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H.H. SHEIKH HAMDAN BIN RASHID AL MAKTOUM

Deputy Ruler of Dubai

UAE Minister of Finance

President of Dubai Health Authority

Patron of the Sheikh Hamdan Award for Medical Sciences

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Cover Art

With the availability of human DNA or protein sequences, early methods of sequence alignment were applied to predict the etiology of a DNA change, whether a disease causing mutation or a neutral polymorphism, to identify regions of similarity that may hint for functional or structural relationships, or assign evolutionary relationships and predict ancient routes of human dispersal.

The availability of complete genome sequences and powerful computational tools offered the possibility to perform global alignment of complete genomes to draw comparisons between genomes of different organisms, to predict coding sequences, to analyze repetitive sequences, to compare chromosomal sequences, and to analyze human sequence variability in health and disease states.

The poster concept for HGM 2011 revolves around present applications of Comparative Genomics to help depicting disease-related variations and study evolutionary relationships among world populations. The poster hosts a second embedded concept where colored lines indicate the main routes for the early dispersal of anatomically modern humans according to the Recent African Origin theory.

Research and Concept: Dr. Ghazi O Tadmouri

Artistic Realization: Mr. Jamal Halloum

MESSAGES

Dr Hanif Hassan Ali Al Qassim

Minister of Health, UAE
Chairman, Board of Trustees,
Sheikh Hamdan Bin Rashid Al Maktoum Award for Medical Sciences

It gives me great pleasure to warmly welcome you here to Dubai and the UAE to conduct your important scientific deliberations in the field of human genomics. Your focus on 'Genomics of Human Diversity and Heritable Disorders' along with the 4th Pan Arab Human Genetics Conference is extremely relevant and of great consequence globally. It is of particular interest to us here in the Arab region, for as many of you are acutely aware, the prevalence of genetic disorders is disproportionately high in our communities. Many factors contribute to this situation and we are looking forward to working with you in the future to address those factors.

Genetic disorders inflict suffering for people who grapple with the long term effects they impose; chronic illness and disability undermine the lives of many. They also impose significant burdens on families and on our social systems, inflicting tremendous human and economic costs. We must reduce our burdens and find solutions for these conditions. It is essential that the work of the Human Genome Organisation and the Centre for Arab Genomic Studies continue with focus and speed. As we have learned about your organization's purpose and mission we see some parallels with our own vision for the UAE; it is appropriate for you to have chosen Dubai as your meeting place. Like you, we are focused on building a new future that embraces the best that technology has to offer and we are embedding that technology in the infrastructure – the DNA - of Dubai. What you see as you travel around this city and the UAE are environments in the building stages. Our DNA is shaping our skeletons and backbones, organizing our systems and movements. Our culture and heritage are rich with the foundations of science and discovery. Like you, we embrace these ideas to help us create a healthier future for our people. We welcome you to explore our country and to be greeted by our Arab culture of hospitality and respect.

We congratulate you on your work and your remarkable achievements to advance medical science by developing new technologies and techniques in the field of human genome therapy. We applaud your efforts to help those struggling with previously untreatable disease. Your work is essential to our individual and collective futures. Your work will reshape the health of individuals and populations around the globe. We are honored to have you here with us. Thank you for your commitment and your dedication. We wish you great success in your deliberations here and in your work ahead.

MESSAGES

Prof Edison T Liu

HUGO President
Executive Director, Genome Institute of Singapore

I wish to welcome all delegates of the HGM 2011 meeting in Dubai. The focus of this conference is on the next generation of genomic technologies and their impact on heritable disorders. The burden of disease from genetic disorders has been significant in many of the countries in this region. However, as we discover genetic causes of subtle phenotypes the level of this burden may formally rise. We have placed HGM 2011 in the Middle East and in particular in the Gulf States in recognition of the critical mass of talent, the significant advances in infrastructure and capabilties in this region, in addition to the medical need. Indeed, in this conference, Ruth Chadwick from HUGO's Ethics and Society Committee will be presenting the conclusions of the deliberations held in Geneva 2010 on the impact of next generation sequencing in our conceptualization of medicine. In addition, we will be describing the next Pan Asian Personal Genome Project. We have several special symposia and workshops that extend our scientific discussions into economic development, ethics, and global collaborative networks. We wish to highlight these advances at the conference and to have HGM 2011 as a venue to enhance collaborations between regional and international scientists.

The pace of change in genomic medicine has been breathtaking, and HUGO is also changing, reflecting both the nature of genomics sciences, and the interests of our membership. We are more global with greater representation from countries who are new entrants in genomic research, and we are more diverse in what we call our intellectual domain. So we encourage all regional scholars in the genomics and genetics field to join HUGO and make your voices heard. HUGO, as an organisation, is advancing. We have launched a new journal the HUGO Journal which is going into its second issue, we have successfully completed several symposia including one on the Genomics of Breast Cancer in 2010, and our plans for HGM 2012 in Sydney are progressing well. I wish you all an exciting conference.

MESSAGES

Prof Najib Al Khaja

Secretary General,
Sheikh Hamdan Bin Rashid Award for Medical Sciences
President, HGM 2011

I am delighted to welcome you to Dubai to attend the Human Genome Meeting 2011, organized by the Centre for Arab Genomic Studies, on behalf of the Human Genome Organisation.

The theme for HGM 2011 is 'Genomics of Human Diversity and Heritable Disorders'; always a topical subject, but more so, given the high burden of monogenic disorders in the Arab World. The inspiring program will include special talks, symposia, expert sessions, working summits, special fora, and exhibitions, which will bring together renowned experts, senior and junior investigators and researchers in genomics and related fields to share basic and translational research as well as educational and social issues. In association with the HGM 2011 meeting, the Centre for Arab Genomic Studies is also organizing its Fourth Pan Arab Human Genetics Conference, bringing together a wide platform of regional and international scientists to discuss common issues in human genetics. I hope that this meeting offers ample opportunities for potential collaborations between the delegates. Other satellite meetings organized in conjunction with HGM 2011 and the 4th PAHGC will be aimed at highlighting advancements in genomics and genetic applications in the region.

On behalf of the Local Organizing Committee, the Centre for Arab Genomic Studies and the Sheikh Hamdan Award for Medical Sciences, I thank you for your participation in HGM 2011, and hope that you have an active, stimulating, and enjoyable conference.

EDITORIALS

Human Genome Organisation

Human Genome Organisation (HUGO) is an international organisation of scientists involved in various aspects of human genetics. HUGO was conceived in 1988 at the first meeting on Genome Mapping and Sequencing at Cold Spring Harbor, New York. From an initial group of 42 scientists from 17 countries, HUGO has increased its membership to over 1,400 members, from over 70 countries in a period of only two decades. Over the years, HUGO has played an essential role behind the scenes for the human genome project. With its mission to promote international collaborative efforts to study the human genome and the myriad issues raised by our increasing knowledge of the genome, HUGO has had noteworthy successes in some of the less glamorous, but nonetheless vital, aspects of the human genome project.

As a truly international organisation, and currently in its 23rd year, HUGO refocused its efforts towards the medical implications of genomic knowledge. Looking forward, HUGO is working to enhance the genomic capabilities of the emerging and developing countries of the world. The excitement and interest in genomic sciences in Asia, the Middle East, South America and Africa are palpable and our hope is that these technologies will help to aid national development and worldwide health.

Mission Statement

> To investigate the nature, structure, function and interaction of the genes, genomic elements and genomes of humans and relevant pathogenic and model organisms;

> to characterise the nature, distribution and evolution of genetic variation in humans and other relevant organisms;

> to study the relationship between genetic variation and the environment in the origins and characteristics of human populations and the causes, diagnoses, treatments and prevention of disease;

> to foster the interaction, coordination, and dissemination of information and technology between investigators and the global society in genomics, proteomics, bioinformatics, systems biology, and the clinical sciences by promoting quality education, comprehensive communication, and accurate, comprehensive, and accessible knowledge resources for genes, genomes and disease; and

> to sponsor factually-grounded dialogues on the social, legal, and ethical issues related to genetic and genomic information and championing the regionally-appropriate, ethical utilisation of this information for the good of the individual and the society.

For further information please visit www.hugo-international.org

EDITORIALS

Sheikh Hamdan Bin Rashid Al Maktoum Award for Medical Sciences

Sheikh Hamdan Bin Rashid Al Maktoum Award for Medical Sciences was established in 1999 under the patronage of H.H. Sheikh Hamdan Bin Rashid Al Maktoum, Deputy Ruler of Dubai and Minister of Finance & Industry, with the objective of honouring scientists from every part of the world who tirelessly pursue distinctive medical research that serves the larger interests of humanity.

The initial focus of the foundation was on two major categories of awards, the International and National categories. In the international category, there were three sections, the Grand Hamdan Award, three Research Excellence Awards and four awards for volunteers in humanitarian medical services. In subsequent years, an additional category of the Arab World Award was introduced followed by an additional award to the UAE category- an award for the Clinical Department in the public sector. Today, the foundation's emphasis is on supporting and encouraging scientific research in the UAE with the provision of research grants. This activity has already yielded excellent results with publications in reputable journals.

The vision of H.H. Sheikh Hamdan Bin Rashid Al Maktoum to alleviate human suffering from genetic diseases in the Arab World crystallized in the establishment of the Centre of Arab Genomic Studies to characterize and prevent genetic disorders and transfigure the future practice of health care in the region. Today the centre is having a fully fledged database called CTGA – CATALOGUE FOR TRANSMISSION GENETICS IN ARABS. Further to the development in this field was the formation of the Arab Council which further extended the activities of this centre to the Arab World. It resulted to the completion of UAE, Bahrain, Oman, and Qatar databases, while work on Kuwait is in the process, and is expected to be completed within this year.

Over the years, the awards have created a rich resource of works by leading researchers and doctors from across the world and believed that a journal could be sustain that would be treasured by the medical community. Hence, the Journal of Medical Sciences was born in 2006, and started publishing as a quarterly publication. Three volume issues of the journal have already been published, while the fourth volume issue is in the stands, available in both print and electronic versions. The journal is also in the process of review by PUBMED international and the Chemical Abstracts, indexed with Index Medicus for the Eastern Mediterranean Region (IMEMR).

The foundation is now in the 7th term of awards and besides enriching scientific research, it has an additional objective of enhancing the nature of scientific interaction between doctors in this country and the overseas medical centres. The subjects of the awards are selected carefully to reflect scientific advances made in the subject. The subject for the Grand Hamdan International Award for 2011-2012 is Neonatal Medicine. Hamdan Award for Medical Research Excellence is the second award in the International category and there are 3 subjects selected and will be award to 3 winners. The subjects are "Fetal Medicine, Nutrition in infants and inborn errors of Metabolism. As per the agenda of the awards, evaluation involves determining the factor will be a research breakthrough in the subject selected for the award, having the potential to have a major impact on healthcare delivery. The systematic way of assessing or evaluating the excellent work or individual who have been nominated for the award on the selected subject have been completed for the last 6 terms were very professional. We expect a good number of excellent nominations from various parts of the world for the current term of 2011-2012. For more information and the details including rules & regulations and how to apply for this award, please visit www.hmaward.org.ae.

EDITORIALS

Centre for Arab Genomic Studies

The Arab World is rich in many genetic disorders; a factor contributed to by the wide-spread norm of consanguinity in the region, selective and environmental factors favoring the persistence of certain genetic traits, and the lack of public awareness towards the early recognition and prevention of inherited disease. As a result, several disease conditions, such as hemoglobin disorders, hypertension, diabetes mellitus, and Down syndrome, among others continue to impact the health system by increased rates of neonatal deaths and morbidity and mortality in children as well as in adults.

The pioneering vision of H.H. Sheikh Hamdan Bin Rashid Al Maktoum, Deputy Ruler of Dubai and UAE Minister of Finance, to alleviate human suffering from genetic diseases in the Arab World crystallized in the establishment of the Centre for Arab Genomic Studies (CAGS) on 25 June, 2003. Since then, the Centre has dedicated itself to the mission of improving human health by characterizing and preventing genetic disorders in Arab countries based on the recent advances in human genetics.

The scientific structure of the Centre for Arab Genomic Studies includes two committees:

1. The Executive Board of CAGS is composed of a number of local scientists and it represents the governing body and the legal trustee of all activities of the centre.

2. The Arab Council of CAGS includes regional scientists and it acts as a consultative body and facilitates the exchange of information on genetic disorders occurring in Arab countries. Countries represented in the Council of CAGS currently include: Bahrain, Egypt, Iraq, Jordan, Kuwait, Lebanon, Oman, Palestine, Qatar, Saudi Arabia, Sudan, and Tunisia.

One of the major projects undertaken by CAGS is the Catalogue of Transmission Genetics in Arabs (CTGA) database, which is a continuously updated, open-access compendium of bibliographic material and observations on human gene variants and inherited, or heritable, genetic diseases in Arabs (www.cags.org.ae). As the database covers country after country in what is the largest scientific effort to define genetic disorders in Arab people, a clearer picture of the pattern of genetic disorders and effective strategies to prevent them, is emerging. Currently, the database hosts entries for nearly 955 genetic disorders and 373 related genes.

CAGS regularly comes out with open access publications, aimed at both the scientific community as well as the public. The Centre's major publication has been its series of books on "Genetic Disorders in the Arab World". This compilation is a consequence of CAGS' work on cataloguing Arab genetic disorders. Thus far, three volumes of these books have been published. CAGS also comes out with articles in scientific journals time and again. At the level of the public, CAGS also published two series of pocket guides on inherited blood disorders and cancers common in the region. These guides contain basic information on the disorders, their causes, and their management, along with some information on the epidemiology of the disease in the Arab World. CAGS has also come out with a handy User's Guide on the CTGA Database which simplifies the database for the end-user.

EDITORIALS

One of the major activities of CAGS is to conduct cutting edge research in the field of genetic disorders seen in the Arab World. One example that clearly demonstrates the efforts undertaken by CAGS towards achieving this objective is project related to the identification of a rare skeletal abnormality in an extended consanguineous family in the UAE early in 2005. Scientists at CAGS conducted extensive clinical and molecular analysis for all affected and non-affected family members in collaboration with other international groups. The genetic depiction for this disorder is expected to bring fresh insights to our understanding of the human genome and pave the way for many similar projects in light of the presence of many non-characterized inherited disorders in Arab populations.

The Pan Arab Human Genetics Conference (PAHGC) is a biennial event organized by CAGS every alternate year. This event provides a common platform to bring together regional and international geneticists to share their knowledge and to discuss common issues. Undoubtedly, the organization of this conference series has been a huge contribution of CAGS towards the study on human genetics in the region and this conference has become one of the most awaited events in the calendar of human genetics. The first edition of the conference, held in 2006, was supported by the Human Genome Organisation (HUGO), and attracted more than 500 delegates. This was the first large-scale event on human genetics to be held in the Arab World, and was a tremendous success in terms of providing a platform for various leading geneticists to work out strategies and set the priorities for research aimed at combating the menace of genetic disorders in the region.

In the near future, CAGS shall witness an expansion of all its activities according to the requirements of its working objectives. The CTGA Database is expected to continue its growth and will continue to cover other countries of the region in its effort to catalogue the entire spectrum of genetic disorders in the Arab World. Consequently, additional volumes of the series of books on “Genetic Disorders in the Arab World” shall be made available following the completion of data collection in new Arab countries. Meanwhile, CAGS will expand its research activities directed at understanding the molecular basis of genetic disorders in the Arab populations. Setting up the required infrastructure to launch the Arab Human Variome Project could also be an interesting initiative to explore. The Pan Arab Human Genetics Conference will continue to be organized regularly as a platform to discuss contemporary issues in genetic research pertaining to the priorities of the region. Hosting the Annual Human Genome Meeting (HGM) of the HUGO in Dubai is another feather in the cap for CAGS, and is expected to provide a significant boost to genetic research in the region.

The support of H.H. Sheikh Hamdan Bin Rashid Al Maktoum has been instrumental in achieving most of the Centre’s objectives. This support has been further reinforced with the establishment of a CAGS genetics award to honor individuals and institutions working in the field with an aim to encourage genetic research in the Arab World. Surely, this task will bring CAGS closer to its mission to build sustainable research activities based upon education and improvement of human health in the Arab World.

HGM 2011 INTERNATIONAL SCIENTIFIC COMMITTEE

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Najib Al Khaja

HUGO PRESIDENT

Edison T Liu

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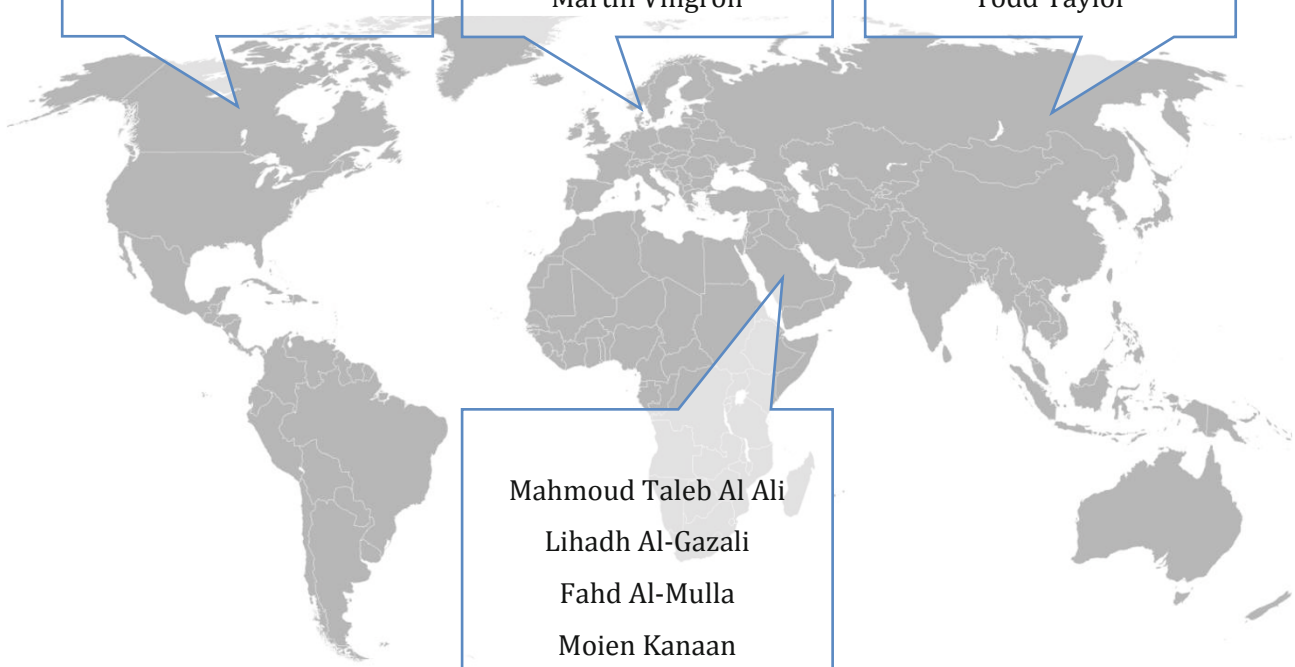

Mahmoud Taleb Al Ali
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Fahd Al-Mulla
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ACKNOWLEDGMENTS

HGM 2011 has received financial support from the following organisations. We would like to extend our utmost appreciation to them for all of their support.

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GENERAL INFORMATION

On-Site Registration

On-Site Registration Desks located at the entrance of Sheikh Maktoum Hall will be operational as per the following schedule:

Sunday	13 March	12.00 NN – 7.00 PM
Monday	14 March	8.00 AM – 5.00 PM
Tuesday	15 March	9.00 AM – 5.00 PM
Wednesday	16 March	9.00 AM – 5.00 PM
Thursday	17 March	9.00 AM – 12.00 NN

The conference bag containing the HGM 2011 Programme/Abstract book and other essential information can be collected at the On-Site Registration Desks.

Badges

Badges will be issued upon registration and must be worn at all times during HGM 2011. Friendly Hosts/Hostesses will be manning each entry point to the scientific sessions and anyone without a badge will be refused entry**.** Replacement badges will incur a charge of USD 20 each. Your badge allows you to attend the scientific sessions on each day and the Welcome Cocktail Reception on Monday, 14 March.

Badges are colour coded as follows:

Blue	–	Speakers and Session Chairs
Red	–	Participants
Green	–	Exhibitors
Black	–	Staff and Volunteers

Travel/Tourist Information

Please drop by the Information Desk at the entrance of Sheikh Maktoum Hall and speak to our friendly representatives for information and booking of sightseeing and excursion tours. HGM 2011 registrants will be offered a 10% discount on the published tour rates.

Welcome Cocktail Reception

The Welcome Cocktail Reception will be held in the Exhibition Area (Sheikh Maktoum Hall) on Monday, 14 March from 6.00 pm – 7.00 pm. All HGM 2011 registrants and their registered accompanying persons are welcome to attend, so please come and support our exhibitors and sponsors while enjoying a cocktail.

Gala Dinner

The HGM 2011 Gala dinner will take place on Wednesday, 16 March. Tickets must be purchased in advance. If you have purchased your gala dinner ticket(s) during the pre-registration process, you will receive your ticket(s) at the time of delegate badge collection. If you have not purchased your ticket(s) but wish to do so, you may still be able to purchase ticket(s) onsite at USD100/each on 13 & 14 March only, subject to availability. Please contact the On-Site Registration Desks for more information.

GENERAL INFORMATION

Food/Drinks

Complimentary tea, coffee, and light refreshments will be provided in the morning and afternoon tea breaks in the Exhibition Area (Sheikh Maktoum Hall). During lunch, delegates can purchase a range of reasonably priced drinks and snacks from the refreshment areas located within the Exhibition Area. Alternatively, you may choose amongst one of the following outlets located within the Dubai International Exhibition Centre, all within walking distance from Sheikh Maktoum Hall.

Blue Bar
Ground floor,
Novotel Hotel Bar
14:00 – 02:00

Café Cream
Ground floor,
Novotel Hotel Coffee Shop
07:00 – 23:00

Chianti‘s
Ground floor,
ibis Hotel
Coffee Shop/Bar
09:00 – 01:00

Chills
Pool, Novotel Hotel
Pool Bar
10:00 – 19:00

Coffee Bean & Tea Leaf
Concourse 1, Hall 1
Coffee Shop
07:00 – 23:00

Cubo
Ground floor,
ibis Hotel A la Carte
12:00 – 15:00/19:00 – 23:00

Entre-Nous
Ground floor,
Novotel Hotel
Buffet/A la Carte
06:00 – midnight

Le Gourmand
Ground floor,
ibis Hotel
Breakfast 06:00 – 10:30

Loop
Concourse 2, Hall 7
Self-service
09:00 – 19:00

Lotus One
Ground floor,
Convention Tower
Fusion, A la Carte
12:00 – 15:00/19:30 – 02:00

Options
Ground floor,
Convention Tower
Indian,
12:00 – 15:00/19:00 – 02:00

Round Table Pizza
Concourse 1, Hall 2
Pizzeria

The Hub
Concourse 2,
Sheikh Rashid Hall Coffee Shop
08:00 – 18:00

Za‘abeel Bistro
Za‘abeel Concourse,
Self-service
09:00 – 19:00

Sponsored Lunch Seminars

During the company sponsored lunch seminars, lunch boxes will be offered to the pre-registered attendees (up to a maximum of 200 lunch boxes per seminar). Priority to attend the seminar and receive the lunchbox will be given to delegates who have pre-registered. But you may still be able to attend in case of no-shows. Please ask the hostess at the entrance of the sponsored lunch seminar hall(s) for information and assistance.

Date	Lunch Seminar	Time	Venue
15 March 2011	Affymetrix Lunch Seminar	12.30 pm - 1.30 pm	Maktoum A
16 March 2011	Agilent Technologies Lunch Seminar	12.30 pm - 1.30 pm	Maktoum A
16 March 2011	Illumina Lunch Seminar	12.30 pm - 1.30 pm	Rashid A
17 March 2011	Bio-Rad Lunch Seminar	12.30 pm - 1.30 pm	Maktoum A

GENERAL INFORMATION

Poster Sessions

All printed posters must be put up on the poster boards by 10 am on Monday, 14 March. Each presenter is required to present their poster at the session specified by their poster number in the Poster directory. Presenters who are not stationed at their poster during the specified session will not be eligible for Poster Prizes.

Poster Session 1	(T)	Tuesday	15 March	12.30 pm - 1.30 pm
Poster Session 2	(W)	Wednesday	16 March	12.30 pm - 1.30 pm
Poster Session 3	(TH)	Thursday	17 March	12.30 pm - 1.30 pm

Springer Poster Competition

HUGO is delighted that Springer, a major publisher of books and journals in the field of genomic medicine - including The HUGO Journal, the Official Journal of the Human Genome Organisation, will be sponsoring a poster competition at HGM 2011. The competition will be judged by members of the HUGO Council and the HGM 2011 International Scientific Committee. Three prizes will be given out and each prize is a one year subscription to various Springer Journal(s) of your choice as well as to The HUGO Journal.

HUGO Gene Nomenclature Committee Nomenclature Poster Prize

The HUGO Gene Nomenclature Committee (HGNC) will again be awarding prizes to the authors of the three posters which contain the HIGHEST NUMBER of approved gene symbols. This will be judged by members of the HGNC team with a score of +1 for use of a correct symbol and -3 for an incorrect one. Each prize is a one year subscription to one Springer Journal of your choice and to The HUGO Journal; the HGNC would like to thank Springer for their sponsorship of this competition.

Chen Award 2011

HUGO wishes to thank Professor Yuan-Tsong Chen and Alice Der-Shan Chen of the Chens‘ Foundation for the honour of once more administering the Chen Award (2011). Please join us to celebrate the achievements and talents in Genomic Sciences in the Asia Pacific region at the Chen Award lecture(s) at HGM 2011.

Getting to HGM 2011

Delegates staying at the HGM 2011 Official Hotels are entitled to our pre-scheduled complimentary shuttle bus service(s) to get to the Dubai International Convention & Exhibition Centre. Please refer to the shuttle service timetable in your delegate bag.

Alternatively, we encourage you to take the recently inaugurated Dubai Metro. The World Trade Centre metro station allows direct access to the HGM 2011 venue from prominent locations around Dubai. The station (number 22) is on the Red Line within Zone 5. Trains run every 7 minutes to all major business, tourist and residential areas, and with options such as Park and Ride, or feeder buses which connect your neighbourhood to the metro. Using the metro not only saves you time and reduces traffic on the roads, but also lowers our carbon footprint which helps us work towards a greener environment. There will be no car park redemption from HGM 2011.

Station opening times: Saturday to Thursday 6am to 11pm
Friday 2pm to midnight

GENERAL INFORMATION

Parking at HGM 2011

Free Car Parking operating on a first-come, first-served basis:

Car Park B (open) - Opposite Convention Gate. Approx. number of car parking spaces: 657
Car Park C (open) - Opposite Convention Gate. Approx. number of car parking spaces: 1457
Car Park D (open) - Opposite Convention Gate. Approx number of car parking spaces: 470
Car Park F (open) - Opposite Zabeel Entrance. Approx number of car parking spaces: 500

Multi-storey Car Park (paid parking)
Level 3 – 6 (covered / Behind Sheikh Rashid Hall / Approx. number of car parking spaces: 996

A nominal parking fee per hour is applicable from 6:00 am to 20:00 pm from Saturdays to Fridays. Parking outside these hours is free, but please note vehicles are not allowed to park overnight or longer. Any vehicle left overnight will incur a penalty fee and DWTC reserves the right to remove all vehicles remaining in the car park after the permitted 24-hour period.

Vehicles are not allowed to park within the _no parking zones‘, and DWTC reserves the right to remove any vehicles that are parked incorrectly or causing obstruction to other road users.Violators will be charged a daily fee plus administration fees.

A parking token is issued on arrival and must be submitted for payment on departure. A lost parking token will be charged in addition to the respective hourly parking charges, and it is not refundable. The grace period between payment and departure from the parking zone is 15 minutes.

Prayer Rooms

A men‘s prayer room is located on level 2 opposite Exhibition Hall 5 and the ladies‘ prayer room is located on level 2 opposite Exhibition Hall 7. Prayer rooms are also available near Za‘abeel Hall.

Lost And Found Office

The Lost and Found office is located on the podium at Convention Gate heading towards Novotel and is responsible for the safekeeping of items that have been found at the premises. Items will be returned to the rightful owner upon presentation of reasonable proof of ownership. HGM 2011 Organizers and DWTC assumes no responsibility for the care and/or protection of any personal belongings left unattended on DWTC property or for the loss, under any circumstance, including theft, vandalism, or malicious mischief of any such belonging. Anybody losing property should report the details to the Lost and Found office as soon as they become aware of the loss. Losses may be reported by phone to: Tel +971 (0)4 308 6440 or in person, and must be followed up with an official report of loss, theft, or disappearance.

Non-Smoking Policy

As per Dubai Municipality law, the entire complex has been declared non-smoking. A fine will be charged to all violators. Smoking is allowed outdoor in designated areas.

GENERAL INFORMATION

Outlets

A wide range of outlets located in are available in Concourse 1 and Concourse 2:

DWTC Business Centre	Concourse 1
Courier service	Concourse 1
Travel agency	Concourse 1
Car rental	Concourse 1
Mobile phones	Concourse 1
Florist	Concourse 1
Jewellery and gift shops	Concourse 1
Banks and ATMs	Concourses 1 & 2
Etisalat	Concourse 2
Pharmacy	Concourse 2
International money exchange	Concourse 2
Signage and graphics	Concourse 2
Post office	Concourse 2

About Dubai

Dubai, the 21st century Arabia, is the ultimate location that offers all HGM 2011 delegates the very best of facilities, easy accessibility, expansive infrastructure, and, above all, a culture of hospitality. It is one of the world‘s most intriguing, ultramodern, and cosmopolitan destinations located at the crossroads of Asia, Europe, and Africa. An enjoyable climate, sparkling nightlife, intriguing culture, and ingrained hospitality are aspects of Dubai that every delegate will enjoy. From the timeless tranquility of the desert to the lively bustle of the city center at Bur Dubai, Dubai offers a kaleidoscope of attractions for visitors. In a single day, guests can experience everything from rugged mountains to sandy beaches; from awe-inspiring sand dunes to lush green parks; from dusty villages to luxurious residential districts; and from ancient souks to ultra-modern shopping malls. The Emirate is both a dynamic international business centre and a laid-back tourist escape. Truly, it is a city where the sophistication of the 21st century walks hand in hand with the simplicity of old Arabia. These contrasts give Dubai its unique flavor and personality, a society of local traditions with an international lifestyle.

Lifestyle

Citizens, expatriates and visitors alike, enjoy a relaxed and pleasant lifestyle. There is virtually no crime, the city is clean and there is a wide choice of modern and spacious accommodation. In addition, Dubai has a choice of cuisine to suit any palate and all pockets. Arabic is the national language. However, English is widely spoken throughout Dubai, so you will have no problem getting around. Dubai is secular and tolerant, freedom of worship is allowed to all religions and Christian churches have existed in Dubai for many years. Alcohol may be consumed at home, in hotels and on licensed club premises. Women can drive and move about freely unaccompanied. There is zero tax on personal and corporate income in Dubai and there are low import duties. Hotels charge a 10% service charge and a 10% municipality fee.

Culture and Heritage

The culture in Dubai is rooted in Islamic traditions that form the UAE‘s national lifestyle. The country‘s Rulers are keen to maintain the emirate‘s culture and heritage and actively support many sporting events that are representative of their past, including falconry, camel racing and dhow sailing.

GENERAL INFORMATION

Visitors Information

Banks: Many international banks are represented by branches in Dubai. Bank hours vary but in general are 0800 to 1400, Sundays to Thursdays and 0800 – 1200, Saturdays.

Business Hours: 0800-1300 and 1600-1930, Sundays to Thursdays. Most of the multinational companies work from 0900-1800 with a one hour lunch break. Government offices: 0730-1430, Sundays to Thursdays.

Exchange Houses: 1000-2200. Shopping malls: 1000-2200, Sundays to Wednesdays and 1000-0000, Thursdays and Fridays.

Climate: The UAE has a sub-tropical, arid climate. May to September is summer, when temperatures range between 40ºC and 48ºC. However, during the winter months, temperatures range from 10ºC to 30ºC. Rainfall is predominantly in winter and amounts to some 13cm annually.

Clothing: Summer clothing may be worn for most of the year but the temperature can drop during the winter. At the pool or on the private beaches, swimwear is quite acceptable, but when in the city and public areas, care should be taken not to give offence by wearing clothing that may be considered revealing.

Credit Cards: American Express, Diners Club, Visa, MasterCard, etc. are generally accepted in the main hotels and shops.

Currency: The monetary unit is the Dirham (AED), which is divided into 100 fils. It is fixed to the US dollar at a current rate of US$1 = Dhs3.675.

Language: The official language is Arabic but English is widely spoken and understood throughout the country.

Alcohol: Alcohol is freely available in hotels, clubs, restaurants and bars. However, many restaurants outside hotels are not permitted to serve alcoholic beverages.

Local Time: Gulf Standard Time: + 4 hours GMT

Photography: Normal tourist photography is acceptable but like anywhere in the world, it is courteous to ask permission before photographing people, especially local women.

Media: There are three English language newspapers published in Dubai. International newspapers, magazines and journals can be bought at bookshops and supermarkets. Dubai has both Arabic and English commercial radio and television stations, as well as access to international satellite TV programming.

Communication: The international dialing code for in-coming calls is +9714. Calls to and from land-lines within Dubai are free of charge and direct dialing is possible to more than 170 countries. GPRS and WAP services are also available. A GSM international roaming service for mobile phones is available for over 60 countries. If your country isn‘t one of them then a service known as ―Wasel” is available. Bring your phone or buy it here and purchase a SIM card (available at most supermarkets, petrol stations and hotels) which enables you to make and receive calls from the UAE. Internet services are also available for non-subscribers from regular phone lines.

Medical: Medical services in Dubai are of an international standard.

GENERAL INFORMATION

Bargaining: Bargaining is expected in the souq and is quite usual everywhere. Vendors will usually drop the price and often quite substantially, particularly for a cash sale.

Tipping and Gratuities: Tipping practices are similar to most other parts of the world. Most restaurants include a 10% service charge, but tipping in general is at the customer‘s discretion.

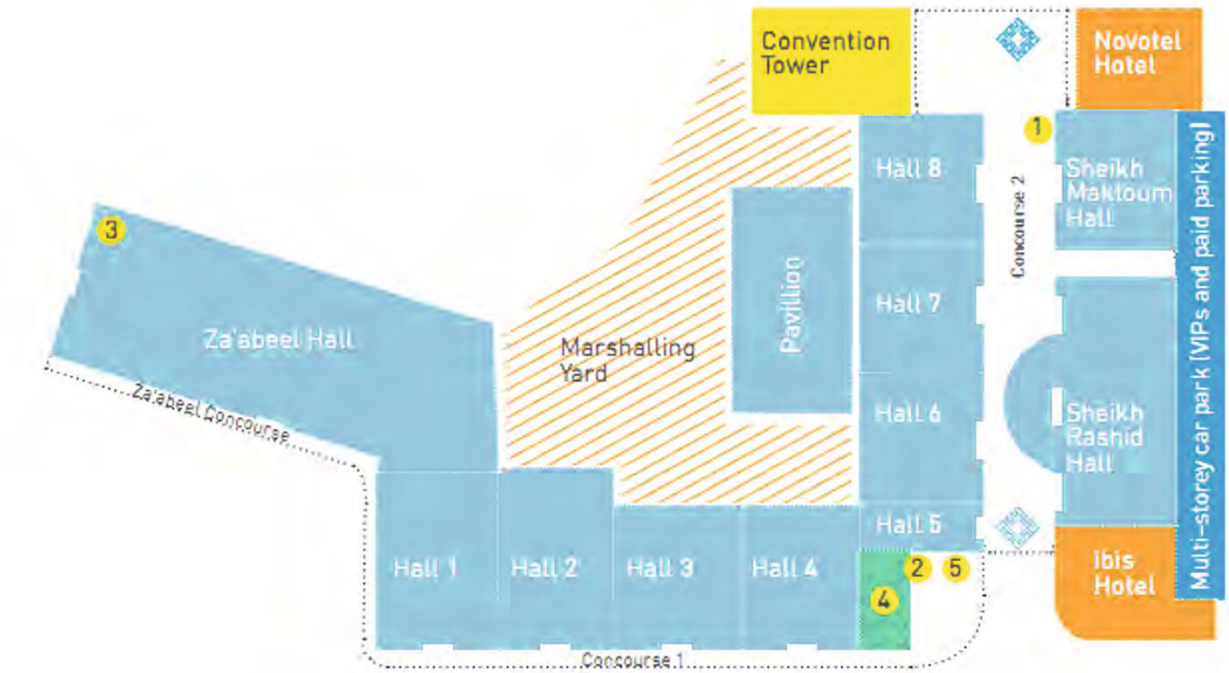
Electricity: The electricity supply in Dubai is 220/240 volts at 50 cycles. Standard, British square three-pin plugs are the norm in most hotels. US-made appliances may need a transformer.

Water: The tap water in Dubai is safe to drink. But locally bottled mineral water is generally served in hotels and restaurants.

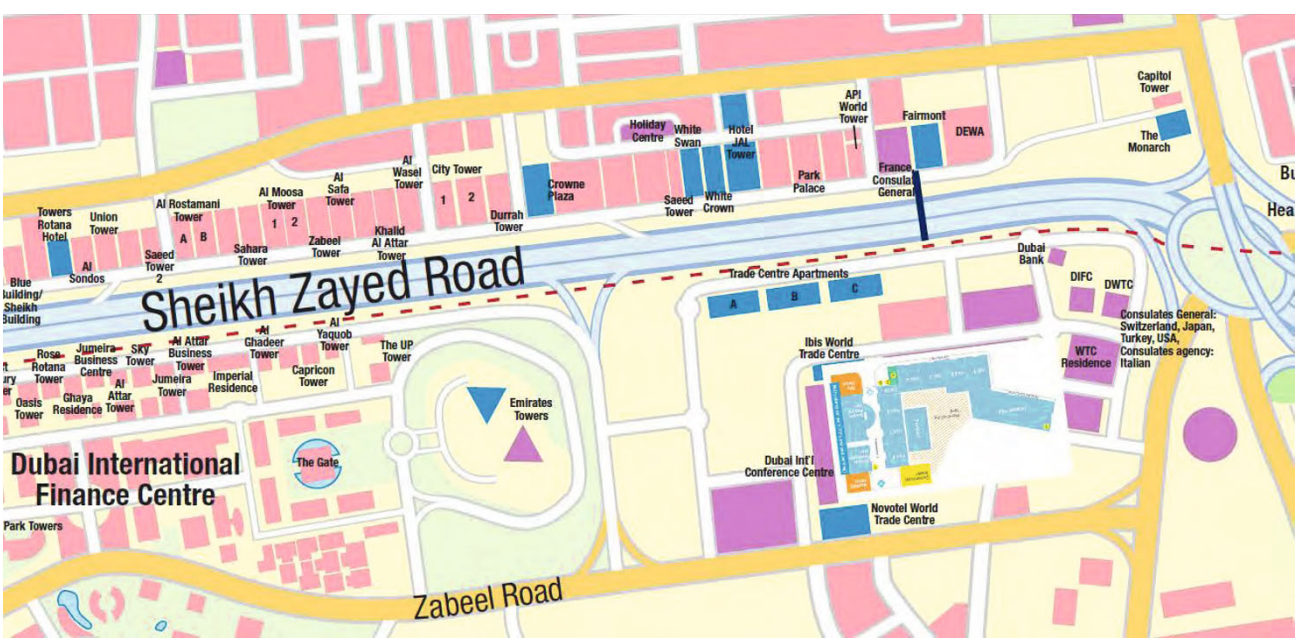
Major Tourist Attractions

Bastakia Area
Burj Al Arab
Burj Khalifa
Deira City Centre
Desert Safari
Dubai Creek
Dubai Festival City
Dubai Fountain
Dubai Mall
Dubai Marina
Dubai Walk
Gold, Spice and Textile Souks
Jumeirah Mosque
Jumeirah Palm Island
Karama District
Mall of the Emirates
Medinat Jumeirah Souk

MAPS



Dubai International Convention & Exhibition Centre (situated in World Trade Center)



Area map

Join us at our Lunch Seminar
March 16th 2011 at 12:30-1:30 p.m.
to hear the latest news on our
Cytogenetics and NGS Product Portfolio.
Come to register at booths #109-110!

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The Measure of Confidence

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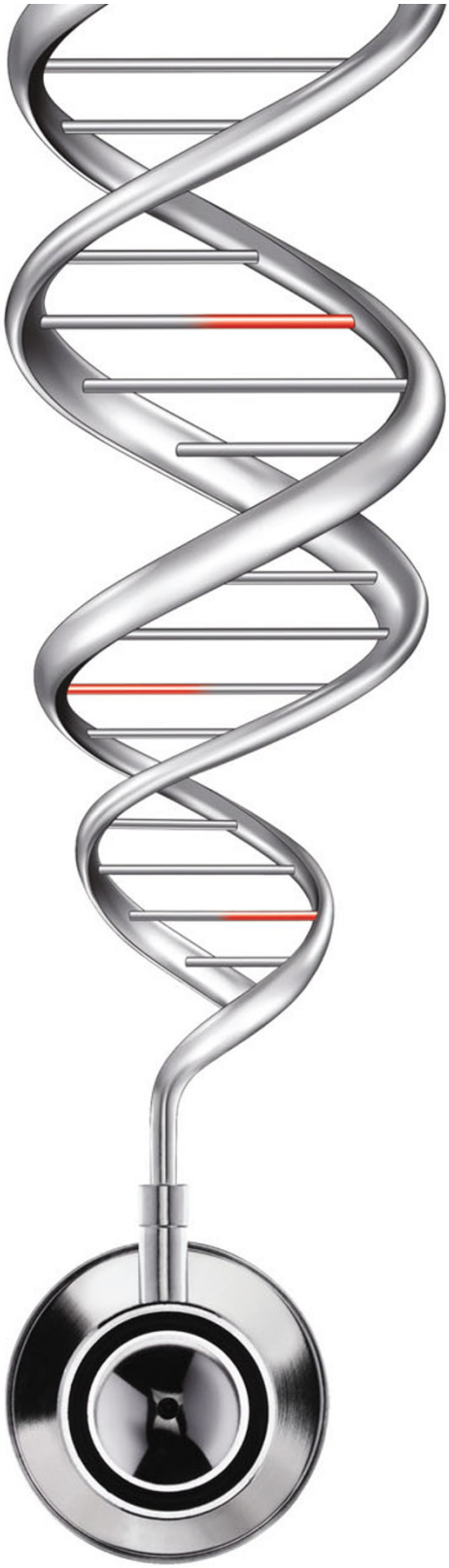

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PROGRAM AT A GLANCE

DAY 1	**14th MARCH 2011**		
10.00 am – 11.00 am	Opening Ceremony		
11.00 am - 12.00 nn	Opening Keynote Lecture		
12.00 nn – 12.45 pm	Featured Talk		
12.45 pm – 2.30 pm	*Lunch Break*	*Press Conference*	
2.30 pm – 6.00 pm	Featured Talks		
6.05 pm – 7.00 pm	*Special message from HUGO President & Welcome Cocktail Reception*		
DAY 2	**15th MARCH 2011**		
9.00 am – 12.30 pm Symposia	RNA and Epigenetic	Genomic Medicine	Genetics of Heritable Disorders
12.30 pm – 1.30 pm	*Lunch Break*		
1.45 pm – 4.45 pm Working Summits	Converging Technologies In Genomics: Opportunities for a Global Economy	Global and Regional Initiatives: Pan Asian Personal Genomics Initiative	Global Ethical and Legal Challenges in Genomics and Genetics
4.45 pm – 6.15pm	Featured Talks		
DAY 3	**16th MARCH 2011**		
9.00 am – 12.30 pm Symposia	From Genome Variation to Personalised Medicine	Inborn Errors of Metabolism and Therapy of Genetic Disorders	Cancer Genomics
12.30 pm – 1.30 pm	*Lunch Break*		
1.45 pm – 4.15 pm Expert Sessions	Mechanism of Genome Sequencing: Setup and Operations of a Facility	Computational Analysis of Genomic Information	The Human Variome Project and the Arab Countries
4.45 pm – 6.15pm	Featured Talks		
7.00 pm – 11.00pm	*Conference Dinner*		
DAY 4	**17th MARCH 2011**		
9.00 am – 12.30 pm Symposia	Computational Biology and Statistical Genetics for the Analysis of Human Disease	Genetics of Deafness & Neurologic Disorders	Advances in Genetics of Heritable Disorders
12.30 pm – 1.30 pm	*Lunch Break*		
1.45 pm – 4.00 pm	Special Forum: Genome Sequencing Landmark Technologies	RIKEN Session: Expanded Universe of Single Cell Biology	
4.15 pm – 5.45pm	Featured Talks		
5.45pm – 6.00pm	Closing Remarks		

14 MARCH 2011 FULL PROGRAM

14 March 2011	Program
10.00 am – 11.00 am	Opening Ceremony & Exhibition Inauguration *Venue: Maktoum B & C*
11.00 am - 12.00 nn	Opening Keynote Lecture Chair: Edison T Liu **Sydney Brenner** Reading the Human Genome *Venue: Maktoum B & C*
12.00 am – 12.45 pm	Featured Talk Chair: Edison T Liu **Jun Wang** Personal Genomes are Personalised *Venue: Maktoum B & C*
12.45 pm – 2.30 pm	*Lunch Break Venue: Exhibition Hall* | *Press Conference*
2.30 pm – 3.15 pm	Featured Talk Chair: Edison T Liu **Veronica van Heyningen** From Disease Genes to Biology via Technology *Venue: Maktoum B & C*
3.15 pm – 4.00 pm	Featured Talk Chair: Edison T Liu **Stephen W Scherer** Clinical Context of Copy Number and Structural Variation in the Human Genome *Venue: Maktoum B & C*
4.00 pm – 4.30 pm	*Tea Break Sponsored by Pacific Biosciences Venue: Exhibition Hall*
4.30 pm – 5.15 pm	Featured Talk Chair: Edison T Liu **Ghazi O Tadmouri** Genetic Disorders in Arabs from Clinical Genetics to Human Genome Variability *Venue: Maktoum B & C*
5.15 pm – 6.00 pm	Featured Talk Chair: Edison T Liu **Mark McCarthy** Type 2 Diabetes Genetics: A Global Perspective *Venue: Maktoum B & C*
6.00 pm – 6.05 pm	Special message from HUGO President, **Edison T Liu** *Venue: Maktoum B & C*
6.05 pm – 7.00 pm	*Welcome Cocktail Reception Venue: Exhibition Hall*
7.00 pm – 10.00 pm	HUGO Council Meeting (By invitation only)
7.00 pm onwards	*Free and Easy*

15 MARCH 2011 FULL PROGRAM

15 March 2011	Program		
9.00 am – 12.30 pm Symposia	**RNA and Epigenetics** Chair: John S Mattick & Sumio Sugano ***Venue: Rashid A***	**Genomic Medicine** Chair: Geoffrey S Ginsburg ***Venue: Maktoum A***	**Genetics of Heritable Disorders** Chair: Hanan Hamamy ***Venue: Maktoum B & C***
9.00 am – 9.35 am	**John S Mattick** RNA Regulation of Human Development, Cognition and Disease	**Geoffrey S Ginsburg** Genomic and Personalized Medicine: Foundations and Applications	**Jianjun Liu** GWAS in Chinese Population: Opportunities and Challenges
9.35 am – 10.10 am	**Yoshihide Hayashizaki** An Expanding RNA World	**Edison T Liu** Genomic Medicine in Cancer Care	**Hanan Hamamy** Consanguinity and Novel Technology: Cracking the Code of Autosomal Recessive Disorders
10.10 am – 10.40 am	*Tea Break Sponsored by Malaysian Genomics Resource Centre Berhad (MGRC)* *Venue: Exhibition Hall*		
10.40 am - 11.15 am	**Yijun Ruan** 3D Chromatin Architecture and Transcription Regulation	**Ingrid Winship** Can Genetic Information Reduce the Burden of Disease?	**A Nurten Akarsu** Molecular Analysis of the Rarest of the Rare: Autosomal Recessive ALX-Related Frontonasal Dysplasias
11.15 am – 11.50 am	**Bing Ren** Decoding the Mammalian Genome	**Tim Sprosen** New Models for Large Scale Biobanks	**Samia A Temtamy** Rare Autosomal Recessive Disorders in Egyptians
11.50 am – 12.10 pm	**Ashraf Dallol** RASSF1A Methylation is Predictive of Poor Prognosis in Female Breast Cancer Patients in the Background of Overall Low Methylation Frequency	**Elza Khusnutdinova** Genome-Wide Association Study of Asthma in the Volga-Ural Region of Russia	**Al-Abri Abdul Rahim** The Origin of Human Lactase Persistence in the Arabian Peninsula
12.10 pm – 12.30 pm	**Sukru Tuzmen** High-Throughput RNAi Based Functional Pharmacogenomics for Drug Target Identification in Cancer Genetics and Applications of Quantitative Real-Time PCR	**Swati Subodh** Genomic Signatures: Leading the Way for Personalized Patient Management	**Sergio Pena** Estimating the Extent of Genomic Identity by Descent in Consanguineous Couples
12.30 pm – 1.30 pm	Lunch Break & Exhibition *Venue: Exhibition Hall*	**Poster Session 1** *Venue: Exhibition Hall*	Affymetrix *Lunch Seminar* *Venue: Maktoum A*
1.30 pm – 1.45 pm	*Change of Room*		

15 MARCH 2011 FULL PROGRAM

15 March 2011	Program		
1.45 pm – 4.45 pm Working Summits	**Converging Technologies In Genomics: Opportunities for a Global Economy (Organised jointly by HUGO and OECD)** Chair: Gerardo Jimenez-Sanchez ***Venue: Maktoum A***	**Global and Regional Initiatives: Pan Asian Personal Genomics Initiative** Chair: Edison T Liu, Henry Huanming Yang, Jong Bhak, Timothy Ravasi & Maude E Phipps ***Venue: Maktoum B &C***	**Global Ethical and Legal Challenges in Genomics and Genetics** Chair: Ruth Chadwick & Aida I Al Aqeel ***Venue: Rashid A***
1.45 pm – 2.15 pm	**Gerardo Jimenez-Sanchez** Opportunities for Genomics in the Knowledge Economy	**Charles N Rotimi** Global and Regional Initiatives: The Human Heredity and Health in Africa (H3Africa) Genomic Initiative (1.45 pm – 2.15 pm)	**Ruth Chadwick** Imagined Futures: Capturing the Benefits of Genome Sequencing for Society
2.15 pm – 2.45 pm	**Iain M M Gillespie** Genomics, Realising the Bioeconomy	**Jong Bhak** PASNP2 Proposal: Pan Asian Personal Genome Project (PAPGP) (2.15 pm – 2.30 pm)	**Ellen Wright Clayton** Dealing with the Tsunami of Genomic Data in the Clinic (2.15 pm – 3.00 pm)
2.45 pm – 3.15 pm	**Edison T Liu** Genomics Engineering and Integrated Cancer Research	**Maude E Phipps** Copy Number Variation in Indigenous Malaysians : A Preliminary Analysis (2.30 pm – 2.45 pm)	**Aida I Al Aqeel** Personalised Translational Medicine in the Developing World, and Knowledge-Based Economy (3.00 pm – 3.30 pm)
3.15 pm – 3.45 pm	**Pierre Meulien** Genomics and Environmental Sustainability	**Henry Huanming Yang** Genomics: The Door to Personalised Medicine (2.45 pm – 3.00 pm)	**Mohsen A F El-Hazmi** The Ethical Aspects of Biomedical Research - The Saudi Law of Research on Living Beings (3.30 pm – 3.50 pm)
3.45 pm – 4.15 pm	**Samir Brahmachari** Integration of Genomics & the Bioeconomy in the Developing World	**Discussions** (3.00 pm – 3.45 pm)	*Teabreak (3.50 pm – 4.05 pm) Venue: Exhibition Hall*
4.15 pm – 4.45 pm	**Neil Jones** Managing Business Complexity and Change in the Genomic Age	**Global and Regional Initiatives: Centre for Arab Genomic Studies** Chair: Mahmoud Taleb Al Ali & Ghazi O Tadmouri (3.45 pm – 4.45 pm)	**Discussions** (4.05 pm – 4.45 pm)

15 MARCH 2011 FULL PROGRAM

15 March 2011	Program		
		Fowzan Alkuraya Autozygome Decoded (3.45 pm – 4.05 pm)	
		Suzanne Al-Bustan Long runs of Homozygosity in the Kuwaiti Population (4.05 pm – 4.25 pm)	
		Annika FM Haywood Initial Assessment of Human Genetic Diversity in the Saudi Arabian Population (4.25 pm - 4.45 pm)	
4.45 pm – 5.30 pm	Featured Talk Chair: Stylianos E Antonarakis **Christopher A Walsh** Rare Causes of Rare Diseases, and Common Diseases, Affecting Human Cognition ***Venue: Maktoum B & C***		
5.30 pm – 6.15 pm	Featured Talk Chair: Stylianos E Antonarakis **Evan E Eichler** Genome Structural Variation, Exome Sequencing and Neurocognitive Disease ***Venue: Maktoum B & C***		
6.15 pm onwards	Free and Easy		

16 MARCH 2011 FULL PROGRAM

16 March 2011	Program		
9.00 am – 12.30 pm Symposia	**From Genome Variation to Personalised Medicine** Chair: Todd Taylor & Howard L McLeod ***Venue: Rashid A***	**Inborn Errors of Metabolism and Therapy of Genetic Disorders** Chair: Habiba Chaabouni-Bouhamed & Dhavendra Kumar ***Venue: Maktoum B & C***	**Cancer Genomics** Chair: Yijun Ruan & Fahd Al-Mulla ***Venue: Maktoum A***
9.00 am – 9.35 am	**Martin L Hibberd** Human - Pathogen Interactions and Their Outcomes, A Tale of Two or More Genomes and Their Variations	**Y T Chen** Translating the Promise of Genomic Medicine into Clinical Reality: Challenges of Pompe Disease	**Mary-Claire King** Genetic Heterogeneity in Human Disease
9.35 am – 10.10 am	**Howard L McLeod** Learning How to Apply the Genome to Guide Therapy	**Gert-Jan B van Ommen** Translational Genomics, Integrating Rare and Common Disease	**Axel Hillmer** Long Span Paired-End-Tag Mapping Reveals Characteristic Patterns of Structural Variations in Cancer Genomes
10.10 am – 10.40 am	*Teabreak* *Venue: Exhibition Hall*		**Lotfi Chouchane** Breast Cancer in Arab Populations: From Cancer-Oriented Genomic and Proteomic Approaches Towards Preventive and Predictive Medicine (10.10 am – 10.45 am)
10.40 am – 11.15 am	**Y T Chen** Pharmacogenomics of Adverse Drug Reactions: Toward Personalised Medicine	**Arthur L Beaudet** Mutations and Possible Epimutations Causing Schizophrenia and Autism	**Douglas Easton** Recent Developments in the Genetics of Breast and Other Cancers (10.45 am – 11.20 am)
11.50 am - 12.10 pm	**Vajira H.W. Dissanayake** The Sri Lankan Personal Genome Project (SLPGP)	**Said Shawar** The Arabic Allele: A Novel 10BP Deletion in the Low Density Lipoprotein Receptor (LDLR) Creates a Premature Stop Codon and Severely Decreases the Expression Levels in Two Unrelated Arab Families with Familial Hypercholesterolemia	**Alessandro Stella** Analysis of Telomere Dynamics in Peripheral Blood Cells from Lynch Syndrome Patients (11.55 am – 12.15 pm)
12.10 pm – 12.30 pm	**Sridhar Sivasubbu** Comprehensive Computational Pipeline for Systematic Analysis and Annotation of Functional Variants in Personal Genomes	**Giriraj Chandak** Maternal 1-Carbon Metabolism in Pregnancy and Offspring Birth Weight: Epidemiological Associations and Mendelian Randomization in Two Indian Birth Cohorts	**Prakash Hande** Mechanism Based Combination Telomerase Inhibition: Implications for Cancer Therapy (12.15 pm – 12.35 pm)

16 MARCH 2011 FULL PROGRAM

16 March 2011	**Program**				
12.30 pm – 1.30 pm	Lunch Break & Exhibition *Venue: Exhibition Hall*	**Poster Session 2**	Agilent Technologies *Lunch Seminar Venue: Maktoum A*	Illumina *Lunch Seminar* *Venue: Rashid A*	President's Luncheon *(By Invitation only)*
1.30 pm – 1.45 pm	*Change of Room*				
1.45 pm – 4.15 pm Expert Sessions	**Mechanism of Genome Sequencing: Setup and Operations of a Facility** *Sponsored by Genome Institute of Singapore* Chair: Yijun Ruan & Xiaoan Ruan ***Venue: Maktoum A***		**Computational Analysis of Genomic Information** *Sponsored by Genome Institute of Singapore & Genome Quebec* Chair: Anthony J Brookes ***Venue: Rashid A***		**The Human Variome Project and the Arab Countries** Chair: Richard G H Cotton ***Venue: Maktoum B & C***
1.45 pm – 2.15 pm	**Yijun Ruan**		**Guillaume Bourque** Changing Landscape of Computational Biology		**Richard G H Cotton** The Human Variome Project: Supporting the Sharing of Genetic Variation Data
2.15 pm – 2.45 pm	**Herve Thoreau**		**Niranjan Nagarajan** Reconstructing Personal and Disease Genomes		**Fahd Al-Mulla**
2.45 pm – 3.15 pm	**Xiaoan Ruan**		**Pauline C Ng** Characterising Individual Genomes		**Lihadh Al-Gazali**
3.15 pm – 3.45 pm	**Atif Shahab**		**Anthony J Brookes** Towards 'Ideal Healthcare': Optimised and Personalised Future Medicine		**Ghazi O Tadmouri**
3.45pm – 4.15 pm	**Axel Hillmer**		**Discussions**		**Discussions**
4.15 pm – 4.45 pm	*Teabreak*				*Venue: Exhibition Hall*
4.45 pm – 5.30 pm	Featured Talk **Charles Lee** Capturing Copy Number Variants (CNVs) from Whole-Genome Next Generation DNA Sequencing: Perspectives from the 1000 Genomes Project ***Venue: Maktoum B & C***				Chair: Todd Taylor
5.30 pm – 6.15 pm	Special Lecture ***Venue: Maktoum B & C***				Chair:Todd Taylor
6.15 pm – 6.45 pm	*Transfer to Hotels*				
7.00 pm – 7.30 pm	*Transfer to Conference Dinner*				
7.30 pm – 11.00 pm	*Conference Dinner* *(Advance Purchased Tickets required)*				

17 MARCH 2011 FULL PROGRAM

17 March 2011	Program			
9.00 am – 12.30 pm Symposia	**Computational Biology and Statistical Genetics for the Analysis of Human Disease** Chair: Anthony J Brookes & Elspeth Bruford ***Venue: Rashid A***	**Genetics of Deafness & Neurologic Disorders** Chair: Moien Kanaan ***Venue: Maktoum A***	**Advances in Genetics of Heritable Disorders** Chair: Lihadh Al-Gazali & Timothy Ravasi ***Venue: Maktoum B & C***	
9.00 am – 9.35 am	**Goncalo Abecasis** Sequencing Thousands of Human Genomes	**Moien Kanaan** Next Generation Sequencing Approaches to Identify Novel Genes Critical For Hearing	**Lihadh Al-Gazali** Molecular Characterization of Birth Defects: United Arab Emirates Experience	
9.35 am – 10.10 am	**Guillaume Bourque** The Role of Genomic Repeats in Gene Regulation, Diversity and Disease	**Doron Lancet** The Genetic and Molecular Basis of Mendelian Diseases in the Israeli Communities Studied by Novel Genomic Strategies	**Andre Megarbane** Linkage Analysis and Cloning of the Gene Responsible of the Leukodystrophy and Oligodontia Syndrome	
10.10 am – 10.40 am	*Teabreak*		*Venue: Exhibition Hall*	
10.40 am – 11.15 am	**Felix Li Jin**	**Faycal Hentati** Phenotypic and Genetic Aspects of Parkinson Disease in Tunisia	**Nasir Al-Allawi** Molecular Characterization of Inherited Hematological Disorders in Iraqis: Trying to Bridge the Gap	
11.15 am – 11.50 am	**Hiroaki Kitano** Systems Biology and Drug Discovery	**Nadezhda Maksimova** Neuroblastoma Amplified Sequence Gene is Associated with a Novel Short Stature Syndrome Characterised by Optic Nerve Atrophy and PelgereHuet Anomaly (11.15 am – 11.35 am)	**Bassam R Ali** ER-Associated Protein Degradation (ERAD) is a Common Cellular Mechanism for Many Genetic Disorders	
11.50 am – 12.10 pm	**Stephen Sherry** NCBI Resources for Medical Genomics Integrate Mutations, Rare Variants and Common Polymorphisms for Research and Clinical Practice	**Fowzan Alkuraya** In Search of Oligogenicity in Bardet-Biedl Syndrome (11.35 am – 11.55 am)	**Anna Rajab** Understanding Genetics of Congenital Generalised Lipodystrophy in the Sultanate of Oman	
12.10 pm – 12.30 pm	**Joseph Terwilliger** GWAS in Large Families from Inbred Populations is Vastly more Powerful Than Case-Control Analysis Under Arbitrary Etilogical Models	**Lin He** Understanding Schizophrenia by GWAS and Next Generation Sequencing (11.55 am – 12.15 pm)	**Khalid Fakhro** Rare Copy Number Variants in Patients with Congenital Heart Disease Identify Novel Genes in Vertebrate Left-Right Patterning	
		Osama Alsmadi Familial Disorders in Middle Eastern Families: Finding the Causing Genes is Just the Beginning of the End (12.15 pm – 12.35 pm)		
12.30 pm – 1.30 pm	Lunch Break & Exhibition *Venue: Exhibition Hall*	**Poster Session 3**	Bio-Rad *Lunch Seminar* *Venue: Maktoum A*	HUGO Committee Meeting *(By Invitation Only)*
1.30 pm – 1.45 pm	*Change of room*			

17 MARCH 2011 FULL PROGRAM

17 March 2011	Program	
1.45 pm – 4.00 pm	**Special Forum: Genome Sequencing Landmark Technologies** Chair: Yijun Ruan & Herve Thoreau ***Venue: Maktoum A***	**RIKEN Session: Expanded Universe of Single Cell Biology** Chair: Mitsuoki Mick Kawano ***Venue: Rashid A***
1.45 pm – 2.15 pm	**Mostafa Ronaghi** Current and Future Outlook of Genomic Technologies	**Yoshihide Hayashizaki** Opening Remarks (1.45 pm – 1.50 pm)
2.15 pm – 2.30 pm	**Han Cao** Rapid Long Range Genomic Analysis at Single Molecule Level Using Disposable Nanochannel Arrays	**Kai Q Lao** Development and Applications of Single Cell RNA-Seq Analysis (1.50 pm – 2.30 pm)
2.30 pm – 3.00 pm	**Radoje Drmanac** Large-Scale Human Genome Sequencing for Genomic Medicine	**Piero Carninci** Lessons From Miniaturization of CAGE Technology to Study Individual Neuron Types (2.30 pm – 3.10 pm)
3.00 pm – 3.15 pm	**Mike Lelivelt** Semiconductor Sequencing for Life	**Milos Pekny** Molecular Signature of Astrocytes by Single Cell Gene Expression Profiling (3.10 pm – 3.50 pm)
3.15 pm – 4.00 pm	**Discussions**	**Mitsuoki Mick Kawano** Closing Remarks (3.50 pm – 3.55 pm)
4.00 pm – 4.15 pm	Teabreak	*Venue: Exhibition Hall*
4.15 pm – 5.00 pm	Featured Talk **Nicholas Katsanis** Merging Medical Resequencing with Functional Data to Understand Disease Architecture ***Venue: Maktoum B & C***	Chair: Felix Li Jin
5.00 pm – 5.45 pm	Closing Keynote Lecture **George Church** Technologies for Collecting and Integrating Genome, Environment and Trait Data ***Venue: Maktoum B & C***	Chair: Felix Li Jin
5.45 pm – 6.00 pm	**Closing Ceremony** - HGM 2012 (Sydney, Australia) - Poster Awards Presentation - Nomenclature Awards Presentation	
6.00 pm	*End of HGM 2011 and see you at HGM 2012*	

Chen Award

CHENs' FOUNDATION

Chen New Investigator Award
(US$5,000 / 2 Awardees)

This award is giving out in recognition of two young scientists, one within the Asia-Pacific region and one globally, who have made significant contributions to the field during their early career years (normally within 15 years from the time of receiving his/her highest earned degree, in the year of the award).

Chen Award for Distinguished Academic Achievement in Human Genetic and Genomic Research

2008
Dr Li Wen-Hsiung

2010
Prof Yusuke Nakamura

Chen New Investigator Award

2010
Dr Ng Huck Hui

Chen Award for Distinguished Academic Achievement in Human Genetic and Genomic Research
(US$10,000 / 1 Awardee)

This award is to celebrate the achievement of a biomedical scientist who has performed extraordinary work in biomedical sciences which has changed the thinking in the field where important technology was developed; and/or has uncovered new insights which brought forth new therapies; and/or whose lifetime contribution has significantly impacted the Asia-Pacific region.

Professor Yuan-Tsong (Y-T) Chen and Mrs. Alice Der-Shan Chen were both originally from Taiwan and have been committed to biomedical research for over 30 years. They recognise the tremendous impact that genetics and genomics have had on the improvement of health and treatment of diseases and wish to establish the Chen Award to celebrate research accomplishments in Human Genetics and Genomics in Asia Pacific. Professor Chen received his MD degree from National Taiwan University (Taipei) and a PhD from Columbia University (USA). He is currently a Distinguished Research Fellow and Director of the Institute of Biomedical Sciences, Academia Sinica, Taiwan, and Professor of Pediatrics and Genetics at Duke University Medical Center (USA).

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PANEL OF INTERNATIONAL SPEAKERS

14 MARCH 2011 | OPENING KEYNOTE LECTURE

L1

Sydney Brenner

President, Okinawa Institute of Science and Technology Promotion Corporation, Japan
Senior Fellow, Janelia Farm Research Campus, HHMI, USA

READING THE HUMAN GENOME

[No abstract is available]

Dr. Sydney Brenner is a Senior Fellow at the Janelia Farm Research Campus of the Howard Hughes Medical Institute (HHMI). He is also a Senior Fellow of A*STAR and Scientific Advisor to the Chairman of A*STAR. Dr. Brenner joined the Medical Research Council (MRC) in 1957, as a member of the scientific staff in the predecessor of the Laboratory of Molecular Biology and served as Director from 1979 to 1986. He was Director of the Molecular Genetics Unit from 1986 to 1992. Dr. Brenner has been a Scientific Advisor to major biotech venture funds, a consultant to multinational companies and was a founder of several start-up companies. His early research was in molecular genetics, working with bacteriophages and bacteria. He is best known for his work in the 1960's; he discovered messenger RNA (with Jacob and Meselson) and, with Francis Crick, showed that the code was composed of triplets. That discovery won him the Albert Lasker Award in 1971 for basic medical research. He introduced the nematode, Caenorhabditis elegans as a model organism for the study of development and the structure and function of a small nervous system. He initiated research on the compact genome of the puffer fish and led the team which published the draft sequence of the genome. Dr. Brenner, who has been hailed as one of the pioneers of molecular biology, has been associated with Singapore‘s Institute of Molecular and Cell Biology (IMCB) since its very beginning and has seen it grow into the world-class institution that it has become today. For his contributions to the development of life sciences in Singapore, Dr. Brenner has received the Distinguished Friends of Singapore 2000 award. Dr. Brenner received his 2nd Lasker Award for Special Achievement in Medical Science to honor him for 50 years of brilliant creativity in biomedical science – exemplified by his legendary work on the genetic code; his daring introduction of the roundworm Caenorhabditis elegans as a system for tracing the birth and death of every cell in a living animal; and his rational voice in the debate on recombinant DNA. He was awarded the Nobel Prize for Medicine in 2002.

14 MARCH 2011 | FEATURED TALK

L2

Jun Wang

Executive Director, BGI, Shenzhen, China

PERSONAL GENOMES ARE PERSONALIZED

It is 10 years since human genome project was drafted, yet we are still asking how genomes will help health care for general people. Recent sequencing revolution has brought affordable personal genomes into practice in terms of cost and throughput, but it remains very difficult to interpret a genome to make sense for the owner. Scientists are still struggling in biomedical genomics studies to get the meaning of every nucleotide in the sequence, while missing heritability in complex diseases confused researchers, and prevented disease modeling, prevention and precaution. Our recent studies have proposed two possible explanations to the missing heritability. First, we have discovered an excess of rare, deleterious SNPs in average human population, which are not designed in current genome-wide association study (GWAS) arrays. Second, we identified extensive structural variations as well as individual-specific sequences among human individuals with potential functional impacts. In all, we believe each human genome is actually highly personalized, or private, as a personal genome. The continuous innovations in the technology would finally prove that by complete de novo assembly of multiple private genomes could we find the key to human genomics for medical genomics and health care.

Jun Wang is the Executive Director of the BGI (previously known as the Beijing Genomics Institute). He was instrumental in the 1999 founding and the growth of the BGI Bioinformatics Department, which is now widely recognized as one of world‘s premier research facilities committed to excellence in genome sciences. Dr. Wang also holds a position as an Ole Rømer professor at the University of Copenhagen. He has authored 100+ peer-reviewed original papers – of which 26 are published in *Nature* (including *Nature* series), and *Science.* Among those 26, WJ is the first author or corresponding author for 19 of them. He has been recognized with an award from His Royal Highness Prince Foundation in Denmark, an Outstanding Science and Technology Achievement from the Chinese Academy of Sciences, Top 10 Scientific Achievements in China, and the prize for Important Innovation and Contribution from the Chinese Academy of Sciences. His research focuses on genomics and related bioinformatics analysis of common diseases and agricultural crops, with the goal of developing applications using this genomic information.

14 MARCH 2011 | FEATURED TALK

L3

Veronica van Heyningen

Honorary Professor, University of Edinburgh, UK
Group Leader, MRC Human Genetics Unit

FROM DISEASE GENES TO BIOLOGY VIA TECHNOLOGY

One of the most profitable approaches to understanding how complex biological systems function is to explore what happens when they malfunction. Many new methods are becoming available for uncovering disease causing genes: simpler SNP arrays can be used for genome-wide association studies, autozygosity mapping as well as for identifying copy number variants are revealed by CGH arrays, while exome sequencing, soon to be followed by whole genome sequencing, uncovers possible disease mutations. Combining this much improved capacity for disease gene identification with careful phenotype analysis in patients, and with the use of a spectrum of model systems, can provide unparalleled insight into biological mechanisms. We can build up a picture not only of individual gene function, but also of gene interactions and system dynamics. Construction of Gene Regulatory Networks is possible following experimental prediction using chromatin immunoprecipitation and binding-site identification. Co-immunoprecipitation of proteins may reveal protein interaction networks. The networks identified are used to verify gene function and to predict further disease gene candidates and targets for effective therapy.

First degree in genetics (Cambridge); DPhil on early gene mapping studies using somatic cell hybrids, with Walter Bodmer (Oxford); Beit Memorial Fellow, MRC Mammalian Genome Unit, Edinburgh; eventually rose through the ranks at MRC Human Genetics Unit, Edinburgh from postdoctoral fellow to group leader and until recently Section Head. Honorary Professor University of Edinburgh, CBE FRS, FRSE, FMedSci. Howard Hughes International Research Scholar 1993-1998. Member of UK Human Genetics Commission 2000-2005. EMBO member 2003. Fellow of the Royal Society 2007. Human geneticist (non-clinical) working on developmental eye anomalies such as aniridia and anophthalmia/microphthalmia. Interested in what detailed analysis of the human phenotypes in individuals with known mutations can tell us about the biological role of the genes involved. Ultimately most human developmental genes need to be explored in model systems and we are currently studying the roles of PAX6 and SOX2 in humans, mice and zebrafish. A major area of endeavour, since the early 1990s, is to understand the mechanisms of long-range regulation of gene expression. Transcription factors like PAX6 and SOX2 show complex spatiotemporal and quantitative control of expression, requiring a large number of strongly sequence-conserved cis-regulatory elements, found upstream, downstream and within the gene. Such regulatory regions can stretch more than a megabase either side of the gene. We are aiming to understand the spatial and functional organisation of these interacting elements (which often function as enhancers in reporter transgenic assays), additively recapitulating the sum of the total gene expression pattern. Expression-associated patterns of open chromatin suggest dynamic genomic organisation. Another emerging interest is in the mechanisms underlying disease with non-Mendelian segregation patterns. We are exploring how other genes and environmental factors affect phenotype modification.

14 MARCH 2011 | FEATURED TALK

L4

Stephen W Scherer

Director, McLaughlin Centre and The Centre for Applied Genomics
The Hospital for Sick Children and University of Toronto, Canada

CLINICAL CONTEXT OF COPY NUMBER AND STRUCTURAL VARIATION IN THE HUMAN GENOME

During the past five-years, copy number variation (CNV) and structural variation (SV) have emerged as highly prevalent forms of genomic variation, bridging the interval between long-recognised microscopic chromosomal alterations and single-nucleotide changes. These genomic differences among humans reflect the dynamic nature of genomes, and account for both natural variations among us and variations that predispose to conditions of medical consequence. I will discuss CNV-SV in their historical and medical contexts, focusing on how these variations can be recognized, documented, characterized and interpreted. I will also discuss how they can cause disease or influence adaptation to an environment. Our recent work on autism spectrum and related neuropsychiatric disorders will also be described to illustrate salient characteristics and residual enigmas of this complex form of genetic variation.

Dr. Stephen Scherer, PhD, holds the GlaxoSmithKline-CIHR Endowed Chair in Genetics and Genomics at The Hospital for Sick Children and University of Toronto. He has made numerous contributions to medical genetics including mapping sequencing and disease gene studies of human chromosome 7. He collaborated with the J. Craig Venter Institute to generate the first genome sequence of an individual ushering in an era of genomic medicine. In 2004, his team co-discovered global gene copy number variation (CNV) and has since shown that CNV is the most abundant type of nucleotide variation of human DNA. His group has also discovered CNV to contribute to the etiology of autism and the Database of Genomic Variants he founded facilitates tens of thousands of diagnoses each year. His work is documented in >275 publications cited some 20,000 times. Dr. Scherer has won numerous honors such as the Steacie Prize, an International Howard Hughes Medical Institute Scholarship, and the Premier Summit Award for Medical Research. He is on the Board of Trustees of Genome Canada and the Human Genome Organisation.

14 MARCH 2011 | FEATURED TALK

L5

Ghazi O Tadmouri

Assistant Director, Centre for Arab Genomic Studies, Dubai, United Arab Emirates

GENETIC DISORDERS IN ARABS FROM CLINICAL GENETICS TO HUMAN GENOME VARIABILITY

Arabs are a panethnicity of peoples of various ancestral origins, religious backgrounds, and historic identities. They originate from the region including Mesopotamia, the Levant, the Arabian Peninsula, and North Africa. The Arab World is the largest geocultural unit in the world after Russia and Anglo-America, with a population exceeding 360 million and spanning more than 14 million square kilometers. According to the Recent Out-of-Africa model describing the origin of modern humans, the region has repeatedly served as a migratory passageway between Africa and Eurasia and has acted as an incubator for the early diversification of non-African lineages. This diversity reflects today with the presence of 955 genetic disease entities among Arabs according to the CTGA Database. This diversity also echoes at the clinical level as observed in the large number of disease groups, affected systems, incidence rates, geographical distributions, clinical subtypes, and disease phenotypes. This latter characteristic is further amplified by the presence of comorbidity in patients from the region with combinations of major disorders including hemoglobinopathies, cystic fibrosis, Down syndrome, G6PD deficiency, and many others. On the other hand, nearly two-third (61%) of genetic disorders in Arabs follow an autosomal recessive mode of inheritance and this is highly attributed to the widespread practice of consanguineous marriages in the region. Certainly, the availability of many consanguineous and extended families in the region has fueled the process of gene identification for various inherited disorders, thus, providing invaluable resources for gene annotation and human genome variation. Recently, the Centre for Arab Genomic Studies initiated a long-term Arab Human Variome Project to document human genome variation in the region with geographically-oriented and disease-oriented perspectives. In a striking example of the spatial distribution of diversity, the State of Qatar, one of the smallest Arab countries in terms of area and population size, exhibited at least 12 novel mutations in 11 different loci. From a disease perspective, two main examples may be noted. (1) The Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene demonstrates a heterogeneous profile in a small region including the neighboring countries of Bahrain, Qatar, the United Arab Emirates, and Oman. In brief, the 2043delG (c.1911delG) mutations is the most common in Bahrain, while c.3700A>G (p.I1234V) is the most common in Qatar, and the c.1647T>G (p.S549R) mutation is commonly observed in Oman and the UAE. (2) beta-Thalassemia exhibits another extreme example of diversity with at least 73 beta-globin mutations leading to the disease in Arab populations. At present, 36% of reported genetic disorders in Arabs remain confined to clinical observations. Efforts to decipher their molecular pathologies will definitely result in high value knowledge base. The organization of such information will have direct implications on genetic counseling, prenatal diagnosis, genotype-to-phenotype correlations, evaluation of individual prognosis, and appropriate patient management.

Dr. Ghazi Tadmouri is the Assistant Director of the Centre for Arab Genomic Studies, a division of the Sheikh Hamdan Award for Medical Sciences (Dubai, UAE). Since March 2010, he is member of the UAE Ministry of Health's Higher Committee for Health Research. In 2004, He launched the CTGA Database for genetic disorders in Arab people and is heading its development team. Dr. Tadmouri is member of the consultancy group supporting the UNDP-Lebanon "Transfer of Knowledge Through Expatriate Nationals" (TOKTEN) Project. He is also a member of many regional research grant review boards, journal editorial and peer review boards, and international organizations. In 1999, he received his Ph.D. degree in Molecular Biology and Genetics from Bogaziçi University (Turkey). In years 2000-2004, he was Assistant Professor of Molecular Biology and Genetics at Fatih University (Turkey). In years 2007 and 2009, he conducted graduate and professional courses and workshops on Bioinformatics at the Arabian Gulf University (Bahrain) and the World Health Organization (Egypt). Dr. Tadmouri is author of more than 35 books and international scientific articles. He presented scientific papers in more than 60 international conferences and workshops. Despite this, Dr. Tadmouri believes that scientific knowledge is only effective when translated into public practice.

14 MARCH 2011 | FEATURED TALK

L6

Mark McCarthy

Robert Turner Professor of Diabetes
Oxford Centre for Diabetes, Endocrinology and Metabolism, UK

TYPE 2 DIABETES GENETICS: A GLOBAL PERSPECTIVE

Ongoing efforts to define additional common variants influencing traits of biomedical importance are motivated by the biological insights that follow the identification of robust causal relationships between genome sequence variation in a given location and the phenotype of interest. Following the initial success of the genome-wide association effort in finding large numbers of susceptibility loci for type 2 diabetes, further success is going to be increasingly dependent on improvements in efforts to extend these studies to a wider range of variants examined in a wider range of populations. For type 2 diabetes (T2D), the DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) consortium has concentrated current efforts on T2D signals in European-descent populations. The Meta-Analysis of Glucose and Insulin-related traits (MAGIC) consortium has focused on variants influencing continuous glycemic traits in non-diabetic individuals. The efforts of these (and other) consortia have contributed to an expansion in the number of confirmed T2D common variant signals to 40, with another 20 or so influencing continuous glycemic traits. At the same time, the results from similar studies conducted in non-European data sets are emerging. These studies are revealing additional loci influencing T2D risk, as well as confirming many of the associations previously reported in European samples. Indeed, there is a great deal of overlap in the common variant GWAS signals for T2D seen in samples collected from different major ethnic groups. This finding argues strongly that the association signals detected by GWAS (which have to date been focused around common variants) are themselves driven by common causal variants that are widely distributed across the globe (most likely since they arose before the spread out of Africa). If so, transethnic fine-mapping approaches should make it possible to narrow down the location of the causal variants, and thereby enhance our ability to connect these association signals with the molecular events through which they influence diabetes risk. I will report on some of our efforts in this respect. The other way in which the term ―global" is relevant here relates to the genome. One of the main challenges in the field right now is to move towards a more complete enumeration of alleles contributing to genetic risk of T2D through extending the spectrum of variants evaluated. Large next-generation sequencing studies now underway should provide the first clues to the roles of low frequency and rare variants to diabetes susceptibility, and again, I will describe some of these studies. The expectation is that these efforts will allow us to address two further challenges which follow from genetic discoveries. First, we need to move from these association signals to understanding of biological mechanisms through identification of the causal variants driving these effects and the genes and pathways through which they operate; and second, we have a duty to translate these discoveries into advances in clinical management of diabetes.

Mark McCarthy is Robert Turner Professor of Diabetes at Oxford University, based at the Oxford Centre for Diabetes, Endocrinology and Metabolism (OCDEM) and at the Wellcome Trust Centre for Human Genetics. His work on the genetics and genomic basis of type 2 diabetes seeks to define the relationship between genetic variation, environment, intermediate phenotypes, and clinical disease, in the belief that such information will translate into a significant impact on clinical care for people with diabetes, through more rational and effective deployment of available preventative and therapeutic modalities. He obtained his medical degree at the University of Cambridge and postgraduate clinical training in general medicine, diabetes and endocrinology at the London Hospital. Following research training with – amongst others – Newton Morton and Eric Lander, he took up an appointment as Senior Lecturer (subsequently Professor in Genomic Medicine) at Imperial College in 1995, moving to Oxford as the Robert Turner Professor of Diabetes in 2002. In the past decade, his group has become established as one of the leading international teams working on the genetics of T2D, with expertise extending from physiological characterisation through to high-throughput genomic analysis and related issues in computational biology. Prof McCarthy currently leads the T2D component of the Wellcome Trust Case Control Consortium, and has been intimately involved in many of the recent discoveries generated by the application of genome wide association approaches to diabetes, obesity and related traits. His group is increasingly involved in efforts to understand how such information can be translated into advances in clinical management, and in extending these studies beyond the European context. He has a strong commitment to the wider research community, having served as a member and chair of the Diabetes UK Research Committee, and on Wellcome and MRC panels. He serves on the Editorial Board of Diabetes, Diabetologia, PLoS Medicine, Human Molecular Genetics and several other journals.

15 MARCH 2011 | CONCURRENT SYMPOSIUM: RNA AND EPIGENETICS

L7

John S Mattick

Professor of Molecular Biology and NHMRC Australia Fellow
Institute for Molecular Bioscience
University of Queensland, Brisbane, Australia

RNA REGULATION OF HUMAN DEVELOPMENT, COGNITION AND DISEASE

It appears that the genetic basis of the programming of human development and cognitive capacity has been misunderstood for the past 50 years, because of the assumption that most genetic information is transacted by proteins. Contrary to the derived assumption that most of the human genome is comprised of evolutionary debris (introns, integenic _deserts', retrotransposon-derived sequences), it is now evident that essentially the entire genome is dynamically transcribed to produce enormous numbers of regulatory RNAs that control gene expression at various levels, including the site-specificity of the chromatin-modifying complexes that underpin developmental trajectories and cognitive function. Increasing numbers of these regulatory RNAs are being shown to be dysregulated in cancer and other complex diseases. It is also becoming evident that the system has evolved extraordinary plasticity via RNA editing, and that this is the molecular basis of environment-epigenome interactions underpinning brain function and influencing the progression of diseases such as type 2 diabetes. Retrotransposons also appear to contribute to genomic, epigenomic and transcriptomic plasticity, and somatic mosaicism, especially in the brain. Thus, apart from the fact that some genes encode proteins, it appears most orthodox assumptions about human genetic information have been incorrect, and that what was dismissed as _junk' because it was not understood will hold the key to understanding human evolution, development, variation, cognition and disease.

John Mattick is the Professor of Molecular Biology and ARC Federation Fellow at the Institute for Molecular Bioscience at the University of Queensland. He did his undergraduate training at the University of Sydney and his PhD at Monash University. He has worked at Baylor College of Medicine in Houston, the CSIRO Division of Molecular Biology in Sydney, and the Universities of Cambridge, Oxford, Cologne and Strasbourg. He was Foundation Director of the Australian Genome Research Facility and the Institute for Molecular Bioscience. He is an Associate Member of the European Molecular Biology Organisation and a Fellow of the Australian Academy of Science.

15 MARCH 2011 | CONCURRENT SYMPOSIUM: RNA AND EPIGENETICS

L8

Yoshihide Hayashizaki

Director, Omics Science Center, RIKEN, Yokohama, Japan

AN EXPANDING RNA WORLD

The first step on the road to knowledge was taken in 1995 when we first glimpsed the RNA complexity. We realized the need of new technologies to construct the full-length cDNA library (Cap trapper method, normalization, subtraction, new cDNA vector and thermoprotection technology of reverse transcriptase using trehalose), and high throughput sequencing (Riken integrated sequence analysis system; RISA) was essential to reach the goal of large-scale data collection. In order to process the data we started to collect people, and the International FANTOM consortium was founded in 2000. The combination of talented people and data have given us millions of full-length cDNA sequences, CAGE tags and ditags, collected in the *de facto* world standard database (5 visits/second). The efforts of the FANTOM consortium have revealed non-coding RNA (ncRNA) as the major product of the genome (53%), and that the actual number of genes is diminished through the history of life science due to gene fusion, but increased by the number of ncRNA. We also learned that 72% of all genes have sense/antisense transcripts. All the discoveries we have made regarding RNA have given us a new view of the central dogma, collapsing the old DNA to protein concept. The double stranded RNA (dsRNA) for RNAi cannot only be created by virus and miRNA and S/AS is a new source of dsRNA. RNA is flexible and regulates gene expression through RNAi and other mechanisms. Now we have found a group of transcription factors that act like a switch between RNAi and regular gene expression by interacting with the RNAi machinery directly. Altogether these new findings dissolve the central dogma into a new picture with new interaction cascade and the unexpected complexity of combined omics.

Yoshihide Hayashizaki received his M.D. and Ph.D. from Osaka University Medical School in 1982 and 1986, respectively. In 1992, he joined RIKEN, and was appointed Project Director for the RIKEN Genome Project in 1995. Since then he has been taken a transversal data-driven approach to analyze transcriptomes by developing unique technologies including a series of full-length cDNA technologies. With this approach, he has established large amount of full-length cDNA clone bank. This activity was followed by organization of FANTOM (Functional Annotation of Mammalian), an international consortium, originally to annotate a large number of cDNA and subsequently expanded to transcriptome and network analysis. FANTOM activities revealed that more than 63% of the genome — not just the ~1.5% fraction that are protein-coding exons — is transcribed as RNA. In 2008, he appointed to the Director of the Omics Science Center. The center was established to link a variety of omics subdisciplines to molecular networks and pathways in order to advance our understanding of biological phenomena as systems at the molecular level.

15 MARCH 2011 | CONCURRENT SYMPOSIUM: RNA AND EPIGENETICS

L9

Yijun Ruan

Senior Group Leader and Associate Director of Genomics Technology & Biology
Genome Institute of Singapore, Singapore

3D CHROMATIN ARCHITECTURE AND TRANSCRIPTION REGULATION

Higher-order chromosomal organization for transcription regulation and coordination is poorly understood in eukaryotes. Using genome-wide Chromatin Interaction Analysis with Paired-End-Tag sequencing (ChIA-PET), we mapped long-range chromatin interactions associated with CTCF and RNA polymerase II in human cells. These analyses revealed that the general landscape of chromosomal organization is largely framed by CTCF function into abundant chromatin looping structures, and such looping conformation provides the topological basis for gene transcription regulation and coordination. We demonstrated that many genes are organized within chromatin complex and are transcribed cooperatively. We also discovered that promoters in spatial proximity could influence each another, implying higher-order combinatorial controls of transcription. Our analyses provide new dimension of combinatorial controls of transcription in eukaryotic genomes. Further study in the new concept of chromatin architecture and transcription regulation will yield new insights of gene transcriptional control in normal and diseased cells.

Dr. Ruan Yijun is currently the Senior Group Leader and Associate Director of Genomics Technology at the Genome Institute of Singapore. His primary interest is to elucidate the structures and dynamics of all functional DNA elements in complex genomes through transcriptome characterizations and genome interrogation. To facilitate such understanding, Dr. Ruan's lab have developed paired-end-ditag (PET) based high throughput and high precision DNA sequencing and mapping methodologies. These sequencing-based measurements are used to address complex biological questions such as how cancer cells progress and how stem cells maintain their unique properties. Another major interest of Dr. Ruan is to discover previously uncharacterized microbial genes and genomes that are relevant to human health. To this end, his lab has established a metagenome analysis capability that includes a filtration system for isolating uncultured microbes, shotgun and PET sequencing of metagenomes to uncover viral and bacterial genome sequences from a variety of environment settings and cavities of the human body.

L10

Bing Ren

Head, Laboratory of Gene Regulation
Lugwig Institute for Cancer Research
Professor, Department of Cellular and Molecular Medicine, University of California, San Diego School of Medicine, USA

DECODING THE MAMMALIAN GENOME

Eukaryotic gene transcription depends on the interplay between transcription factors and the cis-regulatory elements in the genome. While most of the protein coding sequences in the mammalian genome have been found, the cis-regulatory sequences that control their tissue- and temporal-specific expression remain largely unknown. We report the first comprehensive survey of cis-regulatory sequences in a mammalian genome. We use a high throughput experimental strategy to identify transcription factor binding and chromatin modification profiles in a large panel of mouse tissues and primary cells. By analyzing the genomic binding sites of RNA polymerase II, co-activator protein p300, insulator protein CTCF, and two chromatin modification marks H3K4me3 and H3K4me1, we identified over 270,000 cis regulatory sequences including promoters, enhancers and insulator sequences in the mouse genome. This map of cis-regulatory sequences provides functional annotation for over 70% of all the conserved non-coding regions previously identified in the mouse genome. It identifies long-range enhancers for thousands of tissue-specifically expressed genes. It also exhibits a high level of conservation in the cis-regulatory elements between the human and mouse genomes, providing a powerful tool for the annotation of functional elements in the human genome.

Dr. Ren is currently Member of the Ludwig Institute for Cancer Research (LICR) and Professor of Cellular and Molecular Medicine at the University of California, San Diego School of Medicine. He currently leads the San Diego Epigenome Center, one of four NIH-sponsored Reference Epigenome Mapping Centers. He obtained his Ph.D. from Harvard University in 1998, where he studied mechanisms of transcriptional repression under the guidance of Dr. Tom Maniatis. From 1998 to 2001, he continued to research mechanisms of gene regulation and genomics as a postdoctoral fellow in Dr. Richard Young‘s laboratory at Whitehead Institute. During this period he pioneered the ChIP-chip analysis method. When Dr. Ren began his faculty appointment, he combined the ChIP-chip with genome tiling arrays to investigate the mechanisms of gene regulation in human cells. His group is among the first to demonstrate the use of high-resolution genome tiling arrays for mapping *cis*-regulatory elements. His recent works include generation of genome-wide maps of promoters, enhancers and potential insulators in human cells, and the discovery of distinct chromatin modification signatures for promoters and enhancers.

15 MARCH 2011 | CONCURRENT SYMPOSIUM: RNA AND EPIGENETICS

Oral Presentation

L11

Ashraf Dallol

RASSF1A METHYLATION IS PREDICTIVE OF POOR PROGNOSIS IN FEMALE BREAST CANCER PATIENTS IN THE BACKGROUND OF OVERALL LOW METHYLATION FREQUENCY

Dallol Ashraf[1], Buhmeida Abdelbaset[1], Merdad Adnan[2], El-Maghrabi Joudah[3], Al-Thobaiti Fatima[2], Syrjänen Kari[3], Abuzenadah Adel[1], Chaudhary Adeel[1], Gari Mamdooh[1], Al-Qahtani Mohammed[1]
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Breast cancer (BC) is the most common cancer world-wide. BC in the Kingdom of Saudi Arabia is also the most frequent cancer type in the country with ever increasing incidence rates. An interesting feature of this disease is the relatively young age of the affected women. The average age in the present cohort of 100 sporadic cases of invasive ductal carcinomas was 45 years, with a median of 46 years (range between 19-81 years). In an effort to understand the molecular signature of BC in the Saudi population, we undertook this study to profile the methylation events in a series of key genes (RASSF1A, HIC1, CDKN2A, RARB2, ESR1, PGR, PITX2, SFRP1, MYOD1, and SLIT2) using the MethyLight analysis in archival tumor samples. Results: Interestingly, the overall methylation levels were low in this cohort, with only 84% of the cases displaying methylation in one or more of the analyzed genes. RASSF1A methylation frequency was the highest (65%) while there was almost complete absence of methylation in the ESR1 and the CDH1 genes (1% and 3%, respectively). Several statistically significant correlations were identified between specific methylation events and clinical parameters which gained more significance when analysis was limited to the ER+ samples. Although there was no significant correlations between any methylation event and disease-specific survival (DSS), methylation of MYOD1 or RASSF1A was associated with lower disease-free survival (DFS) and increased chance of recurrence. Furthermore, multivariate (Cox) regression analysis identified RASSF1A as an independent predictor of poor prognosis in terms of DFS in this cohort. Conclusion: Our findings provide further evidence on the usefulness of RASSF1A methylation status as an informative prognostic biomarker in BC in Saudi population.

15 MARCH 2011 | CONCURRENT SYMPOSIUM: RNA AND EPIGENETICS

Oral Presentation

L12

Sukru Tuzmen

HIGH-THROUGHPUT RNAi BASED FUNCTIONAL PHARMACOGENOMICS FOR DRUG TARGET IDENTIFICATION IN CANCER GENETICS AND APPLICATIONS OF QUANTITATIVE REAL-TIME PCR (QPCR)

Tuzmen Sukru, Tuzmen Pinar, Yin Holly, Kiefer Jeff, Azorsa David, Mousses Spyro
Translational Genomics Research Institute (TGen), 14409 Settlers Landing Way, North Potomac, USA; stuzmen@tgen.org

A classical technique for determining the function of a gene is to experimentally inhibit its expression in order to examine the resulting phenotype or effect on molecular endpoints and signaling pathways. RNA interference (RNAi) is one of the most recent discoveries of a naturally occurring mechanism of gene regulation, which is triggered by the introduction of double stranded RNA into a cell. This phenomenon can be exploited to down-regulate expression of specific genes by transfecting mammalian cells with synthetic short interfering RNAs (siRNAs). siRNAs can be designed to silence the expression of specific genes bearing a particular target sequence and may potentially be presented as a therapeutic strategy for inhibiting transcriptional regulation of genes, which in such instances constitute a more attractive strategy than small molecule drugs. Low dose drug and siRNA combination studies are promising strategies for the purpose of identifying synergistic targets that facilitate reduction of cell proliferation. Commercially available RNAi libraries have made high-throughput genome-scale screening a feasible methodology for studying mammalian cell systems. However, it is crucial that any observed phenotypic change be confirmed at either the mRNA and/or protein level to determine the validity of the targeted genes. Quantitative real-time PCR (qPCR) is now widely used owing to its simplicity, wide dynamic range of quantification, sensitivity, and precision, for accurate evaluation and validation of gene expression. We describe here a high-throughput screening of RNAi based gene silencing process and qPCR validation of specific transcript levels. In light of such advantageous applications, siRNA technology has become an ideal research tool for studying gene function and holds the promise that siRNA-based therapeutic agents will soon be put to test in clinical trials.

15 MARCH 2011 | CONCURRENT SYMPOSIUM: GENOMIC MEDICINE

L13

Geoffrey S Ginsburg

Director, Center for Genomic Medicine, Institute for Genome Sciences & Policy
Professor of Medicine and Pathology, Duke University Medical Center, USA

GENOMIC AND PERSONALIZED MEDICINE: FOUNDATIONS AND APPLICATIONS

The last decade has seen a steady embrace of genomic and personalized medicine by senior government officials, industry leadership, health care providers, and the public. *Genomic medicine* - the use of information from genomes and their derivatives (RNA, proteins, metabolites) to guide medical decision-making- is a key component of *personalized medicine,* a rapidly advancing field of health care that is informed by each person‘s unique clinical, genetic, genomic, and environmental information. As medicine begins to embrace genomic tools that enable more precise prediction and treatment disease, including ―whole genome" interrogation of sequence variation, transcription, proteins, and metabolites, the fundamentals of genomic and personalized medicine will require the development, standardization, and integration of several important tools into health systems and clinical workflows. These include health risk assessment, family health history, and clinical decision support for complex risk and predictive information. Together with genomic information, these will enable a paradigm shift to a comprehensive approach that will identify individual risks and guide clinical management and decision-making, all of which form the basis for a more informed and effective approach to patient care. DNA based risk assessment for common complex disease, molecular signatures for cancer diagnosis and prognosis, and genome guided therapy and dose selection are just among the few important examples where genome information has already enabled personalized health care along the continuum from health to disease. In addition, information from individual genomes, a fast-moving area of technological development, is spawning a social and information revolution among consumers that will undoubtedly affect health care decision-making. While these and other scientific findings are making their way from the genome to the clinic, the full application of genomic and personalized medicine in health care will require dramatic changes in regulatory and reimbursement policies as well as legislative protections for privacy for system wide adoption. Thus there are challenges both from a scientific and policy perspective to personalized health care, however they will be confronted and solved with the certainty that the science behind genomic medicine is sound and the practice of medicine that it informs is evidence-based.

Dr. Ginsburg, the founding director of the Center for Genomic Medicine, assumed his current position in the Duke Institute for Genome Sciences and Policy in 2004 and was also co-director of the Duke Translational Medicine Institute in 2006. He is also the founding executive director of the Center for Personalized Medicine established in 2010. While at Duke, Dr. Ginsburg has pioneered translational genomics, initiating the first genomic-guided clinical trials as well as developing novel practice models and implementation research for the integration of genomic tools in heath care systems. In 1990, he joined the faculty of Harvard Medical School, where he was director of preventive cardiology, and led a laboratory in applied genetics of cardiovascular disease. In 1997 he joined Millennium Pharmaceuticals Inc, as senior program director for cardiovascular diseases and was eventually appointed vice president of Molecular and Personalized Medicine at Millennium. Dr. Ginsburg research interests are in the development of novel paradigms for developing and translating genomic information into medical practice and the integration of personalized medicine into health care. He has received a number of awards, including the Innovator in Medicine Award from Millennium (2004) and the Basic Research Achievement Award in Cardiovascular Medicine from Duke (2005). He is a founding member and on the Board of Directors of the Personalized Medicine Coalition, a senior consulting editor for *The Journal of the American College of Cardiology,* editor-in-chief for *The HUGO Journal*, and an editorial advisor for *Science Translational Medicine*. In addition he is the editor of *Genomic and Personalized Medicine* (Elsevier) whose first edition was published in 2009. He has been an international expert panel member for Genome Canada and is currently a member of the Board of External Experts for the National Heart, Lung and Blood Institute, the Secretary of Veterans Affairs Advisory Council on Genomic Medicine, the Institute of Medicine‘s Roundtable on Genome-Based Research to Human Health and the National Advisory Council for Human Genome Research. He received his MD and PhD in biophysics from Boston University and completed an internal medicine residency at Beth Israel Hospital in Boston. He pursued postdoctoral training in clinical cardiovascular medicine at Beth Israel Hospital and in molecular biology at Children‘s Hospital as a Bugher Foundation Fellow of the American Heart Association.

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L14

Edison T Liu

Executive Director, Genome Institute of Singapore
Professor of Medicine, National University of Singapore
President, Human Genome Organisation, Singapore

GENOMIC MEDICINE IN CANCER CARE

Genomic medicine involves the provision of medical care that uses the power of genomic knowledge and technologies to resolve complex problems. The fundamental difference between this and older strategies in medicine research is the comprehensiveness and the precision of the analyses afforded by new genomic technologies such as in sequencing, cloning, and genotyping. The new challenge will be the assembly and management of this high volume of data with dimensional complexity. Genomic medicine therefore means computational and systems medicine as well. Operationally, systems biology requires the digitalization of biological output, the computational power to analyze comprehensive and massive datasets, and the capacity to integrate heterogeneous data into a usable knowledge format. There is no field more suitable for genomic strategies in clinical care than cancer. The precision and the completeness of the genomic analysis will allow for the stratification of patients at risk for cancer, for therapeutic resistance, and for drug side effects. This will not only improve care, but also reduce the cost of health care at the systems level. The availability of genome sequences will change the face of biomedical research and of medicine. Individual genomes that do not change in life can be assessed at one time. Therefore one‘s complete genetic profile is accessible potentially as a clinical test. As with other technologies, genome sequencing of this magnitude raises clear legal and social challenges. In the same way that personal computers and the internet has changed our social activities and redefined privacy, the same will be true of personal genomic information. We will describe how genomic approaches are changing our understanding of cancer, as a model system. Our work, at the Genome Institute of Singapore, in transcriptional profiling has led to transcription factor binding site dynamics, and human variations in those binding sites. We employ a strategy of using genomic data to reconstruct systems maps of critical regulatory networks. This integrative approach permits modeling of complex interactions and allowed us to quickly uncover complex mechanisms of drug action. Coupled with the dramatic expansion of disease gene discovery in population studies, we now find that rather than a few genes, hundreds of genes may be involved in the genesis of a single complex disease. Harnessing complexity will be our next great challenge.

Dr. Liu is the Executive Director, Genome Institute of Singapore (Agency for Science, Technology, and Research) and Professor of Medicine, National University of Singapore. He received his degrees (B.S. and M.D.) at Stanford University further oncology and molecular biology training at Stanford and at UCSF. Prior to starting the GIS in 2001, Dr. Liu was the Scientific Director for the Division of Clinical Sciences, National Cancer Institute (USA). Dr. Liu‘s scientific research has focused on the functional genomics of human cancers, particularly breast cancer, investigating the dynamics of gene regulation on a genome scale that modulates cancer biology. He has authored over 260 scientific papers, reviews and books. He is the recipient of a number of awards: Leukemia Society Scholar, 1991-96; Member, the American Society of Clinical Investigations (elected 1995), the Brinker International Award for basic science research in Breast Cancer, 1996; the Rosenthal Award from the American Association for Cancer Research, 2000; the President‘s Public Service Medal for helping Singapore resolve the SARS crisis, and a Doctor of Medicine Sciences *honoris causa,*Queen‘s University, Belfast, 2007. He was elected as a Foreign Associate Member of the European Molecular Biology Organization (EMBO, 2008), and serving his second term as the elected President of the Human Genome Organisation (HUGO). Dr. Liu is also the current Chairman of the Board for the Singapore Health Sciences Authority, health regulatory and blood banking agency for Singapore.

L15

Ingrid Winship

Professor of Adult Clinical Genetics, University of Melbourne
Executive Director Research, Melbourne Health, Australia

CAN GENETIC INFORMATION REDUCE THE BURDEN OF DISEASE?

Genetic data will influence clinical health services and preventive health strategies increasingly in the future. Translating rapidly from biomedical research to health care is an increasing understanding of sequence variation in the human genome. This is facilitated by more accessible, accurate and affordable technologies for genotyping, along with the recognition of the need for informatics expertise to interpret the significance of these changes for human health. Enhanced opportunities now exist to use genetic technologies in a preventive approach to healthcare, in order to reduce the burden of disease. The information generated by whole genome sequencing (WGS) needs correlation with accurate phenotypic data, to provide an understanding of pathogenicity in this context, and the use and utility of genotyping in clinical practice. The combination of better phenotype and genotype data will give new insights into human health and create the platform for preventive strategies, within individuals, families and communities. This creates the basis of precision (or personalized) medicine; likewise, pharmacogenomics is rapidly moving into mainstream medicine. In the past two decades, genetic technologies were used primarily within the pediatric and prenatal approach to rare single gene disorders. Genetics is no longer in the domain of single gene disorders. The International Cancer Genome Consortium is mapping sequence variants across tumor types, putting somatic genetic changes at the centre of cancer diagnosis and treatment for the future. We have established a clinical genetic service for adults in a large general hospital, where the focus of genetic information is on prevention of symptoms and complications of predictable later onset disorders. The practice of preventive genetics in hereditary breast and colon cancer, with the ability to assess and manage risk, has already reduced the incidence of malignancy in some subsets of these common cancers. We have extended the preventive approach to many other disorders, including sudden cardiac death (SCD). Hereditary heart disease may be preventable if detected early. Use of the ~~"~~molecular autopsy", genetic investigation of SCD, may provide an explanation for that death. Risk assessment provides not only information, but the opportunity to offer surveillance and management strategies in the prevention of further untimely death in families. Multidisciplinary and interdisciplinary collaborations between clinical geneticists, medical and surgical experts, genetic counselors, and molecular pathologists enable the management of the proband and the family. At the same time, the Direct- to-Consumer (DTC) market is growing internationally, raising issues about easy access to extensive health information, its potential use and utility, as well as privacy, ownership, and accreditation. Supportive care through genetic counseling is an essential pillar of genetic medicine; its role in DTC cannot be underestimated. The mainstreaming of genetic technologies into health care systems raises a range of ethical, legal, cultural, spiritual, psychological and social issues. An integral part of the inclusion of DNA analysis in a clinical setting is the provision of advocacy for patients in our care, so that the benefits of technology outweigh any potential for harm.

Prof. Winship was appointed as the Inaugural Chair of Adult Clinical Genetics at the University of Melbourne, and Executive Director Research for Melbourne Health in November 2006. She graduated from the University of Cape Town in 1981 then completed postgraduate training in genetics and dermatology before combining an academic position at the University of Cape Town with a clinical position at the Groote Schuur Hospital from 1989-1994. In 1994, she moved to New Zealand to an academic position at the University of Auckland where she later became Prof. of Clinical Genetics and Associate Dean for Research within the Faculty of Medical and Health Sciences. In addition she was Clinical Director of the Northern Regional Genetic Service, a comprehensive genetic service based in Auckland that she initiated in 1995. In 2004, she was appointed as Head of Adult and Cancer Genetics at Genetic Health Services Victoria. Prof. Winship has a wide range of clinical and research interests in inherited disorders, focusing on those with onset in adulthood, including familial cancer, and where foreknowledge of genotype may influence clinical or lifestyle measures to create positive patient outcomes. She has experience in gene discovery and in the translation of such discovery into clinical practice. She has also highlighted societal implications of her discipline with research into the cultural and psychosocial domains of genetic technology and was a member of the inaugural Independent Biotechnology Advisory Council for the Ministry of Research Science and Technology in New Zealand. In Melbourne, Prof. Winship is Chair of the Victorian Cooperative Oncology Group Committee. She is on the Human Genetic Advisory Committee for the National Health and Medical Research Council. She represents Melbourne Health on the Board of the Walter and Eliza Hall Institute, the Mental Health Research Institute, and on the Scientific Advisory Council of the Bio21 Cluster, where she chairs the Hospital Research Directors Forum. Prof. Winship has had an active role in teaching, education and knowledge transfer to professionals, community support groups and society. She has strong community links and is a member of the committee of the Genetic Support Network Victoria.

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L16

Tim Sprosen

Chief Scientific Officer
UK Biobank, UK

NEW MODELS FOR LARGE SCALE BIOBANKS

UK Biobank is a prospective cohort study of 500,000 people from the UK aged 40-69. This large sample size coupled with the rich phenotyping of participants will mean that in the next few decades it will provide uniquely reliable insights into the causes of a wide range of diseases that cause death and misery in old age and beyond. The study has recently completed recruitment of the cohort in around three years and the presentation will review how the lessons learned from UK Biobank and other emerging cohorts can be applied to create a worldwide network of biobanks to better understand the causes of major diseases in different populations.

Tim Sprosen has been Chief Scientific Officer for UK Biobank since August 2004. His responsibilities include the integration and delivery of the scientific activities and clinical operations at UK Biobank. He is also vice-chair of the North West Research Ethics Committee and chair of the governing body of his local primary school in Nottingham. Before joining UK Biobank, he was director of product development and acting director of clinical operations for Health Decisions Limited in Oxford . Tim has also worked as associate director of clinical development for Baxter Healthcare at their European headquarters in Brussels; and as the first clinical trials manager at the Medical Research Council (MRC) headquarters. He has led two US West-coast start-ups to successful first meetings with the Food and Drug Administration (FDA). Tim is also an invited trainer in the area of innovation/lateral thinking and the management of virtual teams. Tim received his BSc in pharmacology from the University of Dundee in 1987 and his MPhil/DPhil from the University of Cambridge in 1990. His post-doctoral research in central nervous system (CNS) electrophysiological studies was undertaken in Cambridge and Oxford . Tim may be the youngest particiant in UK Biobank, having participated on his 40th birthday!

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Oral Presentation

L17

Elza Khusnutdinova

GENOME-WIDE ASSOCIATION STUDY OF ASTHMA IN THE VOLGA-URAL REGION OF RUSSIA

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Asthma is a chronic respiratory disease that is caused by the complex interaction of genetic susceptibility with environmental influences. The aim of our investigation was to identify asthma susceptibility genes in the Volga-Ural region of Russia. The study included unrelated patients with physician-diagnosed asthma and disease-free control subjects different ethnic origin (Russians, Tatars and Bashkirs). Recruitment of cases and matched controls was carried out by the Hospital of the Bashkir Medical State University and Ufa Municipal Hospital No. 21 between 1999 and 2007 years. Asthma patients were diagnosed by pulmonologists on the basis of clinical examination, family and medication history, objective tests of lung function. DNA samples of 358 asthma patients and 369 control individuals were genotyped at the CNG (Centre National de Génotypage, France) as a part of GABRIEL (A Multidisciplinary Study to Identify the Genetic and Environmental Causes of Asthma in the European Community). Whole-genome genotyping was carried out using the Illumina Human610 quad array (www.illumina.com). Statistical tests for association were carried out using PLINK 1.06 software package. In order to control for population stratification, we performed Eigenstrat analysis for cases and controls, removing outliers. After QC filters, 550 915 SNPs genotyped in 330 cases (141 Russians, 120 Tatars, 69 Bashkirs) and 348 controls (145 Russians, 111 Tatars, 92 Bashkirs) were used for testing the association of SNPs to asthma. Initially, we have carried out association analysis of full sample of asthmatics and controls. Some markers on chromosome 17q12 within the ORMDL3/GSDMB locus showed the most statistically significant association in this study ($p \leq 5x10-7$). The maximum association was at the SNP rs7216389 within 1 intron of the GSDMB gene ($p=1.013x10-7$). Six linked SNPs (rs11557467, rs2872507, rs8067378, rs2305480, rs2290400, rs7216389) located within 42 kilobase of the GSDMB/ORMDL3 locus were selected for haplotype analysis. There was a significant association between the haplotype GGAGTT and asthma ($p=3.2969x10-7$). The haplotype TAGACC offered a protective effect against asthma ($p=1.7011x10-6$). The association analysis of the SNPs at the chromosome 17q12 locus taking into consideration ethnic origins of individuals showed important associations of these SNPs with asthma in Russians. The SNP rs7216389 gave the smallest P-value for association with asthma (1.0221x10-5). The T allele frequency of the SNP rs7216389 was 0.649 in Russian asthmatics and 0.465 in controls (OR=2.12). Analyzing of the SNPs on 17q21 in Bashkirs we also found allele frequency differences between case and control groups. Three top SNPs (rs8067378, rs2290400, rs7216389) showed identical allele frequencies in case and control group of Bashkirs (0.572 vs 0.411, respectively) and identical p-values (0.0043). According to the association analysis in Tatars, there was a tendency towards association between the SNPs rs2290400, rs7216389 and asthma. This study provides further data to support the interethnic variations of allele frequency distributions for polymorphic markers on chromosome 17q12. In summary, we have found the association asthma in the Volga-Ural region of Russia with SNPs at the previously reported ORMDL3/GSDMB locus on 17q12. This work was supported by a contract from the European Commission (018996).

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Oral Presentation

L18

Swati Subodh

GENOMIC SIGNATURES: LEADING THE WAY FOR PERSONALIZED PATIENT MANAGEMENT

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Current tools for pathogen characterization are limited in their ability to identify specific regions/epitopes of the genome and in differentiating mixed and recombinant strains. Presence of minor co-infecting pathogen populations maybe missed. Thus there is a need for a robust high throughput assay for whole genome pathogen profiling from patient samples. We report here a comprehensive analysis of different genomes for identification of 'Genomic Signatures'. Over 500 database pathogen genomes were analyzed for each signature development. These genome sequences were clustered by NJ algorithm and MSA of these sequences enabled identification of individual sites. These sites were scored based on various statistical parameters. Drug associated mutations, known and novel, were also included. The sites were distributed throughout the length of the genome to obtain an overall profile. The sites were validated in silico and the results showed 100% accuracy for clinical samples and >98% accuracy for database sequences. The signatures were able to identify recombinants and mixed types, a major limitation in existing methods. An iPLEX based assay was designed on Sequenom Massarray® Platform. The assay identified the mixed/recombinant and pure genotypes with good specificity and was able to detect < 100 copies of the pathogen in the sample. The drug associated mutations could also be reliably identified. We designed the assay on a single chip enabling simultaneous characterization of multiple parameters in these organisms. A genomic signature based profiling of the pathogen can enable their exhaustive profiling in patient samples. This may find application in better patient management.

L19

Jianjun Liu

Senior Group Leader and Associate Director, Human Genetics
Genome Institute of Singapore, Singapore

GWAS IN CHINESE POPULATION: OPPORTUNITIES AND CHALLENGES

GWAS has been widely employed to dissect the genetic basis of common diseases, leading to the identification of an unprecedented number of common disease risk alleles. However, there is a tremendous disparity in term of the representation of different ethnic populations in GWAS efforts, with most of GWA studies performed in Caucasians. Through collaboration with several clinical groups in China, we have carried out a series of GWA studies in the Chinese population and identified a number of novel disease susceptibility genes for psoriasis (Zhang et al. 2009 Nature Genetics), systemic lupus erythematosus (SLE) (Han et al. 2009 Nature Genetics), leprosy (Zhang et al. 2009 NEJM) and nasopharyngeal carcinoma (NPC) (Bei et al. 2010 Nature Genetics). These efforts have provided much needed GWAS data of Chinese population, and more importantly, offered opportunities for the direct comparison of GWAS findings between Chinese and Caucasian populations. In this presentation, the opportunities and challenges for working in Chinese population will be discussed.

Dr. Liu Jianjun is currently the Group Leader and Associate Director of Human Genetics at Genome Institute of Singapore. His main research interest is to understand which and how genetic variants influence disease development. Currently, there are three main research programs in his lab focusing on breast cancer, Parkinson‘s disease and schizophrenia. In the area of breast cancer research, one of Dr. Liu's research focus is to understand how genetic variation within estrogen-related pathways can modify sex hormone-related risk to breast cancer. Dr. Liu's lab is also actively involved in genome-wide association study (GWAS) on both breast cancer susceptibility and prognosis.

L20

Hanan Hamamy

Professor, Human Genetics
Department of Genetic Medicine and Development
Geneva University Hospital, Switzerland

CONSANGUINITY AND NOVEL TECHNOLOGY: CRACKING THE CODE OF AUTOSOMAL RECESSIVE DISORDERS

Rare and novel autosomal recessive disorders have been widely reported from communities with high consanguinity rates, including Arabs, since the main impact of consanguinity is an increase in the prevalence of such disorders. Analysis of data in the Catalogue for Transmission Genetics in Arabs (CTGA), a database on genetic disorders in Arab populations maintained by the Centre for Arab Genomic Studies (CAGS), indicates that among more than 1000 disorders in the CTGA Database, 68% follow a recessive mode of inheritance. Scientifically, a considerable number of genes causing autosomal recessive conditions have been structurally and functionally determined at the molecular level through the joint collaboration of international and Arab scientists; these efforts should continue and expand given the high number of rare recessive disorders in this region.. Technological advances for rapid high throughput genome sequencing (HTS), and for the identification of copy number variants by comparative genomic hybridization (aCGH) offer an unprecedented opportunity to identify genotype-phenotype correlations focusing on autozygosity, the hallmark of consanguinity. The discovery of the functional genomic elements with recessive pathogenic mutations in consanguineous families will lead to a better understanding of the genetic, molecular and biochemical processes underlying a considerable number of autosomal recessive diseases and paves the way towards new forms of diagnostics and future treatment.

Professor Hanan Hamamy is currently affiliated with the Department of Genetic Medicine and Development at Geneva University Hospital. Her research interests focus on community genetics and consanguinity health impact. She has a long experience in genetic counseling in Arab countries mainly Jordan and Iraq where consanguinity rates reach 40% and has encountered many consanguineous families harboring rare or not previously reported autosomal recessive genes. She participated in several World Health Organization consultations and co-authored several WHO publications on community control of genetic and congenital disorders, ethical issues in medical genetics, and prevention of birth defects in developing countries. She has recently organized an international meeting on Consanguinity in Geneva and created a network of collaborations for the utilization of consanguineous samples for the discovery of disease-related genes.

L21

A Nurten Akarsu

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Hacettepe University Medical Faculty
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Gene Mapping Laboratory, Ankara, Turkey

MOLECULAR ANALYSIS OF THE RAREST OF THE RARE: AUTOSOMAL RECESSIVE ALX-RELATED FRONTONASAL DYSPLASIAS

Homozygosity mapping within consanguineous families is a powerful method of localising genes for autosomal recessive disease. It has a higher advantage over classical linkage approach to identify genes in fewer numbers of families and even in single cases per family. Therefore, it is important to create special registries and sample collections to study inbred and endogamous populations. Newly recognised ALX-Related Frontonasal Dysplasia (FND) phenotypes provide ideal examples to demonstrate how SNP array technology and homozygosity information could efficiently be used to identify genetic causes of rare disorders. Frontonasal dysplasia is an outcome of developmental failure of the facial prominences. Facial findings range from mild hypertelorism to severe midline clefts. Genetic aspects of FND are not well defined. Recently, we and others demonstrated that homozygous mutations in Aristaless-like homobox genes (*ALX1, ALX3* and *ALX4*) cause distinctive FND phenotypes in human (*Am. J. Hum. Genet. 2010, 86:78; Hum. Mol. Genet. 2009, 18:4357; Am. J. Hum. Genet. 2009, 84: 698*). According to these findings, *ALX1* expression is essential not only for building the oral and nasal cavities, but also for proper eye development during early embryogenesis. Complete loss of *ALX1* function cannot be compensated for, and frontonasal and palatal development is likely to be disrupted in early stages of development. *ALX4* and *ALX3* expression are related more to regulating the formation of the final shape of the nose.

Dr. Akarsu is a medical geneticist. She obtained her MD (1984) and Ph.D. (1994) from Ankara University. She is currently running the Mapping Facility of Hacettepe University Medical Faculty. Research interests include genetic modeling, mapping and cloning of human disease genes. She completed her two years postdocdoral training in the Surgical Research Center, University of Connecticut Health Center (UCONN) where she identified synpolydacty and congenital glaucoma genes. In 1996, she relocated to Hacettepe University and established the first mapping facility of Turkey. Her laboratory‘s effort resulted in a number of striking studies concerning the identification of genetic localizations and/or genes of rare craniofacial and limb malformations (frontonasal dysplasias, polydactylies, multiple synostosis) and other human disorders (macrophthalmia-coloboma, Limb-Girdle muscular dystrophy and quadrupedal walking in human). Currently, she focuses a combined approach of homozygosity mapping followed by next generation sequencing to study rare recessive disorders. She is also working with large pedigrees overloaded psychosis phenotype.

L22

Samia A Temtamy

Professor of Human Genetics
Founder of Human Genetics in the National Research Centre, Cairo, Egypt

RARE AUTOSOMAL RECESSIVE DISORDERS IN EGYPTIANS

The Egyptian contribution to medicine and genetics is justly reasoned. Ancient Egypt gives us some of the earliest evidence for both congenital and acquired diseases. Although birth incidence studies of congenital malformations have shown that the overall incidence of malformations as a whole is similar to other populations, there is a relative excess of autosomal recessive disorders due to the high rate of consanguinity. Among 200 genetic disorders reported in Egyptians 70% were autosomal recessive. The presentation provides a review of reported rare autosomal recessive genetic disorders among Egyptians with emphasis on their clinical features and molecular bases. Data are collected from available studies, mostly from personal experience of the speaker over the last forty years. Some disorders have been identified for the first time in the world by the speaker. Examples of the novel syndromes are Carpenter syndrome (MIM 201000), Temtamy syndrome of multiple congenital anomaly, mental retardation, agenesis of the corpus callosum, eye colobomas, subluxation of lenses, facial dysmorphism and connective tissue dysplasia (MIM 218340), the syndrome of congenital cataract, hirsutism and mental retardation (CAHMR syndrome MIM 211770) and Temtamy preaxial brachydactyly syndrome (MIM 605282). Autosomal recessive inheritance was suggested or confirmed for some disorders; examples are the Marden-Walker syndrome (248700) and a variant of Adams-Oliver syndrome (218600), and autosomal recessive variants of osteogenesis imperfecta. Molecular studies of rare autosomal recessive disorders in Egyptians also helped in the identification of new gene mutations. Examples are Fanconi anemia (MIM 227650), Ellis-van Creveld syndrome (MIM 225500) the 3M syndrome (MIM 273750), and the Ostrix gene mutation in osteogenesis imperfecta. The recently identified molecular basis of Temtamy preaxial brachydactyly syndrome and of Cenani-Lenz syndrome (MIM 212780) will be outlined. In conclusion, molecular studies defined locus heterogeneity of rare autosomal recessive disorders and increased our knowledge of molecular pathways. Because of the rarity of these disorders, international networking is needed to discover the genes responsible for other rare autosomal recessive disorders which have not yet been identified. Considering ethical regulations, data base registries, backed up with DNA banks should be encouraged. Transfer of recent molecular technologies, at a reasonable cost, is needed from the advanced to the developing world scientists. Large scale functional genomic studies will permit genotype/phenotype correlations. The results will also allow better genetic counseling, carrier detection, prenatal and preimplantation diagnosis necessary for the prevention of such chronic and crippling disorders.

Graduated from Faculty of Medicine Cairo University (December, 1957), DCH (1960). Ph.D. Human Genetics, Johns Hopkins University Baltimore Maryland, U.S.A. (February, 1966), was the first from Egypt, Middle East, Arab World and Africa to obtain this degree. Founder of Department of Human Genetics (1977), later the Division of Human Genetics and Genome Research in 2003. Has more than 250 peer reviewed articles. Coauthor of the Book (The Genetics of Hand Malformations), Temtamy S.A. and McKusick V.A (1978), Alan R.Liss, USA. Author of a book in Arabic (Human Genetics: The present and the future) by Al Ahram Press (1997 and 2009). Author or coauthor of chapters in books, the most recent: (Genetic Disorders among Arab Populations), Editor Ahmed S Teebi, Springer 2010. Discovered new genetic syndromes which were added to the medical literature. Member of the Editorial board of the European Journal of Human Genetics and the World Journal of Medical Genetics. Collaborator with Egyptian Ministry of Health and Population for introducing Human Genetics as a practice and in initiating newborn screening for inborn errors of metabolism in Egyptian newborns. Organized and participated as an invited speaker and gave inauguration lectures in numerous International and National Conferences. President of the National Society of Human Genetics-Egypt, member of IFHGS. Winner of numerous scientific awards: Award of Scientific Distinction in Medical, Pharmaceutical and Environmental Sciences in the National Research Centre (1987),Award of Scientific Appreciation, National Research Centre (1977), Highest State Prize of Merit in Medical Sciences (2000).

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Oral Presentation

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Abdul Rahim Al-Abri

THE ORIGIN OF HUMAN LACTASE PERSISTENCE IN THE ARABIAN PENINSULA

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Recently several genetic variants of the lactase gene [T-13910, G-13915, C 14010…] which are associated with adult lactase persistence (LP) were described and reviewed by Itan et al (2010). The T-13910 appears to be specific to northern Europeans; the G-13915 is specific to Arabs; while Africans seem to have several diverse variants. The aim of this study was to examine the distribution of the G-13915 variant in the Arabian Peninsula and examine its evolutionary origin and possible association with an independent focus of domestication of live stock. DNA samples were extracted from saliva or blood of 648 Omani and 239 Yemeni individuals. The Omani population sample was divided into three ethnic groups: Arabs of Northern Oman, Omani of Asian Origin, and Arabs of southern Oman (Dhofaris). The Yemeni samples were collected randomly from Sanaa University students including individuals from different parts of Yemen. The DNA fragment containing the T-13910 and G-13915 variants was amplified and genotyped using direct DNA sequencing. Genotyping 887 DNA samples showed that the frequency of the G-13915 allele was highest in the southern Arabian population (Dhofaris; 0.72 and Yemenis; 0.56) and completely absent in Omani of Asian Origin. In contrast the allele frequency of T-13910 was extremely low in Omani Arabs (0.01) especially Dhofaris (<0.002) while it was 0.16 among Omanis of Asian Origin. It was also very low among Yemenis (0.002). Using data from several recent publications and data from Oman and Yemen, the distribution of the G-13915 variant was plotted across the Arabian Peninsula and neighboring regions. An interpolation map was drawn using ―Spatial Analyst Extension" of ArcView version 3.2. The map shows that the highest frequency focus is in Dhofar. Radiating from Dhofar, frequencies decrease in all directions, giving evidence of clinical distribution. In conclusion, the data suggest that the origin of the Arab-specific G-13915 lactase variant appears to be in southern Arabia, in particular Dhofar. The high frequency of this variant reflects selective pressure introduced by pastoral practices of early domestication of live stock 5-10 thousand years ago, in the then green and lush Southern Arabia. This may also suggest that the origin of animal domestication in Arabia is quite independent of that in northern Europe.

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Oral Presentation

L24

Sergio Pena

ESTIMATING THE EXTENT OF GENOMIC IDENTITY BY DESCENT IN CONSANGUINEOUS COUPLES

Pena Sergio[1], Carr Ian[2]
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A significant proportion of the case load of genetic counseling involves consanguineous couples, their pregnancies and their offspring. Paradoxically, this is an area in which the ―new genomics" has not yet played a significant informational role. Clinical geneticists are often unable to furnish specific advice to these couples, even when there is already a child affected by an autosomal recessive disease in the family. We have developed IBDelphi, a suite of computer programs that uses genome wide SNP maps (Affymetrix 6.0) of the two members of a consanguineous couple to estimate the extent, size and location of ―identical by descent" (IBD) regions in their genomes. The results can be shown in tabular form and/or the IBD regions can be graphically displayed in the chromosomes. In addition, the software can compare the segments of IBD between two individuals with the autozygous regions of a relative affected by an autosomal recessive disease of unknown cause. Using this knowledge it is possible to calculate the probability of one of their children suffering from the same autosomal recessive disease. The software uses a heuristic algorithm that works by finding SNPs that exclude any possible IBD. It assumes that to be a genuine region of IBD the region must have pre-established minimum size and number of SNPs. It looks for regions that exceed these parameters and ignores smaller stretches. The total length of the non excluded regions is then added up and reported. The accuracy of the algorithm was established using two different data sets. The first was based on estimating pairwise IBD between different members of a large pedigree with varying known coefficients of genetic relationship (CGR). A high significance (P < 10-4) was observed when the total amount of IBD was regressed on CGR. The second data set was composed of pairwise IBD estimates in a random sample of 40 individuals within all populations of HapMap3. The genetic relationship of pairs with unexpectedly high IBD levels was then looked up in the HapMap database. Again, there was a highly significant linear regression of IBD on CGR (P < 10-4). Furthermore, the slopes and Y-intercepts of the two regressions were not significantly different, allowing the data to be pooled. Thus, we obtained a regression equation that permits the software to estimate the coefficient of genetic relationship of any two persons on the basis of the estimated total extent of genomic IBD. These programs are ready for use in clinical settings, improving the quality of genetic counseling of consanguineous couples. (Supported by the Sir Jules Thorn Charitable Trust of Great Britain and CNPq of Brazil).

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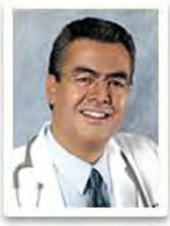

L25

Gerardo Jimenez-Sanchez

Chair, Working Party in Biotechnology, Organization for Economic Co-Operation and Development (OECD)
Chief Scientific Officer, BioFields, Mexico

OPPORTUNITIES FOR GENOMICS IN THE KNOWLEDGE ECONOMY

Genomic sciences have emerged in the last decade as a promising area with significant impact in health, the environment, industry, and other domains of modern life. This has contributed to the development of new interdisciplinary research areas, such as bioinformatics, synthetic biology, nanobiology, computational biology, biomaterials, and systems biology, among others. As with all transformative technologies, expansive economic opportunities will arise from their application. These new fields share convergence, a comparable and underlying research model which brings together engineering and the physical and life sciences, providing a new paradigm that can yield critical advances in a broad array of sectors. We believe that these emerging disciplines, where genomics plays a mayor role, will have an important impact in the world‘s future. That role is even more important today as countries emerge from the recent economic crisis, and seek to build sustainable economies geared toward meeting global challenges in providing innovative healthcare, a cleaner environment and an abundant food supply for a growing population. This summit will examine how the advancement of genomic-related technologies can contribute to a sustainable economic development in the context of the bio-economy, and will point out some challenges that need to be addressed to achieve such goals. The nature of these new technologies is such that all nations, in the developed and the developing world, may benefit from this scientific trend.

Dr. Gerardo Jimenez-Sanchez was born in Mexico City. He is has an M.D. with a Ph.D. in Human Genetics and Molecular Biology from the Johns Hopkins University. He received his training in business administration from the IPADE Business School. He is a certified Pediatrician and a member of the National Academy of Medicine, the American Society of Human Genetics, the American Society of Gene Therapy, the Society for Inherited Metabolic Disease, the European Society of Inborn Errors of Metabolism. He was founder Director General of the National Institute of Genomic Medicine in Mexico, and Chairman of the Working Party on Biotechnology at the Organization for Economic Cooperation and Development (OECD) in Paris. He is the leading investigator in the Mexican Genomic Diversity Project and the Mexican Medical Re-sequencing Initiative. Dr. Jimenez-Sanchez is Chief Scientific Officer of BioFields, Professor of Genomic Medicine at the National Autonomous University of Mexico, and teaches Business in Life Sciences at the IPADE Business School. He was President of the first and second National Congresses of Genomic Medicine in Mexico, and serves as Council member of the Human Genome Organisation (HUGO), as well as on the Board of Directors of the Public Population Projects in Genomics (P3G). He is founder President of the Mexican Society of Genomic Medicine and Regional Editor for Latin America and the Caribbean of the HUGO Journal.

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Iain M M Gillespie

Head of Science & Technology Policy Division
Directorate for Science, Technology and Industry, OECD, France

GENOMICS, REALIZING THE BIOECONOMY

Genomic sciences have emerged in the last decade as a promising area with significant impact in health, the environment, industry, and other domains of modern life. This has contributed to the development of new interdisciplinary research areas, such as bioinformatics, synthetic biology, nanobiology, computational biology, biomaterials, and systems biology, among others. As with all transformative technologies, expansive economic opportunities will arise from their application. These new fields share convergence, a comparable and underlying research model which brings together engineering and the physical and life sciences, providing a new paradigm that can yield critical advances in a broad array of sectors. We believe that these emerging disciplines, where genomics plays a major role, will have an important impact in the world‘s future. That role is even more important today as countries emerge from the recent economic crisis, and seek to build sustainable economies geared toward meeting global challenges in providing innovative healthcare, a cleaner environment and an abundant food supply for a growing population. This summit will examine how the advancement of genomic-related technologies can contribute to a sustainable economic development in the context of the bio-economy, and will point out some challenges that need to be addressed to achieve such goals. The nature of these new technologies is such that all nations, in the developed and the developing world, may benefit from this scientific trend.

Iain Gillespie is Head of the Organisation for Economic Cooperation and Development‘s (OECD) Science and Technology Policy Division. The Division works with the 30 OECD member countries as well as some 70 non-members to develop international consensus on a wide range of scientific and technological policy issues, including those related to emerging technologies such as nanotechnology and biotechnology. The Division is also responsible for OECD‘s work on innovation policy and concomitant country studies. Iain was previously Head of the OECD‘s Biotechnology Division, from its creation in 2005 to its incorporation in the current Science and Technology Policy Division in 2009. Iain worked in academia (UK and Middle East) and in the biotechnology industry (Agricultural Genetics Co Ltd, Cambridge) before joining government service in 1991. He held policy posts in the UK Departments of the Environment, of Health and of Trade and Industry as well as in the Cabinet Office where he ran a small policy unit in support of the UK‘s Chief Scientific Advisor (the now Lord May) developing advice on issues as diverse as climate change, human cloning, the use of scientific advice in policy making and risk. Just before joining OECD, Iain ran the highly successful Pharmaceutical Industry Competitiveness Task Force (PICTF), reporting to the UK Prime Minister. Iain is a scientist by training with a PhD in Microbiology. He also holds an MA in International Relations and European Politics and an MBA with specialisms in knowledge management and innovation. He was educated at the Universities of Edinburgh, London and Kent at Canterbury, as well as the Open University in the UK, and prior to that at George Heriot‘s School in Edinburgh. Iain is a member of the GlobalScot network. He is married with a son.

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Edison T Liu

Executive Director, Genome Institute of Singapore
Professor of Medicine, National University of Singapore
President, Human Genome Organisation, Singapore

GENOMICS ENGINEERING AND INTEGRATED CANCER RESEARCH

Genomic sciences have emerged in the last decade as a promising area with significant impact in health, the environment, industry, and other domains of modern life. This has contributed to the development of new interdisciplinary research areas, such as bioinformatics, synthetic biology, nanobiology, computational biology, biomaterials, and systems biology, among others. As with all transformative technologies, expansive economic opportunities will arise from their application. These new fields share convergence, a comparable and underlying research model which brings together engineering and the physical and life sciences, providing a new paradigm that can yield critical advances in a broad array of sectors. We believe that these emerging disciplines, where genomics plays a mayor role, will have an important impact in the world‘s future. That role is even more important today as countries emerge from the recent economic crisis, and seek to build sustainable economies geared toward meeting global challenges in providing innovative healthcare, a cleaner environment and an abundant food supply for a growing population. This summit will examine how the advancement of genomic-related technologies can contribute to a sustainable economic development in the context of the bio-economy, and will point out some challenges that need to be addressed to achieve such goals. The nature of these new technologies is such that all nations, in the developed and the developing world, may benefit from this scientific trend.

Dr. Liu is the Executive Director, Genome Institute of Singapore (Agency for Science, Technology, and Research) and Professor of Medicine, National University of Singapore. He received his degrees (B.S. and M.D.) at Stanford University further oncology and molecular biology training at Stanford and at UCSF. Prior to starting the GIS in 2001, Dr. Liu was the Scientific Director for the Division of Clinical Sciences, National Cancer Institute (USA). Dr. Liu‘s scientific research has focused on the functional genomics of human cancers, particularly breast cancer, investigating the dynamics of gene regulation on a genome scale that modulates cancer biology. He has authored over 260 scientific papers, reviews and books. He is the recipient of a number of awards: Leukemia Society Scholar, 1991-96; Member, the American Society of Clinical Investigations (elected 1995), the Brinker International Award for basic science research in Breast Cancer, 1996; the Rosenthal Award from the American Association for Cancer Research, 2000; the President‘s Public Service Medal for helping Singapore resolve the SARS crisis, and a Doctor of Medicine Sciences *honoris causa,*Queen‘s University, Belfast, 2007. He was elected as a Foreign Associate Member of the European Molecular Biology Organization (EMBO, 2008), and serving his second term as the elected President of the Human Genome Organisation (HUGO). Dr. Liu is also the current Chairman of the Board for the Singapore Health Sciences Authority, health regulatory and blood banking agency for Singapore.

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Pierre Meulien

President and CEO
Genome Canada, Canada

GENOMICS AND ENVIRONMENTAL SUSTAINABILITY

The challenges facing humankind in protecting the environment are reaching a critical point in our history. The list of issues is long and includes (i) the protection of diminishing fresh water supplies and maintaining them free from contamination (ii) monitoring the planets biodiversity and limiting the disappearance of existing species of flora and fauna (iii) ensuring healthy environments on land and in oceans for the production of crops, livestock and wild and farmed fish for human consumption (iv) the remediation of industrial sites such as mines, used military sites, fossil fuel extraction sites etc. (v) understanding and harnessing the power of microbial communities to detoxicify spills of toxic substances on land ,in oceans and in fresh water reservoirs (vi) issues regarding how we as a population adapt best to the acceleration in climate change. The field of the genome sciences, which has blossomed over the past decade following the successful completion of the Human Genome Project, can provide an impressive array of tools that can be used to monitor the state of play in many of the situations described above and to provide policy makers, regulators, managers of environmentally fragile assets and owners of economically viable concerns, evidence on which to base sound decision making. Specific examples taken from our Canadian portfolio will be used to illustrate this potential which in certain spheres is already becoming reality.

Dr. Pierre Meulien was appointed President and CEO of Genome Canada on October 18, 2010. Prior to this appointment, he served as Chief Scientific Officer for Genome British Columbia from 2007 to 2010. From 2002 to 2007, Dr. Meulien served as the founding CEO of the Dublin Molecular Medicine Centre (now Molecular Medicine Ireland) which linked the three medical schools and six teaching hospitals in Dublin to build a critical mass in molecular medicine and translational research. The Centre managed the Euro 45 Million ―Program for Human Genomics" financed by the Irish government and was responsible for coordinating the successful application for the first Wellcome Trust funded Clinical Research Centre to be set up in Ireland. For over 20 years, Dr. Meulien has managed expert research teams with a number of organizations, including Aventis Pasteur in Toronto (Senior Vice President of R&D), and in Lyon, France (Director of Research). He also spent seven years with the French biotechnology company Transgene in Strasbourg, France as a research scientist and part of the management team. Dr. Meulien‘s academic credentials include a PhD from the University of Edinburgh and a post-doctoral appointment at the Institut Pasteur in Paris.

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Samir K Brahmachari

Director General, Council of Scientific and Industrial Research (CSIR), India
Former Director, Institute of Genomics and Integrative Biology (IGIB), India

INTEGRATION OF GENOMICS & THE BIOECONOMY IN THE DEVELOPING WORLD

Genomic sciences have emerged in the last decade as a promising area with significant impact in health, the environment, industry, and other domains of modern life. This has contributed to the development of new interdisciplinary research areas, such as bioinformatics, synthetic biology, nanobiology, computational biology, biomaterials, and systems biology, among others. As with all transformative technologies, expansive economic opportunities will arise from their application. These new fields share convergence, a comparable and underlying research model which brings together engineering and the physical and life sciences, providing a new paradigm that can yield critical advances in a broad array of sectors. We believe that these emerging disciplines, where genomics plays a mayor role, will have an important impact in the world‘s future. That role is even more important today as countries emerge from the recent economic crisis, and seek to build sustainable economies geared toward meeting global challenges in providing innovative healthcare, a cleaner environment and an abundant food supply for a growing population. This summit will examine how the advancement of genomic-related technologies can contribute to a sustainable economic development in the context of the bio-economy, and will point out some challenges that need to be addressed to achieve such goals. The nature of these new technologies is such that all nations, in the developed and the developing world, may benefit from this scientific trend.

Dr. Samir K. Brahmachari completed a Ph.D. in Molecular Biophysics and specializes in Structural Biology and Genome Analysis. He is presently the Director of Institute of Genomics & Integrative Biology (IGIB), Delhi under the Council of Scientific and Industrial Research, India. Earlier he was a Professor of Molecular Biophysics and genetic Engineering at Indian Institute of Science, Bangalore. Institute of Science, Bangalore. Professor Brahmachari has received many prestigious National and International Awards for his contributions in Science. He is a Fellow of Indian National Science Academy and Indian Academy of Science. He was elected a member of the Human Genome Organisation, 1991 and to the HUGO Council in 2004; member of various Committees, Govt. of India; member, expert group on Human Rights and Biotechnology, United Nations and member of various International Committees. He has also been involved in issues relating to Genomics research, ethics and Human Rights. As a member of the steering committee of the International Human Rights Commission he has contributed to the formulation of the draft guidelines in terms of benefit sharing by the populations that are the part of the research endeavor as resources of genetic material and addressed issues of unethical exploitation of genetic resources of the Third world. He has contributed significantly in promoting industry-academia interactions through novel program of knowledge partnerships and. He heads the Functional Genomics Unit at IGIB. He has demonstrated the structural flexibility of DNA and the role of repetitive sequences in DNA transactions much before the discovery of repeats association with genetic disorders. His work on the structural flexibility of telomeric repeat sequences is one of the well-cited contribution. He has made major contribution in molecular analysis of genetic disorders associated with trinucleotide amplification and repetitive sequence instability. Using a combination of structural biology, computational genomics and population based polymorphism scanning he and his group have provided a novel structural frame work for understanding the etiology of several neurological disorders. One of the outcomes of these efforts has been the demonstration that loss of triplet repeat interruption as the primary step in ataxia SCA 2 which is followed by repeat expansion. Dr. Brahmachari and his group also identified a susceptibility locus on chromosome 22 using a novel positional candidate gene approach for schizophrenia and bipolar disorder patients in the Indian population and have for the first time identified a nonsense mutation in synaptogyrin I gene, a component for presynaptic pathway in schizophrenia patients. His group has developed novel in Silico bioinformatics tools to identify functional signature of hypothetical proteins and novel drug targets. For further details visit http://www.igib.res.in/

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Neil Jones

Affiliate Professor of Strategy at INSEAD, Canada

MANAGING COMPLEXITY AND CHANGE IN THE GENOMIC AGE

The complexity of technological change may lead simultaneously to both specific overestimates of the prospects for success and general underestimates of the eventual scope of feasible achievements. In this talk I draw on existing theory and research to identify some of the dimensions along which technological changes associated with a "bioeconomy" may be complex, in the sense that many elements must be coordinated and controlled for their successful introduction. While such an analysis suggests caution in making specific forecasts, it leaves considerable room for optimism more broadly.

Neil Jones is an Affiliate Professor of Strategy at INSEAD. He joined INSEAD in 2000. From 2005-2010 he was a member of the faculty of the Singapore Management University where he was the founding Academic Director of its MBA Programs. Neil has also held positions as a Visiting Assistant Professor at The Wharton School, and an Assistant Professor at the Ivey School of Business, University of Western Ontario,. He earned his doctorate in Technology and Operations Management at the Harvard University Graduate School of Business Administration and a Masters in Public and Private Management from Yale University. His undergraduate degree, in Physics, was awarded by Memorial University of Newfoundland in his native Canada. Before entering academia, Neil managed consulting projects at McKinsey and Company and practiced geophysics at Amoco Production Company (now BP). Since entering academia he has served on the Board of Directors of the Nasdaq listed Pacific Internet, where he Chaired the Compensation Committee. He is a member of the Advisory Board of aidha, a non-profit provider of financial education to lower income groups in Singapore. Professor Jones has taught Business Strategy and Management widely in North America, Europe, and Asia in both MBA and Executive Programs. He has taught and consulted at a wide range of companies including Fuji-Xerox, IBM, Nokia, 3M, 3i, Sun, Johnson and Johnson, Shell, SAP, Allianz, DKSH, Hewlett-Packard, Alcatel, India Rail, SingTel and United Technologies. He has also designed and taught modules in Strategic Management for members of Boards of Directors and for healthcare management professionals. Recently, he has begun to apply business simulations in his Strategy teaching. Professor Jones‘s research interests are rooted in a wish to understand the strategic implications of technological change. He is especially interested in environments of increasing complexity. His writings have won awards from the Strategic Management Society, the Academy of Management and the Decision Sciences Institute. They have also appeared in the Strategic Management Journal and the Harvard Business Review among other publications. He has designed and taught MBA elective courses and customized Executive Program courses in Technology Strategy, Management of Technological Change and Product Development Performance.

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Charles N Rotimi

Director, Center for Research on Genomics and Global Health at NHGRI/NIH
Senior Investigator, Inherited Disease Branch, NHGRI/NIH, USA
President, African Society of Human Genetics

THE HUMAN HEREDITY AND HEALTH IN AFRICA (H3AFRICA) GENOMIC INITIATIVE

The H3Africa Initiative, currently supported by the National Institutes of Health (NIH) and the Wellcome Trust (WT), aims to facilitate a contemporary research approach to the study of genomics and environmental determinants of common diseases with the goal of improving the health of African populations. To achieve these aims, the H3Africa Initiative aims to create and support the development of the necessary expertise among African scientists, and to establish networks of African investigators. It is anticipated that this initiative will lead to the design of high-quality research in human genomics. More broadly, it is envisaged that the H3Africa research program will develop strategies that will address health inequities in both communicable and non-communicable diseases with the ultimate goal of improving the health of Africans. This presentation will discuss the recommendations of the communicable and non-communicable working groups for H3Africa. These recommendations are currently available as a white paper at http://h3africa.org and will be presented, in a public conference, to the African and the global scientific communities March 4-5, 2011 in Cape Town, South Africa.

Dr. Rotimi is a genetic epidemiologist and a biochemist, is a senior investigator in the Inherited Disease Branch of the NHGRI intramural program. He is the Director of the Center for Research on Genomics and Global Health (CRGGH). The mission of this trans-NIH center is to advance research into the role of culture, lifestyle, genetics and genomics in disease etiology and health disparities. Dr. Rotimi develops genetic epidemiology models and conducts population genetics research that explores the patterns and determinants of common complex diseases in human populations with particular emphasis on populations of the African Diaspora. As a senior investigator and director of the CRGGH, Dr. Rotimi leads a team of researchers across multiple disciplines (Medicine, genetics/genomics, epidemiology, statistics and informatics) to understand the complex interactions between inherited characteristics and environmental factors in disease susceptibility, variable drug response and health disparities. For example, his team conducted the first GWAS of an African American cohort that identified several genetic variants including PMS1, SLC24A4, YWHA7, IPO7, and CACANA1H underlying susceptibility to Hypertension and blood pressure control. His lab also conducted the first and only genome-wide linkage study of Type 2 Diabetes in West Africans (the AADM Study). Dr. Rotimi's lab continues to contribute to the global understanding of human genetic variation and its implication for differential disease distribution, variable drug response and human migration history. He is providing scientific leadership to the new 38M dollar NIH/Wellcome Trust genomic initiative titled –Human Heredity and Health in Africa (H3Africa). He is the current president of the African Society of Human Genetics (www.afshg.org).

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Jong Bhak

Director, Personal Genomics Institute (PGI)
Director, Theragen BiO Institute (TBI), South Korea

PASNP2 PROPOSAL: PAN ASIAN PERSONAL GENOME PROJECT (PAPGP)

PASNP (Pan Asian Personal Genome Project) is an international consortium for mapping genetic diversity of Asian populations. It used about 2000 human samples to genotype them using Affymetrix 50K typing chips. The results were analyzed to show the diversity and possible migration routes of Asians that include Indians and Pacific islanders. PASNP 2.0, the second phase of PASNP will use whole genome sequencing to map all the major ethnic groups in Asia. Any one is welcome to initiate, participate in, and contribute by providing the consortium with funds, samples, and research capabilities.

Jong Bhak is the director of PGI (Personal Genomics Institute), Korea, since 2010. He had been the director of KOBIC (Korean Bioinformation Center) since 2005. He worked on a broad range of bioinformatics problems with interests in computer hardware, operating systems, programming, and applications. He received his BSc. Honours in biochemistry from Aberdeen University in 1994 and his Ph.D. in BioInformatics from Cambridge University in 1997. He joined genetics department at Harvard Medical School in 1998 as a postdoctoral researcher for DNA chip analyses. He worked as a research fellow in EBI from 1999 until 2001. In 2001, he joined MRC-DUNN as a group leader to research geronto-genomics and mitochondrial functions. In 2003, he became an associate professor at KAIST, Korea. He is a proponent of an openfree information sharing in science. He advocates free genomics projects. His group analyzed the first Korean human genome (working with Dr. Seong-Jin Kim) and the first publically available female genome (working with Personal Genome Project). He established Genome Research Foundation jointly with Dr. Seong-Jin Kim, Dr. Byungchul Kim, and Mr. Jinup Goh, to promote the application of genomics to society. GRF, working with PGP, has launched KPGP (Korean PGP) in Korea to sequence analyze 10,000 Korean people to construct reference standard Korean genomes. Also, he is collaborating with Cha medical school, National Cancer Center, and Seoul National University to find cancer specific genomic markers using bioinformatics.

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Maude E Phipps

Professor (Human Genetics)
Jeffrey Cheah School of Medicine and Health Sciences
Monash University, Malaysia

COPY NUMBER VARIATION IN INDIGENOUS MALAYSIANS: A PRELIMINARY ANALYSIS

The world's oldest rainforests of approximately 400 million years ago can be found in Malaysia. Within these rich and verdant habitats dwell some of the last semi-normadic peoples of the South Esat Asian region, the Orang Asli (OA). Although the majority of population of Peninsular Malaysia comprise Chinese, Indians and Malays, it is these indigenous communities who are the descendents of the earliest migrants into this region. Collectively, the OA comprise a little over 0.5% of the population and can be divided into 3 large categories, and within these further sub-groupings based on languages, lifestyles and phenotypes. Working with some indigenous groups, in particular the Negritos, represents a challenge. They live very much in the interior, sometimes in restricted areas that require special police permits for access. Nevertheless, over the years, we have cultivated good working relationships with them. In line with our goals of elucidating genome variation in the various ethnic groups of Malaysia, we undertook a preliminary investigation of copy number variations (CNV) in the OA. We genotyped some 30 individuals from the Temuan, Mendriq and Jehai ethic groups. The Affy SNP 6.0 system that was utilized revealed some unique variants, predominantly in the form of large deletions, some exceeding 1 MB. Some of the variants were present in more than 1 ethnic group, while some appeared to be specific. We are currently proceeding to full investigations with more participants.

Maude Elvira Phipps is Malaysian and a human geneticist who graduated with a B.Sc. Honours (Class 1) in Genetics from the University of Malaya, having completed early work on plasmid mediated antibiotic resistance and virulence factors in bacteria. In 1990, she obtained the Cambridge Commonwealth Trust Scholarship award to pursue doctoral studies at the University of Cambridge, United Kingdom where she researched the molecular genetics of Von Hippel Lindau disease and Chromosome 3p- syndrome. In 1994, she joined the Faculty of Medicine, University of Malaya and contributed substantially to the development of biomedical sciences, specialist training and research programmes. Together with colleagues, she began researching molecular genetics of autoimmune diseases and transplantation mechanisms, in collaboration with researchers the Oxford Transplant Centre and the University of Western Australia, supported by the CICHE and the UNESCO Human Genome Fellowship awards. These efforts resulted in the setting up of a new service for molecular immunogenetics and transplantation matching at the University of Malaya Medical Centre. Her current research focuses on the genomics of *Homo sapien*s to answer questions related to our evolution, migration, morphological development and health. Apart from translational medicine, she is a keen advocate of bioethics education and research programmes in Asia, especially in rapidly developing countries which have placed biotechnology high on their development agendas. She has published extensively in international journals, has been an invited speaker at numerous international meetings and supervised many graduate students over the years. Maude is currently Professor of Human Genetics at the Jeffrey Cheah School of Medicine and Heath Sciences, Monash University (Sunway Campus). She is an active member of the Human Genome Organisation (HUGO), Australian South East Asian Tissue Typing Association (ASEATTA), the UNESCO Bioethics programme. She is a member of the Steering Committee for the Malaysian Bioethics Council, co-chair of the Policy Review Board of the Pan-Asia SNP Initiative and Vice President of the Genetics Society of Malaysia.

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Henry Huanming Yang

President & Professor
BGI - Shenzhen, China

GENOMICS: THE DOOR TO PERSONALISED MEDICINE

The International Human Genome Project (HGP) has opened the door to ―Personalized Medicine", or genomic medicine, by providing the first reference sequence of our genome, as well as new concepts, strategies and powerful tools for OMICS. Even we don't have the consensus for the definition of *Personalized Medicine* yet, we might describe it, just practically and ideally, as ―to have the right diagnosis and the right medicine, at the right time, at the right dose, in the right way for the right disease of the right patient." First of all, *Personalized Medicine* requires personal genome sequence as the basis and starting point. It also requires more knowledge about population-specific genome differences among all the major populations in the world (―the human pan-genomes"), more knowledge about evolution and adaptation of our genomes, as well as the selection by environment and our own life style. It requires more knowledge about the disease-related genome differences, especially about the heterogeneity of diseases. It requires more knowledge about the mirobes, especially pathogens, and metagenomes in different parts in our body and their variations under different conditions, about the host-microbe/pathogen interaction and host susceptibility. In addition, other -omics, such as proteomics, nutrigenomics, metabolomics, and their possible relevance to epigenomics, might be important. Personalized medicine also faces new bioethical challenges. Perhaps one of them is the reconsideration of the ownership of a genome.

Dr. Yang received his Ph.D. from University of Copenhagen, Denmark, in 1988, and his postdoc training in France and USA afterwards. He returned to China in 1994 and co-founded BGI (formerly Beijing Genomics Institute) in 1999. As the co-founders of BGI, he and his collaborators have made a significant contribution to the HGP and HapMap projects, as well as to sequencing and analysing genomes of rice, chicken, silkworm, giant panda, cucumber, and many microorganisms. BGI published the first Asian's genome, human pan-genome, human ancient genome, and human gut metagenoms by means of new-generation sequencing technoloty and innovative bioinformatic tools recently. BGI now has becomes one of the major genomics centers in the world. Dr. Yang has received many awards and honors, including Research Leader of the Year by *Scientific American* in 2002 and Award in Biology by the *Third World Academy of Sciences* (TWAS) in 2006. He was elected as a foreign member of EMBO in 2006, an Academician of Chinese Academy of Sciences in 2007, and a fellow of TWAS in 2008.

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Oral Presentation

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Fowzan Alkuraya

AUTOZYGOME DECODED

Alkuraya Fowzan[1,2,3]
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Consanguineous unions permit the ~~"~~reunion" of ancestral chromosomal segments in a pattern referred to as ~~"~~autozygosity" which is essentially a special form of homozygosity. Modern SNP microarrays have rapidly replaced the historical use of microsatellites for the purpose of tracking autozygous regions of the genome. As a result, high throughput characterization of the entire set of genomic regions that are identical by descent in an individual (autozygome) has become widely available at a very low cost. We draw from our own experience in the study of the autozygome important lessons that showcase the tremendous utility of this unique natural experiment: 1) Disease Gene Mapping: In addition to the traditional linkage analysis and candidate gene sequencing approach which has been the backbone of mapping human disease genes, we show exciting examples from our lab of combining exome and autozygosity data to quickly identify disease genes even from single affected patients. 2) DNA Dispensability: Despite major recent advancements, much remains to be learned about copy number variations and how they relate to health and disease. In particular, there is uncertainty about the phenotypic consequences of homozygosity for apparently benign CNVs. Taking advantage of the consanguineous nature of our population, we show how autozygome efficiently maps dispensable DNA in humans by studying the occurrence of nullizygous events, which represent homozygosity for deletion CNVs, in runs of homozygosity. In addition to unveling our first map of such events, we show the selective bias in the occurrence of such events in the offspring and discuss its biological significance. 3) SNP Annotation: SNP databases are increasingly fed with data on SNPs of unknown population frequency. It is almost certain that some of these SNPs represent true Mendelian mutations whose pathogenicity is masked by their occurrence in a heterozygous state. We demonstrate examples where we found the causative mutation of Mendelian disorders to be variants deposited in SNP databases as variants of unknown frequency. We also discuss how our ongoing efforts to sequence autozygome and deposit the data in public databases can be of tremendous value to the wider genetic community because one can safely assume that variants present in a homozygous state in healthy individual are unlikely to be pathogenic, at least in the Mendelian sense. These and other applications that are becoming increasingly feasible with the recent advancement in sequencing technology will undoubtedly unlock the potential of autozygome as a tool to understand the human genome.

15 MARCH 2011 | **CONCURRENT WORKING SUMMIT: GLOBAL AND REGIONAL INITIATIVES CENTRE FOR ARAB GENOMIC STUDIES**

Oral Presentation

L36

Suzanne Al-Bustan

LONG RUNS OF HOMOZYGOSITY IN THE KUWAITI POPULATION

Al-Bustan Suzanne, Al-Mulla Fahd
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Long runs of homozygosity (ROH) have recently been shown to be ubiquitous in the human genome. However, there is enormous variation among individuals and populations in both the number and length of these runs. Shorter runs reflect the effective population size of an individual's ancestors and are correlated with distances out of Africa. Very long runs arise from consanguinity, a cultural norm for many millions of people across the globe. Arab and other West Asian genomes are poorly studied, although they represent a rich source of genetic variation with significant pockets of genetic homogeneity that have arisen from cultural isolation and inbreeding. Using high density genome-wide scan data, we here describe the patterns of ROH in the Kuwaiti population, including Arabs, many of Bedouin tribal origin, and Arabised Iranians. We compare the levels of homozygosity with other populations from West Asia and elsewhere in the world. We also correlate runs of homozygosity with pedigree inbreeding, and compare the effect of high parental kinship in a West Asian and European population. These long runs of homozygosity have implications for the burden of recessive Mendelian disease in Kuwaitis, and will allow recessive effects on common complex diseases such as heart disease and diabetes to be assessed.

15 MARCH 2011 | **CONCURRENT WORKING SUMMIT: GLOBAL AND REGIONAL INITIATIVES CENTRE FOR ARAB GENOMIC STUDIES**

Oral Presentation

L37

Annika F M Haywood

INITIAL ASSESSMENT OF HUMAN GENETIC DIVERSITY IN THE SAUDI ARABIAN POPULATION

Haywood Annika FM[1], Ghannam Nadia[2], Al-Aqeel Sarah A[1], Incitti Roberto[3], Ballat Hassan M[2], Sharma Kumar[4], Olefsky Jerrold M[4], Frazer Kelly A[5,6], Voolstra Christian R[1], Ravasi Timothy[1,4]
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The genetic diversity of the Saudi Arabian population is not comprehensively understood. Studies have been conducted in order to understand the genetic structure of the Arabian Peninsula and in particular the origins of the Saudi Arabian peoples. These experiments were carried out using either the haploid and maternally inherited mtDNA or the paternally inherited Y chromosome. The results showed that the majority of the lineages have come from African and Asian areas as a result of human migration since the last glacial maxim. While these studies have helped understand the origins of the Saudi people and compared their diversity with their Arab neighbors they are far from comprehensive as whole genome studies are lacking within the Kingdom of Saudi Arabia. Saudi Arabia is the largest country in the region and historically it has been considered a closed country with movement in and out of the country as quite limited. Traditionally the population is thought to be quite homogeneous and 50-60% of marriages are consanguineous, with over 30% being first cousin marriages. However there is a large influx of pilgrims yearly (approximately 3 million during Hajj), mainly from East Asian countries. Because of the strong Saudi oil economy and its large demand of workforce, in present times many stay and this may reduce the apparent homogeneity of this population. Here we report the first survey of autosomal variation in the human population of Saudi Arabia as assessed by Illumina HumanOmni2.5-Quad Bead chip and its comparison with the human genetic diversity of East Asia populations, as recently surveyed by the HUGO Pan-Asian SNP consortium.

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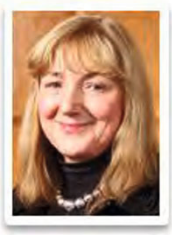

L38

Ruth Chadwick

Director, Centre for Economic and Social Aspects of Genomics (CESAGEN), Cardiff University, UK
Chair, HUGO Ethics Committee

IMAGINED FUTURES: CAPTURING THE BENEFITS OF GENOME SEQUENCING FOR SOCIETY

In the light of rapid advances in sequencing technology it is critical to explore the pathways by which the potential applications could be taken up by society. Ruth Chadwick and Edison Liu obtained generous sponsorship from the Brocher Foundation, Geneva, to bring together a Working Group to write the paper, in December 2010, including expertise from scientific, clinical, social and legal domains. The group's remit was not to investigate every possible use, misuse or application of genomic sequencing, e.g. in the context of criminal justice or behavior modification. The goal was to identify a number of specific _imagined futures' for how the technologies could be used for public good. The Writing Group identified its purpose and commitments in this paper as follows: to focus on clinical utility of sequencing technology, identifying pathways to translation and what would be the requirements for travelling along those pathways with a commitment to delivering scientifically and socially robust technology for the public good. For example, what might be needed in the form of oversight? The group had regard to the uncertainty that accompanies the societal uptake of any technology and the impossibility of *predicting* the future. This uncertainty applies not only to scientific and technological developments themselves but also to future developments in mechanisms of oversight, ethics and regulation. The group identified three imagined futures to explore: clinical indications for whole genome sequencing (WGS); cancer genomics in diagnosis and theranostics; and microbial genomics and metagenomics. This presentation will outline the main conclusions and recommendations of the group.

Ruth Chadwick is Director of the ESRC (Economic and Social Sciences Research Council) Centre for Economic and Social Aspects of Genomics (Cesagen), Cardiff University, UK. She also holds a Link Chair between Cardiff Law School and the School of English, Communication and Philosophy (ENCAP). She has co-ordinated a number of projects funded by the European Commission, including the EUROSCREEN projects (1994-6; 1996-9) and co-edits the journal Bioethics and the online journal Genomics, Society and Policy. She is Chair of the Human Genome Organisation Ethics Committee and has served as a member of several policy-making and advisory bodies, including the Panel of Eminent Ethical Experts of the Food and Agriculture Organisation of the United Nations (FAO), and the UK Advisory Committee on Novel Foods and Processes (ACNFP). She was editor-in-chief of the award winning Encyclopedia of Applied Ethics (1998), of which a second edition is now being prepared. She is an Academician of the Academy of Social Sciences and a Fellow of the Hastings Center, New York; of the Royal Society of Arts; and of the Royal Society of Medicine. In 2005 she was the winner of the World Technology Network Award for Ethics for her work on the relationship between scientific developments and ethical frameworks.

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Ellen Wright Clayton

Rosalind E. Franklin Professor of Genetics and Health Policy
Professor of Pediatrics
Professor of Law
Director, Center for Biomedical Ethics and Society, USA

DEALING WITH THE TSUNAMI OF GENOMIC DATA IN THE CLINIC

At present, most testing in medicine is done to diagnose and treat existing clinical problems. Incorporating genomic data in clinic care may turn this paradigm on its head. In this talk, I will identify some of the challenges presented by obtaining genomic data prospectively, include the certainty of false positives, the dilemmas posed by pleiotropy, and limited availability of resources for follow-up. I will then outline strategies for optimizing the use of genomic data.

Ellen Wright Clayton, MD, JD, received a bachelor's degree from Duke, a master's degree from Stanford, her law degree from Yale, and her medical degree from Harvard. A member of the Vanderbilt faculty since 1988, she is currently the Rosalind E. Franklin Professor of Genetics and Health Policy and Co-Director of the Center for Biomedical Ethics and Society at the Vanderbilt University Medical Center. She is also Professor of Pediatrics and Professor of Law. At Vanderbilt, she directs the Law Emphasis program and teaches in the Patient, Profession, and Society in the medical school and teaches the interdisciplinary course in Bioethics and Law in four schools of the University. Dr. Clayton has focused primarily on issues surrounding the ethical, legal, and social implications of advances in genetics and genomics as both a scholar and a policy maker. She has served on Tennessee‘s Genetics Advisory Council since the early 1990‘s, has participated in numerous policy and academic groups that have considered newborn screening, and is currently conducting research on the impact of false positive results in newborn screening. She has been very involved with the Human Genome Project in the United States, serving as a member of the National Advisory Council for Human Genome Research and more recently as Co-Chair of the Ethical, Legal, and Social Implications Working Group of the International Haplotype Mapping Project. She has also been very involved in ethical issues raised by genetics and genomics research, working with investigators and deliberative bodies around the world. She is currently working with HUGO on implications of whole genome sequencing. She has been instrumental in the development of Vanderbilt‘s DNA biobank and is currently Co-Chair of the Consent and Community Consultation Working Group of the eMERGE consortium, which is studying the use of electronic medical records in genome wide association studies. She has also written about a variety of issues regarding children‘s and women‘s health. A member of the Institute of Medicine since 2006, she has served on the Health Sciences Policy Board, its Advisory Council, and on several IOM Committees, chairing committees to evaluate Title X family planning and to evaluate the safety of vaccines.

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L40

Aida I Al Aqeel

S. Consultant Pediatrics, Medical Genetics and Endocrinology
Principal Scientist, King Faisal Specialist Hospital and Research Centre
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Riyadh Military Hospital, Saudi Arabia

PERSONALIZED TRANSLATIONAL MEDICINE IN THE DEVELOPING WORLD, AND KNOWLEDGE-BASED ECONOMY

Personalized translational Genomics and Stem Cell research in the long-term have major benefits in the society towards the development of new knowledge-based economy (biotechnology production, investment in technology) and the diagnosis, prevention and treatment of many diseases, e.g., cancer, diabetes, neurological diseases and others. Now that we have high density single nucleotide polymorphism (SNP) genomic information available at affordable prices for clinical applications, and with the $1000 genome not far away, we are encountering challenges to the implementation of personalized translational medicine. For example, we recognize that the sequence of the genome is only a part of the information required, and additional ~~"~~omic dimensions" such as transcriptomics and epigenomics must be integrated. In addition, association data on large and adverse populations across these dimensions will be critical to attain highly predictive and personalized diagnostic information. In Saudi Arabia like other countries in the developing world first cousin marriages account for almost 60-70% of all marriages, leading to uniquely common disorders. A review of our patients files over 15 years period, documented more than 150 varieties of neurodegenerative disease among 2,000 children; 27 of which constitute more than half of these files. Some autosomal recessive disorders are common e.g. sickle cell anemia and thalassemia. Others are unique e.g. Al-Aqeel-Sewairi syndrome. Some others are diagnostic challenges, like mitochondrial disorders of which lactic acidosis in the new born is the most common, for which no standard treatment is available. Therefore adapting strategies for the diagnosis and the management of these patients is the most challenging, not only from the clinical aspects but from the psychological aspects. For the last seven years pre- implantation genetics diagnosis and newborn screening for genetics metabolic disorders are the most important preventive programs in Saudi Arabia. The Stem Cell Therapy Program was also established at King Faisal Specialist hospital and research centre with launching of ten projects. These rapidly changing technologies which involve human subjects raise complex ethical, legal, social and religious issues. For example the field of cloning, stem cell research and pre-implantation genetics diagnosis causes debate and challenges not only among scientists but also among ethicists, religious scholars, governments and politicians. There is no consensus on the morality of human cloning, even within specific religious traditions. In countries in which religion has a strong influence on political decision making, the moral status of the human embryo is at the center of the debate. This ethical debate will need to produce acceptable policy and regulatory compromises so that the regulatory burden can be reduced and investors' risk aversion can be overcome. In conclusion, personalized translational medicine should not be limited to diagnostic and prognostic approaches, and must include personalized therapeutic strategies taking into account the psychological aspect of each family in these challenging disorders. From the various genetic techniques available, each country should adopt strategies most suitable to its genetic needs and should prioritize the programs to be used in prevention and biotechnology research that is consistent with the ethical, social and religious values, in the presence of the challenges of having resources and expertise, a based among others. Therefore we will explore the challenges as well as the progress in the implementation of personalized translational genomics in the clinical setting, including diagnostic, and preventive strategies, e.g. pre-implantation genetic diagnosis and new therapeutic strategies like stem cell therapy and their applications for the development of knowledge-based economy.

Awarded the American Federation of Medical Research Outstanding Investigation Award (2002); European Society of Human Genetics Science Award (2005); the 10th International Congress of Inborn Errors of Metabolism Outstanding Physician Award, Japan (2006). I was honored at the House of Commons, United Kingdom, as one of the distinctive international speakers (2007). Nominated for King Faisal International Prize in Medicine (2008). Was given the Distinction Medal by the Crown Prince of Saudi Arabia (2008), also given Distinctive Arab Female Scientist Prize, the Arabian Gulf University (2009). Awarded King Faisal Distinction Wissam by The Custodian of the Two Holy Mosques, King Abdullah Bin Abdul Aziz (2010). I have described a new genetic syndrome, which carries my name. This has been published and reviewed in the prestigious Nature Genetics journal as ~~"~~the first genetic evidence for the understanding of human growth and development". I am actively involved in research and research grants in translational genomics for implementing improved health services , including: (1) Pre implantation Genetic diagnosis for the prevention of genetics disorders, Co-Principal Investigator - involved in 50% of the research activities; (2) Embryonic Stem Cell development for therapy of genetic metabolic disorders - Principal Investigator- awarded 35 millions Saudi Riyals by King Abdulaziz City for Science and Technology; (3) Treatment of Genetics disorders at the molecular level - Principal Investigator, submitted to King Abdulaziz City for Science and Technology. I presented over 100 papers to National and International meetings, been invited to lecture at Havard Medical School; North Western University; Mount Sinai School of Medicine; Yale University; University of California, Irvine, USA; World Health Organization, Geneva; University of Oslo and Medical Advisory Board of Biotechnology, Norway; National Institute of Health, USA; Wellcome Trust Foundation, Cambridge, UK; Biovision International congress, Bibliotheca Alexandria; Human Variome Project meeting, Spain; Tissue Engineering International Congress, Bibliotheca Alexandria. I published over 70 manuscripts in peer reviewed, journals; presented over 100 abstracts and over 100 invited speeches. I have established ethical Frame work for research and patient care in Genetics and Genomics in the Muslim world, published that in Nature Genetics. I also established international policies for the Human Variome project in collaboration with international colleagues.

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Oral Presentation

L41

Mohsen A F El-Hazmi

THE ETHICAL ASPECTS OF BIOMEDICAL RESEARCH: THE SAUDI LAW OF RESEARCH ON LIVING BEINGS

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Advances in molecular and cellular biology research and genetic experimentations opened new avenues that can lead to promotion of health care and disease diagnoses and prevention. Professional and public perception of research on living beings remains an essential dimension of biomedical genetic research. However, the professional organizations, the advocates, the relevant watchdogs and patients' organizations, aware of the pros and cons of biomedical genetic research, are vigilant and have pushed, at local and global arenas, for regulations that pave the way for research as well as maintaining the dignity and safety of living beings. In Saudi Arabia, a Law regulating research on living beings, plants, animals and human being has been developed following the establishments of the National Ethical Committee. The Law was debated at the Ash Shura Council (The Saudi Parliament) with participation of regulators, research and public representatives who managed to arrive at a common position. The Law was subsequently passed by the Cabinet. The Law embedded the National Ethical Committee, outlining the policy and procedures that govern various elements of the Law with Islamic Teachings, Ethical aspects and the prevailing Tradition and Customs in mind. This paper will outline the said Law, its components and the features of relevance. The Law can provide an example for others to develop similar Laws in the Gulf Arabian States and Other Islamic Countries and pave the way for enhancement of Biomedical research in the region.

15 MARCH 2011 | FEATURED TALK

L42

Christopher A Walsh

Investigator, Howard Hughes Medical Institute
Chief, Division of Genetics, Children's Hospital Boston
Bullard Professor of Neurology and Pediatrics, Harvard Medical School, USA

RARE CAUSES OF RARE DISEASES, AND COMMON DISEASES, AFFECTING HUMAN COGNITION

An important unanswered question in genetics is how cognitive abilities are mapped onto genomes. Studies from many laboratories suggest that humans far exceed ‘saturation mutagenesis” for mutations at all possible loci that govern the development of the brain. Many of these mutations create rare (<1 in 10,000 individuals affected) Mendelian syndromes, that are often recessively inherited, and typically most easily studied by analyzing families in which parents have distant shared ancestry. On the other hand, intellectual disability and autism collectively affect up to 2% of the population, yet causal genes are known only in a minority of patients. An increasing amount of data suggests that autism can arise from a heterogeneous collection of rare mutations, including syndromic forms (e.g., Fragile X or *MECP2* mutations), rare quasi-Mendelian forms (*NRXN1*, *SHANK3*, or *NLGN3/4* mutations), recurrent *de novo* copy number variants (CNV‘s, e.g., 22q11 deletions, 16p11.12 deletions or duplications, and 15p11 duplications) and other, diverse CNV‘s. In order to identify inherited mutations associated with autism, our collaborators have recruited >240 families with one or more children affected with autism (>40 with 2 or more affected children) in which the two parents share distant common ancestry, focusing recruitment on countries where cousin marriage is common (including Kuwait, Saudi Arabia, Turkey, Pakistan). Analysis of these families identified a lower incidence of large, *de novo* CNV‘s compared to comparable children with unrelated parents, consistent with an important role for inherited, recessive mutations in children whose parents share ancestry. Some autistic children showed *homozygous* deletions, inherited through both parents from a common ancestor, often involving noncoding DNA near genes involved in neurological function, and suggesting the importance of precise timing and patterns of gene expression. One gene (*SCL9A9*, a.k.a. *NHE9*) near a large deletion seen in a patient with autism with seizures also showed heterozygous point mutations in American children with autism and seizures. High throughput array capture, whole exome, and whole genome sequence analysis reveals additional mutations in unexpected pathways including chromatin regulation, gene expression, and neurometabolism, and also suggest ways in which quasi-recessive genes may interact in ‘complex‘ fashion. Supported by the NIMH, the Simons Foundation, the NLM Family Foundation and the Howard Hughes Medical Institute.

Christopher Walsh is Bullard Professor of Pediatrics and Neurology at Harvard Medical School, Chief of the Division of Genetics at Boston Children's Hospital, and an Investigator of the Howard Hughes Medical Institute. Dr. Walsh completed his MD and PhD degrees at the University of Chicago. After a neurology residency and chief residency at Massachusetts General Hospital, he completed a fellowship in genetics at Harvard Medical School. He joined the faculty at Harvard Medical School in 1993, and has held the Bullard Professorship since 1999. He is formerly Director of the Harvard-MIT combined MD-PhD training program. Dr. Walsh‘s research has focused on the development, evolution, and function of the cerebral cortex, the part of our brain responsible for our highest cognitive abilities. He has pioneered the analysis of human genetic diseases that disrupt the cerebral cortex, including autism, intellectual disability, seizures, and cerebral palsy, identifying genetic causes for more than a dozen brain diseases of children. His research entails worldwide collaborations with physicians and families, especially focusing on countries of the Persian Gulf region, where he has active collaborations in Qatar, Saudi Arabia, Jordan, Kuwait, and the United Arab Emirates. Among his awards are a Jacob Javits Neuroscience Investigator Award from the National Institute of Neurological Disorders and Stroke, the Dreifuss-Penry Award Epilepsy Research Award from the American Academy of Neurology, the Derek Denny-Brown Award and the Jacoby Award from the American Neurological Association, the Research Award from the American Epilepsy Society, and the Wilder Penfield Award from the Middle Eastern Medical Assembly. He is an elected member of the American Neurological Association, the American Association of Physicians, and an elected fellow of the American Association for the Advancement of Sciences.

15 MARCH 2011 | FEATURED TALK

L43

Evan E Eichler

Principal Investigator
Professor of Genome Sciences
Howard Hughes Medical Institute
University of Washington, USA

GENOME STRUCTURAL VARIATION, EXOME SEQUENCING AND NEUROCOGNITIVE DISEASE

Structural variation of the genome is an important aspect in our understanding of human disease and susceptibility to disease. This presentation will focus on the genome-wide discovery, analysis and distribution of copy-number and structural variants within the normal human population and a population of children with intellectual disability. Our analysis will be based on a study of 15,732 children with autism, intellectual disability and congenital heart defects compared to 8,720 adult controls. I will show how high-quality sequence data can be used to predict regions associated with genomic instability as well as the discovery of the molecular basis for more complex neurocognitive disease based on a genomic hotspot model of rare and recurrent copy-number variants. I will present a two-hit CNV model to explain variability in disease phenotypes and show how the evolution of diverse structural haplotypes can act as a premutation state predisposing to recurrent rearrangement. I will contrast these results with more recent exome sequencing from a modest number of sporadic parent-child trios where offspring are diagnosed with autism and/or developmental delay. Our analyses suggest that rare CNVs are collectively common in the population and the presence of multiple events may help to explain the variability in disease manifestation. Combined with exome-based sequencing of patients, we predict that ~45% of sporadic cases of disease may be explained. The analyses are converging on a finite number of neurodevelopmental pathways where gene dosage imbalance in the heterozygous state is sufficient to create a neurological disease state.

Evan Eichler gained his Ph.D. in Molecular Genetics from Baylor College of Medicine in 1995 and a B.Sc., Honors, Biology from the University of Saskatchewan, Canada. He focuses on duplicated regions and structural variation in the human genome. Using computational and experimental approaches, he investigates the architecture of these regions and their role in evolution and disease.

L44

Martin L Hibberd

Senior Group Leader and Associate Director, Infectious Diseases
Genome Institute of Singapore, Singapore

HUMAN-PATHOGEN INTERACTIONS AND THEIR OUTCOMES, A TALE OF TWO OR MORE GENOMES AND THEIR VARIATIONS

The recent advent of genomic approaches for pathogen sequencing and human association testing is starting to enable a more comprehensive understanding of the role of human immune response in determining infectious disease outcomes, why severe disease is usually rare occurrence. These new approaches are leading to the robust discovery of a number of disease susceptibility genes, the beginnings of an appreciation of their connections and are starting to dissect pathogen-specific human responses. In particular, the availability of deep sequencing technologies has revolutionized the field of microbial genomics as we are now able to generate genomic assemblies of tens to hundreds of related genomes in a single project. This dense genetic information from multiple microbial strains is enabling novel insights into their population structures and their evolution, ranging from the delineation of disease outcomes, to transmission patterns. In Singapore, we have teamed up with the Ministries of Health, Environment and Defense; together with local hospitals, to apply this knowledge to infectious disease outbreaks, resulting in unique understandings of human interactions.

Dr. Martin Hibberd BSc(Hons) PhD; Senior Group Leader and associate director, Infectious Diseases at the Genome Institute of Singapore and has adjunct positions at the National University of Singapore and Imperial College (London, UK). Graduated with Honors from Brunel University in 1985 (West London, UK) and received his Doctorate, on the immune-genetics of the human T-cell antigen receptor, from King‘s College, London. Has a broad scientific background spanning both microbial and human determinants of infectious and inflammatory diseases. Previous posts include WHO-funded Senior Microbiologist at the UK‘s central Public Health Laboratories, and for seven years prior to his current appointment he was Lecturer and Senior Lecturer in Pediatric Infectious Diseases at the Imperial College School of Medicine, one of the very top-ranking British universities. Current research interests cover both pathogen and host aspects of infectious disease, understanding how microbial agents causes the observed disease (including pathogen identification and sequence characterization) and why specific individuals are susceptible to the disease (using host genetics on a genomic scale). Approaching infectious disease from these two directions also allows specific host pathogen responses to be investigated (utilizing RNA micro and low density arrays). This work aims to identify key host responses to specific pathogens that could be targeted by new therapies.

L45

Howard L McLeod

Fred N. Eshelman Distinguished Professor
Director, UNC Institute for Pharmacogenomics and Individualized Therapy, USA

LEARNING HOW TO APPLY THE GENOME TO GUIDE THERAPY

The field of pharmacogenomics has seen some exciting advances in the recent past. The Human Genome Project and International HapMap projects have uncovered a wealth of information for researchers. This has lead to the discovery of clinically predictive germline genotypes (e.g. UGT1A1*28-irinotecan, TYMS TSER-fluoropyrimidines, CYP2D6-tamoxifen, CYP2C19-clopidogrel), germline haplotypes (e.g. VKORC1 Haplotype A-warfarin) and somatic mutations (e.g. epidermal growth factor receptor-gefitinib/erlotinib, KRas-cetuximab/panitumumab). The introduction of FDA approved pharmacogenetic tests (UGT1A1*28, CYP2C9/VKORC1, CYP2D6/CYP2C19) and the initiation of genotype-guided clinical trials have provided the first steps towards the integration of pharmacogenomics into clinical practice. However, it is also clear that there are many scientific and non-scientific barriers to clinical application. These include integration of new tests into health systems, changing old habits to allow application of new data, and the reality that the cost of both testing and the therapeutic options are a key driver in health care. As the scientific evidence matures, A team research approach must be more aggressively applied in order to overcome the many obstacles to delivering more careful selection of drug therapy.

Dr. Howard McLeod is Fred N. Eshelman Distinguished Professor and Director, UNC Institute for Pharmacogenomics and Individualized Therapy, University of North Carolina, Chapel Hill. Dr. McLeod holds appointments in the Schools of Pharmacy and Medicine and the Lineberger Cancer Center. Dr. McLeod is also the Principal Investigator for CREATE, a member of the NIH funded Pharmacogenetics Research Network and is a member of the FDA committee on Clinical Pharmacology. He also directs the Pharmacogenetics for Every Nation Initiative, which aims to help developing countries use genetic information to improve National Drug Formulary decisions. Howard has published over 350 peer reviewed papers on pharmacogenomics, applied therapeutics, or clinical pharmacology and continues to work to integrate genetics principles into clinical practice to advance individualized medicine.

L46

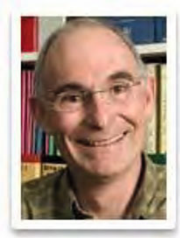
Yuan-Tsoong Chen

Distinguished Research Fellow
Institute of Biomedical Sciences
Academia Sinica, Taiwan

PHARMACOGENOMICS OF ADVERSE DRUG REACTIONS: TOWARD PERSONALISED MEDICINE

Adverse drug reactions (ADRs) account for 6-7 % of all hospital admissions and remain a major clinical problem. Type A ADR is dose-dependent and usually monogenic or oligogenic; an example is warfarin sensitivity, which causes excessive bleeding. A functional promoter polymorphism of vitamin K epoxide reductase complex subunit 1 was found to be associated with inter-individual differences in warfarin dosage and can explain the inter-ethnic differences in warfarin sensitivity. Prospective study of warfarin dosage requirements based on CYP2C9 and VKORC1 genotypes showed that pharmacogenetics-based dosing can improve the time to stable dosing, reduce adverse events and achieve high sensitivity. Type B ADR is usually dose-independent, and historically referred to as being unpredictable and polygenic; an example is drug hypersensitivity. Several recent studies reported strong genetic associations between HLA and susceptibility to drug hypersensitivity. The genetic associations can be drug-specific; HLA-B*1502 is associated with carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN), HLA-B*5701 with abacavir hypersensitivity and HLA-B*5801 with allopurinol-induced severe cutaneous adverse reactions. The genetic association can also be phenotype-specific; B*1502 is associated solely with carbamazepine-SJS/TEN, and not with either maculopapular eruption or hypersensitivity syndrome. Furthermore, a genetic association can be ethnicity-specific; carbamazepine-SJS/TEN associated with B*1502 is seen in Southeast Asians but not in Caucasians or Japanese, which can be explained by the difference in allele frequencies among populations. The strong genetic association suggests a direct involvement of HLA in the pathogenesis of drug hypersensitivity of which HLA molecule presents an antigenic drug for T-cell activation. Pharmacogenomic study identified an unusual form of granulysin secreted by cytotoxic T lymphocytes and natural killer cells responsible for the disseminated keratinocyte death in Stevens-Johnson syndrome and toxic epidermal necrolysis. The high sensitivity/specificity of some genetic markers provides a plausible basis for developing tests to identify individuals at risk for drug hypersensitivity. Application of HLA-B*1502 genotyping as a screening tool for patient taking carbamazepine is now recommended by the Department of Health, Taiwan and by the US FDA.

Professor Yuan-Tsong (Y-T) Chen was originally from Taiwan and has been committed to biomedical research for over 30 years. He recognizes the tremendous impact that genetics and genomics have had on the improvement of health and treatment of diseases and has established the Chen Award, with HUGO, to celebrate research accomplishments in Human Genetics and Genomics in Asia Pacific and around the world. Professor Chen received his MD degree from National Taiwan University (Taipei) and a PhD from Columbia University (USA). He is currently a Distinguished Research Fellow of the Institute of Biomedical Sciences, Academia Sinica, Taiwan, and Professor of Pediatrics and Genetics at Duke University Medical Center (USA). Professor Chen is a physician/scientist, recognized for his work on human genetic disorders. His translational research leads to the development of now standard therapies for two devastating inherited metabolic diseases: a simple and effective cornstarch therapy for severe hypoglycemia in glycogen storage diseases and an enzyme replacement therapy, the first ever treatment, for a debilitating, progressive and often fatal myopathy called Pompe disease. Professor Chen has also identified the genetic basis of and developed DNA-based diagnosis for several major heritable diseases, and more recently, his team in Taiwan has uncovered genes/SNPs associated with drug-induced Stevens-Johnson syndrome and warfarin sensitivity. His latest pharmacogenomic studies of adverse drug reactions paved the way for personalized medicine by preventing drug toxicity with a gene test. Professor Chen is an elected member of Academia Sinica and of the Academy Sciences for the Developing World.



L47

Pierre Renault

Research Director
Micalis Institute, France

THE HUMAN INTESTINAL MICROBIOTA, OUR "SECOND GENOME" AS A FUTURE TARGET FOR PERSONALISED MEDICINE

Human genome encodes key factors directing our development, physiology and ability to undertake adapted responses to environmental conditions. However, our body is colonized by billions of commensal microorganisms, which are more abundant than our own body cells. These microorganisms interact with our body, and plays role in immune system maturation, digestion, nutrient production and assimilation and preventing pathogen overgrowth. These interactions play key roles in our health and well-being. In regards to their role in human physiology and health, these microorganisms are now collectively considered as an organ in our body, and therefore, their genetic content as our "second genome". In the frame of the EU MetaHit and French Micro-Obes projects, we detailed by new sequencing technologies, the nature and the role of this still poorly characterized world. A catalogue of 3.3 millions genes has been established, largely over numbering that of human genes. The analysis of gene variability between individual by deep profiling with the Illumina or SOLiD analyzer was performed for a better understanding in the metabolic potential of human intestinal microorganisms and finding association between specific genes and phenotypes such as particular metabolic disorders. Collectively, human can be colonized by thousands of microbial species and more variants. However, each individual displays a specific microbiota, relatively stable in the lifespan, and composed of several hundreds of species which are drawn out of this large catalog. Therefore, our "second genome" greatly varies in gene composition and abundance. In our work, the number of gene counted by deep profiling averages 540 000 by individual, but may vary between 250 000 and 1000000. Gene association studies have been carried out by comparing gene contents of individuals included in clinical studies targeting obesity and inflammatory bowel diseases (ulcerative colitis, Crohn disease). Association could be revealed between bacterial species and diseases, raising the possibility to design genetic markers for personalized medicine and guide for the discovery of etiological factors. Deep profiling of human intestinal microorganism genomes will provide new insight in factors affecting our health in number of pathologies. Furthermore, studies on the effect of diets, cultural practices and lifestyle affecting the composition of our "second genome" will provide guideline for preventive care and personalized medicine.

Pierre Renault, Ph.D., is Research Director at the Micalis Institute located in Jouy en Josas (Ile-de-France) in the National Institute for Agronomical Research (INRA). Micalis is composed of 29 teams working in Ecosystem, Food Risk and System Biology applied on Food and Health. In particular, it develops researches on the impact on health of human intestinal microorganisms, which could be collectively named our "second genome", and which genetic variability largely encompasses that of our "first genome". P. Renault first worked for 2 years to settle a microbiological laboratory in Yemen. Then he performed a PhD on genetics and physiology of food bacteria. From 3 years he redirected its activities on human intestinal microorganisms that intimately interact with human physiology and may protect or favor metabolic disorders in conjunction of changes induced by diet, lifestyle and health. The BAC team, managed by P. Renault, has a strong background in gene expression and bacterial physiology. It develops metagenomic approaches to establish relationships between components of the human intestinal microbiome and metabolic disorders such as obesity and inflammatory bowel diseases. This includes bioinformatic analysis of data generated by the New Generation Sequencers such as SOLiD and illumina, but also functional approaches on human intestinal microorganisms to pinpoint molecular mechanisms involved in the crosstalk between human and microbiota. These researches may open new ways for personalized medicine.

Oral Presentation

L48

Vajira H W Dissanayake

THE SRI LANKAN PERSONAL GENOME PROJECT (SLPGP)

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With the completion of the Human Genome Project scientists were able to determine the nucleotide sequence of the human genome. Although this laid the foundation to study the genotype and phenotype correlation, evidence was not strong enough to address the phenotypic differences between individual human beings. Personal genome projects address this issue by sequencing and examining the genetic makeup of individual persons. The Sri Lankan Personal Genome Project was aimed at sequencing the genome of a Sri Lankan individual and identifying all the mutations, conserved genetic elements and clinically significance regions in the genome. The genome of the Sinhalese male of Sri Lankan origin was sequenced using Illumina's reversible terminator chemistry. 65.25 Gigabases of raw data was generated. Casava 1.6 was used for base calling. Mapping and Assemblies with Qualities (MAQ) which uses the GRCh37/hg19 build of the Human Genome as the reference was used for genome assembly. The length of non-gapped regions of the reference genome covered by reads was 2.8Gb, which is exactly the length of the reference genome excluding gaps. 99.41% of the reference genome was covered by the Sri Lankan genome and the depth of coverage achieved was 22.52 X. During the base call and assembly process, 2,811,918 Single Nucleotide Polymorphisms (SNPs) and 488,921 Insertion Deletion Polymorphisms (InDels) were identified. Then the data was fed into an advance analysis pipeline where the data was first filtered using the dbSNP 131 build to identify novel variations. Results showed that 250,463 (8.9%) of the Identified SNPs were novel variations. Next, these variations were categorized based on their Genic/Intergenic, Synonymous and Non-Synonymous properties. This second phase of the pipeline presented 18,997 Variations in Exons/CDS regions and 89 variations in noncoding Functional RNAs. Following that if the SNPs were non-Synonymous, potential effects of these variations were studied according to SIFT (Sorting Intolerant from Tolerant) resulting in the identification of 884 variations as damaging non-synonyms. Furthermore, SNPs were compared against the GWAS catalog which resulted in the identification of 1617 variations in GWAS loci. Finally, genomic data was visualized by using GBrowser and made available to the public via www.srilankangenome.net. Acknowledgement: This project was funded by the NOMA Project of the PGIM.

Oral Presentation

L49

Sridhar Sivasubbu

COMPREHENSIVE COMPUTATIONAL PIPELINE FOR SYSTEMATIC ANALYSIS AND ANNOTATION OF FUNCTIONAL VARIANTS IN PERSONAL GENOMES

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Whole genome sequencing of individual humans provides a wealth of information on genomic variations. These studies provide a rich template for identification of common and rare variants conferring disease risks thus leading to an interest in sequencing of both normal as well as individuals with clinical indications. Apart from addressing the question of novel variations in the genome, variation data derived from whole-genome sequencing also reveals a wealth of information on gene disruptions and their potential consequences, in addition to suggesting potential clinical indications, which constitute the preventive and predictive use of whole-genome sequencing. In this study we have generated a whole genome sequence of an individual of Indian origin and then used this genome as a template to develop a systematic workflow for identifying genome scale variants and their consequences, thus laying the template for genome-scale analysis of personal genomes for personalized medicine. We have applied the massively parallel DNA sequencing method to generate the whole genome sequence of a self-declared healthy male of Indian origin. This work provides us with a template male human sequence from the subcontinent, thus adding to the number of individual genomes available till date. We have generated around 82Gb of genome sequence data, which aligned back to the GRCh37/hg19 build of the human reference genome resulting in over 28-fold coverage of the reference genome and representing over 99% of the reference genome. In this process, we have identified over 3 million single nucleotide polymorphisms (SNP) at high confidence and also about 480k small insertion deletions (InDels), many of which are in the coding region of the genome. We have used this data set as a template to analyze and annotate for potential biological implications in terms of the genome variability. We designed a comprehensive computational pipeline for the systematic analysis of clinically relevant variants in the coding and non-coding region of the genome and also compare this with other personal genomes available in the public domain and other known datasets by integrating information on markers on disease predisposition as well as pharmacogenomic markers.

16 MARCH 2011 | **CONCURRENT SYMPOSIUM: INBORN ERRORS OF METABOLISM AND THERAPY OF GENETIC DISORDERS**

L50

Yuan-Tsoong Chen

Distinguished Research Fellow
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TRANSLATING THE PROMISE OF GENOMIC MEDICINE INTO CLINICAL REALITY: CHALLENGES OF POMPE DISEASE

Pompe disease is an autosomal recessive disorder of glycogen metabolism caused by a deficiency of the lysosomal enzyme acid alpha-glucosidase (GAA). Patients present differentially with variable rates of progression ranging from a rapidly progressive course, often fatal by 1 year of age, to a slower, but nevertheless relentlessly progressive course. Prior to 2006, therapy for Pompe disease remained essentially palliative and the natural history of infantile onset Pompe disease was uniformly poor with death occurring usually by age 1 year from cardiomyopathy or respiratory failure. Research on the development of enzyme replacement therapy (ERT) started in the early 70‘s but not until mid 90‘s that the *in vivo* efficacy of ERT was first demonstrated in the Japanese quail with Pompe disease, and then later in the GAA-knockout (GAA-KO) mouse model. Subsequently, pilot human phase I/II studies of recombinant human GAA began in 1999, followed by phase II clinical trials and pivotal trials which eventually leads to market approval of the Myozyme® (alglucosidase alfa, Genzyme, Cambridge, MA, USA) in 2006 and more recently Lumizyme® in 2010 for late-onset patients. The story of a father searching for a life-saving drug for his two children with Pompe disease and the development of this new drug has been adapted to a Hollywood movie entitled ―Extraordinary Measures”. The ERT has dramatically improved the outcome of the disease; however, limitations of the therapy such as high dose and variable skeletal response remain a challenge. Stage of the disease at the time of treatment, CRIM status of the patients and antibody are some important factors contributing to the variable skeletal response. Progress continues to be made in the development of improved therapies for Pompe disease such as a second generation recombinant enzyme, small molecule chaperone therapy, small molecule for substrate reduction and gene therapy.

Professor Yuan-Tsong (Y-T) Chen was originally from Taiwan and has been committed to biomedical research for over 30 years. He recognizes the tremendous impact that genetics and genomics have had on the improvement of health and treatment of diseases and has established the Chen Award, with HUGO, to celebrate research accomplishments in Human Genetics and Genomics in Asia Pacific and around the world. Professor Chen received his MD degree from National Taiwan University (Taipei) and a PhD from Columbia University (USA). He is currently a Distinguished Research Fellow of the Institute of Biomedical Sciences, Academia Sinica, Taiwan, and Professor of Pediatrics and Genetics at Duke University Medical Center (USA). Professor Chen is a physician/scientist, recognized for his work on human genetic disorders. His translational research leads to the development of now standard therapies for two devastating inherited metabolic diseases: a simple and effective cornstarch therapy for severe hypoglycemia in glycogen storage diseases and an enzyme replacement therapy, the first ever treatment, for a debilitating, progressive and often fatal myopathy called Pompe disease. Professor Chen has also identified the genetic basis of and developed DNA-based diagnosis for several major heritable diseases, and more recently, his team in Taiwan has uncovered genes/SNPs associated with drug-induced Stevens-Johnson syndrome and warfarin sensitivity. His latest pharmacogenomic studies of adverse drug reactions paved the way for personalized medicine by preventing drug toxicity with a gene test. Professor Chen is an elected member of Academia Sinica and of the Academy Sciences for the Developing World.

16 MARCH 2011 | **CONCURRENT SYMPOSIUM: INBORN ERRORS OF METABOLISM AND THERAPY OF GENETIC DISORDERS**

L51

Gert-Jan B van Ommen

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Leiden University Medical Center, The Netherlands

TRANSLATIONAL GENOMICS, INTEGRATING RARE AND COMMON DISEASE

Twenty years after the first wave of Mendelian disease gene discoveries, their translation into therapeutic modalities begins to take hold, greatly aided by the increase in biological insights and advancement of technologies of the genomics era. Antisense-mediated reading frame restoration is presently the most promising therapeutic approach for Duchenne muscular dystrophy (DMD). In this approach, antisense oligoribonucleotides (AONs) induce specific exon skipping during pre-mRNA splicing to restore the disrupted open reading frame and allow synthesis of internally deleted, partly functional Becker-like dystrophin proteins. The approach is theoretically applicable to over 70% of all patients. Proof of concept has been achieved in cultured muscle cells from patients carrying different mutation types, in the mdx mouse and dog models and recently in patients as well. In a first trial published in 2007 (van Deutekom et al. NEJM) we showed exon 51 skipping and dystrophin restoration in four patients after local intramuscular AON injections. A subsequent systemic trial has recently been successfully completed by Prosensa, as a multicenter one-month dose-finding trial, using subcutaneous administration. This better route for self-administration was previously tested to be efficient in reaching proper muscle AON levels, with a lower peak circulation level as intravenous administration. The 12 patients enrolled showed a clear dose response, both of skipping and dystrophin restoration, without adverse effects. Our preclinical further research now focuses on the next steps in developing and improving therapy: the development of more refined readouts for therapeutic success using transcriptomics and proteomics technology, and supporting treatments to increase myogenesis. Finally, the success of the exon skipping work in DMD has led us to explore applications to genes affected in other diseases. Thus, the translational steps initially taken for rare diseases will also greatly assist therapeutic development for common disease. Especially in this era of rapidly emerging high-troughput tools and technology, it is becoming increasingly clear that the merging of the fields of complex and rare disease, classically seen as complementary and largely separate, has much to contribute to better defining biology, predict health outcomes and guiding therapy development.

Prof. Dr. Gertjan B. van Ommen, PhD, is head of the Department of Human Genetics of the Leiden University Medical Center (LUMC), and founder of the Leiden Genome Technology Center (LGTC), a principal genomics facility in the Netherlands. He is Director of the Center for Medical Systems Biology (CMSB), one of the four Centers of Excellence established in 2003 by the Netherlands Genomics Initiative, aiming to improve diagnosis, therapy and prevention of common and rare diseases. Van Ommen has as major research interests in neuromuscular and neurodegenerative diseases, with a focus on Duchenne Muscular Dystrophy (DMD), Huntington Disease and the development and application of genome research and diagnostic technology for disease study, diagnosis, therapy and prevention, including the societal aspects of genetic advances. As of 1998, his group has been pioneering the exon-skipping approach for therapy of Duchenne Muscular Dystrophy. After preclinical research in patient cells and mice, this approach is now the potential DMD therapy closest to market. In collaboration with the Leiden biotech company Prosensa, in 2007 the first-in-man proof-of-concept study was performed and in 2009 Prosensa completed the first successful phase I/II systemic trial. Van Ommen is coordinator of the national Dutch biobank integration infrastructure (BBMRI-NL), established in 2009. He is Editor-in-chief of the European Journal of Human Genetics and past president of HUGO and of the European and Dutch Societies of Human Genetics. He is a member of several national, EU and HUGO committees in the fields of genetics, innovative health care, genomics, bioinformatics, biobanking, ethics and intellectual property issues. He participates in several EU FP7 projects including BBMRI, the European biobanking infrastructure, and ENGAGE, analysing GWA studies of approximately 90.000 samples across Europe. He is treasurer of the international Public Population Project in Genomics (P3G), and board member of the Medical Genetics Centre (MGC) and the Centre for Biomedical Genetics (CBG).

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L52

Arthur L Beaudet

Henry and Emma Meyer Professor and Chair
Department of Molecular and Human Genetics
Baylor College of Medicine, USA

MUTATIONS AND POSSIBLE EPIMUTATIONS CAUSING SCHIZOPHRENIA AND AUTISM

Haploinsufficiency for individual genes or chromosomal regions is known to be capable of causing autism or schizophrenia. In addition to the known copy number mutations causing schizophrenia and autism, we have identified novel copy number variations at substantial frequency in the DNA of patients with combined schizophrenia and epilepsy. By analogy, epigenetic silencing of an allele should be the functional equivalent of deletion or loss-of-function point mutation in that allele. We hypothesize that some fraction of autism and schizophrenia cases might be caused by epimutations. A genome-wide analysis of DNA methylation was performed on brain samples from 44 normal individuals, 13 patients with autism and 22 with schizophrenia using the Illumina Infinium human 27 methylation bead chip platform. The CpG island at the 5′-end of *SERHL* was hypermethylated in cerebellum of one autism patient. The CpG island at the 5′-end of *LOC652276,* a hypothetical gene, was hypermethylated in the BA8 region of cerebral cortex of one schizophrenia case. In both instances, the Infinium data were consistent with the interpretation that all controls and other cases were unmethylated at these loci and that heterozygous methylation was present in these two cases. Bisulfite treatment of DNA followed by PCR and sequencing of clones yielded approximately equal numbers of highly methylated and unmethylated clones for each locus which is consistent with the possibility of methylation of one allele but not the other for each locus. No similar cases of gain of methylation were observed in control brain samples. In addition, we also identified more than 100 sites showing hypomethylation in both disease sample sets. This work is being extended using the Illumina Human Methylation 450 DNA Analysis BeadChip and additional autism and schizophrenia samples. Supported by the Simons Foundation Autism Research Initiative (SFARI).

Dr. Beaudet received his M.D. degree from Yale, did pediatric residency training at Johns Hopkins, and was a research associate at the National Institutes of Health before joining Baylor College of Medicine (BCM) in 1971 where he has remained to the present. Dr. Beaudet has made diverse contributions in the field of mammalian genetics including discovery of uniparental disomy in humans and publishing over 250 original research articles. He has argued for the importance of epigenetics in human disease since 2002 (PMID: 12394355) and proposed a mixed epigenetic and genetic and mixed *de novo* and inherited model for oligogenic inheritance in autism (PMID: 15389703). In 2004, Beaudet and a BCM team of investigators were the first in the US to introduce array comparative genomic hybridization (array CGH) into the clinical lab, and they have gone on to play a leadership role in the transformative impact of this technology on clinical genetics. His current work is focused on the role of genomic copy number abnormalities and epigenetic changes in neurobehavioral disabilities, and especially on the importance of the *CHRNA7* gene in intellectual disability, autism, and schizophrenia. Dr. Beaudet is well-known as one of the editors of the *Metabolic and Molecular Bases of Inherited Disease* textbook for the 6th through 8th editions and now the electronic edition, and he has served on many editorial boards and national review panels. He was President of the American Society of Human Genetics in 1998 and is an elected member of the Association of American Physicians and the Institute of Medicine of the National Academy of Sciences. Dr. Beaudet is currently the Henry and Emma Meyer Distinguished Service Professor and Chair in the Department of Molecular and Human Genetics at Baylor College of Medicine in Houston.

16 MARCH 2011 | **CONCURRENT SYMPOSIUM: INBORN ERRORS OF METABOLISM AND THERAPY OF GENETIC DISORDERS**

L53

Chaker Adra

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Stem Cell Therapy Program, Research Centre,
King Faisal Specialist Hospital and Research Centre, Saudi Arabia

GENOMIC, PROTEOMIC AND STEM CELL STRATEGIES FOR DIAGNOSING AND TREATING KIDNEY, CANCER, CARDIOVASCULAR, NEUROLOGICAL AND AUTOIMMUNE DISEASES IN THE GULF REGION AND WORLDWIDE

Accurate diagnosis of the primary cause of an individual‘s kidney disease can be essential for proper management. Certain kidney diseases have similar histopathological features despite being caused by defects in different genes. Two consanguineous Saudi Arabian families in which individuals presented with renal failure and mixed clinical and histological features, initially thought consistent with focal segmental glomerulosclerosis (FSGS) were compared. We applied whole-genome single-nucleotide polymorphism analysis followed by targeted isolation and sequencing of exons using genomic DNA samples from affected members, followed by additional focused genotyping and sequence analysis. We studied members of two apparently related families from Saudi Arabia with kidney disease. The two apparently unrelated families shared a region of homozygosity on chromosome 2q13. Exome sequence from the affected individuals lacked any sequence reads from the NPHP1 gene, located within this homozygous region. Additional PCR based genotyping confirmed that affected individuals had NPHP1 deletions, rather than defects in a known FSGS-associated gene. This analysis demonstrates the power of new high-throughput genotyping and sequencing technologies to aid in the rapid genetic diagnosis of individuals with an inherited form of kidney disease. The aim was to identify genes and differentially expressed proteins that have potential as disease specific biomarkers for kidney disease. This technology will aid in the diagnosis for other genetic and autoimmune related diseases. Functional characterization of these disease associated genes, proteins and stem cells will elucidate our understanding of the pathogenesis of kidney diseases, cancers, neurological, cardiovascular and stem cell diseases in the Gulf Region and throughout the world.

Dr. Chaker Adra is the Director of The Stem Cell Therapy Program at King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia. Chaker Adra is a geneticist, biochemist, molecular and cellular biologist investigating the biology of hematopoiesis, cancer, and the mechanisms of stem cell cycle regulation. Since his childhood, he has been interested in discovering the Laws of Physics and Chemistry as manifested in The Language of Genomes and in Living Organisms. In a series of groundbreaking experiments, he discovered several universal gene families and biochemical and physiological pathways operating in yeast, plants, animals and humans. He cloned and characterized the family of the phosphoglycerate kinase genes and pseudogenes. He identified the phosphoglycerate kinase (PGK) promoter and constructed the PGK Neo Vector. The PGK-Neo Cassette is being used around the world for gene therapy, to engineer transgenic and knockout animals. Almost all laboratories and pharmaceutical companies are engineering mice using The PGK-Neo Cassette to understand the causes of human diseases and find cures for genetic, cardiovascular, neurodegenerative, renal, liver and autoimmune diseases, diabetes and cancer. Most recently he discovered several new cancer and stem cell specific biomarkers. He is the inventor of twelve USA and International Patents.

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Oral Presentation

L54

Said Shawar

THE ARABIC ALLELE: A NOVEL 10BP DELETION IN THE LOW DENSITY LIPOPROTEIN RECEPTOR (LDLR) CREATES A PREMATURE STOP CODON AND SEVERELY DECREASES THE EXPRESSION LEVELS IN TWO UNRELATED ARAB FAMILIES WITH FAMILIAL HYPERCHOLESTEROLEMIA

Shawar Said[1], Al-Drees Mohammad[2], Ramadan Ahmad[1], Ali Najat[3], Al-Fadhli Suad[4]
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Familial hypercholesterolemia (FHC) is a monogenic autosomal dominant disorder caused by defects in the low density lipoprotein receptor (LDLR). To date, more than 1000 mutations have been identified. The worldwide prevalence of heterozygous FHC is 1 in 500, and 1 in a million for the homozygous. Few reports describe FHC mutations among Arab Gulf population. In this study, we describe a novel, previously unreported deletion in the LDLR of two unrelated Arab Gulf families. Materials and Methods: Nineteen patients from two different families were studied using DNA sequence analysis, restriction fragment length polymorphism (RFLP), real-time (RT) PCR and flowcytometry to characterize LDLR and evaluate its expression. Results: DNA sequence analysis of the homozygote individuals (undergoing cholesterol apheresis) showed a novel 10bp deletion in exon 12; (c.1706-1715del.ATCTCCTTCA) leading to a frameshift and a premature stop codon (PSC; TGA) at position c.2084-2086. These results were confirmed using Bgl II restriction enzyme and RFLP. Also, RT-PCR revealed that LDLR mRNA in peripheral blood lymphocytes is 9.30%±6.50 and 17.90%±8.06 for FHC homozygote and heterozygote individuals respectively compared to a healthy family control (100%). The low levels of mRNA correlated with the cell surface protein expression as assessed by flowcytometry. Using LDLR-specific monoclonal or polyclonal antibodies, we found no protein expression at the cell surface of monocytes taken from FHC homozygote persons while the monocytes of heterozygote persons showed reduced cell surface expression compared to that of a healthy family control. Taken together, our results predict a class II LDLR mutation due to a truncated receptor that contains a dysfunctional epidermal growth factor precursor homology domain and the deletion of exons 15-18; i.e. missing the O-linked rich region, the membrane spanning, and the cytoplasmic domains. Conclusions: We identified a novel 10bp deletion followed by a frameshift and a premature stop codon in the LDLR of two unrelated Arab families. We called this possible founder mutation "the Arabic Allele" in contrast to the Lebanese Allele. We predict a significant contribution of the Arabic Allele to the prevalence of FHC among Arabs in general and the Arab Gulf Population in specific. Also, we propose that the severe down regulation of LDLR expression in these patients is due to a cryptic splicing, mRNA nonsense mediated decay and protein misfolding and ER associated degradation of the truncated receptors.

16 MARCH 2011 | **CONCURRENT SYMPOSIUM: INBORN ERRORS OF METABOLISM AND THERAPY OF GENETIC DISORDERS**

Oral Presentation

L55

Giriraj Chandak

MATERNAL 1-CARBON METABOLISM IN PREGNANCY AND OFFSPRING BIRTH WEIGHT: EPIDEMIOLOGICAL ASSOCIATIONS AND MENDELIAN RANDOMIZATION IN TWO INDIAN BIRTH COHORTS

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Circulating homocysteine concentration is a ‗summative index' of 1-Carbon metabolism for which folate and vitamin B12 are essential nutrients. We have shown earlier that mothers of small-for-gestational-age (SGA) babies had higher plasma homocysteine (tHcy) concentrations during pregnancy. We now report the association between maternal tHcy levels and offspring birth weight in two Indian birth cohorts and investigate the causality of this association using Mendelian randomization. We used data from the Pune Maternal Nutrition Study (Pune, India, N=702) and Parthenon Study (Mysore, India, N=526). Maternal demographic, anthropometric and nutritional measurements (folate, vitamin B12, and tHcy concentrations) were made at around 28 weeks gestation, and offspring birth weight was recorded. Both mothers and children were genotyped for two polymorphisms in the MTHFR gene, C677T and A1298C and the interrelationship between the genotypes, maternal biochemical parameters and the offspring birth weight was investigated. Nineteen percent of mothers were hyperhomocysteinemic (tHcy > 10mmol/l), 2% had low folate status (<283 nmol/L for erythrocyte folate and <7 nmol/L for plasma folate) and 58% had low vitamin B12 status (<150 pmol/L). Maternal homocysteine levels were inversely related to offspring birth weight (standardized β= -0.21, p=0.001), while folate concentrations were directly associated (standardized β=0.084, p=0.001). However, plasma B12 levels had no significant influence on the offspring birth weight. Maternal MTHFR C677T genotype predicted higher levels of plasma tHcy (standardized β=0.169, p=0.001) and lower offspring birth weight (p<0.01) independent of maternal body mass index, socio-economic status, gestation at delivery, and newborn sex and its MTHFR C677T genotype (standardised β= -0.069, p=0.01). Higher maternal folate concentrations overcame the birth weight lowering effect of MTHFR 677TT genotype. The other polymorphism A1298C was not associated with any of the biochemical parameters or the offspring birth weight. Maternal 1-C metabolism influences fetal growth and offspring birth weight. Improving maternal vitamin B12 and folate nutrition may help reduce intrauterine growth retardation and its short- and long-term sequela. These observations should promote interest in a public health intervention to improve vitamin B12 and folate status in young girls in India.

16 MARCH 2011 | CONCURRENT SYMPOSIUM: CANCER GENOMICS

L56

Mary-Claire King

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GENETIC HETEROGENEITY IN HUMAN DISEASE

Evolutionary forces on the genome have generated vast genetic heterogeneity in human disease. Mutation introduces many new variants in every generation, some severe enough to cause disease. Such mutations are rapidly selected out of the population but are replaced by newcomers. Current sequencing technologies offer the possibility, for the first time, of finding these mutations and the genes that harbor them.

Mary-Claire King Ph.D. is American Cancer Society Research Professor of Medicine and Genome Sciences at the University of Washington in Seattle. She was the first to prove that breast cancer is inherited in some families, by genomic localization of the gene she named BRCA1. The characterization of inherited breast and ovarian cancer remains her primary research focus. Her other research interests include inherited deafness, genetic influences on schizophrenia, human genetic diversity and evolution, and the application of genomics to human rights problems. Dr. King grew up in Chicago. She received her B.A. cum laude in Mathematics from Carleton College in Northfield, Minnesota, her Ph.D. in Genetics from University of California at Berkeley, and her postdoctoral training at U.C. San Francisco. Her Ph.D. dissertation in 1973 was the demonstration that human and chimpanzees are 99% identical in gene sequences. She served as Professor of Genetics at U.C. Berkeley from 1976-1995. At the University of Washington since 1995, she is American Cancer Society Professor in the Departments of Medicine and Genome Sciences. She has an adult daughter, Emily, who lives and works in Berkeley. Dr. King has served on the Advisory Committee to the Director of NIH, the National Commission on Breast Cancer of the President s Cancer Panel, the National Academy of Sciences' Committee on Science, Engineering, and Public Policy (COSEPUP), multiple National Cancer Institute councils and planning groups, multiple NIH study sections, the Council of the Institute of Medicine, the Advisory Committee for the NIH Office for Research on Women's Health, the Council of the NIH Fogarty International Center, the National Academy of Sciences' Committees on the use of DNA in forensics and on the development of the Department of Defense Breast Cancer Research Program, and as consultant to the Commission on the Disappearance of Persons of the Republic of Argentina. Her lab has carried out DNA identifications for the United Nations War Crimes Tribunals. Dr. King has been elected to Phi Beta Kappa and Sigma Xi, to the American Association for the Advancement of Science as a Fellow, to the Institute of Medicine, to the American Academy of Arts and Sciences, and to the National Academy of Sciences of the USA and as a foreign member of the French Academy of Sciences. She received the Clowes Award in Basic Research from the American Association for Cancer Research, the Jill Rose Award from the Breast Cancer Research Foundation, the Brinker Award from the Susan G. Komen Foundation, the Genetics Award from the Peter Gruber Foundation, the Weizmann Award for Women and Science, the Heineken Prize for Medicine from the Netherlands Academy of Arts and Sciences, and the American Cancer Society Medal of Honor for Clinical Research. She has received honorary doctorates from Carleton College, Smith College, Bard College, Dartmouth College, SUNY, Columbia University, Harvard University, Brown University, the University of Leuven, Yale University, Tel Aviv University, Princeton University, and the University of California Medal.

L57

Axel Hillmer

Research Scientist, Genome Technology & Biology
Genome Institute of Singapore, Singapore

LONG SPAN PAIRED-END-TAG MAPPING REVEALS CHARACTERISTIC PATTERNS OF STRUCTURAL VARIATIONS IN CANCER GENOMES

Somatic genome rearrangements are thought to play important roles in cancer development. Individual tumors frequently exhibit different patterns of somatic mutations, gene copy number variations, differential gene expression profiles, and epigenetic modifications. Most of the currently identified genes associated with cancers contribute to oncogenesis as a consequence of somatic genome rearrangements that result in fusion transcripts or transcriptional deregulation. Recent advances in DNA sequencing technologies render it possible to systematically identify the majority of genomic rearrangements using a genomic DNA paired-end-tag (DNA-PET) sequencing and mapping strategy. This strategy has been applied with short genomic DNA fragments for human genome analysis, but has not been fully exploited for the identification of the different types of structural variations (SVs) and their joint architecture primarily because of cost and the complexity of the analysis. We optimized a long span PET sequencing approach using 10 kb genomic DNA inserts to study human genome structural SVs. The use of 10 kb insert size allows the identification of breakpoints within repetitive or homology containing regions of a few kb in size and results in a higher physical coverage compared to small insert libraries with the same sequencing effort. We have applied this approach to comprehensively characterize the SVs of several cancer genomes. Our analyses revealed that most inversions, deletions, and insertions are germline SVs, whereas tandem duplications, unpaired inversions, inter-chromosomal translocations, and complex rearrangements are overrepresented among somatic rearrangements in epithelial cancer genomes. We demonstrate that the quantitative and connective nature of DNA-PET data is precise in delineating the genealogy of complex rearrangement events. Further, we observe signatures which are compatible with breakage-fusion-bridge cycles and discover that large duplications are among the initial rearrangements that trigger genome instability for extensive amplification in epithelial cancers. With further optimization for the current prototype of DNA-PET analysis and the continuous drop of sequencing cost, we expect this approach to be sufficiently robust and cost effective to be applied in clinical settings for genetic diagnostics of cancer patients.

Structural variants of the human genome contribute to inter-individual differences and certain structural rearrangements can result in severe cell biological malfunction. My first interest is to analyze genome structure alterations which contribute to the development of cancer. To investigate the characteristics of the cancer genome, we use paired-end-ditag (PET) based high throughput DNA sequencing methodologies. The identification of cancer-specific rearrangements will help us to understand the processes involved in tumorigenesis. Another focus of mine is the detailed analysis of structural variants within and across populations. In addition to improving the understanding of the human genome, the structural variants are potential modulators of phenotypic variability and evolutionary advantage. Further, I am interested in genetic variability which contributes to hair loss. In collaboration with the University of Bonn, I work on the genetic basis of male pattern baldness.

L58

Lotfi Chouchane

Professor of Genetic Medicine
Professor of Microbiology & Immunology
Assistant Dean for Basic Science Curriculum
Weil Cornell Medical College in Qatar, Doha, Qatar

BREAST CANCER IN ARAB POPULATIONS: FROM CANCER-ORIENTED GENOMIC AND PROTEOMIC APPROACHES TOWARDS PREVENTIVE AND PREDICTIVE MEDICINE

Shan Jingxuan[1], Mathew Rebecca[1], Mahfoudh Wijden[2], Bouaouina Noureddine[2], Gabbouj Sallouha[2], Abdelhak Sonia[3], Messaoud Olfa[3], Megarbane Andre[4], Jalkh Nadine[4], Al-Bozom Issam[5], Hassen Elham[2], Chouchane Lotfi[1]
[1]Weill Cornell Medical College in Qatar, Doha, Qatar; [2]Laboratory of Immuno-Oncology, University of Monastir, Tunisia; [3]Institut Pasteur of Tunis, Tunisia; [4]University Saint-Joseph, Lebanon; [5]Hamad Medical Corporation, Qatar; loc2008@qatar-med.cornell.edu

Breast Cancer remains one of the leading causes of death among women worldwide. The incidence of the disease has been increasing in Arab populations. The collected data suggest that Arab women may experience an early age of onset and a preponderance of aggressive breast cancer phenotype. Particularly important is the exceptionally high prevalence of inflammatory breast cancer (IBC) in Arab populations. The replication of the associations found between the novel SNPs and breast cancer, revealed by the recent genome-wide association studies, in populations other than Caucasians, such as Arab populations, is essential for the validation of these findings. In this communication, I will summarize recent investigations of breast cancer candidate genes and proteins, which their variation may predict not only breast cancer onset in the Arab populations but also the clinical outcome. The potential identification of proteins/genes associated specifically with the aggressive forms of breast cancer could shed light on the important molecular pathways of metastases and eventually could be translated into alleviate and preventing poor survival outcome of breast cancer.

Dr. Lotfi Chouchane is professor in the departments of genetic medicine, and microbiology and immunology of Weill Cornell Medical College in Qatar (WCMC-Q). Dr. Chouchane received his Ph.D. in immunology from Pasteur Institute of Paris and the University of Paris VII. Following a four-year post-doctoral position at the National Institute of Allergy and Infectious Diseases, National Institutes of Health, in the U.S., he obtained his D. Sc. in human genetics and immunology. He then joined the National Institute of Medical Research in Paris as visiting scientist. Before joining WCMC-Q in July 2005, Prof. Chouchane was at the Faculty of Medicine of Monastir University in Tunisia, where he worked as professor of human genetics and immunology, and chief of the laboratory of immuno-oncology. He was the chair of the department of basic science during the period between 1996 and 2002. Dr. Chouchane is currently the Associate Dean for Basic Science Curriculum, Associate Director of the Molecules Genes & Cells course of the 1st year Medical Program and the course Director of the Human Genetics Course of the 2nd year of the Pre-medical Program at WCMC-Q. His current research interests include the genetics and immunology of multi-factorial diseases including cancer, obesity & Diabetes. Dr. Chouchane is a member of the Human Genome Organisation (HUGO), a member of the steering committee of the WHO consortium of genetics of nasopharyngeal cancer, and a member of the advisory board of the Centre for Arab Genomic Studies of Dubai.

16 MARCH 2011 | CONCURRENT SYMPOSIUM: CANCER GENOMICS

L59

Douglas Easton

Professor of Genetic Epidemiology
Centre for Cancer Genetic Epidemiology
University of Cambridge, UK

RECENT DEVELOPMENTS IN THE GENETICS OF BREAST AND OTHER CANCERS

Common cancers, including breast cancer, exhibit familial aggregation, consistent with substantial variation in inherited susceptibility. Over the past 25 years, the underlying genetic basis for this susceptibility has been increasingly understood. Three important classes of genetic loci have been identified: (1) ―High-penetrance" genes, principally *BRCA1* and *BRCA2*. Mutations in these genes confer a high lifetime risk of breast, ovarian and other cancers. However, mutations in these genes are rare and explain less than 20% of the familial risk of breast cancer. (2) ―Intermediate-penetrance" genes currently include *ATM*, *CHEK2*, *BRIP1* and *PALB2*. Mutations in these genes confer a 2-3 fold increased risk of breast cancer. (3) Common ―low-penetrance" alleles, principally identified through genome-wide association studies (GWAS). There are currently approximately 20 such loci. The most significant such loci, in *FGFR2* and *TOX3*, confer relative risks of 1.2 to 1.3 fold. Altogether, the known loci probably explain 25-30% of the familial aggregation of breast cancer, implying that many additional loci remain to be found. It is unlikely that there any further important high-penetrance loci, but many more lower penetrance loci should be identifiable, through GWAS, large-scale replication studies and resequencing. The mutations in *BRCA1* and *BRCA2* (and, so far, those in the intermediate risk genes) involve inactivating coding alterations. In contrast, the low-penetrance loci are occur in non-coding regions (including ―gene deserts") and are presumably regulatory. Most of these regions have not previously been related to carcinogenesis and point to novel mechanisms. While the risks associated with the common low-penetrance alleles are modest, these risks combine multiplicatively with each other and with *BRCA1* and *BRCA2*. This raises the possibility that common genetic variation may become important in risk prediction, particularly in women with a family history of the disease. There are also important differences in susceptibility by tumor subtype: *BRCA1* mutations predispose predominately to ER-negative ―Basal" breast cancer, whereas many of the low-penetrance loci are specific to ER-positive disease. These pathological differences may have implications both for risk prediction and prevention.

Douglas Easton is Professor of Genetic Epidemiology at the University of Cambridge and a Principal Research Fellow of Cancer Research UK. He is also honorary director of Strangeways Research Laboratory. He received a first class honours degree in Mathematics from the University of Cambridge and a Ph.D. in genetic epidemiology at the Institute of Cancer Research, London. He was elected a Fellow of the Academy of Medical Sciences in 2002. In 2008 he was awarded the inaugural Outstanding Investigator Award for Breast Cancer Research from the American Association for Cancer Research and Susan G. Komen for the Cure. His principal research interests are in the genetic epidemiology of common diseases, especially cancer. His major research contributions have involved the design and analysis of large-scale genetic epidemiological studies, and the development of statistical methodology. He was one of the leading investigators in the mapping of the *BRCA2* breast cancer predisposition gene. He co-founded the Breast Cancer Linkage Consortium, and his work lead to the development of reliable risk estimates for BRCA1 and *BRCA2* carriers, and the development of the first comprehensive risk model for breast and ovarian cancer (BOADICEA). Much of his recent work has focussed on the analysis of common, lower penetrance, variants in cancer. His group co-ordinates the analysis of three large international consortia: the Breast Cancer Association Consortium (BCAC), Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome (PRACTICAL), and the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA). He led the first genome-wide association study (GWAS) in breast cancer, which resulted in the identification of the first common susceptibility variants in this disease, and has co-directed successful GWAS in prostate, endometrial and testis cancer that have led to the identification of multiple genetic variants for these diseases. He is also evaluating the role of rarer variants in breast and prostate cancer, and susceptibility to cancer-related traits including breast density, steroid hormones and telomere length.

16 MARCH 2011 | CONCURRENT SYMPOSIUM: CANCER GENOMICS

L60

Fahd Al-Mulla

Associate Professor and Head of Molecular Pathology
The Health Sciences Center, Faculty of Medicine, Kuwait University, Kuwait

COLORECTAL CANCER GENOMICS: FINDING A CONVERGENCE NEXUS IN A FRACTAL WORLD

Metastasis is a leading cause of death from cancer. However, this field remains poorly explored. Our research aims at utilizing what we term _Functional Fractals‘ to identify metastasis suppressor genes. In order to understand a complex system that involves a large number of interacting components such as cancer metastasis, one needs to determine the type of tissues/data collected, and the technologies/approaches best suited to address cancer heterogeneity and multidimensional signaling pathway perturbations. Current sophisticated technologies paved the way towards our understanding of complex systems and their hierarchical architectural. However, faced with such a magnitude of fragmented data sets composed of hundreds or thousands of genes that are differentially expressed or copy number altered, it remains challenging to identify important players in complex biological or pathological processes such as metastasis. Using functional fractal ideology aided by microarray CGH, we identified a commonly deregulated molecule termed Raf-Kinase inhibitor protein (RKIP) that appears to have an important metastasis suppression characteristic in many cancer types. We show that RKIP may attain such properties by inhibiting several pathways including c-RAF (MAPK), GRK2, NFκB and activating GSK3β. We show that RKIP role in cells is more diverse than previously thought. Funding Agency: Our studies are supported by funds from the Kuwait Foundation for the Advancement of Sciences grant number (2006-1302-07) and Kuwait University grant (MG02/08) and Research Core Facility Grant Number GM01/05 AND GM01/01.

Fahd Al-Mulla received his Medical Doctorate and Ph.D. from Glasgow University in the field of cancer genetics and metastasis. Dr. Al-Mulla is the Director of the Research Core Facility in Kuwait University Health Sciences Center. He heads a Molecular Pathology Unit, which aims at delivering state-of-the-art theranostics. As Assistant Vice President for Research, he headed the office of External Research Collaboration in Kuwait University with a mandate to build collaborative partnerships, invest institutional outputs, generate capital and resources, and promote public awareness as regards to the importance of scientific research outputs in resolving society‘s problems and in expediting the development process. Dr. Al-Mulla is a pioneer in the identification and characterization of metastasis suppressor genes. It is expected that his work will result in the identification of clinically useful cancer biomarkers in the near future.

16 MARCH 2011 | CONCURRENT SYMPOSIUM: CANCER GENOMICS

Oral Presentation

L61

Alessandro Stella

ANALYSIS OF TELOMERE DYNAMICS IN PERIPHERAL BLOOD CELLS FROM LYNCH SYNDROME PATIENTS

Stella Alessandro[1], Bozzao Cristina[1], Lastella Patrizia[1], Ponz de Leon Maurizio[2], Pedroni Monica[2], Di Gregorio Carmela[3], D'Ovidio Francesco[4], Resta Nicoletta[1], Prete Fernando[5], Guanti Ginevra[1]
[1]Medical Genetics Unit, Department of Biomedicine in Childhood, "Aldo Moro" University of Bari, Bari, Italy; [2]Department of Medicine and Medical Specialties, Medicine I, University of Modena and Reggio Emilia, Italy; [3]Department of Laboratory, Pathology and Legal Medicine, University Hospital Policlinico di Bari; Bari, Italy; [4]Department of Statistical Sciences, "Aldo Moro" University of Bari, Bari, Italy; [5]"C. Righetti" Surgery Division, University Hospital Policlinico di Bari, Bari, Italy; alexst@medgene.uniba.it

In Lynch syndrome, also known as hereditary nonpolyposis colorectal cancer (HNPCC), germline mutations in DNA mismatch repair (MMR) genes cause a a highly increased risk of developing cancers mainly in the colon and the endometrium and less frequently in other target organs such as stomach, skin, and genitourinary tract. The management of Lynch patient's, to date, represents a major challenge due to the large variability in age at cancer onset. Several factors, including genetic anticipation, have been proposed to explain this phenotypic heterogeneity but the molecular mechanisms remain unknown. Telomere shortening is a common event in tumorigenesis and has been observed also in different familial cancers. We investigated the possibility of a relationship between telomere length and cancer onset in Lynch syndrome. We measured the mean telomere length with quantitative PCR in peripheral blood of 50 controls, 31 unaffected mutation carriers, and 43 affected patients and correlated it with both the mutated MMR gene and cancer occurrence. The relative telomere length was determined as the amount of telomeric template (T) vs. a single-copy gene (S) to give the T/S ratio in experimental samples using the standard curve. In affected patients, telomere attrition was correlated with age at cancer onset. In all cases, a t-test was used to assess the linearity of the regression. The present study reports, for the first time, an evaluation of the telomere length in patients with Lynch syndrome. Our data show that telomere length in peripheral blood cells of Lynch carriers is not different from that of controls and declines with age in a similar way. On the other hand, affected patients demonstrated accelerated telomere attrition, compared to normal individuals, whereas asymptomatic carriers had a slower decline with age. A significant correlation between telomere length and age was observed in both affected and unaffected carriers (P=0.0016 and P=0.004 respectively) and in MSH2 mutation carriers (P=0.0002) but not in MLH1 mutation carriers. When the T/S values were correlated with the age at onset in the affected patients, a statistically significant different trend was observed for MLH1 and MSH2 carriers (MLH1 r=0.097 P=0.677, MSH2 r=-0.66 P=0.001 and P=0.0072 for the difference). Therefore, in MSH2 carriers the lowest the lowest T/S values were observed in patients with late onset cancer while an opposite trend for longer telomere in patients with delayed onset was present in MLH1. Our data suggest that telomere dynamics are different between MLH1 and MSH2 mutation carriers. Subtle gene-specific mechanisms can be possibly linked to cancer onset and anticipation in Lynch syndrome. Acknowledgements: Supported by grants: a) Regione Puglia contract PE 041CARSO Ricerca Oncologica; b) Fondazione Cassa di Risparmio di Puglia –Identificazione di eventi di splicing associati ai tumori del colon retto" and c) Ricerca Finalizzata Universita di Bari (60%) to AS.

16 MARCH 2011 | CONCURRENT SYMPOSIUM: CANCER GENOMICS

Oral Presentation

L62

Prakash Hande

MECHANISM BASED COMBINATION TELOMERASE INHIBITION: IMPLICATIONS FOR CANCER THERAPY

Hande Prakash, Gurung Resham Lal, Sethu Swaminathan, Lim Shi Ni, Koh Bernard Jing Zhi, Venkatesan Shriram, Gopalakrishnan Kalpana, Sameni Safoura, Khaw Aik Kia, Jayapal Manikandan
Department of Physiology, National University of Singapore, YLL School of Medicine, MD9 2 Medical Drive, Singapore; phsmph@nus.edu.sg

Telomerase reactivation is essential for telomere maintenance in human cancer cells ensuring indefinite proliferation. Targeting telomere homeostasis has become one of the promising strategies in the therapeutic management of tumors. Recent investigations are beginning to indicate the potential of targeting telomerase in brain tumors. In this study, we show the anticancer potential of two different telomerase inhibitors in brain tumor cells (medulloblastoma and glioblastoma). In an integrated approach using multicolor fluorescence in situ hybridization, array comparative genomic hybridization and cDNA micro array analysis, we have determined the genetic makeup of the brain cancer cells used in the study. In addition to the disruption of telomere length maintenance, they decreased tumor cell viability, induced cell cycle arrest and DNA damage. Repair of telomerase inhibitor-induced DNA damage involved activation of DNA-PKcs protein with inhibition of DNA-PKcs activity causing delay in the repair of induced DNA damage. Additionally, telomere dysfunctional foci were more detectable in DNA-PKcs deficient glioblastoma cells as compared to DNA-PKcs proficient glioblastoma cells. The observed therapeutic potential in the brain tumor cells improved when they were combined with the inhibition of certain selective DNA repair factors (such as PARP-1 and DNA-PKcs). We have also observed the radio-sensitisation potential of these telomerase inhibitors in brain tumor cells. Therefore, targeting telomerase in addition to contemporary therapies and/or with inhibition of specific DNA repair pathways would improve the short and long term prognosis of malignant brain tumors. *This research is supported by Academic Research Fund, Ministry of Education, Singapore.

16 MARCH 2011 | **CONCURRENT EXPERT SESSION: MECHANISM OF GENOME SEQUENCING - SETUP AND OPERATIONS OF A FACILITY**

L63

Yijun Ruan

Senior Group Leader and Associate Director of Genomics Technology & Biology
Genome Institute of Singapore, Singapore

MECHANISM OF GENOME SEQUENCING: SETUP AND OPERATION OF A FACILITY

Next-generation sequencing technologies are transforming the field of genomic science and the DNA sequencing based approaches are penetrating in almost every topics of modern biology. Rapid development of sequencing instruments, information framework, and bioinformatic capabilities have made it possible that many institutions and even individual labs can now think of setting up their own DNA sequencing facilities. Therefore, frequent questions floating in the field are: what it takes to set up my own sequencing facility; how to do so; are there tips; and can you help? Yes, a team of experts is assembled in this session to specifically address these questions. Collectively, they will cover: what biological questions can be effectively studied by genome-wide sequencing analysis; how to generate different types and high quality libraries; how to manage the workload and timelines; how to flow sequencing reads around; and how to analyze the data for biological discovery. Don‘t miss it!

Dr. Ruan Yijun is currently the Senior Group Leader and Associate Director of Genomics Technology at the Genome Institute of Singapore. His primary interest is to elucidate the structures and dynamics of all functional DNA elements in complex genomes through transcriptome characterizations and genome interrogation. To facilitate such understanding, Dr. Ruan's lab have developed paired-end-ditag (PET) based high throughput and high precision DNA sequencing and mapping methodologies. These sequencing-based measurements are used to address complex biological questions such as how cancer cells progress and how stem cells maintain their unique properties. Another major interest of Dr. Ruan is to discover previously uncharacterized microbial genes and genomes that are relevant to human health. To this end, his lab has established a metagenome analysis capability that includes a filtration system for isolating uncultured microbes, shotgun and PET sequencing of metagenomes to uncover viral and bacterial genome sequences from a variety of environment settings and cavities of the human body.

16 MARCH 2011 | **CONCURRENT EXPERT SESSION: MECHANISM OF GENOME SEQUENCING - SETUP AND OPERATIONS OF A FACILITY**

L64

Herve Thoreau

Production Leader, Sequencing
Genome Institute of Singapore, Singapore

MECHANISM OF GENOME SEQUENCING: SETUP AND OPERATION OF A FACILITY

Next-generation sequencing technologies are transforming the field of genomic science and the DNA sequencing based approaches are penetrating in almost every topics of modern biology. Rapid development of sequencing instruments, information framework, and bioinformatic capabilities have made it possible that many institutions and even individual labs can now think of setting up their own DNA sequencing facilities. Therefore, frequent questions floating in the field are: what it takes to set up my own sequencing facility; how to do so; are there tips; and can you help? Yes, a team of experts is assembled in this session to specifically address these questions. Collectively, they will cover: what biological questions can be effectively studied by genome-wide sequencing analysis; how to generate different types and high quality libraries; how to manage the workload and timelines; how to flow sequencing reads around; and how to analyze the data for biological discovery. Don‘t miss it!

Herve began to work at Genome Institute of Singapore in 2001. He is the production Leader for Genome Technology and Biology group. The GT&B group is applying cutting edge innovative genomic technologies and next generation sequencing platform to study genome variation and transcription regulation in complex biological systems. Prior to joining Genome Institute of Singapore, Herve worked for 4 years in the French Biotechnology Company, GENSET S.A., as team leader of the Mapping Production group. Herve holds a B.Sc. in Industrial Bio-experimentation from E.S.T.B.A, Paris. Concurrently he is also pursuing graduate studies in Biological Engineering at the Université de Technologie de Compiègne (UTC), conferring the diplôme d‘ingénieur.

16 MARCH 2011 | **CONCURRENT EXPERT SESSION: MECHANISM OF GENOME SEQUENCING - SETUP AND OPERATIONS OF A FACILITY**

L65

Xiaoan Ruan

Manager, Personal Genomics Solutions (PGS)
Genome Institute of Singapore, Singapore

MECHANISM OF GENOME SEQUENCING: SETUP AND OPERATION OF A FACILITY

Next-generation sequencing technologies are transforming the field of genomic science and the DNA sequencing based approaches are penetrating in almost every topics of modern biology. Rapid development of sequencing instruments, information framework, and bioinformatic capabilities have made it possible that many institutions and even individual labs can now think of setting up their own DNA sequencing facilities. Therefore, frequent questions floating in the field are: what it takes to set up my own sequencing facility; how to do so; are there tips; and can you help? Yes, a team of experts is assembled in this session to specifically address these questions. Collectively, they will cover: what biological questions can be effectively studied by genome-wide sequencing analysis; how to generate different types and high quality libraries; how to manage the workload and timelines; how to flow sequencing reads around; and how to analyze the data for biological discovery. Don‘t miss it!

Rapid advance in DNA sequencing technologies has opened brand new opportunities for biomedical researches and clinic applications. The paired-end diTag (PET) sequencing methods, invented by GIS scientists, have been integrated with next-generation sequencer platforms such as 454-GSFLX, Solexa GAII and ABI SOLiD. My current focus is to streamline the existing PET methodologies and develop new sequencing approaches including automated PET pipelines for whole genome, transcriptome, and chromatin interactome analyses. We are actively applying the PET technologies to address broader interests in genomic researches and biomedical implementations, through internal and external collaboration projects. Our ultimate goal is to establish a robust and cost-effective DNA sequencing platform to deliver personalized genomics solutions to all patients and individuals.

16 MARCH 2011 | **CONCURRENT EXPERT SESSION: MECHANISM OF GENOME SEQUENCING - SETUP AND OPERATIONS OF A FACILITY**

L66

Atif Shahab

Software Engineering Manager, Research Computing
Genome Institute of Singapore, Singapore

MECHANISM OF GENOME SEQUENCING: SETUP AND OPERATION OF A FACILITY

Next-generation sequencing technologies are transforming the field of genomic science and the DNA sequencing based approaches are penetrating in almost every topics of modern biology. Rapid development of sequencing instruments, information framework, and bioinformatic capabilities have made it possible that many institutions and even individual labs can now think of setting up their own DNA sequencing facilities. Therefore, frequent questions floating in the field are: what it takes to set up my own sequencing facility; how to do so; are there tips; and can you help? Yes, a team of experts is assembled in this session to specifically address these questions. Collectively, they will cover: what biological questions can be effectively studied by genome-wide sequencing analysis; how to generate different types and high quality libraries; how to manage the workload and timelines; how to flow sequencing reads around; and how to analyze the data for biological discovery. Don‘t miss it!

Atif joined Genome Institute of Singapore in 2007. He currently manages teams responsible for information technology infrastructure and bioinformatics support for next generation sequencing platforms. Prior to joining Genome Institute of Singapore, Atif was a manager in a sister institute, Bioinformatics Institute, A*STAR. Atif graduated with a Bachelors of Engineering and Masters in Computer Science from University of New South Wales, Australia.

16 MARCH 2011 | **CONCURRENT EXPERT SESSION: MECHANISM OF GENOME SEQUENCING - SETUP AND OPERATIONS OF A FACILITY**

L67

Axel Hillmer

Research Scientist, Genome Technology & Biology
Genome Institute of Singapore, Singapore

MECHANISM OF GENOME SEQUENCING: SETUP AND OPERATION OF A FACILITY

Next-generation sequencing technologies are transforming the field of genomic science and the DNA sequencing based approaches are penetrating in almost every topics of modern biology. Rapid development of sequencing instruments, information framework, and bioinformatic capabilities have made it possible that many institutions and even individual labs can now think of setting up their own DNA sequencing facilities. Therefore, frequent questions floating in the field are: what it takes to set up my own sequencing facility; how to do so; are there tips; and can you help? Yes, a team of experts is assembled in this session to specifically address these questions. Collectively, they will cover: what biological questions can be effectively studied by genome-wide sequencing analysis; how to generate different types and high quality libraries; how to manage the workload and timelines; how to flow sequencing reads around; and how to analyze the data for biological discovery. Don‘t miss it!

Structural variants of the human genome contribute to inter-individual differences and certain structural rearrangements can result in severe cell biological malfunction. My first interest is to analyze genome structure alterations which contribute to the development of cancer. To investigate the characteristics of the cancer genome, we use paired-end-ditag (PET) based high throughput DNA sequencing methodologies. The identification of cancer-specific rearrangements will help us to understand the processes involved in tumorigenesis. Another focus of mine is the detailed analysis of structural variants within and across populations. In addition to improving the understanding of the human genome, the structural variants are potential modulators of phenotypic variability and evolutionary advantage. Further, I am interested in genetic variability which contributes to hair loss. In collaboration with the University of Bonn, I work on the genetic basis of male pattern baldness.

16 MARCH 2011 | **CONCURRENT EXPERT SESSION: COMPUTATIONAL ANALYSIS OF GENOMIC INFORMATION**

L68

Guillaume Bourque

Associate Professor, Department of Human Genetics, McGill University, Canada
Director of Bioinformatics, McGill University & Genome Quebec Innovation Center

CHANGING LANDSCAPE OF COMPUTATIONAL BIOLOGY

New sequencing technologies have enabled a wealth of new biomedical applications and promise to revolutionize medicine. In this session I will highlight some of the challenges associated with the computational analysis required to decipher biology from genome sequences and related data that is accumulating at incredible speed. I will also describe some of the computational methods associated with technologies such as ChIP-Seq and RNA-Seq that enable an incredible look into cellular activity.

During his Ph.D., Guillaume Bourque worked on genome rearrangements in evolution and cancer with Pavel Pevzner at the University of Southern California. In 2002, he moved to the University of Montreal to start postdoctoral research on gene regulatory networks with David Sankoff. In 2004, he accepted a position at the Genome Institute of Singapore, where he became Senior Group Leader and Assoc. Director of Computational & Mathematical Biology. At this Institute he helped setup and was responsible for the IT infrastructure, LIMS and analysis pipelines associated with 10 Next-Generation sequencing instruments. In 2010, he moved to McGill University as a faculty member in the Department of Human Genetics and the Director of Bioinformatics at the McGill University and Genome Quebec Innovation Center. His research interests are in functional genomics with a special emphasis on applications of next-generation sequencing technologies.

16 MARCH 2011 | **CONCURRENT EXPERT SESSION: COMPUTATIONAL ANALYSIS OF GENOMIC INFORMATION**

L69

Niranjan Nagarajan

Senior Research Scientist, Computational & Mathematical Biology
Genome Institute of Singapore, Singapore

RECONSTRUCTING PERSONAL AND DISEASE GENOMES

Recent technological advances are rapidly bringing us close to a future where medical treatments can be informed by an individual's unique genetic makeup. In this session, I will present an overview of existing and emerging technologies that are making this possible. I will also outline the computational challenges and the tools currently available for analyzing this information and reconstructing personal and disease genomes, focusing in particular on cancer genomics.

Advances in sequencing technology have changed the landscape of research in Computationally Biology providing researchers with a flood of information about biological sequences. Our research focuses on statistical and algorithmic approaches to make sense of this data and provide biological insights. Some of the areas that we work on include: (1) Genome Assembly - Our ability to study various genomes is dependent on computational tools to reconstruct genomes from noisy experimental data. In recent years, new sequencing technologies have presented both a challenge and an opportunity for the design of new assembly tools and strategies. In our group we look at both de novo and comparative approaches for using sequencing and mapping information to reconstruct various Microbial and Eukaryotic genomes; (2) Pan-genomics - Analyzing and cataloguing genomic differences between individuals of a species (or strains of a microbial species or genus) is critical for understanding the genomic basis for various phenotypes. These differences can be subtle and can sometimes be in unexpected places (repeat elements, intronic regions etc.) and in our work we develop statistical approaches to identify such differences with high confidence; (3) Metagenomics is a new area of study geared towards understanding of microbial communities and their impact on diverse environments - from the human body to entire marine ecosystems. Our work is geared towards the design of novel tools to aid in the analysis of metagenomic datasets (both marker sequences as well as whole genome shotgun sequences).

16 MARCH 2011 | **CONCURRENT EXPERT SESSION: COMPUTATIONAL ANALYSIS OF GENOMIC INFORMATION**

L70

Pauline C Ng

Group Leader, Computational & Mathematical Biology
Genome Institute of Singapore, Singapore

CHARACTERISING INDIVIDUAL GENOMES

Humans differ from each other by ~0.1% at the DNA level. Once these genetic variants have been identified by whole genome or exome sequencing, the challenge is to characterize these variants. In this session, I describe resources and methods to identify functionally relevant variants. I will demonstrate how bioinformatic tools can reveal phenotypic traits of an individual, thus paving the way to personalized medicine.

The major research focus of my group is understanding the relationship between genotype and phenotype. This includes research in personalized medicine, understanding disease mutations, and working with next-generation sequencing technologies and protein sequence. Personalized Genomics: I have analyzed the personal genome of Craig Venter in great detail. I have shown that genome sequencing can help improve individual drug prescriptions by studying Dr. Craig Venter‘s and Dr. Jim Watson‘s genomes. I have also recommended guidelines to direct-to-consumer genetic companies such as 23andMe and Navigenics for improving disease risk predictions. Understanding Disease Mutations: A large proportion of Mendelian disease can be attributed to mutations in coding genes. I created the SIFT algorithm to predict the effect an amino acid substitution has on protein function. The SIFT algorithm is often applied to nonsynonymous variants. Technology: As a Senior Bioinformaticist at Illumina, I designed the content for the microarrays used in genome-wide association studies. Later, I assessed next-generation sequencing technologies to observe what can be expected of the new technologies.

16 MARCH 2011 | **CONCURRENT EXPERT SESSION: COMPUTATIONAL ANALYSIS OF GENOMIC INFORMATION**

L71

Anthony J Brookes

Chair, Bioinformatics and Genomics
Department of Genetics
University of Leicester, UK

TOWARDS 'IDEAL HEALTHCARE': OPTIMISED AND PERSONALISED FUTURE MEDICINE

This talk will argue that the needs of future healthcare can be met in full, and at an affordable cost, only by launching a radical new scientific and technological project that tackles the Information & Communication Technology (ICT) challenges surrounding the knowledge that underpins decisions about personal, patient and community health. Despite excellent progress in disease research, very little of the resulting mass of new knowledge gets through to the patient or their doctor in a convenience and useable format. There are three key reasons for this: 1) Doctors and patients have a limited understanding of modern genetics and other bioscience sub-disciplines. 2) Information produced by research is large in scale, complex in nature, and made up of a poorly resolved mix of true and false positive and negative findings, making it unsuitable for direct clinical deployment. 3) Key clinically useful information is difficult or impossible to locate, since much of it is never reported in structured electronic format, and the portion that is reported is dispersed across multiple data silos often with complex and burdensome data access mechanisms. Bridging this major _ICT gap‘ will require a large-scale and globally orchestrated new discipline to be launched - which we propose to call 'I-Health Informatics'. This should aim to intelligently locate, distil, and repurpose all the key biomedical knowledge, framed in the specific context of a 'health avatar' for each patient, and then place this at the fingertips of doctors, the public, and many other stakeholders, in a real-time and multi-lingual format and mode that they can use it. The system should be 'self-optimizing, to continually generate new and better evidence based upon the outcomes of 'natural experiments' of life/medicine.

Professor Brookes is an internationally recognized leader in genomics and bioinformatics, having made significant contributions to method development, disease and population genetics, DNA variation analysis, and database systems for organizing gene-disease information. His publications include over 140 peer-reviewed articles and reviews, and he has filed 6 patent applications on cloning, genotyping, and DNA analysis. Professor Brookes began his research career in the UK by achieving a first class degree in Medicine and Medical Biochemistry at the University of Manchester, followed by a molecular genetics PhD at the Imperial Cancer Research Fund and the University of London. He then established a research group in the MRC Human Genetics Unit in Edinburgh, where his team was involved in identifying the Presenilin-1 gene that causes Alzheimers Disease. Subsequently, he moved to Sweden, first to Uppsala University where he received Docenture in Genetics, and then to the Karolinska Institute where he was awarded both Docenture and a Professorship in Genome Research. Professor Brookes now holds a Chair in Bioinformatics and Genomics at the University of Leicester in the UK. There, he runs active method development and bioinformatics research groups, and he is Director of the institute's 'NUCLEUS' Genomics Services Core. He coordinates the European FP7-GEN2PHEN informatics project, and runs the 'GWAS Central' (HGVbaseG2P) genetic association database. He is Editor & Chair of Publications Committee for the HUGO Journal, and a member of both the Public Population Project in Genomics (P3G) and the Open Researcher & Contributor ID (ORCID) Technical Working Group. Additionally, he is a Co-Founder and Board Member of the Human Genome Variation Society, and works as communicating Editor for Human Mutation. Other significant achievements include launching and running the international Meeting series on "Human Genome Variation & Complex Genome Analysis" and inventing the Dynamic Allele-Specific Hybridization genotyping technology.

16 MARCH 2011 | **CONCURRENT EXPERT SESSION: THE HUMAN VARIOME PROJECT AND THE ARAB COUNTRIES**

L72

Richard G H Cotton

Senior Principal Research Fellow
Group Leader, Genomic Disorders Research Centre, Australia

THE HUMAN VARIOME PROJECT: SUPPORTING THE SHARING OF GENETIC VARIATION DATA

Genetic diseases are a pressing global health problem that requires comprehensive access to basic clinical and genetic data to counter. The creation of regional and international databases that can be easily accessed by clinicians and diagnostic labs will greatly improve our ability to accurately diagnose and treat patients with genetic disorders. The Human Variome Project is facilitating the creation of these repositories through its *Human Variome Project Country Node* program: automated or semi-automated systems designed to collect every mutation reported by a diagnostic laboratory, clinic or research laboratory in a country and store these within a national repository. HVP Country Nodes have been established in six countries including Kuwait and Egypt. HVP Country Nodes serve three functions: first and foremost, they allow data to be shared amongst the diagnostic labs and clinics in any one country to support genetic testing services for patients; secondly, data from the Nodes can also be shared with gene/disease-specific databases and central variation depositories (e.g. NCBI‘s dbGaP) in a manner that complies with each country‘s existing privacy legislation and ethics obligations. Finally, these repositories allow the genetic burden of disease in individual countries to be quantified, which in turn can be used to better target healthcare planning and policy development.

Richard Cotton initiated the Mutation Research Centre, now renamed the Genomic Disorders Research Centre, in January, 1996 (www.genomic.unimelb.edu.au). He has always been interested in the biochemical genetics of human disease and has recently focused on mutation. Amongst his more notable scientific achievements are the conception, planning and execution of the fundamental experiment, which proved that when two immunoglobulin producing cells were fused, the immunoglobulin of both parental cells were produced in the hybrid. This laid the experimental and theoretical foundation for the widely used monoclonal antibody technique. He also conceived the widely used tetrohydrobiopterin (BH4) load test to identify the serious variants of PKU, but BH4 is currently being trialled in heart disease. He is particularly interested in improving mutation detection technologies to make them cheaper and simpler, so that they can be more widely applied, and holds several patents in the area. A recent development has been a method to detect DNA damaging compounds. Prof Cotton has written two books entitled "Mutation Detection", initiated the journal entitled "Human Mutation", and in 1991 initiated bi-yearly international workshops on Mutation Detection and in 1998, bi-yearly HUGO Mutation Detection Courses. In 1996 he has also started a worldwide initiative (The HUGO Mutation Detection Database Initiative, recently formed into the Human Genome Variation Society (HGVS); www.hgvs.org) to capture and distribute lists of mutations. In June 2005, he was admitted as a Member of the Order of Australia for service to science through genetic research, particularly through the development of technologies to detect gene mutations that underlie birth defects or cause disease and through efforts to document findings. In June 2006, he convened a Meeting, co-sponsored by WHO, which initiated the Human Variome Project (www.humanvariomeproject.org). This project aims to collect worldwide genetic variation and its associated phenotype. He was Treasurer of the Human Genome Organisation (HUGO) and he is author of over 200 scientific papers and three patents.

16 MARCH 2011 | FEATURED TALK

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Charles Lee

Director, Molecular Genetic Research Unit
Associate Professor, Harvard Medical School
Associate Member, Broad Institute of MIT and Harvard
Clinical Cytogeneticist, Brigham and Women's Hospital, USA

CAPTURING COPY NUMBER VARIANTS (CNVS) FROM WHOLE-GENOME NEXT GENERATION DNA SEQUENCING: PERSPECTIVES FROM THE 1000 GENOMES PROJECT

Copy number variation (CNV) is abundant in humans, differing from other variation classes with respect to extent, origin, and functional impact. Despite progress in CNV characterization, the nucleotide resolution architecture of most CNVs remains unknown. We analyzed whole genome sequences of 185 individuals using complementary algorithmic approaches accompanied with extensive experimental validation. This has led to the construction of a population-scale CNV map encompassing 22,025 deletions and 6,000 additional structural variants including mobile element-based insertions and tandem duplications. The breakpoints of many CNVs (53%) were mapped to nucleotide resolution, which facilitated subsequent analyses into their origins and functional impact. This dataset should serve as a resource for future sequencing-based association studies.

Dr. Lee's research unit centers on the use of molecular cytogenetic technologies to study the structure of vertebrate genomes to understand human diseases. He received his doctoral degree from the University of Alberta (Canada) in 1996, was an NSERC research fellow at the University of Cambridge (UK) from 1996-1998, a clinical cytogenetics fellow at Harvard Medical School (USA) from 1998-2001, and then became board certified by the American Board of Medical Genetics in 2002 in Clinical Cytogenetics. Dr. Lee is currently the principal investigator on grants from the National Cancer Institute, the National Human Genome Research Institute, and the National Institute of General Medicine. He has authored / coauthored over 100 publications in top journals such as *Nature, Science, Cell, Proceedings of the National Academy of Sciences USA,* and *Nature Genetics*. He currently chairs the American Society of Human Genetics Program Committee, co-chairs the structural variation analysis group for the International 1000 Genomes Project (www.1000genomes.org), is a regular member of the Genes, Health and Development Study Section at the National Institutes of Health, and serves as an Associate Editor for the American Journal of Human Genetics. Among the fellowships / awards that he has received, he was the recipient of a Ph.D. studentship from the Alberta Heritage Foundation for Medical Research, postdoctoral fellowship awards from both the Medical Research Council of Canada and the Natural Sciences and Engineering Research Council of Canada, the Inaugural Team Award from the American Association for Cancer Research (2007), the C. Thomas Caskey Lectureship from the University of South Carolina (2008), and the George Brumley Jr Award from Duke University (2010). In 2008, at the age of 39, Dr. Lee became the youngest recipient of the Ho-Am Prize in Medicine (also referred to as the "Korean Nobel Prize") for his 2004 discovery of widespread structural genomic variation in the human genome and his seminal contributions to this new field of human genetics.

17 MARCH 2011 | **CONCURRENT SYMPOSIUM: COMPUTATIONAL BIOLOGY AND STATISTICAL GENETICS FOR THE ANALYSIS OF HUMAN DISEASE**

L74

Goncalo Abecasis

Felix Moore Collegiate Professor of Biostatistics
Center for Statistical Genetics, Department of Biostatistics, University of Michigan, USA

SEQUENCING THOUSANDS OF HUMAN GENOMES

Identifying and characterizing the genetic variants that affect human traits is one of the central objectives of human genetics. Ultimately, this aim will be achieved by examining the relationship between interesting traits and the whole genome sequences of many individuals. Whole genome re-sequencing of thousands of individuals is not yet feasible, but advances in laboratory methods (for example, to enable the genotyping of thousands of individuals at hundreds of thousands of SNP sites) and in statistical methodology (for example, to enable accurate correction for population stratification and genotype imputation) have resulted in substantial progress in our understanding of complex disease biology. Here, we discuss practical study designs for the first generation of whole genome sequencing studies. These will enable the examination of 1,000s of individuals at >15 million of polymorphic sites. These studies will be enabled by continuing advances in laboratory technology and statistical methods and should further refine our understanding of complex disease genetics. I illustrate the possibilities both with simulation and with results from ongoing studies.

Goncalo Abecasis is the Felix Moore Collegiate Professor of Biostatistics at the University of Michigan School of Public Health. He has been a faculty member at the University of Michigan since 2001. Previously, he completed a Ph.D. in Human Genetics at Nuffield Department of Clinical Medicine, under the supervision of Professors William Cookson and Lon Cardon. Gonçalo completed his initial training in Genetics at the University of Leeds (in the UK) and at McMaster University (in Canada). Dr. Abecasis' research focuses on the development of statistical tools for the identification and study of genetic variants important in human disease. Software developed by Dr. Abecasis at the University of Michigan is used in several hundred gene-mapping projects around the world. He and his group have made important contributions to our understanding of patterns of genetic variation across the genome and its relationship to a variety of traits, ranging from age-related macular degeneration, to a variety of cardiovascular risk factors, to psychiatric traits. He is currently deploying next-generation sequencing technologies to study the genomes of thousands of individuals.

17 MARCH 2011 | **CONCURRENT SYMPOSIUM: COMPUTATIONAL BIOLOGY AND STATISTICAL GENETICS FOR THE ANALYSIS OF HUMAN DISEASE**

L75

Guillaume Bourque

Assoc Professor, Department of Human Genetics, McGill University
Director of Bioinformatics, McGill University & Genome Quebec Innovation Center, Canada

THE ROLE OF GENOMIC REPEATS IN GENE REGULATION, DIVERSITY AND DISEASE

Next-generation sequencing (NGS) technologies (e.g., ChIP-Seq, RNA-Seq) are now supplanting array-based technologies because of their accuracy, comprehensiveness and cost. Notably, these technologies enable an unbiased look at the functional contributions of the genome including the contributions of repetitive regions. We will present results that demonstrate the ubiquitous role that play repeats in gene regulation. In particular, we will show that species-specific transposable elements have been an important source of new regulatory elements and have contributed more than 20% of the binding sites of OCT4 a key transcription factor in human ES cells. Although it has been recognized for some time that the gain and loss of regulatory elements is a common feature of eukaryotic genomes, these results suggests the that repeats are associated with important human-specific regulatory innovations. Characterization of these innovations will improve our interpretation and our ability to translate findings from animal models. Finally, since many repeat families are highly polymorphic even across individuals, their role in gene regulation is likely to have important implications for susceptibility to a number of diseases.

During his Ph.D., Guillaume Bourque worked on genome rearrangements in evolution and cancer with Pavel Pevzner at the University of Southern California. In 2002, he moved to the University of Montreal to start postdoctoral research on gene regulatory networks with David Sankoff. In 2004, he accepted a position at the Genome Institute of Singapore, where he became Senior Group Leader and Assoc. Director of Computational & Mathematical Biology. At this Institute he helped setup and was responsible for the IT infrastructure, LIMS and analysis pipelines associated with 10 Next-Generation sequencing instruments. In 2010, he moved to McGill University as a faculty member in the Department of Human Genetics and the Director of Bioinformatics at the McGill University and Genome Quebec Innovation Center. His research interests are in functional genomics with a special emphasis on applications of next-generation sequencing technologies.

17 MARCH 2011 | **CONCURRENT SYMPOSIUM: COMPUTATIONAL BIOLOGY AND STATISTICAL GENETICS FOR THE ANALYSIS OF HUMAN DISEASE**

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Felix Li Jin

Haoqing-Fudan Professor
Vice President at Fudan University, China

[No abstract is available]

Dr. Jin received Ph.D in genetics at University of Texas Health Science Center at Houston in 1994. He is now Haoqing-Fudan Professor and Vice President at Fudan University. He is a foreign member of Max-Planck Society and a board member of Human Genome Organisation (HUGO). He serves as an Editorial Board Member in 9 academic journals. He also serves as the President of Shanghai Society of Genetics and the President of Shanghai Society of Anthropology. His research areas include medical genetics and genetic epidemiology, computational biology, human population genetics and genomics. He published 270 articles in journals including *Nature, Science, PNAS, JCI* and *JAMA*.

17 MARCH 2011 | **CONCURRENT SYMPOSIUM: COMPUTATIONAL BIOLOGY AND STATISTICAL GENETICS FOR THE ANALYSIS OF HUMAN DISEASE**

L77

Hiroaki Kitano

Director, Sony Computer Science Laboratories, Inc.
President, The Systems Biology Institute
Principal Investigator, Okinawa Institute of Science and Technology, Japan

SYSTEMS BIOLOGY AND DRUG DISCOVERY

Discovery of drugs and appropriate therapeutic interventions are complex enterprises. It is inherently complex as biological systems evolved to be complex in order to cope with broad range of perturbations and to maintain various functionalities. Multiple coordinated interventions are key for successful drugs to coming decades. The inherent difficulties lies in robustness and fragility associated with disease outbreak and progression as well as host response to therapeutic interventions. The talk addresses issues in the current drug discovery processes, and argues that more systematic approach needs to be taken with principles behind. One option is the use of multi-component multi-target drugs. However, it requires powerful computational approach to overcome its combinatorial explosion problems. It also requires principles that guide the discovery process. Experimental approach such as gTOW (genetic Tug-of-War) shall uncover various mechanistic issues that cause discrepancies between computational and experimental results. At the same time, it requires systematic and well designer engineering process to make the whole enterprise successful and economically viable. Nevertheless, lack of common platform hinders efficient development of tools that can potentially speed up drug discovery process. This talk outlines principles for systems drug discovery, addresses experimental issues, and efforts to develop unified and versatile software platform to enhance the process.

Hiroaki Kitano is a Director at Sony Computer Science Laboratories, Inc., Tokyo, a President at The Systems Biology Institute, Tokyo, and a Principal Investigator at Okinawa Institute of Science and Technology, Okinawa. He received a B.A. in physics from the International Christian University, Tokyo, and a Ph.D. in computer science from Kyoto University. Since 1988, he has been a visiting researcher at the Center for Machine Translation at Carnegie Mellon University. His research career includes a Project Director at Kitano Symbiotic Systems Project, ERATO, Japan Science and Technology Corporation followed by a Project Director at Kitano Symbiotic Systems Project, ERATO-SORST, Japan Science and Technology Agency. He is also a visiting professor of Keio University, a Manager of Division of Systems Biology, Cancer Institute, Japanese Foundation for Cancer Research, and a Founding President of The RoboCup Federation. Kitano received The Computers and Thought Award from the International Joint Conferences on Artificial Intelligence in 1993, Prix Ars Electronica 2000, Japan Design Culture Award 2001, Good Design Award 2001, and Nature‘s 2009 Japan Mid-career Award for Creative Mentoring in Science, as well as being an invited artist for Biennale di Venezia 2000 and Museum of Modern Art (MoMA) New York in 2001.

17 MARCH 2011 | **CONCURRENT SYMPOSIUM: COMPUTATIONAL BIOLOGY AND STATISTICAL GENETICS FOR THE ANALYSIS OF HUMAN DISEASE**

Oral Presentation

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Stephen Sherry

NCBI RESOURCES FOR MEDICAL GENOMICS INTEGRATE MUTATIONS, RARE VARIANTS AND COMMON POLYMORPHISMS FOR RESEARCH AND CLINICAL PRACTICE

Sherry Stephen, Maglott Donna, Phan Lon, Church Deanna, Ward Minghong, Feolo Mike, Kattman Brandi
National Center for Biotechnology Information, NLM, National Institutes of Health, 45 Center Drive, Room 4AN12A, Bethesda, USA; sherry@ncbi.nlm.nih.gov

New high-throughput sequencing and genotyping technologies are rapidly advancing our knowledge of human genetic variation. NCBI serves the worldwide scientific research community by providing comprehensive catalogs and databases of human genetic variation including common polymorphisms, rare variants and clinical mutations. Small variants resolved to the sequence level are cataloged and distributed by dbSNP while larger features are managed by dbVar. All variants are exported in a common XML markup, variation-ref, to facilitate standard use by software tools. As sequencing costs continue to decrease, direct sequencing of population cohorts and disease-affected individuals will become an increasing efficient way to screen for known and novel genetic variants. This has already started with diversity discovery projects like 1000 Genomes and The Cancer Genome Atlas releasing sets of variant calls with global allele frequency estimates falling below 1/1000 individuals, thus blurring the line between conventional common polymorphisms, lineage-specific rare variants, and the individual mutations submitted by Locus Specific Databases. The variation repositories at NCBI accept all such submissions across the full spectrum of mutational classes: simple nucleotide polymorphisms, insertion/deletions, short tandem repeats, copy number variants, and structural variants. When phenotypes can be related to specific variations, such knowledge is stored in a new NCBI resource, ClinVar. When variants are included in a genetic test, information about the availability, scientific basis, and usefulness of the genetic test will be available at the Genetic Testing Registry (GTR). Here we present an overview of our current and planned tools applicable to medical genetics and the management of clinical mutation data. The review will cover the organization of the data and relationship between relevant NCBI resources, markup conventions in NCBI database records for standard characteristics: frequency, clinical significance, validation properties, and cell-type (germline, somatic, neoplastic, etc), new techniques for retrieval and filtering clinical data, and variation detection and QC services NCBI has developed to increase the value of large scale sequencing results.

17 MARCH 2011 | **CONCURRENT SYMPOSIUM: COMPUTATIONAL BIOLOGY AND STATISTICAL GENETICS FOR THE ANALYSIS OF HUMAN DISEASE**

Oral Presentation

L79

Joseph Terwilliger

GWAS IN LARGE FAMILIES FROM INBRED POPULATIONS IS VASTLY MORE POWERFUL THAN CASE-CONTROL ANALYSIS UNDER ARBITRARY ETILOGICAL MODELS

Terwilliger Joseph[1,2,3], Hiekkalinna Tero[1]
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After spending the past decade fruitlessly chasing down the genetic variants which influence common complex diseases using large numbers of unrelated individuals, it is clear that this approach was misguided, and that whole genome sequencing is not likely to help much. In this work, we show that sampling larger families is always more powerful than singletons for detecting allelic association, even treating linkage as a nuisance parameter. We developed software, PSEUDOMARKER, for association analysis conditional on linkage in mixtures of singletons and pedigrees, to maximize the likelihood of the data over parameters describing linkage (recombination fraction) and/or association (marker allele frequencies conditional on risk alleles). We then compare the likelihood maximized over both linkage and association parameters with that maximized over linkage under the assumption of no association. This has previously been shown to lead to statistics equivalent to the haplotype relative risk when performed on triads, to the case-control test of association when performed on singletons. This test retains the appropriate type I error rates under any combination of data structures, independent of linkage, unlike the majority of existing ~~"fa~~family-based association tests", and has significantly higher power in general. To illustrate the gain in power from sampling pedigrees rather than unrelated individuals we compared four simple study designs, each with 4000 genotyped individuals: (a) cross sectional sampling (2000 cases, 2000 controls); (b) triads (1000 triads, 1000 controls); (c) affected sibpairs (800 sibpairs, 800 controls); (d) affected sib-trios (667 trios, 665 controls). For all models we considered the power was highest for sample (d), then (c), then (a), and then (b). For example, if we considered a risk locus with MAF of 0.10, disease prevalence of 0.10, and a relative risk of 4, and a critical p-value of 10-8, the power for these four study designs was (a): 0.05 (b): 0.005 (c): 0.4; (d): 0.99, and note that this test has a null hypothesis of linkage and no association, while a joint test would have much more bias towards families! This is an extreme example, but the trend is the same for all models considered. Case-control approaches were largely pushed in Western Europe, East Asia and North America over the past decade because of the relative ease of collecting large samples, in outbred heterogeneous populations with generally small family size. In the developing world, however, much larger pedigrees from smaller populations are available, and it is hoped that scientists from such countries will not be seduced by fancy technology, but will rather use their superior human resources to design better studies than are possible in the West.

L80

Moien Kanaan

Professor of Molecular Genetics
Dean of Science and Hereditary Research Lab Director
Bethlehem University, Palestine

NEXT GENERATION SEQUENCING APPROACHES TO IDENTIFY NOVEL GENES CRITICAL FOR HEARING

Shahin Hashem, Walsh Tom, Abu Rayan Amal, Nord Alex S, Lee Ming K, Avraham Karen B, King Mary-Claire, Kanaan Moien
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In studies of genetics of deafness, families with inherited hearing loss have been extremely valuable, providing paths to discovery of genes essential to mechanisms of hearing. Until now, such studies have depended on Sanger sequencing of genes in candidate genomic linkage regions. Constraints of PCR-based sequencing have largely limited gene discovery to conventional mutations in known genes in relatively small regions of linkage. The advent of next generation sequencing technology has the potential to dramatically accelerate the pace of gene discovery. We have undertaken three approaches with next generation sequencing to discover novel genes responsible for the deafness phenotype in families with dominant or recessive inherited hearing loss. (1) For families in which hearing loss maps to linkage regions of less than 3 megabases, we tile the entire genomic interval on capture arrays. DNA fragment libraries from the hearing impaired probands are hybridized to the arrays and the enriched portion of the genome is sequenced to approximate 30 fold coverage to reveal the critical allele. (2) For small nuclear families in which hearing loss maps to one or more very large linkage regions, we capture the entire coding region or _exome‘ and approximately 400 miRNAs with in-solution oligonucleotides, sequence to approximately 30 fold coverage, and evaluate all functional variants co-inherited with the phenotype. (3) In order to identify all classes of structural mutations – inversions, translocations, duplications, or deletions – in families unresolved by other methods, we construct large-insert mate-pair libraries from the proband and sequence the entire genome to high clone coverage. Point mutations and small insertions or deletions can be resolved directly. In addition, structural mutations can be resolved from discordant mate-pairs, in which orientation, strand location, or distance apart differs from expected values. The results emerging from these studies indicate that many more novel genes for hearing loss will be discovered in the near future. Supported by NIH grant R01DC005641.

Dr. Moein Kanaan is a professor of Molecular Genetics and a leading Palestinian geneticist. Over the last 18 years, Dr. Kanaan has been investigating the genetically isolated Palestinian population and its high consanguinity rate and identifying the genetic basis for human disorders; these include: hearing loss, skin abnormalities, breast cancer and congenital heart diseases. By studying large consanguineous Palestinian kindred, Dr. Kanaan‘s collaborative work has been able to profile novel and variant alleles undermining hearing loss and Epidermolysis Bullosa in the Palestinian population and just recently mapped and identified a few new hearing loss causing genes. Dr. Kanaan has been a member of the Research Task Force in Palestine. He has many publications to his credit and has participated in many international research effort and scientific networks. Dr. Kanaan is a recipient of many research and scientific awards.

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Doron Lancet

Ralph & Lois Silver Chair of Human Genomics & Head, Crown Human Genome Center
Department of Molecular Genetics
Weizmann Institute of Science, Israel

THE GENETIC AND MOLECULAR BASIS OF MENDELIAN DISEASES IN THE ISRAELI COMMUNITIES STUDIED BY NOVEL GENOMIC STRATEGIES

Novel genomic techniques like DNA next-generation sequencing and advanced genotyping arrays open new avenues in the elucidation of genetic defects causing monogenic disorders. They not only speed up disease gene identification but enable one to systematically tackle previously intractable monogenic (Mendelian) disorders. These are mainly rare disorders not amenable to classic linkage analysis e.g. due to insufficient family size. Most monogenic diseases are caused by exonic mutations or splice-site-mutations changing the amino acid sequence of the coded protein. These mutations can be identified by whole exome sequencing, rendering whole genome sequencing necessary only in special cases. Genotyping-arrays representing ~$2x10^6$ single-nucleotide-polymorphisms (SNP) allow highly accurate mapping of copy number variations (CNVs) and other genome structural variations often representing deletions readily detectable by exome sequencing. Based on these novel techniques we launched a project encompassing several medical centers to decipher the dozens of accumulated families with monogenic diseases. We currently focus mainly on neuronal disorders affecting the central nervous system, including mental retardation, microcephaly and congenital general anosmia (CGA) – an inborn complete loss of the sense of smell. These diseases are observed in various Israeli ethnic groups sometime due to high consanguineous marriages. In collaboration with the Duke Center for Human Genome Variation, we have implemented the most up-to-date sequencing and back-end analyses for sequence mapping, variation detection, and variation filtering. Based on the inheritance mode and family structure, we perform one of several modes of subgenome sequencing, including whole exome sequencing, chromosome X super-exome sequencing (including larger intronic territories and promoter regions), complete gene sequencing of linkage interval content, or system biology based gene groups. In preliminary results we have indicated the validity of our approach, identifying by whole exome sequencing the causative variation in at least one of the first group of 5 diseases studied. We aim at generating novel scientific insights related to the underlying biology of intellectual impairment disorders, as well as much better capacity to cope with genetic testing challenges.

Doron Lancet is Professor at the dept. of Molecular Genetics, and heads the Crown Genome Center at the Weizmann Institute of Science. Previously he headed there the Dept. of Biological Chemistry. He pioneered genome research and infrastructure development, and initiated bioinformatics and Systems Biology efforts at Weizmann and in Israel. A major focus of his research is olfaction, having made some of the first discoveries regarding the molecular pathways of smell reception. He currently studies the genomics, evolution and population genetics of human olfactory receptor genes, focusing on loss of function variations that shape sensory genetic individuality. In addition, as part of the Genome Center‘s research, he studies human disease, collaborativly discovering genes for both monogenic and polygenic disorders, with considerable focus on special Mid-Eastern populations. Presently he is active in implementing 2nd and 3rd generation genome-wide DNA sequencing in the discovery of pathological genetic variations, transcriptomics and pharmacogenetics. In the realm of bioinformatics he developed GeneCards, a world-wide used human gene web compendium, automatically mined from 80 web resources. Lancet is member of the European Molecular Biology Organization (EMBO) and a HUGO council member. He wrote a science column in Israel‘s major daily Haaretz, and continuously delivers public lectures on the impact of genomics. He was awarded the Hestrin Prize (Israel, 1986), the Takasago Prize (USA, 1986), the Wright Award in olfaction (USA, 1998) and the Landau prize in Human genetics (Israel, 2008).

L82

Faycal Hentati

Professor of Neurology
Head of Department of Neurology
Institut National de Neurologie, Tunisia

PHENOTYPIC AND GENETIC ASPECTS OF PARKINSON DISEASE IN TUNISIA

Parkinson‘s disease (PD) is a common neurodegenerative syndrome with age-related prevalence. Generally PD is considered a sporadic illness but ~14% (range 10-30%) of patients have one or more 1st degree relatives with parkinsonism. Recent studies have implicated at least 13 PARK loci in disease pathogenesis. In recent years, several monogenetic causes of parkinsonism have been identified including dominant mutations in alpha-synuclein (SNCA) and leucine-rich repeat kinase 2 (LRRK2; Lrrk2), and recessive mutations in parkin (PRKN), Pten-induced kinase 1 (PINK1), DJ-1 (DJ-1) and ATP13A2. We performed prospective clinical, epidemiological and genetic study of Parkinsonism in Tunisia. This study concerned in total, 1212 structured interviews, clinical examination and blood samples were carried out including 240 patients with idiopathic PD, 91 probands with familial parkinsonism (defined as having one or more affected individuals with 1-3º of blood relationship) and 368 control subjects. Of the 91 probands, 63 kindreds, each containing 2 or more affected individuals, were successfully recruited to include a total of 210 affected and 245 unaffected family members. The 63 kindreds were subsequently genotyped by with 1100 microsatellite markers for linkage analysis. In familial cases Lrrk2 G2019S mutation was found as the cause of parkinsonism in 34/80 (42%) kindreds including 21homozygous patients. In addition this mutation was found the cause of parkinsonism in 30% of l patients without known familial history. There were no significant differences in various clinical parameters between LRRK2 and idiopathic PD, although LRRK2 patients seemed to develop less dementia and more motor dyskenesia. The clinical phenotypes in homozygous and heterozygous Lrrk2 G2019S carriers were comparable. Disease penetrance in Lrrk2 G2019S carriers ranges from ~20% in those younger than 50 years to greater than 80% at 80 years. PRKN mutations were rare, but homozygous inheritance of PINK1 mutations was found responsible of PD in d 14% of kindreds with familial parkinsonism. Homozygous and compound heterozygous mutations in PRKN and PINK1 are most frequently observed in early-onset Parkinsonism in Asians and Caucasians 58. The most apparent difference between LLRK2 and was the younger age at onset in PINK1 homozygous individuals, with an akinetic-rigid presentation without evidence of subsequent cognitive decline or dementia. Parkinson disease displays a high frequency of genetic forms in Tunisia with in particular a large predominance of Lrrk2 G2019S mutation .This gives an opportunity for a detailed phenotypic analysis and gene penetrance study. Comparative genetic studies in the other African countries may help the understanding of the causes of this particular distribution of Parkinsonism in Tunisia.

Professor Fayçal Hentati has directed the Department of Neurology and the Neurobiology laboratory at the National Institute of Neurology (INN) in Tunis (Tunisia) since 1995. He is also the past president of the Medical Council of this Institute. He has been a Professor of Neurology at the faculty of medicine of Tunis since 1990. His training was spent within the Faculty of Medicine of Tunis (Tunisia), Bicetre and Salpétrière hospitals in Paris (France), and Mass General Hospital in Boston (USA). With his group he has been involved in the study of prevalent hereditary neurological diseases in Tunisia for more than 25 years, and has contributed to the description of new genetic entities such as juvenile ALS, ataxia with vitamin E deficiency and limb girdle muscular dystrophy 2I. His research has lead to gene identification of numerous hereditary diseases frequent or specifically encountered in Tunisia (LGMD2C, ALSIN, CMT4A). Various national and international agencies such as American Muscular Dystrophy Association (MDA), Association Française contre les Myopathies (AFM), and the European commission have funded this research. Professor Fayçal Hentati has authored more than 130 scientific publications and is a member of the Editorial board of several scientific journals. He is president of the Tunisian Association of Neurosciences and member numerous scientific associations. He is a TWAS fellow since 2000 and obtained the first Biotechnology Presidential prize (Tunisia) in 2002, the ―Gaetano Conte" prize ―(Italy) in 2001, and is nominated ―Chevalier of the Order of National Merit of Tunisia in Education and Sciences” since 1998.

17 MARCH 2011 | CONCURRENT SYMPOSIUM: GENETICS OF DEAFNESS & NEUROLOGIC DISORDERS

Oral Presentation

L83

Nadezhda Maksimova

NEUROBLASTOMA AMPLIFIED SEQUENCE GENE IS ASSOCIATED WITH A NOVEL SHORT STATURE SYNDROME CHARACTERISED BY OPTIC NERVE ATROPHY AND PELGEREHUET ANOMALY

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Hereditary short stature syndromes are clinically and genetically heterogeneous disorders and the cause have not been fully identified. Yakuts are a population isolated in Asia; they live in the far east of the Russian Federation and have a high prevalence of hereditary short stature syndrome including 3-M syndrome. A novel short stature syndrome in Yakuts is reported here, which is characterized by autosomal recessive inheritance, severe postnatal growth retardation, facial dysmorphism with senile face, small hands and feet, normal intelligence, Pelger-Huet anomaly of leucocytes, and optic atrophy with loss of visual acuity and color vision. This new syndrome is designated as short stature with optic atrophy and Pelger- Huet anomaly (SOPH) syndrome. Our aims were to identify a causative gene for SOPH syndrome. Genome-wide homozygosity mapping was conducted in 33 patients in 30 families. The disease locus was mapped to the 1.1 Mb region on chromosome 2p24.3, including the neuroblastoma amplified sequence (NBAS) gene. Subsequently, 33 of 34 patients were identified with SOPH syndrome and had a 5741G/A nucleotide substitution (resulting in the amino acid substitution R1914H) in the NBAS gene in the homozygous state. None of the 203 normal Yakuts individuals had this substitution in the homozygous state. Immunohistochemical analysis revealed that the NBAS protein is well expressed in retinal ganglion cells, epidermal skin cells, and leukocyte cytoplasm in controls as well as a patient with SOPH syndrome. These findings suggest that function of NBAS may associate with the pathogenesis of short stature syndrome as well as optic atrophy and Pelger-Huet anomaly.

Oral Presentation

L84

Fowzan Alkuraya

IN SEARCH OF OLIGOGENICITY IN BARDET-BIEDL SYNDROME

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Bardet-Biedl syndrome (BBS) is a model disease for ciliopathy in humans. The remarkable genetic heterogeneity that characterizes this disease is consistent with accumulating data on the interaction between the proteins encoded by the 14 BBS genes identified to date. Previous reports suggested that such interaction may also extend to instances of oligogenic inheritance that defies the long held view of BBS as an autosomal recessive disease. We have previously demonstrated the power of autozygosity mapping in identifying disease genes in genetically heterogeneous conditions. Consistent with that notion, autozygosity mapping was an efficient way to identify the underlying mutation in every one of the 29 families, most of which are multiplex, that were enrolled in this study except for the one non-consanguineous family in which a compound heterozygote mutation was identified. However, because our goal in this study was to investigate the magnitude of oligogenic inheritance in BBS, we conducted a comprehensive analysis of all known 14 BBS genes as well as the MGC1203 modifier gene in all affected and unaffected siblings in these families. With close to 30,000 PCR amplicons sequenced and analyzed in the largest study to take this approach thus far, two in trans mutations in a BBS gene were identified in each of the study families for a total of 20 mutations, all but one are novel. In no instance did we observe two mutations in unaffected members of a given family or observe the presence of a third allele that convincingly acted as a modifier of penetrance or even expressivity. Failure to identify two in trans mutations in any of BBS genes in any of the unaffected siblings is highly significant in view of the large size of the families in the study. In addition to presenting a comprehensive genotype/phenotype overview of a large set of BBS mutations, including the occurrence of nonsyndromic retinitis pigmentosa in a family with a novel BBS9 mutation, our study strongly argues against the oligogenic model of BBS in the overwhelming majority of cases.

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Oral Presentation

L85

Lin He

UNDERSTANDING SCHIZOPHRENIA BY GWAS AND NEXT GENERATION SEQUENCING

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Schizophrenia has caused severe problems for Chinese society with such a big population. To study the etiology of schizophrenia that has interested to us for years, we tried a systematical study of its susceptibility genes by genome wide association study (GWAS) and next generation sequencing (NGS). In this work, we recruited a large number of non-family based schizophrenia samples of the Chinese Han population living in different regions and carried out a series of genome-wide studies including SNP and CNV-based GWAS and epigenomics and miRNA-based NGS to dissect genetic risk factors for schizophrenia. In my presentation, I will show more recent advances about hotspots, which are thought to be susceptible to schizophrenia through these approaches. Interestingly, in the follow-up study of ―Rates of adult schizophrenia following prenatal exposure to the Chinese famine of 1959-1961 (JAMA, 2005)", we found that different degrees of methylations appear on between genes determining neural pathways in cases and controls, which may reflect the dating venue for ―dialog" or ―communication" of interaction between metal disorders and environment.

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Oral Presentation

L86

Osama Alsmadi

FAMILIAL DISORDERS IN MIDDLE EASTERN FAMILIES: FINDING THE CAUSING GENES IS JUST THE BEGINNING OF THE END

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We identified a novel homozygous missense mutation (c.196G-T) in the fibroblast growth factor 3 (FGF3) in 21 affected individuals from a large extended consanguineous Saudi family. Affected members were characterized by autosomal recessive syndromic congenital sensorineural deafness, microtia and microdontia. All affected family members descend from one common ancestor. This discovery comes back-to-back to another report on FGF3 involvement in syndromic deafness, and independently confirms the gene‘s positive role in the inner ear development in humans. The c.196G-T mutation results in substitution of glycine by cysteine at amino acid 66 (p.G66C). This residue is conserved in several species and across 18 FGF family members. Conserved glycine/proline residues are central to the ~~b~~-trefoil fold” characteristic of the secondary structure of FGF family proteins and substitution of these residues is likely to disrupt structure and consequently function. This report further document the higher risk of rare Mendelian disorders in the consanguineous families as typically practiced in the Middle Eastern societies. The methodologies and biological implications will be discussed.

L87

Lihadh Al-Gazali

Professor in Clinical Genetics, Department of Pediatrics,
Faculty of Medicine and Health Sciences, UAE University, United Arab Emirates

MOLECULAR CHARACTERIZATION OF BIRTH DEFECTS: UNITED ARAB EMIRATES EXPERIENCE

The United Arab Emirates local inhabitants are tribal in nature with diverse ancestries including Arabs from the south and north of the Arabian Peninsula, Persia, Baluchistan and East Africa. However, about 80% of the current 5 million inhabitants are expatriates from the Asian subcontinent and from Arab and Middle Eastern and European countries. Despite this admixture of populations, intermarriages between these groups are still rare with consanguineous marriages within the UAE local and other Arab and Muslim populations are still the norm leading to the formation of population isolates and indeed the appearance of rare genetic disorders. According to the UAE Ministry of Health Statistics, genetic disorders are the fourth cause of the death in the UAE. In addition, the UAE is currently ranked 6th out of 193 countries in terms of prevalence of birth defects, mainly due to genetic causes. The epidemiology of these birth defects is especially complicated due to the fact that many families and tribal groups have descended from a limited number of main ancestors and the disease genes reflect the sample carried by the founding members. Therefore, while some birth defects are common throughout the population, others are confined to specific villages, families and tribal groups leading to unusual genetic burden on these communities. In addition, there are many birth defects which are unique to this population. Over the last 20 years we have been involved in research into the elucidation of the underlying molecular defects of these conditions. Here we present our experience in identifying the molecular basis of birth defects prevalent in this population.

Dr. Al-Gazali is professor of Clinical Genetics and Pediatrics at the UAE University, Faculty of Medicine and Health Sciences. She obtained her MBCHB from Baghdad University and was trained in Pediatrics and then Genetics in UK (Edinburgh and Leeds). Prof. Al-Gazali is a Fellow of the Royal College of Physician and the Royal College of Paediatrics and Child Health, UK. She is member of several international organizations. Prof. Al-Gazali also made an important contribution in the area of Clinical Genetics, providing a significant amount of information regarding genetic disorders specific to the UAE and the Arab world in general. She has provided important data on the clinical phenotypes and natural history of many genetic syndromes. Her expertise in Clinical Dysmorphology has been widely recognized by the international community. Al-Gazali was profiled in the Lancet in March 2006 for her contribution to Clinical Genetics and research in the Middle East. She is the winner of Women in Science UNISCO-L'OREAL Award for Africa and Arab States for 2008. Prof. Al-Gazali has published more than 140 papers.

L88

Andre Megarbane

Professor, Unit of Medical Genetics, Laboratory of Molecular Biology and Cytogenetics, Faculty of Medicine, University Saint-Joseph, Lebanon

LINKAGE ANALYSIS AND CLONING OF THE GENE RESPONSIBLE OF THE LEUKODYSTROPHY AND OLIGODONTIA SYNDROME

Dentoleukoencephalopathies with autosomal recessive inheritance are very rare. Recently, a large inbred Syrian pedigree was reported with oligodontia in association with a degenerative neurologic condition characterized by progressive ataxia and pyramidal syndrome and abnormalities in the white matter and cortical atrophy. A genome-wide linkage analysis, using the 260k SNPs Affymetrix array was then undertaken and a maximum multipoint lod scores of 5.66 (NPL score = 7.65) was detected on chromosome 10q22 region. This genomic interval contains 95 known genes including the Prosaposin gene (*PSAP)* responsible for metachromatic leukodystrophy, which was excluded. Seventeen additional candidate genes were tested and excluded. Recently, sequencing of a gene allowed the identification of the causative gene in this rare disease, thereby improving the understanding of the physiopathology of this disease. Ten other families collected worldwide were analyzed as well. Mutations were found in 6 of them. We will discuss the results of this study.

He is professor of medical genetics and head of the Medical Genetic Unit, St Joseph University, Lebanon. Dr. Megarbane is author and co-author of more than 200 publications. He is member of the Lebanese National Bioethics Committee, member of the French Society of Genetics and Genetic Counseling, the American Society of Human Genetics, and the European Society of Human Genetics. Dr. Megarbane is member of the editorial board of the European Journal of Medical Genetics and member of the Rammal Rammal Prize Committee. He is recipient of four scientific awards, namely: Abdel Hamid Shuman Award; Rammal Rammal Medal, Mohammad El-Fasi Young Researcher, and Makhzoumi Association Award. Dr. Megarbane has an active research with interest in the domains of mental retardations, dysmorphology, osseous malformations, and others.

L89

Nasir Al-Allawi

Professor of Hematology
Head of Pathology and Hematology/Oncology
Faculty of Medicine, University of Dohuk, Iraq

MOLECULAR CHARACTERIZATION OF INHERITED HEMATOLOGICAL DISORDERS IN IRAQIS: TRYING TO BRIDGE THE GAP

Despite the fact that several inherited hematological disorders are known to be prevalent in Iraq, little was known about their molecular basis until quite recently. My presentation is to review the efforts of our research group over the past few years to pursue this endeavor. Prevalence of β thalassemia varies between 3.7-4.6% among Iraqis. Molecular characterization revealed heterogeneity in the distribution of β thalassemia mutations, even within the same ethnic group. However, IVS-II-1 (G>A) was the most frequent mutation among Kurds, while IVS-I-110 (G>A) was the commonest among Arabs in Northern Iraq. Alpha thalassemia on the other hand, varied in frequency 1-20% in different parts of the country. Studies from Northern Iraq revealed that the most common genotype was ($-\alpha^{3.7}/\alpha\alpha$), followed by the ($-\!\!-^{MED}/\alpha\alpha$). Sickle cell carrier state varied in frequency from 0-6.5%. Haplotype analysis in Northern Iraq revealed that it is associated with the Benin Haplotype in around three quarters of cases. G6PD deficiency has been reported in 6-15.3% of Iraqi males. The Mediterranean and Chatham deficient variants constituted the bulk of the deficient variants both in Arabs and Kurds. Thrombophilic mutations were also investigated. Factor V leiden (G1691A), Prothrombin mutation (G20210A) and homozygosity to MTHFR (C677T) were found in 1-3%, 3% and 8% of healthy individuals respectively. Some of the clinical associations of these mutations were also studied. The presentation will also include an overview of recently introduced regional hemoglobinopathies prevention program of in Northern Iraq, which included premarital screening of 115,188 individuals over more than 3 years.

Dr. Al-Allawi is a Professor of Hematology and the Head of Departments of Pathology and Hematology/Oncology at the faculty of Medicine, University of Dohuk, Iraq. He is also in charge of medical molecular research at the scientific research center of the latter University. Dr. Al-Allawi obtained his MBChB from the University of Baghdad-Iraq in 1980, thereafter his MSc and PhD degrees in Hematology at the Universities of Baghdad and Manchester-United Kingdom. Dr. Al-Allawi trained and practiced at the Manchester Royal Infirmary-UK, Medical City teaching Hospital in Baghdad and finally at Azadi Teaching Hospital in Dohuk-Iraq. His special interest is inherited hematological disorders for which he established a research group which tackled the task of molecular characterization of these disorders in Iraqis. He has authored or co-authored around 40 papers in International and Arab medical journals. He initiated in 2006 a regional Hemoglobinopathy preventive program in northern Iraq (the first in his country), which he is currently supervising.

L90

Bassam R Ali

Associate Professor, Molecular and GeneticMedicine
Leader, Genetics and Development Research Priority Group
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ER-ASSOCIATED PROTEIN DEGRADATION (ERAD) IS A COMMON CELLULAR MECHANISM FOR MANY GENETIC DISORDERS

More than a third of all cellular proteins are targeted to the endoplasmic reticulum (ER) as a first step in their trafficking routes along the secretory pathway to their final cellular destinations. The processes of protein folding, assembly into multi-subunit complexes and export out of the ER are subjected to a stringent quality control system to ensure that only properly folded and assembled proteins exit the ER. Malfolded proteins and unassembled subunits of protein complexes are rejected by this ER quality control system and re-translocated to the cytosol for degradation by the ubiquitin/proteasome. This process has been named ERAD (ER-Associated protein Degradation) and has been implicated in the cellular mechanisms of at least 50 human monogenic diseases including cystic fibrosis. Due to the high stringency of ERAD and the large number of cellular proteins that has to pass through the secretory pathway (~8,000), we reasoned that ERAD should be implicated in the mechanisms of many more human monogenic conditions. We therefore, utilized bioinformatics and data mining approaches and found that at least 45% of all known human disease genes have an ER-targeting signal and consequently we identified many ERAD disease candidates. We validated our predictive approach experimentally by establishing that ERAD is indeed responsible for most of the loss-of-function missense mutations in the genes involved in a number of the identified ERAD disease candidates including Robinow syndrome, Acromesomelic Dysplasia type Maroteaux,Spondylo-Meta-Epiphyseal Dysplasia Short Limb-Hand Type (SMED-SL) and some forms of Hereditary Hemorrhagic Telangiectasia.

Dr. Bassam Ali is an associate professor in Molecular and GeneticMedicine and the leader of the Genetics and Development Research Priority Group at the Faculty of Medicine and Health Sciences, UAE University. Dr. Ali obtained his BSc and MSc degrees from Yarmouk University in Jordan and PhD degree in biochemistry from the University of Cambridge where he was the recipient of Said Foundation scholarship. Subsequently, Dr. Ali worked as at Imperial College London and University College London before joining the UAE University in August 2006. His current research interests are: (1) Elucidation of the cellular and molecular mechanisms underlying human genetic diseases (2) The identification of disease genes responsible for rare recessive disorders in Arab populations and (3) The regulation of cellular trafficking in eukaryotic cells. Dr. Ali published over 40 articles in international refereed journals and he is on the editorial board of the Journal of Medical Sciences. Dr. Ali is a fellow of the Higher Education Academy and a member of several societies including the American Society for Cell Biology and the European Society for Human Genetics.

17 MARCH 2011 | CONCURRENT SYMPOSIUM: ADVANCES IN GENETICS OF HERITABLE DISORDERS

Oral Presentation

L91

Anna Rajab

UNDERSTANDING GENETICS OF CONGENITAL GENERALISED LIPODYSTROPHY IN THE SULTANATE OF OMAN

Rajab Anna[1], Straub Volker[2], Schuelke Markus[3], McCann Liza[4], Seelow Dominik[2], Varon Raymonda[5], Barresi Rita[2], Bachman Sebastian[5], Spuler Simone
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In 25 Omani patients with Congenital Generalized Lipodystrophy generalized absence of adipose tissue was common to all patients. However they do not appear to comprise an entirely homogenous entity. Phenotypic association was noted between the presence of acanthosis nigricans, early onset of metabolic disturbance and severity of phenotype. Children with acanthosis had more prominent delay in development, acromegaloid features, and developed of insulin resistance and hyperlipidemia in early childhood. A search for homozgosity is being carried out. Only four children have found to be homozygous for CGL1, CGL2 and CGL3 loci of 9q34, 11Q13 and 7Q31.1. None of the patients were homozygous for 1q21 involved in partial lipodystrophy (FPLD2). Seventeen affected children neither had acanthosis nor early insulin resistance or markedly delayed development. They have striking abnormalities in both skeletal and non-skeletal muscle with myopathy, muscle rippling and sudden death. Their features included prominence of skeletal muscles, reduced exercise tolerance, venomegaly, infantile hypertrophic pyloric stenosis, disturbance of cardiac rhythm (long-QT syndrome, bradycardia, supraventricular and ventricular tachycardias), cardiomyopathy and impaired bone formation. Homozygosity mapping located the gene within 2 Mbp on chromosome 17 (CGL4). Prioritization of 74 candidate genes with GeneDistiller for high expression in muscle and adipocytes suggested PTRF-CAVIN (Polymerase I and transcript release factor/Cavin) as the most probable candidate leading to the detection of homozygous mutations (c.160delG, c.362dupT). PTRF-CAVIN is essential for caveola biogenesis. Caveola are cholesterol-rich plasmalemmal vesicles are involved in signal-transduction and vesicular trafficking and reside primarily on adipocytes, myocytes and osteoblasts. Functional studies showed absence of PTRF-CAVIN did not influence abundance of its binding partner caveolin-1 and caveolin-3. In our patient's fibroblasts, caveolin-1 failed to localize toward the cell surface and electron microscopy revealed reduction of caveola to less than 3%. The loss of caveola was confirmed by Atomic Force Microscopy (AFM) in combination with fluorescent imaging. PTRFCAVIN deficiency thus presents the phenotypic spectrum caused by a quintessential lack of functional caveola in CGL4 patients. Transfection of full-length PTRF-CAVIN reestablished the presence of caveola which opens prospects for future new therapies in lipodystrophy patients.

Oral Presentation

L92

Khalid Fakhro

RARE COPY NUMBER VARIANTS IN PATIENTS WITH CONGENITAL HEART DISEASE IDENTIFY NOVEL GENES IN VERTEBRATE LEFT-RIGHT PATTERNING

Fakhro Khalid, Choi Murim, Khokha Mustafa, Brueckner Martina, Lifton Richard
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Congenital Heart Disease (CHD) is the most common birth defect, affecting nearly 1% of live births. The high incidence despite a significant reduction in reproductive fitness suggests that some CHD may be caused by dominant de novo mutations, complicating gene discovery by traditional mapping. Further, despite the recognized strong association of CHD with large chromosomal abnormalities, very little is known about which specific dosage-sensitive genes within affected loci are causative. We genotyped 285 patients with Heterotaxy (Htx) - a severe CHD associated with abnormalities in left-right (LR) body patterning - and 991 controls, and detected a 2-fold excess of subjects with novel genic copy number variants (CNVs) in the Htx cohort (14.7% vs 7.4%, p = 1x10-4). Eight of 49 novel CNVs were large chromosomal abnormalities, a four-fold enrichment over the rate observed in controls. Two of these are overlapping deletions in 8p, and encompass a known CHD gene, GATA4, that has not previously been implicated in Htx. The remaining 41 CNVs were smaller events, affecting a total of 68 genes. One of these genes, TGFBR2, was altered twice, once by deletion and once by duplication. While this gene is known to be involved in vasculogenesis and in structural CHD associated with Loeys-Dietz syndrome, it has not been previously implicated in Htx. In the absence of other large cohorts to screen for recurrent mutations, we used Xenopus tropicalis to attempt to implicate specific genes in these novel CNVs in Htx. We found unequivocal orthologs for 22 of 68 genes, and identified by whole-mount in situ hybridization 7 genes with expression in the ciliated LR organizer (gastrocoel roof plate, GRP), a 7-fold enrichment compared with 845 previously studied genes (p < 10-6). Morpholino knockdown of Htx candidates in Xenopus embryos showed striking disruption of heart and gut looping and of expression of the molecular LR marker pitx2 for 5 of these genes (GALNT11, NEK2, NUP188, ROCK2 and TGFBR2), none previously implicated in Htx. We also show that these effects are specific by MO knockdown of 13 other genes from other Htx and control rare genic CNVs, none of which produced a strong effect on LR patterning (p=0.001). Our results identify new genes in CHD and highlight the utility of emerging model organisms in rapidly validating a subset of disease loci suggested by genomic studies.

L93

Mostafa Ronaghi

Senior Vice President & Chief Technology Officer
Illumina, Inc., USA

CURRENT AND FUTURE OUTLOOK OF GENOMIC TECHNOLOGIES

Recent advancements in genomic technologies are changing the scientific horizon, dramatically accelerating biomedical research. For wide implementation of these technologies, their accuracy, throughput, cost, and workflow need to be addressed. In the past seven years, the cost of full human genome sequencing has been reduced by 4-5 orders of magnitude, and reduction will continue by another 10-fold in the next few years. At that cost level, major biomarker discoveries will fuel adoption of the latest genomic technologies for medicine, agriculture, consumer products, and forensics. In this talk, we will discuss Illumina's efforts and provide our perspectives on the future of genomics.

Mostafa Ronaghi, Ph.D., joined Illumina in August 2008 and is responsible for leading internal research programs and evaluating new technologies for the Company. Mostafa is an experienced entrepreneur and was involved in the start-up of four life sciences companies. In 2007, Mostafa co-founded Avantome, a privately-held sequencing company. Before this, he co-founded NextBio, a search engine for life science data. In 2001, Mostafa co-founded ParAllele Bioscience, which was eventually acquired by Affymetrix, Inc., and was involved in the development and commercialization of highly multiplexed technology for genetic testing. In 1997, he co-founded Pyrosequencing AB, which was renamed to Biotage in 2003, and led the company to a successful initial public offering in June 2000 on the Stockholm Stock Exchange. Mostafa was a principal investigator at Stanford University from 2002–2008 and focused on the development of novel tools for molecular diagnostic applications. He serves on the board of directors of Microchip Biotechnologies, NextBio, and Aurora Biofuels. Mostafa earned his Ph.D. from the Royal Institute of Technology in Sweden. Mostafa holds more than 20 pending and issued patents and has written more than 50 peer-reviewed publications in journals and books.

L94

Han Cao

Founder and Chief Scientific Officer
BioNanomatrix, Inc, USA

RAPID LONG RANGE GENOMIC ANALYSIS AT SINGLE MOLECULE LEVEL USING DISPOSABLE NANOCHANNEL ARRAYS

BioNanomatrix, Inc has developed the world‘s first commercial system (nanoAnalyzer® 1000) for high throughput dynamic single molecule level analysis using a high density nanochannel array platform. The core technology consists of a nanofluidic chip with thousands of massively parallel channels of less than 100 nm fabricated on the surface of a silicon chip. Long genomic DNA molecules of 100‘s kbs to multi-megabases can be linearly streamed continuously into these long channels and analyzed individually in a massive parallel fashion. Fluorescently labeled molecular length, sequence and chemical moiety-specific signature at genomic and epigenomic level could be imaged and correlated to a series of quantitative linear patterns at high resolution in standardized format using BioNanomatrix‘s nanoStudio™ and nanoMap™ software suite. This automated, high-resolution, multi-color imaging platform enables a wide range of applications, including direct single molecule level sample quality control, direct DNA damage and chemical modification assessment, accurate genome finishing and assembly, and DNA structural variation analysis associated with diseases, such as cancer. The unprecedented dynamic access to long genomic segments provided by nanoAnalyzer® 1000 system for linearizing and imaging intact native DNA in solution, with the planned affordability, speed and simplicity of the technology is expected to make the routine use of genetic information feasible in broad-ranging applications impacting molecular diagnostics, personalized medicine and daily biomedical research.

Dr. Han Cao founded BioNanomatrix in Oct, 2003 as a spinout of an $ 8 M Princeton University Project funded by Defense Advanced Research Project Agency (DARPA) of US Department of Defense. He is a key co-inventor of the company‘s ground breaking core single-molecule nanochannel array whole genome analysis technology that led to the commercial development of nano*Analyzer*® 1000 system. His diverse experience includes signal transduction pathway study, transgenic and knock-out animal models in cancer and aging, industry scale microarray and genomics technology development, as well as micro/nanofluidics design and fabrication at single molecule and single cell level analysis. He worked in China's National Key Lab of Plant Genetic and Protein Engineering at Beijing University, the Global Plant Genomic Unit of DuPont & Co, Institute for Human Gene Therapy of University of Pennsylvania Medical Center and Department of Electrical Engineering of Princeton University. Dr. Cao is a frequently invited speaker and panelist at international biotech, nanotech and entrepreneurship events. He has been leading multiple NIH and NIST funded projects and served on many NIH grant and contract review panels. BioNanomatrix‘s technology has won Ben Franklin Technology Partner‘s 2008 Emerging Technology Business Award, Frost & Sullivan 2009 Technology Innovation of the year in drug discovery, MIT Technology Review 2009 Top Ten Emerging Technology will change the World, and the company was recently named 2010 top 50 companies to watch by Medical Device + Diagnostics Industry. Dr. Cao was awarded the rising Star of Chinese Entrepreneur in Beijing, Sept 2010. He received his BS degree from University of Science and Technology of China (USTC) and a PH.D. in Molecular Biology from University of Delaware.

L95

Radoje Drmanac

Chief Scientific Officer and Co-founder
Complete Genomics, Inc., USA

LARGE-SCALE HUMAN GENOME SEQUENCING FOR GENOMIC MEDICINE

Based on a novel technology employing unchained-base reading on DNA nanoarrays (Drmanac et al., *Science* 2010), Complete Genomics sequences highly accurate (over 99.999%) genomes and has a highly efficient large-scale, commercial facility capable of sequencing more than 400 genomes per month. The last 300 delivered genomes contained greater than 50x read coverage and diploid calls of over 95% of the genome and the exome. Our five-year plan is to sequence hundreds of thousands complete human genomes and be the first company to achieve the $1000 genome. In addition, we are currently developing an enhancement of our process resulting in clinical-grade genome accuracy including haplotyping. Our sequencing service includes DNA library preparation, sequencing, mapping, assembly, and analysis, as well as various data analysis tools. The data includes easy-to-use lists of annotated genetic variants (SNPs, indels, SNVs, SVs) for each genome. These lists allow scientists to study the genetic basis of any of thousands of different diseases without the cost and labor associated with building, operating, and maintaining large-scale sequencing and computing facilities. Numerous studies with collaborators have been completed and this presentation will show examples of the utility of complete genome sequencing for discovery of novel genes and pathways. The availability of affordable, complete human genome sequencing for hundreds of cases and related controls for each disease of interest--including various types of cancers--promises to revolutionize human biology and medicine and provide the foundation for routine personal genome sequencing.

Dr. Radoje (Rade) Drmanac, chief scientific officer and co-founder of Complete Genomics (NSDQ: GNOM) since 2006, is one of the leading research scientists and inventors in the field of DNA sequencing-by-hybridization (SBH) and genomic microarrays. In 1994, he co-founded Hyseq (later Nuvelo) where, as chief scientific officer, he led the effort to discover and patent thousands of genes which formed the basis of Nuvelo‘s drug development pipeline. Prior to Hyseq, Rade was a group leader at Argonne National Labs from 1991 to 1994 as part of the Department of Energy‘s Human Genome Project. He completed his postdoctoral studies in 1990 in Hans Lehrach‘s group at the Imperial Cancer Research Fund in London. He earned his Ph.D. in molecular biology for the conception and pioneering development of SBH technology from Belgrade University, where he also received B.S. and M.S. degrees in molecular biology.

L96

Mike Lelivelt

Director of Bioinformatics & Software Products
Life Technologies
Ion Torrent, USA

SEMICONDUCTOR SEQUENCING FOR LIFE

Ion Torrent has invented the first device—a new semiconductor chip—capable of directly translating chemical signals into digital information. The first application of this technology is sequencing DNA. The device leverages decades of semiconductor technology advances, and in just a few years has brought the entire design, fabrication and supply chain infrastructure of that industry—a trillion dollar investment—to bear on the challenge of sequencing. The result is Ion semiconductor sequencing, the first commercial sequencing technology that does not use light, and as a result delivers unprecedented speed, scalability and low cost. All of these benefits are a result of applying a technology that is massively scalable, as proven by Moore's Law, to a task that has traditionally used optics-based solutions, which work in a linear fashion: increasing capacity requires increasing the number of signals that must be read resulting in longer run times, higher capital costs and ever more sophisticated optics. By contrast, Ion Torrent semiconductor technology can provide increases in chip capacity without impacting capital costs or runtime. Ion Torrent sequencing uses only natural (label-free) reagents and takes place in Ion semiconductor microchips that contain sensors which have been fabricated as individual electronic detectors, allowing one sequence read per sensor. We will show how the technology has scaled in just a few months from ~1 million sensors in the first-generation Ion 314 chips to ~7 million sensors in the second-generation Ion 316 chips—all while maintaining the same 1- to 2-hour runtime. We will also demonstrate that Ion semiconductor sequencing provides exceptional accuracy, long read length and scalability on a single, affordable bench-top sequencing platform.

Dr. Lelivelt is currently the Director of Bioinformatics and Software Products at Ion Torrent | Life Technologies. His Ph.D. Is in microbial genetics from the University of North Carolina at Chapel Hill and postdoctoral work in yeast genomics at the Univ. of Wisconsin – Madison. Dr. Lelivelt has over 15 years experience in genomics with work history at Affymetrix and Partek.

L97

Kai Q Lao

Principal Scientist
Molecular Biology Department
Applied Biosystems, USA

DEVELOPMENT AND APPLICATIONS OF SINGLE CELL RNA-SEQ ANALYSIS

Dissecting the relationship between genotype and phenotype is one of the central goals in biology and medicine. Cell development is driven and controlled by temporal and spatial changes in gene transcription, followed by translation of the resulting messenger RNAs into proteins. Recent advances in high throughput sequencing technology make it possible to obtain information on single cell transcriptomes at high resolution by RNA-Seq analysis, which can be instructive concerning how individual cells respond to signals and other environmental cues at critical stages of cell fate determination, or when they acquire aberrant phenotype. Essentially all cells within an individual organism share a virtually identical genotype, but the individual transcriptomes reflect expression of a subset of genes, which is determined by their epigenetic state, including DNA methylation and histone modifications. Diverse cell types exhibit a unique transcriptome, which can be used to assess gene regulation network underlying their physiological functions, behavior and phenotype during development in multi-cellular organisms. Combined with live cell imaging and lineage tracing, it will be possible to decipher the full gene expression network underlying physiological functions of individual cells in embryos and adults, and for the analysis of diseases.

Kai Q. Lao is currently Principal Scientist in Genetic Systems, Applied Biosystems, part of Life Technology. Dr. Lao received his Ph.D. from The University of Chicago in 1990. Following his graduation, Dr. Lao moved to California where he had his post-doctoral training in biophysics at Stanford University. Prior joining Applied Biosytems/Life Technologies, Dr. Lao was employed as a visiting scientist at UC Berkeley and a senior scientist at Hoechst/SYVA to develop biotechnology in DNA detection/sequencing. Dr. Lao have authored and co-authored 50+ patents/patent applications and 50+ peer reviewed scientific papers.

L98

Piero Carninci

Leader of the Functional Genomics Technology Team and of the Omics Resource Development Unit
Deputy Project Director of the LSA Technology Development Group
Omics Science Center(OSC), RIKEN, Japan

LESSONS FROM MINIATURIZATION OF CAGE TECHNOLOGY TO STUDY INDIVIDUAL NEURON TYPES

Plessy Charles[1], Salimullah Md[1], Noro Yukihiko[1], Saxena Alka[1], Hayashizaki Yoshihide[1], Lenhard Boris[2], Hensch Takao[3], Gustincich Stefano[4], Carninci Piero[1]
[1]RIKEN Omics Science Center, Yokohama Institute, Japan; [2]Bergen University, Computational Biology Unit, Bergen Center for Computational Science, Bergen, Norway; [3]Harvard Medical School, Boston, USA; [4]SISSA/ISAS International School for Advanced Studies, Neurobiology Sector, Trieste, Italy

To connect gene expression to transcriptional control we link mRNA expression to the promoter elements with cap-analysis gene expression (CAGE) technology. CAGE profiles mRNA expression, as well as other capped non-coding RNA (ncRNAs) by high-throughput sequencing with second and third generation sequencers of short tags corresponding to 5‘ ends of mRNAs. CAGE has allowed comprehensive mapping of human and mouse promoters and to reconstruct transcriptional networks, as well as identifying ncRNAs including antisense. Additionally, CAGE allowed mapping the expression of repeat elements. Analysis of individual cells is of paramount importance to identify the molecular role of RNAs in the cell. We have recently developed nano-CAGE, which is used to profile 1000 or less, and are currently pushing the methods towards single cell. We are also developing robotics and microfluidics to handle single cells. We have collected comprehensive datasets from homogeneously purified neurons. Analysis of mouse olfactory epithelia mapped the promoters for the majority of the mouse olfactory receptor genes. Other projects involve the comprehensive characterization of the A9 dopaminergic neurons of the midbrain, with identification of specific networks. We are further using nanoCAGE on individual neurons types involved in the brain plasticity and on RNAs deriving from subcellular fractions.

Born and Educated in Italy he obtained his doctoral degree at the University of Trieste in 1989. From 1990 to 1995 he developed technologies for DNA extraction and DNA sequencing at Talent, a spin-off biotech. He moved to Japan in 1995 at RIKEN, Tsukuba Life Science center and became tenure researcher in 1997. He has been developing technologies to capture full-length cDNAs, which were used for the construction of the Fantom projects. From 2008 he is a Team and Unit Leader and a Deputy Project Director at the RIKEN Omics Science Center in Yokohama. He has developed technologies to analyze the the transcribed part of the genome (transcriptome), such as the cap-trapper and the CAGE. These technologies have been broadly used in the RIKEN Fantom projects and allowed identifying non-coding RNAs as are the major output of the mammalian genome and providing comprehensive maps of the mammalian promoters. Additionally he developed a miniaturization of CAGE, in order to approach biological problems that for which there is limited amount of starting material. He has published more than 180 papers and book chapters, edited books and is a member of editorial boards of various scientific journals.

L99

Milos Pekny

Professor, Laboratory of Astrocyte Biology and CNS Regeneration
Center for Brain Repair and Rehabilitation
Department of Clinical Neuroscience and Rehabilitation
Institute of Neuroscience and Physiology
Sahlgrenska Academy at the University of Gothenburg, Sweden

MOLECULAR SIGNATURE OF ASTROCYTES BY SINGLE CELL GENE EXPRESSION PROFILING

Brain and spinal cord contain three neuroectoderm-derived cell types: astrocytes, neurons and oligodendrocytes. They all originate from the same multipotent neural stem cells. Traditionally, astrocytes were viewed as a homogeneous cell population that predominantly supports neuronal functions. Recent findings point to many functions of astrocytes in health and disease, including control of the number and the function of neuronal synapses. In contrast to neurons, we have limited knowledge about functional diversity of astrocytes and its molecular basis. To study astrocyte heterogeneity and stem/progenitor cell properties of astrocytes, we used single-cell gene expression profiling in primary mouse astrocytes and dissociated mouse neurosphere cells. The transcript number variability for astrocytes showed lognormal features and revealed that cells in primary cultures to a large extent co-express markers of astrocytes and neural stem/progenitor cells. We show how subpopulations of cells can be identified at single-cell level using unsupervised algorithms and that gene correlations can be used to identify differences in activity of important transcriptional pathways. We identified two subpopulations of astrocytes with distinct gene expression profiles. One had an expression profile very similar to that of neurosphere cells, whereas the other showed characteristics of activated astrocytes in vivo.

Milos Pekny received his MD (cum eminentia) and medical license from Charles University in Prague, Czech Republic, in 1989. He pursued his PhD studies at Uppsala University, Sweden, and received his PhD in 1994. Dr. Pekny's PhD thesis entitled "Studies of the function of platelet-derived growth factor and glial fibrillary acidic protein in vivo. A transgenic approach" was the first doctoral thesis in Scandinavia in which gene targeting (gene knock-out) technology was applied to address developmental processes and disease pathogenesis. Dr. Pekny then moved to the University of Gothenburg in Sweden as a postdoctoral fellow and built his own research group. In 1999 he became Associate Professor in Medical Biochemistry and Director of the Laboratory of Astrocyte Biology and CNS regeneration. In 2005, Dr. Pekny and his laboratory moved to Dept. of Clinical Neuroscience at Sahlgrenska Academy at the University of Gothenburg where he became Professor of Astrocyte Biology in the same year. Prof. Pekny is one of the leading European scientists in the field of astrocytes and CNS regeneration. The research focus of Prof. Pekny‘s laboratory has been on novel strategies for brain repair and regeneration. Pekny‘s laboratory redefined the concept of reactive gliosis in an injured brain (PNAS, 2006). Pekny‘s group with collaborators showed that reactive astrocytes play a key role in CNS trauma and stroke (J. Cell Biol., 1999; J. Neurosci., 2004; JCBFM, 2008) and identified these cells as a potential target for pharmacological intervention. They identified post-traumatic reactive gliosis as a major obstacle to CNS regeneration and demonstrated that the integration of neural transplants and neural stem cells can be largely improved by modulation of astrocyte activity (Nature Neurosci., 2003; Stem Cells, 2007). Prof. Pekny's laboratory has recently used single cell rtPCR for gene expression profiling of astrocytes as a step towards defining their molecular signature (Nucl. Acids Res, 2011). Prof. Pekny is Coordinator for the program ―Novel strategies for brain regeneration after stroke – from lab to patient to population” at the University of Gothenburg. He is a Steering Committee member and leader of the University of Gothenburg node in Marie Curie Training Network ―Neuron-Glial Interactions” (EduGlia.eu) funded by European Commission (2009-2013) and connecting laboratories of excellence in Europe and the Swedish representative and Work Group leader in a EU funded NANONET network. In 2005, Prof. Pekny received the Swedish Eric Fernström‘s Prize for outstanding medical research.

17 MARCH 2011 | FEATURED TALK

L100

Nicholas Katsanis

Director, Center for Human Disease Modeling
Professor, Dept of Cell Biology
George W. Brumley Distinguished Professor of Pediatrics
Duke University, USA

MERGING MEDICAL RESEQUENCING WITH FUNCTIONAL DATA TO UNDERSTAND DISEASE ARCHITECTURE

Defects of the primary cilium and its anchoring structure, the basal body, cause a number of human genetic disorders, collectively termed ciliopathies, since they are characterized by an overlapping range of phenotypes that include retinal degeneration, polydactyly, renal and hepatic fibrosis, obesity and a complex range of cognitive and neurodevelopmental defects. Recent data have also shown that some ciliopathies overlap not only phenotypically, but also genetically by contributing epistatic alleles that can modulate the phenotypic expressivity and penetrance. As such, the primary cilium and its associated signaling represent a useful model to understand the mechanism of total mutational load in a biological system. Towards that end, we have initiated systematic sequencing and functional evaluation of mutations of ciliary genes in a range of ciliopathy phenotypes and, using a large allelic series, have constructed models of epistasis in oligogenic disorders that suggest an intricate interaction between rare and common alleles to modulate penetrance and expressivity. Such studies will ultimately empower the predictive nature of the genotype and inform clinical management and treatment. Importantly, coupling deep medical resequencing with systematic *in vivo* and *in vitro* functional testing offers significantly improved resolution and increased appreciation of the complexity and architecture of genetic disease.

Dr. Katsanis obtained his first degree in Genetics from UCL in London in 1993 and his doctorate from Imperial College, University of London in 1997, where he worked with Dr. Elizabeth Fisher on the genetics of Down syndrome. He then joined the laboratory of Dr. James Lupski at the Dept. of Molecular and Human Genetics, Baylor College of Medicine, where he initiated his studies on the genetic and molecular basis of Bardet-Biedl syndrome. In 2002, he relocated to the Institute of Genetic Medicine, Johns Hopkins University, where he is currently an Associate Professor with appointments at the Departments of Ophthalmology, Molecular Bilogy and Genetics. His research interests continue to focus on the genetic basis of Bardet-Biedl sydnrome, where is laboratory is engaged in the identification of causative genes. In parallel, the Katsanis lab pursues questions centered on the signaling roles of vertebrate cilia, the translation of signaling pathway defects on the causality of ciliary disorders, and the dissection of second-site modification phenomena as a consequece of genetic load in a functional system.

17 MARCH 2011 | CLOSING KEYNOTE LECTURE

L101

George Church

Professor of Genetics, Harvard Medical School
Director of the Center for Computational Genetics, USA

TECHNOLOGIES FOR COLLECTING AND INTEGRATING GENOME, ENVIRONMENT AND TRAIT DATA

The human genome draft completed in 2004 (at 8-fold coverage) was a milestone, but at $3 billion it was not applicable to routine research or diagnostics. Expensive "common variant" association studies also generally failed to produce highly predictive and actionable diagnostics. Since 2004, we have pushed the cost of sequencing down by over a million-fold to $2K cost ($7K price) per 40-fold genome today. This also enables time-series studies of epigenomic and immunogenomic responses to cancers, microbes, allergens, vaccines, etc. Sharing saliva, skin, blood and stem cells and associated genome, environment and trait (GET) data greatly enables commercial and academic research, open-source software and data for interpreting whole and partial genome sequences as well as community tools for diverse phenomics. As the utility of cells, genes, and traits increases, insights come from highly integrative approaches - evaluating individuals in cohorts holistically and computationally, often from outside the clinical specialty of the study, e.g., computer scientists, systems biologists, or educational communities. Progress has been made by consenting volunteers with the understanding of open-access (including tests of comprehension of the consenting materials). Technologies for analysis of single-chromosome haplotypes and single-cell epigenomics include dilution libraries and in situ sequencing.

Dr. George Church is Professor of Genetics at Harvard Medical School and Director of NIH-CEGS and DOE-GTL Genomics Centers. He has pioneered technology innovations early in the development of key fields in chemistry and biomedicine with 10 US Patents granted and several pending. As part of technology transfer to the commercial sector he has served on 22 scientific advisory boards. In 1976, his crystallographic software lead to the first high-resolution folded-RNA structure (a decade before similar structures important for ribozymes, aptamers, and RNAi). That software is still in use 30 years later. He wrote the first automated DNA sequencing software (8 years ahead of other efforts); variations on that software figured into commercial efforts in 1980-1991. Between 1977 and 1984, working with Walter Gilbert (1980 Nobel Prize in Chemistry), he developed the first direct genomic sequencing method. That technology helped inspire the Human Genome Project (HGP). Of a handful of advocates, he was the one who participated in all three meetings in 1984-5 that lead to the HGP start in 1987 at DOE and 1990 at NIH. He obtained the first HGP sequencing grant and 3 years later helped found the Stanford, MIT, and CRI Genome Centers. The CRI group (later GTC, then Agencourt) was (and still is) the only commercial production group of the 7 US centers. GTC completed the first genome sequence sold commercially (the human pathogen, *H. pylori*, in 1994, the year before the first published genome sequence). In 1983-1988, Dr. Church invented the broadly applied concepts of molecular multiplexing and tags, variations of which are present in many high-throughput assays today. A homologous-recombination method from his group is one of the most broadly used, distributed to more than 1000 research groups. He began development of oligonucleotide-array DNA synthesizers in 1990 and has co-developed technologies for innovative array assays with most of the major companies (Affymetrix, Nimblegen, and Xeotron). Recently these have been extended from analysis to synthesis, i.e. assembly and error-correction of genes from multimegabase-scale chips and hence initiating 'synthetic biology' as a new engineering discipline. His group is synthesizing bacterial genomes with new genetic codes, new protein types, and thereby immune to all existing viruses. Dr. Church helped develop and commercialize some of the first "single-molecule" and microfluidics technologies, most recently "Polony" DNA sequencing and has been championing its development for $1000 human genome sequences. This, together with the advances above for unprecedented manipulations of DNA in cells, brings practical personalized medicine considerably closer, along with applications to energy, the environment, and smart materials.

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Dr Alexandra I Blakemore
Editor-in-chief, The HUGO Journal

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PANEL OF INTERNATIONAL CHAIRPERSONS

Aida I Al Aqeel

S. Consultant Pediatrics, Medical Genetics and Endocrinology
Principal Scientist, King Faisal Specialist Hospital and Research Centre
Department of Paediatrics
Riyadh Military Hospital, Saudi Arabia

Awarded the American Federation of Medical Research Outstanding Investigation Award 2002; European Society of Human Genetics Science Award, 2005; the 10th International Congress of Inborn Errors of Metabolism Outstanding Physician Award, Japan, 2006. I was honored at the House of Commons, United Kingdom, as one of the distinctive international speakers, 2007. Nominated for King Faisal International Prize in Medicine 2008. Was given the Distinction Medal by the Crown Prince of Saudi Arabia 2008, also given Distinctive Arab Female Scientist Prize, the Arabian Gulf University, 2009. . Awarded King Faisal Distinction Wissam by The Custodian of the Two Holy Mosques, King Abdullaha Bin AbdulAziz January 2010. I have described a new Genetic Syndrome, which carries my name. This has been published and reviewed in the prestigious Nature Genetics journal as –the first genetic evidence for the understanding of human growth and development". I am actively involved in research and research grants in translational genomics for implementing improved health services , including: (1) Pre implantation Genetic diagnosis for the prevention of genetics disorders, Co-Principal Investigator – involved in 50% of the research activities; (2) Embryonic Stem Cell development for therapy of genetic metabolic disorders- Principal Investigator- awarded 35 millions Saudi Riyals by King Abdulaziz City for Science and Technology; (3) Treatment of Genetics disorders at the molecular level- Principal Investigator, submitted to King Abdulaziz City for Science and Technology. I presented over 100 papers to National and International meetings, been invited to lecture at Havard Medical School; North Western University; Mount Sinai School of Medicine; Yale University; University of California, Irvine, USA; World Health Organization Geneva; University of Oslo and Medical Advisory Board of Biotechnology, Norway; National Institute of Health, USA; Wellcome Trust Foundation, Cambridge, UK; Biovision International congress, Bibliotheca Alexandria; Human Variome Project meeting, Spain; tissue engineering International Congress, Bibliotheca Alexandria. I published over 70 manuscripts in peer reviewed, journals; presented over 100 abstracts and over 100 invited speeches. I have established ethical Frame work for research and patient care in Genetics and Genomics in the Muslim world, published that in Nature Genetics. I also established international policies for the Human Variome project in collaboration with international colleagues.

Lihadh Al-Gazali

Professor in Clinical Genetics, Department of Pediatrics,
Faculty of Medicine and Health Sciences, UAE University, United Arab Emirates

Dr. Al-Gazali is professor of Clinical Genetics and Pediatrics at the UAE University, Faculty of Medicine and Health Sciences. She obtained her MBCHB from Baghdad University and was trained in Pediatrics and then Genetics in UK (Edinburgh and Leeds). Prof. Al-Gazali is a Fellow of the Royal College of Physician and the Royal College of Paediatrics and Child Health, UK. She is member of several international organizations. Prof. Al-Gazali also made an important contribution in the area of Clinical Genetics, providing a significant amount of information regarding genetic disorders specific to the UAE and the Arab world in general. She has provided important data on the clinical phenotypes and natural history of many genetic syndromes. Her expertise in Clinical Dysmorphology has been widely recognized by the international community. Al-Gazali was profiled in the Lancet in March 2006 for her contribution to Clinical Genetics and research in the Middle East. She is the winner of Women in Science UNISCO-L'OREAL Award for Africa and Arab States for 2008. Prof. Al-Gazali has published more than 140 papers.

Fahd Al-Mulla

Associate Professor and Head of Molecular Pathology
The Health Sciences Center, Faculty of Medicine
Kuwait University, Kuwait

Fahd Al-Mulla received his Medical Doctorate and Ph.D. from Glasgow University in the field of cancer genetics and metastasis. Dr. Al-Mulla is the Director of the Research Core Facility in Kuwait University Health Sciences Center. He heads a Molecular Pathology Unit, which aims at delivering state-of-the-art theranostics. As Assistant Vice President for Research, he headed the office of External Research Collaboration in Kuwait University with a mandate to build collaborative partnerships, invest institutional outputs, generate capital and resources, and promote public awareness as regards to the importance of scientific research outputs in resolving society‘s problems and in expediting the development process. Dr. Al-Mulla is a pioneer in the identification and characterization of metastasis suppressor genes. It is expected that his work will result in the identification of clinically useful cancer biomarkers in the near future.

Stylianos E Antonarakis

Professor and Chairman
Department of Genetic Medicine and Development
University of Geneva Medical School, Switzerland

Professor Stylianos Antonarakis is the Director of the Department of Genetic Medicine at the University of Geneva in Switzerland. Before moving to Geneva in 1992 he was a professor at Johns Hopkins University in the USA. His lab has contributed to the genetics of monogenic and polygenic disorders, as well as the functional annotation of the human genome and particularly of human chromosome 21. He is on the editorial board of many high profile journals, received several awards for his research, and has recently served as the president of the European Society for Human Genetics. He has published more than 500 papers in peer-reviewed journals in the last 30 years (h-index 90).

Jong Bhak

Director, Personal Genomics Institute (PGI)
Director, Theragen BiO Institute (TBI)
South Korea

Jong Bhak is the director of PGI (Personal Genomics Institute), Korea, since 2010. He had been the director of KOBIC (Korean Bioinformation Center) since 2005. He worked on a broad range of bioinformatics problems with interests in computer hardware, operating systems, programming, and applications. He received his BSc. Honours in biochemistry from Aberdeen University in 1994 and his Ph.D. in BioInformatics from Cambridge University in 1997. He joined genetics department at Harvard Medical School in 1998 as a postdoctoral researcher for DNA chip analyses. He worked as a research fellow in EBI from 1999 until 2001. In 2001, he joined MRC-DUNN as a group leader to research geronto-genomics and mitochondrial functions. In 2003, he became an associate professor at KAIST, Korea. He is a proponent of an openfree information sharing in science. He advocates free genomics projects. His group analyzed the first Korean human genome (working with Dr. Seong-Jin Kim) and the first publically available female genome (working with Personal Genome Project). He established Genome Research Foundation jointly with Dr. Seong-Jin Kim, Dr. Byungchul Kim, and Mr. Jinup Goh, to promote the application of genomics to society. GRF, working with PGP, has launched KPGP (Korean PGP) in Korea to sequence analyze 10,000 Korean people to construct reference standard Korean genomes. Also, he is collaborating with Cha medical school, National Cancer Center, and Seoul National University to find cancer specific genomic markers using bioinformatics.

Anthony J Brookes

Chair, Bioinformatics and Genomics
Department of Genetics
University of Leicester, UK

Professor Brookes is an internationally recognized leader in genomics and bioinformatics, having made significant contributions to method development, disease and population genetics, DNA variation analysis, and database systems for organizing gene-disease information. His publications include over 140 peer-reviewed articles and reviews, and he has filed 6 patent applications on cloning, genotyping, and DNA analysis. Professor Brookes began his research career in the UK by achieving a first class degree in Medicine and Medical Biochemistry at the University of Manchester, followed by a molecular genetics PhD at the Imperial Cancer Research Fund and the University of London. He then established a research group in the MRC Human Genetics Unit in Edinburgh, where his team was involved in identifying the Presenilin-1 gene that causes Alzheimers Disease. Subsequently, he moved to Sweden, first to Uppsala University where he received Docenture in Genetics, and then to the Karolinska Institute where he was awarded both Docenture and a Professorship in Genome Research. Professor Brookes now holds a Chair in Bioinformatics and Genomics at the University of Leicester in the UK. There, he runs active method development and bioinformatics research groups, and he is Director of the institute's 'NUCLEUS' Genomics Services Core. He coordinates the European FP7-GEN2PHEN informatics project, and runs the 'GWAS Central' (HGVbaseG2P) genetic association database. He is Editor & Chair of Publications Committee for the HUGO Journal, and a member of both the Public Population Project in Genomics (P3G) and the Open Researcher & Contributor ID (ORCID) Technical Working Group. Additionally, he is a Co-Founder and Board Member of the Human Genome Variation Society, and works as communicating Editor for Human Mutation. Other significant achievements include launching and running the international Meeting series on "Human Genome Variation & Complex Genome Analysis" and inventing the Dynamic Allele-Specific Hybridization genotyping technology.

Elspeth Bruford

Project Co-ordinator
European Bioinformatics Institute (EMBL-EBI), UK
HUGO Gene Nomenclature Committee (HGNC)

Elspeth A. Bruford received her Ph.D. mapping retinal diseases at the MRC Human Genetics Unit, Edinburgh. After working in publishing, she moved to University College London in 1998 to join the HUGO Gene Nomenclature Committee, of which she is now the Group Co-ordinator. From 2000-2007 she was also the Managing Editor of the Annals of Human Genetics. In 2007 Elspeth gained funding from the Wellcome Trust and NHGRI to relocate the HGNC to the European Bioinformatics Institute at Hinxton, UK. Elspeth plays an active role in the annotation of the human genome, involving collaborations with all the major genome databases, and attends many international meetings including all of the HGM meetings since 2000.

Habiba Chaabouni-Bouhamed

Professor, Laboratory of Human Genetics, Faculty of Medicine of Tunis;
Service of Hereditary Disorders, Hospital Charles Nicolle, Tunisia

Dr. Bouhamed-Chaabouni is professor of medical genetics in University of Tunis El Manar and Chief of the Department of Congenital and Hereditary Diseases, Charles Nicolle Hospital, Tunis, Tunisia. She is director of the Human Genetics Research Laboratory at the Faculty of Medicine, Tunis. Prof. Chaabouni developed medical genetics courses for undergraduate students in medical schools of Tunisia, for graduated residents in medical genetics and implemented Master

of Sciences in Human Genetics. She implemented genetic counseling clinics and prenatal diagnosis as medical facilities in Tunisia from more than 30 years. Prof. Chaabouni conducted several studies on consanguinity, genetic disorders and genetic polymorphism. She authored and co-authored more than 100 publications in peer-reviewed publications. In 2006, Prof. Chaabouni received the prestigious award of L'Oréal-UNESCO for Women in Science based on her groundbreaking achievements and contributions to scientific progress. In 2007, she received in Italy the International Price ⊣ATIUM tra Europa e Mediterraneo" for Scientific Research. Prof. Chaabouni is member of several organisms working in the field of genetic disorders including Orphanet and the Centre for Arab Genomic Studies. She is also member of several scientific societies.

Ruth Chadwick

Director, Centre for Economic and Social Aspects of Genomics (CESAGEN),
Cardiff University, UK
Chair, HUGO Ethics Committee

Ruth Chadwick is Director of the ESRC (Economic and Social Sciences Research Council) Centre for Economic and Social Aspects of Genomics (Cesagen), Cardiff University, UK. She also holds a Link Chair between Cardiff Law School and the School of English, Communication and Philosophy (ENCAP). She has co-ordinated a number of projects funded by the European Commission, including the EUROSCREEN projects (1994-6; 1996-9) and co-edits the journal Bioethics and the online journal Genomics, Society and Policy. She is Chair of the Human Genome Organisation Ethics Committee and has served as a member of several policy-making and advisory bodies, including the Panel of Eminent Ethical Experts of the Food and Agriculture Organisation of the United Nations (FAO), and the UK Advisory Committee on Novel Foods and Processes (ACNFP). She was editor-in-chief of the award winning Encyclopedia of Applied Ethics (1998), of which a second edition is now being prepared. She is an Academician of the Academy of Social Sciences and a Fellow of the Hastings Center, New York; of the Royal Society of Arts; and of the Royal Society of Medicine. In 2005 she was the winner of the World Technology Network Award for Ethics for her work on the relationship between scientific developments and ethical frameworks.

Richard G H Cotton

Senior Principal Research Fellow
Group Leader, Genomic Disorders Research Centre, Australia

Richard Cotton initiated the Mutation Research Centre, now renamed the Genomic Disorders Research Centre, in January, 1996 (www.genomic.unimelb.edu.au). He has always been interested in the biochemical genetics of human disease and has recently focused on mutation. Amongst his more notable scientific achievements are the conception, planning and execution of the fundamental experiment, which proved that when two immunoglobulin producing cells were fused, the immunoglobulin of both parental cells were produced in the hybrid. This laid the experimental and theoretical foundation for the widely used monoclonal antibody technique. He also conceived the widely used tetrohydrobiopterin (BH4) load test to identify the serious variants of PKU, but BH4 is currently being trialled in heart disease. He is particularly interested in improving mutation detection technologies to make them cheaper and simpler, so that they can be more widely applied, and holds several patents in the area. A recent development has been a method to detect DNA damaging compounds. Prof Cotton has written two books entitled "Mutation Detection", initiated the journal entitled "Human Mutation", and in 1991 initiated bi-yearly international workshops on Mutation Detection and in 1998, bi-yearly HUGO Mutation Detection Courses. In 1996 he has also started a worldwide initiative (The HUGO Mutation Detection Database Initiative, recently formed into the Human Genome Variation Society (HGVS); www.hgvs.org) to capture and distribute lists of mutations. In June 2005, he was admitted as a Member of the Order of Australia for service to science through genetic research, particularly through the development of technologies to detect gene mutations that underlie birth defects or cause disease and through efforts to document findings. In June 2006, he convened a Meeting, co-sponsored by WHO, which initiated the Human Variome Project (www.humanvariomeproject.org). This project aims to collect worldwide genetic variation and its associated phenotype. He is Treasurer of the Human Genome Organisation (HUGO) and the author of over 200 scientific papers and three patents.

Geoffrey S Ginsburg

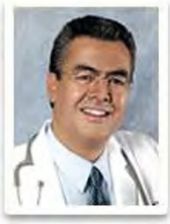
Director, Center for Genomic Medicine, Institute for Genome Sciences & Policy
Professor of Medicine and Pathology, Duke University Medical Center, USA

Dr. Ginsburg, the founding director of the Center for Genomic Medicine, assumed his current position in the Duke Institute for Genome Sciences and Policy in 2004 and was also appointed as a co-director of the Duke Translational Medicine Institute in 2006. He is also the founding executive director of the Center for Personalized Medicine established in 2010. While at Duke, Dr. Ginsburg has pioneered translational genomics, initiating the first genomic-guided clinical trials as well as developing novel practice models and implementation research for the integration of genomic tools in heath care systems. The center focuses on oncology, infectious diseases, cardiovascular disease and metabolic disorders. In 1990, he joined the faculty of Harvard Medical School, where he was director of preventive cardiology, and led a laboratory in applied genetics of cardiovascular disease. In 1997 he joined Millennium Pharmaceuticals Inc, as senior program director for cardiovascular diseases and was eventually appointed vice president of Molecular and Personalized Medicine at Millennium, where he was responsible for developing pharmacogenomic strategies for therapeutics, as well as biomarkers for disease and their implementation in the drug development process. Dr. Ginsburg research interests are in the development of novel paradigms for developing and translating genomic information into medical practice and the integration of personalized medicine into health care. He has received a number of awards for his research accomplishments, including the Innovator in Medicine Award from Millennium in 2004 and the Basic Research Achievement Award in Cardiovascular Medicine from Duke in 2005. He is a founding member and on the Board of Directors of the Personalized Medicine Coalition, a senior consulting editor for *The Journal of the American College of Cardiology,* editor-in-chief for *The HUGO Journal*, and an editorial advisor for *Science Translational Medicine*. In addition he is the editor of *Genomic and Personalized Medicine* (Elsevier) whose first edition was published in 2009. He has been an international expert panel member for Genome Canada and is currently a member of the Board of External Experts for the National Heart, Lung and Blood Institute, the Secretary of Veterans Affairs Advisory Council on Genomic Medicine, the Institute of Medicine‘s Roundtable on Genome-Based Research to Human Health and the National Advisory Council for Human Genome Research. He received his MD and PhD in biophysics from Boston University and completed an internal medicine residency at Beth Israel Hospital in Boston, MA. Subsequently, he pursued postdoctoral training in clinical cardiovascular medicine at Beth Israel Hospital and in molecular biology at Children‘s Hospital as a Bugher Foundation Fellow of the American Heart Association.

Hanan Hamamy

Professor, Human Genetics
Department of Genetic Medicine and Development
Geneva University Hospital, Switzerland

Professor Hanan Hamamy is currently affiliated with the Department of Genetic Medicine and Development at Geneva University Hospital. Her research interests focus on community genetics and consanguinity health impact. She has a long experience in genetic counseling in Arab countries mainly Jordan and Iraq where consanguinity rates reach 40% and has encountered many consanguineous families harboring rare or not previously reported autosomal recessive genes. She participated in several World Health Organization consultations and co_authored several WHO publications on community control of genetic and congenital disorders, ethical issues in medical genetics, and prevention of birth defects in developing countries. She has recently organized an international meeting on Consanguinity in Geneva and created a network of collaborations for the utilization of consanguineous samples for the discovery of disease related genes.



Gerardo Jimenez-Sanchez

Chair, Working Party in Biotechnology, Organization for Economic Co-Operation and Development (OECD)
Chief Scientific Officer, BioFields, Mexico

Dr. Gerardo Jimenez-Sanchez was born in Mexico City. He is has an M.D. with a Ph.D. in Human Genetics and Molecular Biology from the Johns Hopkins University. He received his training in business administration from the IPADE Business School. He is a certified Pediatrician and a member of the National Academy of Medicine, the American Society of Human Genetics, the American Society of Gene Therapy, the Society for Inherited Metabolic Disease, the European Society of Inborn Errors of Metabolism. He was founder Director General of the National Institute of Genomic Medicine in Mexico, and Chairman of the Working Party on Biotechnology at the Organization for Economic Cooperation and Development (OECD) in Paris. He is the leading investigator in the Mexican Genomic Diversity Project and the Mexican Medical Re-sequencing Initiative. Dr. Jimenez-Sanchez is Chief Scientific Officer of BioFields, Professor of Genomic Medicine at the National Autonomous University of Mexico, and teaches Business in Life Sciences at the IPADE Business School. He was President of the first and second National Congresses of Genomic Medicine in Mexico, and serves as Council member of the Human Genome Organisation (HUGO), as well as on the Board of Directors of the Public Population Projects in Genomics (P3G). He is founder President of the Mexican Society of Genomic Medicine and Regional Editor for Latin America and the Caribbean of the HUGO Journal.

Felix Li Jin

Haoqing-Fudan Professor
Vice President at Fudan University, China

Dr. Jin received Ph.D in genetics at University of Texas Health Science Center at Houston in 1994. He is now Haoqing-Fudan Professor and Vice President at Fudan University. He is a foreign member of Max-Planck Society and a board member of Human Genome Organisation (HUGO). He serves as an Editorial Board Member in 9 academic journals. He also serves as the President of Shanghai Society of Genetics and the President of Shanghai Society of Anthropology. His research areas include medical genetics and genetic epidemiology, computational biology, human population genetics and genomics. He published 270 articles in journals including *Nature, Science, PNAS, JCI* and *JAMA*.

Moien Kanaan

Professor of Molecular Genetics
Dean of Science and Hereditary Research Lab Director
Bethlehem University, Palestine

Dr. Moein Kanaan is a professor of Molecular Genetics and a leading Palestinian geneticist. Over the last 18 years, Dr. Kanaan has been investigating the genetically isolated Palestinian population and its high consanguinity rate and identifying the genetic basis for human disorders; these include: hearing loss, skin abnormalities, breast cancer and congenital heart diseases. By studying large consanguineous Palestinian kindred, Dr. Kanaan‘s collaborative work has been able to profile novel and variant alleles undermining hearing loss and Epidermolysis Bullosa in the Palestinian population and just recently mapped and identified a few new hearing loss causing genes. Dr. Kanaan has been a member of the Research Task Force in Palestine. He has many publications to his credit and has participated in many international research effort and scientific networks. Dr. Kanaan is a recipient of many research and scientific awards.

Mitsuoki Kawano

Research Scientist
LSA Technology Development Unit
RIKEN Omics Science Center, Japan

Dr. Kawano received PhD from Nara Institute of Science and Technology (NAIST) in 2002. He then pursued post-doctoral studies as a Visiting Fellow at National Institutes of Health (NIH), National Institute of Child Health and Human Development, and JSPS Research Fellow in Biomedical and Behavioral Researchers at NIH in the laboratory of Dr. Gisela Storz (2002-2006) where he studied small, noncoding RNAs in *E. coli*. In 2006, he joined Functional RNA Research Program, Frontier Research System at RIKEN Yokohama Institute as a research scientist (2006-2008). He is currently a Research Scientist at RIKEN Omics Science Center, and developing technologies to investigate gene expression network at single-cell level, and miRNA and pre-miRNA by deep sequencing. He is also interested in functional small RNAs in sperm that are transmitted to oocyte at fertilization. He is a member of the Research Ethics Committee in RIKEN Yokohama Institute from 2009. Dr. Kawano has received awards including Letter of Appreciation from the President of RIKEN and Nature Chemical Biology Award in the 21st International Mammalian Genome Conference.

Dhavendra Kumar

Consultant in Clinical Genetics
Institute of Medical Genetics, Cardiff University
Genomic Policy Unit, University of Glamorgan
University Hospital of Wales, UK

Professor Dhavendra Kumar is a Consultant in Clinical Genetics at the University Hospital of Wales, Cardiff (UK). He is on the Faculty of the Institute of Medical Genetics, Cardiff University and Genomic Policy Unit, University of Glamorgan in Wales, United Kingdom. He is the lead Clinician for Clinical Cardiovascular Genetics in Wales. After qualifying in Medicine from the King George‘s Medical College, University of Lucknow, India, he completed postgraduate training in Pediatrics with an MD. Since 1980 he has pursued a career in Medical Genetics in the UK. In 1990 he became a Diplomate of the American Board of Medical Genetics. He is a Fellow of the American College of Medical Genetics (FACMG) and Royal Colleges of Physicians (FRCP-London and FRCP-Ireland) and Pediatrics and Child Health (FRCPCH-UK). He has edited/ authored five books- *Genetic disorders of the Indian Subcontinent*-Springer/Kluwer; *Genomics and Clinical Medicine* (Oxford University Press); *Principles and Practice of Clinical Cardiovascular Genetics (*Oxford University Press); *Oxford Specialist Handbook on Inherited Cardiac Disease* and *Genomics and Health in Developing World* (Oxford University Press). He has several publications in peer-reviewed journals of pediatrics and clinical genetics. In 2006, he established and developed a new biomedical journal (*Genomic Medicine-Springer*) that subsequently became the official journal of the Human Genome Organisation (*The HUGO Journal'*). He serves on the editorial board of the HUGO Journal as Editor in Chief and a member of the publications committee of HUGO. He is a member of the HUGO Council. Professor Kumar‘s current clinical and research interests include inherited cardiovascular diseases, applications of genomics in medicine and human health, particularly in improving the health in emerging economies of the developing world. He is currently actively involved in promoting medical genetics and genomics in developing countries through education programs and setting up a database on genomic variation and genetic disorders across the developing world.

Edison T Liu

Executive Director, Genome Institute of Singapore, Singapore
Professor of Medicine, National University of Singapore
President, Human Genome Organisation

Dr. Liu is the Executive Director, Genome Institute of Singapore (Agency for Science, Technology, and Research) and Professor of Medicine, National University of Singapore. He received his degrees (B.S. and M.D.) at Stanford University further oncology and molecular biology training at Stanford and at UCSF. Prior to starting the GIS in 2001, Dr. Liu was the Scientific Director for the Division of Clinical Sciences, National Cancer Institute (USA). Dr. Liu‘s scientific research has focused on the functional genomics of human cancers, particularly breast cancer, investigating the dynamics of gene regulation on a genome scale that modulates cancer biology. He has authored over 260 scientific papers, reviews and books. He is the recipient of a number of awards: Leukemia Society Scholar, 1991-96; Member, the American Society of Clinical Investigations (elected 1995), the Brinker International Award for basic science research in Breast Cancer, 1996; the Rosenthal Award from the American Association for Cancer Research, 2000; the President‘s Public Service Medal for helping Singapore resolve the SARS crisis, and a Doctor of Medicine Sciences *honoris causa,*Queen‘s University, Belfast, 2007. He was elected as a Foreign Associate Member of the European Molecular Biology Organization (EMBO, 2008), and serving his second term as the elected President of the Human Genome Organisation (HUGO). Dr. Liu is also the current Chairman of the Board for the Singapore Health Sciences Authority, health regulatory and blood banking agency for Singapore.

John S Mattick

Professor of Molecular Biology and NHMRC Australia Fellow
Institute for Molecular Bioscience
University of Queensland, Brisbane, Australia

John Mattick is the Professor of Molecular Biology and ARC Federation Fellow at the Institute for Molecular Bioscience at the University of Queensland. He did his undergraduate training at the University of Sydney and his PhD at Monash University. He has worked at Baylor College of Medicine in Houston, the CSIRO Division of Molecular Biology in Sydney, and the Universities of Cambridge, Oxford, Cologne and Strasbourg. He was Foundation Director of the Australian Genome Research Facility and the Institute for Molecular Bioscience. He is an Associate Member of the European Molecular Biology Organisation and a Fellow of the Australian Academy of Science.

Howard L McLeod

Fred N. Eshelman Distinguished Professor
Director, UNC Institute for Pharmacogenomics and Individualized Therapy, USA

Dr. Howard McLeod is Fred N. Eshelman Distinguished Professor and Director, UNC Institute for Pharmacogenomics and Individualized Therapy, University of North Carolina, Chapel Hill. Dr. McLeod holds appointments in the Schools of Pharmacy and Medicine and the Lineberger Cancer Center. Dr. McLeod is also the Principal Investigator for CREATE, a member of the NIH funded Pharmacogenetics Research Network and is a member of the FDA committee on Clinical Pharmacology. He also directs the Pharmacogenetics for Every Nation Initiative, which aims to help developing countries use genetic information to improve National Drug Formulary decisions. Howard has published over 350 peer reviewed papers on pharmacogenomics, applied therapeutics, or clinical pharmacology and continues to work to integrate genetics principles into clinical practice to advance individualized medicine.

Maude E Phipps

Professor (Human Genetics)
Jeffrey Cheah School of Medicine and Health Sciences
Monash University, Malaysia

Maude Elvira Phipps is Malaysian and a human geneticist who graduated with a B.Sc. Honours (Class 1) in Genetics from the University of Malaya, having completed early work on plasmid mediated antibiotic resistance and virulence factors in bacteria. In 1990, she obtained the Cambridge Commonwealth Trust Scholarship award to pursue doctoral studies at the University of Cambridge, United Kingdom where she researched the molecular genetics of Von Hippel Lindau disease and Chromosome 3p- syndrome. In 1994, she joined the Faculty of Medicine, University of Malaya and contributed substantially to the development of biomedical sciences, specialist training and research programmes. Together with colleagues, she began researching molecular genetics of autoimmune diseases and transplantation mechanisms, in collaboration with researchers the Oxford Transplant Centre and the University of Western Australia, supported by the CICHE and the UNESCO Human Genome Fellowship awards. These efforts resulted in the setting up of a new service for molecular immunogenetics and transplantation matching at the University of Malaya Medical Centre. Her current research focuses on the genomics of *Homo sapien*s to answer questions related to our evolution, migration, morphological development and health. Apart from translational medicine, she is a keen advocate of bioethics education and research programmes in Asia, especially in rapidly developing countries which have placed biotechnology high on their development agendas. She has published extensively in international journals, has been an invited speaker at numerous international meetings and supervised many graduate students over the years. Maude is currently Professor of Human Genetics at the Jeffrey Cheah School of Medicine and Heath Sciences, Monash University (Sunway Campus). She is an active member of the Human Genome Organisation (HUGO), Australian South East Asian Tissue Typing Association (ASEATTA), the UNESCO Bioethics programme. She is a member of the Steering Committee for the Malaysian Bioethics Council, co-chair of the Policy Review Board of the Pan-Asia SNP Initiative and Vice President of the Genetics Society of Malaysia.

Timothy Ravasi

Associate Professor of Bioengineering, KAUST
Associate Adjunct Professor of Medicine, University of California San Diego
Head of the Red Sea Laboratory for Integrative Systems Biology, KAUST, Saudi Arabia

Before join KASUT Dr. Ravasi has been the Co-Director of the Systems Biology and Integrative Networks Core at the Scripps NeuroAIDS Preclinical Studies Center (SNAPS). From 2000 to 2005, Dr. Ravasi was a research scientist at the Institute for Molecular Biosciences of the University of Queensland in Australia. Dr. Ravasi is working to develop large-scale, computer-aided models of biological signaling, transcription regulatory networks, and regulatory pathways. He applies new experimental strategies and statistical frameworks with the aim to integrate, model, and visualize the enormous amount of measurements derived from genome-wide experiments, such as ultra-high-throughput DNA and RNA sequencing, proteins and mRNAs expression arising in the wake of Genome Projects. At KAUST Dr. Ravasi is directing the Saudi Arabian SNPs genotyping project. Dr. Ravasi is an active member of the International Immunomics Society, a member of the Functional Annotation of the Mammalian Genomes consortium (FANTOM), the Human Genome Network Project, and a member of the Program Committee for the Dialogue for Reverse Engineering Assessments and Methods (DREAM). In 2005 he was honored with the prestigious position of Permanent Visiting Scientist at the Institute of Chemicals and Physical Research (RIKEN) in Yokohama, Japan. In 2001 he was awarded with the Japan Science and Technology Agency fellowship for the analysis of the mouse genome. He is Dr. Ravasi received his bachelor‘s and doctoral degrees in genetics and bioinformatics from the University of Milan in Italy.

Xiaoan Ruan

Manager, Personal Genomics Solutions (PGS)
Genome Institute of Singapore, Singapore

Rapid advance in DNA sequencing technologies has opened brand new opportunities for biomedical researches and clinic applications. The paired-end diTag (PET) sequencing methods, invented by GIS scientists, have been integrated with next-generation sequencer platforms such as 454-GSFLX, Solexa GAII and ABI SOLiD. My current focus is to streamline the existing PET methodologies and develop new sequencing approaches including automated PET pipelines for whole genome, transcriptome, and chromatin interactome analyses. We are actively applying the PET technologies to address broader interests in genomic researches and biomedical implementations, through internal and external collaboration projects. Our ultimate goal is to establish a robust and cost-effective DNA sequencing platform to deliver personalized genomics solutions to all patients and individuals.

Yijun Ruan

Senior Group Leader and Associate Director of Genomics Technology & Biology
Genome Institute of Singapore, Singapore

Dr. Ruan Yijun is currently the Senior Group Leader and Associate Director of Genomics Technology at the Genome Institute of Singapore. His primary interest is to elucidate the structures and dynamics of all functional DNA elements in complex genomes through transcriptome characterizations and genome interrogation. To facilitate such understanding, Dr. Ruan's lab have developed paired-end-ditag (PET) based high throughput and high precision DNA sequencing and mapping methodologies. These sequencing-based measurements are used to address complex biological questions such as how cancer cells progress and how stem cells maintain their unique properties. Another major interest of Dr. Ruan is to discover previously uncharacterized microbial genes and genomes that are relevant to human health. To this end, his lab has established a metagenome analysis capability that includes a filtration system for isolating uncultured microbes, shotgun and PET sequencing of metagenomes to uncover viral and bacterial genome sequences from a variety of environment settings and cavities of the human body.

Sumio Sugano

Professor, Division of Biosciences
Department of Medical Genome Sciences
University of Tokyo, Japan

Dr. Sumio Sugano is professor at Department of Medical Genome Sciences, Graduate School of Frontier Sciences, The University of Tokyo. He was the leader of FLJ cDNA collection project of Ministry of Economy and International Trade of Japan. Also, he headed the Scientific Research on Priority Areas "Medical Genome Science" of the Ministry of Education, Science, Sports and Culture of Japan. Dr. Sugano's research interests include gene structure and gene expressions, protein functions and application of genomics in disease studies.

Ghazi O Tadmouri

Assistant Director, Centre for Arab Genomic Studies
Dubai, United Arab Emirates

Dr. Ghazi Tadmouri is the Assistant Director of the Centre for Arab Genomic Studies, a division of the Sheikh Hamdan Award for Medical Sciences (Dubai, UAE). Since March 2010, he is member of the UAE Ministry of Health's Higher Committee for Health Research. In 2004, He launched the CTGA Database for genetic disorders in Arab people and is heading its development team. Dr. Tadmouri is member of the consultancy group supporting the UNDP-Lebanon "Transfer of Knowledge Through Expatriate Nationals" (TOKTEN) Project. He is also a member of many regional research grant review boards, journal editorial and peer review boards, and international organizations. In 1999, he received his Ph.D. degree in Molecular Biology and Genetics from Bogaziçi University (Turkey). In years 2000-2004, he was Assistant Professor of Molecular Biology and Genetics at Fatih University (Turkey). In years 2007 and 2009, he conducted graduate and professional courses and workshops on Bioinformatics at the Arabian Gulf University (Bahrain) and the World Health Organization (Egypt). Dr. Tadmouri is author of more than 35 books and international scientific articles. He presented scientific papers in more than 60 international conferences and workshops. Despite this, Dr. Tadmouri believes that scientific knowledge is only effective when translated into public practice. Born on the 8th of November 1969 to a family with roots from the Mameluke cities of Tripoli and Cairo, educated in Beirut and Istanbul, and acquired professional experience in Istanbul and Dubai, Dr. Tadmouri recognizes the Eastern Mediterranean and the Arabian Peninsula to be his large homeland. As a population geneticist, he admires the genetic diversity in the region as well as its unique blend of cultures and languages.

Mahmoud Taleb Al Ali

Director, Centre for Arab Genomic Studies
Dubai, United Arab Emirates

Dr. Taleb Al Ali is a consultant geneticist and head of the Genetics Centre at Al Wasl Hospital in Dubai. He is also an adjacent assistant professor in the Department of Biochemistry at the Faculty of Medicine and Health Sciences, UAE University. Dr. Al Ali graduated in 1987 with a degree in laboratory Medicine from the University of Kentucky and Ph.D. in Biochemistry and Molecular Endocrinology from the University of London Medical School in 1994. He is presently involved in laboratory diagnosis and research in Inherited Metabolic Diseases. He has developed a Department of Metabolic Genetics which Servers the Region.

Todd Taylor

Team Leader, Laboratory for MetaSystems Research Computational Biology
Research Core RIKEN Quantitative Biology Center, Japan

Todd Taylor is Team Leader of the Laboratory for MetaSystems Research at the RIKEN Quantitative Biology Center, in Yokohama, Japan. His team is focused on developing algorithms and high-throughput computational solutions for the understanding of metagenomic environments and single bacterial species, and is involved in the analysis of various human health and environment related microbial communities. He first started working at RIKEN in 1998 as a research scientist, and became team leader in 2002. He received his Ph.D. in Molecular and Medical Genetics from Oregon Health & Science University in Portland, Oregon, where the theme of his research was the "Genetic and Physical Mapping of the Gene for Hallervorden-Spatz Syndrome." As an active member of the International Human Genome Sequencing Consortium, Todd served as coordinator for

chromosomes 11, 18p, and 21. He also helped to coordinate the sequencing of chimpanzee chromosomes 22 and Y. Todd has been a member of HUGO since 1999 and has served on the council since 2006.

Herve Thoreau

Production Leader, Sequencing
Genome Institute of Singapore, Singapore

Herve began to work at Genome Institute of Singapore in 2001. He is the production Leader for Genome Technology and Biology group. The GT&B group is applying cutting edge innovative genomic technologies and next generation sequencing platform to study genome variation and transcription regulation in complex biological systems. Prior to joining Genome Institute of Singapore, Herve worked for 4 years in the French Biotechnology Company, GENSET S.A., as team leader of the Mapping Production group. Herve holds a B.Sc. in Industrial Bio-experimentation from E.S.T.B.A, Paris. Concurrently he is also pursuing graduate studies in Biological Engineering at the Université de Technologie de Compiègne (UTC), conferring the diplôme d'ingénieur.

Henry Huanming Yang

President & Professor
BGI - Shenzhen, China

Dr. Yang received his Ph.D. from University of Copenhagen, Denmark, in 1988, and his postdoc training in France and USA afterwards. He returned to China in 1994 and co-founded BGI (formerly Beijing Genomics Institute) in 1999. As the co-founders of BGI, he and his collaborators have made a significant contribution to the HGP and HapMap projects, as well as to sequencing and analysing genomes of rice, chicken, silkworm, giant panda, cucumber, and many microorganisms. BGI published the first Asian's genome, human pan-genome, human ancient genome, and human gut metagenoms by means of new-generation sequencing technoloty and innovative bioinformatic tools recently. BGI now has becomes one of the major genomics centers in the world. Dr. Yang has received many awards and honors, including Research Leader of the Year by *Scientific American* in 2002 and Award in Biology by the *Third World Academy of Sciences*（TWAS）in 2006. He was elected as a foreign member of EMBO in 2006, and an Academician of Chinese Academy of Sciences in 2007, and a fellow of TWAS in 2008.

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POSTER PRESENTATIONS

TRAVEL AWARDS

P1

A HEURISTIC APPROACH TO THE IDENTIFICATION OF DISEASE GENE REGION USING HAPLOTYPE ANALYSIS

Ahmed Adeel
Department of Computer Science, Quaid-i-Azam University, Islamabad, Pakistan; idealadeel@gmail.com

Identifying the location of disease gene within a human genome is a process of observing the associations of marker alleles in affected and controlled individuals. Haplotype provides useful study for linkage disequilibrium among alleles. Genome scanning using microsatellite markers give effective results in haplotype association studies. The efficacy of disease gene mapping not only depends upon the pattern mining algorithm but also on the choice of markers, chromosomes, threshold value and the strength of association measure used during pattern mining algorithm. It is also important to understand the features of domain in which the algorithm is being applied as the performance of the different algorithms may vary depending on these features. In this paper, we address the problem of gene mapping and translate this problem into disease gene identification problem. We propose a new algorithm that finds the location of a disease gene by mining the allele patterns based on heuristic search. A key assumption that we have followed for haplotype mapping is the non-random association of marker alleles and haplotypes to detect the disease gene. We have developed a novel approach to identify the set of associated marker alleles in the form of haplotype patterns using a heuristic search. We give the frequency score to each pattern and based on the score of each pattern we find the two most frequent markers near the disease susceptibility gene. For our experiments, we have selected three datasets which are generated by Toivonen et al. in 2001. These simulated datasets contains the characteristics of realistic isolated founder population that grow from 300 to about 100,000 individuals over a period of 500 years. Each dataset consists of case-control chromosomes, 101 microsatellite markers and has different disease gene location. Our experimental results are nearly similar to the results of existing algorithm called Haplotype Pattern Mining (HPM) proposed by Toivonen et al. in 2001. We apply a new method on simulation-generated datasets and find the reliable results about disease gene location. Table 1 shows the comparison between observed disease gene location using new algorithm and existing HPM algorithm. Dataset/% Mutation/Location (New algorithm)/Location (HPM algorithm), 1/7.5/M63 to M74/M63 to M72, 2/5/M54 to M70/M60 to M66, 3/5/M47 to M59/M47 to M56. Like HPM proposed by Toivonen at al. (2001) and LinkageTracker algorithm proposed by Lin et al. (2005), our new algorithm does not require any population ancestry information and detects a disease locus if the mutation is present even at below 10% in the DNA samples. In addition, a new algorithm is not bounded with the frequency threshold value in detecting the highly disease associated patterns. The performance of our new method is encouraging and is restricted to the simulation-generated datasets.

P2

DETECTION OF CHROMOSOMAL ALTERATIONS AND BRCA1 GENE POLYMORPHISM IN BREAST CANCER PATIENTS IN TAMIL NADU POPULATION, INDIA

Balachandar Vellingiri[1], Sasikala Keshavarao[1], Arun Meyyazhagan[1], Mohanadevi Subramanium[1], Velmurugan Palanivel[2], Sangeetha Raman[1], Sudha Sellappa[3], Darwadkar Shanawaz[4]
[1]Human Molecular Genetics Laboratory, Department of Zoology, School of Life Sciences, Bharathiar University, Coimbatore, India; [2]Division of Biotechnology, College of Environmental and Bioresource, South Korea; [3]Cytogenetic Laboratory, Department of Biotechnology, Karpagam University, India; [4]KLE Medical University, Bangalore, India; geneticbala@yahoo.co.in

Breast cancer is the most common cancer in women and accounts for between 18-25% of all female malignancies world-wide. In India, the incidence of breast cancer is increasing, with an estimated 82,000 new cases diagnosed annually. Family history is one of the strongest risk factors for developing breast cancer. Genetic predisposition for familial early onset of breast cancer accounts for approximately 5-10% of all breast cancers. The focal aim of the present investigation is to find out the major chromosomal alteration in breast cancer patients and analyze the BRCA1 gene mutation in breast cancer patients, as a molecular marker for diagnosing the disease in Tamil Nadu region. Moreover, follow-up study has been conducted in the year of 2007 to 2010. In the present study 39 breast cancer patients were selected on the basis of CA15.3 marker which is the most widely used serum biochemical tumor marker in breast. The work was carried out in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. After signing a consent form, blood samples (5 ml) was collected and establish the 72hrs cell cultures. In our study satellite formation, deletion and translocation were frequently observed in chromosome 1 and 17. 46, XX, del (13s+-); (46, XX, del (1p-); 46, XX, del (17q-); 46, XX, del (11q-); 46, XX, t (1p+;13q-) ; 46, XX, t(1q+;21q-) ; 46, XX, t(17q-)). The BRCA1 mutations were detected in 8 familial breast cancer patients, out of the 39 breast cancer patients analyzed. The BRCA1 mutation 185 del AG, which results in the generation of a stop codon at position 39 in exon 2 was detected. Identification of the predisposition of the breast cancer BRCA1 gene, speculate that the BRCA1 protein may be useful in the treatment of breast carcinoma as a decision making biomarker for aggressive treatment. In the near future, we can look forward to the identification of novel breast cancer predisposing genes due to rapid advancement of gene discovery technologies. The Identification and functional characterization of such genes will have a significant impact on breast cancer research and early detection.

P3

HUMAN GENOMIC VARIATION IN RELATION TO FUNCTIONALITY: AN ASSESSMENT BASED ON GENIC AND NON-GENIC SEGMENTS

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Over an evolutionary time scale, the structure of the human genome has been strongly influenced by natural selection. However, natural selection is expected to have had differential impacts on different segments of the genome. Hypothesis: Genomic regions with decreasing functionality will exhibit decreasing impacts of natural selection. To test this hypothesis, we have selected five genomic regions of decreasing functionality: (a) Atherosclerosis-associated: Selectin L (SELL); (b) Housekeeping: Glucose-6-phosphate dehydrogenase (G6PD) and Beta-Actin (ACTB); and, (c) two gene-desert regions (GDES1 and GDES2) on chromosomes 2 and 6. We carried out double-pass resequencing of these regions in 72 individuals chosen from 8 socio-culturally and geographically diverse ethnic groups of India to discover genomic variation. We then expanded our investigation of genomic variation by selecting ~60kb segment around three core regions - SELL, ACTB, GDES2, one chosen from each functional category, and genotyping an additional set of 360 individuals chosen from the same 8 populations. We analyzed our data separately and in combination with HapMap data, using a variety of statistical methods (such as, calculation of site-frequency spectra, tests of neutrality, HKA test, network analysis and long-range haplotype tests), to assess genomic variation and the impact of natural selection. Result: (1) Analyses of site-frequency spectra: Compared to expectations under neutral evolution, (a) SELL, exhibited significantly ($p<10-9$) greater intermediate frequency variants, (b) G6PD, showed large deviations; (c) ACTB, showed no significant ($p>0.05$) deviation, and (d) Gene deserts showed marginal deviations ($p=0.01$, for GDES1 and $p=0.03$ for GDES2). (2) Neutrality tests: Tajima D and Fu & Li D* and F* statistics were non-significant ($p>0.1$) for all genomic regions. (3) Median-joining haplotype networks: For (a) SELL, high-frequency modal haplotypes were separated by long branches; multiple star-like phylogenies radiating from larger nodes; (b) G6PD, presence of two predominant haplotypes with some low frequency haplotypes; (c) ACTB, only one predominant haplotype was present; (d) GDES1 and GDES2, high, medium and low frequency haplotypes were all present; these patterns are consistent with neutrality. (4) HKA test: No rejection of neutrality. (5) Low frequency variants were commonly found in gene deserts; genic regions commonly comprised polymorphic variants. (6) Presence of a neighboring gene strengthened the LD structure in the genomic region around the chosen genes. (7) LD structure between HapMap populations and Indian populations were highly concordant for genic regions, but not for gene deserts. (8) LRH test: exhibited significant diversity in long-range haplotype homozygosity structures across populations for all genomic regions. Genomic variation and haplotype structure around the SELL gene (associated with atherosclerosis) exhibited strong impact of natural selection, housekeeping genes - ACTB and G6PD - depicted variable signatures of natural selection, while the nature and extent of variation in and around the gene-desert regions conformed to neutral expectations. These findings are supportive of our hypothesis that impact of natural selection on different segments of the human genome has been variable, and proportional to the functional importance of a segment.

P4

ASSOCIATION OF CYTOTOXIC T LYPMHOCYTE ASSOCIATED ANTIGEN-4 (CTLA-4) 3' UTR CT60A/G AND EXON1 +49A/G SINGLE NUCLEOTIDE POLYMORPHISMS WITH VITILIGO SUSCEPTIBILITY

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Genes involved in common complex diseases such as the autoimmune disorders that affect approximately 5% of the population remain obscure. The gene encoding cytotoxic T lymphocyte associated antigen 4 (CTLA-4) has been suggested as a candidate gene for conferring susceptibility to autoimmunity. Cytotoxic T lymphocyte antigen 4 (CTLA-4) is a negative regulator of T-cell function, which has been suggested to be involved in a wide-range susceptibility to autoimmune diseases including vitiligo. Vitiligo is an acquired pigmentary disorder characterized by areas of depigmented skin resulting from loss of melanocytes; affecting 0.5-1% of the world population. The contribution of genetic factors in susceptibility to vitiligo is exemplified by familial clustering. About 20% of vitiligo patients have at least one first-degree relative affected. Several theories have been proposed to explain the mechanism of vitiligo pathogenesis however, autoimmune hypothesis is well accepted. The aim of present study was to explore exon1 +49AG (rs231775) and 3â€™ UTR CT60A/G (rs3087243) single nucleotide polymorphisms (SNPs) in CTLA-4 gene and to study their associations with vitiligo susceptibility. Interestingly, the G allele of CTLA-4 +49AG SNP was found to be involved in the altered intracellular transport of the CTLA-4 protein and its availability on the cell surface. In addition, the 3' UTR CT60A/G allelic variation was reported to be correlated with lower mRNA levels of the soluble alternative splice form of CTLA-4 (sCTLA-4), suggesting the crucial role of these SNPs in autoimmune diseases. Polymerase chain reaction-Restriction fragment length polymorphism (PCR-RFLP) technique was used for the analysis of these polymorphisms in 376 vitiligo patients and 540 unaffected age-matched controls of Gujarat population where prevalence of vitiligo is alarmingly high (i.e. 8.8%). The genotype and allele frequencies for CT60A/G SNP were significantly differed ($p=0.003$, $p<0.0001$ respectively) between patients and control population whereas frequencies of genotypes and alleles for +49AG SNP did not differ significantly ($p=0.332$, $p=0.997$ respectively) when compared with Chi-square test. Gene expression analysis of CTLA-4 is also being carried out in vitiligo patients and controls and will be analyzed in correlation to the respective genotypes. In conclusion, our recent results suggest that the well documented

CT60A/G polymorphism of CTLA-4 gene may be a genetic risk factor for vitiligo susceptibility in Gujarat population.

P5
POPULATION SUBSTRUCTURE: AN IMPACT ON THE GENES MAPPED TO KALA-AZAR PREDISPOSITION IN ONE ETHNIC GROUP FROM THE SUDAN

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Human genome polymorphism is expected to play a key role in defining the basis of phenotypic differences between individuals. Such variations in the human genome might have a major impact on disease predisposition and on drug responses as well. In this study we aimed to highlight new candidate genes for Kala-Azar predisposition more than those identified in the previous studies. We therefore screen the whole genome of 220 individuals from a highly susceptible Masalit tribe using 400 highly polymorphic microsatellite genetic markers. The members of this tribe live in two different villages: Al Rugab and Um Salala villages located in the heart of Kala-Azar endemic area in Sudan. The multipoint analysis performed for all individuals from the two villages provided evidence for linkage of Kala-Azar susceptibility to 5 regions on chromosome 1p22, 1q31.3, 5q34-35.3, 6q27 and 13q 31.1 ($0.0002<p< 0.05$). 35 additional markers were added and were genotyped in more samples from the two villages. Stratification of families by village revealed village-specific for linkage: in Um Salala at 1p22 and 5q34 (p=1.6x10-4, p=0.047 respectively), in El Rugab at 1q31.1, 5q35.3 and at 6q27 (p=0.007, p=0.002,p=8.95x10-5). Many genes were annotated on these loci of which: .On 1p22: BCL10 activates NF-kappaB in response to antigen-receptor stimulation and DDAH1 increases nitric oxide production. On 6q26-27: DLL1 Play role in T helper 1 induction These results indicate that susceptibility to Kala-Azar might be complex inheritance not only between populations in different geographical regions but also between individuals of the same genetic background and this indicates the vital role of the population substructure in the implication of the disease in different populations and there by demonstrate the importance of understanding population genetic substructure in studying genes that regulate complex diseases.

P6
OCT4-B1, A NEW SPLICED VARIANT OF OCT4, CAN GENERATE A TRUNCATED PROTEIN IN STEM AND TUMOR CELL LINES

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OCT4 is a master regulator of self-renewal and involved in regulating pluripotency in embryonic stem cells (ESCs). In addition to the previously described spliced variants of the gene (e.g. OCT4A and OCT4B), we have recently identified a novel variant of the gene, designated as OCT4-B1. The expression of OCT4-A is limited to ESCs and ECCs, but not expressed in other non-pluripotent cells. While OCT4-B is expressed at low levels, when detected, OCT4B1 is expressed highly in ESCs and ECCs and its expression decreases with the onset of differentiation. OCT4-B1is highly upregulated in various tumors and cell-lines, where it acts as an anti-apoptotic factor. Material and methods: We have designed specific siRNAs to suppress OCT4-B1 expression in stem and tumor cell lines. We have also constructed an HA-tagged OCT4B1, which generates an N-terminal tagged protein, detectable by HA antibody. The transfected cells then were lysed and the expression of HA-OCT4-B1 transcript and protein detected by means of real-time PCR and Western Blotting. Results: Our data revealed that interfering with the expression of OCT4-B1 causes profound changes in the morphology and cell cycle distribution of the cells. Furthermore, Western blotting revealed a protein product with a molecular marker corresponding to OCT4B variant and a truncated protein with a molecular size corresponding to OCT4-B1. Discussion: Our data demonstrated a functional role for OCT4-B1 in apoptosis and tumorogenesis. Our data also revealed that OCT4-B1 could act as a precursor to OCT4B protein and that it could also generate a truncated OCT4-B1 protein.

P7
PROMOTER HYPERMETHYLATION OF DAPK1: A STRONG INDEPENDENT PREDICTIVE FACTOR FOR DISEASE PROGRESSION IN CHRONIC MYELOID LEUKEMIA PATIENTS

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Methylation of CpG islands is a mechanism for the suppression of gene transcription in physiological and pathological settings, including neoplasia. The recently described CpG island methylator phenotype is an alternative tumorigenesis pathway characterized by methylation of multiple promoter regions of tumor suppressor genes harboring CpG islands. Recent studies have shown that CpG island methylator phenotype is very common in leukemiogenesis. The epigenetic changes of TSGs are now recognized as a mechanism contributing to the progression and development of chronic myeloid leukemia (CML). To clarify the role of DAPK1 and P16 in CML progression, we examined the methylation status of DAPK1 in 100 patients with CML using methylation-specific polymerase chain reaction. The study included 100 CML patients, 60 patients in advanced

stage and 40 in initial stage (CP-CML). From each and every patients 5ml peripheral blood sample was collected in 1.6% EDTA vial. Genomic DNA was isolated from peripheral blood samples and approximately 1 mg of DNA was sodium bisulfite-modified and subjected to MSP-PCR. The DNA concentration was determined by spectrophotometry and its integrity was checked by 1.5% gel electrophoresis. The aberrant methylation of the DAPK1 gene was found in 53% (32/60) in advanced stage CML patients and 27.50% (11/40) in initial stage CML whereas the aberrant methylation of p16 gene was found in 31% (19/60) in advanced stage CML patients and 22.50(09/40) in initial stage CML. No correlation was found between DAPK1 gene methylation and the age, hematologic parameters, the types and levels of bcr/abl transcripts of CML patients. However, correlation could be observed between the, loss of molecular and hematological responses, sex and the status of DAPK1 methylation in CML patients (R = 0.374, P = 0.008). Furthermore, there was a significant correlation between DAPK1 methylation and the stages of CML (R = 0.354, P = 0.013). The CML patients in accelerated phase (AP) and blast crisis (BC) had higher frequency of DAPK1 methylation than those in chronic phase (CP) (27% vs. 53%) P = 0.013). In most cases the status of DAPK1 methylation became positive on the transition from CP to AP and BC. These results suggested that DAPK1 promoter methylation might play a significant role in the progression of CML. Comparing the frequencies of p16 methylation between initial and advanced stage CML patients, the results obtained were not significant (37% vs 27%) P = 0.366). Our findings indicate that promoter hypermethylation of DAPK-1 is a marker of progression of CML and provides independent prognostic information on disease outcome.

P8

FAMILIAL HYPOMAGNESAEMIA WITH HYPERCALCIURIA, NEPHROCALCINOSIS (FHHNC) AND SEVERE OCULAR INVOLVEMENT IS CAUSED BY A MUTATION IN THE TIGHT-JUNCTION GENE CLAUDIN 19 (CLDN19) IN A CONSANGUINEOUS PAKISTANI FAMILY

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Familial hypomagnesaemia with hypercalciuria and nephrocalcinosis (FHHNC) is a rare renal tubular disorder complicated by progressive renal failure during childhood or adolescence. Recently, causative mutations in a newly identified member of the claudin multigene family (CLDN19) have been identified in FHHNC patients presented with severe ocular involvement. The objective of the study was to investigate the molecular genetic defect underlying FHHNC with severe ocular abnormalities in a Pakistani consanguineous family. Clinical and biochemical parameters of the proband were studied during the follow up period over five years. Genotyping of seven members of the family including one affected individual was performed by amplifying polymorphic microsatellite marker loci, tightly linked to CLDN16 and CLDN19 genes. To screen for mutations, all exons and splice junctions of the two genes were sequenced directly in an automated sequencer. PCR-RFLP assay and bioinformatics analysis were performed to verify the identified mutation. Genotyping revealed that the proband was homozygous for the marker loci tightly linked to CLDN19 gene. Sequence analysis in the proband revealed homozygosity for a novel missense mutation in exon 3 of the CLDN19 gene (389A>G) resulting in G130D amino acid substitution. Bioinformatics analysis supported the pathogenicity of the identified mutation. Family screening revealed nephrolithiasis in 3/6 (50%) heterozygous carriers of pathogenic mutation. This study supports the fundamental role of claudin19 for magnesium homeostasis, normal tubular structures in the kidney, and undisturbed organization and development of retina.

P9

MICROARRAY ANALYSES OF DIFFERENTIAL GENE EXPRESSION IN RNA INTERFERENCE-MEDIATED URG4 GENE SILENCED HEPG2 CELLS

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Upregulated gene 4 (URG4, GenBank GeneID: 55665), is a novel gene stimulated by HBxAg. Satiroglu-Tufan and her colleagues have discovered URG4 by PCR select cDNA subtraction, using HBxAg-positive and HBxAg -negative HepG2 cells. URG4 is located on chromosome 7 (7p13) and the full-length URG4 clone is 3.607 kb. It encodes a polypeptide of 922 amino acids with a molecular weight of 104 kDa. URG4 is strongly expressed in hepatitis B-infected liver and in HCC cells, where it costained with HBxAg, and weakly expressed in uninfected liver, suggesting that URG4 is an effector of HBxAg in vivo. Over-expression of URG4 in HepG2 and GES-1 cells promotes cell growth and survival in tissue culture and soft agar, and accelerates tumor development in nude mice, suggesting that URG4 may be associated with the onset of tumorigenesis. Over-expression of URG4 in osteosarcoma tissues is well correlated with tumor recurrence and metastasis, as well as with the proliferative activity of osteosarcoma cells. Patients with high expression of URG4 had shorter survival time, suggesting that URG4 may be a valuable prognostic marker in osteosarcoma patients. In the present study, differential gene expression analyses in RNA interference-mediated URG4 gene silenced HepG2 cells have been carried out by Affymetrix Human Genome U133 2.0 Plus chip- microarray platform. (This study has been supported by The Scientific and Technological Research Council of Turkey (TUBITAK), SBAG-104S259).

CANCER GENOMICS

P10

HER2/NEU CODON 655 POLYMORPHISM AS A POTENTIAL RISK FACTOR FOR DEVELOPMENT OF BREAST CANCER

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Human epidermal growth factor 2 (Her2) was proved to play a role in carcinogenesis and prognosis of malignant tumors including breast cancer. In the present study we aimed to investigate the frequency of Her2 Ile 655 Val genotypes and alleles in breast cancer and test the association with different clinicopathological data. Her2 gene polymorphism was analyzed by polymerase chain reaction and restriction fragment length polymorphism, using DNA extracted from venous blood samples withdrawn from 64 breast cancer patients and 86 normal control individuals. Immunohistochemical analysis was done on tissue samples taken from malignant cases during mastectomy to analyze the relation of Her2 polymorphism to protein expression and their effect on clinicopathological criteria as tumor size, histopathological type, histological grade, stage, lymph node involvement and distant metastasis. The frequency of homozygous (Val/Val) and heterozygous (Ile/Val) genotypes were significantly higher in patients (39.1%) than in control group (22%) and they were associated with increased risk of breast cancer incidence (OR= 2.26, 95% CI= 1.1-4.62, Ï‡ 2= 5.09, P= 0.02). moreover there was significant correlation between distant metastasis (OR= 4.7, 95% CI=1.1-15, Ï‡ 2= 4.7, p= 0.03) and Ile 655 Val polymorphism, Val allele was significantly higher in duct carcinoma as compared to other histopathological types (P =0.023), but no significant correlation with other criteria or protein expression. Her2 Ile 655Val polymorphism is a possible risk factor for incidence and metastasis of malignant tumors of breast.

P11

SINGLE NUCLEOTIDE POLYMORPHISMS OF HMLH1 655 A>G, HMLH1 1151 T>A AND P53 CODON 72 IN HEALTHY INDIVIDUALS AND SPORADIC COLORECTAL CANCER PATIENTS: A MALAYSIAN CASE-CONTROL STUDY

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Colorectal cancer (CRC) is unfortunately an all too common lethal disease and is a major health concern that affects men and women equally and showing increase in incidence rates recently. Sporadic colorectal cancer (CRC) is a complex disease resulting from complex interaction between environment and genetic factors. Genetic polymorphisms in genes responsible for the metabolism of environmental carcinogens and those involved in DNA damage repair and cell cycle control may be associated with CRC risk. Genetic association studies on cancer risk have focused on identifying effects of single nucleotide polymorphism (SNPs) in candidate genes among which DNA repair genes are increasingly studied because of their critical role in maintaining genome integrity. Even though polymorphisms in several DNA repair genes have been identified, the risk of these SNPs in development of CRC has not yet been clarified. Hence a case control study was designed to address this issue. Aim: In this case control study, we have investigated whether any of the two polymorphisms (655 A>G and 1151 T>A) in the MLH1 gene and codon 72 polymorphism of P53 gene contribute to colorectal cancer susceptibility, by evaluating the association between each SNP and colorectal cancer risk in Malaysian patients. We conducted this case control study including 260 Malaysian individuals comprising of 130 sporadic CRC patients (76 males and 54 females, mean age 58 years) as well as control group consisting of 130 normal individuals (71 males and 59 females, mean age 49 years). Peripheral blood samples of the study subjects were collected, DNA extracted and genotyping of these polymorphisms were performed using polymerase chain reaction- restriction fragment length polymorphism (PCR-RFLP) technique. Genotypes were categorized into homozygous wildtype, heterozygous and homozygous variant. P53 codon 72 polymorphism showed homozygous wildtype, heterozygous and homozygous variant genotypes among cases and controls but with statistically insignificant difference (p>0.05) in the genotype frequencies among cases and controls. With regard to hMLH1 polymorphisms, the polymorphisms 655 A>G and 1151 T>A, were distributed as homozygous wild type and heterozygous genotypes only among cases and controls, indicating the rare frequency of homozygous variant genotypes in Malaysian population. On evaluating the risk association, the P53 codon 72 homozygous variant, heterozygous genotypes 655 A>G and 1151 T>A of hMLH1 showed higher susceptibility risk (with OR = 1.434, 1.109 and 2.560 respectively) but was not statistically significant. Our results showing lack of significant association with CRC susceptibility risk could be attributed to small samples size, interaction of other polymorphic DNA repair genes and rarity of homozygous variant allele in this population.

P12

ASSOCIATION OF THE C677T POLYMORPHISM IN THE MTHFR GENE WITH RISK OF ORAL SQUAMOUS CELL CARCINOMA

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The C677T mutation in the methylenetetrahydrofolate reductase (MTHFR) gene is associated with reduced enzyme activity, and a significant increase in serum Homocysteine (Hcy) concentrations. MTHFR C677T polymorphism was likely to play an important role in the susceptibility to OSCC. In this case-control study, we examined the role of one of the most frequently studied MTHFR C677T polymorphism at codon 222 in the etiology of oral squamous cell carcinoma (OSCC) and their impact on homocysteine in the south Indian population. We genotyped 150 OSCC patients and 150 controls, using a PCR-RFLP method. The serum total Homocysteine levels were quantitatively detected by using commercial Enzyme immunoassay (EIA) kits from Axis®-shied Diagnostics Ltd, UK. Genotype frequencies of MTHFR CC, CT and TT were 82.7, 16 and 1.3% in the oral cancer patients and 94.0, 5.3 and 0.7% in the controls, respectively. The frequency of CT + TT allele in MTHFR was significantly higher in OSCC patients (17.3%) than in healthy controls (6%), suggesting that individual alleles were associated (p-value 0.003) with OSCC. The mean serum tHcy levels (Mmol/L) <15.0 were slight higher in CT genotype patients (11.51±1.37) than controls (10.6±2.07), where as the mean serum tHcy levels (Mmol/L) >15.0 was higher in cases in all three CC (26.81±7.51), CT (29.26±7.67) and TT (48.85±28.07) genotypes when compared CC (17.85±2.18), CT (17±1.0) and TT (0) with controls. The results of the present study indicate that the polymorphisms in the MTHFR C677T genotype that are reported to modulate homocysteine levels may contribute to oral squamous cell carcinoma susceptibility in south Indian population.

P13

RNA-SEQ REVEALS NOVEL MUTATION SELECTION AND GENE EXPRESSION CHANGES IN OVARIAN CANCER METASTASIS

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The mutation landscape of cancer is known to evolve as different metastases develop. As the cancer spreads, certain mutations are selected for and gene expression changes are needed to adapt to the new environment. We have begun to document the changes that occur as cancer metastasizes using Next-Generation Sequencing of mRNA from ovarian primary tumor and its peritoneal and lymph node metastases. We used data generated using deep-sequencing to evaluate the clonal relationships among primary and metastatic cancers to uncover the natural history of ovarian cancer progression. Using this approach, we have documented numerous Single Nucleotide Polymorphisms (SNP) changes including changes in SNP frequency as the cancer spreads. In combination with gene expression changes these will serve as a powerful tool to begin understanding the continual evolution of cancer in response to new environments.

P14

DETECTION OF SOMATIC COPY NEUTRAL-LOSS OF HETEROZYGOSITY, IN ADDITION TO SOMATIC COPY NUMBER ALTERATIONS IN SPORADIC COLORECTAL CANCER USING GENOME-WIDE SNP MICROARRAY - A MALAYSIAN REPORT

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Colorectal cancer (CRC), the incidence of which is increasing in developed as well as developing countries, progresses through a series of well defined steps, including early and late adenomas, invasive cancer and eventually metastatic lesions. Despite significant amount of data generated regarding genomic events and associated genetic instability that accompany various stages of tumorigenic process, still there remain significant gaps. A better understanding of the molecular events underlying various stages of colorectal carcinogenesis will help in detection and prevention of premalignant lesions. Recently, high throughput genomic technologies have become increasingly useful in defining the genomic events that occur during various stages of colorectal carcinogenesis. We used one such tool - genome-wide SNP microarray, to investigate the whole genomic alterations in tumorous tissues of Malaysian sporadic CRC patients, using Affymetrix SNP microarray. Eighteen histopathologically confirmed sporadic CRC cases (17 moderately differentiated tumor and 1 mucinous tumor tissues) were included in this analysis. DNA was extracted from matched tumor and normal tissues and 250ng DNA from each sample was assayed on the Affymetrix GeneChip Human Mapping 250K NspI arrays according to the manufacturer's protocol. The arrays were washed and stained using Fluidics Station 450 and scanned with GeneChip Scanner 3000. Raw data generated with GCOS were imported into GTC 3.0 and CNAG 3.0 software for paired analysis of copy number and loss of heterozygosity. Copy number (CN) alterations involving both gains and losses were the most frequent genomic alterations observed. CN gains involved chromosome 1q, 7p, 8q, 13q, 20p, and 20q whereas CN-losses involved chromosome 4, 8p, 14q, 15q, 17p, 18p, 18q, and 21. Copy number gain on chromosome 13q and chromosome 20 appeared to be the common event among the tumor samples inconsiderate of tumor stage. Frequency of chromosome 20q gain was found to be higher than 20p, affecting 60% of the tumor samples. In fact, several oncogenes involved in cell migration and mitotic cell division had been identified on 20q. Similarly, the two arms of chromosome 18 showed differences in frequency of copy number loss, wherein CN loss in chromosome 18q was observed to be higher than in the 18p. Another interesting observation was the detection of copy neutral loss of heterozygosity (CN-LOH) or uniparental disomy (UPD) especially involving chromosome 6, 9p, 12,

13q, 17p, 20p, and 21. CN-LOH which is the result of copy loss LOH followed by the duplication of remaining chromosomal segment, has now been recognized as a nonrandom contributing factor to the development of cancer, that went previously unrecognized because UPD karyotype and genotype appears normal when examined by conventional cytogenetic analysis, FISH or aCGH. The fact that CN-LOH also can be detected using SNP arrays makes SNP array more advantageous compared to aCGH. With SNP array, it is possible that many new chromosomal regions which harbor potential oncogenes and tumor suppressor genes and which hitherto has gone unnoticed, can be identified. This will give additional information on the mechanisms of genomic instability and a better understanding of colorectal carcinogenesis.

P15

EVALUATION OF HEALTH EFFECTS AND GENETIC DAMAGE IN ARSENIC EXPOSED POPULATION: A PROSPECTIVE STUDY FROM WEST BENGAL, INDIA

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About 26 million people are exposed to arsenic through drinking water in West Bengal, India. Arsenic contamination in drinking water is a major concern due to its association with multiple cancer risk. Detailed epidemiological survey and genetic study were conducted in arsenic exposed population from three different districts in West Bengal, i.e., North 24 parganas, Nadia and Murshidabad. Now, we have focused for a perspective study to look at the status of health effects as well as cytogenetic damage level, after a gap of four years. It has been observed that, mean arsenic concentration in urine was significantly reduced in this four years gap, which indicates that they are using relatively less arsenic contaminated water. Corroborative with this data, we have found significant overall improvement in arsenic-induced skin lesions, and also reduced cytogenetic damage studied in lymphocyte. However, respiratory troubles, peripheral neuropathy and eye problems were enhanced in the individuals when compared with earlier results. Therefore, it can be stated that, although arsenic content was reduced and skin lesions were improved, some of the internal health effects once occurred, cannot be reversed.

P16

DIFFERENTIAL EXPRESSION OF MICRORNAS IN SERUM BEFORE AND AFTER SURGICAL RESECTION OF COLORECTAL PRIMARY TUMOR

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MicroRNA (miRNA) opens up a new field for molecular diagnosis of cancer. Recent findings that human serum and plasma contains stably expressed microRNAs (miRNA) have revealed a great potential of circulating miRNA signature as disease fingerprints to predict survival. Nevertheless, the role of circulating miRNAs in plasma/serum of cancer patients is not clear. The aim of this study was to investigate whether serum miRNAs expression profile change after surgical resection of colorectal primary tumor. And investigate if these changes in serum miRNA profile can be used as prognostic biomarkers. Using quantitative real-time polymerase chain reaction (RT-PCR), we measured the expression levels of 6 human miRNAs (miR- 21, 18a, -92a, -29a, -16, and -103,) in paired pre and post-operative serum samples from 40 patients with complete surgical resection of colorectal neoplasia. Preliminary analysis in 20 patients showed that all miRNAs were stable and detectable in pre and post-surgery serum samples. Among all the patients, in terms of normalized Ct values, no significant differences were observed when compared both groups (post-operative versus pre-operative). Nevertheless the individual analysis of paired pre and post-operatives serum samples indicate that serum miRNAs levels changed after surgical resection of colorectal neoplasia. The increased or decreased expression of these miRNAs didn't correlate with tumor stage or clinical prognosis; however seems to be associated with the proximal or distal localization of the tumor in the colon. The current analysis in a set of 20 more patients and healthy individuals would allow us to verify these preliminary results. Our findings indicate that serum miRNA levels changes after complete surgical resection. Elucidate the biological meaning of this differential expression profiles could help to a more comprehensive understanding of the potential diagnostic or prognostic use of these markers.

P17

MOLECULAR CHARACTERIZATION OF CO-LORECTAL CARCINOMA OF SAUDI ARABIAN PATIENTS AND IDENTIFICATION OF NOVEL PREDICTORS OF DISEASE OUTCOME

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The traditional staging system is currently inadequate for identifying those patients with colorectal carcinoma (CRC) who carry a high risk for poor outcome. Recent studies suggest that methylation profiling and aberrations in cell cycle checkpoint controllers are a common feature in human malignancies and predict prognosis independent of stage. This study correlated the methylator phenotype of CIMP (5 panel genes) + extra 6 genes and two cell cycle regulators (p27 and p21) protein expression with molecular, clinical and pathological variables in CRC patients to assess their role as prognostic biomarkers. A series of 65 CRC patients were analyzed for CIMP by MethyLight, a quantitative, TaqMan-

based, real-time PCR assay for measuring DNA methylation profiles and p27 and p21 expression in their tumors using immunohistochemistry. RESULTS: Forty-six percent of tumors showed positive nuclear p27 expression, whereas 72% of cases were completely p21-negative. There were no significant correlations between p27 and p21 expression and gender, age, lymph node involvement, stage and grade. However, positive methylator phenotype (CIMP +ve) significantly correlates with the tumor location ($p<0.01$) and p27 (but not p21) expression revealed highly significant correlation with tumor location ($p<0.01$), depth of invasion ($p<0.03$), and lympho-vascular invasion ($p<0.02$). Tumors with high p27 expression showed a higher recurrence rate than tumors with no expression ($p<0.03$). In Kaplan-Meier survival analysis, there was a significant ($p=0.046$) difference in disease free survival (DFS) between p27-positive and p27-negative tumors in favor of the latter. p21 did not show any predictive value of DFS ($p<0.7$). Neither p27 nor p21 did predict DSS in Kaplan-Meier analysis, but DSS time was much shorter for p27-positive tumors. In multivariate (Cox) model, p27 lost its value as independent predictor of DFS, and none of the covariates were independent predictors of DSS. Methylation profile of CIMP panel genes and p27 expression seems to be more powerful than p21 expression in providing useful prognostic information in CRC, particularly in predicting the patients at high risk for recurrent disease. Larger cohort and longer follow-up are needed to fully elucidate the value of p27 (and p21) as independent predictors of disease outcome.

P18

DETECTION OF TELOMERASE ACTIVITY IN ORAL SQUAMOUS CELL CARCINOMA PATIENTS USING PCR ELISA METHOD

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Telomerase is an enzyme that catalyzes the addition of TTAGGG repeats to the end of chromosomes, using its intrinsic RNA component as template. It may be necessary for continuous cell proliferation. Its activity was shown to be expressed in most permanent cell lines and tumors. This enzyme that stabilizes telomere length is reactivated in most of the cancer types. In this study the oral rinse was used because it is a non-invasive method of collecting sample, in addition the previous study showed that telomerase activity was easily detected by body fluid such as urine. Oral cancer is a subtype of head and neck cancer. There are several types of oral cancers, but around 90% are oral squamous cell carcinoma. The aim of this study was to investigate the feasibility detection of telomerase activity level in oral rinse from oral squamous cell carcinoma patients by using a non-radioactive telomerase PCR ELISA method. Forty oral rinse samples were collected from 20 pre and oral squamous cell carcinoma patients and 20 samples were normal subjects. All the patients and normal subjects vigorously swished of normal saline in their mouth and spitted into a falcon tube. Oral rinse was centrifuged and pelleted cell was washed with TE (tris EDTA) buffer. Protein extraction was performed by using protein isolation kit (Roche). Extracted protein was shocked freeze in aliquots nitrogen and stored in -80ºC if not perform Telomeric Amplification Protocol (TRAP) reaction immediately. Quality and purity of extracted protein was analyzed by NanoDrop Spectrophotometer. A ratio of A260/A280 was calculated for protein purity. The extracted proteins with the purity in range of 1.3 to 1.6 OD were selected for TRAP PCR assay. The protein was amplified with P1-TS and P2 primer. The Telomerase activity level was confirmed by nonradioactive photometric enzyme immunoassay, ELISA using microplate reader and the absorbance value at wavelength 450 nm were measured for each sample. The 690 nm wavelength was used as reference. Test absorbance values were reported as the A450 nm reading blank against with reference wavelength of A690 nm. Finally, statistical analysis was done using T-test version SPSS 17.0. It was detected positively telomerase activity in 80.0% (16/20) of pre cancer and oral cancer patients with oral squamous cell carcinoma, while it was positive telomerase activity in 5.00% (1/20) of normal subjects, the statistical difference was significant with $P=0.001$. The study showed that PCR ELISA method provides a highly sensitive nonradioactive photometric enzyme immunoassay detection technique of telomerase activity .Further this study indicates that the evaluation of telomerase activity in oral rinse specimens may provide useful information in the diagnosis of oral squamous cell carcinoma.

P19

HUMAN BREAST CANCER: MASS SPECTROMETRIC INVESTIGATION OF COMPLEX GENOMIC DISORDER

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Complex genetic diseases like Breast Cancer (BC) are one of the most challenging tasks for present age scientists in order to uncover the disease etiology and provide ultimate therapy. Conventional genomic techniques have proved insufficient to deal with the multi-genomic complex diseases such as cancer. In order to understand tumor biology a trans-disciplinary approach is needed to study its genetics, metabolomics, proteomics, cell-cell interactions, tissue morphology, angiogenesis and metastasis. A multimodal analysis provides a wealth of information about cancer proliferation and growth. It holds a great potential to investigate many aspects of carcinogenesis at a time. In a joint project of AMOLF (The Netherlands) and JHU (USA), we combined the advantages of

in vivo and ex vivo imaging techniques and mass spectrometric analysis of genomic expression of human breast cancer cell lines. Our research focus is to find the uncover mechanisms of novel hypoxia-driven signaling pathways which play a major role in tumor angiogenesis, metastasis, radio- and drug-resistance. Breast tumor xenograft models were genetically engineered to express a red fluorescent protein (tdTomato) under hypoxic conditions which allows precise study of tumor microenvironments. With MS analysis we were able to quantify 6000 genes/proteins and hundreds of which were differentially expressed under hypoxic conditions. In addition to MS analysis, various in vivo and ex vivo imaging techniques like MRSI, Xenogen, and MSI were used to localize various biomolecules such as small metabolites, lipids and proteins, directly from the tissue sections. All these data combined together with mRNA expression analysis will expand our understanding of molecular processes occurring in breast tumors and bring us one step closer to successful treatment of this complex disease. MSI has a great potential to become one of the most powerful tools for future breast tumor diagnosis and selection of patient tailored therapy.

P20

THE DETECTION OF 6174DEL(T) MUTATION IN BRCA2 GENE BY MUTAGENICALLY SEPARATED PCR AMONG LIBYAN PATIENTS WITH BREAST CANCER

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Breast cancer is the most common cancer in women, 1 in 10 women worldwide is affected by breast cancer during their lifetime. In 2007, it was the most common cancer in female (16 %) and constituted 35.5 % of all female cancer patients in Western Libya. In 5 to 10% of breast cancer cases, the disease results from a hereditary predisposition, which can be to a large extent, be attributed to mutations in either of the two tumor suppressor genes, BRCA1 and BRCA2. BRCA2 6174del T mutation constitute the most frequent mutant alleles predisposing to hereditary breast cancer in the Ashkenazi Jewish population, with reported carrier frequencies of 1.52%. Here, we investigated the presence of the 6174delT mutation of the BRCA2 gene in Libyan breast cancer women by studying Eighty- five Libyan women affected with breast cancer (23 samples collected from Tripoli Central Hospital and 62 from African Oncology Institute 'Sabratha') in addition to 5 patient's relatives (Healthy individuals). We obtained clinical information, family history and peripheral blood for DNA extraction and analyzed using mutagenic polymerase chain reaction (PCR) for detection of 6174delT mutation in BRCA2 gene. Our results shows that The 6174delT of the BRCA2 gene was not detected either in the (85) patients with breast cancer (18 with familial breast cancer and 67 with sporadic breast cancer) nor in 5 healthy individuals. In conclusion, our present study showed that the 6174delT of the BRCA2 gene is not detectable using mutagenic PCR in the Libyan Breast cancer patients and can be considered exceedingly rare.

P21

C-MYC ONCOGEN OVEREXPRESSION IN EGYPTIAN PATIENTS WITH HEPATOCELLULAR CARCINOMA: ASSOCIATION WITH VIRAL AND/OR SCHISTOSOMA MANSONI INFECTION

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C-Myc protein is a transcription factor that activates expression of a great number of genes through binding on consensus sequences. When c-Myc is mutated, or overexpressed, the protein doesn't bind correctly, this leads to the unregulated expression of many genes some of which are involved in cell proliferation and results in the formation of cancer. The rationale of the present study was to investigate the c-Myc mRNA expression in patients with HCC, and to analyze the relationship between c-Myc mRNA overexpression with the different clinical, pathological and histopathological characteristics of HCC patients with viral and/or Schistosoma mansoni infection. The samples were obtained from 65 patients with HCC (45 males and 20 females). The clinical/pathological data of the patients were determined, including age, sex, viral infections, Schistosoma mansoni infection, biochemical liver function test and Alpha-Fetoprotein levels. Also, the liver tissue samples were subjected for histopathological characterization. The expression of c-Myc mRNA overexpression was determined in blood samples of HCC patients using real time RT-PCR technique. The results revealed that c-Myc mRNA expression was significantly higher in HCC patients previously infected with HCV and/or HBV than non infected patients ($p < 0.05$), The infection with S. mansoni, AFP levels and tumor size were not correlated with the expression c-Myc mRNA in HCC patients ($P > 0.05$). The expression of c-Myc mRNA was significantly higher in tumor grade especially in grades IV and IV ($p < 0.05$). In conclusion, HCV and HBV viruses might play an important role in transactivation of c-Myc mRNA oncogene expression in Hepatocarcinogenesis. c-Myc oncogen was responsible for poor differentiation and advancement of HCC.

P22

THE ROLE OF GENETIC POLYMORPHISM IN ALCOHOL METABOLIZIMNG ENZYMES IN THE SUSCEPTIBILITY TO OESOPHAGEAL CANCER: A STUDY AMONG SUDANESE SUBJECTS

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There are many risk factors associated with the development of esophageal cancer and including tobacco smoking and alcohol consumption. The genes that encode enzymes involved in alcohol metabolism, alcohol dehydrogenases (ADH) and aldehyde dehydrogenases (ALDH2) are polymorphic. In some populations, the high-activity isoforms of ADH (ADH2*2 and ADH3*1) and the low-activity form of ALDH2 (ALDH2*2) have been shown to be associated with alcohol-related carcinogenesis. In this study, the contribution of this polymorphism to esophageal cancer risk has been investigated in 134 Sudanese patients with esophageal cancer and 233 unrelated healthy controls using polymerase chain reaction/restriction fragment length polymorphism analysis (PCR/RFLP). Results There were no significant differences in the frequency distribution of ADH2*2, ADH2*3, ADH3*2 and ALDH2*2 alleles between esophageal cancer patients and healthy controls. The homozygous ALDH2*2/*2 genotype was not observed in any of the subjects in this study. Among the controls, the polymorphic alleles in the alcohol metabolizing genes, ADH2*2, ADH2*3, ADH3*2 and ALDH2*2 occurred at frequencies of 6%, 6%, 25% and 0%. In the Sudanese population, the known variants of alcohol metabolizing genes are not associated with increased risk of esophageal cancer.

P23

GENETIC PROGNOSTIC FACTORS STUDY OF 36 NEUROBLASTOMAS USING SNP MICROARRAY AND FISH ANALYSIS

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Neuroblastoma (NB) accounts for 8% of all childhood cancers and is characterized by its clinical heterogeneity. At the molecular level NB is reflected by copy number variation (gain or loss). Several recurrent molecular markers are used to evaluate the NB prognostic as MYCN amplification, 1p deletion, 11q gain. Here we present our comparative studies of 36 NB pediatric tumor samples challenging obstacles as disease heterogeneity and samples quantity and/or quality. We used Affymetrix Genome-Wide Human SNP (Single Nucleotide Polymorphism) Array 6.0 platform containing 945,826 non-polymorphic probes and 906,000 polymorphic probes for whole-genome scanning. We also established a novel fluorescence in situ hybridization (FISH) panel targeting the prognostic molecular markers for NB. Interphase FISH and SNP arrays results were compared and correlated with the prognosis. There was a strong concordance between FISH panel and SNP arrays. The SNP arrays also allowed the refinement of the chromosomal abnormalities breakpoints and the detection of LOH without copy number variation. Furthermore preliminary SNP arrays results indicate correlation between 14q abnormalities and clinical factors such as tumor grading and evolution. Analysis of 14q abnormalities revealed three genes of interest, MAX, BCL11B and GPHN, which should be analyzed on larger samples.

P24

MULTIPLE GENETIC LOCI MODULATE LUNG ADENOCARCINOMA CLINICAL STAGING

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The main prognostic factor of lung cancer patients' outcome is clinical stage, a parameter of tumor aggressiveness. Our study was conducted to test whether germ-line variations modulate individual differences in clinical stage. We conducted a case-only genome-wide association study (GWAS) using a 600-K single-nucleotide polymorphism (SNP) array in a first series of 600 lung adenocarcinoma (ADCA) patients and in a replication series of 317 lung ADCA patients. GWAS identified 54 putatively associated SNPs, three of which were confirmed in the replication series. Joint analysis of the two series pointed to 22 statistically associated (P <0.01) genetic variants that together explained ~20% of the phenotypic variation in clinical staging (P <2 x 10-16) and showed a statistically significant difference in overall survival (P = 8.0 x 10-8). The strongest statistical association was observed at rs10278557 (P = 1.1 x 10-5), located in the mesenchyme homeobox 2 (MEOX2) gene. These data point to the role of germ-line variations involving multiple loci in modulating clinical stage and, therefore, prognosis in lung ADCA patients.

P25

AN UNUSUAL MOLECULAR PRESENTATION OF ALVEOLAR RHABDOMYOSARCOMA

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Rhabdomyosarcoma (RMS) is the most common type of pediatric sarcoma (23%) classified in two subtypes: embryonal (ERMS) and alveolar (ARMS). At least 70% of the more aggressive subtype, ARMS are characterized by chromosomal translocations t(2;13)(q35;q14) and t(1;13)(p36;q14) and the associated PAX3-FOXO1 and PAX7-FOXO1 fusion genes respectively. The remaining 30% of ARMS failed to exhibit any PAXs-FOXO1 fusions that could be revealed by RT-PCR at the transcript level and/or by molecular cytogenetics at the genomic level. We investigate an atypical ARMS case by comparative genomic hybridization (CGH) array and identified a novel rearrangement involving FOXO1 gene at the chromosomal band 13q14.11. By RT-PCR we did not detect ARMS characteristic fusions PAX3-FOXO1 or PAX7-

FOXO1. Interphasic fluorescence in situ hybridization (iFISH) with break apart and fusion probes confirmed the absence of both fusions but showed multiple copies of the centromeric portion of a rearranged FOXO1 gene suggesting an amplification of a putative fusion gene in the form of double minutes chromosomes or episomes. By CGH arrays we detect the amplification of PAX7 on chromosomal band 1p36.2, the centomeric portion of FOXO1 at 13q14 and miR-17âˆ¼92 microRNA cluster at 13q31.3. Our results suggest a complex rearrangement leading to a negative molecular and iFISH result with fusion probes. This investigation clearly demonstrates the utility of array CGH in detecting ARMS associated amplicons and refining their boundaries in the diagnosis of RMS particularly when FISH or/and molecular techniques are uninformative or negative.

P26
GENETIC MARKERS IN NEUROBLASTIC TUMORS: CISH-MLPA COMPARATIVE STUDY AND GENOTYPE-PHENOTYPE CORRELATION

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Neuroblastic tumors are the most common extra-cranial solid neoplasms in childhood. They became an oncogenetic model due to the wealth of genetic markers. In fact Different duplications and loss of heterozygosity have been reported. These genetic markers allowed patients classification, prediction of their clinical course, pre-treatment risk stratification, and new strategies for risk-based therapies. In this study we focused on the analysis of a large panel of genetic markers in 30 neuroblastoma tumors using both chromogenic in situ hybridization (CISH) and multiplex ligation probe amplification (MLPA). MLPA, multigenomic technique, presents an overview of genomic regions while CISH gives only MYCN amplification rate. Our results showed that MLPA results considering MYCN amplification are validated by CISH analysis. Knowing that neuroblastoma therapeutic strategies are not only based on MYCN amplification, CISH is not sufficient for treatment decision. Combined to CISH, MLPA analysis seems more efficient. MLPA appears very promising for neuroblastome routine diagnosis and has been adopted in our laboratory.

P27
COMPREHENSIVE ANALYSIS OF PAIRED CANCER-NORMAL TISSUE FROM DIGITAL TRANSCRIPTOME DATA

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There are several analysis methods available for massively-parallel short read transcriptome sequencing, however, only a very limited number of tools for a simultaneous analysis of expression level, splice variants, fusion-transcripts, and somatic mutations from whole transcriptome data, especially for the comparison of paired tumor-normal tissues. We developed an integrated platform to perform all these analyses in one go from paired-end mRNA-sequencing data. We applied this approach to several gastric and lung cancer tissues rich in stromal components. Using about 10 to 20 M paired-end mRNA reads from cancer and normal tissue, respectively, we evaluated base mismatches, alignments to different transcripts for each sequence end, and variant specific alignments. Integrating comparative data from paired cancer/normal tissues and quantitative assessment, it was possible to rank the observed variants in order of read number and/or statistical significance. Independent targeted validation, using Mass Spectrometry and RACE sequencing, confirmed the presence of somatic mutations, alternative splicing, and novel fusion transcripts in these cancer tissues. Mass Spec-based analysis of the quantitative representation of particular mutations within tissue genomic DNA revealed that the actual tumor content in various samples was as small as 10-20%. These data show the applicability of this discovery approach in heterogeneous tissue samples, which are very common in actual clinical settings.

P28
A ROLE FOR JMJD6 IN BREAST CANCER

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The pathogenesis of breast cancer involves a multitude of genetic alterations affecting the regulation of cell growth, survival, invasion and metastasis. To discover such novel oncogenes, we analyzed comprehensive gene expression profiles of breast tumors from several breast cancer patient cohorts for correlations between gene expression and distant metastasis-free survival. Jumonji Domain Containing 6 Protein (JMJD6), a histone arginine demethylase was one of the genes associated with poor survival in all cohorts. Immunohistochemical analysis of JMJD6 in tissue microarrays suggested that its high expression significantly correlated with grade and estrogen receptor negativity. In addition, its over-expression in multiple breast cancer cell lines led to increased proliferation, while in contrast, siRNA-mediated knock-down suppressed cell division. Microarray analysis of gene expression changes induced by siRNA-mediated knock-down of JMJD6 suggested that JMJD6 led to increased expression of cell cycle genes including CDC6, CHEK1, and suppression of cell cycle inhibitors like PTEN and TGF- β. We confirmed that siRNA-mediated knock-down of JMJD6 increased TGF-beta 2 secretion whereas JMJD6 over-expression reduced it. Since TGF- β have been implicated in cell cycle arrest in many epithelial cells, we propose that JMJD6 may influence cell growth primarily via this pathway. Further studies to understand the molecular relationship between JMJD6 and TGF- β regulation are underway. These results suggest that the

extrapolation of gene-survival associations in primary tumors to phenotypic analysis in vitro holds promise as a platform for understanding of new mechanisms in tumorigenesis, as well as discover new therapeutic targets.

P29

FAS-670 A/G POLYMORPHISM: A MARKER FOR THE INCREASED RISK OF BREAST CARCINOMA AMONG TUNISIANS

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FAS-670 A/G single nucleotide polymorphism has been demonstrated to affect the expression of FAS gene by altering the transcriptional activity of FAS gene promoter. Downregulation of FAS with resultant resistance to death signals has been found in many cancers. We carried out a population-based case-control study to investigate the biological significance of this polymorphism in breast carcinoma. FAS-670 A/G polymorphism was examined in a Tunisian population of 438 patient with breast cancer and 332 control subjects using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technique. Homozygous FAS-670 GG genotype and FAS-670 G allele showed significant associations with increasing risk of breast carcinoma (OR = 1.89, P = 0.002; OR = 1.38, P = 0.002 respectively). In addition, FAS-670 AG genotype showed an increasing incidence of distant metastasis, but this finding did not reach statistical significance (OR = 1.68, P = 0.06). Regarding prognostic indicators, significant associations were found between homozygous FAS-670 GG genotype, FAS-670 G allele and estrogen receptor status (OR = 2.16, P = 0.04; OR = 1.49; P = 0.03). In conclusion, our data suggest that the FAS-670 A/G polymorphism may be a marker for the increased risk of breast carcinoma among Tunisians.

P30

THE EMBRYONIC STEM CELL-SPECIFIC MICRORNA, MIR-302, IS EXPRESSED IN A RARE SUBPOPULATION OF GLIOMA CELL LINES

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MiR-302s is a cluster of polycistronic microRNAs that are primarily expressed in embryonic stem (ES) cells. MiR-302s promoter is functional during embryonic development, but it is turned off later in the development. Indeed, it has been revealed that ES-associated transcription factors, namely Nanog, Oct3/4, Sox2, and Rex1 have putative binding sites on the miR-302s core promoter region. Additionally, it has been observed that the pluripotency-associated genes are up-regulated ectopically in tumor samples and cell lines. Whether the upstream regulators of miR-302s gene are transcribed and translated in cancer cells, miR-302 promoter should become activated in the cells as well. Here, we tried to expand our knowledge about the expression pattern and functionality of miR302s by evaluating its expression pattern in a series of tumor cell lines by means of real-time PCR. Furthermore, to assess the functionality of miR-302 in cancer and stem cell lines, we cloned its promoter core region upstream of the EGFP and luciferase encoding genes. As a result, we were able to evaluate the functionality of the promoter either in live cells by EGFP reporter or with a higher sensitivity using luciferase assay. Taken together, our data opens up new avenues to further investigate on cancer gene therapy based on suicide-inducing genes regulated by a specific promoter such as miR-302s. Moreover, confirming the expression of ES-specific molecular network in cancer cells would help us in developing therapeutic approaches for interfering with stemness property of cancer cells.

P31

TARGETED NEXT-GENERATION SEQUENCING OF JAK2 SUSCEPTIBILITY HAPLOTYPE TO UNDERSTAND THE EITOLOGY OF MYE-LOPROLIFERATIVE NEOPLASMS (MPN) PHENOTYPE AND PREDISPOSITION

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Myeloproliferative neoplasms (MPN) are clonal disorders of the hematopoietic lineage. There are three types of MPN: polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). The somatic mutation JAK2 (V617F) is present in hematopoietic cells of many MPN patients. In a previous genome-wide study, we (and others) identified an allele at the JAK2 locus (rs10974944) that predisposes to the development of JAK2 (V617F)-positive MPN. We also found that JAK2 (V617F) is preferentially acquired in cis with the predisposition allele (G). This led to several possible hypotheses including haplotype-specific variation in a regulatory motif, genotype-specific splicing, or an increased mutation rate at this locus. To understand the haplotype-specific acquisition of somatic mutation, we carried out targeted sequencing of 300KB haplotype block harboring JAK2 using next generation sequencing technology

(RainDance and SOLiD sequencing). We compared MPN cases that are homozygous for risk allele (GG-MPN cases) with the ones that are homozygous for wild type allele (CC-MPN cases). We found that there is no excess of single nucleotide variants in the JAK2 locus in GG-MPN cases compared to CC-MPN cases using ancestral sequence as reference. However, we further explored the existence of selection pressure at JAK2 using HapMap phase III data and detected an excess of derived alleles at JAK2 when compared to ancestral repeats. To identify the functional variant(s) that results in haplotype-specific mutation acquisition in MPN cases, we are analyzing sequence specific differences (such as motif /regulatory elements) between these two groups of patients. Our study is helpful to understand the etiology of MPN phenotype and predisposition.

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GENETIC VARIANTS OF TNF- α -308G>A AND IL-8 -251T>A ARE ASSOCIATED WITH SUSCEPTIBILITY OF SPORADIC COLORECTAL CANCER IN MALAYSIAN PATIENTS

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Colorectal cancer (CRC), the incidence of which has been increasing worldwide for the past few years, represents a significant cause of morbidity and mortality. Even though the mechanism of CRC development is still unknown, both environmental factors and genetic susceptibility are believed to contribute to the onset of CRC. Recently, chronic inflammation has been linked to increased risk to various types of cancers including CRC. If inflammation constitutes one of the molecular networks underlying susceptibility to CRC, genes which mediate inflammatory response might be a group of candidate genes for CRC predisposition. Allelic variants of the genes involved in inflammatory pathways could be logical candidates as genetic determinants of CRC risk. Tumor Necrosis Factor alpha (TNF-α), Interleukin-8 (IL-8) and Intercellular Adhesion Molecule 1 (ICAM-1) are genes involved in mediating inflammatory response. Polymorphisms have been identified in these genes. So a case control study was designed to investigate the TNF- α -308 G>A, IL-8 -251 T>A and ICAM-1 K469E polymorphic genotype frequencies in healthy controls and CRC patients in Malaysian population and to determine the influence of the polymorphic genotypes on sporadic CRC susceptibility risk. Subjects were recruited from Hospital University Sains Malaysia (HUSM), and other government hospitals under Ministry of Health, Malaysia. In this case control study, we included 146 histopathologically confirmed CRC patients (80 males, 66 females, 57.26 years) and 146 healthy normal controls (76 males, 70 females, 48.91 years). Peripheral blood samples of study subjects were collected, genomic DNA extracted and amplified using appropriate primers and genotyped employing PCR-RFLP followed by sequencing. Genotypes were categorized into homozygous wildtype, heterozygous and homozygous variants. The strength of association between polymorphic genotypes and colorectal cancer susceptibility risk was assessed by Odd Ratio (OR) with corresponding 95 % CI. On comparing the frequencies of TNF-α -308 G>A genotypes of patients and controls, the homozygous variant -308AA was significantly higher in CRC patients (P=0.017) compared to controls. For IL-8 -251 T>A, the frequencies of homozygous variant -251 AA was significantly higher in CRC patients compared to controls, with P value of 0.033. However, for ICAM-1 K469E, the genotype frequencies were not significantly different between cases and controls. On investigating the association of the variant genotypes with susceptibility risk, the homozygous variant of TNF-α -308G>A with OR=3.0077 and the heterozygous and homozygous variants of IL-8 -251T>A with OR of 2.1 and 4.0 respectively, emerged as high risk genotypes. However, ICAM-1 K469E showed no CRC risk association. When analyzed in combination, the homozygous variant genotypes TNF-α -308 AA/ IL-8 -251AA showed remarkably higher CRC susceptibility risk with OR 11.375, (CI 1.1718-110.4238, P=0.036). These results suggest that genetic polymorphisms of inflammation response gene IL-8T251A and TNF-α -308G > A are significantly associated with susceptibility risk in Malaysian CRC patients and could be considered as a potential predisposition risk factors for CRC in Malaysian population. Results are also in favor of inflammation mediated colorectal carcinogenesis pathway.

P33

CYCLOOXYGENASE-2 (PTGS2) -765 G>C POLYMORPHISM: SUSCEPTIBILITY AND PROGNOSTIC IMPLICATIONS IN BREAST CARCINOMA

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Cyclooxygenase-2 (COX-2) is involved in carcinogenesis, immune response suppression, apoptosis inhibition, angiogenesis, and tumor cell invasion and metastasis. The gene for COX-2, designated as PTGS2, carries a common functional polymorphism at position 765 in the 5' transcriptionnal regulatory region, which has been associated with susceptibility to malignant disease. In the current study, we investigated the susceptibility and prognostic implications of the genetic variation in PTGS2 in breast carcinoma. We used the RFLP-PCR to characterize the variation of PTGS2 for 409 unrelated Tunisian patients with breast carcinoma and 305

healthy control subjects. To estimate the relative risks, Odds ratios and 95% confidence intervals were calculated using unconditional logistic regression after adjusting for the known risk factors for breast cancer. Associations of the genetic marker with the rates of breast carcinoma-specific overall survival and disease-free survival were assessed using univariate and multivariate analyses. A highly significant association was found between the homozygous PTGS2 (-765) CC genotype (adjusted OR = 4.09; P = 0.0002) and breast carcinoma. The PTGS2 (-765) C allele manifested a significant association with an aggressive phenotype of breast carcinoma as defined by a large tumor size, a high histological grade, and auxiliary‘s lymph node metastasis. Moreover, the presence of the PTGS2 (-765) C allele showed a significant association with a decreased overall survival (log rank test, P = 0.01) and disease-free survival (log rank test, P = 0.001) in breast carcinoma patients. Our results indicated that the polymorphisms in PTGS2 gene is associated with increased breast cancer risk, as well as disease progress, supporting our hypothesis for COX-2 involvement in breast cancer pathogenesis.

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BRAF MUTATIONS IN THYROID LESIONS FROM WESTERN SAUDI ARABIA

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The objective of the genetic survey on thyroid lesions is to estimate the prevalence of gene mutations in BRAF in non-cancerous and cancerous thyroid lesions arising in the Western Saudi Arabian region. Mutational screen was performed on formalin-fixed/paraffin-embedded as well as fresh-frozen specimens derived from the Pathology Departments of the King Abdulaziz University, Jeddah, and the King Faisal Specialist Hospital & Research Center, Jeddah. Included in the screen were nodular goiters, Hashimoto‘s thyroiditis, follicular adenomas, hyperplastic lesions, follicular thyroid carcinoma (FTC), Hurthle cell carcinoma, papillary thyroid carcinoma (PTC), and follicular variant PTC (PTC-FV). PTC/PTC-FV microcarcinomas (tumor size < 1 cm) were excluded from analysis. Primers flanking the mutational hotspot region of BRAF (exon 15) were used for PCR on genomic DNA. Nested primers were used for sequence reactions and purified sequencing products were resolved by capillary electrophoresis on an ABI PRISM 3130 Sequencer. We identified BRAF mutations in one of 48 follicular adenomas, one of eight FTC, 67 of 110 (61 %) PTC, and 6 of 32 (19 %) PTC-FV. Most of the cases showed the common point mutation in codon 600 leading to substitution of valine by glutamic acid (V600E). Four cases had a point mutation in codon 601 leading to substitution of lysine by glutamic acid (K601E). Rare mutational variants include a 3-base-pair deletion of codon 599 identified in a follicular adenoma and a 3-base pair insertion at codon 600 found in a PTC. No BRAF mutations were revealed in nodular goiter (0 of 25 cases), Hashimoto`s thyroiditis (0 of 5 cases), hyperplastic lesion (0 of 8 cases), and Hurthle cell carcinoma (0 of 5 cases). Patients with PTC and no BRAF in the tumor were on average younger than those with BRAF mutation in the tumor (35.6 years vs. 43.9 years; p = 0.02). Lymph node involvement in PTC was revealed in 75 % of the tumors (38 of 51 cases examined); however, lymph node involvement was independent of the BRAF mutational status. This survey provides the first overview of the prevalence of BRAF mutations in non-cancerous and cancerous thyroid lesions arising in the Western Saudi Arabian region. BRAF mutations were most abundant in PTC and PTC-FV that correlates with similar studies performed in other countries; however, the significance of the BRAF mutational status in regard to clinicopathological features and clinical treatment of the disease is still matter of discussion.

P35

SYNERGISTIC EFFECT AND VEGF/HSP70-HOM HAPLOTYPE ANALYSIS: RELATIONSHIP TO PROSTATE CANCER RISK AND CLINICAL OUTCOME

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Prostate cancer is a complex disorder resulting from the combined effects of multiple environmental and genetic factors. Our previous single locus analysis showed that VEGF and HSP70-hom polymorphisms were significantly associated with prostate cancer susceptibility and prognosis. Both genes encoding these proteins were located on chromosome 6p21, and combining the neighboring SNPs into haplotypes may increase the association with the disease. Three tagging polymorphisms, the HSP70-hom 2437 T/C, the VEGF-1154 G/A and the VEGF-634 G/C SNPs were genotyped in 101 cases and 80 controls. For the combined analysis of VEGF and HSP70-hom, we found a positive gradient in the ORs related to the number of high risk genotypes with a 3.53-fold increase of prostate carcinoma risk (OR= 3.53; P= 0.015). Furthermore, The TAG and CAG haplotypes at positions HSP70-hom, VEGF -1154 and VEGF -634 exhibited a twofold (OR= 0.46; P= 0.014) and a sevenfold (OR= 0.14; P= 0.00005) reduction in prostate cancer risk, respectively. Regarding prostate cancer prognosis, the TAG haplotype had a negative association with the aggressive phenotype as defined by the histopathological grade (OR= 0.28; P= 0.006). Our findings confirm the role of at-risk haplotype across the HSP70-hom/VEGF gene cluster in determining susceptibility to prostate cancer.

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GENETIC POLYMORPHISMS OF CYP1A1, NQO1 AND NAT2 AND RISK OF ORAL CANCER IN NORTHEAST

INDIA: TOBACCO CONSUMPTION AS RISK MODULATOR

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In India, oral cancer is the most common cancer among men and ranks third among women. Northeastern states in India have reported a very high prevalence of aero-digestive tract cancers when compared with other regions of India. In this region, there is widespread chewing habit of tobacco with peculiar fermented betel nut. The quantitative absorption, distribution, metabolism, and excretion of carcinogenic tobacco constituents depend on the activity and efficiency of metabolic and enzymatic detoxification pathways. Most of the carcinogenic chemicals are converted to reactive electrophilic metabolites by the cytochrome P-450 (CYP) superfamily of phase I enzymes. Subsequently, the phase II enzymes detoxify these intermediates by conjugation reactions. Some of the major phase II enzymes are glutathione S-transferases (GSTs), N-acetyletransferases (NAT), and NAD(P)H-quinone oxidoreductase 1 (NQO1). As the population under study has unique betel quid and tobacco consumption habits, we hypothesized that polymorphisms of genes responsible for detoxification of xenobiotics may be associated with risk of oral cancer. The present case control study was performed on 235 histopathologically diagnosed oral squamous cell carcinoma cases and 289 healthy controls collected during the period of December 2005 to 2009. All incident cases willing to participate in the study were recruited from the collaborating centers in Northeast India. The association between polymorphisms in three genes [CYP1A1 (Msp1 and Nco1), NAT2 and NQO1] encoding for xenobiotics metabolizing enzymes and risk of oral cancer were analyzed in these cases. The CYP1A1, NAT2 and NQO1 genotypes were determined by the polymerase chain reaction - restriction fragment length polymorphism (PCR-RFLP) based methods. Tobacco chewing as well as smoking were found to be significantly associated with increased risk of oral cancer (OR=2.78, 95% CI=1.71-4.51, p=<0.001 and OR=1.57, 95% CI=1.05-2.35, p=0.027). Frequency of betel quid chewers were also higher in cases (80%) compared with controls (66%) but when adjusted with other risk factors it conferred only a marginal risk (OR2=1.50, 95% CI=0.92-2.45, p=0.1). Frequency of alcohol consumption higher in cases (37%) as compared to controls (30%), but the difference was not statistically significant. Frequencies of variant genotypes of CYP1A1 2A, CYP1A1 2C and NAT2 were found to be higher in oral cancer cases when compared with controls but this difference was not statistically significant. Frequency distribution of NQO1 genotypes Pro/Pro, Pro/Ser and Ser/Ser was 44.7%, 35.3% and 20% in cases and 59.8%, 26.6% and 13.5% in controls respectively. The difference between cases and controls was significantly higher for both of the variant genotypes, Pro/Ser (OR=1.64, 95% CI=1.04-2.58, p=0.03) as well as for homozygous variants (OR=1.81, 95% CI=0.98-3.32, p=0.06). Tobacco chewing and smoking but not betel quid chewing or alcohol consumption, were found to be the major contributing risk factors for oral cancer. Variant genotypes of NQO1 may play an important role for the genetic susceptibility to oral cancer in Northeast region of India.

P37

COLORECTAL CANCER RISK IS NOT ASSOCIATED WITH INCREASED LEVELS OF HOMOZYGOSITY IN A POPULATION FROM SAUDI ARABIA

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Autozygosity is a term used to denote the presence of two identical haplotypes that are derived from an ancestor shared by both parents, so it essentially represents a special type of homozygosity. Runs of homozygosity (ROH) in the genome is a measure of the extent of autozygosity and is directly correlated with the extent of inbreeding. While the role of ROH in unmasking recessively acting mutations is well established in Mendelian genetics, much less is known about their contribution to more complex disorders such as cancer. Recently, it has been suggested that ROH may contribute to the risk of colorectal cancer (CRC) perhaps through the unmasking of a recessively acting CRC-predisposing mutations in one or more genes. However, this observation could not be replicated. In this study, we examine the role of homozygosity in the CRC risk by asking four specific questions. First, do CRC patients have enrichment for ROH in particular chromosomal regions compared to controls? Second, do CRC patients have longer ROH compared to controls? Third, is there a particular SNP that is more likely to be homozygous in CRC patients compared to controls? And fourth, are CRC patients more inbred than controls? By comparing 48 Saudi CRC patients to 100 ethnically matched controls, all processed on Affy 250SytI SNP Chip platform and analyzed by Partek, we found that the answer is no to all these four questions. We note here that this is the first study to address these questions in an inbred population so the negative results in our study carry more significance than what has been previously reported in the literature. We also note that our subgroup analysis of patients with MSI-positive tumors compared to other groups did not significantly change our results. While these results do not rule out the potential presence of recessively acting CRC-predisposing genes in a small percentage of patients that our relatively small sample size could not capture, they do suggest that such genes are unlikely to account for the disturbingly high incidence of CRC in our consanguineous population and that future research should consider other mechanisms.

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WHOLE GENOME ANALYSIS OF PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA

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Different regulatory mechanisms influence the gene expression and function, and DNA copy number alterations play a key role in these processes. There are widespread copy number variations in the genome of healthy human individuals and numerous variations have been associated with susceptibility or resistance to diseases. In cancer, genes detrimental to tumor growth (e.g. tumor suppressor genes) are likely to be contained in regions of decreased DNA copy number; while genes important for tumor growth or development (e.g., oncogenes) are likely to be contained in regions of increased DNA copy number. Chronic lymphocytic leukemia (CLL) is a malignancy of B-lymphocytes of unknown etiology with a variable clinical course. Prognostic markers stratify patients into groups with good- and poor-risk disease according to the genomic complexity, mutational status of immunoglobulin heavy chain variable region (IgVH) and p53 functionality. Deletions of chromosomal region 13q14, where miRNAs 15a and 16-1 are located, were found to be the most common genomic alteration in CLL (in approx. 60% of cases). Other frequent aberrations currently detected using CLL-specific FISH panel are deletions of 11q22.3-q23.1 including the ATM gene, trisomy 12, and deletions of the TP53 tumor suppressor gene at 17p13. To improve genetic characterization of CLL cells, we performed high-resolution gene copy number analysis of 41 CLL patients using oligonucleotide array comparative genomic hybridization (Human Genome CGH Microarray 4x44K, Agilent). FISH data were available for all samples. In all CLL samples we found at least one alteration compared to referenced sequences. Additional aberrations not detected by FISH were found in the majority of samples (95 %). Complex genomic changes (3 and more abnormalities compared to the reference sequence) were present in 33/41 samples. Deletion of 13q14 was observed in 56% of patients (23/41) and the minimal deleted region contained miR-15a and miR-16-1. One Mb loss in the IGH locus 14q32.33 was found in 22/41 patients reflecting V(D)J recombination events. Interestingly, 37 Mb interstitial loss in the 14q24.2-q32.33 region was identified in 2/41 patients beside other alterations. Both of them have the same break point at the telomeric side. The presence of genomic alterations could influence the prognosis of CLL patients and therapy option and nowadays belongs to the essential diagnostic tool in leukemia patients. Whole genome CGH microarrays are expanding the known genomic regions of importance in CLL and allow these regions to be evaluated in the context of a genome-wide perspective. This method could help identify new prognostic markers of the disease and uncover mechanism of genomic changes evolution during course of the disease, thus bringing new insight into CLL pathogenesis. This work was supported by research project MSMT MSM0021622430 and research grants IGA MZ CR NS10439-3/2009 and NT11218-6/2010.

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QUANTITATIVE REAL TIME-PCR TAQMAN AND FLUORESCENCE IN SITU HYBRIDIZATION (FISH) APPROACHES TOWARDS DETECTION OF TERT GENE AMPLIFICATION IN A LEUKEMIC CELL LINE (K562) AND NORMAL CELLS

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Telomerase reverse transcriptase (TERT) gene serves as a catalytic component in telomerase enzyme which its activity is detectable in more than 80% of human tumors. Amplification of TERT gene which is located on chromosome 5p15.33 may act as one of the important mechanisms for oncogenic activation. High expression or activity of telomerase in malignant cells has been associated with copy number gain or amplification of TERT gene. Although various molecular strategies are available for detecting the gene amplification in tumor samples, reliable method is essential to be used in diagnostic purposes. We employed a quantitative Real time-PCR TaqMan and Fluorescence in situ Hybridization (FISH) assays to detect TERT gene amplification status in a leukemic cell line (K562) and normal cells; and to elucidate the concordance results obtained from these two assays. The K562 cell line was maintained in an appropriate culture media and the preparation of cell pellet was carried out using 5 X 106 cells. A total of 10 peripheral blood samples were obtained from healthy individuals and the genomic DNA were extracted from the blood and also K562 cell pellet using a commercial kit. A quantitative real time- PCR (qPCR) assay was performed using TaqMan probe and a set of primers for TERT (target gene) and ATP10A (reference gene) designed by Primer Express 3.0 software. The assay was performed in duplicate consisted a standard curve, a no-template control, 20 ng of DNA calibrator, and 20 ng of unknown samples (normal and K562 cells). The results were analyzed by 7500 Software v2.0.4 and the level of amplification (N) was calculated. In the interphase FISH analysis, dual-color assay probe was used which covered the genomic region encoding TERT (red signal) together with a specific sequence of EGR1 (green signal) at 5q31 to facilitate chromosome identification. Both normal and K562 cells were prepared on slides according to the conventional cytogenetic method and followed with FISH procedures recommended by the probe supplier. Our results showed that the level of TERT gene amplification detected by qPCR was observed in K562 cells with the N value was ranged 3 to 4 as compared with average N value of less than 2.5 in normal samples. The FISH signal pattern was observed as two green signals and two red signals (2G2R) in normal cells, while more than 90% of K562 cells showed either 2G3R or 2G4R signal patterns. Both qPCR and FISH assay were successfully optimized in detection of TERT gene copy number status in K562 and normal cells. The findings obtained from these assays were concordant which indicating the presence of low grade amplification of TERT gene in K562 cells as previously reported. Thus, our study suggested that the qCR assay is rapid and useful to be applied as a potential reliable diagnostic tool in clinical samples.

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ALLELIC TRANSCIPT IMBALANCE OF MGMT DETERMINES THE RESISTANCE FOR ALKYLATING AGENTS IN THE TREATMENT OF BREAST CANCER

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Genomic regions that regulate gene expression are major causes of human diversity and may also be important susceptibility factors for complex diseases, traits and repairing. O-6-methylguanine-DNA methyltransferase (MGMT) acts to repair inappropriately methylated guanine residues in DNA. Chronic exposure to alkylating/methylating agents can lead to increased MGMT activity and MGMT expression protects from spontaneous G:C to A:T transition mutations. Inactivation of MGMT increases efficacy of alkylating agent against cancer. Deficiency in MGMT are more susceptible both to the toxic effects of alkylating antitumor agents and to tumor induction by alkylating carcinogens, while in transgenic models, mice expressing increased levels of MGMT are more resistant to alkylating carcinogens and also have a lower frequency of spontaneous tumors. In humans, MGMT is expressed at different levels in different tissues and there is considerable inter-individual variation in the activity levels in particular tissues. However, the causes of inter-individual differences in expression levels are unclear, in particular, whether there is a genetic component for this variability. On the other hand, Unequal expression of the alleles of autosomal genes (allelic expression imbalance; AEI) has long been known in tumors where it reflects somatic alterations at the DNA level, such as amplification, deletions, duplications or translocations, and the deregulation of epigenetic control mechanisms. These processes are hallmarks of tumor development. In this context, the present study has been undertaken to evaluate whether or not observed the variation in the expression of MGMT alleles at different levels among 253 cases (breast cancer patients) and 264 controls which determines the status of the reparation of this gene MGMT due to alkylated chemotherapeutic agents in breast cancer women by the analysis of RT-PCR-RFLP of mRNA which will enable to relate to the prevention and treatment of cancer in man. Marked differences in the relative abundance of the MGMT transcripts encoded by the two MGMT alleles were observed higher in patients than the cases. The extent of the differences were up to 48-fold and this is considerably higher than the average reported. The expression of these two alleles demonstrated allelic imbalance with a variation in cases and controls which in turn reflect in the treatment of alkylating chemotherapeutic treatment among the breast cancer patients. The basis of allelic expression differences could be the clonal expansion of a cell carrying a mutation in one allele and this allele expression imbalance may be exclusively due to epigenetic modifications of cis acting elements, as observed in imprinted genes, indicating that there is a genetic component to inter-individual variation of MGMT levels and that at least some of this variation maps close to or within the MGMT locus.

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EXPLORING THE VALUE OF CONVENTIONAL CYTOGENETICS, FISH AND RT-PCR IN DIAGNOSIS, PROGNOSIS AND CLINICAL MANAGEMENT OF CHRONIC MYELOID LEUKEMIA PATIENTS

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Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder resulting from neoplastic transformation of hematopoietic stem cells.CML is associated with the presence of a recurrent chromosomal translocation the t(9;22)(q34;q11) (Philadelphia [Ph‘] chromosome) that creates a hybrid BCR-ABL oncogene. For the identification of t(9; 22)(q34; q11), conventional cytogenetics is sufficient but at times, lack of good mitotic index, difficulty in aspirating bone marrow and complex translocations brings relevance to molecular techniques such as FISH (Fluorescent In Situ Hybridization) and RT-PCR (Reverse Transcriptase Polymerase Chain Reaction). Here we examined 92 CML suspects (Median age: 38; M: F=2.9:1), attending the OP clinics of the Regional Cancer Centre. Conventional cytogenetics revealed presence of Philadelphia chromosome in 83.6% (77/92) cases. The chromosomal abnormalities at diagnosis and during treatment were recorded and grouped. Additional abnormalities observed are double Ph‘, structural abnormalities (i(21)(q10),2q-,6q+,12q-,16q-,21q-,20p-), monosomy (-8,-7,-9,-10,-17-21,-X), trisomies (+6,+7,+8,+15,+16,+17,+18,+19,+21), ring chromosomes, endoreduplication and cases with atypical ploidy status. Of the 92 cases, 7.6% (7/92) cases were negative for Philadelphia chromosome, of which, 3 cases showed unusual chromosomal abnormalities. RT-PCR was performed for 80/92. The bcr-abl gene status of all the cases matched the cytogenetic profiles except one case, where a Philadelphia negative case was found to be fusion gene positive. Atypical fusion transcript was also observed in one case. The RT-PCR performed on 8.6% cytogenetically un-analyzable cases (8/92), revealed the presence of fusion transcript in 6 of them. FISH was performed on 20 cases, including the 12 cases for which RT-PCR could not be done, in 2 cases for confirming double Phâ€™ and in one cytogenetically negative but molecularly positive case. Using BCR/ABL dual colour dual fusion FISH probe [Spectrum Orange:ABL locus(O), Spectrum Green:BCR locus(G), Yellow Signal:BCR-ABL/ABL-BCR fusion(F)], 200 interphase nuclei/metaphase were analyzed per sample. The OGFF was the typical pattern for CML. To our surprise, FISH analyses revealed sub-microscopic deletions of the der(9) in 50%(10/20cases) CML patients with various signal patterns including OGGF, OOGF, OGF and admixed patterns which are indicative of deletion of ABL, BCR and ABL-BCR respectively on der(9). A new OOGGF pattern with atypical karyotypic and molecular profile was found in two cases. OGF

pattern was the most recurrent observation (5/20).The evaluation of the prognostic significance of the cases with atypical FISH patterns showed a slight preponderance towards loss of cytogenetic response and accelerated phase CML, except OOGGF patterns showing good response to drug. Additional abnormalities are considered as poor prognostic marker against Ph' chromosome, which is a good prognostic marker. One reason for the cytogenetically, Philadelphia (Ph') negative CML is attributed to the presence of cryptic translocations which masks the constitution of Ph' chromosome. In addition to complex translocations, sub microscopic deletions on der(9) needs further validation in a larger cohort to justify its prognostic importance. This study points towards the clinical and research utility of using the above techniques at diagnosis and at regular intervals for grouping patients based on karyotype, FISH signal patterns and fusion transcripts to postulate a new formula for prognostic risk stratification of CML patients.

CLINICAL GENETICS

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DNA METHYLATION OF REGULATION REGIONS OF HUMAN TUMOR SUPPRESSOR GENES: STUDY BY BLSI- AND GLAI PCR ASSAYS

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DNA methylation in mammalian genomes regulates expression of genes. Aberrant DNA methylation of promoter and/or first exon regions of human tumor suppressor genes results in these genes silencing and plays a key role in tumor initiation. BlsI- and GlaI-PCR assays have been developed to study DNA methylation and include DNA hydrolysis with unique methyl-directed site-specific DNA endonuclease BlsI or GlaI, respectively, followed by PCR with primers designed for DNA region of interest. In this work we have applied BlsI- and GlaI-PCR assays to determine methylation of promoter and first exon regions of RARB, SEPT9, IGFBP3, CEBPD, MGMT, DAPK1 and RASSF1A tumor suppressor genes in malignant cell lines HeLa, Raji, U-937, Jurkat and control fibroblast cell line L-68. GlaI-PCR assay has shown a methylation of RARB regulation region in DNA from all malignant cell lines, but not in DNA from control L-68 cells. BlsI-PCR assay has demonstrated an absence of the regulation regions methylation in control fibroblast cells. GlaI- and BlsI-PCR assays have revealed different methylation patterns of studied regulation regions in malignant cell lines HeLa, Raji, U-937 and Jurkat. According to the results of BlsI-PCR assay 1) each GCGCNGCG(C/T) site, located in regulation regions of tumor suppressor genes, is methylated in at least one malignant cell line; 2) DNA preparations from malignant cell lines have shown either an absence of methylation or a complete DNA methylation of these sites. A comparative analysis of 7 DNA fragments within regulation regions has been made and revealed a presence of direct repeats around site GCGCNGCG(C/T).

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REPORT ON CLASS II HISTOCOMPATIBILITY (HLA-DR & DQ) ANTIGENS IN A SUBPOPULATION OF ARAB PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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This report is the second of its kind on Arab patients with lupus .We reviewed the HLA- DR and DQ phenotypes of 37 patients from the Arabian peninsula and Southern Mediterranean region . Results were compared to those of healthy controls. HLA -DR 3 displayed significant disease association; 18 (51.5%), vs. 156 (26%) in contols (p= 0.001, RR 2.96, 95% CI 1.58 -5.58). HLA-DR 2 was next in frequency but failed to reach statistical significance; 16 (43%) vs 182 (30%) in controls p= 0.10. The broad antigen was present in only 1 patient and the DR -2 splits of DR- 15 and 16 formed the rest. HLA-DR 4, and DR-5 were of noticeably, low prevalence in the patients (8 and 2.5%) compared to (25.5%, p=0.01 and 34%, p=0.0001) among controls respectively. HLA-DQ2 showed positive association with patients (60%), versus (35.5%) in the controls (p=0.006, RR 2.56 & 95% CI 1.327-4.940) whereas DQ3 appeared as the least likely disease-associating antigen (34% in patients vs.57% in controls, p=0.005, RR 0.40 & 95% CI 0.204-0.798). HLA-DR3/DQ2 and DR 2/DQ1 haplotypes were found in 48.5% & 43% respectively, p=0.8. Therefore, the MHC class II of this cohort is not associated with specific entity of antigens and haplotypes. This would support the notion of shared susceptibility in the line of predisposition to lupus among various ethnic groups. Further substantiation is required by studying larger cohorts and this work paves the way towards such a goal.

P44

NOVEL MUTATIONS IN CRYGB GENE IN A CONSANGUINEOUS KUWAITI FAMILY WITH AUTOSOMAL DOMINANT CONGENITAL CATARACT REVEALED GENETIC AND CLINICAL HETEROGENEITY

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Congenital cataract is a clinically and genetically heterogeneous lens disorder. Herein a Kuwaiti family diagnosed with autosomal dominant congenital cataract (ADCC) across three generations screened to explore the disease locus and causative mutation. Family members were clinically characterized by a complete eye examination. Three various phenotypes; lamellar, anterior polar and complete cataract were detected in this family. Whole genome linkage analysis (Affymetrix 250K) revealed Locus 2q34-36.1, harpers CRYBA2 gene, with the highest LOD score of 1.505. CRYBA2 gene screened by direct sequencing and revealed no alteration in the coding region or the exon-intron boundaries in patients. Therefore, locus 2q33-q37 with the next highest LOD score (1.489), harpers γ-crystallin gene cluster CRYGA, B, C and D, was considered. All γ-crystallin gene were screened for mutation by cloning and sequencing. Two novel heterozygous deletions; g. intron1 (58delG) and c. 72delC in exon2 and a novel tri-nucleotide polymorphism g. intron1 (11-13 GGT>AAA) were detected in CRYGB. Heterozygous g. intron1 (58delG) detected in 4 affected members with lamellar cataract. Heterozygous c. 72delC detected in 2 affected members, one with anterior polar cataract while the second (80yrs old) exhibited an extreme cataract phenotype. It was difficult to predict whether the cataract found in this patient was due to old age or c. 72delC mutation. In addition, one patient had a complete cataract found to be a compound heterozygote with c. 72delC and g. intron1 (58delG) mutations. The novel, tri-nucleotide polymorphism g. intron1 (11-13 GGT>AAA) was found to be maternally inherited to two affected daughters while the mother showed no clear eye abnormality. Therefore, the involvement of this polymorphism in ADCC is not clear. The c. 72delC mutation results in a truncated protein of 43 aa which preserved the first 24 aa of wild type protein, a frame shift generating 19 random amino acids, before a translation termination at position 130. We are presenting the first ADCC case reported having complex mutation in CRYGB gene. The genetic heterogeneity resulted in clear clinical presentation of the disease. This case will advance our understanding of the genotypic-phenotypic correlation of ADCC.

P45

MOLECULAR GENETIC DIAGNOSIS OF GENETIC DISEASES IN KAZAKHSTAN

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Gene diagnostics is a new area of medicine that uses molecular genetic methods for early diagnosis, choice of preventive medication and individual approach to the patient. In the Republic of Kazakhstan in the laboratory of medical genetics at the base of the Scientific Center for Obstetrics and Gynecology and Center for Molecular Medicine are diagnosed phenylketonuria, cystic fibrosis, and Duchenne/Becker miodystrophy. The aim of our study was detection in the genome of a patient known mutations phenylketonuria, cystic fibrosis, and Duchenne/Becker miodystrophy. Molecular genetic analysis of mutations in PAH - phenylalanine (R408W, R261Q, R252W, IVS10-11, IVS12 +1, R158Q, P281L, IVS14 +5), mutations in the gene CFTR (delF508, del21kb, delI507, 1677delTA, 2143delT, 2184insA, 394delTT, 3821delT, L138ins), mutations in fragments of 19 different exons and the promoter region of the dystrophin gene (MPA1 and MPA2) carried out using PCR technique. The average frequency of phenylketonuria in Kazakhstan is equal of 1:19227. In the research presented the spectrum and frequency of a PAH gene mutation in Kazakhstan were studied. DNA from blood of 20 patients with phenylketonuria and their parents has taken for investigation. The results of study have shown four mutations: R408W in 13 of 40 chromosomes with mutation (frequency 0,325), mutation R261Q in 4 of 40 chromosomes with mutation (0,100), IVS12nt1 in 2 chromosomes (0,050) and mutation IVS10nt546 also in two chromosomes (0,050). Besides, we have revealed described earlier (Dworniczak et al., 1990) neutral polymorphism V245V in 7 exon of a PAH gene. The frequency of cystic fibrosis in different populations and nations in Kazakhstan vary considerably. Accordingly to Nazyrova (2006) it is 1 per 8000 births. We carried out the molecular genetic diagnosis of 111 family members with cystic fibrosis. 33% of investigated have found mutation delF508, 19% - possessed mutation Del21kb, 16% - have found 394delTT, 13% possessed 3821delT- and 13% - del507 and 6% - have found mutation 1677delTA. Miodistrofiya Duchenne-Becker. 20 patients with clinical symptoms of progressive muscular dystrophy miodistrofii were examined. The results of study have shown the presence of deletions in 9 patients. 44% of them contained del50 (271bp) MPA2; 33% - del6 (242bp), del13 (238bp) MPA2 and del43 (357bp) MPA1; 22% - del44 (268bp), del45 (307bp), del51 (388bp0, del52 (113bp) MPA1 and del47 (181bp) MPA2; and 11% contained del8 (360bp), del17 (416bp), del19 (459bp) MPA2 and del53 (212bp) MPA1. Application of molecular genetic techniques provided new opportunities for diagnosis of hereditary diseases. The results of the study presented have clearly indicated that examination of mutant alleles in patients and their families or investigation of alleged heterozygous carriers with pathological mutations provided good possibility for prenatal diagnosis of the fetus. This is an important factor for prevention of hereditary diseases in families.

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MECP2 GENE MUTATION ANALYSIS IN IRANIAN PATIENTS WITH RETT SYNDROME

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Rett syndrome is a neurodevelopmental disorder of the grey matter of the brain that affects girls almost exclusively. The clinical features include small hands and feet and a deceleration of the rate of head growth (including microcephaly in some). The signs of this disorder are most easily confused with those of Angelman syndrome, cerebral

palsy and autism. The X-linked dominant inheritance of RS has been mapped to the gene that encodes the methyl-CpG-binding protein-2 (MECP2) at Xq28. Approximately 80 percent of deleterious MECP2 mutations are sequence changes, while large deletions of MECP2 may comprise up to 15 percent of causative mutations. Samples of 11 patients were analyzed in Sarem woman hospital for MECP2 mutations. The patients were reviewed by pediatric and clinical geneticist, and the probable diagnosis of RS was based on clinical features and disease progression. Genomic DNA was extracted using standard procedures from the samples. PCR was performed to amplify all the three exons of MECP2 gene in 8 fragments, using published primers and conditions with some modifications. PCR products were purified and introduced to direct sequencing. Sequencing results were compared with reference to the normal human genomic MECP2 sequence. Of the 11 patients, 6(54%) had pathogenic mutations, which included 6 different mutations. Altogether, there were one missense mutation (c.916 C>T in genome / p.R306C in protein level), one stop codon mutation (c.502C>T / p.R168X), one insertion (c.703-704 ins G / p.W718fs), and one nonsense mutation (p.R294X), and one with large rearrangement in exon4, and finally one with familial mutation. Rett syndrome exists in different parts of the world. Prevalence of Rett syndrome is approximately one in 10,000. In this study we detected pathogenic mutations in 54% of the patients. This is a rather low percentage of found mutations compared to the other studies where the range is between approximately 60-80%. However, several studies have also reported quite low mutation occurrence, between 35% and 55%. The discrepancy in our and in former studies is most probably a result of the use of different diagnostic procedures in making a diagnosis.

P47

ASSESSMENT OF APOPTOSIS IN CRYOPRESERVED HUMAN SPERMATOZOA

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The presence of high rate of apoptosis in spermatozoa may be responsible for male factor infertility. Cryopreservation of sperms is a routine methodology in assisted reproductive centers. However, it may have negative impact of sperm parameter, including apoptosis. The purpose was to investigate the rate of apoptosis in cryopreserved sperms of fertile and infertile men. Semen samples from young fertile (n=17) and infertile (n=17) men were analyzed according to WHO criteria. Sperm parameters of concentration, motility, morphology, and viability were assessed using Makler chamber and Geimsa staining, The rates of apoptosis was also evaluated with TUNEL staining technique and light microscopy for both groups of fertile and infertile. All samples were then cryopreserved using vitrification-cryoloop and stored in liquid nitrogen for 1 week. After thawing, the aforementioned parameters were assessed blindly. The rates of progressive motility of sperms decreased significantly in both groups of men after cryopreservation. The rate of sperm apoptosis in fertile men increased insignificantly from 16.41±4.53% to 24.76 ±5.03% after vitrification. In infertile patients, however, the sperm apoptotic rate increased from 23.50±8.31% to 34.29±10.02% following vitrification (P<.05). Cryopreservation of human spermatozoa also significantly reduced the sperm viability and morphology in both groups. Cryopreservation had negative impacts on parameters of human spermatozoa. It also enhanced the rate of apoptosis in germ cells, especially in infertile men. However, cryopreservation has advantage, as long term storage of human sperms become feasible.

P48

NO POLYMORPHISM OF CTLA4 GENE AT POSITION OF EXON 1 WITH SCHIZOPHRENIA POPULATION IN AND AROUND COIMBATORE, SOUTH INDIA

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The focal aim of the present study was carried out to investigate the association of a polymorphism of the Cytotoxic T-lymphocyte antigen-4 (CTLA-4) gene, at position 49 of exon 1, with schizophrenia population in coimbatore south India. Among these patients diagnosed with schizophrenia according to DSM-IV, 102 patients who met the selection criteria were recruited for the study. Equal number of control was selected from same subject area but they are not affected with any genetic disorder in past year and also they are not taking any treatments and drugs for any disease. DNA was extracted from whole blood using phenol chloroform method and the CTLA-4 gene region was amplified by polymerase chain reaction. Molecular genotyping was performed by single strand conformation polymorphism (SSCP). The genotype and allele distribution in patients with schizophrenia was not significantly different from that seen in the control group. This study suggests a there is no polymorphic role of the CTLA-4 gene polymorphism at position 49 of exon 1 for schizophrenia in the south Indian population, although the detailed mechanisms remained to be elucidated.

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CONGENITAL MALFORMATIONS PREVALENT AMONG EGYPTIAN CHILDREN AND ROLE OF GENOMICS IN ITS PREVENTION

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The possible role of genomics in uncovering genetic susceptibilities and helping prevention of congenital malformations (CMs) require in depth epidemiological studies and cost effective analysis. CMs is a type of congenital disorder which is primarily structural in nature and which is present at time of birth. They affect 3-4% of all live births and many elective pregnancy terminations or spontaneous

abortions. Most CMs are thought to have a multifactorial etiology (interaction between genes and/or environmental factors. In this study we tried to assess for the first time the frequency and nature of CMs among Egyptian children as well as the associated risk factors. I will also try to discuss the future role of genomics in its prevention. Subjects & Methods: Charts of children with CMs (13,582), aged 0-18 years were extracted from 660,280 child attending the Pediatric Hospital Ain-Shams University, Cairo, Egypt during the period 1995-2009. This is the main Hospital in the North Eastern region of Cairo, and all children with CMs attend this hospital for investigations and proper diagnosis. Reports of physical examination and investigations (echo-cardiogram, abdominal ultrasonography, CT brain, and chromosomal study) of these children were also studied. Major malformations were classified according to ICD-10 classification. Maternal, paternal and neonatal risk factors were studied and compared to a control group (5000 mothers of normal children of same age group). Results:- The frequency of CMs was 20/1000 with more affection in males. The commonest system involved was the central nervous system, followed by chromosomal anomalies, genital, urinary, musculoskeletal, circulatory, eye, ear, face and neck. Among the maternal risk factors were multiparity, age of mother above 35y, maternal illness, exposure to pollutants and drug intake during the first 3 months of pregnancy with low intake of multivitamins and folic acid. Fathers above 50 years and consanguineous marriage were among the risk factors as well as birth weight of patients below 2.5 kgs. All these results will be discussed. Future role of Genomics in Prevention of CMs:- Genomics has many tools including pathogenomics, pharmacogenomics, nutrigenomics and bio-informatics. Pathogenomics will reveal the molecular background of CMs to identify candidate genes and interactions of those genes with each other and the persons‘ environment. Pharmacogenomics identifies variant genes affecting the response to drugs and chemicals and which would be expected to increase their teratogenecity in at risk individuals and it should be applied to study drug induced birth defects. Nutrigenomics will identify genetic variations and nutritional requirements for genome stability. Bio-informatics will allow interpretation of biological data in a meaningful context. This will help to offer new diagnostic methods and new approaches for prevention and therapy. All these items will be discussed.

COMPUTATIONAL GENOMICS AND ANALYSIS OF HUMAN DISEASE

P50
GENOMICSCLOUD: NEXT GENERATION SEQUENCE ANALYSIS USING HIGH PERFORMANCE CLOUD COMPUTING

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Over the past decade, the decoding of the genomes of various organisms has sparked an extraordinary biological revolution. The information and technology of genomics is transforming our understanding of evolution; the mechanisms of disease, the relationship between heredity and environment, and our ancient connection with all forms of life. But large comparative genomics studies and tools are becoming increasingly more compute-expensive as the number of available genome sequences continues to rise and we look at organisms with larger genome size. GenomicsCloud with its alternative computing architectures such as high performance computing and cloud computing techniques, will help alleviate this increasing pressure and enable fast, large- scale, and cost-effective comparative genomics strategies. GenomicsCloud is a commercial scale genome computing center powered with a suite of HPC accelerated bioinformatics assembly and analysis tools for doing end to end downstream bio- informatics and bio-statistical analysis for next generation sequencing data. Some of the tools offered by GenomicsCloud such as Cloud-MAQ, RNA-Seq to Gene Models are highly parallel and scalable. Cloud-MAQ is a cloud computing tool to build assembly by mapping short reads to reference sequences. RNA-Seq to Gene models is a pipeline to discover gene models from RNA- Seq data. GenomicsCloud's collaboration of genomics research and cloud computing will lead to better and faster access to information about genes, which in turn will help in better understanding of the complexity of life, diagnosis of new diseases, as well as in discovering new drugs and vaccines.

P51
NTRFINDER: AN ALGORITHM TO FIND NESTED TANDEM REPEATS

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We introduce the algorithm NTRFinder to find a complex repetitive structure in DNA we call a nested tandem repeat (NTR). An NTR is a recurrence of two distinct tandem motifs interspersed with each other. We propose that nested tandem repeats can be used as phylogenetic and population markers. An algorithm for finding Nested Tandem Repeats is introduced. We have tested our algorithm on both real and simulated data, and present some real nested tandem repeats of interest. We discuss how one of these may assist in determining the cultivation prehistory of the ancient staple food crop taro (Colocasia esculenta).

P52
SURVEY OF FOXP2 TARGETS FOR EVIDENCE OF POSITIVE SELECTION

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Forkhead Box P2 (FOXP2) is a highly conserved transcription factor with a fork head DNA-binding domain that plays an important role in cell fate during embryonic brain development. While mutations in this gene have been associated with difficulty in learning and impaired speech, the pattern of nucleotide polymorphisms in modern populations suggests that it has been the target of positive (Darwinian) selection during recent human evolution. The objective of this study was to look for evidence of selection in modern humans that might have followed in response to FOXP2 adaptations. We investigated whether or not there was an enrichment for positive selection in any of the ~500-600 FOXP2 target genes that have recently been identified by chromatin immunoprecipitation genomic screening (ChIP-CHIP surveys) in fetal brain tissue and neuronal cell lines. FOXP2 targets were matched with a list of control genes in the Ensembl Archives database (Ensembl 54: NCBI Build 36) for gene length, GC content and average recombination rate. Positively selected genes were identified based on the summary statistics generated for each non-overlapping ~10 kb window across the genome using the low coverage (Pilot 1) data of the 1000 Genomes Project (http://www.1000genomes.org/ page.php) in four HapMap populations (CEU _ Utah residents with European ancestry; CHB _ Han Chinese from Beijing; JPT_ Japanese in Tokyo and YRI_ Yoruba from Ibadan, Nigeria). These statistics included Tajima‘s D, Fay and Wu‘s H, and a composite likelihood ratio test that uses the allele frequency spectrum to compare the likelihood ratios of selection versus the neutral model. Non-parametric analyses (Mann-Whitney U and permutation tests) were used to compare whether the summary statistics were significantly different between the FOXP2 targets and control sets. A small but significant proportion of FOXP2 target genes associated with neuronal function appear to be enriched for positive selection in the 1000 Genomes Project (Pilot 1) data set. If validated, these would be candidates for genes contributing to human-specific speech and language abilities. This pipeline can be used to analyze signals of selection in any chosen set of genes that may be involved in any biological processes or molecular function.

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GENETIC VARIABILITY OF MTRNR2L GENES AMONG PATIENTS WITH ISCHEMIC STROKE AND PARKINSON'S DISEASE: FUNCTIONAL IMPLICATIONS

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We have recently identified several humanin (HN) peptides encoded within the nuclear genome that may differ in their neuroprotective potential. Aim: To assess genetic variability of MTRNR2L HN-encoding genes in Polish patients with neurodegenerative disorders, including ischemic stroke and Parkinson's disease (PD), and to identify potential functional correlates in cell-culture models. We identified a c.38C>T substitution causing the Thr13Ile amino acid exchange within the MTRNR2L5 gene coding for HN5. The Ile13-HN5 variant was significantly more frequent in patients with PD compared to stroke and normal control groups. High throughput genotyping analysis of 128 SNPs within MTRNR2L and other neuro-protective genes using OpenArray technology is under way. Live cell imaging experiments on cultured human endothelial cells exposed to pro-apoptotic agents showed that the synthetic Thr13-HN5 peptide provided significantly more protection against the mitochondrially-mediated apoptosis than the Ile13-HN5 variant. The effects of Thr13-HN5 were comparable to those of the potent HNG derivative, which served as a gold standard. The Ile13-HN10b allele may be a risk factor for mitochondrial dysfunction in the setting of the pro-apoptotic stress, and may contribute to the risk of certain neurodegenerative disorders such as Parkinson's disease. Supported by the N R13 0038 04 grant from the Polish Ministry of Science and Higher Education.

P54

DISCRETE PARTICLE SWARM OPTIMIZATION FOR SOLVING 2D AND 3D HP PROTEIN FOLDING PROBLEM

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How a protein (chain of amino acids) folds plays a key role in the field of protein research and proteomics. It can help us to analysis of the function of the proteins. As a matter of fact, protein folding is the last step in deciphering the genetic code of organisms. One way for simplifying the protein folding problem, is hydrophobic-polar (HP) model. The HP model is based on hydrophobic energy can fold the chain of protein sequence, in a way that the hydrophobic amino acids to be in the interior part of folded protein. In this paper, a novel approach so-called Discrete Particle Swarm Optimization (DPSO) has been used for optimizing the HP model to achieve the native state or a state with the lowest energy in an environment. Introduced method can be used in both 2D and 3D HP protein folding problem. Each particle in DPSO will have _n-2‘ dimension that _n‘ is equal to length of our amino acid chain. Every particle in DPSO implicates one way of protein sequence folding. Each dimension in 2D HP model can have 3 situations; S (as straight), R (as right) and L (as left) and 5 situations in 3D HP; S (as straight), R (as right), L (as

left), U (as up) and D (as down). The supposed algorithm will search between possible folding shapes and will choose the particle (shape of folding) with best fitness. Fitness function for proposed approach is the energy of boundary between hydrophobic amino acids which are close to each other but not consecutive in a sequence. Energy will be calculated for each particle. The results show that the proposed approach is accurate and has a fair good speed.

P55
STUDY OF GENOMIC AND BIOLOGICAL COMPLEXITIES USING NETWORK ANALYSIS

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Complex network has emerged as a new field which has witnessed a boom since the last decade, as observed by the exponential number of the papers being published in this domain. Complex networks have been used to model a variety of multifaceted real systems-- from domains as diverse as social, technological, biological, and others. Once a complex system has been modeled as a network, different network analytic measures can be applied to discover hidden patterns, motifs, sub-graphs, structural features and principles governing the organization of the system. Recent studies have shown that there is considerable value-addition in modeling biological complex systems as networks which enables the scientists to study the system from a completely new perspective. However, the rate-limiting step in these studies has been the conversion of the real data (such as that from high through-put yeast 2-hybrid experiments) into network formats. This can be a daunting task for the life-scientists because of the availability of varied complex networks analysis tools which accept a number of different network formats. Understanding these formats can also be difficult due to the unavailability of data formats at a unified platform. Moreover, determination of the format suitable for particular task can also be a problem. In this study, we first analyzed the most commonly used complex network formats from a biological perspective, describing their minor details, syntax, strengths/weaknesses, purpose, and analyzing them on the basis of the loading and processing times. As an example, we took the protein-protein interaction dataset of yeast and converted it into all the available formats and subjected them to complex network analysis. Our results suggests that for larger datasets, Pajek.net is the most suitable format because of its size compatibility, less memory usage, and less processing time required; whereas, Pajek.mat was suitable for smaller datasets since the file size increased exponentially with the increase in nodes. This was because the edges/links in this format are represented in the form of n x n adjacency matrix which increases the size of the file, subsequently increasing the loading and processing time. Moreover, the processing of Pajek.mat and .dat file required a lot of memory which is normally not available in regular life science computer labs. Currently, we are utilizing the network approach to study the complexities of the genome at the RNA level. Successful creation of computational tools to allow this will open up new avenues of research into the structural topography of RNA networks critical for their structure and function.

P56
DETECTING TRACES OF NATURAL SELECTION IN HUMAN TYR LOCUS

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Melanin, the major component of human skin color, is an organic polymer which comes in two types: a red-yellow pheomelanin and a black-brown eumelanin. Variation in human skin and hair color can be largely explained by the levels and ratio of the two forms of melanin. Many different genes involved in pigmentation are characterized, but only a fraction of them controls skin pigmentation directly, e.g. MC1R, TYR and SLC24A5. Population genetic studies on MC1R gene, the best studied locus, reflect a very unusual pattern of variation in African and non-African populations. Diversity in this gene is considerably lower in Africans comparing to non-Africans. This is surprising as haploid loci reflect opposite situation: diversity is largest in Africa where all non-African mtDNA and Y-chromosomal variation is rooted. This striking pattern of MC1R variation could be explained by the fact that eumelanin is photoprotective, but pheomelanin is not. Mutations which decrease the eumelanin vs pheomelanin ratio, might be therefore deleterious in (near) equatorial areas with high UV level, resulting in the increased skin damage and vitamin B folate photolysis. In contrast to (near) equatorial areas, loss of function is tolerated in Europe and eastern Asia, where UV level is considerably lower. MC1R mutations, which would result in the elevated pheomelanin level and thus decreased UV protection, could be positively selected in Europeans and eastern Asians to increase UV-induced vitamin D synthesis. Therefore, human skin color is a trade-off between skin light enough to permit UV radiation penetration for vitamin D synthesis, but dark enough to reduce UV induced vitamin B folate photolysis and skin damage. Tyrosinase (TYR) is one of the key players in human skin pigmentation. To explore the extent of genetic variation of this gene in human populations and to identify possible targets of selection we sequenced in a global sample approximately 24kb including exons, introns and the 5' UTR, as it has been proposed that variation at these regions may account for the intraspecific morphological diversity. We checked for the neutrality using Tajima's D and HKA tests under the assumption of various demographic models. We further compared our results with empirical re-sequencing data and simulated neutral loci. Finally, we genotyped our re-sequencing plus additional worldwide samples with Illumina platform and checked for the selection with different ‐long-range haplotype" and other whole-genome methods. We have detected signatures of natural selection in TYR locus in all studied non-African populations. Positive Tajima's D values point to balancing selection, which maintains excess polymorphism relative to the neutral expectation. Study results

concur with the idea of functional relaxation in pigmentation genes among non-African populations.

P57
NEW METHOD FOR HUMAN DNA SEQUENCING USING HMM AND OVERLAP AND SAVE METHOD

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Today one of the most important issues in biology is DNA sequencing. especially Human DNA Sequencing (HDS).So far several method have been proposed for DNA sequencing, that a very popular of them is Hidden Morkov Model (HMM).We think that HMM can be useful method for DNA sequencing. Here we try to improve the performance of HMM. The performance of previous methods that used HMM in DNA sequencing are not very satisfying and have some drawbacks. For example these methods normally, don't achieve a good estimate for all length of sequence and don‘t spot the coding and non coding regions. In this paper we proposed a new method for HDS that use an HMM modeling with the overlap and save method. Overlap and save method have been used in signal processing for filtering the real time signals and long length signals. For validation of our model we choose chromosome 22 of human which has about 49 million base pairs. We divide this chromosome into 4900 equal segments (N=4900), each segment contains 10000 bps. For training of our system we choose 100 segments randomly from N segments for the training set. (n=100). Now, let we have a string as a length of 1 million bps that is our training set. We again divide this string into 8 equal segments, each segment contains 125000 bps and is called frame for frame k; k=1, 2, 3… 8. Each frame is chosen such that it has overlap with two other neighbors (next and previous frame).we divide our training sequence into k frames because our initial experiments show that if we investigate our sequence locally is more effective and accurate, overall than investigate the sequence globally. The value of overlap is 5000 bases. We consider for each frame a HMM and calculate the transition and emission probability with the Baum-Welch algorithm. M1, M2, M3,....., M8 are the corresponding HMM for frame K1, K2, K3...., K8, respectively, and Mxy is the HMM that its parameters is obtained by averaging from the parameters of Mx and My. For example by averaging from the transitions and emissions probabilities of M1 and M2, the transitions and emissions probabilities of M12 is obtained. From this averaging we get M12, M34, M56, M78 and with repeat this averaging between M12, M34 and M56, M78 the M1234 and M5678 is obtained. At finish, we obtain a total hmm from the two lasted hmms, which named Mtotal. We test Mtotal on the chromosome 22. Initial experiments show a good estimate for all of the length of chromosome.

P58
STATISTICAL ANALYSIS OF CHIA-PET CHROMATIN INTERACTION DATA FOR CANCER GENOMES

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We recently developed the Chromatin Interaction Analysis with Paired-End Tag (ChIA-PET) sequencing strategy for the identification of transcription factor binding sites and chromatin interactions in a global, de novo, and high-throughput manner. This technique has raised the new challenges in statistical analysis of ChIA-PET data to identify bona fide binding sites and chromatin interactions. One of the main challenges is to differentiate noisy PETs from signal PETs. The noisy PETs are probably from the random ligations of DNA fragments from different molecular complexes, and are called as chimeric data. The signal PETs are from the real intra-molecular DNA fragments of the individual chromatin interactions, and are called as non-chimeric data. Four statistics are proposed to help us to resolve the challenge: (1) the percentage of chimeric data in the total PETs of one ChIA-PET library based on linker barcode sequences, (2) the percentage of intra-chromosomal PETs vs. inter-chromosomal PETs, (3) the span distribution of the intra-chromosomal PETs from chimeric and non-chimeric data, and (4) the span cutoff for intra-chromosomal interaction clusters. The analysis results showed that random ligation (observed from the chimeric data) is really the main noise source in the ChIA-PET data. By comparing the non-chimeric data and the chimeric data, high-confidence chromatin interaction data can be extracted. We applied our analysis and ChIA-PET Tool on ChIA-PET RNAPII libraries from five different cancer cell lines, and identified high-confidence binding sites and interaction clusters. Comparing the binding sites and interaction clusters from different cell lines, we identified the common and cell-line specific binding sites and interactions, which can help us to understand the mechanism in the cancer cells.

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GDIT: A COMPREHENSIVE CLINICAL, EPI-DEMIOLOGICAL AND GENETIC DATABASE OF THE TUNISIAN POPULATION

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Databases of mutations causing Mendelian diseases play a crucial role in research, diagnostic and genetic health care and can play a role in life and death decision. Because of the existence of population-specific mutations for single gene disorders, there is an urgent need for country/population-specific databases. As no available resource on genetic diseases affecting the Tunisians exists, we aimed to provide to users (clinicians, researchers and patients) all data published on genetic diseases in Tunisia from scientific publications extracted from PubMed, OMIM and other resources, including

those of the grey literature, in a comprehensive database. More than 300 genetic disorders affect the Tunisian population were reported; mainly due to recessive genes (62.9%). Their classification shows that the congenital malformations (30.5%), metabolic disorders (23%) and diseases of the nervous system (17%) were the major groups of genetic diseases affecting the Tunisian population. Four hundred thirty nine mutations were described as the cause of the 50% reported genetic disorders affecting the Tunisian. The database integrates, in addition to clinical, epidemiological and molecular data from the Tunisian population, mutations that were identified in neighboring populations as of North Africa and the Middle East. Our database, by its rich content, will be a valuable decision making tool for researchers and clinicians; will facilitate molecular diagnosis of Mendelian disorders and will help evaluate the burden of genetic diseases on public health and establishment of preventive programs. This comprehensive resource will be useful not only for research in Tunisia, but also in the other North African and Middle Eastern populations. Therefore, we hope that the integrated data will not be for better access but also for knowledge discovery. The database is actually under construction using the Model-View-Controller architecture implemented in the open-source PHP web framework Symfony and will be freely available for users.

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CHANGES IN THE EXPRESSION OF TGF-β VARIANTS IN TISSUES AND CELLS EXPOSED TO MUSTARD GAS

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Sulfur mustard (SM) is a chemical warfare agent with cytotoxic, mutagenic, and vesicating properties. It effectuates cutaneous blisters, respiratory tract damage, eye lesions and bone marrow depression. Biological actions of SM occur through -at first hand- alkylation of cellular targets (DNA, RNA, protein, lipid and small electrophilic molecules such as glutathione). Cells exposed to SM confront problems in DNA replication, transcription and translation, which are manifested as necrosis/apoptosis, or alteration in several pathways including cell cycle control, cell adhesion, morphogenesis, repair, and inflammatory response. Transforming growth factor-b family (TGF-β) are multipotent cytokines modulating cell growth, proliferation, differentiation, recognition, apoptosis, inflammation, cellular homeostasis and angiogenesis. Altered expression of TGF-β and/or mutation in its signaling pathway has been linked to numerous diseased states, including cancer, inflammation and fibrosis. As these conditions are seen in Iranian veterans, we hypothesized that TGF-β signaling might play a pivotal role in SM-induced pathogenesis. Normal human fibroblasts were maintained in RPMI medium (37°C, 5% CO2). Near-confluent cultures were used for SM exposure. 50, 150, and 300 micromoles of SM, in fresh medium without serum, were added to cell cultures for different times (30, 60, 960 min). After RNA extraction and cDNA synthesis, expression of TGF-β variants was assayed using real time PCR. Expression of TGF-β variants was also evaluated in skin biopsies from Iranian veterans. TGFβ1 and TGFβ2 were both over-expressed in skin biopsies. In exposed fibroblasts, TGF-β1 was initially (t = 30 min) down-regulated in a dose-dependent manner, but was over expressed at 16 hrs post exposure. TGF-β2 was down-regulated at both time points, and TGFβ-3 was upregulated at 60 min post-exposure. Battlefield exposure to sulfur mustard results in early and late effects, especially on skin and lungs. As signaling pathways like IL6-78, VEGF, EGFR, TNF-α, and TGF-β have been indicated in skin and lung complications, determining the changes in the expression of TGF-β could have potential benefits in treatment of SM-exposed patients.

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TRANSCRIPTION FACTORS BINDING AND CHROMATIN LANDSCAPE IN BREAST CANCER GENOME: CHIP-SEQ ANALYSIS

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Epigenetic modifications play important role in regulation of gene expression and affect transcription factors binding. Access of regulatory proteins such as TF to DNA is regulated by chromatin and is an important aspect in controlling transcriptional regulation of specific gene loci and TF function. To study gene expression regulation and interplay with chromatin modifications in breast cancer genome we used recent ChIP-seq data in MCF-7 and T47D human breast cancer cell lines and recently available data from ENCODE project. Chromatin landscape and, in particular, histone H3 modifications, have cell-specific effects on availability of TF binding sites and recruitment of RNA Pol II complexes. Recent studies have demonstrated chromatin remodeling even in terminally differentiated normal cells and advanced-stage melanoma and breast cancer cells, in context-dependent responses to alterations in their microenvironment. Using high throughput sequencing technologies in combination with chromatin immunoprecipitation (ChIP-seq), we constructed and analyzed chromatin landscape maps in MCF-7 based on several activation marks, including activation modifications H3K9ac, H3K4me1, H3K4me3 and repressive marks H3K27me3, H3K9me3. We further analyzed these in conjunction with genome-wide binding profiles of ER, FOXA1 and p53. Estrogen receptor (ER) is regarded as a major factor in breast cancer and FoxA1 has been found to function as a pioneer factor in the recruitment of ER to gene regulatory regions. We used extensive search of co-motifs in regions proximal to ChIP-seq binding peaks in reference human genome. Binding motifs of transcription factors AP-1, SP1 and E2F1 were found among co-activation factors. To

show that this was an unbiased analysis of genome-wide maps we developed software to test statistical significance of associations between chromatin modifications. The impact of chromatin configuration (as combinations of histone modification marks) in determining both ER binding site selection and their association with gene induction or repression by ER was explored by statistical tools. Predictive logistic regression model for ERÎ± binding was constructed. Clustering of regions with activating and repressive histone marks in MCF-7 genome revealed strong co-localization of activating histone modifications and TF binding sites. Positive correlation between ChIP binding intensity of ERÎ± and open chromatin conformation was shown. In more general approach we studied association between nucleosome occupancy (predicted by DNA sequence as well as experimentally estimated by sequencing) and affinity of transcription factor binding measured by ChIP-seq. To complete analysis of gene-targets of TF binding we used gene network databases. Network analysis of cancer-related genes proximal to ER binding sites was fulfilled using STRING protein interaction database, Ingenuity Pathway Analysis (IPA) and SkyPainter Interactome software. We found clusters of genes having common chromatin activation pattern. Together, our data shows that TF binding following gene activation in cancer genome is associated with activating chromatin modifications specific for cell lines that could be used as powerful predictive tool.

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UAE MUTDB: THE UNITED ARAB EMIRATES MUTATION DATABASE

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The current United Arab Emirates residents are extremely heterogeneous with diverse ethnic and national backgrounds. The national population constitutes less than 20% of the total population with large communities from India, Pakistan, Philippines, Iran, Arab and Middle Eastern countries and smaller communities from the UK and other western countries. Genetic conditions are highly prevalent in the local and other Arab populations due to the high rates of consanguinity. The molecular causes of a significant number of those conditions have been elucidated but there is no database available. Therefore, the aim of this project is to construct such database and make it publically available. The data of the mutations reported among UAE residents have been collected from published literature as well as unpublished data supplied by researchers at the UAE University. The relational database was designed using Microsoft Access and is composed of several tables appropriately designed to store mutation data. The UAE MutDB website was created with ASP web programming language. The UAE MutDB web interface is designed to be as easy to use as possible. Each gene has been assigned its own 'homepage', where all other links are located. Each homepage contains a table detailing the type and number of mutations, with hypertext links to the mutation pages. In addition, tables containing details on entries categorized by phenotype with links to OMIM entries matching these phenotypes. The database is searchable by gene name, Gene ID and Protein Sequences. The database facilitates the retrieval of results in ―Text" and ―Table" formats. The UAE MutDB will be highly useful to the local, regional and international scientific community interested in genetic conditions among Arabs. This database will be particularly useful for diagnostic and research purposes. Furthermore, this database will complement the database maintained by the Centre for Arab Genomic Studies in Dubai.

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DISCOVERY OF NOVEL GENETIC CHANGES IN TONGUE CARCINOMA AND MATCHED LEUKOPLAKIA USING SHORT- AND LONG-MATE PAIR LIBRARIES WITH NEXT-GENERATION SEQUENCING

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Accumulation of multiple genetic changes over a period of time drives the development of tumor. Next-generation sequencing and DNA microarray studies provide a high-throughput approach to understand the roles of various changes associated with cancer. Several types of tumors and tumor cell lines have been sequenced using next-generation sequencers in the last 2-3 years generating thousands of novel SNVs, indels and structural variants [1-8]. Oral cancer is the most common subtype of the head and neck cancers in human, with a worldwide incidence in greater than 300,000 cases [9]. The disease is an important cause of death and morbidity, with a 5-year survival of less than 50% [9]. As a part of larger translational cancer research initiative, we have started sequencing pairs of tongue tumors and their associated pre-cancerous lesions from the same patients in order to catalogue all types of genetic changes. The aim of the initial study is to discover changes associated with tumor progression in tongue. Following histopathology studies, we have sequenced whole exomes and genomes from tongue tumor and matched normal and leukoplakia lesions with both short- and long-insert paired-end libraries respectively by using Solexa sequencing-by-synthesis platform. Systematic approaches were made to align reads from short- (used for SNVs & indel calling) and long-insert (used for structural variation detection) libraries using gapped alignment. In-house scripts were written and several filters were applied to select novel somatic cSNPs, indels and SVs followed by in silico prediction of the phenotypic effect of cSNPs on the translated mutated proteins. Pipeline tools were optimized to attain significant sensitivity in detecting SNVs and structural variants. Based on our analysis, we binned variants into different tiers. We plan to discuss in

detail our strategy for finding novel somatic SNVs, indels and structural variations followed by experimental validation in oral tongue tumors along with their effects on tumor progression.

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MECHANISMS OF DISEASE: A GENOME-WIDE SEARCH FOR SPLICE TRANSLATIONAL EFFICIENCY POLYMORPHISMS (STEPS) AND ANALYSIS OF GENOMIC CONFOUNDING

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Genome-wide association studies (GWAS) have transformed genetic studies of disease susceptibility, identifying many variants that may tag functional polymorphism nearby. Previous research into the insulin gene discovered a polymorphism influencing splicing efficiency and causing retention of a non-coding intron in the 5' untranslated region (UTR). This extension of the UTR was associated with increased insulin levels, suggesting a relation to disease phenotypes through differential protein quantity, whilst maintaining protein quality. Our analyses searched public genome annotation data to discover and assess candidate variants located in motif regions of non-coding introns (5' splice site, 3' splice site and branch point sequence) which may act as functional moderators of alternative splicing through splicing efficiency and correlate with reported disease association. Transcript sequences containing candidate variants were analyzed for evidence of splice motif recognition (through splicing prediction algorithms) and alternative splicing in expressed sequence tags (ESTs). Candidate polymorphisms with population frequency data were analyzed with publicly released genome-wide association data sets of common diseases for association through linkage disequilibrium. In addition, gene-variant associations from a catalogue of published GWAS results were analyzed to check for potential genomic confounding, where alternative genes exist at greater physical distances, but lesser linkage or linkage disequilibrium distances, such that alternative functionality is tagged by the reported variant. These results were crosschecked with splicing variants and an online visualization tool was developed for future analyses. This in silico study revealed many candidate polymorphisms in splicing motif regions of 5' UTR introns, with 21 candidates showing EST evidence of alternative splicing containing the polymorphism as well as population frequency data. These results suggest potentially many intronic polymorphisms contributing to splicing efficiency. While, none showed strong evidence of being explanatory of any leading GWAS hit, functional studies and studies of the wider range of genetic influences in both polygenic and monogenic disease will be necessary further to clarify the impact of STEPs variants. We also developed a database and browser to examine recombinational as well as physical gene proximity to reported GWAS hits. Of 1907 gene-variant associations published, 55 variants were discovered where recombination was lower between the identified variant and a physically more remote gene than the one initially reported, highlighting potential for genomic confounding amongst reported associations, through misassociation of a gene with a tagged variant.

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A NEW MATHEMATICAL MODEL FOR RELATIVE QUANTITATION OF GENE EXPRESSION BY REAL-TIME RT-PCR USING SYBR GREEN DYE

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Quantitation of mRNA expression levels using real-time reverse transcription PCR is increasingly used to verify DNA microarray results and to investigate the physiological changes in gene expression pertinent to residual tumors or minimal residual disease. Several mathematical models were developed for computing the relative expression ratio of a target gene versus a reference (housekeeping) gene and these models were based on normalization of differences in threshold cycles (CT) in test and control samples. These models are more reliable in real-time PCR employing gene-specific fluorescent probes, where fluorescence is a function of amplicon copy number. However, a crucial problem exists in relative quantification of gene expression by real-time PCR employing the intercalating SYBR Green I fluorescent dye that binds to double-stranded DNA. In this case, not only amplicon copy number but also amplicon length and non-specific amplification products contribute to the overall fluorescence. Therefore, the relative expression ratio based on threshold cycles will not be optimally computed by using the available models. In this study, a new mathematical model for relative quantification is described for real-time RT-PCR using SYBR Green dye. Consistent with PCR-efficiency correction, this new model relies on a correction factor to correct for the variation in amplicon length. This correction has been proved useful for quantifying low gene expression levels and for determining the relative expression ratio of a target gene versus a reference gene in test and control samples.

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USING MULTI-OBJECTIVE GRAVITATIONAL SEARCH ALGORITHM (MOGSA) FOR BI-CLUSTERING OF GENE EXPRESSION MICRO-ARRAY DATA

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With the advent of microarray technology, there has been a substantial progress in gene expression studies. Using of microarray technology unlike other previous methods that have studied only one gene allows us to survey thousands of genes simultaneously. On the other hand, this technology has generated great amounts of data which needed to be analyzed. One way of analyzing this data is biclustering which helps

clustering both genes and conditions simultaneously. Several algorithms have been applied to this problem in the literature, however the clustering problems are still challenging. Since in biclustering there are several objectives that are contradictory with each other, so normally we need a multi-objective optimization algorithm for solving this problem. Recently, many studies have been done on the use of swarm intelligence algorithms such as Particle Swarm Optimization (PSO) in data clustering. In this paper, we will use a different method called Gravitational Search Algorithm which is based on swarm intelligence in dealing with data clustering. This algorithm was inspired by the notions of mass, gravity and gravitational forces. In this algorithm a set of agents (masses) search the space randomly and each agent affects other agents, proportional to its mass and distance to other agents. The initial numerical results gained through this algorithm on the benchmark dataset show the efficiency of this algorithm in solving microarray biclustering problem, and it compares with MOPSO results favorably.

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TRANSCRIPTIONAL PROFILING OF HOST CELL RESPONSE TO VIRAL RESPIRATORY TRACT INFECTIONS: TARGETING INFLAMMATORY RESPONSE AND VIRUS MATURATION

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A global disease burden study predicted that in 2020, chronic obstructive pulmonary disease and lower respiratory tract infections (RTIs) will rank third and fourth among death causes. Major viral pathogens, other than influenza A, contributing to RTIs are human rhinovirus (RV) and human respiratory syncytial virus (RSV). Both viruses induce pro-inflammatory mediators of lung epithelial pathways. Often it is the host response to the infection rather than the cytopathicity of the virus that lead to lower RTIs and exacerbation of asthma. Lack of approved vaccines and limited availability of antiviral drugs require new strategies focusing on the suppression of inflammation and viral maturation process. The latter is accompanied by host plasma membranes rearrangements and alterations in lipid content. Since the molecular mechanisms are poorly understood we started to examine differences in molecular pathways of in vitro host responses as well as differences in response to RV and RSV. Here we report a R/Bioconductor analysis of relevant host genes by RSV infection using genome-wide (HG-U133 Plus 2) temporal gene expression profiles to improve the understanding of RSV infection dynamics and pathway cross-talk associated with RSV-mediated lipid raft microdomain changes. Mfuzz clusters with significantly upregulated transcripts in early phases of infection were as expected associated with cytokine receptor signaling, peptide transport, protein kinase phosporilation, transcription factor regulation among others. For example, CDC25 and other M-phase associated transcripts were down-regulated in early phases of infection might be the result of RSV-induced p38 MAPK activation. In later phases, genes associated with Golgi transport vesicle coating processes, sterol and cholesterol biosynthesis, including transcription factor SREBF2 and peroxisomal membrane localized ABC transporters were significantly enriched. The observed convergence of these genes and interconnections of activity have important implications for selecting targets to dampen the inflammatory response and prevent virus maturation.

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MMP-1, 2, 8, AND 9 IN TEAR FLUID OF MUSTARD GAS EXPOSED PATIENTS WITH CHRONIC DRY-EYE SYMPTOMS

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There are much more victims with chronic eye injuries due to Mustard gas during the Iraq- Iran war. Eyes are the most vulnerable organs to sulfur mustard gas Dry eye is a prevalent chronic complication in these patients. In less than 1% of patients with battlefield exposure to sulfur mustard, a delayed type of ulcerative keratopathy may develop; leading to late-arrival blindness. There is much evidence to suggest that MMPs play a vital role in several physiological and pathological processes. The purpose of this study was to compare the levels of MMP-1, 2, 8, and 9 in tear fluid of people exposed to mustard gas compared to normal group. Various biochemical reactions and alterations in DNA structure can explain cytotoxic and mutagenic properties of sulfur mustard. This study is performed in Baqiyatallah Hospital, Tehran, Iran, in 2009 and In this study 25 of patients who were exposed to mustard gas and had chronic dry eye symptoms were compared to 25 patients as control group consisting of 25 people who had common chronic dry eye symptoms with blepharitis and 25 healthy people as normal group. The level of MMP-1, 2, 8, 9 in tear fluid of people of these three groups was assessed by ELISA. Double sandwich ELISAs for human MMP 2, 8, and 9 and TIMP 1 and 2 were performed with commercial kits (Ray Biotech, Germany), according to the manufacturer‘s protocol. The results for levels of MMP-1(P=0.8) and MMP-2 (P=0.54) in tear fluid of patients in comparison with normal group do not indicate any significant difference. On the other hand the calculated levels for MMP-8(P=0.002) and MMP-9 (P=0.01) in tear fluid of patients in comparison with normal group shows a significant increase. The effects of exposure to mustard gas on eyes of chemical-injured veterans destroy meibomian glands which paves the way for evaporative dry-eye. As a result MMPs in tear fluid of these patients increase which eventually elevates the MMPs levels in tear fluid and results in later eye-impairments.

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COMPLEX NETWORK DATA SOURCES AND PARAMETERS FOR DISEASE SPREAD ANALYSES

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Complex network analysis (CNA) is a powerful computational tool to investigate the dynamics of structural patterns. We can extend CNA to understand disease dynamics effectively. For example, knowledge from the genetic interaction data can be used to discover patterns in disease diffusion processes through social interactions or CNA can be used to investigate the effects expected from diseased genotypes on social networks. CNA can be used to study correlations between genetic and disease networks as well. However to correlate many types of interaction data, there is a dearth of publicly-available reliable data. There are two areas of complex networks, i.e., complex network generation and complex network analysis. The verification, validation and study of both of them are solely dependent on the underlying data on which they are executed. However the scarce and dispersed data sources of complex networks on worldwide web act as a bottleneck to the research process and slow down the pace of research. Further complexity arises since most research studies give partial access to data in the form of different analytical parameters and analyze data in tabular formats, images or supplementary materials, etc. The present study conducted a review of the current complex network data sources with a focus on the quantitative tools of network theory used to unravel various disease spread networks. We discovered three types of complex network data sources according to the type of origin besides the accessibility issue. The first are the knowledge repositories that include databases of different journals, such as Science Direct, Pub Med, etc. that have some publicly accessible versions of data used in each study. These repositories have special contracts and policies with the authors of the studies that apply to their modification or usage in future by other people as well. The second type of repository includes numerous complex network centers associated with universities and scholars of domains which provide limited access to selected studies through online established labs and databases. The third type of repository belongs to surveys for different studies which are being performed at all times. The surveys can be either specific for some study in which data is gathered according to the need of that particular study, or might be large surveys performed over long periods of time, such as the Framingham Heart Study, which can prove helpful in a number of studies. Small studies hardly have their data accessible, but we found that large survey studies did offer accessibility through online contact via application forms, etc., and proper acknowledgement. Here, we provide an integrated source of current complex network data sources to increase the pace of research in the domain. Since most of the studies do not make available their research data, we suggest that some public version of data must be made accessible with a proper acknowledgement policy. Finally, our analysis reveals that clustering analysis, degree distribution and component distribution are the most popular and significant measures of network theory for the analysis of disease spread networks.

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GENOMEBREAK: A VERSATILE COMPUTATIONAL TOOL FOR GENOME-WIDE RAPID INVESTIGATION, EXPLORING THE HUMAN GENOME, A STEP TOWARDS PERSONALIZED GENOMIC MEDICINE

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It was long believed that Human Genomes are similar to each other by 99.9%. Recent studies by researchers across the globe have confirmed this to be slightly less to around 99.5% identity. This research unravels further discovery that the identity between two different persons genome could be less than 95%. More than 5% of structural variation in the human genome such as CNVs, SNPs, etc. opens up more promise for the world of personalized genomic medicine as this gives clue as to why some individual are more prone to diseases than others, why some individuals have no or reduced effect on drugs, while some are incurable. The work presents a bioinformatics tool developed called GenomeBreak which handles genome wide variation detection robustly doing extensive calculations which would otherwise take years to investigate in order of few days, plotting the variation in a map for further deduction. Now that sequencing of genomes have become relatively cheaper by the advent of inexpensive technologies, the bottleneck lies more in the analysis of the genome for which the software tools such as GenomeBreak finds great applicability.

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DETERMINATION OF GENE'S EXPRESSION STRENGTH INFLUENCE ON FUNC-TION/PROCESS/COMPONENT IN COMPARISON TO OTHER EXPRESSED GENES

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The purpose of the study is to reveal the strength of the relationship between gene expression level and their molecular functions, biological processes and cellular components (terms described in Gene Ontology database) in comparison with other genes involved in analyzed feature (e.g. disease). The study is based on the data obtained from microarray experiments stored in Gene Expression Omnibus database and the relationship between features of gene and its product. Information about the expression level of specified genes and their GO database features allows making a comparison between control and affected groups (e.g. affected group with muscular dystrophy). The calculation is carried out by the application of Z-association coefficient. Z-correlation measurement expresses the dependence between two families of events: Aj and Bi where Aj: genes or group or genes-clusters and Bi: e.g., stages of disease. The coefficient is defined on the basis of the dependent events probabilities and gives information about dependence between particular gene

and stages (eg. disease or process). This measure can help reveal dependences that were difficult to discover formerly. This approach was applied also in other genome analysis. Experimental procedure consists: - retrieval of the strength of gene connection with particular feature: Function, Process, Component from GPL file (taken from Gene Expression Omnibus database) - retrieval of gene expression level from GDS file - counting the average gene expression based on the samples (for affected and unaffected separately) - Function/Process/Component gene contingency tables expressing the influence of gene on specified feature creation. Z-coefficient is used to compute the data. - comparing data and extraction of the differences between control and affected groups - strength of the relationship between gene expression level and the features described in Gene Ontology database assessment. The study provides the algorithm for further investigation of the influence of the gene expression level on Function, Process or Component. This approach allows identification of the characteristics of gene profile as well as those genes with the strongest influence on the examined feature (high level of expression does not mean high correlation with analyzed feature). Calculation procedure, which is based on the real expression data, is expected to give suggestion for medical doctors in designing treatment procedure.

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EXONS AS UNITS IN THE IDENTIFICATION AND VISUALISATION PROTEIN REGIONS

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The purpose of the study is the presentation of the tool oriented on identification and visualization of protein regions encoded by exons. Exon-intron classification is taken as a base for discovering coded regions and presenting them on 2D and 3D protein models. Secondary aim is carried out by preliminary screening of the dataset, which is connected with gene underlying the cancer process in this example. It reveals protein regions (secondary structures, domains) which are encoded by more than one exon. Presented tool provides the following features: - color-coded graphical display of the proteins structure (secondary structures and domains in 3D) is correlated with the corresponding exons - visualization of the exon-intron structure of gene which codes the protein with unknown 3D structure Algorithm of procedure steps: a) obtaining exons parts from nucleotide sequences taken form GenBank (*.gb) and corrected by CDS parameter b) comparing amino acid sequences taken form GenPept (*.gp) with the sequence from the previous step for the confirmation of their compatibility c) revealing the differences between sequences from step a) and sequences received from structure data taken from Protein Data Bank (*.pdb) by using bl2seq tool d) determination of secondary structure e) listing of aminoacid sequences, secondary structures and assigning exon number to proper positions of examined sequences f) visualization of proteins with exons as a unit of 3D structure There are numerous web tools that arise in the context of gene structure analysis. Most of them are unfortunately not accessible or do not work for the new structure of proteins. Presented tool is easy to use and can be downloaded for free (http://www.bioinformatics.cm-uj.krakow.pl). Preliminary analyses with the developed application may serve as an example dedicated to those who study exons' representation in proteins (both 2D and 3D). Moreover, it might be also used as an helpful in a study of the relationships in different organisms for investigating the evolution of exon representation in protein domains.

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A CONSTRICTED PARTICLE SWARM OPTIMIZATION METHOD FOR PAIRWIS ALIGNMENTS OF BIOLOGICAL SEQUENCES

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Alignment of biological sequences is a very useful tool for conservation analysis in biology and genome research. Also, it can be used in searching biological databases, and prediction of unknown protein sequences' structure/function, and in building of phylogenetic trees of similar DNA or protein sequences. However, pairwise alignment of sequences is one of the most difficult problems in biology. So far, different approaches have been introduced to solve this problem. In this paper, a Constricted Particle Swarm Optimization (CPSO) method uses constriction coefficient in the form of integer values has been proposed to solve this difficult problem. In this kind of PSO as opposed to the conventional PSO, constant terms (C1 and C2) are omitted and instead of them the random terms which are chosen between zero and especial constant in each iteration is used, also, inertia weight presented in new form which is tuned by two parameters: k and Ï†. The important point is that this PSO requires no explicit limitation as upper bound Vmax. In our proposed approach, best score for pairwise alignment is achieved by moving gap symbols through the sequences randomly using introduced PSO. Also, in order to update positions and velocities of particles, binary format has been used. To do this, 'zero' has been considered as gap symbol and 'one' has been used instead of base symbols (such as: A, T, C and G). Something that should be mentioned is; no base symbols should be omitted in updating step, therefore, in each iteration, alignment solutions are checked whether sequence of all symbols in the biological sequence remain in initial format or not. Using proposed approach, results show that this algorithm can present very quick and precise solutions; also, it is predicted that it can be used for Multiple Sequence Alignment (MSA).

P74

HUMAN ALU REPEATS STUDY: CONSTRUCTION OF ALIGNED DATABASE AND THE SOFTWARE DEVELOPMENT

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Earlier we have studied a human DNA digestion in silico and constructed diagrams of the chromosomal DNA cleavage at different short DNA sequences, which are recognition sites of known restriction endonucleases. Comparison of the calculation data and patterns of human DNA hydrolysis with restriction enzymes has shown a very good coincidence of theoretical and experimental results. Analysis of the DNA cleavage diagrams has shown that visible bands in patterns of genomic DNA hydrolysis, which correspond to DNA fragments less than 300 bp in length, are formed mainly due to cleavage of Alu repeats. A set of Alu repeats, which belongs to SINE group of DNA repeats, is one of the most abundant and well characterized repetitive elements in human genome. A total number of Alu repetitive elements in human genome is about 10%. In our work we have constructed a database of aligned Alu repeats, which consists of 1197 thousand sequences and about 440 million bps. We have proposed a method of restriction analysis of aligned Alu repeats, which is much easier than a study of whole human genome (> 3 billion bps in length). Developed software allows carrying out DNA cleavage calculation on standard PC for several hours and the obtained results well correspond to the theoretical patterns of total genomic DNA cleavage and to experimental data of chromosomal DNA hydrolysis.

P75

AN AUTOMATED PIPELINE FOR DETECTING HUMAN GENETIC VARIATIONS FROM NEXT-GENERATION SEQUENCING DATA

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The advancement of high throughput sequencing technologies has provided researchers with unprecedented opportunities to address many important biomedical problems. Large-scale resequencing projects, e.g. 1000 Genomes, TCGA, and ESP etc, have been initiated to extend our knowledge of single nucleotide polymorphisms (SNPs), short insertions/deletions (INDELs) and structural variations (SVs) and relate these variants to human diseases. The amount of NGS data submitted to public repositories such as Short Read Archives (SRA) is growing exponentially and submissions represent a wide array of technology platforms and sequence collection strategies. To process and analyze such enormous data with complexity for variation detection in a uniform and efficient manner is a challenge requiring a standard pipeline. In collaboration with investigators at Boston College and the University of Michigan, NCBI continues to develop a framework Variation Discovery and Annotation Pipeline. The pipeline generates quality input sequence data from SRA, checks sample identities, aligns the read data with the human reference genome sequences, refines the mapping of placed reads (base quality recalibration and duplicate mark etc), and calls SNPs, INDELs, and SVs according to data availability and project-specific policies. A centrally implemented pipeline streamlines the data processing workflow for the data generated by next-generation sequencing technologies. Currently, this NIH-based pipeline has been used for processing the 1000Genomes main project and TCGA datasets.

P76

A GENOME-WIDE STUDY OF POPULATION STRUCTURE AND INDIVIDUAL ADMIXTURE IN KAZAKHS: IMPLICATIONS FOR GENETIC HISTORY AND GENE MAPPING

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As many human populations settled at Central Asia, Kazakhs demonstrate an array of mixed anthropological features of east Eurasian (EEA) and west Eurasian (WEA), indicating a possible scenario of biological admixture between already differentiated EEA and WEA populations. However, their complex biological origin and genomic make-up, as well as gene flow from surrounding populations over the past millennium are not well understood. In the attempt to decipher their genetic structure and population history, we conducted, to our knowledge, the first genome-wide study of the Kazakhs residing in Xinjiang. Analysis was performed using over 900,000 genome-wide single nucleotide polymorphisms (SNPs) and 600 copy number polymorphisms (CNPs) in 47 unrelated Kazakhs and made comparisons with world-wide populations. We show that Kazakhs are genetically distinctive from Uyghurs in terms of their overall genomic make-up, although both populations showing substantial admixture of EEA and WEA ancestries. Based on genome-wide random markers and ancestry informative markers (AIMs), the ancestry contributions in Kazakhs were estimated to be 61% from EEA and 39% from WEA, respectively. Only modest variation in admixture proportions was observed among individuals, indicating a lack of recent and continuous gene flow from well-differentiated EEA and WEA populations. The interactions of EEA and WEA ancestries in Kazakhs could be dated back to 1,400 years ago, assuming average 20 years per generation. We concluded that the present-day Kazakhs can be considered as an admixed population by genomic make-up, and the admixture features of Kazakhs hold great promise to applications of admixture mapping and advance genetic-based medical research. We finally constructed a genome-wide admixture map with ancestry informative SNPs and CNVs for gene discovery using admixture mapping in Kazakhs.

GENETIC ASSOCIATION STUDIES

P77

ASSOCIATION OF APOLIPOPROTEIN E (APOE), METHYLENETETRAHYDROFOLATE (MTHFR) GENOTYPES, LIPIDS LEVELS AND ALZHEIMER DISEASE IN AN ALGERIAN POPULATION

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Alzheimer's disease (AD) is the most common form of neurodegenerative dementia and affects up to 15 million people worldwide. Although no single cause of AD has been identified, recent research has suggested that several pathogenetic factors influence risk and expression. The aim of the study was to investigate the association between apolipoprotein E (Apo E), methylenetetrahydrofolate (MTHFR) genotypes and lipids as risk factors for Alzheimer disease (AD) in a population-based Cross-sectional study of ageing living in Constantine, Algeria. Of an original sample of 187 referrals to a neurology clinic specializing in memory disorders, 63 were given a diagnosis of AD (mean age 73, 47 ± 7, 61 years, mean MMSE 20.0 + 5.7) according to (DSM IV - NINCDS – ADRDA) criteria; and 124 cognitively normal subjects (control group, mean age 67,17 ± 10,84 years). ApoE and MTHFR gene were amplified by polymerase chain reaction (PCR) in a DNA thermal cycler (Genius) using respectively the forward: (5'- AAC AAC TGC CCC CGG TGG CG -3') and the reverse: (5'- ATG GCG CTG AGG CCG CGC TG-3') primers as previously described (Richard et al. 1994). (5'-TGA AGG AGA AGG TGT CTG CGG GA-3') and (5'-AGG ACG GTG CGG TGA GAG TG-3') (Abbate et al. 1998). The ApoE allele frequencies of AD cases and controls were 5.5% vs. 7.2% for ε2, 63.5% vs. 83.9% for ε3 and 31% vs. 8.9% for ε4. The AD patients compared with controls subjects had significantly higher mean of Total Cholesterol (TC) (191 ± 37 mg/dl vs. 175 ± 37mg/dl, $p<0.05$), LDL-C (122 ± 29 mg/dl vs. 110 ± 32 mg/dl, $p<0.05$) levels in men and lower HDL cholesterol with mean values of (37 ± 08 mg/dl vs. 44 ± 07 mg/dl, $p<0.05$) in men and (42 ± 08 mg/dl vs. 47 ± 08 mg/dl, $p<0.05$) in women respectively, whereas the triglycerides mean values were no significant in our study population. The carriers of allele ε4 and ε3/ε4 subjects compared with ε3/ε3 are associated with an increased incidence of AD with odds ratio of 5.01[95%CI, 2.36 to 10.71] $p<0.001$ and 3.86 [95%CI, 1.72 to 8.72] $p<0.001$, respectively. These results indicated that AD patients with APOE-ε4 allele have a distinct plasma lipid profile and carrier of this allele with high (TC), LDL-C and low levels of HDL-C may be more susceptible to AD. No significant association of MTHFR C677T allele and genotype with AD was observed in total samples.

P78

STRIKING PAUCITY OF HLA-B27 IN THE ENDOGENOUS POPULATION OF UAE AND ITS IMPACT ON DISEASE-ASSOCIATIONS

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This presentation basically spans over the previous and present prevalence of the B27 antigen among healthy Emirati Arabs (UAE natives) and compare it to others reported in individuals from the rest of the Arab world. It also extends to the relevance to ankylosing spondylitis (AS). The antigen was rare (1/201, 0.5%) in 1995 and surveys from 2007 revealed that it had remained as such (prevalence 0/109, 0%), p=1. This exceedingly rare antigen subsequently reflected on the paucity of B27 + ve AS cases too. However, the antigen was present in 31/201, (8.5%) and in 2/ 125 (1.5%) in other healthy Arab expatriates from the Eastern Mediterranean region, P= 0.006 and in 7.5 and 4 %, p=0.2 in the healthy Asian expatriates in these two populations respectively. In all patients with spondyloarthropathies, the antigen was present in 5/86 of the Emiratis (6%), one of which was a B27+ve AS , 22/98 (22.5%) in expatriate Arab patients , p=0.001, and in 19/73 (26%) in the expatriate Asian patients. Cumulatively, the B27 was present in 27 / 184 (14.5%) among Arab patients vs the 26% in Asians, p = 0.04. In the population of AS patients specifically, B27 was found in 1/14 (7%) in Emiratis vs, 15/28 (53.5%), p= 0.005. The presentation also provides clinical models of the above. The data obviously support the inter- and intra-racial disparity of B27 prevalence in the healthy and patient studied populations. The rarity of B27 in Emiratis makes any possible contribution to the diagnosis of AS is rather negligible. Cases of B27 positive AS are likely to be encountered in expatriate patients from Eastern Mediterranean region and Asians. Finally, since the observations were first made more than decade ago, the time gap had little or no impact on the profile of B27 in the endogenous population of UAE.

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CHARACTERIZATION OF A NOVEL DOMAIN IN THE DNA DAMAGE CHECKPOINT PROTEIN RAD9

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Specific region(s) in Rad9 are responsible for the biological functions of the protein. This idea was established when active domain- deleted protein has been tested in terms of biological activity against DNA lesion causing agent- treated fission yeast. Yeast cells with Rad9 (Δ50-74)-c3xHA appeared to be not able to tackle the impact of the cytotoxic agent camptothecine (CPT). Using PCR, the needed domains and points were deleted and mutated. The protein is to undergo the

practical procedure through which the assumed hypotheses are to be tested. A complete domain was deleted from M50.HA and Y61, T52 single point mutations, FF57, 58AA and T52 and Y61 double point mutation were carried out on the full length Rad9. The activity of new proteins were tested in terms of their abilities to tackle the defective effect of DNA damaging agents, so that the importance of the mutated domain and points to the activity of full length Rad9 and M50 would be able to be revealed. It has been found that without the point mutated and the domain deleted, neither M50.HA nor Rad9.HA could make it possible for yeast cells to survive while under the effect of those DNA damaging agents which were CMP, HU and UV light respectively. These findings were concluded via choosing practical techniques involving acute and chronic survival tests.

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A GENOME WIDE SEARCH FOR TYPE 2 DIABETES SUSCEPTIBILITY GENES IN ARAB FAMILIES

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Type 2 Diabetes (T2D) is currently the fastest growing debilitating disease in the world. In the United Arab Emirates (UAE), it has been estimated that one out of five people between the ages of 20 to 79 lives with this disease. Due to an increasing prevalence of T2D in the region, lifestyle management strategies with an emphasis on prevention are required. Determining genetic risk factors can also make an important contribution to understanding the processes leading to disease. A genome wide association study (GWAS) using a family based association test (FBAT) in an extended family of 178 members from the UAE (66 diabetic and 112 healthy individuals) were genotyped using the Illumina Human 660 Quad chip array was undertaken in order to identify gene(s) and mechanisms associated with disease. The study revealed 21 new association signals from single nucleotide polymorphisms (SNPs) within five genes (RBM47, KCTD8, GABRB1, SCD5 and PRKD1). Six SNPs within PRKD1 on chromosome 14 were found to be most strongly associated with T2D in this Arab population. It has been suggested that PRKD1, a serine/threonine kinase, plays an important role in insulin secretion. The strongest statistical evidence for this new association signal was from rs10144903 in intron 1 of PRKD1, with the overall estimate of effect returning an odds ratio of 3.72 (95% confidence interval, 1.28-10.82; p-value = 3.92E-06). This study is the first GWAS for T2D in families of Arab descent, and these findings may provide important insights into the pathogenesis of T2D in Middle Eastern populations. Comparative analysis with other ethnic groups could assist in dissecting the mechanisms that cause the disease.

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MOLECULAR DETECTION AND GENOTYPING OF CYP2D6*10 AMONG FILIPINOS

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Cytochrome P450 (CYP2D6) is one of the major drug metabolizing enzymes involved in the biotransformation of many clinically important medications including opioid analgesics. CYP2D6 enzyme activity varies considerably within a population. Particularly, CYP2D6*10 allele is more common among Orientals than among Caucasians. A recent study among Chinese individuals showed that the allele frequency of CYP2D6*10 was about 37-70%. Phenotypic expressions include individuals with ultrarapid, extensive, intermediate, and poor metabolizer status. It has been shown that the various phenotypes have profound effects on the efficacy of drugs as well as its adverse reactions. The present study aimed to optimize PCR-RFLP technique for the detection and genotyping of CYP2D6*10 gene among Filipinos. Genomic DNA samples were obtained from healthy participants and patients with chronic pain, with diagnosed cancer pathology stages 1 to 4. All study participants were referred to the Pain Management Center and gave informed consent prior to enrolment. Results: The restriction enzyme HphI was determined to cut the 325-bp amplicon. Of the 65 DNA samples, 13 (20%) were identified as homozygous for the wild type, 33 (51%) were identified as heterozygous, and 19 (29%) were identified as homozygous for the mutant allele. The calculated allele frequencies in Hardy Weinberg equilibrium were 0.45 and 0.55 for the CYP2D6*10 dominant and recessive alleles, respectively. Our results showed that majority of the Filipino study participants were heterozygous for the intermediate allele (51%). PCR-RFLP provides a useful technique for detection and genotyping CYP2D6*10 among Filipinos. The allele frequency of CYP2D6*10 in this study was comparable with other Asian populations. Individuals heterozygous for the intermediate allele were found to be the predominant genotype among Filipinos in this study.

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ATRX IS REQUIRED FOR SERTOLI CELL SURVIVAL AND ANDROGEN RECEPTOR-DEPENDENT SPERMATOGENESIS

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X-linked ATR-X syndrome in males is characterized by mental retardation, facial dysmorphism, alpha thalassemia and urogenital abnormalities including small testes with scattered seminiferous tubules. Although the chromatin remodeling protein ATRX is widely expressed during development, how ATRX mutations cause these highly specific clinical features is not well understood. To investigate the mechanisms underlying the testicular defects observed in ATR-X syndrome, we generated ScAtrxKO mice with Atrx specifically inactivated in the somatic Sertoli cell lineage of the mouse testis. ScAtrxKO mice have very small testes with discontinuous seminiferous tubules, the result of Sertoli cell apoptosis during fetal life. Postnatally, spermatogenesis was delayed, and spermatogenesis defects ranging from meiotic arrest to the absence of germ cells were evident in adult ScAtrxKO mice. The expression of the key spermatogenesis gene, Rhox5, and two other Androgen Receptor-dependent genes, Spinlw1 and Cldn3, was significantly down-regulated in ScAtrxKO testes. Moreover, the ATRX and Androgen Receptor proteins physically interact in the testis and co-operatively activate the Rhox5 promoter in a transfected Sertoli cell line. In summary, our data show that ATRX has distinct functions in Sertoli cells; as a survival factor during fetal testis development and as an Androgen Receptor cofactor during spermatogenesis. Recruitment of ATRX by tissue-specific transcription factors could be a novel mechanism by which ATRX controls the developmental processes that are defective in ATR-X syndrome.

P83

ROLE OF ABCB1 GENETIC VARIANTS IN PREDISPOSING RISK TO EPILEPSY AND PHARMACORESISTANCE

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Epilepsy is a common neurological disorder, constituting a heterogeneous group of disorders characterized by recurrent unprovoked epileptic seizures due to widely different etiologies afflicting approximately 5 per 1000 population the world over. Thirty percent of the epilepsy patients continue to be pharmaco-resistant, despite optimal Anti epileptic Drugs (AED) therapy. Over expression of multidrug transporters in blood barrier is implicated in pharmaco-resistance of epilepsy, which may lead to limited penetration of AED to brain. ABCB1 gene product, P-glycoprotein, is one of the ATP-dependent multidrug transporters, reported to be over expressed in epileptic brain. The variants in the ABCB1 gene were reported to alter the expression of p-gp, in addition to other factors, and in turn affect the transport rates of the AED. The variants in the ABCB1 gene, viz: - C3435T, G2677T, and C1236T, in genotypic, allelic and haplotypic combination were found to be associated with pharmaco-resistant epilepsies although with conflicting results among studies in different population, which may be due to heterogeneous phenotypes of epilepsy patients studied, variable definition of pharmaco-resistant epilepsies used and related to ethnic and racial differences between the populations investigated. The present study aims to compare the prevalence of four ABCB1 variants viz: - rs1202168 (+139C/T), rs1128503 (1236C/T), rs2032582 (2677G/T, rs1045642 (3435C/T) and its haplotypic association between homogeneous phenotypes of mesial temporal lobe epilepsy with hippocampal sclerosis (prototype of pharmaco-resistant epilepsies, n=203), juvenile myoclonic epilepsy (prototype of pharmaco-responsive epilepsies, n=175), and normal healthy controls (n=262), belonging to the Kerala population, South India. Genotyping was done by PCR-RFLP and was confirmed by sequencing. Allele, genotype and haplotype frequency were computed among the cohorts. All the SNPs genotyped in controls were within the Hardy-Weinberg equilibrium. The rs1045642 (3435C/T) variant was seen to be significantly associated in genotypic and allelic combination, when normal healthy control were compared with pharmaco-resistant and pharmaco-responsive cohort independently. Increased representation of T alleles was observed in the patient groups, which is in contrast to observation in European studies. When both the patient cohorts combined, were compared with normal healthy controls, T allele of rs1045642 (3435C/T) was seen to be associated in allelic and genotypic combinations with patient population and thereby suggesting for conferring risk of developing epilepsy. More over T allele association is seen to extend in haplotypic combinations too. None of the other ABCB1 variants were seen to be significant when pharmaco-resistant and pharmaco-responsive cohorts were compared. Results suggests ABCB1 C3435T variants are more prevalent in epileptic patients compared to non-epileptic subjects and more frequent in pharmaco-resistant cohort, of Kerala population, and can be a plausible candidate gene to predict pharmaco-resistance and predisposition to develop epilepsy.

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APPLICATION OF GENTREPID AS A DISCOVERY TOOL IN GENOME-WIDE ASSOCIATION STUDIES OF COMPLEX DISEASES

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Genome-wide association studies (GWAS) aim to identify the genetic architecture of complex diseases by using genotyping arrays to test a large number of SNP markers for disease correlation. However, the typical GWAS approach to identifying the disease-causing gene appears to be inadequate with very few results per study. This may be a due to the genotype platform, population or poor gene prediction methodologies. Here we analyzed data from the Wellcome Trust Case Control Consortium on seven disease phenotypes: bipolar disorder, coronary artery disease, Crohn‘s disease, hypertension, rheumatoid arthritis, and type I and type II diabetes. We used the Gentrepid candidate gene prediction

system to select likely gene candidates associated with SNPs of less stringent statistical thresholds than applied in the original analysis and an alternate SNP to gene mapping assumption. We used four different significance thresholds to associate SNPs with phenotypes. In the phenotypes that did not have many highly significant SNPs such as BD and HT, the modestly and weakly significant sets were capable of replicating known loci. We explored 6 different SNP mappings, 3 distance based and 3 proximity based. Predictions were made using protein domains and pathway information of known disease genes or by searching for enrichment of these features within the search space. For each phenotype, Gentrepid was able to extract known disease genes and predict novel plausible disease genes in known and novel, WTCCC-implicated loci. The results show the approach is feasible and may be a valuable discovery tool on other GWAS data.

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EMPLOYMENT OF THE PROTEIN KNOWLEDGE BASE FOR DATA ANALYSIS IN GENOME-WIDE ASSOCIATION STUDIES

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Genome-wide association studies (GWAS) aim to identify the genetic basis of complex diseases by using genotyping arrays to test a large number of SNP markers for disease correlation. The next step of identifying the causal gene is not straightforward. The details of genomic architecture are not well understood and the SNP itself may not be causal but merely in linkage disequilibrium with the causal SNP. Other factors, such as the population-based nature of the study, make the association data noisy. To examine the effect of genetic architecture, we explored six different SNP-to-gene mapping approaches. To account for noise in the data, we take the cream of the data, the top 0.2%, and resift this data using the biomolecular knowledge base using two independent modules based on pathways and homology. The data shows more generous mappings have higher enrichment ratios suggesting the implicated SNP may be further from the disease gene than is commonly used in analysis of GWAS data. As shown previously, pathway-based data makes informative predictions both when benchmarked against disease genes identified using a candidate gene approach as well as genes identified through a more agnostic approach. More interestingly, domain based homology information was not informative when benchmarked against known genes, but was effective when benchmarked against WTCCC genes, suggesting either bias in selection of previous candidates or pathway-based data, or larger contribution of gene homologs to complex diseases than Mendelian diseases.

P86
DECIPHERING THE GENETIC AFFINITIES OF THE CENTRAL INDIAN TRIBES

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Madhya Pradesh is one of the largest Indian states located in the central part and is homeland of several tribal groups. There are less detailed genetic studies on the populations inhabited in this region. Therefore, this study is an attempt for an extensive characterization of the maternal as well as paternal ancestries of three tribal populations, namely; Bharia, Bhil and Sahariya of Madhya Pradesh using Y chromosome and mitochondrial DNA markers. Y chromosome biallelic markers revealed high frequency of Austroasiatic specific M95-O2a haplogroup in Bharia and Sahariya and M82-H1 and M17-R1a in Bhil. Mitochondrial DNA analysis showed higher diversity with some older sublineages of M haplogroup and prominent R lineages in all the three tribes. The results obtained reveal strong genetic affinity of Bharia (a Dravidian speaking tribe) with the Austroasiatic (Mundari) group rather than the Dravidian or the Indo-European groups. The gene flow from Austroasiatic group is further confirmed by their Y-STR where we determined their founder haplotype from the Mawasi population which is an Austroasiatic speaking tribe. Sahariya showed admixed genetic package of Indo-European and Austroasiatic populations and the Bhil exhibited Indo-European specific haplogroups.

P87
VARIABLE ASSOCIATIONS OF KLINEFELTER SYNDROME IN CHILDREN

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KF is characterized by heterogeneity in the degree of expressed phenotypes. Objective: to ascertain the variable phenotypes of Klinefelter syndrome in children. We present eight klinefelter patients, their age ranged from 2 to 11 years (mean 6.63). Subjects were meticulously examined for evidence of dysmorphology. Intelligence quotient was estimated. Cytogenetic analysis revealed 47,XXY karyotype in all patients. The following was detected: Dysmorphism in 5/8, micropenis in 4/8, the left testis was nonpalpable in 4/8, short stature in 4/8, congenital cardiac malformations in 4/8, seizures in 4/8, mental retardation in 5/8, growth hormone deficiency in 2/8, hypothyroidism and delayed bone age in 1/8. Our study demonstrated a variable association of mental retardation, dysmorphism, micropenis, undescended testis, seizures, congenital heart defects, and growth hormone deficiency among Egyptian patients with Klinefelter syndrome. This merits further study to facilitate earlier diagnosis and better management to improve their quality of life.

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GENETIC AND GENOMIC APPROACHES TO IDENTIFY ARSENIC INDUCED TOXICITY AND CARCINOGENICITY

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In West Bengal, India, although a large number of individuals are exposed to arsenic through drinking water but only less than 15 to 20% of total arsenic exposed individuals showed arsenic induced skin lesions. So it is assumed that genetic variations might play an important role in arsenic induced toxicity and carcinogenicity. Major genetic and genomic approaches have been made to find out the cause of arsenic susceptibility and the different genes responsible. For this reason the Chromosomal Aberrations (CA), Comet assay and challenge assay were performed and single nucleotide polymorphisms (SNPs) studies were carried for a number of genes that may involve the different pathways in arsenic metabolism and detoxification SNPs of p53 gene, PNP, ERCC2 and XRCC3 genes were also analyses. Individuals with p53 codon 72 Arg/Arg genotype is over represented in the skin lesions individuals indicating that this genotype is more susceptible to arsenic induced toxicity. Lys/Lys genotype in the ERCC2 polymorphism was almost five fold over represented in the arsenic induced hyperkeratosis skin lesions group when compared to no skin lesions group. In each of these cases, individuals with risk genotype were found to have significantly higher genetic damage functionally validating our associations. In case of XRCC3 T241M Polymorphism, presence of at least one M allele (M/M or T/M) was protective towards development of arsenic-induced skin lesions, as also towards arsenic-related peripheral neuropathy and conjunctivitis. A significant correlation was observed between protective genotype and decreased frequencies of chromosomal aberrations. Results of DNA repair studies through Challenge and Comet assay shows that the individuals with arsenic induced skin lesions have suboptimal DNA repair capacity and are hence inefficient in combating the DNA damage induced by chronic arsenic exposure. Thus the above results indicate that the sub-optimal DNA repair and the genetic variations are responsible for arsenic induced toxicity and carcinogenicity.

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FUNCTIONAL VARIANT IN SCN1A GENE AND RESPONSE TO TREATMENT IN EPILEPSY

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SCN1A gene codifies voltage-gated sodium channels (Nav1.1) which is a target for some antiepileptic drugs (AEDs) such as carbamazepine (CBZ) and sodium valproate (VPA). The purpose of this study was to determine whether the intronic IVS5N+5 G>A polymorphism is associated with response to CBZ or VPA in Malaysian epilepsy patients. The IVS5N+5 G>A polymorphism was genotyped in 643 epilepsy patients (47% drug-resistant) who were on CBZ or VPA monotherapy by using matrix-assisted laser desorption/ionization time of flight (MALDI-TOF) mass spectrometry. The A allele was less common in the Malay drug-resistant patients (47%) than drug-responsive subjects (71%) who were on VPA monotherapy. There was a significant allele and genotype association between SCN1A IVS5N+5 gene polymorphism and response to VPA in Malays with generalized epilepsy. This study demonstrated that Malays A allele carriers with generalized epilepsy were less prone to resistance to VPA than G allele carriers.

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A GENOME-WIDE ASSOCIATION STUDY OF CHRONIC HEPATITIS B IDENTIFIED NOVEL RISK LOCUS IN A JAPANESE POPULATION

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Previous genome-wide association study (GWAS) has identified variants in the HLA-DP locus associated with chronic hepatitis B (CHB) in Asians; however, only 179 cases and 934 controls were genotyped in the first step. Here, we performed a second GWAS of 519,747 SNPs in 458 Japanese CHB cases and 2,056 controls. We confirmed the significant associations between CHB and variants in HLA-DP locus (rs9277535 and rs3077, P<5x10-8). We also detected strong associations at 13 loci with p-value of less than 5x10-5 after adjustment with rs9277535. We analyzed these loci in three replication panels (2,213 CHB cases and 4.440 controls) from Japan and found significant association of two novel SNPs in MHC region (overall p-value of 6.26x10-24 to 3.99x10-37). Conditional association analysis with rs3077 and rs9277535 suggested that the associations observed in two SNPs are independent from HLA-DP region (p-value of 2.86x10-18 to 3.49x10-27). Individuals with seven or eight risk alleles (OR = 5.27, 95 CI% = 4.17-6.65) have an approximately fourfold increase in CHB risk compared to those with three or less risk alleles (OR = 1.18, CI% = 0.9-1.54). These data indicated that genetic variants in MHC region contribute to the risk of persistent HBV infection and provide a novel insight into disease pathogenesis.

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ASSOCIATION OF INSIG2 RS7566605 POLY-MORPHISM WITH OBESITY-RELATED PA-RAMETERS IN MALAYSIAN MALAYS

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Obesity is a global epidemic. INSIG2 gene is a protein coding gene on chromosome 2q14.2. Single nucleotide polymorphism (SNP) of Insulin-induced gene 2 gene (INSIG2) rs7566605 was recently found to be linked with obesity in many different populations. In this study, we investigated association between this SNP with obesity and obesity-related parameters which included Body Mass Index (BMI), body weight, height, waist circumference (WC), hip circumference (HC), waist hip ratio (WHR), systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (TC), High Density Lipoprotein-Cholesterol (HDL-C) and Low Density Lipoprotein-Cholesterol (LDL-C). Six hundred and forty nine (649) Malaysian Malays were subjects of the study. Genotyping was carried out using Real-Time PCR Taqman® single nucleotide polymorphism genotyping assay and data were analyzed using SPSS 16. GC heterozygotes in the non obese and obese groups were 51% and 46% respectively. The frequency of GG homozygotes in non obese and obese groups were 32% and 33% respectively. CC homozygotes in both non obese and obese groups were 17% and 21% respectively. The genotypes were in Hardy-Weinberg equilibrium. Linear regression analysis showed significant associations between INSIG2 rs7566605 SNP with log-transformed WHR (age and gender unadjusted) (additive model: p=0.039; R=0.081) (recessive model: p=0.034; R=0.083) in the Malaysian Malay subjects. There is no significant association between the above mentioned SNPs with log-transformed BMI nor with any other obesity-related parameters. In conclusion, INSIG2 rs7566605 SNP is associated with central obesity in Malaysian Malays.

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HTRA1 IS A POTENTIAL CAUSATIVE GENE FOR AGE-RELATED MACULAR DEGENERATION: EVIDENCES FROM THE PROTECTIVE EFFECT OF A VARIANT

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Age-related macular degeneration (AMD) is a leading cause of severe visual impairment and blindness in most developed countries, affecting about 50 million elderly worldwide. Although AMD-linked locus has long been reported on chromosome 10q26, there are critical debates on the causative gene (HTRA1 or LOC387715) in this region. In this study, we genotyped a HTRA1 insertion-deletion (indel) variant (34delCinsTCCT) in the Hong Kong Chinese cohort and replicated in another Chinese cohort. The properties of this HtrA1 variant were also investigated. The frequency of 34delCinsTCCT indel allele in both cohorts was higher in control subjects than in exudative AMD patients (p = 2.67x10-4), indicating a protective effect with odds ratio of 0.248. This protective effect was validated by the differential haplotypes of the 34delCinsTCCT indel allele with the risk A allele of rs11200638. Enhanced expression of wild type HtrA1 reduced cell viability and increased cell apoptosis in ARPE-19 cells; in contrast, ARPE-19 cells expressing HtrA1 indel variant had higher cell viability, lower cell apoptosis and were less responsive to anoikis, supporting its protective role. In addition, HtrA1 indel variant was more endoplasmic reticulum localized than the wild type in ARPE-19 cells. These results suggested that HTRA1 could be a potential disease-causing gene for AMD in the 10q26 region.

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THE ROLE OF GENE POLYMORPHISMS IL10, TCRA AND FCGRIIIA IN THE DEVELOPMENT OF RHEUMATOID ARTHRITIS IN KAZAH POPULATION

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Rheumatoid arthritis is a chronic inflammatory autoimmune disease with a significant genetic component, so the current is the study of genes responsible for various stages of pathogenesis of RA. We have studied in Kazakh population the polymorphism of RA candidate genes, using PCR assay FcGRIIIA gene (missense mutation T559G, 2 allelic variants Phe/Val) and PCR - restriction fragment length polymorphism assay: TCRA (identification of 8 CA-repeat alleles, from 186 to 200 n.p.) and IL10 (missense mutation in the promoter region of the gene IL-10 C627A, if a nucleotide C (4 restriction fragment size – 351, 85, 42 and 8 n.p.), if nucleotides A (5 restriction fragment size – 240, 111, 85, 42 and 8 n.p.). Subjects: 79 female RA patients and 81 healthy controls Kazakh nationality. The RA diagnosis was placed under the criteria of American College of Rheumatology diagnostic criteria for RA (1987). We observed in RA patients accumulation genotype 240/240 IL10 gene and less 351/351 genotype in comparison with the control in Kazakh population ($\chi 2$ 8.6, p=0.013). Analysis of the frequencies of IL10 alleles showed a decrease of 351 alleles in RA patients (48.5%, p<0,05, OR 0.33) compared with control group (64.6%, p<0,05, OR 1.9). Polymorphism of dinucleotide CA-repeat TCRA gene showed marked differences in the prevalence of allelic variants of TCRA gene in two compared samples ($\chi 2$ 18.2, p<0.001). Allele 192 is probably protective for Kazakh population (3.3% in the RA group and 13.0% in the group of healthy controls, p=0.004, OR 0.23), while allele 198 predictive value (16.4% in the RA and 5.5% in controls, p = 0.05, OR 3.4). Noted the low number of individuals with genotypes containing the 192 allele among RA patients compared with controls (6.5% and 23.3%, p = 0.02, OR 0.23) and higher, compared with the control group, the number of individuals with 198 allele in RA patients (29.5% and 9.6% respectively, p = 0.006, OR 3.9). The frequency of homozygous F/F gene FcGRIIIA among RA patients was 31.0%, heterozygote F/V – 59.1%, and homozygous V/V – 9.9% against 17.8%, 66.7%, 15.5% among healthy controls, respectively. Among the RA patients marked accumulation of

homozygous F/F (OR 27.2) and a decrease in the number of homozygous V/V (OR 0.6). The data obtained allow us to consider homozygous for F allele as a risk factor, whereas homozygosity for the V allele - as a protective factor for RA. Thus, these results allow the use of Kazakh as a predictive factor for development of RA 240 allele of the gene IL10, allele 198, genotype 198/198 TCRA gene and genotype F/F gene FcGRIIIA. As a protective factor of RA in Kazakh stands 351 allele of the gene IL10, allele 192, genotype 192/192 TCRA gene and genotype V/V gene FcGRIIIA.

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GENE-ENVIRONMENT AND GENE-GENE INTERACTIONS IN SUSCEPTIBILITY TO HEAD AND NECK CANCER IN ASIAN INDIANS

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Cancer is a common multifactorial disease that can be considered neither purely genetic nor purely environmental. It is becoming clearly evident that single gene or single environmental factor cannot explain susceptibility to complex diseases such as head and neck cancer that mainly results from complex interactions between many genetic and environmental factors. In this study, we applied the multi-factor dimensionality reduction (MDR) method to explore potential gene–environment and gene–gene interactions that may contribute to predisposition to head and neck cancer in Asian Indians. We genotyped 203 patients with head and neck cancer and 201 healthy controls for thirteen functional polymorphisms in tobacco metabolizing genes CYP1A1, CYP2A13, GSTM1 and UGT1A7 using PCR-RFLP method, real time PCR quantitative assay and denaturing high performance liquid chromatography followed by direct sequencing. CYP1A1 3801 CC (P 0.01), GSTM1 single copy (1/0) (P<0.001) and null (0/0) (P <0.0001) genotypes were found to be associated with increased risk of head and neck cancer while CYP2A13 heterozygous genotype for T478C/T494C conferred protection to head and neck cancer (P 0.003). Further, we observed significant gene-gene interactions between GSTM1 copy number variants, CYP1A1 T3801C and UGT1A7 T622C variants among smokers. MDR approach showed that three factor model, including smoking status, CYP1A1 T3801C and GSTM1 copy number variants conferred more than fourfold increased risk of head and neck cancer (OR 4.89; 95% CI: 3.15-7.32, p <0.01). These results support the hypothesis that genetic variants in tobacco metabolizing genes may contribute to head and neck cancer risk through gene-gene and gene-environmental interactions.

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MONOSOMY OF 1P36 DELETION SYNDROME SCREENING IN PATIENTS WITH DEVELOPMENTAL DELAY AND FACIAL DYSMORPHISM

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Deletion of the distal end of the short arm of chromosome 1(monosomy 1p36) is a micro deletion syndrome which is estimated to be one of the most common terminal deletions in the population with an incidence of 1: 5000 live birth. The syndrome of 1p36 deletion is known to affect fetal phenotype giving rise to a postnatal syndrome characterized by dysmorphic features, mental retardation, neurodevelopmental delay and associated structural abnormalities e.g. visual affection, audio logical manifestations, cardiovascular and gastrointestinal manifestations. The study was conducted on 21 patients attending the human Genetics Department Clinics, National Research Centre with features suggestive of 1p36 deletion syndrome. Our aim was to detect 1p36 deletion by history taking regarding pedigree, consanguinity and age of parents, milestones of development either it is normal or delayed, thorough clinical examinations with laying stress on the presence of developmental delay, mental retardation and facial dysmorphism. Laboratory investigations were carried out in the form of GTG banding, high resolution analysis and fluorescent in Situ Hybridization (FISH) technique. The entire 21 patient were fulfilling the most common clinical features and medical problems previously described with 1p36 deletion syndrome. They were 13 males and 8 females with a female to male ratio of 1:1.6. Their age ranged from 20 days to 12 years with median age of 1.5 years. By GTG banding, all cases revealed normal karyotype of 46, XX in 8 patients (38%) and 46, XY in 13 patients (62%). Fluorescence Insitu Hybridization (FISH) analysis results revealed no deletion in all the studied cases (100%) at the stage of metaphase. At the stage of interphase, 18 cases (85%) showed no deletion, while in 3 cases (15%) deletion was detected. Results of our study clarify that the diagnosis of 1p36 deletion syndrome is suggested by clinical findings and confirmed by detection of a deletion of the most distal band of the short arm of chromosome 1 (1p36).Conventional GTG banded cytogenetic analysis; high resolution banding and FISH with subtelomeric region-specific probes can diagnose monosomy 1p36.With the introduction of array CGH technology to the clinical laboratory setting, there will be a facility to diagnose and confirm the diagnosis of patients with monosomy 1p36 syndrome who carry interstitial deletions of varying sizes and levels of complexity within the common 10 Mb deletion region.

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ASSOCIATION OF THE FAAH, GSTP1 AND SOD2 FUNCTIONAL GENETIC POLYMORPHISMS WITH METHAMPHETAMINE DEPENDENCE IN A MALAYSIAN POPULATION

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Methamphetamine is a highly addictive psychostimulant that has surged in popularity worldwide from the last decade. Recent studies suggest that the FAAH P129T genetic polymorphism is significantly associated with drug addictive traits while the rs4880 genetic polymorphism of the SOD2 gene could be associated with the risk of developing methamphetamine-induced psychosis (3). The Ile105Val in GSTP1 gene was suggested to be significantly associated to both methamphetamine dependence and methamphetamine-induced psychosis (2). The objective of this study is to determine the association between the FAAH P129T polymorphism, GSTP1 Ile105Val, SOD2 rs4880 polymorphism with methamphetamine dependence and occurrence of methamphetamine-induced psychosis in the Malaysian population. In this study, the subjects recruited were 246 male methamphetamine-dependent subjects and 229 male controls from four different ethnicities, namely, Malay, Chinese, Kadazan-Dusun, and Bajau. PCR-RFLP method was utilized for genotyping and validation was carried out by direct sequencing. The result of this study indicated that when comparing the both genotype and allelic frequency between subjects who were dependent on methamphetamine with those who were not, the FAAH P129T polymorphism showed a significant association with risk of methamphetamine dependence in the pooled subjects (genotype, P=0.001; allelic, P<0.001; OR=2.017). When stratified according to the ethnic groups, significant association was also found in the Malay and Chinese ethnic group (genotype, P=0.001; allelic, P<0.001; OR=2.829 and genotype, P=0.002; allelic, P<0.001; OR=3.685 respectively). For the SOD2 rs4880 polymorphism, statistical analysis showed that there was no significant association between this polymorphism with methamphetamine dependence in the pooled subjects. However, significant differences were found in the SOD2 rs4880 polymorphism between Chinese methamphetamine-dependent subjects and control subjects (genotype, P<0.001; allelic, P=0.019; OR=2.556) as well as Kadazan-Dusun (genotype, P<0.001). Furthermore, our finding showed that the Malay ethnic group but not the other ethnic groups, showed significant association between the GSTP1 Ile105Val polymorphism and methamphetamine dependence when comparing the allelic frequencies (P=0.019; OR=1.915) but not the genotype. In conclusion, our findings suggest that the P129T polymorphism of the FAAH gene may contribute to methamphetamine dependence in the Malay and Chinese ethnic groups, and in the pooled subjects, whereas the rs4880 polymorphism of the SOD2 gene may contribute to methamphetamine dependence in the Chinese and Kadazan-Dusun ethnic groups. However, only the Malay ethnic group showed significant association between Ile105Val polymorphism of the GSTP1 gene and methamphetamine dependence. Nevertheless, these three polymorphisms did not appear to be involved in the development of psychosis in these subjects.

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GENETIC ASPECTS OF THE RECURRENT MISCARRIAGE IN KAZAKH POPULATION

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The recurrent miscarriage (RM) of pregnancy is known as one of the most social significant problem in obstetrics and has a multifactorial background. The aim of this research was to detect the contribution of some genetic predisposition factors of RM in Kazakh population. Among 100 couples with RM in anamnesis in the Kazakh population cytogenetical G-banding assay was performed. The polymorphisms of genes of coagulation system (A506G) FV и (G20210A) FII, (4G/5G) PLANH1; folate metabolism genes (C677T, A1298C) MTHFR; (A66G) MTRR and (A2756G) MTR; II phase of detoxification system – (del) GSTM and GSTT; (Ile105 VaI; Val114 Ala) GSTP1 were detected by PCR, RFLP followed by digestion with specific restriction enzyme. Study was carried out in a group of 200 women with 2 and more spontaneous early abortions in anamnesis and 150 women with normal reproductive function. All were Kazakhs and comparable in age and somatic anamnesis. Results: The frequency of chromosomal abnormalities among patients with RM was 7.5%, out of them translocations (13.3%), deletions (6.7%), inversions (6.7%), chromosomal polymorphisms - 73.3%. The most important contribution in RM was determined for unfavorable genotypes of FII и FV coagulation factors, carriers of which increase the risk of RM in 4-18 times, antiphospholipid syndrome (APS) in 5 times. Significant differences between women with RM and control group in frequencies of 677TT and 1298CC genotypes (MTHFR), 66GG (MTRR) and 2756GG (MTR) were found, which increase risk of RM in 2.5-8.3 times. The significant association unfavorable polymorphisms of folate metabolisms genes with risk of Down syndrome and defects of neural tubes (DNT) among fetuses were confirmed. Conclusions: we observed the significant genetic input of chromosomal abnormalities and mutant genotypes in RM, APS, DNT, suggesting that this genotypes cause hyper coagulation, increase the toxic product concentration and endothelial dysfunction. Diagnostic algorithm, preconceive prophylaxis were worked out, in order to increase the effectiveness of RM therapy.

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THE ASSOCIATION STUDY OF EARLY ONSET TYPE 2 DIABETES MELLITUS IN THE HAN CHINESE POPULATION OF TAIWAN

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The incidence of early-onset type 2 diabetes mellitus (T2DM) is increasing worldwide and is strongly associated with the rise of obesity in children, adolescents and young adults. Although several T2DM relative genes were identified by GWAS studies, only a few studies aimed to examine the effect of the risk polymorphisms on the age at diagnosis of T2DM. The

purpose of this study is to investigate whether the genes polymorphisms of ATP-binding cassette transporter A1 (ABCA1), lipoprotein lipase (LPL) and peroxisome proliferator-activated receptor gamma, coactivator 1 alpha (PPARGC1A) are associated with early onset T2DM in the Han Chinese population of Taiwan. A total of 999 T2DM cases (281 subjects had early-onset T2DM: diagnosed age 20-45 years and 718 subjects had late-onset T2DM: diagnosed age≧45 years) were recruited from China Medical University Hospital (CMUH), Taiwan. Blood samples were taken for DNA extraction from T2DM subjects. The gene polymorphism was genotype by polymerase chain reaction in each patient. In our database, more males, younger age and subjects with higher body weight, longer disease duration and lower C-peptide value were found in early onset DM subjects. The significance of 5 SNPs, 3 on ABCA1 with P value of 0.031 (rs3904998), 0.039 (rs2254884) and 0.037 (rs3847304) and 2 on PPARGC1A with p value of 0.019 (rs4550905) and 0.042 (rs4235308) were significantly associated with the age at diagnosis of type 2 diabetes. However, the association between LPL gene polymorphism and early onset T2DM was not observed. In addition, the mean value of insulin was significant different among the different ABCA1 gene polymorphisms in early onset T2DM patients. Our observations suggest that the genetic variation of ABCA1 and PPARGC1A might be useful for the detection of subjects genetically susceptible to early-onset type 2 diabetes in the Chinese population of Taiwan.

GENETICS OF CARDIOVASCULAR AND METABOLIC DISORDERS

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RARE METABOLIC DISORDERS IDENTIFIED IN THE NEWBORNS OF UAE

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Metabolic disorders are one of the major concerns in newborns. Physicians and Pediatricians all around the world are trying to convince parents to screen their babies for metabolic disorders after they are born. Newborn screening is one of the primary tools that can help to avoid fatal and permanent damage of a child. The screening has been in place in various parts of the world for last few decades but the recent advancement of Tandem Mass Spectrometry opened the door to a new era by allowing the pediatricians to detect more than 50 metabolic disorders in children. 5,000 newborn samples from various private hospitals have been processed for Newborn screening analysis with Tandem Mass Spectrometry and routine biochemical analyses to identify the rare metabolic disorders in the people of UAE (Both native and expatriates). As the samples are from private hospitals and the facility is utilized mostly by the expatriates, it is observed that 0.4% of the Asian population out of the 5,000 samples had positive results for various metabolic disorders and the similar conditions were observed in 0.02% of Arabs. The result of the screening also shows that 0.34% of the babies had G6PD deficiency, 0.02% of them had congenital hypothyroidism, 0.02% acycarnitine profile disorders and 0.04% suffers from hemoglobinopathies. The study introduces that rare metabolic disorders like acylcarnitine profile disorder (SCHAD) that is not commonly identified with the routine analyses also exist in the mixed population of UAE. Our study indicates that more extensive research needs to be done to identify these rare conditions in the region. Pediatricians and clinical geneticists must be informed immediately after the identification of the disease for further diagnosis and start the treatment without delay to avoid future sufferings.

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REVERSIBLE CAUSE OF CARDIOMYOPATHY INPEDIATRIC AGE GROUP

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Objective: To report unusual reversible cause of cardiomyopathy .Clinical Presentation and Intervention: A 21 months old boy admitted to our hospital through Emergency Department with history of penile enlargement and progressive darkness of skin for the last 10 months, family history of similar problem. Clinical examination showing good body belt with weight of 13kg in75th percentile height 92cm which is above97th Percentile, high BP 139/90 above 95th percentile, hyperpegmentaion of gum with darkness of skin , facial acne, penile enlargement with 8,7cm length above 90th percentile with scrotal hyper pigmentation (testicular size pre pubertal with no pubic hair) Laboratory investigation showing high ACTH 507pg/ml (normal range 5-60pg/ml) with low serum cortisole 42.4nmol/L (55-248nmol/L), 17hydroxyprogesrerone 67nmol/l(0.3-2.5nmol/L), androstendione more than 70nmol/L (2.4-12.6nmol/L) Testosterone 5.49nmol/L high for his age (0.1-1.12nmol/L) FSH 0.5mIU/ml, LH 0.3mIU/ml, deoxycorticosterone was not available, advanced bone age 5-6 years, echocardiography showing mild dilated cardoimyopathy. Patient diagnosed as case of congenital adrenal hyperplasia, 11betahydroxlase deficiency, hydrocortisone treatment started with anti hypertensive medication. In 9 month follow-up wean of antihypertensive medication, repeated echocardiography was normal, acne disappear, skin darkness and hyperpegmentation improved and patient currently receiving hydrocortisone tablet 5mg AM and 2.5mg PM. Conclusion CAH type 11betahydroxylase deficiency can be missed especially in male until present with complications such as that related to hypertension, hypocortisolism and/or androgen excess that leads to precocious puberty, all these can be avoided by checking BP in well baby clinic visit.

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MELANOCORTIN 4 RECEPTOR GENE POLYMORPHISM AND ASSOCIATION WITH CHOLESTEROL LEVELS IN MALAYSIAN MALAYS

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Melanocortin-4 receptor (MC4R) is a G-protein coupled receptor which regulates appetite and body weight. Mutations in the MC4R gene cause the monogenic form of obesity. MC4R mutations result in early onset of obesity. This study was aimed to investigate the MC4R rs2229616 polymorphism (Val1031Ile) and its association with obesity-related parameters in a Malaysian Malay population. This study involved 649 subjects. Obesity-related parameters were collected. Buccal swabs were collected for extraction of genomic DNA. The genotyping was performed using real-time PCR system. The results showed that 5% of the non obese and obese groups were GA heterozygotes respectively. The frequencies of GG homozygotes in non obese and obese groups were 95% in both. No AA homozygotes mutant was found in both non obese and obese groups. The genotypes were in Hardy-Weinberg equilibrium. Significant associations were observed between MC4R rs2229616 SNP with LDL cholesterol (age and gender adjusted) (additive model: p= 0.032; R=0.140) and with total cholesterol (age and gender adjusted) (additive model: p=0.002; R=0.179). There is no significant association between the MC4R rs2229616 SNP with BMI. In summary, the MC4R rs2229616 polymorphism is associated with cholesterol levels in Malaysian Malays but not with any other obesity parameters.

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ASSOCIATION OF CHROMOSOME 9P21 POLYMORPHISM WITH CORONARY ARTERY DISEASE IN WESTERN INDIANS

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Indians have a high propensity to develop Coronary Artery Disease (CAD) and it has been estimated that 60% of the worlds‘ cardiac population will be in India by the year 2020. In this context it is very important to evaluate the new markers especially genetic variants in the Indian population, which is a heterogeneous group. Genome-wide studies have implicated SNPs in 58kb region of chromosome 9p21 to be associated with CAD. In the current study we have evaluated the association of SNP rs10757278 at the 9p21 locus with CAD in Western Indians. Genotyping for rs10757278A/G was done by direct sequencing in 215 cases with confirmed CAD and 150 controls. Significantly higher frequency of the G allele was seen in cases as compared to controls 0.64 vs 0.53. The G allele showed association with risk of CAD (OR 1.589; 95% CI 1.177-2.146; P 0.003). The association is explained by the recessive model of inheritance. Addition of the 9p21 allele to Framingham risk score FRS, resulted in a shift of 17% of individuals from the low risk category to the intermediate-low (>5% to <10% 10-year risk) and 7% from intermediate-low to intermediate-high (>10% to <20% 10-year risk) categories. In conclusion the rs 10757278 A/G SNP at the 9p21 locus is significantly associated with the risk of CAD in Western Indians.

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APOLIPOPROTEIN E POLYMORPHISM IN GENERAL POPULATION AND IN PATIENTS OF ISCHEMIC AND HEMORRHAGIC STROKE IN CONSTANTINE CITY

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Apolipoprotein E has been one of the most thoroughly studied genetic polymorphism, particularly for its effects on lipid profiles. Several epidemiological studies have identified that plasma concentrations of low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, and triglycerides (TG) are important predictors of myocardial infarction MI and coronary heart disease. Apolipoprotein E, a 299-amino acid, 34-kDa molecular weight is polymorphic and exist in three protein isoforms designed E2, E3, and E4 encoded by three alleles ε2, ε3, and ε4. These three apoE isoforms differ from each other by amino acid substitution at either amino acid 112 or 158. These three isoforms determine the six genotypes (e2/e2, e4/e2, e3/2, e3/e3, e4/e3, and e4/e4. ApoE is a constituent of several classes of plasma lipoprotein: very low-density lipoproteins (VLDL), high-density lipoproteins (HDL), intermediate density lipoproteins (IDL), and Chylomicrons, and plays a key role in regulating plasma cholesterol and triglyceride homeostasis functioning as ligand for LDL-receptors, LDL-receptor related protein. However there are no reports investigating apoE gene polymorphisms in Algerian patients. We therefore done the present study to estimate the frequency of apoE genotype and alleles in healthy subjects and in patients with cerebrovascular disease as well the prevalence of disease associated with particular apoE genotypes and alleles. Mean level of lipid, as well as genetic of Apolipoprotein E (apoE) were determined in control (509) and in CVD (205) including cerebral infarction (63%) and cerebral hemorrhage (37%) in subjects in Constantine, a selected population of east of Algeria. The apoE allele frequencies of patients ICVD and controls were 3.1% vs. 5.0 % for ϵ2, 81.8% vs. 84.3% for ϵ3, and 15.1% vs. 10.5% for ϵ4. The patients compared with control subjects had statistically significantly higher mean cholesterol (1.96+0.47 mg/dl vs 1.82 +0.40 mg/dl p< 0.05) and LDL-C (1.28 ± 0.43mg/dl), vs (1.09 ± 0.27 mg/dl , p< 0.01), and lower HDL cholesterol with mean values of (0.37 ± 0.11 mg/dl vs 0.44 mg/dl p< 0.01). Those patients who carried the apoE/e4 allele, had an association with cerebral infarction but not with cerebral hemorrhage, the carriers of allele ϵ4 and ϵ3/ϵ4 subjects compared with ϵ3/ϵ3 are associated with an increased incidence of ICVD with odds

ratio 1.56 [95% CI, 0.98 to 2.46] p< 0.05 and 1.72[95% CI, 1.8 to 2.75] p< 0.05 respectively. These data establish APOE genotype as a relatively strong predictor of recurrent ischemic stroke and further support an important biological role for this genotype.

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CLINICAL, CYTOGENETIC AND MOLECULAR STUDIES IN EGYPTIAN CHILDREN WITH CONGENITAL HEART DISEASE (CHD)

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The cardiovascular anomalies responsible for congenital heart disease (CHD) are common birth defects and are a leading cause of infant mortality, morbidity. CHD is a primary feature of many genetic syndromes, but genetic causes of non-syndromic CHD are increasingly being recognized. CHD affects at least one in 100 live births. It ranges widely in severity, from tiny holes between heart chambers that close naturally, to life-threatening abnormal structures such as hypoplastic left-heart syndrome. Recently identified disease genes for syndromes associated with congenital heart disease are also increasing. These gene discoveries are being rapidly translated into meaningful genetic testing, improving the diagnosis and prognostication for CHD. To date, very few studies were performed in Egypt for studying the genetic basis of CHD. This study included 500 cases with CHD out of total 8000 cases referred as genetic disorder to the Clinical Genetic Department of the NRC during a period of 6 years (2004-2010). It aims to identify at risk families and types of syndromes with CHD, identify types of chromosomal anomalies causing these diseases & study the spectrum of mutations in known candidate genes. Chromosomal analysis was performed on 200 cases. Molecular studies were carried out for 189 cases. Mutation detection was done using PCR/ SSCP and DNA sequencing. Associated malformations as known syndromes included Russell Silver, Jacobsen, Noonan, Costello, Apert, Kamptomelic dysplasia, McKusik Kaufman, Rubinstien-Taybi, William, Holt-Oram & Roberts. Chromosomal anomalies reported are trisomy 21, trisomy 13, trisomy 18, 46, XY, t (14;18), 46, XYt (8;9), 47, XX, + mar; 46, XX del 11q ,46, XX, dup13q, 47, XXX, 45, X, 47XXY, 46, XX, inv(18). DNA sequencing of NKX2.5 gene revealed two different mutations in two unrelated patients. Sequencing of GATA4 gene in patients with TOF has shown polymorphism in exon 6 at nucleotide 53423 (A-G) in 5 patients out of 19 cases. The genetic investigation results of Nkx2.5 gene concluded the presence of missense mutation in one out of 19 TOF cases (5.3%), two missense mutation in two out of 35 ASD cases (5.7%) and one silent mutation in one out of 35 ASD cases (2.9%). Results of GATA4 gene concluded the presence of two silent mutations in two out of 19 TOF cases (10.5%), and three SNPs in 9 out of 19 TOF cases (47.4%). Results of 22q11.2 critical DiGeorge region (CDGR) concluded the presence of microdeletion in 6 out of 18 DiGeorge/ VCF syndrome cases (33.3%). Results of PTPN11 gene concluded the presence of Polymorphism -21 (C>T) in one out of 16 NS cases (6.3%).

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BIOCHEMICAL AND GENETIC MARKERS FOR CORONARY HEART DISEASE IN SAUDI PATIENTS

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This study was designed with the aim of identifying markers, both biochemical and genetic, that could identify, presymptomatically, individuals susceptible to the development of coronary artery disease (CHD) in Saudis. This investigated group included 106 individuals (males: 64; females: 42) suffering from CHD and 369 healthy adult controls (males: 162; females: 207). Blood samples, collected from fasting individuals, were analyzed for biochemical parameters [renal, bone, liver function tests, electrolytes, lipids and lipoproteins, apolipoproteins, insulin, coagulation parameters, leptin and Lp(a)]. The DNA was extracted and used for the analysis of angiotensin converting enzyme (ACE) gene, SA gene, glycogen synthetase gene, glucokinase gene, and paraoxinase (PON) gene polymorphisms. ACE genotypes DD, ID and II were identified and showed extensive polymorphism. The frequency of II genotype was higher (11.7 % vs 2.13%), while the DD genotype occurred at a lower prevalence (48.3 % vs 56.03%), in CHD patients compared to the control. The frequency of SA genotype A1A1 was significantly higher in the CHD patients (56.06 % vs 40.0%), while that of A1A2 was significantly lower (42.42% vs 59.2%) compared to the normal control group (p<0.05). Paraoxonase (PON) and glycogen synthase genotypes did not show any significant difference in the patients with CHD and normal controls. The CHD patients showed elevations of Lp(a), leptin, urea, creatinine, alanine amino transferase (ALT), creatinine phospho kinase (CPK), lactate dehydrogenase (LDH), cholesterol, triglyceride, low density lipoprotein (LDL) and LDL-cholesterol, apolipoprotein (apo) B, fibrinogen and apartial thromboplastin time, while apo A1, high density lipoprotein (HDL) and HDL-cholesterol were significantly lower (p<0.05). Majority of the patients (>85%) had Lp(a) > 30 nmol/l and the levels of Lp(a) correlated positively with cholesterol level (p < 0.005) and platelet count (p < 0.02). Leptin level was significantly more than in the control group and it correlated positively with weight and body mass index (BMI) (p < 0.05). The paper will present these results in Saudi CHD patients to identify the most reliable marker.

P106

PARKIN MEDIATED UBIQUITINATION AND DEGRADATION OF MUTANT GLUCOCERE-BRIOSIDASE VARIANTS: A POSSIBLE LINK BETWEEN GAUCHER DISEASE AND PARKINSON DISEASE

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Mutations in the glucocerebrosidase (GCase)-encoding gene lead to accumulation of gucosyl-ceramides, manifested as Gaucher disease. We have shown that mutant GCase variants present variable degrees of ER retention and undergo ER associated degradation (ERAD) in the proteasome. The ERAD process requires specific E3 ligases, which ubiquitinate the misfolded enzyme before its elimination in the proteasome. Gaucher mutations have been recently identified as a major cause for Parkinson disease. An association between Gaucher disease and Parkinson disease has been demonstrated by the concurrence of Parkinson disease in Gaucher disease patients and the identification of GCase mutations in probands with sporadic Parkinson disease. One of the genes involved in Parkinson disease is parkin, encoding an E3 ubiquitin-protein ligase. Parkin also functions in the ERAD of misfolded ER proteins, and it is up-regulated by unfolded-protein response (UPR). Loss of parkin function leads to accumulation of its substrates, which is deleterious to dopaminergic neurons in Parkinson disease. We, therefore, tested the possibility that the association between Gaucher disease and Parkinson disease reflects the fact that parkin acts as an E3 ligase of mutant GCase variants. Our results showed that mutant GCase variants associate with parkin. Normal parkin, but not its ring finger mutants, affects the stability of mutant GCase variants. Parkin also promotes the accumulation of mutant GCase in aggresome like structures and is involved in K48 mediated polyubiquitination of GCase mutants, indicating its function as their E3 ligase. In transfected COS cells, parkin and mutant GCase co-localized in perinuclear-aggresome-like structures. In skin fibroblasts that derived from Gaucher patients there was an association between parkin and mutant GCase, as tested by co-immuno-precipitation analyses. Moreover, the degree of mutant GCase ubiquitination in these cells was mutation-dependent. Taken together our results implicate that the ERAD process of mutant glucocerebrosidase in dopaminergic cells affects degradation of normal parkin substrates, leads to their accumulation and to development of Parkinson disease.

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SNP DISCOVERY AND HAPLOTYPE ANALYSIS OF ANGIOTENSIN I CONVERTING ENZYME (ACE) GENE AND ASSOCIATION WITH ESSENTIAL HYPERTENSION IN ASIAN INDIANS

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Angiotensin I Converting enzyme (ACE) gene is one of the leading candidate genes for hypertension. Studies on the association of ACE insertion/deletion (I/D) polymorphism and the risk of developing essential hypertension (EH) have generated inconsistent information in different ethnic populations. This study was designed to search for new polymorphisms in the ACE gene in Asian Indians and to test whether these specific variants and haplotypes were associated with susceptibility to EH. Using a systematic approach, we searched the 8 exons (along with their Intron-Exon junctions and part of intronic fragments) of ACE gene for sequence variants in North Indians. Five variants were identified using DHPLC and DNA sequencing. These five variants plus one bi-allelic Insertion/Deletion polymorphism in the ACE gene (ACE I/D) were examined for association with EH in 300 essential hypertensive patients and 300 age- and gender-matched normotensive controls. Pearson's $\chi 2$ or Fishers Exact test was used for statistical comparisons between the study groups. Haplotypes were generated by the PHASE version 2.1 and Linkage disequilibrium was estimated using Haploview (Version 4) software. We identified 2 novel single nucleotide polymorphisms (SNPs) (ss#52049498 and ss#52049499) along with two novel Insertion-deletion polymorphisms (ss#52084171 and ss#52084172) in ACE gene in our population. ACE I/D polymorphism was found to be in linkage disequilibrium with a SNP (rs11658531) in UTR region of ACE. Genotype and allele frequency of ACE I/D and SNP rs4316818 were significantly different between hypertensives and controls ($p<0.02$, $p<0.004$ and $p<0.005$ respectively) and associated with disease (OR). Haplotype analysis revealed significant higher frequency of haplotype GCICTA in hypertensives as compared to controls and was associated with increased risk of EH (OR 3.1, $p<0.01$). Haplotype (GCITAG) was observed only in EH group. Frequency of two haplotypes (GCDTAG and CCICTA) was higher in controls as compared to hypertensives and associated with decreased risk of EH ($p<0.006$, OR 0.30; $p<0.02$, OR 0.17). Table: Haplotype frequency in hypertensive group and controls. Haplotype/Hypertensives/Controls/Odds Ratio/Fishers Exact Test (p-Value), GCDTAG/15.081/36.574/0.30/0.0006, GCITAG/8.398/*/*/0.007, GCICTA/14.28/5.163/3.09/0.05, CCICTA/1.701/10.638/0.17/0.18. In conclusion, a specific haplotype of ACE gene polymorphisms is associated with an increased risk of EH in Asian Indian population.

P108

IDENTIFICATION OF A LOCUS FOR RECESSIVE DILATED-CARDIOMYOPATHY ON CHROMOSOME 2 BY LINKAGE ANALYSIS IN A BEDOUIN FAMILY

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Cardiomyopaties are the most common disorders resulting in heart failure. Dilated cardiomyopathy (DCM), a disorder characterized by cardiac dilatation and reduced systolic function, is the most frequent cause. However, recessive neonatal isolated dilated cardiomyopathy has scarcely been associated with a mutation. We have identified patients with acute DCM in one tribe with consanguineous family of the Bedouin population. Three subfamilies contain five patients and four healthy siblings were investigated. The disease appears to be familial, with an autosomal recessive pattern of

inheritance. SNPs array and then linkage analysis was performed using polymorphic microsatellite markers to confirm the linkage region on chromosome 2[2q35-2q36.3] with 10cM and to construct the haplotypes. The highest lod score for this region was 3.5 with two point analysis.

P109

MODELLING SINGLE NUCLEOTIDE POLYMORPHISMS IN THE HUMAN AKR1C1 AND AKR1C2 GENES: IMPLICATIONS FOR FUNCTIONAL AND GENOTYPING ANALYSES

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Enzymes encoded by the AKR1C1 and AKR1C2 genes are responsible for the metabolism of progesterone and 5□-dihydrotestosterone (DHT), respectively. The effect of amino acid substitutions, resulting from single nucleotide polymorphisms (SNPs) in the AKR1C2 gene, on its enzyme kinetics were determined experimentally by Takashi et al. We used homology modeling to predict and analyze the structure of AKR1C1 and AKR1C2 genetic variants. The experimental reduction in enzyme activity in the AKR1C2 variants F46Y and L172Q is predicted to be due to increased instability in cofactor binding, caused by disruptions to the hydrogen bonds between NADP and AKR1C2, resulting from the insertion of polar residues into largely non-polar environments near the site of cofactor binding. Other AKR1C2 variants were shown to involve either conservative substitutions or changes taking place on the surface of the molecule and distant from the active site, confirming the experimental finding that these variants do not result in any statistically significant reduction in enzyme activity. The AKR1C1 R170C variant is predicted to have no effect on enzyme activity for similar reasons. Thus, we provide further insight into the molecular mechanism of the enzyme kinetics of these proteins. Our data also highlight previously reported difficulties with online databases.

P110

IN SILICO PREDICTION OF MYBPC3 SPLICE-AFFECTING DNA VARIANTS IN FAMILIAL HYPERTROPHIC CARDIOMYOPATHY

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Pre-mRNA splicing is an important step in the expression of the >90% eukaryotic genes that have introns interrupting their coding sequences. The splicing process generates some of the molecular diversity in the human genome and so provides a myriad of templates that are crucial for sustaining the complexity of human physiology. However, DNA variants that affect splicing can be under diagnosed during routine DNA analysis. They can be ignored because of their ―silent" appearance based on the genetic code, or frequently overlooked due to their intronic locations. There is evidence indicating some missense or nonsense mutations can actually act like as a splice-affecting variant. In order to gain experience in decoding the splicing implications of DNA variants for future large scale analysis, we took 158 known MYBPC3 mutations in familial hypertrophic cardiomyopathy (FHC) as a model for in silico analysis using a web tool called ―Automated Splice Site Analyses". Eleven (7.0%) and 36 (22.8%) of the variants were predicted to have a significant impact on splicing and a potential effect on exonic splicing enhancers or cryptic splicing site, respectively. The changes of information contents (Ri) were carefully studied in 7 intronic variants at +4 or +5 nt after a splicing donor site or 13-41 nt before a splice acceptor site and were compared with 15 mutations at the canonical splice sites. The in silico tool successfully predicted all these non-coding changes and their various effects including: (1) reduced interaction with the spliceosome, (2) activation of a cryptic site or (3) destruction of a branch point. The predicted effects have been demonstrated in our as well as other researchers' in vitro experiments. Our study has confirmed the important role of in silico predication in efficiently identifying the potential splice-affecting DNA variants among a sea of neutral polymorphisms without overloading the experimental analysis. In silico analysis will also be crucial for interpreting the data from massively parallel sequencing based DNA testing as well as applying antisense-mediated splicing modulation as a therapeutic intervention.

GENETICS OF DEAFNESS AND NEUROLOGICAL DISORDERS

P111

TRANSCRIPTOME EVOLUTION AND DISTINCT GENE EXPRESSION PROFILES OF BRAIN AGING AND ALZHEIMER'S DISEASE-LIKE PATHOLOGY IN THE PRIMATE MICROCEBUS MURINUS

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Aging is the primary risk factor of neurodegenerative disorders such as Alzheimer's disease (AD). However, the molecular events occurring during brain aging are extremely complex and still largely unknown. New approaches such as transcriptomic approaches are required to unravel the complex biology of brain aging and neurodegenerative disease. For a

better understanding of these age-associated modifications, animal models as close as possible to humans are needed. In this study, we analyzed the transcriptome of the temporal cortex (TC) of *Microcebus murinus*, a relevant primate model for aging and AD studies because some of them present, as they age, ß-amyloid plaques and cortical atrophy, which are pathognomonic signs of AD in humans. We compared the transcriptomes of TC of 6 young adults, 10 healthy old animals and 2 "AD-like" animals using human oligonucleotide microarrays (Affymetrix HG U113 plus 2). These data were analyzed by different statistical tools such as ANOVA, significance analysis of microarrays (SAM), principal component analysis (PCA), Cluster and Treeview softwares. Functional categorization was applied to classify genes according to their cellular functions based on Gene Ontology (GO) consortium and EASE Analysis Systematic Explorer software. The gene expression data of 14,911 genes, detected present in at least 3 samples, were analyzed. Using ANOVA (p-value 5%), we identified 695 genes differentially expressed during healthy aging and AD-like. About one third of these genes showed similar changes of expression in healthy and ―AD-like" aging, whereas more than two thirds showed opposite changes in these two groups in comparison to young animals. By SAM, 47 genes were identified with the most significant changes in their expression comparing the 3 groups of animals. In addition, PCA showed that each group is distinct from others, and hierarchical clustering indicated that each group showed a specific expression profile. These data were validated by real time PCR on several of the most significant up-regulated expression during aging such as NSFL1C implicated in synaptic transmission, UBE1DC1 and RPL36 in protein metabolism, NDUFB8 in mitochondrial metabolism, SCAND1 in lipid metabolism, WASL and MAP2K1 in transduction signals, HINT1 and CSNK1G1 in transcription regulation. Functional categorization showed that epigenetic and metabolic pathways, notably protein synthesis, presented the most important dysregulation during aging and AD. In addition, most of these genes were up-regulated in healthy old animals and down-regulated in __AD-like" animals. These data suggested the existence of compensatory mechanisms during physiological brain aging that disappeared in "AD-like" animals. In conclusion, transcriptomic analysis represents a relevant approach to investigate molecular changes occurring during complex process like aging and AD. Because we identified distinct and specific profiles for each group, these patterns represent a specific signature specific for each group. These results open the way to new exploration of physiological cerebral and "AD-like" aging in primates.

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ATAXIA TELANGIECTASIA-LIKE DISORDER (ATLD) IN SAUDI ARABIA: MRE11 GENE MUTATIONS, FREQUENCY AND CELLULAR RADIOSENSITIVITY

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Ataxia telangiectasia like disorder (ATLD) is a rare variant of ataxia telangiectasia (A-T) that shares a number of clinical features and similar cellular characteristics. These conditions are typically diagnosed at young age at about the time the affected children start to walk. A-T and ATLD patients develop progressive cerebellar ataxia which is required for their clinical diagnosis. Genetically, the ATLD is caused by mutation in the hMRE11 gene located at 11q21. The function of Mre11 protein is linked to Nbs1 protein which is mutated in Nijmegen breakage syndrome (NBS) and both are members of the Mre11/Rad50/Nbs1 (MRN) complex involved in different DNA healing mechanisms due to innate processes or in responses to damage induced by ionizing radiation and radiomimetic chemicals, including complexing with chromatin and with other damage response proteins, formation of radiation-induced foci, and the induction of cell cycle checkpoints. ATLD is very rare with, at present, only 16 confirmed cases, 4 in the UK, 2 in Italy and 10 in Saudi Arabia. The patients were either homozygous or compound heterozygous for 5 different mutations. The 10 Saudi Arabian patients were related to 3 independent families and represent the largest ATLD cohort. Genetically, the patients were homozygous for a novel missense mutation, a G to C change at nucleotide 630 of the Mre11 gene. The resulting amino acid change at position 210 (Trp to Cys) leads to destabilization of the MRN complex. The high number of Saudi ATLD patients with this particular mutation would suggest noticeable frequency of carriers in the Arabic peninsula. This may have impact on premarital and pre-implantation screening to limit genetic diseases and to provide informed genetic counseling. This paper will review data on ATLD mutations and concentrate on those related to the specific Mre11 G630C mutation found in Saudi Arabia including allelic frequency, cellular radiosensitivity and the impact on genetic screening. Supported by KFSH&RC grants 2000 031 and 2040 025.

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CYTOGENETIC ABNORMALITIES FOUND AMONG THE AUTISM PATIENTS IN AND AROUND COIMBATORE CITY, TAMILNADU, INDIA

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Autism is a neurodevelopmental disorder characterized by clinical, etiologic and genetic heterogeneity. It is often associated with other conditions, such as disorders of the CNS (tuberous sclerosis), developmental delay, attention deficit, epilepsy, and anxiety and mood disorders. The prime aim of the present study was to identify the chromosomal aberrations with autism patients in Coimbatore region. In order to investigate the possible cytogenetic damage in autism patients, peripheral blood lymphocyte culture (PBLC) method was carried out on the lymphocytes of 31 autism patient samples and equal number of controls was selected, based on the detailed questionnaire. Moreover, the present investigation has been conducted in the year of 2008 to 2010. In the present

study volunteers provided blood samples (5 ml) to establish cell cultures at 72 h. For karyotyping, 100 complete metaphase cells from each subject were evaluated using Trypsin – Giemsa Banding method. In our study chromosomal alterations were frequently observed in chromosomes 2, 3, 7, 15, 16 and X (2q32, 3q25-q27, 7q31-q35, 15q11-q13, 16p13, Xp22, and Xq13). The chromosomal aberration frequency among 31 subjects was: 2/31 [6%] supernumerary markers; 7/31 [22%] deletions; 1/31 [3%] duplication; 1/31 [3%] inversions; 2/31 [6%] translocations. In the present study, chromosomal aberrations showed higher degree in experimentals compared to controls (P<0.001). In conclusion, in this pilot study, we observed the chromosomal instability in peripheral blood lymphocytes may be a potential biomarker in autism patients. This is the first study, which documents the spectrum of chromosomal changes in Coimbatore population.

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MOLECULAR, AUDIOLOGICAL AND POPULATION FEATURES OF AUTOSOMAL RECESSIVE DEAFNESS 1A (DFNB1A) IN YAKUT POPULATION ISOLATE FROM EASTERN SIBERIA

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Hereditary forms of hearing impairment (HI) causing by GJB2 (Cx26) mutations are the frequent sensory disorders registered among newborns in various human populations. In this study we present data on the molecular, audiological and population features of autosomal recessive deafness 1A (DFNB1A) associated with the donor splicing site q.-3179 (IVS1+1G>A) mutation of GJB2 gene in Yakut population isolate of the Sakha Republic (Yakutia) located in Eastern Siberia (Russian Federation). The Yakut population exhibits high frequency of some Mendelian disorders which are rare in other populations worldwide. Mutational analysis of GJB2 gene in 86 unrelated Yakut patients with congenital HI without other clinical features has been performed.
In this study we registered a large cohort of Yakut patients homozygous for the q.-3179 (IVS1+1G>A) mutation (70 unrelated deaf subjects in total). Detailed audiological analysis of 40 deaf subjects with genotype q.-3179 (IVS1+1G>A)/q.-3179 (IVS1+1G>A) revealed significant association of this genotype with mostly symmetrical bilateral severe to profound HI (85% severe to profound HI versus 15% mild to moderate HI, p<0.05). The extremely high carrier frequency of the q.-3179 (IVS1+1G>A) mutation (11.7%) from six investigated populations has been found in Yakut population. Reconstruction of 140 haplotypes with q.-3179 (IVS1+1G>A) mutation demonstrates the common origin of all mutant chromosomes found in Yakuts. The age of mutation was estimated to be approximately 800 years. These findings characterize Eastern Siberia as the region with the most extensive accumulation of the q.-3179 (IVS1+1G>A) mutation in the world as a result of founder effect. The study was supported by Russian Foundation for Basic Research (09-04-01123-a), Federal Programs "Scientific and educational staff for innovative Russia" #02.740.11.0701 for years 2010-2012, #16.740.11.0190 and #16.740.11.0346 for years 2009-2013, the A.I. Ivanov Sakha Republic President Grant for Young Researchers in Medicine for 2009 year (03.02.2010 #71-p) and the State Scholarship of the Academy of Sciences of the Sakha Republic (Yakutia).

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GENETIC BACKGROUND OF COCHLEAR IMPLANT PATIENTS WITH INNER EAR MALFORMATION (MONDINI DYSPLASIA, ENLARGED VESTIBULAR AQUEDUCT- AND PENDRED- SYNDROME)

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Pendred syndrome (PDS), an autosomal-recessive disorder is characterized by sensorineural deafness and goiter. This syndrome is one of the most common forms of syndromic deafness. Hearing loss is prelingual in the majority of the cases, only a subset of patients has a progressive hearing loss later in life. The deafness is associated with temporal bone abnormalities ranging from isolated enlargement of the vestibular aqueduct (EVA) to Mondini dysplasia, a more complex malformation that also includes cochlear hypoplasia. PDS is caused by mutations in the SLC26A4 gene. The SLC26A4 gene is expressed in the non-sensory epithelia of the inner ear. Recently an additional gene FOXI1 was described which may also be responsible for Pendred-Syndrome and Mondini dysplasia. The FOXI1 gene is involved in the transcriptional control of the SLC26A4 gene. In this study we analyzed 127 patients with EVA and hearing loss to distinguish between Pendred-, EVA syndrome and Mondini dysplasia. Individual exon and intron transitions of the SLC26A4 and FOXI1 gene of patients were PCR sequenced. A genome-wide linkage analysis was accomplished using the 50 K genotyping. In the analyzed patients with Pendred syndrome and/or enlargement of the vestibular aqueduct, a total of twenty-one different SCL26A4 mutations were detected, by contrast mutations could not be detected in the FOXI1 gene. In the SLC26A4 gene a mutation could not be detected in 42 % of the cases. With a genomewide SNP analysis, of these families it was possible to identify potential new gene loci responsible for the Enlarged Vestibular Aqueduct Syndrome and Mondini dysplasia. Conclusions: These results suggested in contrast to the literature that the FOXI1 gene is not the main factor involved in Pendred- and enlarged vestibular aqueduct syndrome. Our results indicate evidences of an accessory gene for the enlarged vestibular aqueduct syndrome and especially for Mondini dysplasia.

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OVEREXPRESSIOIN OF NT3 AND TRKC AND KNOCKING-DOWN THE EXPRESSION OF P75 GENES IN RAT BONE MARROW STROMAL CELLS AND EVALUATING ITS EFFECS ON TRANSPLANTATION IN A RAT MODEL OF SPINAL CORD CONTUSION INJURY

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Spinal cord injury (SCI) often induces loss of motor and/or sensory function below the level of injury. The adult spinal cord is able to spontaneously respond to SCI, and do so by anatomically reorganizing axonal connections and generating new precursor cells. Transplantation of stem/progenitor cells could enhance these endogenous repairs by generating new neurons and glial cells. Because of the complex clinical nature of SCI, future efficient treatments have to combine different approaches of treatments including: (1) tissue or cell transplantation, (2) providing growth-stimulating factors including neurotrophic factors, and (3) blocking factors which inhibit neural regeneration. Bone marrow stem cells (BMSCs) are easy to isolate and could be applied as autologous transplantation. They also have tropisms for sites of disease and can synthesize neurotrophines and differentiate into neuronal and glial cells. But, the potential success of the transplantation process nevertheless depends on the long-term survival and synthetic activity of the grafted cells in their new environment. p75, known as the death receptor, is involved in neurotrophin-induced apoptosis, especially when Trk receptor is not available. Furthermore, according to our previous results, p75 expression is initiated upon the induction of neural differentiation in bone marrow stem cells. On the other hand, neurotrophines are the primary regulators of neuronal survival and death in the CNS. According to our previous studies, BMSCs express both NGF and BDNF before and after neural differentiation, while no detectable expression of TrkC and NT-3 was observed in these cells in vitro. Therefore, the aim of our study is to merge cell transplantaion, neurotrophic factor provision, and apoptosis inhibition strategies by NT3 and TrkC overexpression and p75 suppression in rat BMSCs in order to increase their functional activity and survival rate after transplantation. To achieve this goal, NT3/TrkC, and p75-siRNA expressing bone marrow stem cells were produced. Transgene expression was confirmed at RNA level. Apoptosis and cell cycle changes of these cell lines were evaluated using flow cytometry after neural differentiation. MTT assay was used for analyzing viability of the cells. Finally, transplantation of the cells into SCI rat models, histological studies, behavioral testing and statistical analysis was performed. Flow cytometry and MTT assay revealed diminished apoptosis and increased survival in transfected BMSCs. Transfected BMSCs were able to survive at the site of implant, and they could improve functional behavior after grafting into lesion site of spinal cord injured rats. Our results demonstrated that genetically modified BMSCs could be a better candidate for treatment of SCI.

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ROLE OF MONOAMINE METABOLIZING ENZYME GENE POLYMORPHISMS IN PARKINSON'S DISEASE DEVELOPMENT IN BASHRORTOSTAN REPUBLIC OF RUSSIA

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Parkinson's disease (PD) is the second most common age-related neurodegenerative disorder, characterized by the progressive loss of substantia nigra pars compacta dopamine neurons and the consequent decrease in the neurotransmitter dopamine. The etiological factors involved in the development of PD remains incompletely understood, but there is considerable evidence that a combination of genetic susceptibilities and environmental factors plays a critical role in disease pathogenesis. The aim of the investigation is to search the genetic factors and neuropsychological abnormalities in Parkinson's disease development. During clinical and genetic research of Parkinson's disease we've examined 620 PD samples, aged 48-83 (mean 62 years) and 630 healthy individuals, aged 46-82 years (mean 62 years), from Bashkortostan Republic of Russia. Psychological investigation of 319 PD was carried out. All patients exhibited at least two of the four principal signs of PD: resting tremor, rigidity, bradykinesia, or postural-reflex impairment. Exclusion criteria included prior history of multiple cerebrovascular events or other causes of Parkinsonian symptoms (e.g., history of brain injury or tumor, encephalitis, etc). Controls were matched for age, gender, ethnic origin and area of residence. All subjects gave consent to being included in the study. The association analysis of PD with polymorphic variants of monoamine metabolizing enzyme genes was performed taking into consideration ethnic origin of examined individuals (Russians, Tatars, Bashkirs), form of the disease, severity level and age of manifestation, as well as presence or absence of neuropsychological abnormalities. The following genes were analyzed: tyrosine hydroxylase TH (VNTR in 1 exon), catechol-O-methyltransferase COMT (Val108Met) and a dopamine receptor DRD4 (VNTR in 5 ' UTR '-areas). The most important results have been received in COMT gene analysis. COMT is the principal enzyme responsible for metabolic deactivation of L-dopa which is necessary to provide more continuous and sustained delivery of dopamine. Levodopa (L-dopa) - a pro-drug of dopamine - is used to elevate striatal levels of the neurotransmitter and remains the gold standard drug for treatment of the symptoms of PD. The analysis of COMT gene gave the evidence concerning the influence of Val108Met polymorphism on PD development: genotype *H/*H and allele *H, determining synthesis of the enzyme with high activity, may be considered as genetic markers of the increased risk contributing to development of PD in Bashkortostan Republic as a whole and to the most severe PD form, in particular. Genotype *H/*H and allele *H were also risk markers for the development of such neuropsychological abnormalities as personal anxiety, depression, dementia, whereas the genotype *L/*H, defining average activity of COMT, made protective impact, reducing

risk of PD development, especially until 60 years. The comparative analysis of the investigated polymorphic loci of TH and DRD4 genes has not revealed significant differences between PD samples and controls. The observed association of COMT genotypes and alleles with PD susceptibility and its role in modulating disease manifestation reiterates the importance of dopamine pathway in sporadic PD etiology in general and potential therapeutic implications of COMT in particular.

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GENETIC ANALYSIS OF SLC2A1 GENE CODING GLUCOSE TRANSPORTER GLUT1 IN TURKISH IGE PATIENTS

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Epilepsy is one of the most common neurological disorders with prevalence of 1% and approximately 30% of all epilepsy cases are classified as idiopathic generalized epilepsy (IGE). Generalized seizures are clinically characterized by absence, tonic, clonic and myoclonic by oneself or in different combinations. On the basis of seizure type and age of onset, the international classification (ILAE) identifies four main sub-syndromes: childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME) and IGE with tonic-clonic seizures. Twin studies demonstrate that genetic factors have significant impact on the etiology of IGEs. The underlying genetic factors for absence epilepsies in human are presently unknown as a result of complex inheritance model. Many of the genes that involve in IGE code for ion channels but syndromes with epilepsy mainly caused by genes that are related to cortical development, mitochondrial function and cell metabolism. Newly identified each ~~"e~~pilepsy gene" provides a better understanding of the molecular basis of brain function. In uncommon cases with Mendelian inheritance of IGE, it has recently been connected with glucose transporter type 1 (GLUT1) deficiency. GLUT1 is responsible for glucose entry into brain, across the blood-brain barrier and its defect leads to insufficient level of cerebral glucose. GLUT1 is encoded by the solute carrier family 2, member 1 (SLC2A1) gene. Generalized epileptiform activity can be seen in the cases with GLUT1 deficiency syndrome is due to heterozygous mutations in SLC2A1 gene. In this study, we will present the data obtained by screening 17 IGE patients with absence seizures for SLC2A1 gene mutations via DHPLC and direct DNA sequencing in 10 fragments.

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VAL153ILE MUTATION AND THE HEREDITARY HEARING LOSS

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Hereditary hearing loss is a very common birth defect, affecting one in ~1000 infants, which is characterized by impressive genetic heterogeneity with more than 130 loci already described. Mutations in the Connexin 26 (GJB2) gene are the predominant cause of hereditary hearing loss and wide spectrum of mutations and polymorphisms have been reported within this gene. There are some common mutations worldwide affecting normal hearing, however there are few mutations that remain controversial in proving their role in population wise pathogenesis. Val143Ile (c.457 G>A) substitution occurs in a transmembrane domain of Connexin 26 that has been in some cases, implicated as pathogenic mutation, whereas in some other cases reported as benign polymorphism. Here we report an extensive analysis combining population and computational study that gives possible indication about the role of this controversial mutation. This study involves population and genetic analysis of existence of this mutation in 450 normal individuals from South India, which revealed the frequency of this mutation in normal population. Further, we extended the study by utilizing the computational approaches to model this mutation with available crystal structure of GJB2 protein. We have also modeled other mutations with the Val143Ile to elucidate the role in a compound heterozygous form. This study would help in understanding the role of this divisive mutation in pathogenesis and also would extend the understanding of knowledge of population specific heterozygote advantage.

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MUTATION DETECTION IN GJB2 IN IRANIAN CHILDREN WITH HEARING LOSS RECEIVING COCHLEAR IMPLANT TREATMENT

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In genetic assessment of hearing impairment, 46 genes and 81 genetic loci have been identified yet and this numbers are increasing. Mutation in GJB2 gene is the most common mutation which had been found in children with non syndromic hearing loss and had been presented as predominant cause of inherited sensorineural deafness. GJB2 gene encodes gap junction channel protein 26 (Connexin 26) which allowing direct communication between the cells. Cochlear implantation (CI) is one of the hearing rehabilitation in patients with complete hearing loss and nowadays most of children with dominant or recessive congenital hearing loss are candidates of this therapeutic method. Present study had two main purposes, firstly genetic assessment of children who were referred for CI and secondly, whether type of mutation is important factor in treatment of included children? During present study, connexin 26 gene analyses was performed on 42 children with nonsyndromic hearing loss who were referred to Baqiyatallah hospital for CI. All probands had prelingual deafness (early onset). Genomic DNA was extracted from peripheral blood

and the coding sequence of the Connexin26 gene was PCR amplified and sequenced using standard methods. In the present study we analyzed the coding region of the connexin26 gene in 42 children with non-syndromic hearing loss and found two homozygote and four heterozygote 35delG mutation in them. Treatment response was assessed in our patients with 35delG mutation. According to results of Speech Intelligibility Rating (SIR), it seems that treatment response of children with homozygote mutation was better than heterozygote patients. Deafness in our patients had an autosomal recessive inheritance pattern and according to this pattern, we must see only homozygote mutations in patients but in four patients, mutations were heterozygote. There are some explanations for this phenomenon. DFNB1 locus has two genes Cx26 and Cx30, and deafness might inherit by genetic defects in each of these genes. Some studies on deaf children reports better speech performance after cochlear implantation in persons with GJB2-related deafness. Results of our study showed that cochlear implantation must be considered suitable choice for treatment of children with GJB2-related deafness. Mutation screening for finding deafness causing mutations in GJB2 gene is a useful predictor of post-implantation speech perception. Mutation screening allows us to have better pre-implantation counseling.

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MULTIPLE CONGENITAL ANOMALIES DUE TO A TERMINAL GAIN OF 16P; A CASE REPORT

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Gain of chromosomal material often results in various clinical consequences depending on the size and part of chromosome. We report on a patient from Indonesia with terminal gain of 16p13.3p13.13 recognized by 250k SNP array, presenting with multiple congenital anomalies (MCA) and developmental delay (DD). Distinct facial anomalies included microcephaly, asymmetric face, high forehead, excess of scalp whorl, sparse eyebrows, telecanthus, strabismus, upslanting palpebral fissures, prominent and low-set ear, short nose, high-arched palate and wide-spaced teeth. An epileptic seizure was reported and confirmed by an abnormal EEG pattern. Arterial Septal Defect type II was found and confirmed by Doppler examination. Clinical features will be compared and discussed with reported cases. Chromosome analysis showed a normal 46,XX karyotype. SNP array demonstrated a terminal gain of 11.5 Mb in 16p13.3p13.13 (1217 SNPs, more than 50 genes). Terminal loss of 1pter was also detected although not statistically significant. In conclusion, we reported a patient with distinct facial anomalies with neurological and cardiac anomalies. A chromosomal imbalance in this case was detected by SNP array only, indicating that cases of MCA and DD with normal karyotype should be followed with SNP array.

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INHERITED DISEASES OF THE NERVOUS SYSTEM IN ARABS

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The study of nervous system disorders among Arabs has usually a low profile because of the increased research interest in widespread ailments including cardiovascular disorders, cancers, and congenital malformations. Besides, nervous system disorders do not usually appear among the main causes of mortality in the region because they tend to be more of chronic and disabling natures. In order to raise the profile of nervous system disorders, we queried the Catalogue of Transmission Genetics in Arabs (CTGA) Database using its Power Search mode and found out records for 103 inherited disorders of the nervous system in Arab populations including 72 inherited in an autosomal recessive mode. Among Arab countries where the Centre for Arab Genomic Studies (CAGS) completed its survey, Oman leads with 24 of these disorders. In countries where CAGS surveys are ongoing, Tunisia leads with 22 disorders. Interestingly, among these two countries only one common nervous system disorder occurs and all the others represent private entities. In fact, apart from the common neuro-genetic disorders, there are 62 nervous system disorders each of which occurs privately in one population, but not in the others. These include such rare conditions as several non-classical forms of amyotrophic lateral sclerosis, hereditary spastic paraplegia associated with thin corpus callosum, and several rare forms of ataxia. In addition, many new neuronal disorders have been identified in Arab families, such as spastic cerebral palsy with microcephaly and mental retardation, a new autosomal recessive disorder of leukodystrophy, a distal hereditary motor neuropathy (HMN-J), and an autosomal recessive muscular dystrophy. On the other hand, the presence of large and extended families from the region has also eased the molecular characterization of such disorders. In fact, many nervous system disorders have been mapped and/or have had their underlying genetic mutation identified in Arab patients. In most cases, such studies have made use of patients from the Maghreb countries (Tunisia, Algeria, and Morocco) or Lebanon. Such linkage and fine mapping studies include the linkage of ataxia with selective vitamin E deficiency, Duchenne-like muscular dystrophy, limb girdle muscular dystrophy (types 2B and 2I), giant axonal neuropathy, and congenital muscular dystrophy 1A. In many instances, nervous system disorders with apparently common clinical features tend to reveal different genetic pathologies reflecting the complexities of the processes governing this system; e.g., spastic paraplegias (SPG24, SPG28, SPG18, SPG30, and SPG35) and Charcot Marie Tooth disease (types 4A, 4B1, 4B3, 4C, 4F, 4H, and 2B1).

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MOWAT WILSON SYNDROME; FIRST CASE IN QATAR IDENTIFIED BY ARRAY COMPARATIVE GENOMIC HYBRIDIZATION (ACGH)

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Mowat-Wilson syndrome (MWS) is a recently delineated mental retardation syndrome usually associated with multiple health defects and characterized by typical facial gestalt. Approximately 200 cases have been reported worldwide predominantly in Europe and North America. The syndrome occurs as a result of heterozygous mutations or deletions in the zinc finger E-box-binding homeobox 2 gene, ZEB2, previously called ZFHX1B (SIP1) located on the long arm of chromosome 2 at 2q22. The spectrum of mutations includes point mutation (81%), intermediate and large mutations (17%) or large scale rearrangements (2%). We report the first case of MWS in Qatar. The 2 year old female patient has features of MWS. The array comparative genomic hybridization (aCGH) analysis was performed by 44k ISCA design oligonucleotide platform. The patient was found to have a de novo deletion of ~500kb at 2q22. The routine chromosome analysis was normal. The aCGH is a relatively new technology, which has revolutionized the field of clinical genetic diagnostics. The aCGH can detect unbalanced chromosomal aberrations including microdeletion, microduplication, aneuploidy, unbalanced translocations, and subtelomeric and pericentromeric copy number alterations throughout the genome. Unlike conventional cytogenetics, aCGH can detect deletions and duplications smaller than 5 megabases and, in contrast to single-color FISH, can scan for multiple aberrations simultaneously. This case emphasizes the value of array CGH to detect or characterize chromosome rearrangements in patients with mental retardation with/out dysmorphic features and multiple congenital anomalies.

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MOLECULAR GENETIC ANALYSIS OF THE MITOCHONDRIAL ATP SYNTHASE 6 GENE IN EGYPTION CHILDREN WITH NEUROPATHY, ATAXIA, RETINITIS PIGMENTOSA/MATERNALLY INHERITED LEIGH'S SYNDROMES

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Neurogenic muscle weakness, ataxia and retinitis pigmentosa (NARP) and maternally inherited Leigh's syndrome (MILS) are genetically heterogeneous, neurodegenerative disorders that predominantly affect children and lead to death within months or years. Clinical features of NARP may include peripheral neuropathy, retinitis pigmentosa, cerebellar atrophy and less frequently epileptic seizures and deafness. MILS is dramatically characterized by bilateral subacute lesions of the basal ganglia. The mitochondrial oxidative phosphorylation system, the source of ATP production in most tissues, consists of the electron transport chain complexes (I-IV) and the ATP synthase (ATPase) (complex V). Genetic alterations disturbing the components of this complex enzymatic system can lead to insufficient energy supply and result in various mitochondrial disorders. Subunits 6 and A6L of complex V are encoded by the mitochondrial genome, while all of the other subunits are encoded by nuclear genes. Several point mutations in the mitochondrial ATPase 6 gene (T8993G/C, T9176C) were associated with these syndromes. This study aims at the contribution to the establishment of a rational molecular approach to these syndromes. Also, to obtain insights into the molecular pathogenesis of these disorders among five Egyptian pediatric patients presented to the Cairo University Pediatric Hospital with the clinical suspicion of these mitochondrial syndromes. Methods: Clinical examination, Pedigree analysis, basic laboratory and radiological examinations of five probands had been reported. Total nuclear and mitochondrial DNA were extracted from the peripheral blood leukocytes of the probands and apparently healthy age and sex matched controls. ATPase 6 gene was amplified and directly sequenced. Sequencing analysis results were compared with the revised Cambridge Reference Sequence (rCRS). All sequence variants were compared with the MITOMAP database and the Human Mitochondrial Genome Database. Sequencing analysis of the mitochondrial ATPase 6 gene revealed distinct sets of benign polymorphisms. Testing for the most common pathogenic point mutations could be used as initial non invasive simple screening test for the mitochondrial syndromes, however ,negative results does not exclude the disease. Involvement of nuclear and other mitochondrial genes rather than mitochondrial ATPase 6 gene should be considered in the molecular pathogenesis of the NARP/MILS syndromes. Targeted molecular diagnosis based on the histochemical and the biochemical analysis of the mitochondrial respiratory chain enzymes makes the molecular evaluation of pediatric mitochondrial disorders much easier.

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THE ROLE OF CYTOKINES IN MESIAL TEMPORAL LOBE EPILEPSY

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Epilepsy is a multifactorial disorder which effects % 1-3 of people worldwide. Mesial temporal lobe epilepsy (MTLE) is the most common form of syptomatic epilepsies with pharmacologically tenacious partial onset seizures. In MTLE it

is thought that various genes and signaling pathways take place due to presence of complex changes in hippocampus during the pathogenesis of disease. The inflammation period in this pathogenesis has been exhibited by the studies of animal models. In this study, we used hippocampus materials which are obtained from post amygdalohippocampectomy period after medical indication of 4 women and 5 men patients who are diagnosed with mesial temporal lobe epilepsy and resistant to antiepileptic treatment applied in convenient time and combinations. RNA samples, isolated from these tissues were used for the synthesis of cDNAs by reverse transcriptase PCR method, in order to quantify the inflammation-related gene expressions by real-time PCR. As control tissue, hippocampus material were taken during autopsy from 9 different cadaver of which the reason of death excluding neurological reasons. In the normalization of results, abl and cyclophilin genes were used Relative expression values were calculated with deltaCt method. Results were compared statistically by using "Mann-whitneyU" test. In the analysis of the expression levels of IL12, IL10, IL6, it has been depicted that these genes do not show any significant differences in the materials of epileptic versus autopsy tissues (P=0.73, P=0.59, P=0.24). On the other hand, it is determined that the expression of IL1-β, TNF-α, IFN-γ and TGF-β in patients indicate significant increase according to healthy controls (P=0.001, P=0.0006, P=0.007, P=0.027). In addition to these, there was no expression of IL1-α, IL2 and IL17 detected neither in patients nor in healthy individuals. Results in this study show that an increased level of inflammation-related gene expression participates in the pathogenesis of mesial temporal lobe epilepsy.

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MOLECULAR GENETICS OF AUTOSOMAL RECESSIVE MENTAL DISORDERS IN CONSANGUINEOUS PAKISTANI FAMILIES

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Mental disorder or mental illness is a complex term which is a behavioral or psychological pattern associated with disability that occurs in an individual and is not a part of normal development or culture. Mental disorders are generally classified into neurological disorders and learning disabilities or mental retardation. Incidence of mental disorders is relatively high in Pakistan because of high consanguinity. Hallervorden-Spatz syndrome (HSS) also called neuro-degeneration with brain iron accumulation (NBIA) encompasses a group of progressive extrapyramidal disorders characterized by iron accumulation in the brain. In the present study, we identified five large consanguineous Pakistani families with autosomal recessive mental retardation and one with autosomal recessive Hallervorden-Spatz syndrome (HSS) having multiple affected births. Purpose of the study was to improve the understanding on protective measurements for mental disorders. Nucleic acid (DNA) was extracted and subjected to STS (Single tagged sequence) marker analyses for mapping of homozygosity in known genes and known loci regions using a fluorescence three primer method. All families were excluded for all known genes and loci regions. For HSS family (consists of three loops), detailed clinical examination including brain MRI was made for two affected from two loops. Both affected individuals showed phenotype of HSS. Further its three loops were subjected to the Genome wide scanning using SNP6.0 array for detection of homozygous regions. No shared homozygous region was found for all three loops and even for any two loops while five homozygous regions were found for a single central loop. By checking genotypes for these three loops, no match was found for compound heterozygosity. PANK2 gene was sequenced as a candidate for this family but no mutation was found. All these analyses made the molecular genetics of MR6 very complicated and suggest several possible molecular etiologies; it could be compound heterozygous, have three different mutations or be digenic. This complexity of HSS needs advanced molecular studies including exome sequencing and next generation sequencing using DNA capture enrichment to understand the molecular genetics of this disease phenotype.

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THE ROLE OF VERSICAN AND COLLAGEN TYPE I ALPHA2 POLYMORPHISMS IN INTRACRANIAL ANEURYSMS IN A SOUTH INDIAN POPULATION

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Intracranial aneurysm is one of the major causes of stroke that affects 2% of the population. It accounts for 500000 hemorrhagic strokes annually in the mid life (median age 50), often resulting in death or severe neurological impairment. Aneurysmal SAH patients have a mortality rate as high as 40% to 50%. The etiology of idiopathic intracranial aneurysms is yet to be established and remains controversial. SAH from aneurysmal rupture supports genetic cause, either directly or in conjunction with predisposing environmental factors like hypertension. Tensile strength of arteries is provided by arterial collagen and Versican gene product that plays a critical role in ECM remodeling. The collagen alpha2 (I) gene (COL1A2) is located on chromosome 7q22.1 and Versican (CSPG2) is located on chromosome 5q are positional and functional candidate gene for intracranial aneurysm. Using case-control study design, six SNPs of COL1A2 (rs42524, rs421587, rs2621215, rs760043, rs411717, rs420257) and two SNPs of CSPG2 gene (rs173686 and rs251124) were analyzed for association of polymorphism with intracranial aneurysms in south Indian population. Study population contained 175 cases and 175 controls. Genotyping was done by PCR-RFLP and was confirmed by sequencing. Allele, genotype and haplotype frequency were computed among the cohorts. All the SNPs genotyped in controls were within the Hardy-

Weinberg equilibrium. Significant association was observed with rs251124 for both genotype (p =0.0000219) and allelic (p=0.00183) combinations. CC genotype was found to have a protective effect. The SNP in COL1A2 gene, rs411717 was found to be significantly associated with genotype risk (p= 0.00458). Haplotypes involving C allele of rs411717 were seen to be significantly associated in patient population in two loci (p =0.001763) and three loci (p =0.00437) combination. Linkage Disequilibrium pattern was found to be significantly different in cases and control. The SNP rs42524, located in exon 28 which was functionally significant and associated in Japanese population found no association with intracranial aneurysm in our population. Our study indicates CSPG2 and COL1A2 are promising candidate genes in predisposing to intracranial aneurysm in south Indian population.

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INVESTIGATING THE EXPRESSION OF APOPTOSIS RELATED GENES IN MESIAL TEMPORAL LOBE EPILEPSY

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Epilepsy is a syndrome characterized by recurrent spontaneous seizures due to neuronal hyperactivity in brain with an incidence of 1%. Temporal lobe epilepsy (TLE) is one of the most frequent types of intractable epilepsy and it comprises 50% of all partial epilepsies. Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS), one of the most common types of TLE, is characterized by seizure generation from the mesial temporal lobe. Although the etiopathogenesis is unknown, changes in synaptic and axonal reorganization have been reported during the course of HS. Complex alterations leading to hippocampal pathogenesis of MTLE suggests involvement of various genes and signaling pathways.Temporal lobe surgery (amigdalahippocampectomy) for histopathological studies have provided a way to study epileptogenesis. The most common neuropathological finding is sclerosis in ammon horn, especially due to neuronal loss in CA1, CA3 and CA4 regions. Recently, the role of apoptosis in neuronal loss leading to development of MTS has been shown. The supporting evidence in patients with MTS includes reactive gliosis observed in pathologic specimens, and changes in the expression of apoptotic genes shown mostly in model organisms. In response to harmful stress, cells induce apoptosis which is also known as programmed cell death. Seizures can induce neuronal damage and activate biochemical pathways associated with apoptosis. Initiation of apoptosis has been broadly separated into processes involving the extrinsic pathways, such as those mediated by death receptors of the tumor necrosis factor (TNF) family (TNFR1, Fas) and the intrinsic pathways, which are initiated by disturbances to intracellular organelle homeostasis particularly at the mitochondrial membrane (especially Bcl-2 superfamily members). In this study, we have investigated gene expression levels for both extrinsic and intrinsic pathways in human hippocampal material obtained from 10 patients with intractable TLE compared to 9 control samples obtained from cadaver hippocampal tissues, via real time RT-PCR with TaqMan probes. Our study with human brain makes it particularly distinctive from previous studies with model organisms.

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MALFORMATIONS OF CEREBRAL CORTICAL DEVELOPMENT IN EGYPTIAN PATIENTS: CLINICO-RADIOLOGICAL AND GENETIC STUDIES

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Malformations of cerebral cortical development (MCD) are heterogeneous group of abnormalities cause by both genetic and epigenetic factors and often presents with developmental delay and seizures. The aim of this work is to present and correlate clinical, neuroimaging, cytogenetics and molecular characteristics of MCD encountered in Egypt. Over a period of 5 years we identified ninety-seven patients from 71 families with MCD with consanguinity rate 77.3%. Patients were classified according to the three overlapping stages of cortical development; defects cell proliferation, migration and cortical organization. Defects in cell proliferation; hemimegalencephaly (n=7), 5 of them was related to different neurocutaneous syndromes and focal cortical dysplasia (n=2) manifested with intractable seizures. Defects in cell migration as classical lissencephaly (LIS) (n=11), Miller-Dieker syndrome was in 2 cases with specific facies and microdeletion of the critical region 17p13.3 identified by FISH analysis. Three of 7 cases were linked to LIS1 gene. Interestingly, we identified 2 sibs from first cousin parent with classical LIS supporting the possibility of presence of an autosomal recessively inherited classical LIS. Cobblestone LIS was 12 cases; isolated cobblestone complex was in 3 families with normal muscle and eye with exclusion of all related genes as POMT1, POMT2, POMTnG1, Fuktin, Fuktin-related, Large genes. Walker-Warburg syndrome was in 3 families and muscle eye brain disease was in 2 families. Lissencephaly and cerebellar hypoplasia (LCH) (n=10), two families seemed to be related to RELN gene mutation which was only identified in one of them, where both sibs had interestingly homozygous balanced reciprocal transclocation 7:14 causing disruption of RELN gene. One family had homozygous mutation in VLDLR gene, and the last family had a unique pattern of LCH, specific features and congenital heart disease. Lissencephaly and ambiguous genitalia were identified in 2 male patients; nevertheless, none of them was linked to ARX gene. LIS was also present in 3 families (4 cases) with Neu Laxova syndrome. Bilateral periventricular nodular heterotopias were in 5 patients, two of them were female sibs from consanguineous parents with macrocephaly and specific facial features and another patient had classic features of Donnai-Barrow syndrome. Polymicrogyria (PMG) was presented in 24 patients. Perisylvian PMG (n=3), one of them was linked to 22q11.2. Generalized PMG (n=10), bilateral frontopariental PMG (n=10), 4 families were due to homozygous mutation in GPR56 gene and a single patient had a parasaggital

polymicrogyria. Congenital infection like syndrome was assigned in 11 cases (6 families), 4 families had band like calcification (BLC) and PMG, 3 of them underwent molecular analysis and found to be linked to occludin (OCLN) gene. A single case had classical LIS and bilateral basal ganglia calcification with exclusion of known genes causing LIS and another case with simplified gyral pattern, cerebellar hypoplasia and unique pattern of calcification. Schizencephaly (n=9) was either open lip, bilateral and symmetrical in 2 patients or unilateral in 7 patients. This study illustrates the wider phenotypic spectrum of MCD and verifies the implication of single gene inheritance as a possible genetic etiology in most of these disorders.

GENETICS OF HERITABLE DISORDERS

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UROMODULIN GENE VARIANT IS ASSOCIATED WITH BETTER KIDNEY FUNCTION AND DECREASED RISK TO TYPE 2 DIABETIC NEPHROPATHY

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About 30% of individuals with type 2 diabetes (T2D) develop persistent albuminuria, with declining renal function, and are at an increased risk for microvascular complications like Diabetic nephropathy (DN). Recently the Uromodulin locus encoding the most common protein in human urine has been found associated with kidney function in Hypertensive patients with chronic kidney disease (CKD). In the present study we examined the association of the common variant of the Uromodulin (UMOD) gene with type 2 diabetic nephropathy and renal function. UMOD variant rs13333226 was genotyped in a case control set-up including 4,888 unrelated type 2 diabetic individuals (with and without nephropathy) from Sweden (Scania Diabetes Registry) using the ABI Real time TaqMan allelic discrimination assay. The G/G genotype of rs13333226 was associated with a decreased risk of nephropathy (OR: 0.8; 95%CI: 0.69-0.91; p=0.001) after correction for confounding factors like age, gender, bmi, SBP, kidney function, smoking and diabetes duration. The same genotype was also associated with a better kidney function (estimated glomerular filtration rate (eGFR) Beta: 0.13; $p< 0.0001$) in the overall study cohort. The present study highlights that common variant of the UMOD gene is protective towards DN susceptibility in type 2 diabetics.

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AUTOSOMAL RECESSIVE SILVER-RUSSEL SYNDROME IS ALLELIC TO 3-M SYNDROME WITH NOVEL MUTATIONS IN CUL7 AND OBSL1 GENES

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Intrauterine growth retardation (IUGR) is a nonspecific finding that occurs in approximately 0.17% of all live-births. However, IUGR can also be a significant feature of many recognized genetic syndromes including Silver-Russel syndrome (SRS), Three M syndrome (3-M), Dubowitz syndrome and Mulibrey nanism. Differentiation of 3-M syndrome from autosomal recessive SRS has been difficult because of the phenotypic variability of the latter. Limb length asymmetry is seen in over half of those with SRS, but not in individuals with 3-M syndrome. Characteristic radiologic findings of 3-M syndrome are not present in SRS. Mutations in CUL7 and OBSL1 genes have recently been shown to cause 3-M syndrome. We used single nucleotide polymorphism (SNP) microarrays to investigate the cause of phenotypic features of SRS that shows autosomal recessive inheritance in three consanguineous families, two from United Arab Emirates (UAE) and one from Jordan. Subsequently, direct DNA sequencing was performed on CUL7 and OBSL1 genes, which are located within the mapped regions. Novel mutations in both genes were found including two mutations in OBSL1 [c.1119G>C (p.W373C) and c.681_682delinsTT (p.Q228X)], and a nonsense mutation in CUL7 [c.203G>A (p.W68X)]. In addition, a 6 nucleotide deletion in CUL7 [c.649_654delAGCCGC (p.217_218delSR)] was found in a consanguineous family from UAE that had the typical features of 3-M. In this article we question the identity of the autosomal recessive SRS and suggest that all apparently recessive SRS families should be tested for mutations in CUL7 and OBSL1.

P132

CONGENITAL DEFECTS DUE TO CONSANGUINITY

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Parental consanguinity results in an increased risk of having offspring with congenital anomalies which has been reported in many countries. Enormous data sources are available online which provide useful insights on the effects of consanguinity as an etiological risk factor for congenital defects, but these studies focus on a particular congenital defect in a particular population. This study was undertaken to analyze the congenital defects trend associated with consanguinity in

different populations; i.e., which congenital defects were most studied and which were less studied in target populations, followed by the development of a prototypical model of congenital defects due to consanguinity based on statistics applied on real data in less studied populations. The target populations in this study included populations from Egypt, India, Israel, Oman, Pakistan, Saudi Arabia, and United Arab Emirates (UAE) -- regions with high rates of consanguinity. The information gathered included detailed demographic, medical, statistical and other relevant information about the occurrence of congenital defects due to consanguinity from the year 1992 to 2010. An extensive assessment of the literature revealed that in the Saudi population, more studies were conducted on congenital heart defects compared to any other congenital defect. In UAE, most of the studies focused on thalassemia, but little attention was paid towards chromosomal abnormalities. However, higher frequencies of chromosomal abnormalities were studied in Oman and India. Congenital deafness was the only congenital defect which was equally studied in all the target populations. Higher rates of studies which focus on congenital malformations of the central nervous system and schizophrenia associated with consanguinity was found in Israeli Arabs and Egyptian rather than Indian, Saudi, or Pakistani populations. In Pakistan, more studies have been conducted on individuals with increased risk of Progressive Encephalopathy (mental retardation), congenital heart disease, and children with cleft lip and palate associated with consanguinity. All these studies target particular domain and population, and conclusions have been drawn by using statistical methods. Different modeling and simulation approaches have been used to develop models that enable the study of particular system at a desired level of specification. The models contain various parameters of the system which helps to adjust system capabilities according to the available data. The variation in these parameters can provide an insight into the trends of a particular system applicable worldwide. Unlike statistical models that provide statistical data for the particular region and particular disease, simulation models provide a unified model applicable in most circumstances regarding a particular disease. Therefore, by customizing simulation models according to the particular disease, statistical data of one population can be applied to the less studied one in order to analyze the behavior of a particular disease. Simio is a rapid modeling, discrete-event simulation software which is extensively used to model healthcare, manufacturing, and airlines management systems. Currently, we are using Simio software to develop simulation models to study the congenital defect trends associated with consanguinity based on statistics applied on real data in less studied populations followed by its validation.

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A MTDNA MUTATION SCREENING STUDY PERFORMED ON NEONATAL PATIENTS HAVING EARLY INFANTILE SEVERE LACTIC ACIDOSIS

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The reason for morbidity and mortality in the early infantile primary lactic acidosis patients lies with the involvement of organs such as liver, brain, sometime heart. . The geneticist and the neonatologist remain helpless since no information for its pathogenesis exists precluding a rationalistic therapy or preimplantation genetics diagnosis or prenatal diagnosis. In this study we performed mtDNA mutation screening study for patients having severe lactic acidosis during neonatal period. In three patients we have identified mutations in ATP synthase 6, cytochrome c oxidase I and cytochrome B genes. Clinical course of the patients, detailed bioinformatics analysis on the deleterious effects of the mutation, and likely mechanisms of the disease caused by these mutations and potential management plan to help these families are discussed.

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TOWARDS THE IDENTIFICATION OF A RECESSIVE CONGENITAL NYSTAGMUS GENE USING COMBINED HOMOZYGOSITY MAPPING AND EXOME SEQUENCING STATEGIES

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Congenital or Infantile Nystagmus (CN) is a rare neurologic inherited condition. It presents as disabling conjugate horizontal oscillations of the eyes. This disorder can be transmitted in an X-Linked fashion, as a consequence of FRMD7 or GPR143 genes mutations. To date, several loci have also been identified in autosomal dominant forms of CN, but no causative gene could be identified. Recessive CN was exceptionally described and has, to date, never been investigated by genetic analyses. We present here an attractive strategy to identify the autosomal recessive CN gene in a French family with an a priori high probability of consanguinity. Recently, this strategy was successfully applied in another very rare condition called Diaphanospondylostosis where consanguinity was suspected (Funari et al, AJHG 2010). In this family, three girls were born from healthy, apparently unrelated parents. Two of the girls have CN. Close geographic origin of the grandparents and the rarity of recessive CN were suggestive of consanguinity. We first performed High Density genotyping of the three girls with Illumina 610K SNP arrays, followed by Homozygosity Mapping analysis using HomozygosityMapper (Seelow et al, PNAS 2009) and PLINK (Purcell et al, AJHG, 2007). This genome-wide analysis confirmed our hypothesis of hidden inbreeding. It allowed us to infer the level of consanguinity of the sibship, using various methods of homozygosity-by-descent estimation (Polasek et al, BMC genomics 2010). It also revealed three runs of homozygosity (ROH) shared by only affected cases: two of them, 54 Megabases and 12 Megabases in length respectively are localized on chromosome 12. The third block, 21 Megabases in length, lies on chromosome 6. A great number of smaller intervals between 1-7 Megabases in length were also shared by the affected sisters. These results led us to adopt

a high-throughput sequencing strategy of any ROH, in order to determine whether one of these intervals contained a CN mutation. We thus combined our results with Exome Sequencing in the sibship, using Illumina paired-end sequencing technology. Systematic search of homozygous mutations, associated with a candidate-genes approach, provided three good candidates for further analysis. The next step of our strategy will consist in crossing references from (1) other rare recessive or sporadic CN cases we are actually recruiting, (2) population studies: we will analyze the candidate variants in large panels of control populations (400-1000 population-matched controls), (3) expression data: we will perform exhaustive expression analysis of our genes set in a focused normal human tissues panel (retina, optic fibers, and several brain regions including optic area). We demonstrate by this approach that crossing data and combining new genomic technologies is an efficient way to identify causative genes in very small sets of patients and in very rare conditions where traditional genetic analysis cannot be held.

P135

SPECTRUM OF GENES CAUSING CONGENITAL NEPHROTIC SYNDROME IN SAUDI ARABIA

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Nephrotic Syndrome (NS) is characterized by heavy proteinuria, hypoproteinaemia, and oedema. Congenital nephrotic syndrome (CNS) is NS occurring within the first 3 months of life and may suggest an inherited condition. Inherited NS is genetically heterogeneous. To date defects in at least eight genes have been recognized; NPHS1, NPHS2, ACTN4, CD2AP, WT1, TRPC6, LAMB2 and PLCE1. Proteins encoded by these genes influence the function of the podocytes and the slit diaphragm. The Saudi Arabian population has a tribal structure and the overall rate of consanguineous marriage is reported to be 58%, with regional variations. In such a population, the identification of mutations in known recessive disease genes is a robust method of diagnosis and will improve clinical management. To determine the frequency of inherited NS, sixty cases of CNS from Saudi Arabia were screened for mutations in the following genes NPHS1, NPHS2, PLCE1, KIRREL1, LAMB2, and CD2AP. We found that the most common genetic cause of CNS in our cohort was mutation of NPHS2 accounting for 15 % of cases. Common mutations included V260E, R168H, and V180M. The second most common cause was mutations of PLCE1, whilst that of NPHS1, LAMB2, and CD2AP remained rare.

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ADVANCES IN MOLECULAR DIAGNOSIS OFGENETICS DISEASES IN KUWAIT

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Nowadays, diagnostic molecular biology techniques are the fastest growing area of laboratory medicine leading to understanding of how structural variations in DNA and RNA are associated with the development of the genetic diseases. New technologies have contributed to the dramatic acceleration in our capacity to investigate the genetic components of hereditary diseases. Many genes responsible for monogenic diseases have been successfully isolated and used for a case or carrier diagnosis of those diseases. Although genes that cause complex diseases, such as cardiovascular disease, asthma or osteoporosis are being studied and isolated, but it will take time before using these results in clinical practice due to the complex city of interaction between genetic and environmental risk factors. Using recent and sensitive molecular techniques, Kuwait Medical Genetic Center is now serving a large number of patients having monogenic hereditary disorders and their families with a well experienced staff members and very well equipped molecular lab aiming for accurate diagnosis of affected cases and carriers, genetic counseling and also to perform genetic studies in this area of the world. Moreover the lab offers a DNA banking facility for genetic diseases with uncharacterized genes for future investigations and also can do screening of any gene for unknown mutation detection with special arrangement. A lot of single gene disorders mutations are diagnosed now in KMGC molecular lab as: Neuromuscular disorders (SMA, Limb Girdle and myotonic dystrophy), metabolic disorders as (Sanjad Sakati, Gaucher), mitochondrial diseases like (MERFF, MELAS and Leigh syndromes), blood diseases as (thalassemia, Sickle cell anemia, haemochromatosis), neurodegenerative diseases as (Metachromaic leukodystrophy, Batten), and sex Differentiation disorders like (21-hydroxylase deficiency, Androgen insensitivity syndrome, Turner syndrome). In addition many other diseases are also diagnosed as Fragile-X, sensory neural hearing loss, Norrie disease, and Down syndrome.

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THE PREVELANCE OF FMR1 PREMUTATION/FULL MUTATION ALLELES IN JORDANIAN PATIENTS WITH COGNITIVE IMPAIRMENTS, MENTAL RETARDATION, OR PREMATURE OVARIAN FAILUER (POI)

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The fragile X syndrome (FXS) is defined as a loss of function disorder. An expansion of a CGG repeat in the 5' untranslated region of the fragile X mental retardation 1 (FMR1) gene (chromosome locus Xq27), results in the deficit of the FMR1 gene-specific product. The diagnosis of FMR1-related disorders depends on the detection of an alteration in the FMR1 gene, including normal range alleles (6-50 CGG

repeats), large sized permutations (50-200 CGG repeats), and full mutations (>200 CGG repeats). Although several studies have been conducted to investigate the phenotype-genotype relationship in different populations, precise prevalence figures of the FMR1 premutation and full mutation alleles, and their association with FMR1-related disorders in Arab populations, are lacking. We report on a series of 97 Jordanian subjects presenting symptoms ranging from learning disabilities to severe mental retardation, and 8 Jordanian POI patients, all of which were examined for the number of CGG repeats within the FMR1 gene between 2000 and 2010. 49 Subjects were examined by southern blot analysis, using the Stb 12.3 probe for hybridization on EcoRI - EagI double digested DNA. 43 subjects were examined by PCR, using primers flanking CGG expansion in the FMR1 5‘ UTR. The amplification products were run on automated sequencer. 13 subjects, including the 8 POI patients, were examined by both techniques. Among the 97 cognitively impaired/mentally retarded subjects, 10 males and 1 female carried the fully mutated allele (>200 CGG repeats), and surprisingly none carried the premutated allele (50-200 CGG repeats). Interestingly, 6 of these symptomatic, full mutation carriers are unrelated, randomly referred for testing individuals with familial origins from the city of Karak south of the capital Amman. Among the POI subjects examined, only one female carried a premutated allele (76 CGG repeats). In addition, 21 and 29 subjects have a CGG repeat allele in the range of 20-30 and 30-40 respectively, whereas 6 subjects only have a CGG repeat allele in the range of 40-45. Although further analysis is necessary, preliminary data indicates that Jordanian patients with mental retardation are carriers of the FMR1 full mutation, whereas patients showing cognitive disabilities are within the normal polymorphic range. In addition FMR1 premutations seem to be uncommon in sporadic cases of POI with no family history of FXS.

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A GENOME-WIDE LINKAGE STUDY OF BIPOLAR DISORDER IN A LARGE MULTIGENERATIONAL FAMILY FROM BRAZIL

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Bipolar Disorder (BP) is a complex disorder characterized by recurrent episodes of mania and depression. There is substantial evidence from family, twin, and adoption studies for the importance of genes in influencing susceptibility to BP. However, with the exception of some loci of small effect uncovered by meta-analysis of genome wide association studies, linkage and association studies have repeatedly failed to produce consistent and replicable findings for BP. The aim of our study is to localize and identify genetic variants that contribute to the development of BP. by conducting a whole-genome linkage scan for susceptibility loci for BP in a large multigenerational family from Brazil. Following the identification and verification of BP linkage region(s), it is our aim to identify the mutations within the region(s) that may be contributing to the development of BP using sequencing approaches. METHODS: This Brazilian Bipolar Family (BBF) includes 916 family members, 330 of whom have been screened using the Structural Clinical Interview for DSM-IV (SCID) and Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS). Seventy-one members (21%) are affected with BPI, BPII, Schizoaffective affective disorder/bipolar type (SA), and Recurrent Major Depressive Disorder (MDD). Three-hundred and thirty family members have been genotyped using the Affymetrix human mapping10K array. Using parametric and non-parametric linkage approaches we have tested the co-segregation between BP and Single Nucleotide Polymorphism (SNP) markers in the Brazilian Bipolar family using different disease and transmission models. Parametric linkage analysis identified a novel susceptibility locus for bipolar disorder on chromosome 3q22.1 with a recessive mode of transmission.

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ASSOCIATION OF CYTOTOXIC T-LYMPHOCYTE ANTIGEN 4 GENE POLYMORPHISM WITH LATENT AUTOIMMUNE DIABETES IN ADULTS

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Latent autoimmune diabetes of adults (LADA) is a subgroup of diabetes, somewhere on the borderland between type 1 and type 2 diabetes. LADA is characterized by a late-age onset and relatively mild progression, but with unmistakable signs of autoimmunity, the most predominant are glutamic acid decarboxylase(GAD65), islet cell antibodies(ICA) and insulin antibodies (IA-2). The cytotoxic T lymphocyte antigen-4 (CTLA-4) is a co-stimulatory molecule expressed on activated T lymphocytes and is an important negative regulator of T-cell activation. Since defects in T cell regulation are believed to underlie the basic etiology of endocrine autoimmunity it is possible that defects in CTLA-4 expression or function may predispose to other autoimmune disorders. Objective: To detect the presence of islet cell autoantibodies (GAD65 & IA2) in clinically diagnosed type II patients with view to be classified as having LADA and to evaluate the impact of allelic variants of the CTLA-4 gene in those LADA patients. GAD65, ICA and IA-2 autoantibodies were evaluated in 264 clinically characterized type two diabetic patients (more than 35 years), who had been on oral therapy for at least three months. The polymorphism of CTLA-4 gene in LADA patients were then studied using CT60 A/G SNP and the CTBC217_1 C/T SNP comparing to similar number of normal controls. Thirty-two patients (12.1%) were positive for the three autoantibodies. In those patients, It was found that the CT60 GG genotype (p=0.003) and the CTBC217_1 TT genotype (p=0.005) were significantly associated with LADA but the healthy controls did not have such polymorphisms. This study revealed that LADA prevalence increases dramatically and misclassified into Type2diabetes resulting in serious complications and false treatment monitoring. Moreover, not only type 1 diabetes but also LADA is associated with CTLA-4 gene polymorphisms. The age and

general symptoms are not adequate to classify diabetes mellitus; hence pancreas autoantibodies should be examined routinely for diabetic patients. The role of CTLA-4 gene in the pathogenesis of LADA is open and needs further investigations.

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GENETIC ASSOCIATION STUDIES IN ARAB POPULATIONS: STATUS AND FUTURE INSIGHT

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With a close look on the non communicable diseases in the Middle East, one sees a striking prevalence of genetic disorders of both monogenic and polygenic types. What is more striking is the timid achievements that originate from the Arabian population genetic research, however for the last few years significant genetic reports have started to emerge bringing a new era of research into the region and that needs further nourishment. Genome-wide association studies (GWAS) is a modern genetic method that can quickly scan across the whole genome, in many individuals, for genetic markers including single nucleotide polymorphisms (SNPs) and copy number variations (CNVs). Variations observed in these genomic markers can be used to assess the underlying genetics as well as the risk of disease development. In recent years, this approach has been heavily and successfully used in many populations, in which disease loci and genes were identified and characterized. Disorders studied through this method include obesity, diabetes, coronary artery disease, cancer, asthma and mental illness. Such achievements are attributed to both the recent advancements in sequencing and genotyping technologies, in addition to the analytical tools which together made it possible to query on the sophisticated genetic and environmental factors that contribute to, or associate with, these complex diseases. Regarding the genetic association studies in the Mediterranean Arab countries, several studies were conducted on Arab populations in which one or few SNPs were genotyped in relatively small size cohorts of cases and controls. Both positive and negative associations were reported from these studies, and hence further research is warranted to address the genetic architecture of diseases in this region. To date, only limited linkage analysis studies (and not GWAS) have been conducted in the Arabian countries according to our knowledge. Not only key studies are lacking, but the utility of the existing genetic arrays for the Arabian genetic research is arguable on the bases of array marker representation. The state and knowledge on the genetic association studies in the Arabian countries and the link with the global genetic research will be discussed.

P141
MANGANESE SUPEROXIDE DISMUTASE ACTIVITY, BENIGN AND BREAST CANCER

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The problem of MnSOD microheterogeneity in patients with breast tumors is interesting. In this study, Manganese Superoxide Dismutase (MnSOD) activity was evaluated in breast cancer and benign females Thirty six females and seven control attending King Hussein Medical City (2007-2008) and Hamzah Hospital (2010) were enrolled in this study; twenty one were histopathologically diagnosed with breast cancer, and fifteen were benign patients. MnSOD enzyme activity was determined using an indirect competitive inhibition assay and MnSOD gene polymorphism using PCR and gel electrophoresis. MnSOD enzymatic activity (94.8 Â± 32.6) was significantly lower in malignant breast tumors than those in benign tumors (245.34 Â± 62.8) among Val/Val patients. At the same time, MnSOD enzymatic activity was significantly lower in malignant breast tumors (39.19 Â± 7.33) than those in benign tumors (94.8Â± 32.6) among Ala/Val patients. MnSOD enzymztic activity was lower among Val/Val cancerous females compared to benign females and MnSOD enzymztic activity was lower among Ala/Val cancerous females compared to Val/Val cancerous females. MnSOD gene polymorphism Ala/Val may be considered as risk factors that are involved in breast cancer development and progression, so further investigations are needed to evaluate the role of MnSOD in breast cancer etiology.

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COGNITIVE EVOLUTION IN HOMO SAPIENS: A COMPARISON AND CROSS-CONNECTION WITH HOMO NEANDERTHALIENS

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Homo Neanderthaliens is the most recent hominid which, according to recent evidences, coexisted in several parts of the world with Homo Sapiens. And so it was expected that the detailed information of Neandertal may give insight into human evolution more vibrantly. One very conspicuous area of the analysis has been human cognition and brain evolution. It has been known from fossil evidences that Neandertal brain size was larger than human. And previous study suggested that Neandertals attained their larger adult brains via higher growth rates rather than via an extended growth period. After Recent success in sequencing Neandertals genome it has been found that several changes have taken place in modern-day-human comparing to the Neandertalâ€™ss genome. One such comparison has catalogued 11 non-synonymous but non-fixed substitution changes in coding sequences of genes (ASPM, PCNT, MCPH1, GLI3, RAI1, UCP1, EVC, COBA1, MYO1C, WRN, ABCAC) hypothesized to be important in human evolution. For these changes the Neandertal shows more similarity to other apes, like Chimpanzees. In this study, all those genes harboring the changes in 11 positions were analyzed using protein interaction analysis tools and databases like string (http://string-db.org) and Biogrid (http://thebiogrid.org/). Of them, it was found that ASPM, PCNT, MCPH1, RAI1, GLI3 are associated to brain

development and functionality. The non-synonymous changes in these genes in modern day human indicate their significances in human brain and cognition adjustment. And it was found from other analyses using SNPs- and mutation - databases that the ancestral stages of these genes in Neandertals actually favored the greater growth rate of the brain in postnatal stages. However, their cognitive and intellectual status remained lower because of the lessened functional ability of the larger brain. One very interesting finding was the ancestral stage of the UCP1 gene in Neandertal. This protein is only expressed in brown adipose tissues (BAT) which functions to produce heat. One very popular hypothesis for Neandertal bigger brain is their habitation in cold environment. The ancestral sate of the UCP1 gene might have roles in heating the bigger brain and body.

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MOLECULAR GENETIC ANALYSIS OF INHERITED ALOPECIA IN PAKISTAN

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There are several forms of inherited isolated alopecias with variation in age of onset and severity. The main cause is consanguineous marriages in Pakistan. There are many consanguineous families with different types of alopecia including autosomal recessive hypotrichosis, congenital atrichia with papular lesions, autosomal recessive woolly hair and alopecia universalis, and others. Unfortunately, there is no therapy for majority of such genetic disorders. However, these disorders can be controlled through carrier screening, genetic counseling, mutation detection and prenatal diagnosis. To establish such programs it is mandatory to understand the molecular basis of these disorders. In this study we ascertained eight consanguineous alopecia families with multiple affected members from Punjab and northern part of Pakistan. The disease segregates in all families in autosomal recessive fashion. We used candidate gene approach for this study and selected five genes like HR, P2RY5, LIPH, DSG4 and FOXI3. Linkage analysis was performed by PCR using the STR (short tandem repeats) microsatellite markers for the known loci. Five families showed linkage to P2RY5 gene, two families with LIPH gene whereas only one family of Alopecia linked to HR gene. Direct sequencing of the PCR products carried out and identified the pathogenic mutations. We found a mutation in P2RY5 gene in five families with autosomal recessive wooly hair (ARWH). Haplotype analysis identified same disease haplotype in all these families which showed the common ancestor for them. Along this mutation, we also identified two recurrent mutations in LIPH and one in HR genes. This research will help in the establishment of carrier screening and prenatal diagnosis tests for prevention of above diseases and to understand the molecular basis involved in the gene function.

P144
THE DSD EXOME PROJECT

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Disorders of sex development (DSD) are defined as congenital conditions in which the development of chromosomal, gonadal, or anatomical sex is atypical. DSD covers a wide spectrum of phenotypes. 46,XY DSD includes 46,XY complete or partial gonadal dysgenesis, or undervirilisation or undermasculinization of an XY male. Ovotesticular DSD refers to an individual with both ovarian and testicular material present in the same or different gonads and 46,XX testicular DSD refers to an XX male with testes. Other forms of DSD include cloacal extrophy, severe hypospadias, vaginal atresia, and as part of other conditions such as Mayer-Rokitansky-Kuster-Hauser syndrome, Smith-Lemli-Opitz syndrome or genito-palato-cardiac syndrome. It has been estimated that a molecular diagnosis is made in only around 20% of DSD, except in cases where the biochemical profile indicates a specific steroidogenic block. These conditions are refractile to classic genetic approaches since familial cases are rare and the sex determination, as a developmental process, is not evolutionary well-conserved. The analyses of candidate genes has had limited success. We have used a whole exome sequencing approach on 6 cases of 46,XY DSD and 46,XX DSD with or without somatic anomalies. The associated somatic anomalies included autism, learning difficulties and congenital heart disease. We identified potential disease-causing mutations associated with these phenotypes. In one example, a 46,XY girl who presented with gonadal dysgenesis and learning difficulties and who was born to consanguinous parents carried two missense mutations in the FOG2 gene, one homozygous other heterozygous. Murine Fog2 mutations are associated with a complex phenotype that includes anomalies of testis development. Functional studies indicated FOG2 protein carrying both the mutants exhibited aberrant biological activity. These data indicate the key role of FOG2 in human testicular development and identify a new genetic cause of human 46,XY DSD. The analyses of other DSD patients included in this study revealed several potential pathogenic mutations that included MAP kinase genes and a nonsense mutation in the TTN gene that is associated with congenital heart disease. These data highlight the power of an exome sequencing approach to understand the genetic basis of complex disorders that are difficult to study by classical approaches.

P145
A NOVEL DELETION MUTATION IN PROTEOGLYCAN-4 UNDERLIES CAMPTODACTYLY-ARTHROPATHY-COXA-VARA-PERICARDITIS

(CACP) SYNDROME IN A CONSANGUINEOUS PAKISTANI FAMILY

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Camptodactyly-arthropathy-coxa-vara-pericarditis (CACP) syndrome is an autosomal recessive condition that mostly affects joints and tendons, but can also affect the pericardium, which is a surface surrounding the heart. The CACP syndrome is caused by mutations in a secreted proteoglycan 4 (PRG4) gene which expresses in skeletal as well as non-skeletal tissues. In the present investigation we have described a large pedigree with multiple affected individuals segregating CACP syndrome in an autosomal recessive manner. Genome wide homozygosity mapping using 250K array revealed a large homozygous region on chromosome 1 carried by all the affected individuals. This region contains the previously described PRG4 gene involved in CACP syndrome. Sequence analysis of PRG4 gene in affected individuals of the family, presented here, revealed a 2 base pair deletion (c.2816_2817delAA) predicting a frame shift mutation (p.Lys939fsX38). To our knowledge probably this is the first mutation identified in PRG4 gene in a Pakistani family.

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POLYMORPHISMS AND PROTEIN LEVELS OF INTERLEUKIN-17A AND F IN SAUDI ASTHMATIC

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Interleukin 17 is associated with several inflammatory conditions, including asthma and polymorphisms in both IL17A and IL17F may contribute to either susceptibility or resistance to asthma as these polymorphisms may influence the expression of the gene product. We investigated possible association between five polymorphisms in interleukin 17 (IL17) gene [(rs17880588 (G/A) and rs17878530 (C/T) of IL17A, and rs763780 (T/C), rs11465553 (T/C) and rs2397084 (G/A) of IL17F)] and asthma development in Saudi population and studied the effect of these polymorphisms on the plasma levels of IL17A and 17F in asthmatics versus controls. The study group included 100 asthma patients and 102 ethnically matched controls. Genotyping was performed on purified DNA using RT-PCR with specific primers and probes. Levels of IL17A and IL17F proteins were measured in plasma by ELISA. Genotyping results showed that AG heterozygotes of rs17880588 of IL17A were significantly higher in the control group compared to the asthmatics ($p < 0.005$); none of the other SNPs examined showed any significant association. Levels of IL17A and IL17F proteins were both higher in asthmatics; levels of IL17A protein were 2.242Â±0.099 in control versus 2.752Â± 0.287 pg/ml in patients, whereas levels of IL17F protein were 236.01Â±38.28 in control versus 700Â±201.078 pg/ml in patients. The difference was statistically significant for IL17F ($p = 0.025$) based on the t-test. Levels of IL17A and IL17F correlated positively and significantly in the patients group ($p < 0.01$). This paper will present the results of our studies in Saudis and will discuss the results in the light of reports from other populations.

P147

THREE NEW POLYMORPHIC MUTATIONS ACCOUNT FOR THE PREVALENCE OF GLUCOSE 6 PHOSPHATE DESHYDROGENASE (G6PD) DEFICIENCY IN TUNISIA

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Erythrocyte (G6PD) deficiency is one of the most well known human genetic defects causing hemolytic anemia. A previous study on G6PD deficiency (our study) was carried out on Tunisian deficient subjects (11 females and 30 males). According to this study using PCR-RFLP seven different mutations have been found with the prevalence of G6PD A-variant. Focusing on the part of the gene between exon 5 to exon 8 by PCR-SSCP of coding regions followed by direct sequencing of abnormal pattern, three new mutations were detected. Two of them are polymorphic intronic mutations. The first is IVS-V 655C>C/T was found in 4 female subjects with mild deficiency of class III variant. The second is IVS-VIII 43 G>A, found in 3 male subjects with mild deficiency of class III variant. The third mutation is in the exon region so that it changes the primary structure of the molecule. It is cited for the first time and was named G6PD Tunisia. This variant affects the exon 7of the gene at genomic position 15435 G>T. It‘s cDNA position is 93 G>G/T it changes arg 246 to leu. This mutation was found in one heterozygote female with deficiency of class II who have had hemolytic anemia due to ingestion of fava beans. Finally, G6PD med variant, reported before in 3 cases, was found in 5 other cases (4 heterozygote females and one male hemizygote). These findings enlarge the spectra of mutations to be 10 variant mutations characterizing the Tunisian population and contribute with hemoglobin gene research in our laboratory to trace the whole genetic map of Tunisian population. On the other hand this study helps in fastening the diagnostic of G6PD deficiency after a long time to be ignored at the molecular level.

P148

ASSOCIATION OF CHROMOSOME 9P21 POLYMORPHISM WITH CORONARY ARTERY DISEASE IN WESTERN INDIANS

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Indians have a high propensity to develop Coronary Artery Disease (CAD) and it has been estimated that 60% of the

worlds‘ cardiac population will be in India by the year 2020. In this context it is very important to evaluate the new markers especially genetic variants in the Indian population, which is a heterogenous group. Genome-wide studies have implicated SNPs in 58kb region of chromosome 9p21 to be associated with CAD. In the current study we have evaluated the association of SNP rs10757278 at the 9p21 locus with CAD in Western Indians. Genotyping for rs10757278A/G was done by direct sequencing in 215 cases with confirmed CAD and 150 controls. Significantly higher frequency of the G allele was seen in cases as compared to controls 0.64 vs 0.53. The G allele showed association with risk of CAD (OR 1.589; 95% CI 1.177-2.146; P 0.003). The association is explained by the recessive model of inheritance. Addition of the 9p21 allele to Framingham risk score FRS, resulted in a shift of 17% of individuals from the low risk category to the intermediate-low (>5% to <10% 10-year risk) and 7% from intermediate-low to intermediate-high (>10% to <20% 10-year risk) categories. In conclusion the rs 10757278 A/G SNP at the 9p21 locus is significantly associated with the risk of CAD in Western Indians.

P149

AN EXOME STRATEGY TO IDENTIFY THE GENETIC BASIS OF NONSYNDROMIC INTELLECTUAL DISABILITY IN A CONSANGUINEOUS LEBANESE FAMILY

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Intellectual disability (ID) (formerly mental retardation) is a lifelong condition characterized by impairment of cognitive and adaptive skills, and affects about 1-3% of the general population. Genetic causes are found in approximately two-thirds of cases with known etiology. Nonsyndromic intellectual disability (NSID) is the diagnosis of ID individuals without additional physical or neurological abnormalities. Linkage and cytogenetic analyses have led to the identification of 29 X-linked and 6 autosomal recessive genes (PRSS12, CRBN, CC2D1A, GRIK2, TUSC3, and TRAPPC9) associated with NSID, which together account for less than 10% of cases of NSMR. NSID reports are scarce in the literature due to broad genetic heterogeneity and small family sizes in Western populations. Recently, whole-exome sequencing combined with stepwise filtering methodologies was demonstrated as an approach to identify the genes underlying Mendelian disorders. We have recruited a consanguineous Lebanese NSID family with three affected siblings who have prior normal standard karyotype and Fragile-X molecular testing. Clinical history, three-generation pedigree, dysmorphologic and neurologic examinations were obtained from the family. Affected siblings presented with dysarthria, action tremor, gait disturbances, and learning difficulties. We used SOLID V4 platform (Applied Biosystems) for whole exome sequencing to identify novel genes associated with this condition. Capture process has been done by â€˜Agilent SureSelect Human All Exon' kit, which covers >37 Mb of the human genome. We are in the process of analyzing data. The results of this study will shed light on the genes required for processes that are crucial for the development of intellectual and cognitive functions. In addition they will allow improvements in diagnostic testing, genetic counseling, and therapeutic interventions in the future.

P150

GABRG2 MUTATION ANALYSIS IN TURKISH CHILDHOOD ABSENCE EPILEPSY PATIENTS

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Childhood absence epilepsy (CAE) which is a subtype of idiopathic generalized epilepsies (IGEs) is characterized by non-convulsive epileptic seizures that has typical features of brief (14-20s) and sudden loss of consciousness with a generalized synchronous, bilateral, 2.5-4 Hz spike and slow wave discharge (SWD) in the electroencephalogram (EEG). The first mutation was identified in the GABRG2 gene that codes Î³2 subunit of GABAA receptors in a family with CAE and febrile seizures. Second mutation IVS6+2TÃ G in GABRG2 was found again in a CAE and febrile seizure family. The mutation disrupting a putative splice site probably results in protein truncation. The sequence analysis of 85 CAE patients revealed nine intronic variations seven of which were novell. As depicted by ASSP and ESEfinder tools these variations do not affect the splicing process except the IVS2+6TÃ G variation that created a crytic splice site (gt donor site) with a higher score compared to the wild type site as calculated by AASP. The cyrptic splice site causes a premature stop codon at the amino acid 60 (Pro60X) thus a truncated protein. It was not detected in 160 control samples and in other CAE patients screened in this study. The synonomous exonic change n.897T>C alters an ESE site. Functional studies are required to unravel the effect of both alterationsInterestingly the novel IVS5+55TÃ G transversion was identified in four of the CAE patients and also in the control group. The new SNP is probably specific to Turkish population therefore was submitted to pubmed (rs55712126). In conclusion, despite the apparent role of GABA receptors in absence seizures, only two probable causative mutations has been identified in 85 CAE patients indicating the involvement of other genes in the pathogenesis of absence seizures.

P151
INDIVIDUAL GENOME VARIABILITY OF PATIENTS WITH ANKYLOSING SPONDILITIS

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The purpose of our research was to find genetic factors of autoimmune arthropathies. During this research comparative genotyping of two Russian cohorts was performed, both of which combine HLA-B27 positive individuals. Among a large number of MHC genes it was the HLA-B27, which was strongly associated with autoimmune arthropathies. Also few other candidate genes were involved in the development of pathogenesis. Association with ankylosing spondylitis (AS) was shown for several non-MHC genes. Most of those genes take part in various immunological processes such as differentiation and antigen presentation. In this research we study variability of candidate genes - ERAP1 and KIRs especially in Russian Caucasian population. Within multigene KIR locus association of activating KIR3DS1 and inverse association of inhibitory KIR3DL1 alleles of killer immunoglobulin-like receptor KIR3D gene with AS were found for cohorts under comparison. To better understand how KIR3DL1/3DS1 gene determines susceptibility to AS, we analyzed the frequencies of alleles and genotypes encoding functional (KIR3DL1*F) and non-functional (KIR3DL1*004) NK-receptors. Also we analyzed an association of several most associated with AS coding-region SNPs in the ERAP1 gene with that KIR3D alleles. We genotyped KIR3DS1, KIR3DL1*F, KIR3DL1*004 alleles and 5 ERAP1 SNPs (rs2287987, rs30187, rs10050860, rs17482078, rs27044) in 70 AS patients and 83 HLA-B27-positive healthy controls from the Russian Caucasian population by SSP-PCR. It was the KIR3DL1*F allele frequency and not KIR3DL1*004 that was found to be low in the AS cohort. KIR3DL1*F/KIR3DS1 KIR3DL1*F/KIR3DL1*F genotype frequencies were found to be higher (34,3% vs 19,3%, p = 0,04, OR = 2,17) and lower (20,0% vs 39,8%, p = 0,01, OR = 0,38) in the AS cohort respectively, while KIR3DL1*F/KIR3DL1*004 genotype frequencies were nearly equally presented in both cohorts. Considerable differences in alleles frequencies within patients vs control cohort were shown for 3 of 5 SNPs under investigation. Using the EM-algorhitm we reconstructed 3-marker haplotypes that distinguish with high probability two cohorts due to differences in the haplotypes frequencies. In such a way both the sensitive, CCT, haplotype and the protective, TTC, ones were predicted. To verify the calculation we determined genuine frequencies of 5-marker haplotypes in AS cohort by haplotyping of individual cDNA samples. As a result presumably risk CCT haplotypes of ERAP1 gene was detected in 65 of 69 examined AS patients genomes. Although no correlation of ERAP1 SNPs and KIR3D alleles carriage was detected, we discover certain allelic forms of both genes that are significant genetic factors for AS in Russian population. We forecasted ERAP1 risk haplotype CCT (rs17482078/10050860/2287987) and demonstrated that its frequency detected within AS cohort reaches 88%. Also our result suggest significant role of KIR3DL1 lymphocyte-membrane expression insufficiency in AS pathogenesis.

P152
CLINICAL AND CYTOGENETIC STUDY OF A CASE WITH FAMILIAL CHROMOSOMAL TRANSLOCATION

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We report on a 6-year-old female patient presenting with muscle weakness, facial dysmorphism, average mentality (IQ is 80). She had low birth weight, developmental delay, hypotonia and hyporeflexia and difficulties in climbing the stairs. EMG revealed axonal polyneuropathy affecting both upper and lower limbs. The cytogenetic findings by GTG-banding and fluorescence in situ hybridization revealed 46,XX,t(12;14)(q14;q23). She was the child of non-consanguineous parents, the mother's karyotype was normal 46,XX while the father‘s karyotype was the same as his daughter 46,XY,t(12;14)(q14;q23), her sister‘s karyotype was also 46,XX,t(12; 14) (q14;q23). Fluorescence in situ hybridization (FISH) was used to elucidate the breakpoints and Array-CGH was done for the patient to confirm the balanced translocation. This case is compared with previously reported patients with similar translocations. This observation is of interest for it shows the importance of molecular cytogenetics in the study of balanced translocation with abnormal phenotype. Detailed correlations between chromosome aberrations and their phenotypes are of invaluable help in localizing genes for axonal polyneuropathy.

P153
HOMOZYGOSITY FOR A NOVEL MISSENSE MUTATION IN THE LEPTIN RECEPTOR (P316T) GENE IN TWO EGYPTIAN COUSINS WITH SEVERE EARLY ONSET OBESITY

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Congenital deficiency of leptin receptor is a very rare cause of severe early-onset obesity. To date, only 9 families have been reported in the literature to have mutations in the leptin receptor gene. The clinical features include severe early onset obesity, severe hyperphagia, hypogonadotropic hypogonadism, T cell and neuroendocrine/metabolic dysfunction. Here we report two cousins with severe early onset obesity and recurrent respiratory tract infections. Their serum leptin levels were elevated but they were within the range predicted by the elevated fat mass in both siblings. Direct sequencing of the entire coding sequence of leptin receptor gene revealed a novel homozygous missense mutation in exon 6, P316T. The mutation was found in the homozygous form in both cousins and in the heterozygote state in their parents. This mutation

was not found in 200 chromosomes from 100 unrelated normal weight control subjects of Egyptian origin using PCR-RFLP analysis. In conclusion, finding this new mutation in the LEPR beside our previous mutation in the LEP gene implies that monogenic obesity syndromes may be common in Egyptian population owing to the high rates of consanguineous marriages. Further screening of more families for mutations in LEP, LEPR, and MC4 receptor might confirm this assumption.

P154

TUMOR NECROSIS FACTOR-BETA (TNF-B) IS SUSCEPTIBLE TO SCHIZOPHRENIA DISORDER IN THE EGYPTIAN POPULATION

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Conflicting results have arisen among different ethnic populations with regard to the ability of tumor necrosis factor (TNF) to control the development of psychiatric disorders. Schizophrenia (SCZ, OMIM #181500) is a chronic psychiatric disorder marked by psychotic symptoms, alterations of thought, affect, volition and behavior. Consanguinity might represent a risk factor for psychoses in some Middle Eastern countries. This unreeled study was undertaken to investigate the possible role of the TNF-β +252A>G polymorphism for susceptibility to schizophrenia. Sixty Egyptian patients with SCZ according to DSM-V criteria (http://www.psych.org/MainMenu/Research/DSMIV/DSMV.aspx; Diagnostic and Statistical Manual of Mental Disorders) on the basis of clinical interviews, clinical examination and family history and 40 healthy controls, were selected from database records of Institute of Psychiatry, Faculty of Medicine, Ain Shams University, Cairo. Genotyping all individuals was performed using polymerase chain reaction (PCR) and enzymatic assay. The mean age ± standard deviation was 45.0 ± 9.5 years). Consanguinity rates are significantly elevated among Egyptian SCZ patients (SCZ: 46.6%, controls: 19.8%, p-value< 0.0001). Family history of SCZ with thyroid disorders, significantly more frequent among cases with SCZ (p< 0.05. Genotypes and allele distributions of the TNF-β polymorphism in patients with SCZ were significantly different from those of the controls. Subjects with the +252G allele had an increased risk for schizophrenia (66.7%, p= 0.001, Odds Ratio= 1.76, 95% CI= 1.27-2.45). Similarly, The GG genotyoe was the most frequent among subjects with SCZ phenotypes. TNF-β polymorphism might susceptible to Schizophrenia in Egyptian population.

P155

OPHTHALMOLOGIC MANIFESTATIONS OF FABRY DISEASE IN MEXICO

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Fabry Disease (FD) is an inherited disorder caused by deficiency of α-galactosidase A with accumulation of globotriacilceramide. Cornea verticillata and vessel tortuosity can occur in an early stage of the FD affecting almost all hemizygous (HMG) men and more than 70% of heterozygous (HTG) women. Ocular involvement can lead to an early diagnosis making the role of an ophthalmologist important in the study and detection of this disease. In Mexico there are no previous reports that describe these findings in patients with FD. Aim: Describe eye abnormalities in FD patients in Mexico. We described on a cross sectional study patients with FD of both sexes with clinical variables of FD such as age, gender, date of diagnosis of FD, enzyme level of α-galactosidase A, genotype, history of concomitant medication, different findings both in anterior and posterior segment of the eye. We included 9 patients, 5 HTG and 4 HMG with a mean age 36.5±14.6 years, all diagnosed with FD at 32.2±14.5 years, with 5 different mutations, 5 on treatment of beta agalsidase, 3 with alfa agalsidase and 1 patient without enzyme replacement therapy, visual acuity 20/20 was attained in 44% of eyes, the most common ocular findings in anterior segment were cornea verticillata in 3 patients, conjuntival vessel tortuosity in 7 patients, cataract only in 1 HMG eye; in posterior segment were retinal vessel tortuosity in 2 patients, and changes in the retinal pigment epithelium in 1 HTG patient. None of the patients had history of concomitant medication that caused cornea verticillata. This report is the first in Mexico about ophthalmological findings on FD patients and It shows the presence of ocular features that can be detected with a non invasive method at a routine medical consultation by general ophthalmologists leading to an early diagnosis and treatment onset by other specialists impacting on the progression of the FD.

P156

MUTATION DETECTION OF BREAST BRCA1 GENE USING FLUORESCENCE UN-PROBE TECHNIQUE

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The Breast Cancer Anti-estrogen resistance-1 (BRCA1) located at (chr 17q21) is one of the tumor suppressor genes and plays an important role in repairing DNA damage. Abnormal BRCA1 gene produce un-functional protein can leads to breast cancer. Using of the single nucleotide

polymorphism (SNP) detection technologies take a place recently in research. Using of fluorescently labeled oligonucleotide probe(s) to detect SNPs in targeted nucleic acid sequences has been raised. We report the first use of Cy5 (Cyanine dyes) and TAMRA (rhodamine dyes) uni-probes to detect the wild type and mutant SNPs of the BRCA1 breast cancer gene. The fluorescence changes according to the hybridization of the probes to the complementary target nucleic acid was gave differences , which help to differentiate between the wild target and the mutated .The synthetic oligonucleotides and genomic DNA extracted from blood samples were tested as target sequences. The fluorescence emission spectra, fluorescence anisotropy values and DNA melting curves showed significant differences that help to differentiate between wild and mutated (SNPs) targets. The mutations were (170-190, G>T) and (290-310, G>T) alleles. The results obtained are promising for the future applications in genetic testing and molecular diagnostics.

P157

BRCA1 AND BRCA2 MUTATIONS IN TUNISIAN FAMILIAL BREAST AND OVARIAN CANCER

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In the Tunisian population, a limited number of BRCA1/2 germ line mutations types have been detected in hereditary breast and ovarian cancer. These mutations are poorly described in western databases and it has been suggested that these mutations could be specific for the Tunisian population, with ethnically and geographical origin. In the present work we have looked for these founder mutations in 47 Tunisian breast and/or ovarian cancer patients, most of them belonging to breast and/or ovarian cancer families. Blood specimens from the 47 Tunisian patients were collected at the Salah Azaiz Cancer Institute of Tunis. Four belongs to ovarian cancer specific families, 33 to breast specific families and 3 to ovarian/ breast families. Exons 11 (HI: 2592-3191 and LM: 3621-4214), 20 and 5 of BRCA1 and exons 10 and 11 (14, 15: 5546-6182) of BRCA2 were sequenced (Applied 3130). In our series, 8/47 (17 %) patients had deleterious mutations in BRCA1 or BRCA2 genes. Four patients had a BRCA1 mutation: 1 with 3871insT stop 1254 (HGVS : c3752 dup T, p.Cys1251 leufsX4), 2 with 5382insC stop 1829 (HGVS : c.5266dupC , p.Gln 1756ProfsX74) and 1 with 4160delAG stop 1354 (HGVS : c.4041delAG, p.Gly 1348AsnfsX7). Interestingly, 4 patients had the same BRCA2 mutations: 1538delAAGA stop 458 (HGVS: c.1310_1313delAAGA, p.Lys437IIefsX22). Four unclassified variants were also detected in our series. In this limited Tunisian population, and studying part of BRCA1 or BRCA2 genes, we found a high frequency of mutations (17%); we confirmed the presence of BRCA1 c.4041delAG, BRCA1 c.5266dupC and of BRCA2 c.1310_1313delAAGA mutations. Moreover, we found twice the BRCA1 c.5266dupC mutation that is frequently described in western countries.

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DELINEATION OF PHENOTYPE IN TWO PEDIATRIC KLINEFELTER SYNDROME MOSAICISMS, NOT PREVIOUSLY DESCRIBED BY LITERATURE

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Klinefelter syndrome (KS) has an incidence of approximately 1/1000 in the general men population. It was first described in 1942 by Harry F. Klinefelter, and associated to an extra X chromosome by Jacobs and Strong in 1959. Diagnosis in pediatric age is difficult, unless hipogonadism is present. Only 10% of KS patients are diagnosed before puberty. We describe the phenotypic characteristics of two pediatric patients with cytogenetic diagnosis of KS mosaicism. We present two unrelated KS cases in 6 and 7 year-old males. Propositus 1: 7 years-old male, product of second pregnancy, full-term, from non consanguineous parents. Anthropometry: weight 29,600 g (97 percentile), height 135 cm (97 percentile), cephalic perimeter 53.2 cm (97 percentile). Chromosome complement: 46 XY (44%), 47 XXY (56%). Propositus 2: 6 years-old male, product of first pregnancy, full-term, from non consanguineous parents. Anthropometry: weight 25,300 g (97 percentile), height 130 cm (97 percentile), cephalic perimeter 52.6 cm (97 percentile). Chromosome complement: 49 XXXXY (86%), 47 XXY (56%). Common characteristics: Dolichocephaly, straight-thick hair, prominent frontal region, inverted V eyebrows, slanting palpebral fissures, hypoplastic nasal tip, broad nose, long philtrum, high palate, large ears, webbed neck, low implantation of hair, teletelia, mild mental retardation, and language disorders. 10 - 20% of total KS are mosaics; pediatric diagnosis is rare due to the lack of symptoms and signs. The variable phenotypes observed in KS mosaics depend on the number of abnormal cells and their distribution. Qureshi and Thurairajan reported a 49 XXXXY with high myopia, and Hata et. cols. with significant dental alterations. Clinical suspicion is required in childhood for an early diagnosis and the adequate patient‘s management.

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GENOME WIDE ASSOCIATION STUDY: SNPS ASSOCIATED WITH CORONARY ARTERY DISEASE IN NORTH INDIAN POPULATION

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Coronary artery Disease (CAD) is arguably the largest cause of mortality and morbidity worldwide. The incidence of CAD is increasing at an alarming rate, especially in developing countries like India were CAD tends to occur at a much earlier age. Like any other complex disorder, genes, environment (including diet) and their interaction play critical role in the manifestation of CAD. In terms of diet India is unique since a large proportion of Indians adheres to a strict vegetarian diet and thus is deficient in vitamin B12, a micronutrient sourced only from animal products. We had earlier reported that CAD is associated with vitamin B12 deficiency in Indian population. In spite of the extremely high rate of CAD till date there is no report of genome wide association studies (GWAS) from India focusing on the CAD or its risk factors. Thus, the aim of our study was to identify the SNPs that could be potentially associated with CAD and/or its risk factors in Indian population. All the CAD cases and controls were either collected from the All India Institute of Medical Sciences or from different parts of North India. The study was performed after obtaining necessary ethical clearance. Biochemical parameters like vitamin B12, folate, homocysteine, holo-transcobalamin, lipid profile, and others were measured using standard techniques. For the GWAS we used Illumina Omni express chip containing 731,442 SNPs and genotyped 1122 individuals (469 angiographically proven CAD and 653 controls) belonging to Indo-European linguistic group. PLINK software (v 1.02) was used for statistical analysis. During quality control analysis we found 5912 SNPs did not pass the SNP quality control filter. Further 9672 SNPs were removed for not following the Hardy Weinberg equilibrium. About 69977 SNPs were found to have Minor Allele Frequency <1% and hence were removed from the first analysis. The remaining 630440 SNPs were used for case-control association analysis with quantitative traits. Preliminary analysis revealed a few SNPs to be significantly associated with CAD with one in chromosome 12 being the most significant. To the best of our knowledge this is a novel finding. The possible biological underpinning of the SNP though remains enigmatic. On performing quantitative trait analysis with the control population we found SNPs to be associated with biochemical parameters some of which remained significant even after multiple correction using Bonferroni correction and False Discovery Rate (FDR) adjustment. Some SNPs were found significantly associated with CAD and other biochemical parameters in North Indian population. While a few of these have been previously implicated in CAD, many are novel. In future these SNPs will be used for further validation in large population.

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ACCOUNTING FOR GENETIC HETEROGENEITY IN HOMOZYGOSITY MAPPING: APPLICATION TO MENDELIAN SUSCEPTIBILITY TO MYCOBACTERIAL DISEASE

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Genome-wide (GW) homozygosity mapping (HM) is a powerful method to locate rare recessive Mendelian mutations. However, statistical power decreases dramatically in the presence of genetic heterogeneity. We applied an empirical approach to test for linkage accounting for genetic heterogeneity by calculating the sum of positive per-family multipoint LOD scores (S) across all positions, and obtaining corresponding empirical P-values (EmpP) through permutations. The statistical power of the approach was found to be consistently higher than the classical heterogeneity LOD (HLOD) by simulations. Among 21 first-cousin matings with a single affected child, for 5 families linked to a locus of interest and 16 families to other loci, S/EmpP achieved a power of 40 % vs. 28 % for HLOD at an Î± level of 0.001. The mean size of peak linkage regions was markedly higher for true loci compared to false positive regions. The S/EmpP approach was applied to a sample of 17 MSMD consanguineous families leading to the identification of two mutations in IL12RB1 and TYK2 from the largest of 6 linkage regions at P < 10-3. The S/EmpP approach is a flexible and powerful approach that can be applied to linkage analysis of families with suspected Mendelian disorders.

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INCIDENCE, GENETICS AND CLINICAL PHENOTYPE OF PERMANENT NEONATAL DIABETES MELLITUS IN NORTHWEST SAUDI ARABIA

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Permanent neonatal diabetes mellitus (PNDM) in the Caucasian population has an incidence of about 1 in 260,000 live births and is most commonly due to mutations in KCNJ11 and ABCC8. The incidence, genetic etiology and phenotypic features in non Caucasian populations are not well defined. Aims: The aim of this study was to define the incidence and the genetic etiology of PNDM in Al-Madinah region of Saudi Arabia. Patients with PNDM diagnosed between 2001 and 2010 from the whole region were identified and clinically phenotyped. Sequencing of KCNJ11, ABCC8 and INS were done initially on all subjects and EIF2AK3, GLIS3, SLC2A2, SLC19A2, GCK, IPF1 and NEUROD1 genes were sequenced according to the clinical phenotype. Seventeen Patients from 11 consanguineous families were diagnosed with PNDM and the incidence was 1 in 21,196 live births. Six different

mutations in 4 genes were identified in 14 (82.4%) patients. Of these, 3 were novel and no patient had KCNJ11, INS or ABCC8 mutations. These children had PNDM as part of known autosomal recessive syndromes including Wolcott Rallison (41.1%), neonatal diabetes and hypothyroidism (29.4%), thiamine responsive megaloblastic anemia (5.8%) and Fanconi-Bickel syndrome (5.8%). Two patients with isolated PNDM and one with iDEND (intermediate developmental delay, epilepsy and neonatal diabetes) syndrome had no identifiable cause. Al Madinah region has the highest reported incidence of PNDM worldwide. In this region with high consanguinity, PNDM has different genetic etiology, and in the majority of cases presents as a part of rare familial autosomal recessive syndrome rather than in isolation.

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KATP CHANNEL MUTATIONS ARE NOT THE MOST COMMON CAUSE OF PERMANENT NEONATAL DIABETES IN ARAB POPULATION

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Mutations in the KCNJ11 and ABCC8 genes that encode the pancreatic KATP channel are the commonest cause of permanent neonatal diabetes (PND) in Caucasian populations. Most of these patients achieve improved glycemic control on oral sulfonylureas. However recent data suggested an ethnic variation in the genetic etiology of this condition. Aim: To define the genetic causes of PND in Arab patients and compare with a British cohort tested in the same laboratory. Patients with PND of Arab origin were identified from the data-base of the Exeter Peninsula Molecular Genetics Laboratory, UK and were etiologically classified. A comparison in the genotype and phenotype between Arab and British cohorts with PND who were referred to the same centre around the same period was made. Seventy-one Arab probands from 13 countries were referred between years 2006-2010. The male to female ratio was 1.6 and the median age of diabetes presentation was 7 weeks (range 0 -26). Genetic causes for PND were identified in 67.6% of these patients. Recessive mutations in EIFK2A2 gene were the commonest cause of PND in this cohort (21.1%) followed by INS (14%). The frequency of other gene mutations were as follows: KCNJ11 (7%), ABCC8 (5.6%), GCK (4.2%), FOXP3 (4.2%), PTF1A, GLIS3, SLC19A2 (2.6% each) and SLC2A2 (1.4%). Compared to the British cohort, the majority of Arab children were the product of consanguineous marriage; their PND had different genetic causes and presented as part of rare genetic syndromes rather than in isolation. In Arab population PND has variable and different etiology compared to Caucasian; therefore careful assessment to detect extra-pancreatic features is important to guide the genetic testing. Although mutations in the KCNJ11 and ABCC8 genes are not the commonest cause of PND in Arab population, testing for these mutations is important as those with positive results can be switched from insulin to oral sulphonylureas.

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CHOICE OF SPOUSE AND POPULATION GENETIC STRUCTURE IN THE KINGDOM OF MOROCCO

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The choice of spouse has direct consequences on the distribution, structure and heterogeneity of a population's gene heritage. The aim of this study is to describe the mate choice pattern, focusing on the geographical endogamy in Rabat city (north-west of Morocco) in order to assess the level of reproductive isolation (or openness) of the community studied. The study was conducted within a randomly selected sample of Rabat's population. Various types of endogamous marriages were measured, based on the spouses' place of birth, place of residence at the date of marriage and geographical origin (810 couples). The results show a strong tendency towards geographical endogamy of nuptiality. This tendency is important among couples within parental generation. The results of intergenerational comparisons can be concluded to a significant decrease of endogamy rates from parental generation to current generation ($p<0,001$). The homogamy index method confirms this decrease. However, the values obtained do not exclude the importance of this marital behavior among the younger generation.

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IS SOUTHPAW AND AMBIDEXTERITY A GENETIC INFLUENCE? A RANDOM STUDY IN SCHOOL CHILDRENS IN BANGALORE, KARNATAKA, INDIA

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Southpaw and ambidexterity individuals have been ubiquitous in human populations, exhibiting geographical frequency variations. Evolutionary explanations have been proposed for the persistence of the handedness polymorphism. Southpaw is the rare hand preference and ambidexterity is still more rare preference, could represent an important strategic advantage in heredity. However, the fact that Southpaw and ambidexterity occurs at a higher and low frequency respectively indicates that some evolutionary costs could be associated with these two traits. Overall, the evolutionary dynamics of this polymorphism are not fully understood. Here, we point out that hand preference is heritable, and report how hand preference is influenced by genetic factors. Thus, perspectives on the persistence of this polymorphism in humans are gathered highlighting the necessity for an assessment of left-hander and ambidexterity on genetic basis and also consequence of socio-cultural pressures. Thus the present

study implies that left-handed is maternal and ambidexterity is not much clear of its inheritance and further exploration is necessary before a definitive explanation can be offered.

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LINKAGE ANALYSIS OF HAEMODYNAMIC PARAMETERS REVEAL SIGNIFICANT AND SUGGESTIVE LOCI DURING MENTAL AND PHYSICAL STRESS AND DURING SLEEP, IN EXTENDED OMANI ARAB PEDIGREES OF 'THE OMAN FAMILY STUDY'

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We performed a genome-wide scan in a homogeneous Arab population to identify genomic regions linked to blood pressure (BP) and its intermediate phenotypes during mental and physical stress tests. The Oman Family Study subjects (N=1277) were recruited from five extended families of ~10 generations. Haemodynamic phenotypes were computed from beat-to-beat BP, electrocardiography and impedance cardiography using the Task Force Monitor (TFM, Austria). High (HF) and low (LF) frequency bands of autonomic parameters were deduced using spectral analysis of R-R intervals .Ambulatory blood pressure was measured using a validated monitor (Schiller BR 102). Multi-point linkage was performed for resting, mental (word conflict test, WCT) and cold pressure (CPT) stress and their reactivity scores (âˆ†), using variance components decomposition-based methods implemented in SOLAR. Genome-wide scans for BP phenotypes identified quantitative trait loci (QTLs) with significant evidence of linkage on chromosomes 1, 3, and 12 for WCT-linked cardiac output (CO, LOD=3.1), heart rate (HR, LOD= 3.2) systolic and mean BP (LOD=3.5 and 3.1) respectively. Evidence for suggestive linkage for WCT was found on chromosomes1, 3, and 17 for left ventricular ejection time (LVET, LOD=2.2) for HR (LOD=2.3), diastolic BP (LOD=2.4) respectively. CPT- significant linkage was detected for Left ventricular work index and sympathetic LF in the same region of Chr 17 (LOD =3.3 and 2.7, respectively). CPT - suggestive linkage was found for HR and LVET in the same region of chr22 (LOD= 2.3 and 2.8, respectively) for systolic BP chr 9 (LOD=2.29), for stroke volume on chr7 (LOD=2.36) and for CO on chr19 (LOD=2.55). Evidence for significant linkage was also found for systolic BP % sleep dip in chr 8 (LOD= 3.6). Mental stress revealed the largest number of significant and suggestive loci for normal BP reported to date. The study of BP and its intermediate phenotypes under mental and physical stress and for 24 hours may help reveal the genes involved in the pathogenesis of essential hypertension.

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CFTR MUTATION SCREENING IN TUNISIAN POPULATION

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Cystic fibrosis transmembrane conductance regulator (CFTR; OMIM: 602421) gene is known to be implicated in Cystic fibrosis (CF; OMIM: #219700), the most common autosomal recessive disorder in the Caucasian population (1/2500). The aim of this study was to determine the frequencies of mutations in CFTR gene in Tunisian patients according to the clinical suspicion. We screened 60 patients for CFTR mutations. Patients were referred to our laboratory for very heterogeneous motifs encompassing CF, bronchietasis and bilateral absence of the vas deferens (CBVAD). 32 mutations were analyzed using Cystic Fibrosis Genotyping Assay from Abbott. Overall, CFTR mutations were detected in 10 % of the patients, while no mutations were detected in 90%. Knowing that the Abbott test sensitivity in North African population doesn't exceed 71% it seems very interesting to develop additional molecular strategies to carry out CFTR mutation screening in remaining patients.

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MOLECULAR DIAGNOSIS OF NEONATAL HYPOTONIA

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The neonatal hypotonia is a decrease in muscle tone active and / or passive. It is the call sign of many diseases of the newborn and infant. Taking into account the diseases covered by a molecular diagnosis certainty and with neonatal hypotonia as a major clinical sign, we are interested in three neurological disorders: Prader Willi syndrome (PWS), which is associated with genomic imprinting and abnormalities in genetic affecting the region 15q11q13; spinal muscular atrophy type I (AMSI), an autosomal recessive neuromuscular disease caused in 98% of cases with a deletion homozygous exon 7 plus or minus exon 8 of SMN1 gene located in 5q13 and myotonic dystrophy type 1 (DM1), an autosomal dominant disease, due to an expansion and unstable trinucleotide CTG in the untranslated region 3'UTR gene encoding myotonic dystrophy protein kinase (DMPK) located in 19q13.3. The aim of our work is to establish a molecular diagnosis strategy of neonatal hypotonia with neurological origin (SPW, AMSI, and DM1). Our study was performed in 27 newborns referred to our laboratory for neonatal hypotonia. We carried the diagnosis of PWS by both MS-MLPA techniques and TP-PCR, for AMSI we have deployed the technique of PCR-RFLP, for the DM1, both

techniques of TP-PCR and QMPSF were used. Patients without clinical suspicion of predilection were investigated with all these techniques. The PWS diagnosis was confirmed in only one patient. Among 17 patients with AMSI suspicion this diagnosis was confirmed for only 7. For the remaining 19 patients, none of the 3 molecular diagnostics (AMSI, DM1 and SPW) could be confirmed and etiology of neonatal hypotonia is to unveil. Our work provides clinicians a strategy for the diagnosis of neonatal hypotonia. However, this strategy remains incomplete and a multitude of other etiologies will have to be explored.

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MACROPHAGE MIGRATION INHIBITORY FACTOR (MIF) AS A POTENTIAL THERAPY FOR COLCHICINE NON-RESPONDERS OF FAMILIAL MEDITERRANEAN FEVER (FMF) PATIENTS

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FMF is an autosomal recessive disorder highly prevalent around the Mediterranean Basin. Colchicine, a prophylactic drug for FMF, is effective in preventing FMF fever attacks (FA) in the majority of patients while 20%-30% of FMF patients are partially or totally non-responders to colchicine. MIF is a potent pro-inflammatory cytokine that plays an essential role in many inflammatory and autoimmune disorders. Blocking MIF tautomerase active site with small pharmacophores has been successfully used to suppress many autoimmune and inflammatory disorders. The role of MIF in FMF pathogenesis and the effect of MIF inhibition have not been evaluated. In this study, we investigated the effect of MIF reversible inhibitor ISO-1 on the expression of IL-1β, TNF-α, IL-10 and MIF from peripheral blood lymphocytes (PBL) of FMF patients during FA. The ethics committee of our institution approved this study. ELISA assays and real time PCR (RT-PCR) were used to determine protein and mRNA expression levels of IL-1β, TNF-α, and IL-10 in FMF PBLs during FA before and after MIF inhibition. Also, mRNA of MIF was determined under the same conditions in these patients. Our results were compared to age and sex matched healthy controls. Using ELISA assays, PBLs taken from FMF patients during FA, secrete 4-6 folds higher of IL-1β, TNF-α, and IL-10 compared to those from healthy matched controls. We determined a non-toxic optimal dose of 100uM and incubation time of 24hr for ISO-1 inhibition. ISO-1 significantly inhibited (50-70%) the secretion of IL-1β, TNF-α, and IL-10 to the media of cultured PBLs during FA. Interestingly, this inhibition returned the levels of assayed cytokines to that during remission. The mRNA level of IL-1β, TNF-α, IL-10, and MIF was 1.5-2.0 folds higher during FA in FMF patients compared to healthy individuals. Also, ISO-1 inhibited mRNA of all four cytokines between 30- 50% as determined by RT-PCR, after ISO-1 inhibition. Conclusions: To our knowledge, this is the first report investigating the effect of MIF inhibition on the expression of TNF-α, IL-1β, Il-10, and MIF from PBLs of FMF patients. Different inhibition percentage of mRNA and protein secretion is likely due to different regulatory mechanisms employed during transcription and translation. Cytokine storm is the cause of fever, nausea and fatigue during immune reaction, i.e., FMF FA. The balance between pro- and anti-inflammatory cytokines usually determines the severity, duration and extent of inflammation. Thus, IL-10 elevation during FA is to counter the actions of IL-1β and TNF-α and to prevent host tissue damages. Our results indicate that MIF is a major regulator of IL-1β, TNF-α, and IL-10 at the protein secretion and transcriptional level. We predict that this regulation is mediated by transcription pathway and transcriptional factors such as NF-kB. Taken together, our data suggests the possible use of ISO-1 as a therapeutic agent in treating FMF patients especially during the fever attacks.

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THE LOW PENETRANCE OF RETINOBLASTOMA FOR THE V654L MUTATION IN RB1 GENE

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Retinoblastoma is caused by compound heterozygosity or homozygosity of retinoblastoma gene (RB1) mutations. In germlinal retinoblastoma, mutations in RB1 gene predispose increase cancer risk during development and segregates as an autosomal dominant trait with high penetrance (90%). In this study, we screened 30 family members from a certain families using high resolution melting assay (HRM) and DNA direct sequencing. We evaluate the phenotype and penetrance of a germ-line mutation of RB1 gene in a large Taiwanese family. The molecular analysis and clinical details of this family showed phenotypic variability associated with certain V654L mutation in exon 19 of RB1 gene in 11 individuals. The phenotype varies from asymptomatic to unilateral tumor. Only 4 individuals (2 males and 2 females) developed unilateral retinoblastoma, which results in calculated low penetrance of 36% (4/11). The age of diagnosis varied from 16 to 46 years, with an average of 30 years old. In particular, none of them relatives in this family exhibited the variable severity and bilateral retinoblastoma. The diseased-eye ratio (DER) for this family was 0.36, lower than current estimates. This suggests that the RB1 V654L mutation was itself insufficient to develop the retinoblastoma.

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MOLECULAR DIAGNOSIS OF FRAGILE X SYNDROME IN A COHORT OF MENTAL RETARDATION PATIENTS IN SAUDI ARABIA

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Fragile X syndrome is the most common form of inherited mental retardation. Its frequency is estimated to be approximately 1/1,500 for affected males and 1/2,500 affected females. The disease is caused by expansion of a CGG trinucleotide tandem repeat at the 5' untranslated region of the FMR1 gene located at Xq27. Aim: to establish a molecular genetics technique for the molecular diagnosis of cases affected with fragile X syndrome. Subjects &Methods: The study included a total of 37 cases, 31 males and 6 females with mental retardation, their ages ranged between 7 months to 27 years; 25 normal subjects were used as controls. Other family members were included: 3 mothers, 3 sisters and 3 fathers. Bisulfite treatment of DNA was followed by molecular testing using two different techniques. First: PCR was performed using two sets of primers, one set of primers was specific for amplifying methylated C residues in affected males and the other pair of primers was designed to amplify the unmethylated repeats in healthy males. The second technique used the real time PCR based on methylation-specific melting curve analysis (MS-MCA) for detection of methylation status of the FMR1 promoter region. Results of PCR using methylated and unmethylated PCR primers revealed (3/19) affected and (16/ 19) unaffected individuals respectively. Results for real time PCR revealed single low melting peak in (25/31) indicating unmethylated FMR1 gene, and hence unaffected males, and high melting peak (6/31) indicating affected males. All control subjects has shown low melting peaks indicating normal gene. The real time PCR technique proved to be more sensitive, reliable and rapid for the diagnosis of cases with fragile X syndrome. No female cases or carriers could be detected by both techniques. The technique can be applied for the exclusion of FRAX syndrome in the setting of diagnosis of patients with mental retardation.

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ESCAPE FROM INACTIVATION: THE X-FACTORS THAT MATTER

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X chromosome harbors 4091 transcripts (NCBI Map Viewer-build 37.2). Most of them have been nailed as genes. Some are just hypothetical genes or transcript with no known functions yet. Many genetic disorders have been implicated with X-linked genes. Many cancer genes have also been mapped on this chromosome. In spite of this revelation, X chromosome has remained enigmatic for researchers even after the completion of Human Genome Project. Dosage compensation, the way of balancing the gene contents of male and female mammals is also quite cryptic. Genes once thought to be inactive are now being evident to escape from inactivation and the number is increasing with the availability of more sophisticated methods and techniques to detect this process. Here, it is proposed that X-linked genes escape inactivation in a tissue specific manner. Not all genes escape inactivation in all tissues. However the genes that reside on pseudoautosomal region are the most escaped genes and it does not create severe problems. But the genes that residing outside the pseudoautosomal regions, when escape inactivation, may cause disease from over and/or misplaced expression as they were supposed to be silent or express at low level only. This misplaced expression leads to dysregulation of the cellular processes which cause cancer or other anomalies. In this study, microarray data (from web repository) of a male X chromosome, a female inactive X chromosome and an active female chromosome has been analyzed which has brought out many candidate genes that may have important role in this phenomenon.

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GENOMIC, INTERACTOMIC AND REACTOMIC PROFILING OF SOMATIC GENOME VARIATIONS IN THE BRAIN ASSOCIATED WITH NEURODEGENERATIVE DISEASES

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Chromosome instability (CIN) is associated with neurodegeneration in ataxia-telangiectasia (AT) and Alzheimer's disease (AD) (Iourov et al., 2009). Here, we have attempted to determine cellular and molecular basis of this relationship. High-resolution interphase molecular cytogenetic and in silico analyses showed that CIN involves specific chromosomal loci in the AT cerebellum: 14q12 (FOXG1B, NOVA1), 7p14, Xp22.1, Xp22.3 (FRA7C, FRAXB, FRAXC). To get more insights into genomic mechanisms of AT neurodegeneration, we performed analyses of these loci by an original in silico approach based on comparative studying of genomic and epigenomic databases. The locus of chromosome 14 more commonly disrupted in the AT cerebellum was found to contain 19 genes of known function and expression profiling. Two genes - FOXG1B and NOVA1 - were found to be highly expressed in the human brain (especially, in the cerebellum) throughout ontogeny. This led us to propose FOXG1B and NOVA1 to be candidate genes for disruption produced by CIN in the AT cerebellum. Remaining loci were not demonstrated specific candidate genes being, however, adjacent to common fragile sites (FRA7C, FRAXB and FRAXC). This supports observations that ATM (AT gene) regulates fragile site stability. Moreover, since we show non-random genomic loci recurrently disrupted by CIN, our data suggest programmed somatic genome recombination during differentiation and maturation of neural cells in the human. We further performed a proteomic (interactomic/reactomic) study analyzing either loci disrupted by CIN or crucial intracellular processes in context of our data. Genes disrupted in the AT cerebellum interact with SMAD pathway (SMAD2, SMAD4 at 18q21.1) of TGF-beta response, required for proper apoptosis and cell cycle progression. Additionally, these data implicate that neuronal-specific alternative splicing is likely to be affected in AT (NOVA1 disruption). Reactomic study suggested that G1/S DNA damage checkpoint p53-dependent pathway is altered by ATM mutations only without additional CIN effect. According to our and literature data, it is supposed that G2/M DNA replication checkpoint pathway should be primarily affected in the AD brain. However, neither

interactome nor reactome evaluation has elucidated elements playing a role in this pathway that have been found to be involved in AD brain-specific CIN. Therefore, we concluded that neurodegeneration in the AD brain is mediated by DNA-replication-independent aneuploidization and chromosome specify is achieved by natural selection during brain ontogeny. We conclude that bioinformatic and proteomic analysis is a required addition to studies discovering mechanisms of complex multisystem disease. Supported by BMBF/DLR (RUS 09/006) and DFG (LI 820/18-1).

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ASSOCIATION OF VITAMIN D RECEPTOR GENE POLYMORPHISM AND GROWTH PARAMETERS IN EGYPTIAN RACHITIC CHILDREN

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Prevalence of nutritional rickets in developed countries appears to be rising. Rickets in infants is attributable to inadequate vitamin D intake and decreased exposure to sunlight. Some studies reported association between bone metabolism and vitamin D receptor (VDR) polymorphism. The aim of this study is to examine the association between (VDR) gene polymorphism and vitamin D deficiency rickets in Egyptian children and assess its relation to growth parameters. The study was performed involving 42 children aged 4 months to ten years with history of rickets (cases) and 48 children with no history of rickets (controls) collected from the out patients clinic of Al-Azhar hospital, Al-Azhar university. The Molecular aspect studied VDR gene ApaI, FokI and TaqI polymorphic sites. The biochemical detection of alkaline phosphatase, calcium and phosphorous in addition to growth parameters were studied in both patients and controls. The study showed that A (Apa-I) allele was more frequent in patients than control (56% vs 43%), while allele frequency for Fok-I and Taq-I are more or less similar. The FF and tt VDR genotypes were associated with lower serum phosphate levels in patients. The FF VDR genotype was associated with reduced height. Patients had significant lower values in phosphate level and higher values in alkaline phosphate level compared to controls. When the genotypes of all polymorphisms were combined, the most frequent genotypes were AaFfTT in patients and AaFFTT in controls. There is a correlation between VDR gene polymorphism, biochemical and growth parameters in Egyptian rachitic children. The study suggests that VDR might play an important role in growth delay, but a less marked role in the development of rickets.

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GENETIC POLYMORPHISMS -590 C/T AND INTRON 3 INDEL IN INTERLEUKIN 4 GENE ARE IN ASSOCIATION WITH VITILIGO IN GUJARAT POPULATION

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Vitiligo is a common depigmenting disorder resulting from the loss of functional melanocytes in the skin. Autoimmunity has been suggested to play a major role in the pathogenesis of the disease. Vitiligo has also been frequently associated with other autoimmune disorders. In India, Gujarat and Rajasthan states have the high prevalence of the disease i.e. ~8.8%. Our studies have shown that 66% of Gujarat vitiligo patients possess autoantibodies against melanocytes. Cytokines are low molecular weight glycoproteins involved in the regulation of our immune system. Cytokine imbalance has been shown to play a major role in the pathogenesis of several autoimmune disorders. Genetic polymorphisms in cytokine genes may be responsible for their altered protein levels, which may lead to immune dysfunction. The present study focuses on genetic polymorphisms in Interleukin-4 (IL-4), which is involved in stimulation of activated B-cells and T-cell proliferation, and the differentiation of CD4+ T-cells into Th2 cells. IL-4 gene polymorphisms have been shown to be associated with many autoimmune disorders. We have examined for a C/T promoter polymorphism (rs2243250) at -590 position using Polymerase Chain Reaction-based restriction analysis (RFLP) using endonuclease AvaII and a 70 bp Insertion or deletion (INDEL) sequence in the Intron-3 region of IL-4 gene using PCR. For this study 500 healthy controls and 350 vitiligo patients of Gujarat were examined. Genotype and allele frequencies for both the studied polymorphisms were found to be significantly different ($p<0.0001$) in vitiligo patients and controls suggesting the positive association of these polymorphisms with vitiligo susceptibility. This is the first report showing the positive association of the IL-4 Intron3 INDEL polymorphism with vitiligo. The gene expression analysis is also being carried out for IL-4 and its levels will be compared with the respective genotypes in patients and controls. In addition, we also estimated serum IL-4 levels in 50 patients and 50 controls using sandwich-ELISA which demonstrated that patients with susceptible genotypes (TT/II) for -590 and INDEL polymorphisms had significantly elevated levels of IL-4 ($p<0.043$) as compared to wild type genotypes. Thus, in conjunction with the possible genotype-phenotype correlation our study proposes that IL-4 may play a crucial role in susceptibility to vitiligo in Gujarat population.

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BETA-THALASSEMIA MUTATIONS IN THE KURDISH POPULATION OF NORTHEASTERN IRAQ

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β-Thalassemias (β-thal) are hereditary defects in the rate of synthesis of β-globin chains of hemoglobin, which are widely distributed throughout the world, with considerable frequencies in the eastern Mediterranean countries, including Iraq. Kurds are an ethnic group inhabiting a region known as Kurdistan, which includes adjacent parts of Iran, Iraq, Turkey and Syria. Sulaimaniyah is a large province lying in northeastern Iraq region bordering Iran, with a population of around 1.5 million of mostly ethnic Kurds. β-thal carrier state is common in this province with a prevalence rate of 4.1% and thal-major is an important problem in this part of the country, with more than 500 registered patients in the only thalassemia center in the province. Therefore, this study was initiated to determine the spectrum of β-thal mutations in this previously uncharted part of the country. Every other subject diagnosed as β-thal minor between 1st Sept to 31st of Dec 2008 by the Sulaimaniyah Provincial Premarital Screening Center-Northeastern Iraq, was enrolled in this study. During this period a total of 264 subjects were diagnosed as β-thal minor based on having a combination of the low MCV (mean corpuscular volume) (<80 fL) and/or low MCH (mean corpuscular hemoglobin) (<27 pg) values with a high or borderline Hb A2 fraction (Hb A2>3.5%). Alternate subjects from the latter group (132 subjects) were enrolled for the purposes of this study, adequate DNA obtained from 123 out of them. Genomic DNA was extracted from white blood cells by phenol-chloroform. The DNA was amplified in a multiplex polymerase chain reaction (PCR), followed by hybridization to specific wild and mutant oligoprobes using β-Globin StripAssay (ViennaLab Diagnostics, Vienna, Austria). This StripAssay designed to detect 20 β-thal mutations which are encountered in Mediterranean countries. Samples in which no mutations could be identified at that stage were further analyzed by sequencing the entire β globin gene at the Kariminejad-Najmabadi Pathology & Genetics Center, Tehran, Iran, using two sets of primers (sense, anti sense, F primer and R primer). A total of 11 different β-thal mutations were identified in the studied samples, of which eight representing 96% of mutated β-globin genes. The most common mutations among our patients were IVS-II-1 (G>A) (25.2%), IVS-I-110 (G>A) (19.5%), codon 8 (-AA) (15.4%), and codon 8/9 (+G) (12.2%). The next four most frequent mutations were IVS-I-5 (G>C), codon 5 (-CT), IVS-I-6 (T>C) and IVS-I-1 (G>A) with frequencies of 8.1, 7.3, 4.1 and 4.1%, respectively. Three other mutations, codon 39 (C>T) (1.6%), codon 44 (-C) (1.6%) and codon 15 (0.8%) were present in frequencies below 2%. All mutation except one (Codon 15) were identified by the reverse hybridization StripAssay. The latter mutation was characterized by DNA sequencing. Thirty nine out of 123 subjects (31.7%) carried β+ (IVS-I-110, IVS-I-6, IVS-I-5), while the rest were carriers of β0 mutations. In a country like ours an effective prenatal diagnostic program is paramount to eliminate the thalassemia health burden on our community.

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BEYOND SEQUENCING AND FUTURE TRENDS

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A new method of analyzing nucleic acid sequences and protein sequences was developed to decrypt the information at the genetic/protein sequences as a natural human language. In the sense as when we write the alphabet in special order, we get a word that has special meaning in a language. The order of the alphabet letters is unique to each given natural language word. The natural human languages follow specific rules by which alphabetic letters are ordered in sequences specific to a language. In this paper, we consider nucleic/protein codes as alphabetic letters of the cell genetic language. By selecting a known human natural language (Arabic language) as a model, we attempt to establish the rules of the genetics language of the cells. This selected language of the study presents a key feature, its letters showed a great similarity with the distribution of genetic/protein codes. Calculated using mathematical methods, words and sentences can be represented in the language study by equations and 2D and 3D graphs. In this article, we present a mechanism by which the Arabic language has its specific features and from which we can find mechanisms for reading and analyzing the fundamental language of any organism genome. We also tested a non-Arabic language using alphabetic Arabic letters by equation and graphs representation to deduce its rules on cellular languages.

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CLINICAL AND MOLECULAR ANALYSIS OF SPINAL MUSCULAR ATROPHY IN ALGERIAN PATIENTS

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Spinal muscular atrophy (SMA) is one of the most common autosomal recessive disorders, characterized by degeneration of anterior horn cells in the spinal cord, and leads to progressive muscular weakness and atrophy. SMA is clinically divided into four subtypes depending on age at onset and clinical course. Genetic linkage studies have mapped responsible genes for all clinical types of SMA to chromosome 5q13, homozygous deletion in SMN1 gene causes the disease but the clinical severity may be modified by copy number of homologous gene SMN2 as well as the extent of deletion at SMN locus. In the present study, to elucidate the correlation between genotype and clinical severity in SMA patients, we analyzed the molecular genetics features of 92 Algerian patients with SMA, from 57 unrelated families. All patients fulfilled the diagnostic criteria of SMA as defined by the International SMA Consortium. Genomic DNA was extracted from peripheral blood following the conventional procedures. Deletions of exons 7 and 8 of the SMN gene were analyzed by an enzyme digestion assay. NAIP gene analysis was performed by PCR amplification of exon 4 and 5. SMN2 gene copy number analysis was carried out by the use of a quantitative PCR-based assay. The patients were classified into type I SMA (20 patients), type II (16 patients), Type III (53 patients) and

type IV (3 patients). 43 of the 57 SMA families (75.43%) were homozygous for SMN1 deletion of exon7 and 8 (type I, type II, type III and type IV). NAIP exon 4 and 5 were deleted in 15 cases (4/14 type I, 2/10 type II, 9/31 type III, 0 type IV), of 57 SMA families. In all patients with a NAIP deletion of exon 4 and 5, there was also a SMN1 deletion of exon 7. Frequency of NAIP deletions were significantly higher in type I patients than in type II or III patients. Also SMN2 copy numbers were higher in SMA type IV and SMA type III than in type I and type II. This increase in copy number of SMN2 gene may be responsible for the less severe form of SMA with late onset of symptoms. Our results are compatible with the data of the literature.

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GENETIC ARCHITECTURE OF HUMAN METABOLISM

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Metabolic markers such as circulating lipoprotein and glucose levels are well known risk factors for cardiovascular diseases and diabetes. During the past years their genetic determinants have been studied extensively. Here we present results from a large-scale genome-wide study on over 200 metabonomic markers. We have analyzed 1H NMR metabonomic profiles of over 9000 Finnish individuals with over 6 600 000 genotyped or imputed genetic markers from five population cohorts. The 1H NMR is capable of measuring 138 metabonomic parameters from blood serum and lipid extracts. The data consists of different lipoprotein variables, lipid measures and small molecules. In addition to direct measures, we also conducted a genome wide association study for further 78 ratios of most interesting metabolites. The GWAS on 6.6 million SNPs were performed for 216 phenotypes using SNPTEST. We set a stringent level of significance by dividing the nominal significance level of p = 5*10-8 by the number of phenotypes used although some of the phenotypes are quite highly correlated resulting to a significance level of 2.31*10-10. In total, 14 novel loci were significantly associated with a metabolite or a ratio of metabolites. We had whole blood expression data available from 517 individuals where we could detect possible eQTLs for the associated SNPs. Five of the 14 novel loci had a significant eQTL associated with the SNP. Nine of the novel associations were for amino acids or small molecules. For example, a locus containing SPRYD4-gene was associated with the ratio of glucose and glutamine suggesting for a previously unknown role in glucose/glutamine metabolism for this gene as it was an eQTL for the associating SNP. A novel locus in chromosome 4 was associated with a large number of lipoprotein measures as well as serum albumin levels. The SNP is located near the albumin gene and was associated with serum triglycerides, various LDL, VLDL measures, ApoB and serum free cholesterol. Although there are case reports of analbuminemia, hypercholesterolemia and hyperlipidemia caused by mutations in the albumin gene, this is the first time when variation found in normal population is shown to affect all three measures at this locus. A SNP, which was an eQTL for FCGR2B and FCGR2A genes, was associated with the cholesterol ester content of the large HDL particles. These genes have been linked to atherosclerotic plaques in mice. As a conclusion, using a novel design combining genomic, metabolomic and transcriptomic data we were able to identify fourteen novel loci affecting human metabolism in European populations. These novel variants provide basis for further functional studies and the metabolic biomarker candidates for studying risk of clinical end points.

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WHOLE EXOME SEQUENCING OF A FAMILY AFFECTED WITH CHRONIC INTESTINAL PSEUDO-OBSTRUCTION DISEASE

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Chronic intestinal pseudo-obstruction (CIPO) is a severe digestive syndrome characterized by derangement of gut propulsive motility which resembles mechanical obstruction, in the absence of any obstructive process. It is one of the most important causes of chronic intestinal failure both in pediatric (15%) and adult cases (20%). CIPO is generally sporadic, but familial forms have also been described with autosomal dominant, autosomal recessive and X-linked transmission. We performed whole-exome sequencing in two affected siblings along with the affected father, and the unaffected mother. The sequencing was done using the Illumina-Solexa platform following enrichment of exonic sequences using Nimblegen whole-exome array. An autosomal dominant mode of inheritance was assumed to identify disease causing gene(s). Moreover, called variants were filtered to exclude those identified in dbSNP130 or HapMap databases. We genotyped the identified variants in 376 unaffected controls. After excluding those variants found in controls, we identified 136 candidate genes. Seven of them have loss of function because they have either stop or splicing site mutations. We are currently sequencing these candidate genes in a set of 50 CIPO patients to confirm their involvement in the disease.

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GENETIC POLYMORPHISMS IN PROMOTER REGION OF TNF-α GENE MAY CONFER SUSCEPTIBILITY TO VITILIGO IN GUJARAT POPULATION

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Cytokines are important mediators of immunity, their response due to imbalance or deficiency in the cytokine network may largely determine autoimmune disease susceptibility and severity. Tumor Necrosis Factor- α (TNF- α), a multifunctional cytokine, is involved in the promotion of inflammatory responses and plays a critical role in the pathogenesis of several autoimmune diseases. TNF- α is a paracrine inhibitor of melanocytes which is secreted by neighboring keratinocytes and it may play an important role in vitiligo pathogenesis. Vitiligo is an acquired pigmentary disorder characterized by areas of depigmented skin resulting from loss of melanocytes. It affects 0.5-1% of the world population however, in India Gujarat and Rajasthan states have the highest prevalence of the disease i.e. ~8.8%. The contribution of genetic factors in susceptibility to vitiligo is exemplified by familial clustering. Though vitiligo is extensively addressed in the past five decades, its etiology is still being debated. The three prevailing hypotheses for the pathogenesis of vitiligo are the neurochemical, autoimmune and oxidative stress hypotheses. But none of them explains the entire spectrum of this disorder. Genetic polymorphisms in the promoter region of TNF- α are involved in the regulation of its expression, and are found to be associated with various autoimmune diseases. We have made an attempt to understand the autoimmune pathogenesis of vitiligo by assessing the TNF- α gene promoter polymorphisms and its expression levels in vitiligo patients compared to unaffected controls of Gujarat. We have investigated five polymorphisms i.e., -238 (G/A; rs361525), -308 (G/A; rs1800629), -857 (C/T; rs1799724), -863 (C/A; rs1800630) and -1031 (T/C; rs1799964) at the promoter region of the TNF- α gene for their role in the susceptibility to vitiligo by a case - control study involving 307 patients and 516 healthy age-matched controls in Gujarat population. Polymerase chain reaction-Restriction fragment length polymorphism (PCR -RFLP) technique was used for the analysis of these promoter polymorphisms. Overall, the distribution of the genotype frequencies and allele frequencies of TNF- α promoter polymorphisms (TNF- α -238: $p=0.002$ and $p<0.0001$, TNF- α -308: $p=0.013$ and $p<0.0001$, TNF- α -857: $p=0.025$ and $p=0.040$, TNF- α -863: $p=0.002$ and $p<0.0001$, and TNF- α 1031: $p=0.012$ and $p=0.037$) were significantly different between vitiligo patients and controls. Gene expression analysis of TNF- α is also being carried out in vitiligo patients and controls and will be analyzed in correlation to the respective genotypes to establish their genotype-phenotype correlation. In conclusion, our results suggest that the well documented promoter polymorphisms of TNF- α gene may be a genetic risk factor for vitiligo susceptibility in Gujarat population.

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ANALYSIS OF IL-10 GENE POLYMORPHISM AT POSITION -592(C/A) IN RHEUMATOID ARTHRITIS PATIENTS IN INDIA

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IL 10 is a type II potent and broad spectrum anti-inflammatory cytokine. It is a key regulator in limiting the inflammatory response that could otherwise cause tissue damage and is essential for homeostasis of immune system (immune tolerance, T-cell, dendritic cell development and differentiation of B cells). Its role has been established in various models of infection, inflammation and in cancers. IL-10 gene is 4.7 Kb in size and is located on chromosome 1q21-32 and signals through a two receptor complex consisting of two copies each of IL-10 receptor R1 and R2.It is produced by many varieties of immune cells, the four major producers are T helper type 2(Th2) cells, subsets of regulatory T cells (Tr1, Th1 & Th17 cells), CD8+ T cells, monocytes and stimulated macrophages. Many studies have discussed the link between IL-10 promoter haplotypes to susceptibility or severity to several diseases including Rheumatoid Arthritis (RA). Aim: To analyze the polymorphism in IL-10 gene at position -592(C/A) and compare them with matched controls since the data is scanty in Indian RA patients. 120 RA patients attending a tertiary care rheumatology centre in Hyderabad were included.120 age and gender matched controls residing in the same city were selected. The study was approved by institutional ethical committee and all subjects gave their consent to participate. The male: female ratio was 1:4 in both the study groups, 60% of RA cases were Rheumatoid Factor positive. Blood samples were collected and DNA was isolated by a rapid non-enzymatic method by salting out the cellular proteins by dehydration and precipitation with saturated sodium chloride solution (Nuremberg and Lahari; 1991). The polymorphism was analyzed using PCR-RFLP method. Result: Category/CC/CA/AA/Total, RA/42(35%)/58(48.3%)/20(16.6%)/120, Controls/32(26.6%)/59(49.1%)/29(24.1%)/120. Frequency of C allele in RA cases and controls were 0.59 and 0.51, respectively. The frequency of A allele in RA cases and controls were 0.40 and 0.48 respectively. No significant difference was observed in the frequency of C and A alleles in RA and controls.

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PREVALENCE OF C677T AND A1298S POLYMORPHISMS OF MTHFR GENE, A66G OF MTRR GENE AND A2756G OF MTR GENE AT KAZAKHS

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MTHFR, MTRR and MTR genes encode key enzymes of folate metabolism. The role of polymorphisms of these genes in the pathogenesis of cardiovascular diseases including obstetric complications, chromosomal disease and neural tube defects in the fetus has been revealed in some populations. Prevalence of polymorphisms folate cycle depends on the ethnicity of individuals. The aim of tour study was to establish population frequencies of C677T and A1298S polymorphisms of MTHFR gene, A66G of MTRR gene and A2756G of MTR gene at Kazakhs. The polymorphisms C677T, A1298C MTHFR; A66G MTRR and A2756G MTR of genes of folate

metabolism were detected by PCR, RFLP followed by digestion with specific restriction enzyme. Frequencies of polymorphisms of the MTHFR gene set based on the molecular-genetic study of 300 unrelated individuals of the Kazakhs. The frequencies of C677T polymorphism at Kazakhs were: CC – 59.1%, CT – 39.4% and TT – 1.6%. The frequencies of A1298C polymorphisms at Kazakhs were: AA –55.2 %, AC – 38.4% and CC – 6.4%. Frequencies of polymorphisms of the MTRR and MTR genes set based on the molecular-genetic study of 105 unrelated individuals of the Kazakhs. The frequencies of A66G polymorphism of MTRR gene were: AA – 63.8%, AG – 30.5% and GG – 5.7%. The frequencies of A2756G polymorphism of MTR gene at Kazakhs were: AA – 65.7%, AG – 29.5% and GG – 4.8%. We compared our results of research with data from studies of other ethnic groups. Kazakh population, as well as Canadian Inuit, South African and sub-Saharan African, show the lowest TT homozygous genotype of C677T MTHFR polymorphism in this study. According to a previous report of other authors the Mexican population has a highest frequency of TT genotype (34.8%). The prevalence of CC homozygosis of A1298C MTHFR polymorphism wasn't rare amongst Kazakhs and has no significant differences from other world populations. Frequencies of GG homozygous genotypes of MTRR and MTR genes were lower than the same frequencies in European populations.

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HB FONTAINEBLEAU [A21 (B2) ALA-PRO] - FIRST AND RECURRENT OBSERVATION OF A VERY RARE HEMOGLOBIN VARIANT IN THE UNITED ARAB EMIRATES

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During the recently launched National Hemoglobinopathies Screening program that has so for covered over 10,000 cases in the United Arab Emirates, several hemoglobin variants were observed, some of which are rare. Occurrence of these rare abnormal hemoglobins (Hb) often poses a problem in both laboratory diagnosis and genetic counseling of such individual cases. Hb Fontainebleau is very rare silent mutant hemoglobin first reported in 1989 in a publication from France on a family with Italian origin. After this a second case was reported from New Zealand in an adult male of Iraqi origin in 2009. To the best of our knowledge, there have been no subsequent publications on this variant. We have the occurrence of eight unrelated cases of Hb Fontainebleau [a21 (B2) ALA-PRO] as a very interesting observation. Our observation is not only the first of its kind in the Arab World, but also emphasizes the fact that it could be relatively a frequent variant in this region. The diagnosis of Hb Fontainebleau was confirmed at molecular level [a2 Gene Codon 21 GCT (Ala) - CCT (Pro)] in all these cases. We observed a characteristic chromatographic pattern on HPLC that suggests the possibility of this variant. In this report we also present on clinical and hematological parameters of this hemoglobin variant, which appears to be a very rare one elsewhere in the World.

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UPDATE FROM POPULATION SCREENING PROGRAM FOR COMMON INHERITED BLOOD DISORDERS IN UNITED ARAB EMIRATES

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Genetic blood disorders represent a major public health problem in this region. Several factors contribute to the wide prevalence of genetic disorders in the region and this includes the lack of public measures directed towards the early recognition and prevention of inherited disease. UAE Genetic Diseases Association (UAEGDA) is a non-profit organization established under the patronage of H.H. Sheikh Nahyan Mubarak Al Nahyan, the UAE Minister of Higher Education and Scientific Research, with main aim to control and prevent population-specific genetic disorders prevalent in the United Arab Emirates. UAEGDA first initiated a massive public awareness campaign under its first project –Emirates free from new births of children with Thalassemia disease by the year 2012". This effort resulted in inclusion of Sickle cell and Beta-Thalassemia screening as mandatory test under the UAE Federal Pre-Marital legislation program that active since the year 2005. In the year 2007, following a generous support from its chief patron and strategic partners, UAEGDA started offering free genetic counseling and free laboratory services to the entire community. Through this project, UAEGDA aims to identify carriers of various hereditary blood disorders including Sickle cell and Beta-Thalassemia particularly in pre-marital age group and the student community studying in various universities and colleges across the country. We present here on our experience in population screening of over 10,000 individuals wide across the country.

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IMPACT OF APOE E2 BUT NOT OF E4 ALLELES ON PLASMA LIPID CONCENTRATIONS IN THE ALGERIAN POPULATION

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Among countries which experience an epidemiological transition at present, Algeria is of great interest because it has been suggested that the age-adjusted incidence rate of coronary deaths would be comparable to those observed in Western countries (Garros et al. 1980). Hence, in order to measure the

prevalence of major cardiovascular risk factors in this population, we performed a case-control study of myocardial infarction based on the Algerian population living in Oran which allowed us to compare the lipid profile between cases and controls (Médiène et al. 2001). In the present work, our aim was to evaluate the impact APOE E2/E3/E4 polymorphism on the plasma lipid concentrations in the Algerian population in which a particular lipid profile has been previously characterized. A sample of 194 men aged 25 to 64 years, residing in Oran and born in Northwest of Algeria, and whose parents and grand-parents were born in Algeria, were eligible for inclusion in the study. The subjects were recruited between 1994 and 1995 and were randomly selected from the lists of household addresses obtained in the census service (Office National de Statistiques). The APOE E2/E3/E4 genotypes were characterized by in vitro DNA amplification followed by an enzyme digestion step of the PCR products, as described elsewhere (Hixson et al. 1990). Concerning the APOE E2/E3/E4 polymorphism, the frequencies of the APOE E2 and APOE E4 alleles were 7.2% and 12.3%, respectively. In Algeria, the frequency of the APOE E4 allele was expected to be comparable to that observed in the Southern European countries. When compared with the APOE E3/E3 frequent genotype, the presence of the APOE E2 allele was associated with reduced plasma concentrations of cholesterol (-22%; p=0.0036), LDL-C (-30%; p=0.0015), and APOB (-23%; p=0.0045), and with increased concentrations of APOE (+33%; p=0.0009). Interestingly, no difference in plasma concentrations of lipids and apolipoproteins could be associated to the APOE E4 allele. These results are in contrast with those of numerous studies which have mainly suggested that the APOE E4 allele is associated with higher levels of total cholesterol, LDL-cholesterol and APOB (Pablos-Mendez et al. 1997). Gene-environment interactions may contribute to the discrepancies observed between studies, including ours. As a matter of fact, the association of the APOE E4 allele with elevated serum cholesterol levels is greater in populations consuming diets enriched in saturated fat and cholesterol (Moreno et al. 2009). Altogether, these data suggest that the absence of association between the E4 allele and lipid levels in our Algerian sample may be at least in part related to the local diet which was characterised in 90's by a low consumption of proteins and a low energy intake (Karamanos et al. 2002). To test this hypothesis and considering the rapid evolution of food habits in Algeria, we planned to compare the present data to those obtained in a sample of the population being recruited.

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NEONATAL SCREENING AND MOLECULAR GENETIC CHARACTERIZATION OF G6PD DEFICIENCY IN ALEXANDRIA, EGYPT

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Glucose-6-phosphate dehydrogenase deficiency is the most common human enzymopathy, affecting more than 400 million people worldwide. Polymorphisms of the G6PD gene are numerous with most mutations identified are point mutations. In a population with high prevalence rate, early detection of the enzyme deficiency by neonatal screening is desirable in order to take appropriate measures to prevent the complications of hemolysis and jaundice. This study aimed at screening newborn infants for G6PD deficiency to allow early detection of the disease and estimate the prevalence of G6PD deficiency among neonates in Alexandria. Also it aimed at detecting the G6PD gene alleles; Mediterranean (C563T) and A-(A376G, G202A) and their frequencies and identifying the heterozygote carriers among available females in each family, at gene level. Finally, it aimed to offer proper genetic counseling for G6PD deficient patients and their families. The present study was conducted on 1100 leftover bloodspots on filter paper cards collected for the 'National Program of Neonatal Screening for Congenital Hypothyroidism' in Alexandria. All these neonatal blood samples were screened for G6PD deficiency using the fluorescent spot test. All G6PD deficient newborns were recalled and subjected to confirmation of the detected result. Those confirmed G6PD deficient neonates together with another 10 G6PD deficient patients referred from Al-Shatby Pediatric University Hospital were subjected to history taking and clinical genetic examination. Both groups were included in the molecular study using PCR/RFLP technique for detection of the three common G6PD gene mutations; C563T, A376G and G202A, and identification of heterozygote carriers among available female relatives of cases. The results of this study revealed the following: - Among 1100 neonatal blood samples, male to female ratio was 0.89:1. - Ten males were proved to be G6PD deficient with an estimated prevalence of 1.9% among male neonates and 0.9% among neonates in general. - Among the 10 G6PD deficient neonates: one (10%) suffered from neonatal jaundice which indicated the use of phototherapy. - Among the 10 symptomatic G6PD deficient patients, referred from Al Shatby University Hospital: 8 were males and 2 were females. The first attack of hemolysis was most commonly (60 %) triggered by ingestion of fava beans. Five patients (50%) developed neonatal jaundice (4 males and 1 female). - The G6PD Mediterranean allele (C563T) was detected in 40.0% of cases, while G6PD A- allele (A376G/G202A) was detected in 35.0% of cases. In 25% of cases none of the mutations were detected. Among the 19 female relatives of the cases with known mutations, one was identified to be heterozygous carrier of Mediterranean allele and 2 were identified to be heterozygous carrier of G6PD A- allele (A376G/G202A). The conclusions are: - G6PD deficiency is one of the common enzyme defects among neonates in Alexandria with potential life threatening complications. - Newborn screening is an essential preventive measure against death and disability caused by G6PD deficiency. - Both Med (C563T) mutation and A- (A376G/G202A) allele represent the most common mutations among G6PD deficient patients in Alexandria.

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FREQUENCY OF NPHP1 GENE DELETION IN TUNISIAN POPULATION

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Genetically transmitted renal diseases constitute a significant part of the renal problems in childhood and adolescent. Familial juvenile nephronophthisis NPHP (MIM 256100) is a well known and common hereditary renal disease especially in places with a high rate of consanguineous marriages as in the Middle East or in North Africa. NPHP accounts for 6 to 10% of end renal disease in children. NPHP is genetically heterogeneous. Ten genes responsible for different types of NPHP have been identified: NPHP1 to NPHP9 and NPHP11.NPHP1 mutations were found in 30-85% of juvenile NPHP in Europe. The major NPHP1 gene defect is a large homozygous deletion. Aim: To determine frequency of NPHP1 gene deletion in a sample of patients with clinical pictures of tubulo-interstitial kidney disorder and chronic renal failure and to establish a standardized scheme for the genetic diagnosis of NPHP in Tunisian population. A Sample of 94 patients belonging to 86 unrelated families was evaluated. 73 healthy parents were also included in this study. All patients have clinical pictures of nephronophthisis (35) and or tubulo-interstitial kidney disorder. Genomic DNA was isolated from blood and PCR was carried out with a set of 6 STS markers to detect the gene deletion. If the deletion is not present we have to search for homozygosity at the NPHP1 loci by genotyping one patient of each non homozygous deleted family using 4 microsatellite markers. Patients showing homozygosity for markers within the NPHP1 gene region will be screened for mutation in the 20 NPHP1 exons. NPHP1 gene deletion was observed in 17 unrelated patients. All of these patients have the same large deletion encompassing the entire gene. Frequency of NPHP1 gene deletion is calculated as 20% of all unrelated patients, and 48, 5% of the 35 cases of strongly suspected NPHP. For the 69 patients without deletion, no homozygosity for markers within the NPHP1 gene region was proven. NPHP1 is the most frequent NPHP in Tunisia. This study shows that gene deletion can be taken as proof of the diagnosis in the all NPHP1 cases.

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IDENTIFICATION OF NOVEL MUTATION IN COL1A1 GENE IN PATIENT WITH OSTEOGENESIS IMPERFECTA FROM RUSSIA

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Osteogenesis imperfecta (OI) is a system disorder characterized by wide phenotypic variation, most of which is bone fragility. The majority of patients (about 90%) with a clinical diagnosis of OI have mutations in COL1A1 or COL1A2, the genes encoding α 1 (I) or α 2 (I) chains of collagen type I -the major structural protein found in bone. We aimed to define mutations and polymorphisms and to check a possible interaction effects or relations between them and to define risk development of fractures. We examined 40 patients from 35 families with OI and 50 healthy controls. The analysis of COL1A1 gene was carried out. Controls were matched for age, gender, ethnic origin and area residence. All samples were screened using SSCP analysis and direct DNA sequencing of all exons of COL1A1 gene. Results: we have identified previously unreported mutation of COL1A1-c.967G>T (p.Gly323X)/1- novel nonsense mutation in heterozygous state in proband and her mother, which leads to premature termination codon. The proband has normal height, 5 fractures, blue sclera and minimal functional limitations. The proband hasn‘t dentinogenesis imperfecta. We also have identified mutations, which have been described previously c.1081C>T (p.Arg361X), c.1243C>T (p.Arg415X) and c.2869C>T (p. Gln779X), which lead to stop codon. Two frameshift mutations were found in 2 unrelated patients: c.579delT (p.Gly194Val fsX71) and c.2444delG (p.Gly815AlafsX293). Nonsense and frameshift mutations both lead to quantitative decrease in type I procollagen. All mutations which we found were associated with a mild form of the disease (OI). We have also identified 18 polymorphisms in COL1A1 gene, which have been reported earlier. Two unknown changes (c.643-36delT and c.957+10ins), which functional role should be determined, were identified in 1 proband. Three polymorphisms (-1997G/T, -1663indelT and +1245 G/T) in 5' region of COL1A1 gene were shown to be associated with high risk of fractures. -1997G/T genotype was shown to be the factor risk of fracture development (OR=2.38, 95%CI 1.06-5.34), while -1997G/G genotype might be considered as a protective one (OR=0.4, 95%CI 0.19-0.98). Allele and genotype frequencies distribution in +1245G/T and -1663indelT polymorphisms between OI patients and control group were not statistically significant. Statistically significant differences were demonstrated to genotype combinations of COLIA1 polymorphisms -1997G/T, -1663indelT and +1245G/T between individuals with OI (29) and control group (150). Genotypes combination -1997G/T+-1663I/D+1245G/T was associated with high risk of fracture development (OR=11.84, 95%CI 2.06-68.09), while combination -1997G/G+-1663I/I+1245G/G- was shown to be protective (OR=0.45, 95%CI 0.22-0.95). The frequencies of remaining polymorphisms appeared to be the same as in controls. In conclusion, 6 mutations were identified in 6 unrelated probands with OI, four of them were nonsense (1 mutation previously unreported), two - frameshift mutations. We have identified 18 polymorphisms, only 3 polymorphisms in 5' region of COL1A1 gene were associated with frequencies of fractures. These polymorphisms contribute to the fragility of the bones, remaining polymorphisms were neutral. We have also found unknown changes in COL1A1 gene which role should be determined.

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MOLECULAR GENETIC ANALYSIS OF PAKISTANI FAMILIES WITH CRIGLAR-NAJJAR SYNDROME

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Crigler-Najjar syndrome (CN), characterized by severe unconjugated hyperbilirubinemia, is caused by deficiency of

UGT isoform 1A1 (UGT1A1). To study the molecular genetic cause of Criglar-Najjar syndrome in three consanguineous Pakistani families (A, B and C), genotyping of 9 individuals was carried out by using polymorphic microsatellite markers that are closely linked to the UGT1A1 gene on chromosome 2q37.1. The results revealed that probands in the three families were homozygous for the markers (D2S1279, D2S2234, and D2S407) suggesting linkage to the UGT1A1 locus. Sequence analysis of the coding exons and splice junctions of the UGT1A1 gene revealed three novel mutations, which were analyzed by bioinformatic mutation analysis. In the proband of family A, a homozygous A > G transition at nucleotide position 1329 was identified predicting tyrosine to cysteine amino acid substitution in the protein. The proband of family B showed homozygous G to A transition of nucleotide 746 predicting aspartic acid to asparagine amino acid substitution. An insertion of four base pairs (1262_delAGCC) was identified in proband C leading to premature stop codon at amino acid position 260 of the protein. In each case, the mutation was present in the heterozygous state in obligate carriers within the family. All the mutations were confirmed by bidirectional DNA sequencing. We did not detect any other mutation in the UGT1A1 gene in the probands of the families studied. In addition, these mutations were not detected in 100 ethnically matched healthy control individuals, suggesting that none of them was a neutral polymorphism. The promoter analysis showed that proband of family A, has A(TA)7TAA sequence, while probands B and C have normal (A(TA)6TAA) promoter sequences. Our report expands the mutation spectrum of the UGT1A1 gene and the data should be helpful for genetic counseling of the affected families.

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KCNE1 GENE SCREENING IN MOROCAN PATIENTS WITH SYNDROMIC DEAFNESS

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Deafness is an etiologically heterogeneous trait with a wide variety of genetic and environmental causes. It is generally considered that genetic factors account for at least half of all cases of profound congenital deafness, which can be classified in two categories dominant or recessive according to the mode of inheritance and in two types syndromic or non-syndromic according to the presence or absence of some other specific clinical features. Syndrome of Jervell and Lange-Nielsen combines congenital deafness with bilateral lengthening of the QT interval of the electrocardiogram than 500 ms. This lengthening of the QT interval is responsible for ventricular tachycardia, torsades and ventricular fibrillation resulting clinically by syncope or sudden death. Patients with this syndrome very rare combination of congenital deafness with severe cardiac arrhythmias are generally limited survival in the absence of treatment and are derived mostly from consanguineous parents. Both genes are KVLQT1 (voltage-gated potassium channel, KQT-like subfamily, member 1) which forms voltage-gated potassium channels and the gene KCNE1 (potassium voltage-gated channel, Isk-related family, member 1, which encodes the beta subunit of the potassium channel responsible for the current IKS. We report here the first study for syndromic deafness in one Moroccan family with cardiac arrhythmias and congenital deafness. Sequencing of KCNE1 gene revealed that this family was actually harboring the transition A/ G at position 112. This mutation was present in heterozygous form in probands and in normal hearing patients. This result confirms that the mutation A/G was not implicated in deafness in Moroccan families but it considered as polymorphism because the function of protein was intact.

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GENETIC DISORDERS IN THE STATE OF QATAR

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Qatar, as all other Arab countries, has a very high rate of consanguinity, female fertility, and maternal age, resulting in a preponderance of genetic disorders. We undertook a study on genetic disorders reported from Qatar for inclusion in the Catalogue for Transmission Genetics in Arabs (CTGA) Database. This follows the successful collection of similar data from the United Arab Emirates, Bahrain, and Oman. The methodology involved a targeted search of PubMed as well as regional non-indexed journals followed by a more intensive manual screening. The completed survey yielded data for 113 genetic disorders in the Arab population of Qatar. Many of these disorders, such as thalassemias, Down syndrome, systemic lupus erythematosus, diabetes mellitus, and neural tube defects, were found to be common between Qatar and its neighboring Gulf Cooperation Council countries. On the other hand, 43 disorders are found to be private for the Qatari population. This adds up to a long list of 127 private disorders in Oman, 111 in the United Arab Emirates, and 41 in Bahrain. Besides, unlike the general assumption that more autosomal recessive (61%) than autosomal dominant (28%) disorders occur in Arab populations, in Qatar, similar to Bahrain, both autosomal dominant and autosomal recessive disorders were found to occur at almost the same rates (45% and 47%, respectively). A large proportion of the diseases in the Qatari population belong to the category of congenital malformations and chromosomal abnormalities (24%), followed by endocrine, nutritional, and metabolic diseases (15%), diseases of the blood and the immune mechanism (including hemoglobinopathies and blood cancers, 11%), neoplasms (10%), and diseases of the nervous system (9%). While analyzing the incidence rates of these diseases, it is obvious that Down syndrome and hydrocephalus achieved the highest rates in Qatar. In certain instances, some other disorders have attained world record values in Qatar, such as classical homocystinuria demonstrating an incidence of 1:1800 and a carrier rate of about 6% of the Qatari population. Moreover, the survey also resulted in the availability of data on 27

associated gene loci. This translates to molecular studies being performed on about one-fourth of genetic diseases reported in the country and indicates the presence of an urgent need to focus efforts on the study of the molecular etiologies leading to these disorders in at-risk families.

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NOVEL CLN2 GENE MUTATION IN AN INDIAN FAMILY WITH LATE INFANTILE NEURONAL CEROID LIPOFUSCINOSIS

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Neuronal ceroid lipofuscinosis (NCL) also known as Batten disease is a heterogeneous group of neurodegenerative disorders characterized by accumulation of ceroid-lipopigment inclusions in neurones and most other cells. The major clinical features include progressive cognitive and motor deterioration, seizures and vision loss. Most of the damage is caused by accumulation of autofluorescent lipopigments resembling ceroid and lipofuscin. NCL affect both males and females, and has worldwide prevalence of 1 in 20,000-100,000 people. Several recessive families and sporadic cases with variable clinical presentation have been reported. Numerous loss-of-function mutations have been identified in the ceroid lipofuscinosis, neuronal gene (CLN2) in NCL individuals from various ethnic groups. We have investigated a NCL family with an apparent autosomal recessive mode of inheritance. The family is originally from the Indian state of Kerala consists of two affected females born to a non-consanguineous parents. The age of onset was two-three years manifested by progressive degenerative disorder, microcephaly, seizures, regression of milestones, complete vision loss and were bed ridden near the age of 5 years. A detailed clinical investigation was performed including electron microscopy of axillary skin and muscle biopsy and brain MRI analysis. The patients were found with deficient in pepstatin insensitive lysosomal tripeptidyl peptidase 1 (TTP1). Genomic DNA from both the affected children and parents were PCR-amplified for regions covering the entire coding sequence and splice junctions of the CLN2 gene. The Sequence analysis of CLN2 gene revealed a novel homozygous splicing mutation IVS4-->5G-->A in both the affected children; however the parents were found to be heterozygous. The mutation changes G to A at fifth position in intron 4 of the CLN2 gene. This mutation was not observed in normal controls from the same geographic region. It is expected that the NCL phenotype in the present family is due to the present splice variant. Further prenatal diagnosis of subsequent pregnancy revealed a heterozygous fetus. A detailed clinical data, mutation spectrum of CLN2 gene and genotype phenotype correlation will be presented.

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FUNCTIONAL VARIANT WITHIN ITGAM ASSOCIATED WITH SYSTEMIC LUPUS ERYTHEMATOSUS: FROM PEDIGREE-BASED LINKAGE ANALYSIS TO MULTIETHNIC ASSOCIATION STUDY

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Systemic lupus erythematosus (SLE) is an autoimmune inflammatory disease with a relatively strong genetic component (sibling risk ratio, s, 30). Our previous genome-scan meta-analysis using 9 independent genome-wide linkage results identified 16p12.3-q12.2 as the second-strongest SLE linkage signal. To identify SLE susceptibility gene(s) under this linkage signal, we performed case-control association analysis in individuals with African and European ancestries. Using a trans-ethnic mapping approach, we identified a novel non-synonymous variant, rs1143679, within ITGAM gene associated with SLE susceptibility. Recently, using genome-wide association approach, 3 studies independently confirmed association between SLE susceptibility and theITGAM-ITGAX region. Therefore, based on thse available data, we hypothesize that multiple independent, possibly ethnic-specific predisposing, variants within the ITGAM-ITGAX region are associated with SLE. Our objective is to perform a comprehensive analysis to assess whether single or multiple causal variants from the ITGAM-ITGAM region are involved in SLE susceptibility across 4 independent data sets (N=12,098). Data sets include 2 European-derived populations, European-American (EA) (3980 cases/3546 controls) and UK: (445/ 588), as well as 2 African-derived populations, African-American (AA) (1511/ 1759) and Gullah (GH) (135/134). We used both real genotyped data and the 1000Genomes Project data as a reference panel to impute SNPs in this region. This approach allowed analysis of virtually all common SNPs (at least five-fold increase in marker density over HapMap) within the ITGAM-ITGAX region. Imputation-based association analyses were performed for single- and multiple-SNP based haplotypes. To correct for population stratification effect in association, we used 343 ancestry informative markers and applied both logistic regression and principal component analysis. LD patterns and conditional logistic regression analysis were performed to assess the independence between SNPs. A meta-analysis was performed to obtain an overall odds ratio and p-value. To assess the functional significance of the associated variant, we compared the mRNA and protein expression between the risk and non-risk homozygous individuals. We genotyped 32 SNPs from the ITGAM-ITGAX region. We identified 195 SNPs in CEU and 281 SNPs in YRI from 1000Genomes database. Once rare (minor allele frequency<3%) SNPs were removed 167 (CEU) and 226 (YRI) SNPs were available for imputation based analysis. Although our analysis identified multiple associated variants, based on LD structure and subsequent conditional analysis the best significant SNP was identified as rs1143679 in all 4 populations (EA p=1.3E-30, UK p=5.7E-9, AA p=2.5E-9, GH p=0.004). Meta-analysis results are significant, the overall p-value, using all datasets are: p=3.6E-46 (OR=1.69, 95% CI (1.58-1.82)). However, we could not

identify other SLE predisposing variants besides rs1143679. Finally, we also we also identified the significant difference in mRNA ($p<0.03$) and protein ($p<0.002$) between risk (AA) and non-risk (GG) individuals. Our comprehensive imputation-based association analysis re-confirmed the exon-3coding SNP, rs1143679 (R77H), explained the entire ITGAM-SLE association. ITGAM discovery is a perfect example for a causal variant identification that is associated with increased susceptibility to SLE, a complex and clinically heterogeneous autoimmune disease.

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CONSANGUINITY AND CONGENITAL ANOMALIES IN A HOSPITAL POPULATION

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Consanguinity is common in Pakistan. In a study by Hussain and Bittles (1998), 60% of Pakistani marriages are consanguineous and out of these 80% are first cousins. Autosomal recessive disorders are related to consanguinity, and approximately 30% of sporadic undiagnosed cases of mental retardation, congenital anomalies and dysmorphism may have an autosomal recessive etiology with risks of recurrence in future pregnancies. The objective of the study was to determine the number of consanguineous unions in parents of children born with congenital anomalies. The study population comprised of 70 pregnant women coming for delivery/termination to Obstetrics Department, Federal Services Hospital, Islamabad, Jan 2004-June 2004. In the study sample consanguineous couples were 70% and 30% non-consanguineous. In consanguineous unions 60% were first cousins. The majority of congenital anomalies encountered were neural tube defects 58.57% (anencephaly 38.57%, spina bifida 12.85%, and meningocele 7.14%). Etiologically most of congenital anomalies are autosomal recessive and multifactorial. In the study sample 84% of patients were from urban areas and 16% were from rural areas. Majority of patients were illiterate or educated only up to primary level and belonged to lower socioeconomic class. The congenital anomalies encountered were autosomal recessive with risk of recurrence in subsequent pregnancies. Genetic counseling could be beneficial for consanguineous couples. There is a need to educate public on harmful effects of inbreeding especially in developing countries with high consanguinity rate and limited financial resources.

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USE OF FOLIC ACID AMONG PREGNANT WOMEN WITH CONGENITAL ANOMALIES IN A HOSPITAL POPULATION

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The prevalence of Neural Tube Defects is high in Pakistan. Daily consumption of a supplement containing 400 μg of folic acid before and during the first trimester of pregnancy has been shown to be effective in preventing both the occurrence and recurrence of Neural Tube Defects. The study population comprised of 70 pregnant women coming for delivery/termination to Obstetrics Department, Federal Services Hospital, Islamabad, Jan 2004-June 2004. Among the congenital anomalies neural tube defects were 58.57 %.(anencephaly 38.57%, spina bifida 12.85%, meningocele 7.14%). In the study sample 10% of women took iron, or multivitamin Preparations. Dietary intake of food containing folic acid was inadequate. Folic acid awareness was 10 % and knowledge regarding role of folic acid in prevention of neural tube defects was zero percent. In the study sample 84% of patients were from urban areas and 16% were from rural areas. Majority of patients were illiterate or educated only up to primary level and belonged to lower Socioeconomic class. The level of folic acid awareness, knowledge and use of folic acid is extremely low. Efforts including public health campaigns aimed at increasing the awareness, knowledge and periconceptional use of folic acid are urgently need both in rural and urban areas with special emphasis to less educated low socioeconomic class.

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A NOVEL MUTATION OF BSCL2 GENE IN A PATIENT WITH BERARDINELLI LYPODYSTROPHY SYNDROME

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Congenital generalized lipodystrophy (CGL) is a rare autosomal recessive disease that is characterized by a near-complete absence of adipose tissue from birth or early infancy. Mutations in the BSCL2 gene are known to result in CGL2, a more severe phenotype than CGL1, with earlier onset, more extensive fat loss and biochemical changes, more severe intellectual impairment, and more severe cardiomyopathy. We report a 4-years girl with hypertriglyceridemia, speech delay, muscle hypertrophy, overgrowth, bilateral genicomasty, massive hepatomegaly, umbilical hernia, coarse hair and acanthosis nigricans. Hepatomegaly was noticed, and histological examination of a liver biopsy specimen suggested extensive fatty changes. According to clinical symptoms Berardinelli lypodystrophy syndrome was diagnosed. Methods Blood sample was taken from patient for DNA analysis and different exons and splice junctions of BSCL2 and BSCL1 gens was sequenced. The result was homozygous mutation of c.150_212+28delinsGAA in BSCL2 gene. This deletion of 91 base pairs deletes the 3‘ end of exon 2 and the consensus sequence of intron 2. Absence of mutation in BSCL1 was noted. The process of adipocyte differentiation is compromised

in patients with Beradinelli-Seip congenital lipodystrophy owing to diminished expression of the regulatory genes involved, which pioglitazone treatment partially rescues. Prelamin A accumulation establishes a link with other types of familial lipodystrophies, as familial partial lipodystrophy.

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CONSANGUINITY AMONG ARABS AND ITS IMPACT ON CLINICAL GENETICS AND GENOME ANNOTATION

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Consanguineous marriages have been practiced since the early existence of modern humans. Until now, consanguinity is widely practiced in several global communities. Arab populations have a long tradition of consanguinity due to sociocultural factors and display some of the highest rates of consanguineous marriages in the world. For this reason, we carried out a comprehensive review to assemble consanguinity rates among Arabs and to figure out the effect of consanguinity on reproductive health in the region. There is accumulating evidence, from studies of Arabs and other populations, that consanguinity exerts a continuous impact on some reproductive health parameters, such as postnatal mortality and rates of congenital malformations. The association of consanguinity with other reproductive health parameters, such as fertility and fetal wastage, is controversial. The main impact of consanguinity, however, is an increase in the rate of homozygotes for autosomal recessive genetic disorders. Worldwide, known dominant disorders are more numerous than known recessive disorders. However, data on genetic disorders in Arab populations, as extracted from the Catalogue of Transmission Genetics in Arabs (CTGA) Database, indicate that two-third of genetically transmitted diseases in Arabs follow an autosomal recessive mode of inheritance (586 of 955 diseases). Definitely, this particular distribution reflects on the practice of clinical genetics in the region especially in genetic counseling, prognosis, and patient management. Yet, the availability of many consanguineous families from the region continues to help scientists in the identification of the genes responsible for many inherited diseases, both common and rare. The CTGA Database indicates that more than 60 genes were identified in families from the region. Undoubtedly, these studies resulted in great contributions with respect to genome annotation and to unraveling the extent of genome variability in the region.

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CLINICAL AND MOLECULAR GENETIC ANALYSIS OF HEREDITARY LOOSE ANAGEN HAIR SYNDROME IN A LARGE MULTIGENRRATIONAL FAMILY

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Loose anagen hair syndrome (LAHS: OMIM 600628) is a rare non-inflammatory hereditary hair disorder seen among children. It is characterized by anagen hairs of abnormal morphology that are easily and painlessly pluckable from the scalp with a gentle hair pull. The estimated prevalence of LAHS is ~ 2 to 2.25 per million individuals. The condition is usually isolated and the clinical presentation includes hair is generally sparse, thin, slow growing and naturally does not grow beyond the nape of the neck that seldom requires cutting. It affects both the genders equally. We have studied one large Indian LAHS pedigree, with an autosomal dominant mode of inheritance and full penetrance. The family consists of 70 individuals including 27 affected (15 males and 12 females). All affected had typical characters of loose anagen hair syndrome without skipping of generation was observed. The expression of the phenotype was first apparent from 1 to 4 years of age. A hair pull test of all affected individuals extracted multiple hairs easily and painless and there were no sign of scalp inflammation or scarring. Microscopic examination was also consistent with LAS. Majority of the affected members including all females never cut their hair, however few males has the history of seldom cutting their hair. Cytogenetic analysis of four affected individuals did not show any abnormality. Mutation search in exons and splice junctions of potential candidate gene SHOC2 was excluded by direct sequence analysis. A genome-wide linkage analysis using polymorphic microsatellite markers with an average spacing of 5 cM was carried out on 11 affected 15 normal individuals of this pedigree. Detailed clinical descriptions and the results of our genome-wide linkage scan with genes of interest will be presented.

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LINKAGE ANALYSIS AND EXOME SEQUENCING OF FAMILIES WITH SPLIT-HAND/FOOT MALFORMATION WITH LONG-BONE DEFICIENCY

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Split hand/foot malformation with long-bone deficiency (SHFLD) is a rare, severe limb deformity characterized by tibia aplasia with or without split-hand/split-foot deformity with an incidence of ~1 per million live births. Genomic regions with evidence of linkage for SHFLD were identified at three chromosomal regions including two of our earlier

identified loci (SHFLD1, MIM 119100; SHFLD2, MIM 610685) at 1q42.2-q43 and 6q14.1 respectively, in a large Arab consanguineous family (UR078; Am.J.Hum.Genet; 80: 105â€—11,2007), which most likely contain novel susceptibility genes for autosomal SHFLD1 and SHFLD2. In order to identify the genes responsible for these two autosomal loci, we performed exome sequencing using the SOLiD™ system at x200 coverage. We prioritized our mutation search within the linkage region between SNP markers rs1124110/rs535043, and rs623155/rs1547251 respectively. In addition, we have recently ascertained several multigenerational SHFLD families of different geographic region. Genome-wide linkage analysis of three selected large families (UR079, UR080 and UR083) using high-density SNP array excluded previously identified SHFLD1 and SHFLD2 and SHFLD3 loci and yielded novel digenic loci each in two distinct families (UR080 and UR083) indicating that SHFLD is highly heterogeneous. Additional clinical details of the affected individuals from newly studied families, the detailed results of our linkage scan with genes of interest in the novel linked chromosomal regions and exome sequencing data of SHFLD1 and SHFLD2 in selected individuals in Arab family will be presented.

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DEALING WITH GENETIC DISEASES IN OMAN

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Autosomal recessive conditions are by far commonest single gene diseases and remain the major contributors to childhood morbidity, mortality and handicap in the Sultanate of Oman. Common Recessive Disorders are discussed in view of collaborative research and the application of molecular genetic technology. The strategies developed for the prevention of genetic diseases in the Sultanate of Oman have been ethically compatible with the cultural and social make up, religious beliefs of the population, and the legal system of the country. The planning of the genetic service currently is guided by the population research in genetics which has shown high level of consanguinity and distinct geographical variation of genetic disease frequencies. The role of basic research in this planning process is discussed.

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THE MOLECULAR-GENETIC STUDY OF CONGENITAL ADRENAL HYPERPLASIA IN BASHKORTOSTAN REPUBLIC (RUSSIA)

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Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders of adrenal steroidgenesis in which 21-hydroxylase deficiency accounts for over 95% of cases, which is caused by various mutations of the CYP21A2 gene, encoding the steroid 21-hydroxylase enzyme. More than 100 mutations causing 21-hydroxylase deficiency have been identified. We studied 87 patients with CAH from Bashkortostan Republic. The patients were divided into 2 groups according to clinical findings: salt wasting (SW) (N=42) and simple virilizing (SV) (N=45) forms. Mutations of the CYP21A2 gene were revealed in 71.82% of the studied CAH-chromosomes. The mutations were distributed as follows: delA2orLGC (27.62%), R356W (16.02%), I2splice (11.6%), I172N (7.18%), Q318X (4.97%), V281L (2.76%), P30L (1.1%) and P453S (0.55%). The mutations frequency distribution in the CYP21A2 gene in 2 groups of patients with classical disease forms showed statistically significant differences. Salt wasting form patients demonstrated delA2orLGC of the gene CYP21A2 twice more often than simple virilizing form patients (37.65% and 19.32%, respectively, $\chi2$=6.28, p=0.012), mutation R356W – 2.6 times (23.53% and 9.09% respectively, $\chi2$=5.62, p=0.018), mutation I2splice – 2.9 (16.47% and 5.68%, respectively, $\chi2$=4.1, p=0.43), and mutation Q318X – 8.3 times more often (4.41% and 1.14% respectively, $\chi2$=4.44, p=0.04). The mutation I172N, on the contrary, was more typical for SV patients than SW patients (13.64% and 1.18%, respectively, $\chi2$=7.95, p=0.005). Mutations P30L and V281L were detected only in SV patients. Thus, we have been able to detect the spectrum of diagnostic significant CYP21A2 gene mutations typical for SW and for SV forms in CAH patients. We found 7 CAH-patients who carried 3 mutations, two of which formed a cluster: Q318X+R356W (2.87%, 5/174), I172N+Q318X (0.57%, 1/174), delA2orLGC+V281L (0.57%, 1/174). Such mutations linkage, or cluster, was inherited by patients from his/her mother or father. The clusterization of mutations on one chromosome inside nucleotide sequences of gene it is characteristic for gene CYP21A2. One of vivid examples of linkage mutations in this gene is the cluster from 3 missence-mutations - I236N, V237E, M239K - in 6th exon, known as E6cluster.According to literature data, different mutation clusters were identified in patients from various countries, specific for each region. This complex of alleles probably resulted from large conversions or multiple mutations events. Besides, in 4 parents we identified mutation clusters, which have not been inherited by their affected children (I172N+Q318X, I2splice+Q318X, delA2orLGC+V281L). Molecular-genetic investigation of 87 CAH families from Bashkortostan Republic showed that 63% were completely informative, 15% were partially informative for the direct DNA-diagnostics. 22% of CAH families from Bashkortostan were absolutely non-informative. As a result of this, further molecular-genetic investigations using direct sequencing of the whole active CYP21A2 gene and indirect DNA-diagnostics with the help of hypervariable DNA-loci and haplotypes are needed. Thus, studying of molecular-genetic nature CAH represents the doubtless scientific and practical importance in respect of use of the received data for differential diagnostics of its various forms, medical and genetic consultation and prenatal diagnostics.

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A GENOME-WIDE LINKAGE STUDY OF HIGH-GRADE MYOPIA IN A LARGE INDIAN FAMILY

SUPPORT FOR THE MULTIFACTORIAL THRESHOLD MODEL OF INHERITANCE

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Myopia, also known as shortsightedness, is hereditary and environmental factors are also extremely important. It is often found in early childhood. In myopic subjects, the image of distant objects falls in front of the retina, either as the eye is too long (axial myopia), the cornea is too convex or the index of refraction of the lens is too high (refractive myopia). The estimated prevalence of high grade myopia is ~2.5 to 9.6% in the elderly world population. However, it varies with age, sex, race, occupation, country, ethnicity, environment, and other factors. Its highest prevalence rates are in Asians, in whom almost 50 to 80% of the adult populations are myopic. The incidence of Myopia is increasing in all parts of the world. Until, 17 myopia loci on different chromosomal regions have been identified in patients of various geographic origins. However, to date no disease-causing mutations in any gene(s) have been identified. We have ascertained 72 extended high myopia families from various parts of world and majority are from India. A genome-wide SNP-based high-density linkage scan was performed using Affymetrix Human SNP Array on a selected Indian family (UR-034) with multiple affected individuals. The Indian Pedigree (UR034) with isolated, non-syndromic myopia, in which the condition appeared to segregate as an autosomal dominant trait and the degree of myopia was variable ranging from –8 to –20 D with majority >8.0 D. In order to map the myopia locus in these families, we performed linkage analysis on 22 genomic DNA samples (10 affected and 12 normals) using a genomewide high density Affymetrix Human SNP array. Nonparametric linkage analysis identified three novel loci in family UR-034 at 4p15.32-4p14 ([NPL] 3.2; p = 0.008789), 11p11.2-11q12.1 ([NPL] 3.5; p = 0.008789) and 13q14.11-13q21.1 ([NPL] 3.2; p = 0.008789) between SNP markers rs1376184/rs1863325, rs950105/rs1376486 and rs347405/rs956122 respectively. The SNP-based copy number analyses did not reveal any variation in the linked genomic regions. The present study provides first report of evidence with multifactorial inheritance for high-grade myopia susceptibility loci in Indian family. It also, suggests that a SNP-based procedure provides increased genomic coverage and better overall information content in contrast to microsatellite markers. Further research is needed to understand role of multifactorial inheritance and how myopia can be prevented and/or treated.

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CASE REPORT: LERI WEILL DYSCHONDROSTEOSIS

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Leri Weill Dyschondrosteosis (LWD) was first described by Leri and Weill in 1929, who reported patients with short stature, skeletal abnormalities and Madelung deformity. To date, seven cases in Mexico have been described. It mainly is caused by a pseudoautosomal mutation in SHOX and SHOXY regions. The patient is a 12-year-old female, product of the third pregnancy, full term, from non consanguineous parents. Her weight at birth was 2.7 kg (percentile 3), and height of 47 cm (percentile 3). Her psychomotor development was normal. At physical examination she showed a disproportionate short stature. Phenotype reveals dolichocephaly, triangular face, broad frontal region, brushy eyebrows in 1-2 thirds and rare distal end, inner epicanthal, almond eyes, high nasal bridge, malar hypoplasia, broad nose, dental malocclusion, pronounced philtrum and pillars, mesomelic limb shortening, Madelung deformity and genu varum. Radiography shows radial and tibial shortening with a partial non-limiting radial subluxation. Family History: 5 affected family members in 3 generations. Actual anthropometry: Weight 30 kg (percentile 3), height 136 cm (percentile 30), cephalic perimeter 55.5 cm, armful 123.7 cm, lower segment 74 cm, upper segment 47 cm. The Leri Weill Syndrome, also known as Dyschondroesteosis, is a pseudoautosomal dominant disorder that causes short stature, mesomelic limb dysplasia and a characteristical malformation known as Madelung deformity. It is caused mainly by SHOX gene mutation located in the pseudoautosomal region 1 (PAR1). This entity is more severe in women, probably due to sexual hormones. 60% of the patients present mutation of the SHOX gene, while the rest remain unknown. It is believed to be located in PAR1, where deletions could strengthen the diagnosis of LWD. The LWD (OMIM #127300) is an autosomal dominant disorder with an incomplete penetrance, caused by a pseudoatosomal gene deletion region 1 (PAR1). The aim of this case report is to present the clinical manifestations of LWD. The molecular detection of the pseudoautosomal region 1 (PAR1) is important, excluding the SHOX gene deletion.

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LOWRY COFFIN SYNDROME: REPORT OF A FAMILIAR CASE

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Coffin-Lowry Syndrome (CLS; OMIM 303600) was first described in 1966, although the name was designated until 1975 by Temtamy. CLS with X-linked dominant inheritance is caused by mutations in the RPS6KA3 gene locus Xp22.2-p22.1, which encodes RSK2, a growth factor-regulated serine-threonine kinase. The clinical features include mental retardation, characteristic facies, dentition abnormalities, pectus excavatum/carinatum, kyphosis/scoliois, puffy hands, tapering fingers, short-hyperconvex nails, articular hyperlaxity, and sometimes cardiovascular complications. The estimated incidence of CLS is 1 in 50,000 to 1 in 100.000, nevertheless 70-80% have no family history of CLS. To date 128 mutations of CLS have been reported. We describe a 27-year-old Mexican male with physical and developmental findings consistent with CLS: mental retardation, coarse facies, soft hands, drumstick terminal phalanges, and skeletal deformities. Physical examination exhibits small stature, brachycephaly, prominent frontal region, arched eyebrows, hypertelorism, inner epicanthal, slanting palpebral fissures, broad nose, high nasal bridge, large mouth, pectus excavatum, micrognathia, large ears, hyperlaxity of joints, scoliosis, spina bifida, and flatfoot. The patient presents severe mental retardation with normal 46 XY karyotype. The mother is similarly affected with a less evident phenotype. The present work describes a familiar case of CLS. The mother exhibits mild clinical features due to the Lyon inactivation phenomenon. RSK2 mutations have not been reported in Mexico, therefore we plan to perform molecular studies on this family.

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CYTOGENETIC ABNORMALITIES FOUND AMONG THE FEMALES SUSPECTED FOR MENTAL RETARDATION IN AND AROUND COIMBATORE CITY, TAMIL NADU, INDIA

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Mental retardation is a condition, not a disease, nor should it be confused with mental illness and is an important health problem all over the world. The prime aim of the present study was to identify the chromosomal alterations in females with mentally retarded patients in Coimbatore region. In order to investigate the possible cytogenetic damage to the mentally retarded patients, a G-banding method was carried out on the lymphocytes of 72 female experimentals and equal number of female controls selected. Experimentals and controls were selected based on the detailed questionnaire. In the present study volunteers provided blood samples (5 ml) to establish cell cultures at 72 h. For karyotyping, 100 complete metaphase cells from each subject were evaluated. The detection of an increasing number of recognizable syndromes such as Down syndrome, Turner syndrome associated with chromosomal anomalies 45,XO; 46, XX,13s+; 47, XXY; 46, XX+21; 46,XX,13s+ ; 46, XX,21s+; 45 ,XO/46,XX, 45,XO/46,XX was found among the female of the city through the chromosomal analysis of the subjects. In the present study exhibit chromosomal aberrations showed higher degree in experimentals compared to controls (P<0.001). In conclusion, to point out that, the systematic study of mental retardation is very rewarding with an accurate diagnosis in the proband and with proper genetic counseling, one can alleviate the misery of many parent and also can reduce the birth of affected offsprings in the family subsequently.

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CHARACTERIZATION OF VWF GENE EXPRESSION FOLLOWING 1110-1G/A MUTATION IN A TYPE 3 VON WILLEBRAND DISEASE FAMILY

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Type 3 von Willebrand disease(vWD) is a rare congenital disorder which inherited as an aoutosomal recessive trait. It is caused by the mutation in vWF gene located on short arm of chromosome 12. This gene produces a multimeric glycoprotein with a crucial role in haemostasis. vWF forms a bridge between subendothelium and platelet to make a clot. It also serves as a carrier for coagulation factor 8. The type 3 mutations can be scattered through the entire gene. To date, over 100 mutations have been found that most of them are null alleles. Among them, splice site mutations are responsible for 15-20% of the defects. The mutation 1110-1G/A in the acceptor splice site of intron 9 was previously reported. In this study using RT-PCR and Real- time RT-PCR we characterized the expression of mutant alleles in a family of type 3 von willebrand disease. A family consisting of 2 vWD type 3 patients and their parents and 12 normal controls were included in the study. Fifteen ml of peripheral blood was obtained from each patients, their heterozygous parents and normal controls. Total RNA was extracted from Platelet rich plasma (PRP) of each sample using RNeasy plus minikit (Qiagen). Total mRNA was reverse transcribed into cDNA using QuantiTect reverse transcription kit (Qiagen). Two primer sets were designed to amplify two different fragments on VWF cDNA. The expression of GAPDH gene was also analyzed as reference gene. Each sample was tested by conventional RT-PCR and quantitative Real-time PCR. The expression of vWF gene was detected in the patients and heterozygous parents. Corresponding bands of vWF gene fragments were revealed by gel electrophoresis for all samples in RT-PCR assay. There was no significant difference between the expression level of vWF mRNA in patients with splice site mutation 1110-1G/A and normal controls as quantified by Real-time PCR analysis. Although, some nonsense mutations in vWF gene lead to its mRNA degradation via Nonsense Mediated Decay (NMD), splice site mutations are less likely to enhance degradation pathways. This kind of mutations may cause the exon skipping and result in the deletion of the next exon. The present study has revealed the expression of vWF mRNA comprising 1110-1G/A mutation and further investigation needs to be done to determine the effects of this mutation on vWF exon 10 splicing.

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ASSOCIATION OF ACE GENE POLYMORPHISM AND ELECTROLYTE HOMEOSTASIS IN DIABETIC NEPHROPATHY

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Diabetes clustered with nephropathy has been the leading cause of deaths due to end stage renal disease globally. The renin-angiotensin system (RAS) has an established link with the pathogenesis of various metabolic etiologies. The findings on involvement of Angiotensin-I Converting Enzyme (ACE) gene polymorphism as well as electrolytes abnormalities have been inconsistent. Moreover, the possible association between insertion (I)/deletion (D) polymorphism of ACE gene and nephropathy in diabetes has not fully explored. This study investigated the possible association of I/D polymorphism of ACE gene and electrolytes disturbances in diabetic patients with and without nephropathy. Sixty diabetic patients with nephropathy and 60 without nephropathy were selected for the study followed by informed consent. Fasting blood samples were analyzed for serum electrolytes, glucose, HbA1c, levels. Polymerase Chain Reaction (PCR) was used to genotype the DNA isolated from the patients for ACE I/D with the help of specific primers. Diabetic patients without nephropathy showed a significant rise serum potassium and calcium levels while serum sodium and magnesium levels were low as compared to controls. The ACE ID, DD and II genotypes were distributed as 35/60 (58.33%), 18/60 (30%) and 07/60 (11.67%) respectively. In diabetic patients without nephropathy serum sodium, calcium and magnesium levels were low. The ACE I/D alleles were distributed as ID, 30/60 (50%), DD, 05/60 (8.33%) and II, 25/60 (41.67%). The homozygous deletion allele (DD genotype) was found in 05/60 (8.33%), heterozygous deletion allele (ID genotype) was found in 30/60 (50%) and homozygous insertion allele (II genotype) was found in 25/60 (41.66%) in diabetic patients without nephropathy. In diabetic patients with nephropathy, homozygous deletion allele (DD genotype) was found in 18/60 (30%), heterozygous deletion allele (ID genotype) was found in 35/60 (58.33%) and homozygous insertion allele (II genotype) was found in 07/60 (11.67%). It is shown that the distribution of D allele is significantly higher in patients of persistent nephropathy (70%) along with disturbed serum electrolyte levels as compared to diabetic patients with normal albuminuria or without nephropathy (58.33%). It is suggested that the appearance of ACE gene D allele polymorphism is metabolically associated with an altered electrolytes homeostasis which may be considered as strong risk factor for the progression of diabetic nephropathy in diabetes.

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A PRELIMINARY INVESTIGATION OF THE SUBUNIT ORGANISATION OF THE RECOMBINANT 2-OXOGLUTARATE DEHYDROGENASE (OGDC)

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OGDC is a mitochondrial assembly that is involved in the TCA cycle and is increasingly implicated in the etiology of various neurodegenerative diseases linked to oxidative stress including Alzheimer's and Parkinson's disease. The basic organization of the OGDC is directed by the self-assembly of 24 copies of dihydrolipoyl succinyltransferase (E2o) to form a cubic core, to which multiple copies of 2-oxoglutarate dehydrogenase (E1o) and dihydrolipoamide dehydrogenase (E3) bind non-covalently. The mammalian E2o is unusual in lacking any obvious E3 or E1o binding domain. In this study, E2o and E3 were successfully over-expressed and purified. Initially it was confirmed that E2o and E3 do not interact with each other on gel filtration although stable association of all 3 constituent enzymes occurs in the native complex. Full-length E1o was also cloned successfully and got sequenced, although it proved impossible to achieve detectable expression in our E. coli BL21 host system. Previous studies employing subunit-specific proteolysis have identified the extreme N-terminal segment of E1o as a key region involved in the maintenance of complex stability and integrity and is required for E2 and E3 binding. To investigate this region in more detail, three N-terminal E1o fragments of decreasing size were over-expressed, one in His-tag form (193 amino acids) and two as E1o-GST fusion proteins (166 and 83 amino acids). In co-expression, purification and gel filtration studies, it was found that all these N-terminal truncates of E1o appeared capable of interacting with E2o although problems were encountered with rapid degradation and unambiguous identification in some cases. However, Western blotting revealed conclusively that even the shortest N-terminal E1o fragment (83 amino acids) was able to enter into a stable association with E2o. Owing to difficulties with rapid degradation and/or solubility of the E1o truncates, it remains to be determined whether this N-terminal region of E1o can also interact with E2o in a post-translational fashion and whether it is directly involved in mediating E3 binding.

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GENOME WIDE SCREEN REVEALS BIOLOGICAL BASES FOR ENVIRONMENTAL CONTROL OF LIPID LEVELS

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Recent GWA studies described 95 loci controlling serum lipid levels. These common variants explain ~25% of the heritability of these phenotypes. To date, no unbiased screen for gene-environment interactions for lipids has been reported. We screened for gene-environment interactions influencing circulating blood lipids in a meta-analysis of genome-wide

association data from 19 population-based cohorts of individuals with European ancestry (total number of samples 15,600-32,600 depending of the trait and environmental factor used). The lipids studied were high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), total cholesterol (TC), and triglycerides (TG), and the environmental factors of interest were alcohol consumption, smoking, gender, waist-to-hip ratio (WHR), and body mass index (BMI). First stage results with p<1Ã—10-6 were replicated using additional eight cohorts consisting of more than 14,000 samples. A locus near the PCDH7 gene (rs6448771) showed an interaction with WHR on TC with a combined p-value of 9.08x10-9. A 10% increase in WHR was estimated to elevate TC by 0.14 mmol/L (CI 0.10-0.18) for carriers of the AA genotype, 0.20 mmol/L (CI 0.16-0.24) for AG carriers, and 0.22 mmol/L (CI 0.15-0.29) for GG. Additionally, four SNPs showed interactions among loci previously associated with lipid levels (after Bonferroni correction for 130 tested SNPs). Inclusion of interaction effects into genetic predictive profile led to significant increase in proportion of lipids variance explained. Key-node analysis revealed PKC-alpha, PKC-epsilon, IGF-1R, and a number of other molecules as potential mediators between environmental exposure and genes which are co-regulated in response to these. Interestingly, keynode analysis of ‗environmentally sensitive‘ loci revealed similar keynodes, potentially suggesting limited number of regulatory molecules involved in the environmental response. A genetic variant rs6448771 modifies the relationship between waist-to-hip ratio and total cholesterol. The effect of waist-to-hip-ratio is over is 60% stronger for individuals carrying two copies of the G allele than individuals carrying two A alleles. Accounting for gene-environment interaction allows better prediction of lipid levels. This opens up possibilities for targeted intervention strategies for people characterized by specific genomic profiles. Identified regulatory molecules, which are likely to translate the environmental stimuli into organism‘s lipids response may be used as targets for development of drugs, which are likely to be most beneficial for people under certain environmental exposure and having specific high-risk gene-environment profile.

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WHOLE GENOME LINKAGE ANALYSIS IN A LARGE CONSANGUINEOUS TURKISH FAMILY WITH IDIOPATHIC GENERALIZED EPILEPSY

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Epilepsy is a complex neurological disorder that affects 1% of the world's population. Among different forms of epilepsies, idiopathic generalized epilepsies (IGE), constituting up to 40% of all epileptic syndromes, are characterized by bilateral and synchronous generalized seizures in the absence of detectable brain lesions or metabolic abnormalities. Thus, the primary etiology for this disorder is believed to be genetic. In this respect, the proposed study includes a large highly inbred consanguineous family with multiple IGE affected individuals with an ultimate aim in identifying a new epilepsy gene that would help us delineate the molecular mechanisms of this disease, eventually leading to improved diagnostics and treatment tools. Physical, neurological and EEG examinations were performed on the subjects recruited with information on family history. These examinations revealed 5 affected individuals, a mother with three children and their cousin, who exhibit varying types of seizures including absence, generalized tonic-clonic and myoclonic seizures. Along with these individuals, 4 unaffected individuals from this family were genotyped using Illumina Infinium HumanLinkage-12 Genotyping BeadChip (6090 SNPs). The genotype data were delineated using easyLinkage software platform, where Mendelian genotyping errors were determined using PedCheck, two and multipoint lod scores were calculated under the assumption of autosomal recessive inheritance via SuperLink and SimWalk, respectively, and haplotypes were constructed through GeneHunter. These analyses revealed a promising locus on chromosome 2p12, which was further analyzed through fine-mapping with additional microsatellites spanning a region of 75.36Mb-78.52Mb. However, microsatellite alleles were heterozygous in the 3 affected sibs rejecting linkage under autosomal recessive inheritance. The future objectives include dense SNP genotyping of the family members in an attempt to unravel small regions that may have been overlooked. Additionally, acquisition of better clinical follow-up and characterization of both affected and unaffected individuals will enable other possible inheritance models for genotype analyses. Once a gene locus is mapped, positional candidate genes will be screened for causative variations.

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ROLE OF GENES ENCODING ALCOHOL METABOLIZING ENZYMES IN ALCOHOL LIVER DISEASES: FIRST INDIAN STUDY

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Chronic and excessive alcohol ingestion is one of the major causes of liver disease in India. The genetically determined differences in alcohol metabolizing genes have been associated with alcoholic liver disease (ALD). However, specific genetic abnormalities for susceptibility to alcohol abuse and the development of ALD have not been firmly established. This is the FIRST study to elucidate the polymorphism of alcohol dehydrogenase, aldehyde dehydrogenase, and cytochrome p450 in patients of alcoholic liver disease and compare them with alcoholic controls in Indian population All patients registered under ALD clinic were worked up with supporting endoscopic, and radiological evidence from patients of Gastroenterology department at All India Institute of Medical Sciences with equal number chronic alcoholics/alcohol-dependent(ALC) male subjects satisfying DSM 1V criteria derived from the Diagnostic Interview for Genetic Study (DIGS), with >18 years of age were inducted in the study. Detailed clinical and demographic history was recorded. The

genetic polymorphism of ADH2, ADH3 ALDH2 was studied in patients of alcoholic liver disease (ALD) and alcoholics (ALC) using PCR/RFLP method. Majority of the alcoholic liver disease patients in the study were sick requiring emergency admissions. Mean duration of symptoms was 10.71 months prior to admission. Ascites (87.7%) and jaundice (87.5%, with bilirubin>1.5) were the commonest examination findings. Hepatomegaly (37%) and splenomegaly (26%) were also present in substantial number of patients. ADH2 was monomorphic for ADH 2*1allele in both groups. A significant difference was seen in allelic/genotypic frequencies of ALDH2 between ALC & ALD patients. In case of ADH3, majority of patients in both groups were heterozygous for ADH3-1/3-2. Conclusion Functional polymorphism of the gene coding for the ALDH enzyme affects the propensity to develop ALD and ALC in Indian population. The important finding of the study was the high frequency of the ALDH2*2/*2 genotype (amongst ALC and ALD) being a risk-conferring polymorphism in Indian population as compared to other Asian countries. Present study revealed association of ALDH2 gene polymorphism in patients of alcoholic liver disease.

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FREQUENCY OF CYSTIC FIBROSIS ΔF508 MUTATION IN ADULT AND ELDERLY CAUCASIAN POPULATION OF NORTH ASIA AND ITS ASSOCIATION WITH COMMON CHRONIC DISEASES

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The study was aimed at the analysis of the frequency of cystic fibrosis major mutation F508 in adult and elderly Caucasian population of North Asia and its association with common chronic condition and related phenotypic traits. The prevalence of ΔF508 mutation of cystic fibrosis gene (CFTR) significantly varies in different Caucasian populations of Eurasia. The frequency of ΔF508 is low in Finno-Ugrian and Baltic populations and high in some Central European and Scandinavian population (Wennberg et al., 1994). Single origin hypothesis determines the interest to further extension of the spectrum of studied Caucasian population particularly in borderline areas of their historical areal. Controversial data on the clinical importance of ΔF508 carrier state also dictate the need of further accumulation of relevant data in large population surveys. Presence of CFTR gene ΔF508 mutation was analyzed in 9397 participants of the HAPIEE project (http://www.ucl.ac.uk/easteurope/hapiee.html), aged 45-69, men/women - 45,6%/54,4. The studied group presents randomly selected samples from Caucasian population of West Siberia largest industrial center Novosibirsk. Data on presence of different chronic diseases, their risk factors and associated phenotypic traits were collected for all participants. These data include relevant questionnaires on the presence of cardiovascular, gastroenterological, endocrine, pulmonary and some other diseases. Traditional risk factors were analyzed including estimation of external respiratory function. DNA was extracted for all participants and presence of ΔF508 was analyzed by standard method. CFTR gene ΔF508 mutation in heterozygous state was found in 109 persons including 42 men (38.5%) and 67 women (61.5%). Observed frequency of heterozygous ΔF508 mutation carriers (1:86) was higher than in Northern Sweden (1:200) and Lithuanians (1:143) and lower than in Southern Scandinavia (Denmark; 1:38). Corresponding estimated homozygous genotype frequency is 1; 1:29730. Presence of ΔF508 was associated with bronchial asthma (2.5% in non-carriers and 8.7% in carriers) and alterations in respiratory function (26.5% in non-carriers and 50% in carriers). No association was found with other chronic diseases and risk factors. The frequency of CFTR gene ΔF508 mutation in adult and elderly North Asia Caucasian population is higher than in populations of Finno-Ugrian and Baltic origin and close to intermediate range for other Caucasians. Similar to some other reports heterozygous ΔF508 mutation state is associated with chronic pulmonary disturbances in studied population. This work was supported in part by Wellcome Trust Grant to HAPIEE consortium.

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LARGE-SCALE SOMATIC GENOME ALTERATIONS MEDIATED BY CHROMOSOMAL MOSAICISM IN CHILDREN WITH MENTAL RETARDATION AND AUTISM: A MOLECULAR CYTOGENETIC EVALUATION

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Low-and medium level of chromosomal mosaicism leading to large scale genomic alterations in definite cell lineages of the body was documented in 3-5% children with mental retardation and in 5-15% children with autism (Vorsanova et al., 2007; Yurov et al., 2007). It was proposed that development genomic instability due to increased rate of chromosome nondisjunction at early stage of ontogenesis, disrupted mitotic check-point control and failures of apoptotic clearance of aneuploid cells could play a leading role in pathogenesis of these common neurodevelopmental psychiatric diseases (Iourov et al., 2010). Here using high resolution molecular cytogenetic approaches (Interphase Multiprobe FISH [IMFISH] and Interphase Chromosome Specific MultiColor Bandind [ICS-MCB] we have determined Chromosome Instability Index (CIN) in cultured lymphocytes of peripheral blood of children with idiopathic mental retardation (n=157) and idiopathic autism (n=160). Totally more that 2 million cells were monitored in double-blinded analysis. Low level mosaicism was found in 5.7% of children with mental retardation and 15% children with autism. More frequently, mosaic cell lineages were presented by aneuploidy involving chromosomes X, 18, 15, and 9. Index Chromosome Instability (CIN) in cultured lymphocytes for these two groups was determined as 1.24 and was similar for CIN calculated

earlier for normal embryonic tissues (1.45) (Yurov et al. 2007). Thus, there is striking evidence for low-level mosaicism to result from CIN generated during early embryonic development. In general, abnormal cell populations should be cleared by programmed cell death. However, this process can be hindered due to either endogenous (failed cell cycle control/chromosome missegregation) or endogenous (irradiation/mutagenic or aneugenic substances) effects affecting aforementioned molecular and supramolecular pathways. Together, our data indicate that large-scale somatic genome alterations generated during prenatal development are an appreciable source for pathogenic intercellular genome diversity associated with brain dysfunction in mental retardation and autism. Supported by BMBF/DLR (RUS 09/006) and DFG (LI 820/18-1).

P214

DYNAMIC VARIATION OF GENE-EXPRESSION REVEALS THE INSIGHTS OF DOWN SYNDROME

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Down Syndrome (DS) caused by trisomy of chromosome 21(HSA21) is the most common genetic cause of mental retardation in human. Some previous studies have reported that dysregulated expression of HSA21 genes may lead to DS phenotypes, but the mechanisms of the process remained elusive. We used Human Exon microarray to characterize the whole transcriptomes of peripheral lymphoblastoid cells in children (10 DS patients and 15 controls) and peripheral blood cells in neonates (5 DS patients and 7 controls), respectively. By Student t test analysis and qPCR validation, a total of 427 genes, including 370 genes on Non-HSA21 and 57 genes on HSA21, showed significantly expression difference between DS and control groups of the children, 79.8% (341/427) of these gene over-expressed in the DS patients. While, 149 genes with 11 on HAS 21 expressed differently in DS and controls of neonates, 59.7% (89/149) up-regulated in the DS. There are only 22 dysregulated genes, including 9 HSA21 genes, existed in both age phases. Through KEGG pathway analysis, we identified 9 pathways affected significantly by dysregulated genes in children group, such as focal adhesion, cell adhesion molecules, regulation of actin cytoskeleton, B cell receptor signaling pathway, Graft-versus-host disease, Natural killer cell mediated cytotoxicity, and Primary immunodeficiency. On the contrary, 3 involved pathways (Leukocyte transendothelial migration, Cell adhesion molecules and Systemic lupus erythematosus) were found in neonates. Our results explored the whole transcriptomes in the peripheral blood cells of DS patients and showed an obvious dynamic variation with patient age. The functional annotation indicated that the dysregulated genes and pathways are closely related to the cell signaling, proliferation, migration and immune response, which disrupt the phenotypes of DS.

P215

DELETION MUTATIONS IN STEROID SULFATASE (STS) GENE UNDERLIE X-LINKED ICHTHYOSIS IN THREE LARGE PAKISTANI FAMILIES

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X-linked recessive ichthyosis (RXLI) is a rare genodermatosis characterized by the appearance of large, thick, tightly adherent, dark-brown scales on upper and lower extremities of affected individuals. In majority of patients with RXLI entire Steroid Sulfatase (STS) gene and flanking sequences have been found deleted. AIMS: To search for pathogenic mutations in STS gene in Pakistani population affected with RXLI. In the present investigation we have studied three large Pakistani families with 38 individuals affected with RXLI. DNA samples of all available affected and unaffected individuals were PCR amplified and then subjected to agarose gel electrophoresis and DNA sequencing. Agarose gel and DNA sequence analysis of PCR-amplified products have detected a complex double deletion in a family with 14 affected individuals. Affected individuals of the other two families showed deletion of the entire STS gene. To our knowledge, this is the first report of STS gene deletions from Pakistani population.

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GENETIC VARIATIONS IN TYPE 2 DIABETES MELLITUS AND SUSCEPTIBILITY TO NEPHROPATHY

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Diabetic nephropathy is the leading cause of end-stage renal disease worldwide. A genetic basis for development of kidney disease has been long-postulated. We investigate variations in HFE, SLC12A3, CCR5 and ELMO1 genes in type 2 diabetes mellitus (T2DM) with and without nephropathy. We examined 658 subjects; 181 subjects with established diabetic nephropathy (DN), 178 with longstanding T2DM but no kidney disease (DM), 102 with kidney disease not due to diabetes (KD) and 197 healthy control (HC) for variation in HFE (187C>G and 845G>A), SLC12A3 (+78 G>A), CCR5 (59029G>A) and ELMO1 (18+9170 A>G) genes. Polymorphism analysis was performed by PCR-RFLP and Taqman genotyping assays. The duration of diabetes was 9.3 ± 6.3 and 13.8 ± 7.0 years ($p<0.0001$) in DM and DN group respectively. Cholesterol, triglyceride, HbA1c values were significantly more in DN as compared to DM ($p=0.004$, 0.05, and 0.01). Neuropathy and retinopathy were also more frequent in DN ($p<0.0001$) group. The genotype frequencies of the various genes are given below: Genotype/DMn (%)/DNn (%)/KDn (%)/HCn (%), HFE 187C>G/CC/152 (85.4)/162 (89.5)a/89 (87.25)/162 (82.23)b, CG/26 (14.6)/19 (10.5)/13 (12.75)/13 (17.77), GG/0 (0)/0 (0)/0 (0)/0 (0), SLC12A3 (+78

G>A)/GG 163 (91.57)/Y161 (88.95)/89 (87.25)/166 (84.26)Z, GA/14 (7.86)/17 (9.39)/12 (11.76)/28 (14.21), AA/1 (0.56)/3 (1.65)/1 (0.98)/3 (1.52), CCR5 (59029G>A)/GG/79 (44.38)/74 (40.88)e/41 (40.19)/96 (48.73)f, GA/74 (41.57)/76 (41.98)/52 (50.98)/81 (41.11), AA/25 (14.04)/31 (17.12)/9 (8.82)/20 (10.15), ELMO1 (18+9170 A>G)/AA/72 (40.2)/70 (38.9)/41 (40.2)/84 (42.6), AG/84 (46.9)/79 (43.9)/42 (41.2)/84 (42.6), GG/23 (12.9)/31 (17.2)/19 (18.6)/29 (14.8), P=0.04ab, p=0.04ef,p=0.03yz We did not find any difference in the frequencies of any of the SNPs between DM and DN groups. Differences were noted between groups with and without diabetes. SLC12A3 +78GG and CCR5 59029AA genotypes were significantly more frequent in diabetics (p=0.05, OR: 1.60, {95%CI: 1.04-2.85} and p=0.02, OR: 1.72, {95%CI: 0.97-2.63}, respectively). The other intergroup differences were as follows: HFE187C>G (p=0.04, OR: 1.84, 95% CI: 0.97-3.5), CCR5 59029G>A (p=0.04, OR: 1.83, 95% CI: 0.96-3.49) in DN compared to HC and SLC12A3 +78G>A between DM and HC (p=0.03, OR: 2.03, 95% CI: 1.01-4.11). We did not find any difference in the frequencies of the studied polymorphisms between individuals with T2DM with or without nephropathy. Several SNPs however, show altered frequencies in those with T2DM compared to those without diabetes.

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ASSOCIATION OF APOLIPOPROTEIN E POLYMORPHISM TO CLINICAL HETEROGENEITY OF MULTIPLE SCLEROSIS

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Apolipoprotein E (APO E) is an ubiquitary apolipoprotein involved in the metabolism of cholesterol, Recently, APO E allele distribution has been investigated in multiple sclerosis (MS), an autoimmune disease characterized by infammatory demyelinating lesions and by a clinical course variable from relapsing remitting (RR) to chronic progressive (CP). And an association between the course of MS and the APOE e4 allele was found. The aim of our study was to explore the relationship between APOE polymorphism and susceptibility to, and clinical phenotypes of, MS among Algerian Arab subjects. Eighty nine individuals (28 male, 61 female, mean age 37, 56±10.04 years) with sporadic MS and 250 healthy controls (100 male, 150 female, mean age 38, 45±9.32 years) were included in our study. The diagnosis of MS was made according to Mc Donald et al 2001. The MS patients had detailed clinical and laboratory evaluations and APOE genotypes were determined in all the subjects (patients and controls) by validated PCR methods. Control subjects were selected from the database of the Immunogenetic Unit DNA Bank of the Constantine University Hospital. At diagnosis the mean age was 37, 56 ± 10.04 years. The most common presenting symptoms were unilateral visual loss or blurring (18%), numbness and paraesthesia of legs, arms, face, and/or multiple sites (24.71%), diplopia (2.2%), and unsteadiness of gait and/or ataxia (10.11%). The disease course was classified as relapsing–remitting (78.8%), relapsing–progressive (12.5%). Homozygous E3 was the most frequent genotype (75.3%). One (1.1%) patient and 2 control subjects were homozygous for E4. There were no significant differences in allele frequencies between patients and controls, although there was a trend towards lower E2 frequency in the patients (p=0.08). Additionally, there was no difference in frequencies in E4 between patients and controls. Discussion: Recently, APO E polymorphism has been investigated in MS patients and an association emerged between the APO E4 allele and a more rapid progression of disability in MS. In the present study the APO E genotype frequency distribution in multiple sclerosis population analyzed was not significantly different from controls population. The relationship between APOE polymorphism and susceptibility to MS and its clinical phenotype is controversial.

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SOMATIC GENOME INSTABILITY IN THE ATAXIA-TELANGIECTASIA BRAIN: EVIDENCE FOR AGE-DEPENDENT INCREASE IN ANEUPLOIDY AND CHROMOSOME BREAKS IN DEGENERATING CEREBELLUM

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Genomic instability due to DNA-damage and -repair defects can be considered as unified genetic mechanism leading to variety of neurological disorders. However, the role of genome and chromosome instability in neurodegeneration and human brain aging is poorly understood. Here we monitored the integrity of interphase genome in neuronal cells of the brain in ataxia-telangiectasia (AT; OMIM #208900) - monogenic neurological as well chromosome instability disease characterized by progressive cerebellar degeneration and premature aging. Application of IMFISH and ICS-MCB techniques with extended set of DNA probes for different chromosomes (1, 7, 8, 9, 11, 14, 16, 17, 18, 21, X and Y) allowed us the identification an dramatic increase in aneuploidy and non-random breaks affecting chromosomes 7,14 and X in neural cells of the AT cerebellum (Iourov et al., 2009). Genome instability has more severely affects the cerebellum that the cerebrum, and, therefore, has mosaic expression in the AT brain. Moreover, an age-dependent increase in aneuploidy and chromosome breaks specifically involving chromosomes 7, 14 and X was observed in the AT cerebellum. Paradoxically, the increased longevity in AT patients was found to be in direct proportion to the percentage of chromosomally abnormal neural cells in the cerebellum. To solve this paradox we proposed two alternative hypotheses. (1) Overproduction of immature neural cells with unrealized chromosome breaks and aneuploidy takes place exclusively during early brain development. These chromosomally aberrant cells might be resistant to clearance throughout

ontogeny and, therefore, survive until the death of the AT patients. (2) An age-dependent increase in the percentage of chromosomally defective cells be could explained by abnormal developmental neurogenesis in the degenerating cerebellum during brain aging. Therefore, we should postulate that adult neurogenesis occurs in the diseased AT cerebellum. We speculate here that the longer the lifetime of AT individuals, the bigger amount of immature neuronal-like cells is accumulated in the degenerating cerebellum. Thus, the persistence and age-dependent accumulation of neural cells with chromosome breaks during ontogeny (even immature and chromosomally abnormal) could protect the diseased cerebellum against dramatic cell loss and, therefore, partially prevents the progression of neurodegeneration. These results indicate that somatically acquired chromosome damage may represent an important genetic phenomenon mediating cerebellar degeneration and accelerating brain aging. Supported by BMBF/DLR (RUS 09/006) and DFG (LI 820/18-1).

P219

GERMLINE MUTATION AND EPIMUTATION ANALYSIS OF HUMAN MISMATCH REPAIR GENES, MLH1 AND MSH2 IN MALAYSIAN LYNCH SYNDROME PATIENTS

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Colorectal cancer is the most common gastrointestinal cancer in Malaysia and hereditary non-polyposis colorectal cancer (HNPCC) also called as Lynch syndrome accounts for approximately 1-5% of all colorectal cancers. It is characterized by an autosomal dominant inheritance with multiple members affected in families, high gene penetrance (85-90%) and early onset of colorectal cancer and extracolonic cancer such as endometrial cancer. Dominantly inherited germline mutations in a group of DNA mismatch repair (MMR) genes mainly MLH1 and MSH2 are responsible for the majority of Lynch syndrome cases. Based on Revised Bethesda Guidelines, we identified 30 families in which multiple members are affected with colorectal and extracolonic cancers and also with an early age of disease onset. Our objectives were to analyze the protein expression profile of MMR protein, MLH1 and MSH2 using immunohistochemistry, to screen for germline mutations in MLH1 and MSH2 gene using dHPLC and also to explore the role of MLH1 germline epimutations in those patients who showed absent expression of MLH1 protein in the tumor but no germline mutations identified in the MLH1 gene. Paraffin tissue blocks were selected from colorectal cancer and adjacent non-neoplastic (normal) colon of resected colorectal specimens for immunohistochemical analysis of MMR protein expression. Peripheral blood from Lynch syndrome patients was collected and DNA was extracted using commercialized kit and all the 19 exons and 16 exons of MLH1 and MSH2 genes respectively, were PCR amplified using appropriate primers. Amplicons were screened for mutations by dHPLC and mutation was confirmed by DNA sequencing. Patients who showed no MLH1 expression in the tumor and no germline mutations identified in the MLH1 gene were screened for methylation of the MLH1 and EPM2AIP1 promoter by methylation-specific PCR and combined bisulfite-restriction analysis. Absent expression of MLH1 and MSH2 protein was observed in 3 and 4 respectively out of 30 Lynch syndrome patients. However, no germline mutation has been identified in MLH1 gene. However, MLH1 promoter polymorphism, -93G>A was identified as a frequent occurrence among these patients. But mutational analysis revealed the germline mutation in MSH2 gene (13.3%) and importantly a novel mutation, transversion mutation c.2005G>C which resulted in a missense mutation (Gly669Arg), transversion mutation in exon 1, c.142G>T which resulted in a nonsense mutation (Glu48Stop) and splice-site mutation, c.2006-6T>C which was adjacent to the exon 13 of MSH2 gene. To the best of our knowledge, this is the first study reporting on the DNA MMR genes mutation among Malaysian Lynch syndrome patients. The study is being continued to investigate the frequency and pattern of other DNA MMR gene mutations in Malaysian Lynch syndrome patients and to establish a MMR gene mutation database of Malaysian Lynch syndrome kindreds.

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ASSOCIATION ANALYSIS OF AGT (M235T) GENE POLYMORPHISM WITH DIABETES, DIABETIC NEPHROPATHY AND NEPHROPATHY IN PAKISTANI POPULATION

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AGT(M235T) polymorphism is well studied polymorphism of RAAS (Renin Angiotensin Aldosterone) pathway in relation to diabetes and hypertension. Objectives: To investigate the possible involvement of AGT (M235T) polymorphism with hypertension, diabetes, and Stroke in Pakistani as well as in DIABHYCAR (DIAbetes, HYpertension, Cardiovascular events AND Ramipril) group of French population. We determined the AGT (M235T) polymorphism using a Taqman analysis. For this purpose, total 3115 patients of DIABHYCAR and 195 total subjects of Pakistani population in four groups DN (60), Control (45), Diabetics (50) and nephropathy group (40) was analyzed. Results are presented as means+/-SD. Groups were compared using the chi-2 and for continuous variables using parametric (Student‘s t test, ANOVA) for the AGT polymorphism. AGT (M235T) polymorphism is not associated with diabetes and diabetic nephropathy in Pakistani population with P value 0.46 and 0.40. Similarly they also do not give any association with blood pressure in any of the four groups mentioned above. In our French cohort of 3115 subjects AGT (M235T), we found

significant association with the systolic and diastolic Blood pressure in males with P value 0.01 and 0.04 respectively while in females we do not find any association with P value 0.94 and 0.57. In French Cohort we also found the significant association with Stroke in males with P value 0.03. These results support the hypothesis that AGT gene plays a role in predisposition to hypertension and stroke as in French population. For Pakistani subjects we do not find any association with diabetes and hypertension.

GENOME DATABASES

P221
ENSEMBL GENOME BROWSER

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The Ensembl project (http://www.ensembl.org) provides an infrastructure that integrates high quality annotation on chordate and selected eukaryotic genomes. Genomic assemblies display comprehensive, evidence-based annotation (including the GENCODE human gene set) with a wealth of additional data, such as sequence variations and whole genome alignments, available for human, mouse, and other species including those used in biomedical research. The Ensembl genome browser integrates data from numerous ancillary databases: polymorphisms and other sequence variation from dbSNP, somatic variation from COSMIC, protein domains from Pfam and InterPro, protein annotation from UniProt, etc. Ensembl delivers whole genome alignments: pairwise alignments and comparisons across multiple species (including 6 primates, 34 eutherian mammals, and 5 teleost fish). Homologies are determined through construction of phylogenetic gene trees, and a first glimpse of where gene-regulatory features may be on a genome wide scale is found in Ensembl's regulatory build, an analysis and integration of ENCODE data (amongst other datasets). Alongside the human genome, nearly 60 other genomes are supported with gene sets and whole genome alignments, along with identification of gene orthology and protein families. Ensembl data are accessible through an interactive web site (www.ensembl.org), and ftp site providing flat files, direct database querying through MySQL, a set of Perl APIs and BioMart, a powerful data-mining tool used by programmers and non-programmers alike. Moreover, Ensembl has introduced widely useful tools such as Variant Effect Predictor to annotate functional consequences and show matching dbSNP IDs of user-inputted SNPs and indels. An assembly conversion tool is also included, to support users who need to convert coordinates to the most up-to-date genome. Feedback from user surveys, our helpdesk, and worldwide courses keeps us up to date with the data and tools Ensembl users require.

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TWO GENOMIC REPOSITORIES AT THE EBI: EGA & DGVa

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The European Bioinformatics Institute (EMBL-EBI) hosts several genomic databases and provides solutions for the permanent archiving and distribution of data resulting from biomedical research projects. The European Genome-phenome Archive (EGA; http://www.ebi.ac.uk/ega) focuses on personally identifiable genetic and phenotypic data (genotypes, structural variants and whole-genome sequences). The EGA contains exclusive datasets collected from individuals with accompanying consent agreements that authorize a controlled data release for specific research use or to bona fide researchers. The EGA project is governed by strict protocols to ensure that data is managed, stored and distributed in a secure manner that respects the consent agreements. For all data archived in the EGA system, the data access decisions remain with the data producing organization. Researchers authorized by the appropriate data access-granting organization may access over 18Tb of data from 75000 samples. The Database of Genomic Variants archive (DGVa; http://www.ebi.ac.uk/dgva) is a public repository for archiving, accessioning and distribution of public structural variations at the individual level. It accepts submissions, accessions the variants at the sample and study level and grants a stable identifier that can be used for publication. The data archived in the DGVa will be integrated to other resources at the EBI such as the Ensembl genome browser. DGVa is the peer archive of dbVar an the NCBI and has implemented the same accessioning model. DGVa also collaborates extensively with the Database of Genomic Variants (DGV), which is based at the University of Toronto. Currently data covering nine different species are represented in DGVa.

P223
DEVELOPMENT OF BIOINFO-PORTAL TOOL FOR THE ANALYSIS OF GENOMIC AND PROTEOMIC DATA

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The recent explosion of biological data and the concomitant proliferation of distributed databases make it challenging for biologists and bioinformaticians to discover the best data resources for their needs, and the most efficient way to access and use them. For the biologist, running bioinformatics analyses involve a time-consuming management of data and

tools. Users need support to organize their work, retrieve parameters and reproduce their analyses. They also need to be able to combine their analytic tools using a safe data flow software mechanism. Finally we have designed a system, Bioinfo-Portal, to provide a flexible and usable web environment for defining and running bioinformatics analyses. It embeds simple yet powerful data management features that allow the user to reproduce analyses and to combine tools using an adobe flex tool. Bioinfo-Portal can also act as a front end to provide a unified view of already-existing collections of bioinformatics resources. Users can analyze genomic and proteomic data by using the tools that has been integrated in the portal (tools for alignments, dotplots, motif detection, domain analysis, profile searching and tertiary structure prediction). The sequences that user obtained from portal‘s nucleotide and protein databases easily analyzed by the portal tools on the same interface in no time. User can also take benefit from the animations.

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DATA BASE FOR GENETIC DISORDERS (GENE ASSIST)

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Registry is a system for collection, storage, registration, record-keeping, and referral of genetic data, materials, or resources, including patient and disease data, DNA bank for the preservation of genetic stocks and strains. It includes genetic disorder clinical registry, DNA bank, genetic resource, repository and biomedical registry. Aims of the project: 1. Establishment of database for genetic disorders. 2. Establishment of centralized collection of data and biological samples to provide the essential raw material for both current and future research projects. 3. Data base registry encoding the information of more than twenty seven thousands files of genetic disorders referred to the genetic clinic recorded over twenty five years and to be continued for the new patients. These data are recorded using special computer program (Gene Assist) constructed by Dr. Khaled Helmy. 4. To develop DNA repository for genetic diseased patients (DNA bank for genetic disorders). 5. Develops and provides educational materials and newsletters for patients, families and health professionals. Results and discussion: 1. The use of the Egyptian program for data base entry (Gene Assist). This system proved to be efficient for genetic disorders data base and modified to be easy in data entry. 2. Registration of 5734 files was accomplished through last two years. 3. The collection of DNA samples after consent of the patients, approved from the Medical Ethical Committee- National Research Centre. 4. Initiation of DNA bio-bank. 5. Recording final accurate diagnosis for most of the patients. 6. Establishment of intranet between the different departments and the clinic of human genetics through ten computer units and server. 7. Starting some diagnostic programs including the entered data. 8. The development of the searchable screens, e.g. search screen on pedigree and different clinical manifestations. 9. The development of diagnostic expert system for some common genetic disorders, e.g. we started with craniosynestosis and disorders of sex development. The achievements of the project are: The choice a good efficient Egyptian system for data entry for genetic disorders (Gene Assist), an intranet connection between the Human Genetics Departments, all the requirements for establishment of DNA bio-bank and the use of interred data for putting diagnostic and teaching programs.

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DOMAIN ARCHITECTURE COMPARISON AS A TOOL FOR THE IDENTIFICATION AND CORRECTION OF MISPREDICTED PROTEIN-CODING GENES

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Recent analyses have shown that the exact genomic structure of protein-coding genes of higher eukaryotes is correctly predicted for only about 60 % of the genes. In our previous work we have developed the MisPred protocol that used five distinct routines for identifying mispredicted entries based on the principle that a protein/gene sequence is likely to be incorrect if some of its features conflict with our current knowledge about protein-coding genes and proteins. Here we present a new routine of the MisPred approach, the Domain Architecture Deviation routine. The rationale of this approach is that since genomic rearrangements leading to domain architecture (DA) change of orthologous proteins are rare evolutionary events deviation of DA of closely related orthologs may be more likely to be due to errors in gene prediction than to genomic rearrangement. To estimate the contribution of errors in gene prediction to differences in DA of predicted proteins we have used the high quality manually curated UniProtKB/Swiss-Prot database as a reference. Comparison of the DA of UniProtKB/Swiss-Prot sequences of worm, fly, zebra fish, frog, chick, mouse, rat and orangutan with those of human Swiss-Prot entries have identified few cases where orthologs had different DA, although the percentage with different DA increased with evolutionary distance. In contrast with this, comparison of the DA of human, orangutan, rat, mouse, chicken, frog, zebra fish, worm and fly RefSeq, EnsEMBL or NCBI's GNOMON predicted protein sequences with those of the corresponding/orthologous human Swiss-Prot entries identified a significantly higher proportion of DA differences than in the case of the comparison of Swiss-Prot entries. Analysis of representative samples of orthologous RefSeq, EnsEMBL or NCBI's GNOMON predicted sequences with DAs different from those of their Swiss-Prot orthologs confirmed that the higher rate of DA differences is due to errors in gene prediction. Our studies confirmed that DA comparison is a valuable component of the MisPred protocol in as much as it helps the identification of mispredicted sequences and it is also a useful component of our FixPred protocol that corrects mispredicted sequences.

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FORMATION OF EUROPEAN GENETIC VARIATION - COMPLEX SIGNALS FROM NEOLITHIC-ASSOCIATED MITOCHONDRIAL LINEAGES

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Although our current knowledge about the beginning of the presence of modern humans in Europe can be marked by their initial arrival some 45-50 kya from the Middle East, little is known about potential demographic movements that have shaped their genetic variation throughout archaeological cultures such as Aurignacian, Gravettian, Solutrean etc. The role of climatic changes such as Last Glacial Maximum (LGM) and its gradual retreat, Younger Dryas and finally the Holocene –climatic optimum", are understood only in very general terms of gene flows from the Near/Middle East and, possibly, from Central Asia, to Europe. Recent progress in the analysis of ancient DNA, in particular from the early Central European Neolithic period-the so-called Linear Pottery Culture around 7500 ybp-allowed to identify mtDNA haplogroup N1a as a likely marker for the incoming Near East farmers, potentially alongside with some other mtDNA variants (Haak et al. 2005, 2010). Yet so far the understanding of the phylogeography of haplogroup N1a has remained vague. Therefore, we have analyzed a sample base of 32000 mtDNAs for the presence of N1a lineages, where we identified 187 samples. Out of them, we sequenced completely 41 mtDNA genomes. Together with 18 N1a sequences present in public databases, we constructed full-genome tree of 59 genomes, representing their variation in Northwest and East Africa, Arabia, the Near East, East and West Europe, as well as India and Central Asia. The topology of the obtained phylogenetic tree and coalescence calculations of individual subclades, carried out using different molecular clock rate estimates, reveal that the N1a genomic variants sampled in Europeans belong actually to four different subclades of this ancient, pre-LGM branch of marco-haplogroup N that has split into individual subgroups often long before the Holocene and the spread of agriculture to Europe, while the only exclusively Near Eastern-African subcluster coalesces even before the LGM. On the other hand, coalescence times (in fact, signals from the beginning of expansions) of some of the European or largely European-specific subclades of N1a suggest time windows, broadly corresponding to the spread of agriculture in Europe. Yet the problematic aspect of the finding is that we could not reveal any obvious nested cladistic structure that could be convincingly interpreted as an expansion from the Near East. Furthermore, a subclade that brings together East European and further eastwards N1a genomes seems to offer an expansion signal corresponding rather to the earlier, pre-Holocene postglacial phase than to the mid-Holocene neolithization. Taken together, full-genome analysis of human mtDNA haplogroup N1a, frequent among the early mid-European Neolithic farmers, carriers of the Linear Pottery Culture, reveals a much more complex scenario of its ancient spread over a wide geographic span than expected from a simple neolithization models. We will consider the results in a broader scale picture of the history of genetic structuring of the area under discussion.

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RESOURCES FOR PROTEOMICS IN EMBRYONIC STEM CELLS

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Remarkable progress in human genetics has identified mutations in numerous genes that are linked with disease. However, the limitation of these discoveries is that genetics only identifies individual genes without placing them into pathways. To achieve this, it is essential to identify the physical relationships of these genes to other genes by proteomic mapping under physiological conditions. Towards this end, we have developed an in situ protein tagging strategy based on recombinase mediated cassette exchange (RMCE) in mouse embryonic stem cells (mESCs) harboring gene trap induced multipurpose alleles of individual genes. Several ESC lines with suitable gene trap insertions in disease genes were recovered from the existing gene trap resources (GGTC and EUCOMM) and subjected to RMCE using an incoming hygromycin-P2A-LAP tag cassette defined as a portable exon by upstream splice acceptor (SA) and downstream splice donor (SD) sites. Since the portable exon is flanked by heterotypic Frt/F3 recombinase target sites (RTs) that are identical to the RTs inserted into the gene trap loci, the incoming construct can effectively recombine with these loci in presence of FLPo recombinase. Accordingly, selection for exchange cassette insertions in hygromycin yielded correctly recombined ESC clones with an efficiency of seventy percent. In these clones, the portable exon was correctly spliced to the endogenous exons of the trapped gene, thereby leading to the expression of LAP tagged versions of the wild type proteins. Subcellular localization the LAP-tagged proteins closely mirrored the localization of the corresponding wild type proteins. Mass spectrometric analysis of immunoprecipitates identified several known and unknown interaction partners in each case. Despite extensive manipulation, the ESC retained their pluripotency as shown by the generation of a mouse line by microinjection into blastocysts. Overall, the experiments confirm the suitability of the in situ protein tagging methodology for high throughput proteomic mapping of proteins expressed in trapped ESC lines.

GENOME SEQUENCING

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CYTOGENETIC AND MOLECULAR GENETIC CHARACTERISATION OF THE B-CELL PRECURSOR ACUTE LYMPHOBLASTIC LEUKAEMIA CELL LINE MHH-CALL-2

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Paediatric B-cell precursor acute lymphoblast leukaemia is a common haematological malignancy accounting for approximately one third of all childhood malignancies. This disorder may be further subcategorised and the prognosis may differ depending on the genetic subgroup. Therefore correct genetic classification is vital for patient treatment and survival. High hyperdiploidy (51-67 chromosomes) occurs in 25-30% of patients and is associated with a superior prognosis. With cell lines being difficult to maintain, in vitro studies are rare. MHH-CALL-2 is the only established high hyperdiploid cell line, and we herein perform an in-depth study of its cytogenetic and molecular genetic features. Herein we reveal that the MHH-CALL-2 cell line in fact originated as a near-haploid (23-29 chromosomes) leukaemia which is masked by a doubling of the whole chromosome content, giving it a typical high hyperdiploid DNA index of 1.14 with a 51,XX,+X,+18,+der(18)t(15;18)(q13.1;q22.1),+21,+21 karyotype. It did not harbour mutations in any of the oncogenes NRAS, KRAS, PTPN11 and FLT3, nor were any of the well-known translocations t(12;21), t(9;22), t(1;19) or 11q23 involved. However, the novel translocation t(15;18)(q13.1;q22.1) was identified. Patients with near-haploidy generally have a poor prognosis and correct identification of near-haploid cases masquerading as high hyperdiploid is therefore important. As the abnormalities harboured by the MHH-CALL-2 cell line are well described herein, it is expected to be useful for future studies.

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SURESELECT(XT) FOR TARGETED VARIATION DISCOVERY AND VALIDATION: SINGLE WORKFLOW, MULTIPLE APPLICATIONS

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Deep sequencing of targeted regions of the genome has revolutionized the discovery of rare variants associated with disease. To provide a single robust, versatile workflow for targeted genomic analysis by second-generation sequencing, we developed the SureSelectXT system that combines DNA isolation, sequencing library preparation, target enrichment, and sample indexing/barcoding. Enriched libraries are ready for direct sequencing on Illumina or SOLiD platforms, and compatibility is also shown with the 454 platform. The target enrichment component is accomplished by the hybrid capture method (Gnirke, et al.) using long high-quality biotinylated RNA probes that are complementary to user-defined regions of the genome. We show performance data on a growing number of pre-defined catalog probe sets, including comprehensive All-Exon designs for human and mouse, the Kinome, and new novel content. Custom and catalog designs, ranging from 0.2 to 50+ Mb, show high performance as measured by specificity of capture, coverage depth, uniformity of coverage, and duplicate read counts. We also demonstrate the effectiveness of spiking novel content into catalog designs to create a customizable All-Exon or Kinome 'Plus' definition. In addition to DNA applications, we illustrate the use of SureSelect with RNA-Seq to identify novel transcript variants within defined regions of interest. For optimal use of sequencing capacity, we introduce enhanced methods for indexing/barcoding samples for multiplexed sequencing in a single analysis lane. Using this integrated SureSelectXT system, we accurately detect SNPs and indels of varying sizes while maintaining allelic balance. Based on our results, we propose a novel approach for variant discovery: using SureSelect catalog designs for variant discovery, followed by the design of smaller focused custom libraries for SNP validation and region profiling. To accommodate studies with large sample cohorts, we illustrate the performance of SureSelectXT on the Automated Bravo Liquid Handling Platform. Significant time savings and process efficiencies are realized while maintaining the high performance characteristics of the manual protocol. Altogether, our data demonstrate a highly robust, accurate, and flexible SNP discovery/validation pipeline for efficient, cost-effective analysis of genomic variation.

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RELATIONSHIP BETWEEN ENDOTHELIAL NITRIC OXIDE SYNTHASE GENE POLYMORPHISMS AND THE RISK OF MYOCARDIAL INFARCTION IN THE ALGERIAN POPULATION

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Endothelial nitric oxide synthase (eNOS), the enzyme in charge of nitric oxide production, plays a crucial role in vascular biology. However, the impact of single nucleotide polymorphisms (SNPs) affecting the gene encoding for eNOS (eNOS) on coronary artery diseases remains under debate and no data were available at present in populations originating from Maghreb. Our purpose was to evaluate the association between the eNOS -786T/C and +894G/T SNPs and (i) the risk of myocardial infarction (MI) and (ii) variations in systolic

(SBP) and diastolic (DBP) blood pressure values. Concerning MI, the SNPs were characterized in a case control study (70 cases vs 68 controls) based on the male population originating from Oran, Algeria. The associations with blood pressure values were assessed in an enlarged control group including 115 male subjects. Since the -786T/C SNP could not be associated to MI, the genotype distribution of the +894G/T genotypes significantly differed between MI cases and controls (p=0.025). The risk of MI (odds ratio) associated to the +894G/T SNP was estimated to 1.2 (95%CI=[1.03;1.32]). The haplotype analysis confirmed this association and the absence of impact of the -786T/C SNP. On the other hand, no consistent association was shown between the two SNPs and SBP or DBP. As observed in other populations, the eNOS +894G/T SNP was associated with MI in the Algerian population but the mechanism underlying the effect could not be related to variations in blood pressure.

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RE-SEQUENCING OF HUMAN SAMPLES: COMPARING AND COMBINING DIFFERENT LIBRARIES, SEQUENCING TECHNOLOGIES AND SOFTWARE TOOLS

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Strategies for sequencing human genomes and transcriptomes need to be designed based on the goals of the project, e.g.to study effects on the DNA and amino acid sequence or on gene regulation and expression. A variety of experimental outlines for a complete analysis by an integrated approach with different libraries and sequencing technologies will be shown. Libraries: Starting with genomic DNA, libraries with small (300 bp) and large (up to 8 kb) inserts to identify SNPs and rearrangements can be prepared. Depending size of the target region and number of samples, different enrichment technologies can also be applied to sequence a specific subset of eukaryotic (including human) or bacterial genomes. Smaller regions can be amplified using classical PCR approaches. Standard enrichment kits for exons can be customized to target all exons, including additional specific regions of interest. Using GATC‘s proprietary tagging protocol it is possible to multiplex samples for sequencing. Transcribing RNA into cDNA is another procedure for transcriptome analysis. For a quantitative analysis, UTR libraries are used to generate expression profiles. Regulatory studies can be performed with ChIP-, MeDip- and small RNA libraries. Sequencing technologies: The Illumina HiSeq 2000 provides the industry's highest sequencing output, quality and fastest data generation rate. This can be optimally used in combination with different paired end and mate pair libraries as well as enrichment strategies, especially for multiple samples. GATC‘s tagging system allows barcoding of samples and multiplexing of any number of samples. For regulatory studies, the shorter reads of the HiSeq 2000 fit perfectly. Amplicons can either be sequenced on the Roche GS FLX machine or with the classical Sanger technology to obtain longer reads (in average 400 bp for the GS FLX and up to 1,000 bp for Sanger). With the new Pacific Biosciences PacBio RS real time single molecule sequencer, long reads in the range of Sanger sequencing and so-called strobe reads (multiple sub-reads spaced across a long single molecule) can reveal multiple types of genetic variation, such as large-scale rearrangements, as observed in cancer. In addition, direct sequencing of methylated and other modified bases will be possible. Proprietary bioinformatic analyses: GATC offers a wide range of bioinformatic solutions for genome assembly, transcriptome analysis and other studies. Proprietary tools are used for the analysis and handling of Next Gen sequencing data, while third party tools are available for optimized de novo assembly or improved hybrid assemblies. The combination of different tools and stepwise approach enables to get all information out of the data. High quality results will be obtained by optimally combining several library preparation methods and the newest Next Gen technologies with state-of-the-art bioinformatics. Thus, the deepest analysis of data and as a consequence, the most robust analysis of the sequence you are working on, will be achieved.

GENOME VARIATION AND PERSONALISED MEDICINE

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ASSOCIATION OF IL-4 -590 T/C AND IL-4 RECEPTOR Q551R GENE POLYMORPHISMS IN PATIENTS WITH ACNE VULGARIS

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Acne vulgaris is a common skin disorder. The complete etiology of this disease remains to be identified but it seems that aberrant expression of cytokine genes might be one of its inducing factors. The association between genetic polymorphisms related to interleukin 4 promoter (IL-4 -590 T/C) and its receptor (IL-4R Q551R, A/G) genes in patients with *acne valgaris* was investigated in the present study. This study involves 95 acne patients recruited from the Outpatient Dermatology Clinics of Qassim University, Saudi Arabia, and their results were compared with 87 normal healthy volunteers of same age and gender matched from the same locality. Genomic DNA was extracted from peripheral blood using the Magna pure DNA system. Single nucleotide polymorphisms (SNPs) related to IL-4 590 T/C and IL-4R Q551R (A/G) genes were determined by real-time PCR. A significant difference was observed between the frequencies of polymorphisms related to IL4-R gene and IL-4R polymorphic genotypes (p=0.0). Furthermore, acne cases showed higher frequencies of the combined genotypes IL-4_CC, CT or TT with the IL-4R_GG genotype. However, cases subgroups related to severity of disease or response to treatment showed no

significant difference in the frequencies of all studied IL-4 and IL-4R genotypes (p>0.05). In conclusion, present study provides an evidence for a significant association of IL-4 receptor Q551R (A/G) with IL-4 -590 T/C genetic polymorphisms in *acne vulgaris* with the susceptibility rather than the severity of disease among Saudi affected subjects.

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MENDELIAN VS. MULTIFACTORIAL: RE-CONCILIATION NOT IMPOSSIBLE

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Our understanding of the relationship between genes and diseases has evolved significantly from a point where single gene-single disease approach dominated the field to the current appreciation of the complexity that underlies the genetics of all human diseases including so called ―Mendelian diseases". It is well established now that there is no such thing as ―single gene disease" because of the effect of many modifiers (genetic and environmental) on the final phenotype. However, it remains conventional to refer to disorders in which a mutation of a single gene is usually sufficient to cause the phenotype as Mendelian disorders. The recent decade has witnessed an explosive phase in the history of mapping Mendelian genes with more than 1,000 of the estimated 4,000 or so Mendelian disorders have been solved at the gene level. While much novel biology has been learned in the course of studying these genes, a significant gap remains in our knowledge of how these genes relate to the more common diseases that are of interest to the wider medical community. In order to address this gap, our lab has been pursuing three lines of investigations: 1- Extrapolating data from syndromic forms of common phenotypes to their non-syndromic counterpart. We show exciting examples of the genes we identified in patients with rare syndromic forms of cleft palate and retinal vascular disease and how variants (common and rare) in these genes can predispose to non-syndromic cleft palate and diabetic retinopathy, respectively. 2- Similarly, we have launched the Carrier Phenome Project in which we carefully phenotype carriers of Mendelian mutations we identified in the lab to see if they are more likely than the general population to develop some related phenotypes. We believe this is an exciting window to look into the contribution of rare variants to common diseases. 3- Most excitingly, we have been actively pursuing Mendelian diseases that faithfully phenocpy common phenotypes. We share the exciting identification in our lab of two genes that underlie very rare Mendelian forms of keratoconus and type I diabetes mellitus, and their contribution to these very common phenotypes. In sum, we believe the above and other approaches that bridge the gap between Mendelian and multifactorial domains of human genetics are critically needed as the field moves fast to the adoption of personal genomics where solving each piece of the human genome puzzle counts.

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DNA BASED BIOMARKERS TO PREDICT RESPONSE TO CHEMOTHERAPY IN GASTRIC CANCER

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Gastrointestinal cancers remain a significant cause of morbidity and mortality. While increasing therapeutic options have improved outcomes for many patients, they have also complicated treatment decision-making. Hence, there is an immediate need for prognostic and predictive markers that could improve treatment significantly by identifying patients who may or may not require a given therapy, and determining those most likely to benefit from a therapy. Treatment regimen based on 5-FluoroUracil (5-FU), cisplatin and taxanes are the most widely used chemotherapeutic drugs for Gastric cancers. However, not all patients respond to treatment with these drugs. Genetic Polymorphisms have been attributed to the inter-individual differences in drug effect. These polymorphisms include mutations; variation in the number of tandem repeats and single nucleotide polymorphisms. The genes affected by these polymorphisms alter the pharmacokinetics of the chemotherapeutic drugs. This review aims at surveying 8 such genes that affect the response of the patient to the drugs mentioned above. It also includes a note on methods to identify the best candidates for such analysis. The genes attributed to inter-individuals differences in outcome are thymidylate synthase and dihydropyrimidine dehydrogenase (DPD) for 5-Fluorouracil; ERCC1, ERCC2, Xeroderma Pigmentosum D, glutathione S transferase P1 for cisplatin and cytochrome P450 genes for taxanes. Polymorphism analysis in these genes would predict the response of a patient to the chemotherapeutic drugs. It can be further extended into categorizing patients into positive and negative drug response categories. In a clinical setting, the outcome of patients undergoing different drug regimens can be predicted using the patient‘s DNA sample, enabling physicians in drug-decision making.

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PSYCHOLOGICAL IMPACT OF GENETIC TESTING FOR CANCER PREDISPOSITION IN A SPANISH MULTICENTRE COHORT VISITING GENETIC COUNSELING UNITS (IMASS COLLABORATIVE GROUP)

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For the last 15 years, genetic testing for cancer predisposition has been available. Technological advances and personalized medicine are moving towards allowing genetic testing to

general population for common genetic changes in order to identify individuals at risk. This genetic information is about possibilities and not certainties as many of the new genetic tests available. Thus, genetic testing raises complex distress issues and psychological impact of these genetic studies is an under-researched area in many populations. Here we present data regarding the psychological impact on Spanish individuals who fulfilled criteria for BRCA1/2 genetic testing who participated in a prospective, longitudinal and multi-centre questionnaire-based study. Demographic and clinical information were collected and anxious and depressive symptoms (HADS scale) were completed at 3 different stages: 1) before genetic testing, 2) three months after the disclosure of the genetic result and 3) one year later. The absence of other validated instruments to evaluate the psychological impact of genetic studies in Spanish language makes this scale the most appropriate for our purpose. A total of 365 individuals visiting any of the four genetic counseling units participating in the study were enrolled. Median age of the individuals was 43 (18-88) and 313 (86%) were females. There were 155 healthy individuals (42%) and 210 cancer patients (58%). Regarding the genetic test result, 114 (39%) were BRCA1/2 mutation carriers, 65 (22%) were non-mutation carriers (negative result) and 113 (39%), were non-informative. The level of studies of 159 individuals (44%) was under university, while 206 (56%) had a high education level (university). Univariate analyses have been performed based on the result of the genetic study to analyze if the three different type of results affect the short term (three months) and/or medium term (one year) anxiety and depression level. We have observed a statistically significant decrease in the anxiety level (p=0.01) of individuals with a negative result 3 months after receiving the genetic result, which return to basal level after one year. In addition, no differences are present in the median values of the HADS scale for anxiety and depression level in the other two groups (positive and non-informative individuals), neither at the short term or medium term stages. Although multivariate analyses taking into account other predictive factors and a long term study are needed, our data support that there are non-adverse effects for the psychological well-being of individuals tested for BRCA1/2. Towards the next personalized medicine era, genetic testing offered in the context of genetic counseling units it appears not to be counterproductive for the anxiety and depression symptoms.

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THE GENETICS OF BRAHMIN'S 'GOTRA' SYSTEM IN SOUTH ASIA

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The tribal and caste populations of Indian subcontinent practice a high level of endogamy which is also apparent in their genetic studies. The gotra (where all the individuals belonging to a group claim their paternal ancestry to a single sage) system is the major element considered among Brahmins. Various ritual practices performed by them are related to their gotra. The marriage pattern is also restricted among certain gotras. Apart from that the origin of Brahmin populations has been a source of major controversy until recently. To address such issues, we analyzed the mitochondrial DNA of 484 Brahmin individuals belonging to two major Brahmin groups of North India. The interpopulation comparison revealed a local South Asian maternal origin of Brahmin populations. The haplotype sharing among different gotras was in complete concordant with their marriage pattern. Moreover, the study of 650,000 SNPs among Brahmins and non-Brahmins communities suggests common ancient founders. Thus, the prehistoric practice of such marriage pattern explicitly gathered similar maternal genome among certain gotras.

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SEQUENCE VARIATIONS OF THE METHYLENE TETRAHYDROFOLATE REDUCTASE GENE (C677T AND A1298C) AND TRADITIONAL RISK FACTORS IN THE ETIOLOGY OF CORONARY THROMBOSIS IN SOUTH INDIAN POPULATION

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Methylene tetrahydrofolate reductase (MTHFR) plays a significant role in methionine metabolism. MTHFR deficiency is inherited as an autosomal recessive trait. In South India, with lower dietary intake of folate, MTHFR deficiency could be a significant risk factor for a number of defects, e.g. vascular events. Polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) was employed to study the two common MTHFR polymorphisms namely 677 C>T and 1298 A>C. We have investigated the incidence of the C677T and A1298C methylene tetrahydrofolate reductase (MTHFR) gene single nucleotide polymorphisms (SNPs) in the South Indian population with a total number of 319 individuals. Among the 152 MI cases and 167 controls, we found that the MTHFR 677TT genotype is absent in the control group, the MTHFR 677CT genotype among 35(22.4%) cases and 08(4.8%) controls, and the MTHFR 677CC allele among 115(73.7%) cases and159(94.6%) controls .Analysis was also done for the MTHFR1298A→C SNP. The results identified the MTHFR 1298CC genotype in 16(10.3%) cases and 01(0.6%) controls, the MTHFR 1298AC genotype in 56(35.9%) cases and 27(16.2%) controls, and the MTHFR 1298AA genotype present in 80(51.3%) cases and 139(82.6%) controls. The CC vs. AA genotype showed statistical significance in patients compared to controls ($\chi 2$=21.59, Odds ratio 27.8, p <0.00001). The CC vs. AA+AC genotype showed statistical significance in patients compared to controls ($\chi 2$=15.5, Odds ratio 19.53, p <0.001).The C vs. A allele also showed significantly higher frequency in patients in comparison with controls

($\chi 2$=43.57and Odds ratio 4.2, p< 0.0001). The results of this study indicate that the MTHFR A1298C SNP is more prevalent among the south Indians when compared to the MTHFR C677T SNP, suggesting a possible role of MTHFR A1298C in the pathogenesis of heart diseases.

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POLYMORPHISM OF THE THIOPURINE S-METHYLTRANSFERASE (TPMT) GENE AMONG LIBYAN POPULATION

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Thiopurine S-methyltransferase (TPMT) is a cytosolic enzyme that catalyzes the S-methylation of 6-mercaptopurine and azathioprine. Low activity phenotypes are correlated with polymorphism in the TPMT gene. Patients with low or undetectable TMPT activity could develop severe myelosuppression when they are treated with standard doses of thiopurine drugs. Since ethnic differences in the TPMT gene polymorphism have been demonstrated worldwide, its assessment in the Libyan population is worthwhile. Here, to investigate the TPMT gene polymorphism, a total of 296 Libyan (246 healthy adult blood donors and 50 children with acute lymphoblastic leukemia), from 3 different Libyan regions (Tripoli, Yifran, and Tawarga), using polymerase chain reaction (PCR)-RFLP and allele-specific PCR-based assays were analyzed for the TPMT gene, *2 (G238C), *3A (G460A and A719G), *3B (G460A) and *3C (A719G) variants. Our results shows that the TPMT variants associated with low enzymatic activity, were detected in 2.7% (8 in 296) of Libyan individuals and the frequency of total mutant alleles was 1.35 %, that who had a heterozygous genotype (TPMT*3A in three subjects 0.51%; TPMT*3C in five subjects 0.84%). No TPMT*2 and TPMT*3B allelic variants, and no homozygous or compound heterozygous mutant alleles were detected. The normal allele (wild-type) was found in 98.65% of studied individuals. In conclusion, here, we reported the presence of the TPMT*3C and *3A mutant alleles in the Libyan population.

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EVOLUTIONARY GENETICS OF HUMAN DRUG METABOLIZING GENE: CASE OF NAT2

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Evolutionary analysis of drug metabolizing gene helps in understanding the pattern of drug metabolism and adverse drug reactions. The genetic basis of drug metabolism lies on the fact that not all individuals can equally respond to a particular drug. The differences in inter-individual variation to drug response are much greater than variation within individual. The primary reason behind the inter-individual variation is polymorphism in drug metabolizing gene that modifies the activity of enzyme involves in drug metabolism. Drug metabolism is an important mechanism of transformation of lipophillic form of drugs to hydrophilic form to enhance their elimination. On the other hand, when drugs are not eliminated from the body it accumulates inside the cells causing bioconcentration of drugs at higher level. That results in increased toxicity, adverse drug reactions, and susceptibility to various diseases. Thus, understanding the human variation that leads to alteration in drug metabolizing enzyme activity is beneficial for human for the development of _Personalized medicine‘. The development of a personalized medicine, where the genotype of an individual is determined in order to adapt the therapeutical scheme to avoid therapeutic failure and adverse drug reactions. In addition to the drug metabolizing gene the genetic diversity of some putatively neutral DNA fragments are important to study the demographic history and population structure of Indian population. The genetic diversity in a population are the product of many layers of demographic and evolutionary events acting on timescales including colonization, migration, population expansion, mutation , genetic drift and selection. The complex of diversity of India has resulted due to the influence of westernization which in turn results in increased prevalence of genetic diseases associated with life style and diets. Modern humans were evolved in Africa around 200kya and migrated to Eurasia (40-80 kya) and Americas (15-30 kya). The migration of modern humans out of Africa is still a question. India acts as a corridor for the dispersal of modern humans out of Africa. For this study we have taken 8 putatively neutral DNA fragments from X chromosome to establish the neutrality standard. DNA sequence data from non-coding regions reflect human history more accurately than coding region. The genetic diversity of India on the basis of these eight loci is compared with worldwide data. Various other population genetics parameter will be discussed.

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CYP3A GENOTYPES IN BANGLADESHI TUBERCULOSIS PATIENTS

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Variation in the CYP3A enzymes, which act in drug metabolism, influences circulating steroid levels and responses to half of all drugs metabolized by oxidation. Cytochrome P4503A is involved in metabolizing of more than 60% of all drugs used in humans. The purpose of this study is to investigate the genotype and allelic frequencies of CYP3A in Bangladeshi Tuberculosis (TB) patients which may help for individualized drug dosing and improved therapeutics.

Genotyping was done using the extracted genomic DNA from 90 TB patients followed by amplification of target alleles by PCR. Amplified alleles were then digested by restriction enzymes (MboII, XcmI, BsmAI, ClaI, HinfI, HpyCH4III, and RsaI) followed by gel electrophoresis and sequencing to identify the targeted alleles namely CYP3A4*1B, CYP3A4*2, CYP3A4*4, CY3A4*5, CYP3A4*6, CYP3A4*10, CYP3A4*18, and CYP3A5*3. In TB patients, no samples were positive for CYP3A4*2, CYP3A4*4, CYP3A4*5, CYP3A4*6, CYP3A4*10, and CYP3A4*18 alleles. One sample was found to be heterozygous for CYP3A4*1B (1.11%). The wild homozygous (CYP3A5*1/*1) genotype frequency was 7.78%, the heterozygous (CYP3A5*1/*3) frequency was 42.22% and the homozygous mutant (CYP3A5*3/*3) frequency was 50% in Bangladeshi TB patients. The present study is the first investigation describing genetic polymorphisms of CYP3A among Bangladeshi TB patients.

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IS ENTERAL DISBIOSIS CORRECTION EFFECTIVE IN PATIENTS WITH HAEMOPOESIS DERANGEMENT?

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Ineffective folates utilization usually is conditioned by digestive mal-absorption of them (genetic failure of biotransformation) or by failure of the folic acid metabolites synthesis by physiologic intestinal microflora. It‘s not exceptional that folates uptake is damaging in conditions of enteritis, that are often appear as satellites of massive antibacterial therapy, without which the Oncohematology is unthinkable. In clinics of our Research Institute it was carried out a commonly accepted scheme of correction of the folic acid shortage (control group), that is folates enriched diet + folic acid daily injection by 1-2 mg. Lab tests are demonstrating that in 23 patients with folates low level (from 41 of patients who have met the folates supplementation) the mentioned folic metabolism marker was recovered, that is the taken steps for folic level correction appeared successful in just half (56,1%) of general number of cases. Ineffectively resulted the completion of the standard scheme of treatment was probably associated with the non-effective absorption of folates containing substances due to the (methyl-tetra-hydro-folate-reductase) MTHFR genes mutation or due to the pathological status of the digestive microflora. At the same time in 40 patients of hematologic dept. of our clinics, who have the reduced level of serum folates and accompanying state of disbiosis, and to whom it was assigned the two week long course of probiotics administration (studied group) the situation turned to be the differing one. Later in this group patients it was assessed the microflora specter. In 26 of them (65.0%) it‘s shown the considerable qualitative and quantitative normalization of microflora indicators. Moreover, the data is demonstrating that in 19 patients of that 26 for which the microflora correction was effective, that is in 73.1% of treated persons there was the statistically authentic elevation of the blood serum folates level. The obtained data let us to judge that in the considerable number of studied patients (73.1%) the normal specter of digestive system microflora in a large extension is conducting the efficacy of the folic metabolites exchange. These data let us conclude that the level of folates in the blood serum of those patients who have genetically caused malabsorbtion of folic acid in the digestive tract, that is MTHFR genes mutations, could not be corrected by mean of microflora status correction.

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DETECTING COPY NUMBER VARIANTS ASSOCIATED WITH HYPERTENSION-RELATED TRAITS IN THE LARGE-SCALE KOREAN POPULATION

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Recently a number of genomic variants associating SNPs with susceptibility to human common complex diseases such as hypertension and Type 2 diabetes have been reported through genome-wide association studies (GWASs). Even though some CNV studies reported association with several complex disorders, a number of CNV data are relatively small as compared with that of SNP data for these common complex diseases. Moreover, previous GWASs reported some associations of SNPs with blood pressure (BP) and body mass index (BMI) from the Korean population [cho, hong], but no association studies with CNV and these traits were reported so far. In this study, we ascertained 2,206 CNV regions (CNVRs) from the 3,274 community-based Korean population using the Affymetrix genome-wide Human SNP array 6.0 platform and undertook a logistic regression analysis of CNVs with two hypertension-related traits such as BP and BMI. Of the 3,274 subjects in this study, 1,725 subjects (602 cases and 1,123 controls) and 3,212 subjects (1,112 cases and 2,100 controls) were selected for the association analysis with BP and BMI, respectively. Genome-wide association studies of CNV found two loci encompassing previously known hypertension-related genes - LPA (lipoprotein, Lp(a)) and FABP2 (fatty acid binding protein 2) - with suggestive P-values (0.0334 for LPA and 0.0443 for FABP2).

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FINE-SCALE SURVEY OF COPY NUMBER VARIANTS IN THE REFERENCE DNA USING ULTRA-HIGH RESOLUTION ARRAY CGH

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In company with single nucleotide polymorphism (SNP), copy number variation which is the most abundant form of structural variation provides a valuable understanding of the

human diversity. In the most CNV studies, a DNA from a single individual such as NA10851 or NA15510 was used as reference sample. However, homozygously deleted region of reference sample can often lead to erroneous CNV detection of a test sample. Therefore, it is essential to avoid biased CNV calls which are affected by CNV region of the reference sample through the genome-wide survey of CNV regions in its sample. In this study, we ascertained CNVs from the commonly used reference DNA (NA10851) sample. To do this, we used not only a NimbleGen HD2 42M aCGH and a NimbleGen HD2 3×720K aCGH, but also whole-genome sequencing data (NA10851, with 28.3× coverage) and NA10851 CNV region obtained from the Genomic Medicine Institute (GMI). Moreover, 25 Korean pooled DNA samples were used for a reference to minimize reference CNV effect and Genome Alteration Detection Analysis (GADA) program was used to detect the CNVs. From the 2,487 CNVs detected by GADA, 127 falsely detected CNVs, 362 CNVs located in segmental duplication regions, and 490 CNVs which were affected by Korean CNVs were filtered out. Finally, 1,508 putative CNVs of NA10851 were discovered. These CNVs were comprised of 490 novel CNVs and 1,017 CNVs overlapped with GMI data. Our results will be a useful resource to catalog accurate CNVs of reference DNA and to provide valuable insight of discovering unbiased CNV call.

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THE ARAB HUMAN VARIOME PROJECT: INITIAL OBSERVATIONS FROM TWO PILOT STUDIES

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Genetic studies in Arab populations have significantly contributed to the elucidation of the genetic basis of both common and rare disorders and provided an invaluable resource of human genome variation. Proper organization of human disease-causing gene variants is an essential tool to guide patient care in the region into the age of personalized medicine. In accordance with the spirit of the international Human Variome Project, the Centre for Arab Genomic Studies (CAGS) initiated the Arab Human Variome Project with an aim to establish a database platform to record the full spectrum of disease-causing gene variations in Arab populations. Accordingly, we conducted a pilot phase that focused on the collection of geographical-oriented and disease-oriented disease-causing gene variants in the region. During the period between years 2009 and 2010, CAGS conducted a data collection phase to document genetic disorders described in the Arab population of Qatar. Published reports referring to gene loci were carefully reviewed to extract detailed disease-causing mutation data. Gene data were standardized according to the recommendations of the Human Genome Organisation's Human Gene Nomenclature Committee. This attempt resulted in the availability of comprehensive mutation data for 18 genetic disorders in the Arab population of Qatar. In brief, the majority of recorded mutations are noted as novel or rare entities, hence, providing evidence for the genetic heterogeneity in the region. Similarly, independent variants occurring in the same gene resulted in variable expression of the clinical severities of associated disorders and contributed to the clinical heterogeneities observed in the populations of the region. On the other hand, beta-thalassemia, a common disorder in the region, was selected to initiate a collection of disease-oriented gene variants. The survey resulted in the generation of detailed data on the distribution of 73 beta-thalassemia mutations (49 point mutations, 18 short deletions, 4 insertions, and 2 deletions/insertions) in 17 Arab populations from studies comprising a total of 6,183 beta-thalassemia alleles. Countries covered by this survey include: Algeria, Bahrain, Comoros, Egypt, Iraq, Jordan, Kuwait, Lebanon, Morocco, Oman, Palestine, Qatar, Saudi Arabia, Syria, Tunisia, UAE, and Yemen. Of the 73 beta-thalassemia mutations the 10 most common ones among Arabs comprise nearly 78% of all beta-thalassemia alleles. These mutations are, in decreasing order: IVS-I-110 (c.93-21G>A), Cd 39 (c.118C>T), IVS-I-5 (c.92+5G>C), IVS-I-6 (c.92+6T>C), IVS-I-1 (c.92+1G>A), IVS-II-1 (c.315+1G>A), 25bp IVS-I-3' deletion (c.93-21_96del), Cd 6 (c.20delA), Cd 5 (c.17_18delCT), and Cd 8 (c.25_26delAA). The information pooled from this pilot survey does mark just the beginning of a long-term and ambitious project by CAGS to depict human genome variation in Arab populations and understand the genetic processes leading to inherited disorders in the region.

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VARIANTS IN CHOLESTEROL RELATED GENE PREDISPOSES INSULIN RESISTANCE INDEPENDENT OF OBESITY

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Type 2 diabetes mellitus (T2DM) is recognized as one of the leading health problems throughout the world. Patients with T2DM in Asia have different clinical phenotypes from other populations and are characterized as low BMI and limited insulin secretary capacity. Previously, we have reported KCNJ15 as an Asian specific susceptibility gene for T2DM and here we show a cholesterol related gene under the same linkage peak on chromosome 21, as a newly identified T2DM susceptibility gene. Direct sequencing for the promoter and all exons of this gene was performed. The replication studies for associated SNPs in the initial sample set were conducted with a new Japanese panel (cases 779, controls 1,500), a Korean panel (cases 756, controls 628), a Danish panel (cases 3,531, controls 4,885) and a UK panel (cases 1,999, controls 1,502). Genotype-phenotype correlations were analyzed with mRNA levels and a cholesterol synthesize marker, desmosterol/cholesterol ratio, in healthy volunteers. Clinical and metabolic parameters (BMI, HOMA-IR and HOMA-β scale) were assessed in T2DM cases by genotype. Four SNPs

in the open reading frame and four SNPs in the 3 prime untranslated region were found to have minor allele frequencies of greater than 1% in the variation screening. Genotyping of these eight SNPs and an intron tag SNP in the first sample set consisting of 96 patients and 200 controls revealed that 6 SNPs (4 SNPs were in absolute LD) were significantly associated with T2DM. Three SNPs (P = 1.7 x 10-3, OR = 1.2; P = 1.1 x 10-4, OR = 1.19; P = 1.8 x 10-6, OR = 1.26) were replicated in Asian (Japanese + Korean) panel and one SNP was replicated in both Asian and Caucasian (Danish + UK) panels (overall P = 2.0 x 10-6, OR = 1.16). The mRNA level of the subjects with the risk haplotype was significantly higher than those without risk haplotypes (n = 28, P = 0.031) and the desmosterol/cholesterol ratio was significantly higher in those with the risk haplotype than in without risk haplotype (n = 28, P = 0.013). T2DM patients carrying the risk haplotype showed low BMI and high HOMA-IR (n = 229, P = 0.028), while there was no significant difference in HOMA-β. Because this cholesterol related gene is expressed in liver and adipocytes abundantly, variations of this gene may contribute to link between visceral adipose tissue and liver in glucose homeostasis. A genome wide linkage analysis in Japanese followed by fine mapping of the candidate region on chromosome 21 has identified a cholesterol related gene as a T2DM susceptibility gene. The association was replicated in Asian and Caucasian populations.

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VIRTUAL PATHOLOGICAL HEART OF THE VIRTUAL PHYSIOLOGICAL HUMAN (VPH2)

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VPH2 aims to develop a patient-specific platform improving the management processes of heart diseases by definition of the severity and extent of the disease in patients with post-ischemic left ventricular dysfunction (LVD). One major task is the integration of clinical, biological and genetic data, retrieved from medical records and laboratories research results. The project involves the development of tools for collecting, storing, analyzing and linkage of heterogenic data. Here we present the genetic data generated for use within the VPH2 platform. We aimed to assess the prevalence of genetic variants in patients with chronic systolic heart failure and different degrees of reverse LV remodeling after cardiac resynchronization therapy (CRT) in a multicentre case-control study. One-hundred-56 patients implanted with CRT were enrolled and DNA was prepared from mononuclear blood cells. Lack of benefit from CRT in terms of reverse remodeling was used to categorize the population as responders/non-responders. Reverse remodeling (CRT responders) was defined as a decrease from baseline at follow-up echo 6 to 12 months after CRT in LV end-systolic volume >15%. Patients DNA was subsequently genotyped for 44 genetic variants using TaqMan technology. Relative allele and genotype frequencies have been compared by chi-square test between responders and non-responders. P-values <0.05 have been considered statistically significant. Chi-square test for categorical variables and Student's t-test or Mann-Whitney test for continuous variables were used to compare the demographic characteristics in both groups. Non responder (NR, n=76) and responder (R, n=80) groups were well balanced for variables known to affect outcome after CRT: age (NR 62 [56-71] vs R 65 [57-71], p=ns), symptom severity (NYHA class II NR 26% vs R 32%, p=ns) and ischemic etiology (NR 55% vs R 52%, p=ns). NR phenotypes were significantly associated with C allele of rs5443 (NR 75% vs R 60%, p=0.013) within the heterotrimeric GTP-binding protein (GNB3) and the C allele of rs3766031 (NR 93% vs R 81%, p=0.006) within the β-subunit of Na+/K+-ATPase (ATP1B1). We identified two genetic variants to be significantly associated with the CRT non-responder phenotype within our study population, which was used for data mining purposes within the VPH2 project. Both variants reside within genes involved in signal transduction processes (GNB3 and ATP1B1), suggesting an impaired response of patients to the applied therapeutical treatment due to altered protein activity. Recently, molecular functional analysis of GNB3 has suggested C825T (rs5443) to create a novel splice variant and an in-frame deletion of 41 amino acids from the wild-type protein. The β-subunit of ATP1B1 is required for the correct cellular enzyme location and its stability and translation is proposed to be a crucial regulatory step in determining the abundance and activity of the enzyme.

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GENOME-WIDE ANALYSIS OF 36 ETHNICS GROUPS FROM NORTHERN EURASIA

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In-depth research of genetic diversity in humans provides the keys to evolutionary history of our species and has fundamental implications for genetic dissection of common diseases, forensic science and anthropology. Here we characterize the genetic variation 36 populations of Eurasia using genome-wide SNPs set. Genotyping was performed with the use of Illumina 370duo, 370quadro or 610quadro arrays on 3300 population samples originating from across Russia, Eastern Europe and Central Asia. The data were combined with HapMap set of 180 samples. This resulted in genotypes of 3478 people that represent different ethnic groups ranging from East Europe to Japan including Eastern Europe, Caucasus, Central Asia, Ural, Siberia, North-East and East

Asia. Using 188668 SNPs with minor allele frequency higher than 10%, we have confirmed a major East-West gradient from Western Europe to East Asia as the first principal component (PC) of the genetic diversity. The second PC identified a North-South gradient although due to large geographic regions occupied by Siberians it was less pronounced. We found that 20 random SNPs were sufficient to predict PC1 value with 90% accuracy and 650 SNPs were sufficient for PC2 prediction. All SNPs were ranked on a basis of their input into genetic diversity of Northern Eurasia population that resulted in final list of 35509 SNPs with genotypic correlation r<0.2 for each pair of them. PCA and admixture analysis using ranked SNPs produced indistinguishable patterns to those obtained with 188668 SNPs. Genome-wide linkage disequilibrium analysis reveals several very long linked SNPs blocks against the background of small average size of blocks. We also found genomic region surrounding TNK and MSRA genes that are associated with obesity and waist circumference which produce invariantly high linkage disequilibrium values among European population. The results of this study are encouraging for the use of shared control samples in Northern Eurasia case/control studies. With or without the origin of the samples, it should be possible to locate a cohort of case samples on a genetic origin map on the basis of their genotypes, and use this information to select a suitable set of control samples for the study. Generation of list of ranked SNPs opens intriguing possibilities to accomplish population genetics studies with significantly decreased number of markers which can be allocated on the same microarray in custom designed focused studies.

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WHY GWAS FAILED AND WHY WE SHOULD HAVE KNOWN BETTER

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Fifteen years ago, Risch and Merikangas proposed that the gene mapping for complex traits could be efficiently performed using case control sampling with large numbers of individuals screened for large number of markers (though they admitted family studies would be more powerful). This motivated development of technologies that place rapid and inexpensive whole genome sequencing on the horizon, representing the possibility for complete information about all inherited sequence variation in any individual. At the time we pointed out that this would only be useful if the risk factors had high attributable risk, which to us seemed highly unlikely under any reasonable evolutionary model. 10 years ago, debate raged about the plausibility of the common variant/common disease model, defined by Reich and Lander (2001) as ―the conjecture that the genes responsible for most of the risk of common diseases, such as hypertension, heart disease and asthma have simple allelic spectra", which implied that ―causes of diseases could be found by association studies using common gene variants". They further came up with a ―hard prediction" that this would be the case. Goldstein wrote in 2003 that ―those worried that genetic association studies would be of limited value because of the rarity of common variants that influence common disease should be reassured", and in 2005, Collins was predicting that by 2010, ―predictive genetic tests will be available for a dozen common conditions". At HGM2001 in Edinburgh, it was suggested that we needed to do GWAS for traits like breast cancer because the population attributable fraction of BRCA1 and BRCA2 mutations was too small to be useful, and that we needed to find the common variants that caused breast cancer in most people. 10 years later, many variants have been identified, but their combined attributable fraction is less than BRCA1 and BRCA2. Some might call the accomplishments of the HapMap and GWAS era enormous, but judged against the standards laid out by those who promoted it a decade and more ago, clearly this is not the case. It is highly unlikely, for example, that the infamous Wellcome Trust Case Control Consortium would have been funded had the actual results achieved been what was promised in the grant application. So here we are a decade later, in what Ken Weiss refers to as a state of Western Zen, where no means yes, and no we did not find what we expected means yes, give us more money. Papers abound discussing the ―missing heritability" of complex traits, when the results fit almost perfectly with what evolutionary theory predicted massive numbers of variants of miniscule individual effect size. Nothing is 'missing' at all, of course, unless one clings to 'faith-based science' in the face of contradictory evidence.

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FREQUENCIES OF ADH1B*47HIS ALLELE IN NORTHERN AFRICA AND SOUTH WEST ASIA POPULATIONS

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ADH1B*47His allele of alcohol dehydrogenase gene is found more rare among individuals affected by alcoholism and considered to be protective against alcoholism. The allele protective effect is based on faster conversion of ethanol into toxic acetaldehyde resulting in discomfort after alcohol consumption because of elevated level of the toxic stuff in the organism. ADH1B*47His allele frequency is the highest in populations of China and Japan (70%-80%), and rather low for Europeans (8%). A local maximum of the protective allele frequency is found in populations of South West Asia, where the allele frequencies vary from 12.5% for Turks to 68% for Samaritans (Osier et al., 2002; Li et al., 2007; Borinskaya et al., 2009). South West Asia supposed to be the place of origin of the ADH1B*47His allele (Osier et al., 2002; Han et al., 2007). Exact position of the frequency maximum is not determined yet. We have established ADH1B*47His allele frequencies for small cohorts from the following countries: Morocco, Palestine, Lebanon, Iraq, Jordan, Egypt, Yemen, Syria, and Oman. Blood or buccal swab samples were collected from Moscow students born in these countries under

informed consent procedure. Maximum frequencies of the ADH1B*47His allele were found in the cohort from Iraq (25%) and Jordan (31%). According to published and our own data the frequency of the ADH1B*47His allele seems to grow from Turkey to the Central or South part of Arabian Peninsula. The gained data are covering white spot on the allele frequency map for ADH1B*47His allele in the putative region of its origin. Supported by ―Gene Pools and Genetic Diversity" Program of Russian Academy of Sciences.

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THE INVESTIGATION OF 17- Y CHROMOSOME STR AND MT-DNA ANALYSIS OF ANATOLIAN POPULATION

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Turkey has a special location in between Europe and Asia. Longstanding human presence and by the effect of social traditions, the genetic structure of populations inhabiting Turkey is quite complex. In this study, to characterize the patterns of genetic diversity of Turkey (Anatolia)113 unrelated Turkish males from 7 different geographic regions are analyzed for variation at 17 Y-chromosome specific STR loci (DYS19, DYS389I, DYS389II, DYS390, DYS391, DYS392, DYS393, DYS385a/b, DYS438, DYS439, DYS456, DYS458, DYS635, Y GATA H4, DYS437 and DYS448). A total of 112 haplotypes were observed in the 113 individuals studied, of which 111 (99.1%) were unique. The most common haplotype was observed in 2 (1.77%) individuals. The overall haplotype diversity for the 17 Y-STR loci was 99.81%, and the discrimination capacity was 99.11%, indicating a high potential for differentiating between male individuals in this population. Mitochondrial DNA (mtDNA) variation was also studied among the same individuals. We analyzed the first, second and third hypervariable region of mitochondrial DNA control region (position 16024-16383, 40-400, 430-576 respectively). The Y-STR results were compared with mtDNA sequence data to study possible differences in male versus female genetic-variation patterns in the Turkish population.

GENOMIC MEDICINE

P251
MODULAR SYNTHESIS AND DNA BINDING OF NOVEL OLIGOHETEROCYCLES

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There has been interest in heteocyclic systems as sequence-selective DNA minor groove binding agents (and some as RNA binding agents), such as dimeric benzimidazoles related to Hoechst33258 (and trimeric equivalents), and oligopyrroles (and benzimidazole-imidazole chimeras). More recently, some examples of symmetrical dimers or linked dimers, have been reported with similar targets, and at least some evidence of structures with potential for targeting G-quadruplexes. Developing new methods to generate novel bis- and oligobenzimidazoles and evaluation as nucleic acid binding agents is thus of interest. This contribution will describe synthesis of several families of novel oligoheterocyclic systems, designed to provide a modular approach to provide a range of new ligands types, categorized based on heterocyclic orientation, separation and various functionality of linkers incorporated, for example including compounds of the generic types shown. Additionally, other series of dimers, trimers, and tetramers will be described. Data on evaluation of binding for an array of structures in the above classes to a series of target DNA sequences (containing various length (AT)n sections) will be presented, leading to identification of novel DNA-binding ligands in several structural families with sub-micromolar affinities.

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CEREBELLAR GENETICS: THREE RARE DIAGNOSES FROM THE ARABIAN PENINSULA

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Over the past two decades, recent advances in our understanding of cerebellar neuroanatomy, along with evidence from research in functional neuroimaging, neurophysiological and neuropsychological fields, have expanded our view of the cerebellum from that of a simple coordinator of autonomic and somatic motor function to more widely accepted notion that the cerebellum is involved in modulation of cognitive functioning and language processing. Objective: To define the neurological, neuroradiological and genetic characteristics of familial cases with mental retardation (MR) and cerebellar involvement. Three different Saudi families with prominent cerebellar involvement and MR were identified through the genetic clinic at King Faisal Specialist Hospital and Research Centre (KFSHRC), Riyadh, Saudi Arabia. Formal neurological and neuroradiological evaluations were performed. Different genetic techniques were used as warranted including homozygosity mapping, linkage analysis, MLPA, array CGH, X inactivation study, and full gene sequencing. The study was approved by the IRB at KFSHRC. The first family of four boys and one girl was affected with XLMR. The boys had moderate MR, seizure disorder, facial dysmorphism, and cerebellar vermis hypoplasia. The girl had mild MR, seizures, and mild cerebellar hypoplasia. A novel

deletion of at least exons 7-15 was identified by PCR analysis and MLPA of the OPHN1 gene. The array CGH further delineated approximately 68 kb deletion of the 7-15 exons and nearly half of intron 15. In addition, X inactivation confirmed random pattern in the girl. The second family has two affected boys with moderate MR and cerebellar ataxia. The brain MRI showed well-defined abnormal T2 hypointensities within the globi pallidi and the substantia nigra bilaterally suggestive of premature iron depositions; and diffuse cerebellar atrophy. Because of the iron deposition in the basal ganglia, PANK2 gene sequencing was performed and was normal. PLA2G6 for suspected infantile neuroaxonal dystrophy showed a novel homozygous mutation (c673C>T, pH225Y). The parents were confirmed as carriers for this mutation. The third consists of seven affected members with variable cerebellar ataxia and mild MR from a large consanguineous family. Homozygosity mapping and linkage analysis revealed a high LOD score (5.1) region on 8q that harbors the CA8 gene. Full sequencing of the CA8 demonstrated a novel homozygous c. 484G>A (p.G162R) mutation in all affected members, and the parents were heterozygous. The neuroradiological assessment revealed novel findings. The MRI of the brain showed volume loss of the cerebellum and white matter abnormalities in the perittrigonal areas of variable degree. In addition, FDG PET revealed hypometabolic cerebellar hemispheres, temporal lobes and mesial cortex. Besides describing the second family in the literature, this report further delineates the neurological CA8 phenotype. We present three rare causes of MR and cerebellar involvement from Saudi Arabia. It is hoped that this report will increase the awareness about these neurogenetic disorders among geneticists and neurologists.

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PREVALANCE OF Y CHROMOSOME MICRO-DELETIONS OF IDIOPATHIC AZOOSPERMIC AND SEVERLY OLIGOSPERMIC INFERTILE MEN IN IRAQI POPULATION

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Male factor infertility, is considered as a major contributor in the prevalence picture (10- 30 %) of infertility. Spermatogenic process is directly encoded by the genes which are located on the long arm of Y-chromosome (Yq), which proved to be a hot spot for deletion mutations. The objective was to provide information on the type and prevalence of microdeletions in infertile Iraqi males, indication for testing, genotype-phenotype correlation. Fifty two cases of idiopathic oligospermic and azoospermic infertile Iraqi males were selected for this study. Case selection was based on case history, Semen analysis, clinical examination, endocrinological, and cytogenetic study. The STS primers tested on each subject DNA by multiplex PCR were SY84, SY86 (AZFa); SY127, SY134 (AZFb); SY254, SY255 (AZFc) and SY14 (SRY) as an internal control. Seven of fifty two cases (7/52, 13.4 %) showed deletion of at least one of the STS markers; Five cases of which had a complete AZFc deletion (two of which were brothers) and two cases had a partial Seven of fifty two cases (7/52, 13.4 %) showed deletion of at least one AZFc deletion. Two cases of the complete AZFc deletions were further overlapped by Partial AZFb deletions. The study concluded that there is a relative high prevalence rate of AZF microdeletions within the Iraqi population. AZFc deletion performing the major type of deletion (50%) in comparison with other deletions. All AZF deletions represent high expressivity and penterance rate. AZF interval deletions in family history negative cases indicate that it was a de novo deletion.

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IN SILICO TOOLS FOR IDENTIFICATION, CHARACTERIZATION AND COMPARISONS OF CORYNEBACTERIUM PSEUDOTUBERCULOSIS PATHOGENICITY ISLANDS (PAIS)

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C. *pseudotuberculosis* is a Gram positive pathogen, non esporulatin and pleomorphic, Belongs to Actinobacteria group and causative agent of Caseous Lymphadenitis (CLA). CLA causes caseous lymphadenitis in lymphatic glands and/or abscesses in superficial lymph nodes and subcutaneous tissues of sheep and goats. The treatment of this disease with antibiotics is not effective and the commercial vaccines licensed for use in sheep do not confer protection on goats. Therefore, it is very important to characterize the virulence factors of C. *pseudotuberculosis* in order to create more efficient vaccines. The virulence genes are frequently harbored by Pathogenicity Islands (PAIs) which are responsible for the high virulence and genomic plasticity of several pathogenic bacteria. The comprehension of bacterial heterogeneity and the elucidation of the processes that takes bacteria to this high plasticity are very important for evolutionary, epidemiologic and phylogenetic studies. PAIs of C. *pseudotuberculosis* were identified by means of PIPS, a software that performs analyses using different strategies based on the classical features of PAIs, like: Codon Usage (Colombo SIGI_HMM) and G+C content deviations (Artemis: annotation tool); presence of virulence factors (mVIRDB), flanking tRNAs (tRNAscan_SE) and transposases (ENTREZ database); and absence on *Corynebacterium glutamicum*, close related non pathogenic bacterium (ACT: Artemis Comparison tool). A manual curation was realized on 14 Putative PAIs automatically identified by PIPS to refine the results. A comparative analysis of 7 PAIs manually curated will be presented harbouring genes such as fagA,B,C and D operon (iron acquisition), pld gene (phospholipase D - sphingomyelinase action) and PAI 3 of *Corynebacterium diphtheriae* shading new lights that could assist directed strategies for production of more efficient vaccines against CLA.

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GENETIC VARIANTS OF BMPR-II AND ELEVATED VASOCONSTRICTORS ASSOCIATE WITH HIGH-ALTITUDE PULMONARY EDEMA

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A large population is settled at Himalayas and millions travel to this region from other parts for various reasons such as adventure, sports and duty-bound. Hence, it is imperative to have detailed knowledge of HA physiology and its genetics so as to take preventive health measures at HA. High-altitude (HA) adaptation/mal-adaptation is a multifactor trait involving several pathways. As PH is a marked feature of various HA disorders such as High-Altitude Pulmonary Edema (HAPE), we hypothesized the contribution of transforming growth factor-β pathway in the pathogenesis of HAPE; hence, investigated the contribution of Bone morphogenetic protein receptor-II (BMPR-II) polymorphisms to hypobaric hypoxia. In addition, the plasma levels of serotonin and 8-isoprostane were also estimated. In a case-control design, age- and gender-matched unrelated 150 HAPE-resistant healthy males (HAPE-r) and 150 HAPE patients (HAPE-p) were recruited for the study. Clinical characteristics such as Body mass index (BMI), Blood pressure (BP), arterial oxygen saturation (SaO2) and pulse rate (PR) were measured. Among the biomarkers, the plasma serotonin and 8-isoprostane levels were measured by commercially available kits. Genotyping was performed by SNAPshot. Statistical analyses were performed using SPSS 16.0 and EPIINFO 6 software. The analysis of variance revealed that the clinical characteristics SBP, MAP and SaO2 differed significantly between HAPE-p and HAPE-r ($P<0.05$). The multivariate-regression analysis after adjustment with age, sex and BMI revealed the genotype frequencies of rs6435149 and rs7589059 of BMPR-II differing significantly ($P<0.05$) between HAPE-p, and HAPE-r, wherein mutant alleles both T of rs6435149 and rs7589059 associated with risk of HAPE ($P=0.05$). The logistic-regression analysis revealed over-representation of the haplotype, GGTC, in HAPE-p hence served as risk haplotype (OR=3.4, 95% CI=2.4-5.5); conversely, haplotypes GGCT, GATT and AGCT were overrepresented in HAPE-r. The plasma levels of serotonin and 8-isoprostane were significantly higher in HAPE-p when compared with HAPE-r ($P<0.01$) suggesting of a stronger vasoconstriction process in the patients. Two BMPR-II polymorphisms individually and as haplotype, also the higher levels of the two biomarkers, serotonin and 8-isoprostane associated with the risk of HAPE.

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MORPHOLOGICAL CHARACTERIZATION OF SEMEN ABNORMALITIES N THE DROMEDARY CAMEL (CAMELUS DROMEDARIUS)

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The dromedary camel (Camelus dromedarius) species is of great importance in Gulf States. They are widely used for meat, milk consumption and racing. The camel industry in Oman and GCC is mature and prosperous and in many instances provide generous returns to owners, for example camel milk is priced and sold in the market at a premium compared with milk originating from dairy cows or goats. This is due to its high nutritional value which is comparable, if not better than that of cow milk. However, a major limiting factor in expanding camel herds is the low survivability of sperm post collection and cryopreservation leading to extremely low fertility. Studies over routinely used cryopreservation media revealed some sperm abnormalities. For example egg yolk- and milk-based extenders, frequently used extenders in semen cryopreservation, were recently shown to be a source of sperm defects upon thawing. Cryocapacitation and incidence of contamination, because of proteins of animal origin, are the main side effects of those extenders. The objectives of this experiment is to optimize camel semen cryopreservation method and improve survivability, using two new extenders which contain animal protein origin substituent and to use the superiority of electron microscopy (EM) to assess the degree of abnormalities caused by traditionally practiced camel semen cryopreservation methods. Semen samples were collected during the breeding season with an artificial vagina (AV) then heat treated and liquefied enzymatically. After that, samples were cryopreserved in a defined milk factor extender, INRA96, without adding cryoprotectant agent. For post thawing sperm quality analysis, frozen straws (0.5 mL) were thawed in a water bath at 37°C and then emptied into a tube. Data were generated by placing 10μL onto the preheated (37°C) counting chamber. Semen was evaluated for key fertilization traits such as motility, progressive velocity, track speed and sperm linearity using the Hamilton-Thorne software, USA. One mL aliquots were processed for transmission and scanning electron microscopy. Standard EM protocol was optimized to fit camel semen specimens. While samples for scanning electron microscopy (SEM) were primarily fixed over night in karnovsky‘s fixative, two hour only was used for transmission electron microscope (TEM). After primary fixation and buffering, secondary fixation of both was carried with 1% osmium tetroxide for 2 hours. Chemical (Hexamethyldisilazane) drying was used for SEM instead of critical point drying. Our results with TEM indicates severe acrosome destruction, membrane abnormalities, mitochondrial sheathe disruption, axonemal alterations, head-mid piece breakage, poly tails, and some other types of tail abnormalities. SEM results showed other types of defects such as knobbed head, tail clumps, cracked tails and head-mid piece connection, heads free of tails. Our findings are highly correlated with the low fertility rates resulting from artificial insemination (AI) with post thawed camel semen.

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A POSSIBLE PROTEUS SYNDROME CASE

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We described a patient originally from Yemen with a possible case of Proteus Syndrome. Father and mother are cousins. There is not family history of similar condition. It started since birth having right hemi-hypertrophy. The child was born having dark discoloration of the skin that is scattered throughout the body except the face and front of left trunk and lower limbs. There was also brownish discoloration of the lower limb especially in the back of left thigh. The child was born with edema that appears mostly in the neck. Also in the front and back of trunk, the swelling started since birth and has intermittent course, as when they appear they start to grow gradually until they reach to variable size not exceeding (4.5 cm length into 4.5 cm width) and then they regress until they disappear in variable duration that can be estimated in a range of 1-4 months. The swellings are firm, not tender, and not attached to the skin. The fingers of the right foot are bigger than in the left side; the second finger is almost double in size and width than the other fingers. There is presence of a subcutaneous mass 3x3 cm in the right hychondrium that appear 1 year ago and grew for three months. Proteus Syndrome is a disorder of mosaic postnatal overgrowth of unknown etiology. It generally begins in infancy and can involve any tissue of the body. Commonly involved tissues include connective tissue and bones, skin, central nervous system, and the eyes. Diagnosing of PS is difficult and the diagnostic criteria are controversial. The overgrowth of PS is progressive and can be difficult to manage. The progressive overgrowth most commonly causes severe complications. The manifestations are typically asymmetric and the location of it varies remarkably among the patients. Some patients have limited extent of the manifestations, which can make diagnosis difficult. Bone, connective tissue and fat are the most commonly involved tissues. Effective management requires knowledge of the wide array of manifestations and complications of the disorder and a team approach that includes the geneticist, pediatrician, general surgeons, orthopedic surgeons, dermatologist and others. Happle, in 1986, suggested that PS was caused by a somatic mutation, and the tissues derived from that clone manifested the symptoms of PS, and that the mutation is lethal in non-mosaic state. This would explain the lack of recurrence in sibs or in offspring of affected patients, the existence of discordant monozygotic twins and the absence of diffusely affected patients. On the basis of this model and clinical experience, parents of the patients have a very low recurrence risk for this condition. We will present pictures and X-ray of the patient, and listen to other colleagues for possible differential diagnosis and management in this case, which is one of the first reported in Saudi Arabia.

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NEUROIMAGING GENETICS: NEW PERSPECTIVES IN RESEARCH ON EMOTIONAL COMPETENCIES AND AFFECTIVE DISORDERS?

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Recent advances in molecular biology and neuroimaging have provided a unique opportunity to explore the relationships between emotional behavior, its neuronal correlates and their genetic underpinnings. It had been shown that defined dimensions of emotional competencies (e.g. empathy, emotion regulation) are influenced by environmental factors such as stress as well as by genetic factors. However, complex, polygenetic hereditary transmissions coding for these heterogeneous, clinically defined phenotypes may be better identified using endophenotype or whole-genome-wide association approaches. This reviewing talk will focus on recent findings investigating the interaction between the neuroimaging endophenotypes, circumscribed emotional behavior and the modulatory effect of genes.

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LMP-1 ROLE IN INFLAMMATORY SIGNALING CASCADE VIA INHIBITION NF- κB PATHWAY

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LIM Mineralization Protein-1 (LMP-1) is an intracellular osteoinductive protein that recently was found to have anti-inflammatory properties. We have reported that LMP-1 suppresses NFκB activation in the murine macrophage preosteoclast cell line RAW 264.7. The aim of this study is to investigate the anti-inflammatory effect of LMP-1 in human monocyte THP-1 cells. In response to inflammatory signals THP-1 cells differentiate from monocytes to functional macrophages. Inflammatory signals initiated by ligand binding to Toll-like receptors (TLRs) or cytokine receptors (TNF-α, IL-β) lead to NFκB pathway activation and consequent release of inflammatory mediators. THP-1 cells were seeded at 300X104 in T-75 flasks and incubated overnight in RPMI medium containing 10% FBS. Cells were transfected for 8hrs with a NFκB luciferase reporter construct, treated with TATLMP-1(0.25 or 0.5 nM) for 30min and then incubated for 24 h with TNF-α (5ug/ml). TATLMP-1 treatment of THP-1 cells did not affect their viability. Conditioned media (CM) were collected and used to assess cytokine production by ELISA. Cellular lysates were harvested to determine NFκB activity by dual luciferase assay. We found that (1) NFκB luciferase activity was reduced by 83% in response to LMP-1 pretreatment, (2) the suppression of NFκB resulted in a significant reduction of pro-inflammatory cytokine (IL-1β, IL-8, INF-γ and TNF-α) release compared to controls. LMP-1 exerted its suppressive effect in a dose dependent manner. Similar results were obtained when THP-1 cells were stimulated with TLR ligands(LPS or Pamsc3K) or other recombinant cytokines, such as IL-1β, suggesting that the inhibitory activity of LMP-1 on the NFκB pathway is independent of specific ligand/receptor interaction. We hypothesize that the suppressive effect of LMP-1 is exerted on cytosolic targets upstream of the NFκB complex. Further

studies to identify the exact target molecules and the mechanistic action of LMP-1 are under investigation. In conclusion, we show that LMP-1 possesses a potent anti-inflammatory activity by suppressing NFκB activation, suppressing release of pro-inflammatory cytokines.

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ASSOCIATION OF CTLA4, PTPN22 AND CYTOKINE GENES POLYMORPHISMS WITH AUTOIMMUNE THYROIDITIS IN TATAR POPULATION

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Autoimmune thyroiditis (AITD) is one of the urgent problems of modern endocrinology. Current evidence suggests that susceptibility to AITD is likely to be influenced by the combined effects of several genes and their interactions with environmental factors. It's known a list of potential candidate genes are associated with the development of AITD that includes CTLA4 and PTPN22, also genes of pro- (TNF-α, IL1β, IL6) and anti-inflammatory (IL4) cytokines. We analyzed the association of polymorphic loci +49A/G,-318C/T and-1661A/G of CTLA4, 1858C/T of PTPN22,-308A/G of TNF-α, +3953 C/T of IL1β,-174G/C of IL6 and -590C/T of IL4 with the risk of AITD in the female population of the Republic of Tatarstan (RT) (137 women with AITD, the control group included 161 women without thyroid pathology). DNA samples were obtained from whole blood by phenol-chloroform extraction. Analysis of polymorphisms of genes carried by SSP-PCR. Data were analyzed using UNPHASED 3.1. The analysis of the distribution of allele and genotype frequencies of polymorphic markers of +49A/G, -318C/T and -1661A/G of CTLA4, polymorphic locus 1858C/T of PTPN22 showed an increasing of homozygous genotype GG and allele G of the polymorphic loci +49A/G in patients with AITD, as well as the genotype A/G and allele G of polymorphism-1661A/G (OR 1.84 CI 2.31-1.4, 2.0-1.1 CI and 1.52 (respectively)). The distribution of frequencies of combinations of genotypes for the three polymorphic loci of CTLA4 gene showed that the maximum risk occurs when the presence of heterozygous genotypes of the promoter region and homozygous for the polymorphic allele G of the exons of the gene (OR 7.87 CI 2.03-3.25), and the combination of genotypes including the normal allele has a protective effect (OR 0.25 CI 1.21-1.89), whereas a polymorphism 1858C/T of PTPN22 is not associated with AITD in this sample. Analysis of polymorphic loci showed the presence of the association of genotype GG for polymorphism-1661A/G of CTLA4 with hypothyroidism, and increased T allele of polymorphism-318C/T in patients with hyperthyroidism, an increasing of genotypes GG and AG of polymorphic loci +49A/G and-1661A/G CTLA4 gene in individuals with elevated levels of antibodies to TPO and to Tg. It's shown, allele G (OR 2.03, CI 0.065-0.075), genotypes GG (OR 3.53, CI 0.081-0.066) and AG (OR 2.85, CI 0.33-0.08) for polymorphic locus-308A/G of TNF-α, are markers of genetic predisposition to AITD with moderate activity of autoimmune process. The frequency of allele A is significantly increased in healthy individuals (OR 0.3, CI 0.06-0.07) (P <0.05). The polymorphic allele C (OR 3.00, CI 0.063-0.065) and the CC genotype (OR 2.08, CI 0.031-0.078) of 3953C/T of IL1β are associated with AITD hypertrophic forms of first degree and with moderate activity of autoimmune process. Carriers of T allele (OR 0.07, CI 0.065-0.063) and TT genotype (OR 0.04, CI 0.075-0.056) were significantly more common in healthy Russian women. C allele (OR 3.00 CI 0.063-0.065) and the CC genotype (OR 2.08, CI 0.031-0.078) of polymorphism -590C/T of IL4 are markers of predisposition to AITD with moderate activity of autoimmune process.

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GENETIC ASSOCIATION STUDY OF AGT AND AGTR1 GENES POLYMORPHISMS IN PATIENTS WITH HYPERTENSIVE LEFT VENTRICULAR HYPERTROPHY

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Left Ventricular Hypertrophy (LVH) is an independent risk factor for the development of clinical events such as heart failure, cardiac arrhythmias, stroke and cardiovascular mortality. Whilst initially LVH is a physiological response to hemodynamic and/or biomechanical stress in hypertension, with cardiac remodeling, it compromises the prognosis of these patients. LVH can be reversed with some anti-hypertensive agents. Losartan, an angiotensin receptor blocker, has this ability and is associated with clinical benefit. Although losartan acts on the renal-angiotensin system (RAS), findings on genetic association studies of the RAS related candidate genes remained inconclusive. An ongoing study attempts to map the genetic factor contributes to the pathophysiology of LVH. In this paper, we report the allele and haplotype frequencies of two major genes of RAS namely, AGT and AGTR1 in hypertensive LVH patients in Malaysia. 80 subjects were recruited from a large ongoing epidemiology study conducted in Malaysia. Comprehensive clinical data of these participants were obtained and an echocardiographic examination was conducted. Hypertensive patients (systolic blood pressure ≥ 140 mmHg, and/or diastolic blood pressure ≥ 90mmHg) with LV wall thickness ≥ 11 mm, were included in the case group while those hypertensive patients who did not develop LVH acted as controls. The study was approved by the institutional ethics committee. All subjects provided the informed and written consent to the study. Genomic DNA was extracted and subjected to Illumina 660W SNPs array genotyping. 14 SNPs from the genes AGT (5 SNPs) and AGTR1 (9 SNPs) were isolated from the whole-genome data obtained. Allele, genotype and haplotype frequencies were calculated. Allelic and haplotype p-values ware calculated by Fisher‘s exact test and risk association was estimated. Four SNPs namely rs16857796, rs11715829, rs12496794, rs6776194 were monomorphic across all subjects genotyped. rs6776194 was reported as polymorphic in Chinese Beijing

samples from HapMap (MAF 0.012); while the remaining three were population specific SNPs, consistent with the frequencies from public database (dbSNP). Minor allele frequencies (MAF) ranged from 0.01 (rs17807087) to 0.36 (rs9878692). Nine polymorphic SNPs of the AGT and AGTR1 genes were pooled and haplotype analysis was performed. 41 haplotypes were found from the nine polymorphic SNPs. The haplotype frequencies ranged from 0.13 (TTCCACGAAG) to 0.008. Fisher exact tests examined on the polymorphic SNPs, genotypes and haplotypes found no association with LV wall thickness - Minimum P values observed were 0.126 (SNP rs1500858); 0.13 (rs1500858, genotype AA); 0.12 (haplotype TTTTACAAAT) respectively. This preliminary finding gave us an early indication that the effect of the renal angiotensin system (RAS) to the development of LVH may be indirect. However, the initial finding may be affected by the small number of samples. Genome-wide analysis is currently ongoing attempts to map the molecular pathway(s) that contribute to the pathogenesis of hypertensive LVH.

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EFFECTS OF GENETIC VARIANTS OF CCR5 CHEMOKIN RECEPTORS ON ORAL SQUAMOSE CELL CARCINOMA

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This study was conducted to evaluate the effect of genetic variants of CCR5 chemokin receptors in the pathogenesis of oral squamous cell carcinoma. A total of 127 patients (76 male - 51 female, between 23-83 years old), with the diagnosis of oral squamous cell carcinoma, who were followed-up in the Department of Oral Diseases were included in the study. The control group was composed of 104 healthy individuals (38 male - 66 female, between 34-81 years old) requiring dental treatment. The control group had no history of cancer. CCR5 59029 and CCR5-delta 32 genes polymorphism were assessed with PCR method in the peripheral blood samples of both groups. For all statistical tests, the standard SPSS 11.0 for windows was used. For determination of the genotype and allele frequency difference between the groups, chi-square and Fisher‘s test were used. For the comparison of demographic features between the groups, student t tests and Annova were used. Male prevalence, lack of oral hygiene, alcohol intake and smoking were statistically higher in study group than in control group. CCR5 59029 genotype and allele prevalence were statistically higher in study group. AA genotype and A allele were higher in control group, where GG genotype and G allele frequency were higher in study group. CCR5 59029 GG genotype was found statistically higher in the later stages of cancer (P: 0,025). The probability that the tumor diameter is greater than 4 cm increased 2.18 times in patients with GG genotype (P:0,059) and 2.34 times in patients with G allele (GG + AG genotypes) (P:0,083). Keratinization presence was 3.52 times more in patients with CCR5 59029 G allele (P: 0,010). However patients with AA genotypes demonstrated 3.57 times more defense against keratinization (P: 0,010). There was no statistically difference in the prevalence of CCR-5 delta 32 genotype between the groups. CCR5-delta 32 II genotype was statistically higher in patients with history of cancer in the families (P: 0,029). Furthermore, CCR5-delta 32 D allele was statistically higher in the later stages of cancer (P: 0,010). As a result, genetic variants of CCR5 chemokin receptors were found to be associated with later stages of oral squamous cell carcinoma.

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ETHOS PERSPECTIVES ON GENOMICS AND THE DEVELOPING WORLD: THE NIGERIAN CASE STUDY

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In March 2002, the Advisory Committee on Health Research of WHO issued a report on the implications of genomics in the developing countries, and the role they have to play (as was done for the South Americans) in ameliorating a fractional imbalance while also aiming at harnessing global genomics. However, in recognizing the potential of genomics in improving health, the unprecedented advances in the science of genomics and its actions, plus its widely predicted revolutionary prevarication – as we look at these realities, how then can we present and apply this scientific knowledge to our global world? Also, while proffering solutions in some genomic problem domain via culminating a positive evolvement of human genome, where do developing countries (for example Nigeria) stand in this revolutionary emancipation? As we mull over this thought, the question of geographical negligence troubles the mind and quakes one to vomit truth. Of no doubt, the supply of genomic tools and data are vital to understanding and tackling infectious diseases in developing countries. But often we receive reports of an infidelity in the supply of genomic apparatus to these regions. Scientists in these countries often lack the equipments and resources to undertake a substantial research in genomics. And this is where this paper hopes to come-in as succor. The researcher hopes to suggest affable solutions to this problem. This will be exclusively done by applying the research questions of ―What", ―Why", and ―How" – just as follows: 1. What is the future or hope of maintaining a univocal or unified balance in global managerial genomics, and what should be the expected contributions of these developing countries in advancing the science of genomics? 2. Since the under-developed countries have over the years lacked trained and qualified bioethicists, scientists, geneticists and sufficient regulatory infrastructures, to deal with genomic issues, (a.) Why is it so important for this ―lack" to be met? And (b.) why is the discipline of genomics typical to the developed countries and then atypical to under-developed countries? Also (c.) why are students of these developing countries (like Nigeria) not embracing this concrete discipline? 3. How can we come in as Individuals, Research bodies, Scholars, Bioethicists, Scientists, Researchers, Medical Practitioners, and Geneticists, to work-out this problem of parity, to give scientism hope, and rekindle

the joy of many in these under-developed nations where the discipline of genomics has been condoned for hollow reasons? The researcher then hopes to challenge folks with these resolving questions in order to bring about a balanced polarity. Based on this background, some ethical questions will also be asked and answered empirically and theoretically so as to help readers grapple the relevance and implication of this crucible study as we consider the ineffable challenges and opportunities facing Nigeria and other developing countries alike as they begin to harness the science of genomics.

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SINGLE NUCLEOTIDE MISMATCH BETWEEN TEMPLATE AND PRIMER LEADS TO MISGENOTYPING OF HETEROZYGOTE AS HOMOZYGOTE

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Most of the genotyping methods till now are dependent on polymerase chain reaction (PCR). Rational designing of primer is one of the key issues for a successful PCR and thus the sequencing and genotyping method. Here, the effects of mismatch primers on the accuracy of genotyping were explored. A large-scale misgenotyping was observed when heterozygotes at NAT1 single nucleotide polymorphisms (SNPs) (rs1057126 and rs15561), determined by TaqMan method, were cross-validated by sequencing method using a primer having an unintentional single nucleotide mismatch. The same primer, without mismatch, can determine heterozygous genotype correctly. Highest (100%) and lowest (0%) misgenotyping were observed when the mismatch was at the 3rd and 15th nucleotide positions from 3' end of the primer, respectively. This indicates a relationship between position of the mismatch and frequency of misgenotyping. Homozygotes can be genotyped correctly irrespective of mismatch position in the primer. Similar results were observed for two other SNPs (rs12947788 and rs12951053) at TP53 in a different sequence context. The possible explanation could be that a single nucleotide mismatch within a primer amplifies preferably one of the two alleles of heterozygote in the PCR product and, thus, homozygote is observed in the sequencing chromatogram. Therefore, along with the other PCR parameters, perfect matching of primer with template strand is a key issue to get correct genotype. So it is suggested to design the primer from the template sequence where SNP(s) is/are absent. The importance of the work lies on the fact that mismatch primer induced misgenotyping may lead the investigators to report faulty allele or genotype frequency. This result also cautions the researchers from using mismatch primer in PCR-RFLP to create a restriction site and identify alleles in heterozygote samples.

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PROGNOSTIC SIGNIFICANCE OF THE PROLINE FORM OF P53 CODON 72 POLYMORPHISM IN BREAST CARCINOMA

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Several reports have noted epidemiological differences in the prevalence or prognostic significance of p53 mutants with arginine (R) or at the codon 72 polymorphism (R72/P72) in certain cancer types but few studies have examined the prognostic value of the codon 72 polymorphism of the p53 gene in Breast cancer patients. Therefore, this study assessed the prognostic value of proline /proline phenotype of codon 72 p53 in Breast cancer patients. Aims and objectives: -To standardize a rapid mutation specific assay for the detection of p53 codon 72 polymorphism in Breast cancer patients and controls. -To study the frequency of TP53 R72P (215G>C) in Arg/Arg, Pro/Pro and Arg/Pro phenotypes in Breast cancer patients and controls. -To study the distribution of TP53 R72P (215G>C) or Arg/Arg, Pro/Pro and Arg/Pro phenotypes in Breast cancer patients with respect to clinical stages, estrogen /progesterone receptor status, menopausal status and erbB2 expression. A case-control study was conducted with 60 breast cancer patients including 34 women with reproductive group and 26 postmenopausal women and ranged in age from 28 to 80 years and 60 healthy controls. The genotyping of DNA samples from the different patient series and population controls was done using ASO-PCR .The group included p53Arg72Pro polymorphism was examined in their association with breast cancer risk. Results: We investigated the effects of the germ-line single nucleotide polymorphisms TP53 R72P (215G>C) which occurs at codon 72 of exon 4, with two alleles encoding either arginine (CGC) or proline (CCC) on breast cancer susceptibility. The distribution of Arg/Arg, Pro/Pro and Arg/Pro phenotypes in Breast cancer patients and controls was 50%, 23%, 27% and 30%, 17%, 53% respectively. Pro/Pro homozygotes were found more frequently in advanced stage (50%) than the early stages (13%). The distribution of initial clinical stage, tumor size, estrogen receptor or progesterone receptor status, menopausal status, or erbB2 expression was also studied among the different polymorphic variants. The significantly higher frequencies of pro/pro homozygotes were found in Erb2 positive case (23%) than the negative cases (12%).The significantly higher frequencies of pro/pro homozygotes were reported in ER/PR +ve cases (50%) than the ER/PR negative patients (12%). Comparing the frequencies of pro-pro homozygotes with respect to age, the significantly higher frequencies pro-pro homozygotes were reported in menopausal group (29%) than the younger group (14%). Furthermore, in multivariate analysis, p53 codon 72 polymorphismwas found to be a strong predictor of pathologic response (odds ratio 6.7, 95% confidence interval, 1.4-31.2; P =0.016). The higher frequency of the Pro/Pro phenotype of p53 is associated with an increased incidence of advanced stage, ER/PR +ve, menopausal group and Erb2 positive cases in Indian patients with breast cancer. These results suggest a significantly reduced survival for 72P homozygous breast cancer patients. The finding of codon 72 genotype as an independent prognostic marker for breast cancer warrants further studies.

P266
TOXICOGENOMICS "GOALS, CHALLENGES AND APPROACHES"

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Scientists, regulators, and the public all desire efficient and accurate approaches to assess the toxicologic effects of chemical, physical, and biologic agents on living systems. Yet, no single approach exists to analyze toxicologic responses, a difficult task given the complexity of human and animal physiology and individual variations. The genomic knowledge and new technologies that have emerged in the post-genomic era promise to inform the understanding of many risks as well as enlighten current approaches and lead to novel predictive approaches for studying disease risk. Toxicogenomics is defined as the application of genomic technologies to study the adverse effects of environmental and pharmaceutical chemicals on human health and the environment. Toxicogenomics combines toxicology with information-dense1 genomic technologies to integrate toxicant-specific alterations in gene, protein, and metabolite expression patterns with phenotypic2 responses of cells, tissues, and organisms. Toxicogenomics may lead to information that is more discriminating, predictive, and sensitive than that currently used to evaluate toxic exposure or predict effects on human health. Specifically, toxicogenomic technologies may be applied to improve cross-species extrapolation in the analysis of chemical hazard, identify susceptible subpopulations, assess effects of early life exposures to chemicals, analyze compounds‘ modes of action, screen for potential toxic responses, refine exposure assessment, and analyze biologic effects of combined exposures or mixtures. Applying toxicogenomic technologies to these important problems in toxicology can improve understanding and minimize adverse effects of environmental exposures and drugs and contribute to a knowledge base of toxicity end points. To date, applications of toxicogenomic technologies in risk assessment and the regulatory decision-making process have been exploratory. Although they clearly have great potential to affect decision making, toxicogenomic technologies are not ready to replace existing required testing regimes in risk assessment and regulatory toxicology. However, toxicogenomic technologies are assuming an increasing role as adjuncts to, and extensions of, existing technologies for predictive toxicology. Toxicogenomics can provide molecular level information and tests that add to the ―weight of the evidence" for or against the safety of specific environmental toxicants and drugs. Ultimately, toxicogenomic technologies are envisioned to be more sensitive and more informative than existing technologies and may supplant some approaches currently in use, or at least be a component of batteries that will replace certain tests.

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A NEW ERA IN CLINICAL GENETIC TESTING FOR MATURITY ONSET DIABETES OF THE YOUNG (MODY)

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Genetic testing for MODY has become a routine procedure allowing to perform not only the family screening to detect at risk relatives but also to set up proper treatment and discriminate from type 2 diabetes (T2D) whose symptoms are often overlapping. Up to now, 11 types of MODY had been delineated, caused by 11 different genes. We have investigated by conventional Sanger sequencing 140 subjects affected by MODY for the genes GCK, HNF1α, HNF4α and HNF1β, known to be associated with the disease and detected causative mutations in 41% of them. We are now sequencing the negative cases by next generation sequencing for a set of target genes indicated as good candidate by genome-wide associated studies performed in both MODY and T2D. Between the analyzed cases, e.g., we found a pathologic variation in the IPF1 gene (p.Pro33Thr c.97C>A) in a subject with incidental finding of glycosuria. This mutation alters both the function of DNA binding and the transcriptional activation of IPF1. The same mutation was present in his father and grand-father, with T2D diagnosis. Defects in this gene are the cause of pancreatic agenesis, which can lead to early onset diabetes mellitus insulin-dependent. In our cases ultrasound has excluded agenesis or hypoplasia of pancreas, indicating that this gene should be tested not only in the presence of pancreas defects, but also in familial cases of MODY/DT2. We will present further results coming from the study of the Î² cell pathways involved in monogenic forms of diabetes that may have implications for many forms of diabetes in adults. Next-generation sequencing technologies are becoming the first tier for an immediate understanding of the molecular basis of most diseases. Altogether, these efforts should to better understand the disease pathogenesis, find new targets for clinical therapy, and allow prediction of the disease.

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ANALYSIS OF CFTR AND AZF POLYMORPHISMS IN INFERTILE MEN IN RELATION WITH OTHER ABNORMALITIES

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Male infertility has been associated with several genetic and non-genetic conditions. At the genetic level, male infertility can be caused by chromosome aberrations or gene mutations. The presence and types of Y chromosome microdeletions (YMD) and cystic fybrosis transmembrane conductance regulator (CFTR) gene mutations as genetic cause of male infertility have been described. The aim of this study was to determine the prevalence of compound genetic abnormalities in patients who are carriers of cystic fibrosis polymorphism and to compare our results to similar patients reported in the literature. A total of 109 infertile men were enrolled in this study: they were identified to be carriers of cystic fibrosis transmembrane regulator (CFTR) gene polymorphism. The screening for Y chromosome microdeletions in the azoospermia factor (AZF) region was performed by multiplex PCR analysis. The screening of the CFTR gene was performed by direct sequencing. Additional genetic testing for karyotype abnormlities was performed. Three patients (2.75%) out of 109 were identified in our database to have compound genetic abnormalities. One patient had 5T/5T while the other had 6T/6T and the third had 9T/9T. The three patients had deletions of AZF a+b or AZFa+b+c regions. There were no karyotype abnormalities identified in our database. An additional four patients with compound CFTR mutations and Y chromosome microdeletions were identified in the literature. Three patients in the literature had compound CFTR mutations and karyotype abnormalities. Compound genetic abnormalities in CFTR mutation patients can be a contributing factor when abnormal spermatogenesis is encountered. A secondary genetic etiology should consider in these types of patients.

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CGH-ARRAY CHARACTERIZATION OF TWO PATIENTS WITH RING CHROMOSOME 22

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The syndrome of deletion 22q13.3 or syndrome of Phelan-McDermid (MIM 606232) is characterized by a neonatal hypotonia, a somatic growth delay, a severe retardation of language in association to an aggressive and autistic behavior as well as a minor facial dysmorphism consisting often of an epicanthus, big dysplasic ears, long eyelashes and thick eyebrows, with sometimes dental malocclusion and hypertelorism. This syndrome can result either from a simple deletion of the region 22q13.3 or an unbalanced translocation as well as in cases of ring chromosome 22. We report here, the results of our investigation in two 5 years old children, with moderate mental retardation, severe speech delay, hypotonia and minor cranio-facial dysmorphism. Cytogenetic exploration of both patients using FISH, revealed a ring chromosome 22 de novo. CGH-array investigation showed in both a deletion of the minimal critical region 22q13.3 involving ARSA, SHANK3, ACR and RABL2B genes. This loss was confirmed using FISH and mapped between ARSA and 22q tel probes. The majority of neurological features in the syndrome of deletion 22q13.3 result mainly from the haplodeficiency of SHANK3 gene, the reason of which we think that our patients' phenotypes and particularly, mental retardation, speech delay and hypotonia were a direct consequence of the deletion of this gene.

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ETS1 ASSOCIATION ANALYSIS IN ASTHMATIC MEXICAN CASES

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Asthma is an inflammatory chronic airway disease which shows a high prevalence in Mexican population. Actually epidemiological studies suggest that nearby to 15% of the childhood population have asthma. Increasing evidences show that this disease has a high complex genetic background. Genome-wide association studies are contributing to identify polymorphisms in novel genes implicated in the pathogenesis of asthma. The present study was undertaken to identify new candidate genes associated with asthma in Mexican-Meztizo pediatric patients. Three hundred and twenty four unrelated asthmatic patients from four tertiary Medical Center from Mexico City and 420 healthy blood donor controls were included. A genome-wide association study was performed in 120 cases and 120 controls using microarrays DNA (Affymetrix V 6.0). Thereafter, validation was carried out in the 324 cases and 420 controls. Data analysis was performed by HELIX TREE (GOLDEN HELIX), FINNETI, HAPLOVIEW and STATCALC softwares. The genome-wide association analysis showed the strongest p-values at 5q23.3 and 11q24.1 regions. Three of the SNPs at the 5q23.3: rs4497423 (p= 2.14x10-6), rs1940745 (2.14x10-6) and rs12795392 (p= 9.61x10-6) were located near to ETS1 gene. Because ETS1 has been implicated in asthma physiopathology, the validation analysis was performed including these three SNPs and two additional SNPs located in the 3'UTR ETS1 region: rs1128334 and rs4937333. However, no significant differences in the distribution of those five SNPs between cases and controls were observed. These data suggest that ETS1 gene is not associated with asthma susceptibility in Mexican population. However, further studies are needed to rule out the implication of the ETS1 gene in asthma etiology.

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CANCER CLINICAL DIAGNOSTIC APPLICATIONS WITH MICROARRAYS: VIRTUAL KARYOTYPING WITH SNP ARRAYS

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Chromosomal copy number alterations have been used to guide the management of cancer patients for decades and there are many well-established, clinically validated applications for such techniques. In addition, cancer cells have a propensity to develop copy-neutral loss of heterozygosity (LOH), which is not detectable by conventional karyotyping, array comparative genomic hybridization, or FISH. SNP array karyotyping provides dramatically better resolution than conventional karyotyping, does not require culture, performs well on paraffin-embedded samples, and readily detects copy-neutral LOH, making it a powerful new addition to our molecular oncology tool box. Examples of the clinical impact of SNP array karyotyping will be presented and considerations for routine clinical use of the platform will be discussed.

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A POSITIVE ASSOCIATION BETWEEN T102C POLYMORPHISM OF THE 5HT2A GENE AND BIPOLAR DISORDER

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Bipolar disorder is mental illness that affects thought, perception, mood and behavior of a person. Both genetic and environmental factors have been claimed to be involved in the pathogenesis of the disorder. One of the genes that have been implicated is the serotonin 2a (5HT2A) receptor gene that have been known to play various roles in neurocognitive functions. There have been numerous findings that have found association between 5HT2A gene and bipolar disorder in terms of etiology and drug response. In this study, we investigate the association between the T102C polymorphism of the 5HT2A gene, and bipolar disorder in the Malaysian population. The T102C polymorphism was genotyped using Taqman Genotyping Real-time PCR method in 183 subjects with bipolar disorder (case) and 336 subjects without the condition (control). The probe sequence for the SNP was designed and optimized to be reverse complement to the target sequence. Assessment of the T102C polymorphism in the pooled patients showed that 16.8% of the subjects were of the A/A genotype, 50.8% were A/G, and 32.4% were G/G genotypes. In control subjects, 34.6% were of the A/A genotype, 46.4% were A/G, and 19% were G/G genotypes. In terms of allelic frequency, 42.2 % of the patients were of the A allele, and 57.8% of the patient were G allele. In the control subjects, 57.8% were of the A allele and 42.2% were of the G allele. There was a significant difference in both genotype ($p<0.001$) and allelic frequencies ($p<0.001$, OR=0.532, 95% CI: 0.410~0.690) between case and control subjects for this SNP. We stratified the Malaysian population into 3 major ethnic groups namely, the Malay, Chinese and Indian to see the effect of this SNP on each ethnicity. Results of the study revealed significant differences in both genotype ($p<0.001$) and allelic ($p<0.001$, OR=0.396, 95% CI: 0.251~0.625) frequencies in the Malay. In addition, significant association was also observed in the Chinese in terms of genotype ($p= 0.035$) and allelic ($p= 0.011$, OR= 0.557, 95% CI= 0.354~0.878) frequencies. However, no association was found between case and control subjects in Indian ethnic group ($p>0.05$). The finding from this study suggests that the T102C polymorphism of the 5HT2A gene is a susceptible gene in the development of bipolar disorder in the multiethnic Malaysian population, especially in the Malay and Chinese ethnic groups.

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FCGR3B COPY NUMBER VARIATION & HOST SUSCEPTIBILITY TO VASCULAR LEAKAGE IN DENGUE HEMORRHAGIC FEVER

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Dengue is a serious public health threat in many countries around the world. It is estimated that 50-100 million cases of severe dengue requiring hospitalization occurs annually. Approximately 500,000 of these cases manifested as DHF/ Dengue Shock Syndrome (DSS) with more than 20, 000 deaths worldwide. Dengue deaths occur usually as a complication of severe vascular leakage. The mechanisms that lead to this severe leakage are still unknown. Recent studies suggested the potential role of Fc gamma receptors (FCGRs) in the pathogenesis of dengue. In the present study, we examined the copy number variations of the FCGR3B genes in a select dengue patient population in Malaysia. Total cell DNA was extracted from dengue patients' whole blood. CNV genotyping was performed either using the Sequenom Mass Spec, or the quantitative PCR (qPCR) with SYBR Green fluorescent dye assay (Bio Rad). In qPCR analysis, the Relative quantification was used to analyze relative changes in CNV by comparing the fold change ratio of targeted gene and reference gene. Data from both Sequenom and qPCR were analyzed using Student t-test. Eighty samples of patients suspected with dengue were used. Forty-seven (47) were from patients who showed signs of vascular leakage (case) and 28 with typical dengue fever symptoms without vascular leakage (control). During the analysis, 4 samples were excluded as they did not pass the QC or failed in genotyping experiment. Results from the study suggested that 75% of the subjects showed normal FCGR3B copy number (CN=2). Of the total 47 cases with vascular leakage, 5 had FCGR3B CN loss and 8 with CN gain. There was no significant association between CN loss and CN gain with vascular leakage when independently analyzed. However, when subjects with CN gain and CN normal were pooled against those with CV loss, a weak association ($p=0.04$) was found suggesting CN loss with lack of vascular leakage. The

importance of FCGR in various autoimmune and inflammatory diseases has been well-documented. Here we showed a potential association between CN loss of the FCGR3B and protection against vascular leakage in dengue. It is possible that the loss of FCGR3B could affect the antibody-dependent enhancement (ADE) of dengue in secondary infection resulting in reduced possibilities of induction of vascular leakage. Further studies with much larger sample size however, will be needed to confirm this finding.

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ALL-TRANS-RETINOIC-ACID (ATRA) UPREGULATES REDUCED CD38 TRANSCRIPTION IN LYMPHOBLASTOID CELL LINES AND FRESH LYMPHOCYTES

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Evidence suggests that oxytocin may contribute vulnerability to autism spectrum disorders (ASD). Recently, a new player in the oxytocin story was revealed by maternal behavior studies in a CD38 knockout mouse model. These animals were characterized by deficits in social behavior that could be restored by oxytocin. Two recent association studies further strengthened the notion that CD38 is a factor in risk for ASD. In a first study, we reported that CD38 expression was reduced in lymphoblast cell (LBC) lines from ASD subjects. Since CD38 is induced by all-trans-retinoic acid (ATRA; vitamin A), we tested the hypothesis that ATRA would ‗rescue' ASD LBC lines and restore normal levels of CD38 expression. Altogether, 42 ASD LBC lines and 80 parental lines were grown for 48 hours in the presence and absence of 0.1 µM ATRA. We replicate our first findings that LBC lines derived from ASD subjects compared to their parental lines showed reduced expression of CD38. Most importantly, in vitro treatment with ATRA rescued ASD cell lines and restored CD38 expression to greater than parental levels. Notably, there was a significant positive correlation between CD38 expression in LBC cell lines and scores in the Vineland Adaptive Behavior Scale (VABS) in ASD subjects. Additionally, a single SNP (rs6449182; C>G variation) in the intronic CpG island harboring the retinoic-acid response element was associated with CD38 expression in parental cell lines. To further examine the potential role of CD38 as an informative biomarker for autism and deficits in social behaviors, ATRA induction of CD38 in fresh lymphocytes was studied in a non-clinical population using quantitative expression assays. Our provisional findings in a group of 21 normal subjects demonstrated that ATRA induces CD38 gene expression. Interestingly, fold increase of CD38 mRNA content upon treatment with ATRA was negatively correlated with CD38 basal expression level ($r=-0.66$, $p=0.001$). Nominally significant ($t=2.27$, $p=0.039$) association was observed between CD38 SNP rs6841880 and scores on the Systemizing Quotient (SQ). Genotype TT, corresponding to higher SQ, was also associated with lower basal level of CD38 mRNA transcripts ($t=2.03$, $p=0.056$). These results are consistent with what we observed in lymphoblastoid cells from ASD subjects viz. CD38 mRNA levels are positively correlated with social skills. Our study provides a valid basis to achieve pharmacologic up-regulation of CD38 with retinoids, and suggests the intriguing hypothesis that this class of compounds might be a potentially novel drug for future treatment of ASD.

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HOLOPROSENCEPHLY IN AN ISOCHROMOSOME 18Q FETUS: A CLINICO- CYTOGENETIC STUDY

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Isochromosomes 18q are rare chromosomal anomaly. The phenotype is in the majority of cases described as very similar to trisomy 18 or Edward syndrome and appears in the classical form with one centromere and two q arms as a result of a mirror duplication of two genetically identical arms. A 38-year-old Tunisian woman was referred our centre for pregnancy termination at 27th weeks because discovering of holoprosencephaly at second trimester fetal ultrasonography. Fetal autopsy, a karyotype on amniocytes and FISH on paraffin embedded fetal tissue were performed The foetal autopsy showed an oseo-tracheal fistula, a diaphragmatic hernia, lobulations anomalies of the liver, with an hypoplasy of the left liver, a complex malformation of the heart and holoprosencephaly. The karyotype on cultured amniocytes showed a 46,XY, i18q formula. The interphase FISH on paraffin embedded tissue showed 2 centromeres of chromosome 18 indicating a monocentric iso18q. The manifestations of 18q trisomy is dysmorphism syndrome with severe heart malformations, pseudohermaphrodism, limbs, urogenital and anal malformations. In the other hand, the manifestation of 18p monosomy is growth retardation, facial dysmorphism, mental delay, holoprosencephaly, hypopituitarism and genital anomalies. Patients with isochromosome18q present features of these both chromosomal anomalies. Most cases of iso chromosome 18q were de novo and when they are inherited, maternal origin was found in 90% of cases. Our presentation demonstrates the importance of perinatal cytogenetic analysis in malformed fetuses in order to uncover underlying genetic disorders. As showed previously our cases share features of both trisomy and monosomy 18, and holoprosencephaly especially is correlated to the loss of the TGIF gene located on 18p.

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THE 11Q23 DELETION SYNDROME (JACOBSEN SYNDROME): A CORRELATION GENOTYPE - PHENOTYPE

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The Jacobsen syndrome is characterized by a distal deletion of the long arm of chromosome 11 and variable phenotypical expression. The most common clinical features include pre- and postnatal growth retardation, psychomotor retardation, and a characteristic facial dysmorphism. Abnormal platelet function, thrombocytopenia or pancytopenia are usually present at birth. Patients commonly have malformations of the heart, kidney, gastrointestinal tract, genitalia, central nervous system and skeleton. Ocular, auditory, immunological and hormonal anomalies may be also present. Here, we describe the cases of 2 young girls referred for poly-malformative association including thrombocytopenia and facial dysmorphism. A cytogenetic and molecular cytogenetic study was performed for the patients and their parents. The first patient is a 6 months old girl with facial dysmorphism, interventricular septal defect, intestinal malformations and thrombocytopenia. The second patient is a newborn girl with facial dysmorphism, interventricular septal defect, bilateral syndactyly of the fourth and fifth toes, left pyeloureteral duplication, and thrombocytopenia. The karyotypes of the two patients showed de novo11q23 deletions confirmed by the fluorescence in situ hybridization using 11q telomeric probe. Diagnosis of Jacobsen syndrome is based on clinical findings especially intellectual deficit, facial dysmorphism and thrombocytopenia and confirmed by cytogenetic analysis. The deletion was usually telomeric with a proximal breakpoint within or telomeric to subband 11q23.3. It‘s size ranges from 7 to 20Mb including three genes, ETS-1, FLI-1, NFRKB and the TGF1 gene resulting in hematologic and growth retardation as seen in our cases .About 20% of children die during the first two years of life, most commonly due to complications from congenital heart disease, and less commonly from bleeding, that‘s why management should be multi-disciplinary. For patients who survive the neonatal period and infancy, the life expectancy remains unknown.

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GENETIC-EPIDEMIOLOGIICAL STUDY OF PERSONALITY DISORDERS IN A HOSPITAL POPULATION

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Personality Disorders, according to ICD 10(who 1992) comprise of deeply ingrained and enduring behavioral patterns manifesting as inflexible responses to personal and social conditions. Etiology of Personality Disorders remains an enigma and mode of transmission unknown. Family and Twin data indicate that susceptibility to Personality Disorders may influence by an incompletely penetrant major gene in some families and perhaps by multiple genes of unknown varying effect in others. The study sample consisted of 189 patients diagnosed for Personality Disorders in Outpatients‘ Department of Psychiatry, PIMS, Islamabad. Total number of females was 107 (56.61%) and males 82 (43.38%). Sex ratio=100:76.63, $\lambda 2$ =3.3; P>0.02. Age at diagnosis ranged from 4-67 years, with 41.21%of patients falling in 10-19 age cohort. The total number of inbred marriages were106 (56.09%) and outbred marriages are 83 (43.91%) The coefficient of Inbreeding (F) for Personality Disorders is F=0.0318 and that of control sample is F=0.0273 (80) Genetic studies; There were 55 (29.10%) patients with disease in family, 12 (6.34%) with mental illness other than PD in family. 120 (63.49%) were sporadic cases. Out of 55 positive PD families, 47 are offspring of first cousin marriages. In sporadic cases there are 41(21.69%) patients from first cousin unions. Genetic heterogeneity was observed in the inheritance of Personality Disorders. Out of 55 positive PD families there are 18(9.52%) pedigrees that depict Dominant inheritance. There are 37 (19.58%) pedigrees showing Autosomal recessive inheritance. Familial cases were 03 (1.59%). Stressful life events were precipitating factors in 122 (64.55%) patients while in 67 (35.45%) no untoward event triggering the onset of disease was reported. Low paid Government servants and laborers are most affected with schizophrenia, and prevalence is more in the less educated class. This study shows consanguinity as an important factor in the onset of Personality Disorders and is a fertile base for further molecular genetic studies to locate genes contributing in the development of illness.

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GENETIC-EPIDEMIOLOGY, CONSANGUINITY AND PATTERNS OF INHERITANCE OF SCHIZOPHRENIA IN HOSPITAL POPULATION

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Schizophrenia is characterized by profound disturbances of cognition, emotion and social functioning. Lifetime risk within the general population of approximately 1%. Genetic epidemiological studies have shown that the syndrome has a high heritability, and significant genetic component to its etiology. The disease is complex and heterogeneous and the precise underlying neurobiological mechanisms remain largely unknown. To study consanguinity, epidemiology and patterns of inheritance of schizophrenia in a hospital population. The study is based on 78 diagnosed schizophrenic patients. The data were collected from the outpatient Department of Psychiatry, Pakistan Institute of Medical Sciences, Islamabad. Results Affected Males were more in number than females (100:119.75) but the difference between the two sexes is not significant. There were 35 unmarried patients and 43 married patients. The mean age at diagnosis of unmarried female patients is 16.14± 1.01 years and that of unmarried male patients is 19.42± 2.52 years, but the difference is not significant. Among married patients, the mean age of diagnosis of female patients is 29.70±2.12 years. Married Male patients

were inflicted with the disease significantly earlier than females (19.76±2.39 years). (t=3.11, p<0.001) The inbred marriages in this study are 60.25% (n=47), of which first cousin unions are 33 (25.74%) The inbred marriages are significantly higher in number as compared to outbred couples (2 =3.89; p < 0.01). The coefficient of inbreeding (F) calculated for total sample of schizophrenia patients was F=0.0472 and that of general population was F=0.0273. There were 31 family members inheriting schizophrenia and of these 21 families were inbred marriages, and 17 were first cousin unions. In this study three groups based on family history of patients were formed. Positive group; where patients immediate relatives had the same (n=31; 39.75%) disorder: Negative group where same disorder was not present in family but some other mental disorder was diagnosed in the family (n=01; 1.28%). Third group where occurrence of disease was sporadic. (n=46; 58.97%) Genetic heterogeneity was observed in the inheritance of schizophrenia. There were 12 (15.38%) families ascertained for recessive inheritance whereas 15 (19.23%) showed autosomal dominant pattern and 5 (6.41%) families showing dominant inheritance with intra family incomplete penetrance. There were 46 cases sporadic cases (58.97%) Low paid Government servants and laborers are most affected with schizophrenia, and prevalence is more in the less educated class. This study shows consanguinity as an important factor in the onset of schizophrenia illness and is a fertile base for further molecular genetic studies to locate genes contributing in the development of illness.

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CHARACTERISATION OF MUTATION IN APOB GENE IN PATIENTS WITH FAMILIAL HYPERCHOLESTEROLAEMIA IN MALAYSIA

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Familial hypercholesterolaemia (FH) is an autosomal dominance genetic disorder characterized by high cholesterol levels, specifically very high low-density lipoprotein (LDL) cholesterol levels in the blood which associated with premature coronary artery disease (CAD). Heterozygous FH is a common genetic disorder, occurring in 1:500 people in most population. With a population of 28 million in Malaysia, it is estimated that 50,000 individuals are affected and majority of whom are under diagnosed. Many FH patients carry the mutations in the LDL receptor (LDLR) gene that encodes the LDLR protein, which normally removes LDL from the circulation, or apolipoprotein B (APOB) gene, which is the part of LDL that binds with the receptor; mutations in other genes are rare. However, mutation in specific site of APOB gene which reduces their affinity for the LDL receptor, leading to hypercholesterolemia was referred as Familial defective apolipoprotein (FDB). With the same prevalence in most population as in FH, the FDB heterozygotes clinical picture is indistinguishable from that in heterozygous FH and 2-5% leads to misdiagnose in certain population. In Asian population, there is still insufficient data regarding the misdiagnosed of FBD in FH patients and FDB have also been poorly characterized. Objective: To screen and confirm the mutation site of LDLR binding domain in APOB gene among the FH patients. This observational cross-sectional study involved 56 FH patients of definite FH and possible FH (46 Malays & 10 Chinese) and 52 age-matched normocholesterolemic controls. Diagnosis of FH was based on the Simon Broom criteria. Anthropometric indices (body mass index [BMI], waist circumference [WC] and waist hip ratio [WHR] and blood pressure were measured and documented. Blood samples were separated, stored and analyzed for fasting serum lipid (total cholesterol [TC], triglycerides [TG], low density lipoprotein [LDL-c] and high density lipoprotein [HDL-c]), plasma glucose, renal profile, liver function tests and urinalysis by standard automated laboratory techniques. DNA extraction was performed using commercially available kit (Promega Maxwell) and purity was determined by spectrophotometer (Nanodrop ND1000). Genotype amplification by polymerase chain rection (PCR) (Eppendorf MasterCycler) as employed to amplify four established common mutation located at exon 26 of the APOB gene (codon 3482-3589). PCR products were then analyzed using capillary gel electrophoresis (Agilent Bioanalyser). DNA sequencing was performed for all patients Applied Biosystem DNA Sequencer). Mutation on APOB gene (codon 3482-3589) was not found in all 56 samples of FH diagnosed patients. Conclusions: This preliminary result of 56 FH patients found that there is no mutation of the specific codon that leads to FDB. Nonetheless, this result is to sparse to make any conclusion at the moment due to i) limited number of samples; ii) possible putative mutations located at other parts of the gene; iii) gene-gene interactions. Study is currently ongoing with a larger sample size and other candidate genes.

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ASSOCIATION OF TLR8 COPY NUMBER VARIATION BUT NOT TLR9 WITH SYSTEMIC LUPUS ERYTHEMATOSUS SUSCEPTIBILITY IN MEXICAN PEDIATRIC POPULATION

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Toll-like receptors (TLR) play a critical role in innate immune response. TLR7 and TLR8 recognize RNA and TLR9 DNA molecules derived from viruses. However, they may also recognize endogenous nucleic acids within immune complexes and in pathological conditions it can result in autoimmunity. Recently, we have shown that TLR7 copy number variations (CNVs) are associated with childhood-onset systemic lupus erythematosus (SLE) susceptibility in Mexican population, and suggested that it may be through the induction of INF-α. We investigated if there are CNVs in TLR8 and TLR9 genes and if they contribute in the genetic component of SLE in Mexican pediatric population. We performed a case control association study in 328 Mexican pediatric SLE, 269 (82%) were female and 59 (18%) were male. As a healthy control group we included 403 gender matched blood bank donors (85% female

and 15% male). Determination of CNVs of TLR8 and TLR9 genes were performed by real time PCR using the ΔΔCt method. Expression levels of TLR8, TLR9 and INF-α were determined in 31 patients. Additionally, to test the activity of INF-α, we stimulated in vitro Wish cells with the serum of patients and determined the expression levels of three genes specifically induced by INF-α; MX1, PKR and IFIT1. We found a significant increase in the relative TLR8 gene copy number (CN) in pediatric SLE patients compared with controls (P = 0.0065). However, when we stratified by gender, logistic regression analysis showed an association only in the female group (P = 0.0008). Female patients having > 2 copies of TLR8 (3 to 5) showed an OR = 1.66 (95% IC = 1.39-1.98). On the other hand, despite CNVs of TLR9 were found, no significant differences were observed between cases and controls (P = 0.529). TLR8 and TLR9 mRNA levels correlated significantly with TLR8 and TLR9 CN (P = 0.002, r = 0.55; P = 0.0001, r = 0.065, respectively). Nevertheless, only TLR8 expression levels correlated with INF-α expression levels (P = 0.017, r = 0.49) and with the INF-α activity (P = 0.008, r = 0.54). Our results show that the gene dosage of TLR8 but not of TLR9 is a risk factor for pediatric SLE and suggest that TLR8 may be involved in the pathogenesis of SLE through the induction of INF-α.

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A GENOME-WIDE ASSOCIATION STUDY IDENTIFIED VARIANTS REGULATING TOTAL PROTEIN SERUM LEVELS THROUGH REGULATION OF IGG AND IGA SERUM LEVELS IN THE JAPANESE POPULATION

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The genome-wide association study of the biochemical and hematological traits in the Japanese population identified the SNP rs4273077 in TNFRSF13B to be strongly associated with total protein serum levels (P= 4.5 X 10-10), but not associated with serum albumin (P= 0.076), suggesting another fraction of serum total protein would associate with this variation. Here we performed GWAS for non-albumin protein values in 9043 individuals and identified 3 SNPs in two loci which cleared the genome-wide significance level of 5X10-8 (P= 5.54 X 10-17, 1.8 X 10-12 and 7.01 X 10-9). We further tested the association of these SNPs with gamma-globulin fractions (IgG, IgA, IgM, and IgE), the second abundant serum protein group following albumin (constituting about 30% of the serum total protein) using data from more than 2000 individuals. As a result, we identified significant association of these SNPs with both IgG (P=0.0014, 0.0015, and 0.00074) and IgA serum levels (P=0.014, 0.002, and 0.0076). The identified SNPs were also tested for association with two autoimmune disorders; systemic lupus erythematosus (SLE) (n=1084) and IgA nephropathy (IgAN) (n= 370). Interestingly, we detected significant association of all SNPs with IgAN (P= 0.001, 0.002, and 0.024, O.R= 1.30, 1.28, and 1.19, respectively) and 2 SNPs with SLE (P= 0.003 and 0.021, O.R= 1.17 and 1.12, respectively). Our findings indicated an important role of these genetic variations in the regulation of immunoglobulin production and autoimmunity.

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GENE-GENE INTERACTIONS IN THE RISK OF NONSYNDROMIC CLEFT LIP WITH OR WITHOUT CLEFT PALATE IN KOREANS

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While environmental factors are known to play important role in the occurrence of oral clefts, previous family studies have suggested that multiple genes (3-7 loci) are likely to interact epistatically in the occurrence of oral clefts. Past two decades, several candidate genes have been reported to be associated with oral clefts. However, different candidate genes have been suggested to be associated with oral clefts in Caucasian and Asian populations. To identify risk factors for non-syndromic oral cleft, we analyzed the demographic, environmental exposure status and other clinical characteristics for 258 isolated, non-syndromic oral cleft case-parent trios in Korea. We also genotyped for the single nucleotide polymorphism (SNP) markers of candidate genes reported previously to test gene-gene interactions using 142 case-parent trios with non-syndromic cleft lip with or without palate (CL/P). These included IRF6, MTHFR, MSX1, TGFA, and TBX22. We performed both conditional logistic regression analysis and non-parametric PGMDR to test gene-gene interaction. Characteristics such as sex, mother's education, mother's exposure to chemicals, and father's alcohol drinking were different by the type of oral cleft (e.g. family history, p=0.033). Gene-Gene interactions among candidate genes, for instance, MTHFR and MSX1 were evaluated and the results will be shown in detail. Interactions among multiple susceptibility genes and the relevant gene-environment interactions may explain a large fraction of the heritability of non-syndromic oral cleft.

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HOW MUCH OF THE INTERACTION BETWEEN GENETICS AND ENVIRONMENT AGGRAVATES A DISEASE DURING EXPOSURE TO HA?

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Since time unknown, high-altitude (HA) has attracted mankind for various reasons; as a consequence most of the high mountains have been widely trekked/travelled. In the process, mankind suffered of local calamities and HA disorders, however it did not deter and succeeded in overcoming odds by establishing permanent residence to these high mountains. Furthermore, the sea-land residents travel to these altitudes for various reasons in spite of threats to life due to extreme environment; alongside in package came adaptation or HA diseases viz, Acute or chronic mountain sicknesses, High-altitude pulmonary hypertension, HA pulmonary edema (HAPE) and HA cerebral edema (HACE). Clinical and physiological aspects associating with aggravation of a health condition during travel are well established; whereas, genetic approach in identifying functional variants has added considerable knowledge in elucidating an individual‘s susceptibility. Here, we provide an example of the susceptibility of an individual during travel to a hitherto hidden disorder which surfaces upon exposure to a new environment such as hypobaric hypoxia of HA. The candidate gene and high-throughput approaches have achieved considerable success in elucidating individual‘s predisposition and provided insight into the dynamics of genome-evolution. Confluencing both the traditional and contemporary approaches, we investigated several candidate genes viz: Angiotensin I converting enzyme (ACE), Angiotensinogen (AGT), Endothelial nitric oxide synthase (NOS3), Aldosterone synthase (CYP11B2), Endothelin-1 (EDN1) and Adrenergic, beta-2-, receptor, surface (ADRB2) in healthy native Himalayan-highlanders (HLs) and sojourners i.e. High-altitude pulmonary edema-resistant control (HAPE-r) and HAPE-patient (HAPE-p). In addition, the relevant biomarkers were also estimated. We illustrate our relevant findings, which once established may influence predisposition and therapeutics. Individual allele/genotype, haplotypes, genotypes/gene-gene interactions and their correlation with pertinent biomarkers were analyzed. Further in a genome-wide study, we compared >4000 SNPs distributed across the entire genome of two ethnically similar populations contrasting altitude residence. The allele/genotype distribution at the same locus varied significantly among these groups. The alleles ACE I (rs4646994), NOS3 894G (rs1799983) and 4b, EDN-1 2288G (rs2070699) and CYP11B2 –344T (rs1799998) were higher in HLs than HAPE-r ($p<0.05$). Whereas, over-representation of D, 894T and 4a, and 2288T alleles was obtained in HAPE-p (p between 0.03 and 0.002) when compared against HAPE-r. Genotype-interactions revealed over-representation of GGbb of NOS3, II/GG of ACE/END1 in HAPE-r than HAPE-p ($p<0.05$). The higher ACE activity, endothelin and aldosterone levels and lower nitric oxide level correlated with respective variants in HAPE-p ($p<0.0001$). The MDR model depicted ADRB2 polymorphisms 46A/G (rs1042713), 79C/G (rs1042714) and 523C/A (rs1042718) as the best disease predicting combination; whereas, greater power was demonstrated by ADRB2 haplotypes to predict HAPE. The genome-wide comparison corroborates difference in SNPs of genes or regions close to the above candidate genes. The participation of vascular homeostasis genes in adaptation to HA environment is perceptible. The high throughput genetic tools have laid a platform to diagnose genetic markers of predisposition to HA adaptation/mal-adaptation.

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WHOLE TRANSCRIPTOME ANALYSIS OF CD34+ HEMATOPOIETIC STEM CELLS DURING LINEAGE SPECIFIC CELL DIFFERENTIATION: TOWARD A MOLECULAR PORTRAIT OF HUMAN HEMATOPOIESIS

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Hematopoietic differentiation is strictly regulated by several exogenous factors and the frequency and functional impact of alternative splicing in stem cell differentiation process are yet to be determined. Disruptions of the intricate sequences of transcriptional activation and suppression of multiple genes can cause hematological diseases, such as leukemias, myelodysplastic syndromes (MDS), or myeloproliferative syndromes (MPS). Elucidating the pattern and sequence of gene expression during normal hematopoietic cell development may help to unravel the disease-specific mechanisms in hematopoietic malignancies. In this study using an vitro hematopoietic model system, CD34+ human stems cells isolated from healthy individuals were selectively induced in vitro with the lineage-specific cytokines, such as erythropoietin (EPO), granulocyte colony-stimulating factors (G-CSF), granulocyte macrophage colony-stimulating factors (GM-CSF) and thrombopoietin (TPO). Microarray and RNAseq based whole transcriptome analysis was performed on these differentiated cells to delineate the modulations in gene expression and alternative splicing events if any during lineage-specific hematopoietic cell differentiation. Gene level analysis on the Human 1.0 ST exon arrays indicated that during lineage specific cell differentiation more than 900 genes showed significant modulation in their level of expression. Analysis of the exon arrays for alternative splicing during erythropoiesis, granulopoiesis and megakaryopoiesis, identified 86 genes that include CAST, ATP5H, CLMN, EPHX1, GAB1, PTPRA, RGS3, SLC25A3, STAB1, TPD52L2,VWF to be significantly spliced during differentiation. RNAseq analysis corroborated with the microarray data on to a large extent both at the gene level ($R=0.72$) and exon level ($R=0.58$) analysis of selected genes. Our data thereby provides several new insights into understanding differentiation and proliferation of human stem and progenitor cells. This knowledge on the nature of stem cells and the molecular process by which these cells acquire their specific cell fate shows great promise to the success of cell-based therapies.

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THE DEVELOPMENT OF A SIMPLE AND RAPID DIAGNOSTIC TEST FOR GAIN AND LOSS OF FUNCTION DEFECTS IN FIBROBLAST GROWTH FACTOR-23 (FGF-23)

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FGF-23 is a recently discovered hormone that regulates the homeostasis of inorganic phosphate (Pi) and vitamin D. Mutations that generate a loss of function in FGF-23 cause a commonly prevalent disorder in the Middle East and Africa known as Familial tumoral calcinosis (FTC). Gain of function mutations in the hormone cause autosomal dominant hypophosphatemic rickets (ADHR). To date, the only method to diagnose defects in FGF-23 is DNA sequence analysis. In this investigation, we report a rapid and simple method to diagnose gain or loss of function in FGF-23 using amplification refractory mutation system (ARMS)-PCR. We employed in vitro site-directed mutagenesis, ARMS-PCR and DNA sequence analysis to produce a rapid diagnostic test for FTC and ADHR due to defects in FGF-23. Results: In vitro site-directed mutagenesis was used to create seven different mutations in FGF-23 that cause FTC and two other mutations that cause ADHR. The mutated sequences were confirmed by DNA sequence analysis. We designed ARMS specific primers to identify each of the mutations and we optimized the conditions required to run the procedure. To validate our diagnostic method, we tested two large Middle East clans clinically diagnosed with FTC. Our results indicate the successful use of this method to diagnose defects in FGF-23. This diagnostic method simplifies and accelerates the detection of FTC and ADHR due to mutations in FGF-23 in an area where the DNA sequence analysis is costly and not commonly found. The high prevalence of FTC is most likely due to high rates of consanguinity in this area. For this reason, the development of rapid and simple methods of diagnosis for genetic diseases is important in prenatal genetic screening and to identify carriers of the disorder and conduct proper counseling to those individuals. We are working on a high resolution melt (HRM) diagnostic method to detect other genes associated with FTC and can supplement ARMS-PCR.

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SNPS IN NFKB1 GENE ARE ASSOCIATED WITH JUVENILE RHEUMATOID ARTHRITIS

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Juvenile rheumatoid arthritis (JRA) is the most common rheumatic disease in childhood. Strong evidences suggest that the etiology of the disease involve both genetic and environmental factors. NFKB1 is a major transcription regulator of immune response, apoptosis and cell-growth control genes. Over time, evidence has accumulated implicating NFKB1 as a mediator of autoimmunity and potential therapeutic target for treating autoimmune diseases. On this way, we analyzed five single nucleotide polymorphisms (SNPs) located on intron 1 of NFKB1 gene. Analysis in silico showed that these 5 SNPs can have a biological implication affecting an enhancer. Objective: To determine whether SNPs located in the NFKB1 gene (NFKB1_1; rs3774933T/C, NFKB1_2; rs3774937T/C, NFKB1_3; rs3774938A/G, NFKB1_4; rs1587213C/T, NFKB1_5; rs1587214C/T) are associated with susceptibility to JRA in Mexican population. This study included 215 patients (127 female and 88 male) with JRA, which met the ACR criteria. A group of 430 (254 female and 165 male) unrelated healthy controls were included. Genotyping was carried out by 5' exonuclease assay (TaqMan). The association test, Hardy-Weinberg Equilibrium (HWE) and haplotypes, were evaluated using EPIDAT, FINETTI and Haploview softwares, respectively. Both cases and controls were in HWE. Differences between cases and controls were observed when we compared the genotype and allele distributions (NFKB1_1T/C, OR 0.69, p=0.004; NFKB1_2T/C, OR 0.67, p=.001; NFKB1_3A/G, OR 0.66, p=.0009; NFKB1_4C/T, OR 0.69, p=.004 and NFKB1_5C/T, OR 0.67, p=.001). The haplotype CCGTT, carrying all minor alleles, showed protection with JRA (OR 0.66, p=0.002). Pairwise linkage disequilibrium (LD) between SNPs showed a r2 > 0.90. The SNPs NFKB1_1T/C, NFKB1_2T/C, NFKB1_3A/G, NFKB1_4C/T, NFKB1_5C/T and the CCGTT haplotype were associated with JRA. It is possible that these SNPs can be important in the biological function of NFKB1. Acknowledgements: This study was supported by the Consejo Nacional de Ciencia y Tecnología (CONACYT: SALUD-S0008–2005–1).

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MOLECULAR STUDIES AMONG WOMEN FROM UNITED ARAB EMIRATE WITH BREAST CANCER

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Breast cancer is the leading cancer among females and comprises 18.4 % of all female cancer cases in United Arab Emirate (UAE). The mortality rate as high as 44%, compared with 10-15% for USA. It accounts for 28% of all female deaths. Women from UAE tend to develop breast cancer at least a decade earlier than their counterparts in Western countries which may indicate a high genetic factor. Women who carry BRCA1 mutations have a probability about 80% for developing breast cancer, and 40 to 60% for developing ovarian cancer during their lifetime. Literature on the genetic predisposition of breast cancer is very limited in UAE. The aims of this study were to: 1. Investigate and analyze the role of genetic factor in breast cancer from UAE patients with either early-onset breast cancer (at age </= 45 years) or a positive family history. 2. The possibility of setting up a screening and diagnostic laboratory. 3. Drug formulation for breast cancer treatment. In collaboration with GMC (Ajman), Tawam (Alain), Al Wasl (Dubai) Hospitals and Shaikh Khalifa Medical City (Abu Dhabi) peripheral blood samples will be

collected from women with either early-onset breast cancer or a positive family history of breast cancer. Mutations will be detected from BRCA1 gene by Protein Truncation Test (PTT) and Denature High Performance Liquid Chromatography (DHPLC) followed by gene sequencing.

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EGYPTIAN CYTOGENETIC EXPERIENCE: ROLE OF GTG AND FISH IN IDENTIFICATION AND DIAGNOSIS OF GENETIC DISORDERS

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In view of an increased risk of having recurrent abortion, congenitally abnormal children and carriers, genetic counseling is greatly required. A total of 4362 cases having different genetic disorders were referred from genetic clinics to the Human Cytogenetic Department for chromosomal studies over a period of 5 years. We aimed to use FISH for definite diagnosis of some genetic disorders, submicroscopic deletions, sex chromosomes abnormalities, cryptic translocation and complex chromosomal rearrangements. According to the referral cause, cases were categorized into: genetic counseling representing 15% of the whole referred cases, CNS malformation and developmental delay representing 10.4%, Down syndrome representing 9.3%, premarital counseling representing 8.8%, short stature representing 8.5%, repeated abortion representing 7.5%, mental retardation representing 6.4%, ambiguous genitalia representing 5% and dysmorphic cases representing 4.11%. All cases were subjected to standard cytogenetic technique GTG- banding and special techniques for some cases according to the provisional diagnosis, chromosomal analysis was performed to the parents of cases with chromosomal aberrations. Our result showed that 17.77% of all studied cases had various chromosomal abnormalities, of which aneuploidy was the most common and represented 67%, trisomy 21 represented 52.5% and sex chromosome abnormalities represented 17.65%. Cytogenetic abnormalities were further investigated by Fluorescence in situ Hybridization using various FISH probes for confirmation, identification and precise diagnosis of the detected chromosomal abnormalities in 600 cases (10%). Probes used were locus specific (LSI) for 107 cases for identification of microdeletion syndromes (Prader-Willi, William, DiGeorge/VCF, Miller-Diecker, Kallman and Cri du chat) and deletion of specific loci (cavernous hemangioma and icthyosis), sex chromosome abnormalities for 40 cases, centromeric CEPX/Y for 30 cases, identification of autosomal markers for 15 cases, translocation confirmation of 10 cases, telomeric, all human telomeres, total subtelomeric panel and cancer FISH. Our studies demonstrate that FISH analysis is often required in an efficient manner and in conjunction with other techniques for accurate diagnosis and confirmation of genetic disorders and greatly facilitating phenotype-genotype correlation, management and genetic counseling.

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GENOTYPIC AND ALLELIC FREQUENCIES OF THE P53BP1 GLU325ASP AND OF P53BP1 GLY412SER IN ASSOCIATION WITH BREAST CANCER RISK

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Breast cancer, is a common type of cancer, with over two million newly diagnosed cases annually worldwide. In Sudan breast cancer is the most common cancer comprising 34% of all cancer patients. The functionally defective mutations in BRCA1 and BRCA2 genes are responsible for up to 5% of all breast cancer patients, while other genes (so-called low penetrance genes) account for the remainder of breast cancer patients. Among those possible low penetrance candidate genes for breast cancer is P53PB1 gene. Since single-nucleotide polymorphism (SNP) is the most frequent and most subtle genetic variation in the human genome and has great potential for application to association studies of complex diseases such as that of breast cancer the aim of this study was to evaluate the role of P53BP1 polymorphisms in breast cancer predisposition in Sudanese breast cancer patients and in breast cancer risk at the population level. This is a case control study where we genotyped a total of 81 breast cancer patients and 91 age matched healthy controls for 2 SNPs in P53BP1 tumor suppresser gene namely Glu 353 Asp or 1236C G [db SNP rs560191] and Gly 412 Ser [db SNPrs689647].The role of these polymorphism in breast cancer susceptibility were investigated using both conventional genotyping technique and high throughput Tag Man allelic discrimination method (SNP scoring methods) using Real-Time PCR technique. Data on clinical features and demographic details were collected. The association between the case-control status and each. Since time unknown, high-altitude (HA) has attracted mankind for various reasons; as a consequence most of the high mountains have been widely trekked/travelled. In the process, mankind suffered of local calamities and HA disorders, however it did not deter and succeeded in overcoming odds by establishing permanent residence to these high mountains. Furthermore, the sea-land residents travel to these altitudes for various reasons in spite of threats to life due to extreme environment; alongside in package came adaptation or HA diseases viz, Acute or chronic mountain sicknesses, High-altitude pulmonary hypertension, HA pulmonary edema (HAPE) and HA cerebral edema (HACE). Clinical and physiological aspects associating with aggravation of a health condition during travel are well established; whereas, genetic approach in identifying functional variants has added considerable knowledge in elucidating an individual‘s susceptibility. Here, we provide an example of the susceptibility of an individual during travel to a hitherto hidden disorder which surfaces upon exposure to a new environment such as hypobaric hypoxia of HA. The candidate gene and high-throughput approaches have achieved considerable success in elucidating individual‘s predisposition and provided insight into the dynamics of genome-evolution. Confluencing both the traditional and contemporary approaches, we investigated several candidate genes viz: Angiotensin I converting enzyme (ACE), Angiotensinogen (AGT), Endothelial nitric oxide synthase (NOS3), Aldosterone synthase (CYP11B2), Endothelin-1

(EDN1) and Adrenergic, beta-2-, receptor, surface (ADRB2) in healthy native Himalayan-highlanders (HLs) and sojourners i.e. High-altitude pulmonary edema-resistant control (HAPE-r) and HAPE-patient (HAPE-p). In addition, the relevant biomarkers were also estimated. We illustrate our relevant findings, which once established may influence predisposition and therapeutics. Individual allele/genotype, haplotypes, genotypes/gene-gene interactions and their correlation with pertinent biomarkers were analyzed. Further in a genome-wide study, we compared >4000 SNPs distributed across the entire genome of two ethnically similar populations contrasting altitude residence. The allele/genotype distribution at the same locus varied significantly among these groups. The alleles ACE I (rs4646994), NOS3 894G (rs1799983) and 4b, EDN-1 2288G (rs2070699) and CYP11B2 –344T (rs1799998) were higher in HLs than HAPE-r ($p<0.05$). Whereas, over-representation of D, 894T and 4a, and 2288T alleles was obtained in HAPE-p (p between 0.03 and 0.002) when compared against HAPE-r. Genotype-interactions revealed over-representation of GGbb of NOS3, II/GG of ACE/END1 in HAPE-r than HAPE-p ($p<0.05$). The higher ACE activity, endothelin and aldosterone levels and lower nitric oxide level correlated with respective variants in HAPE-p ($p<0.0001$). The MDR model depicted ADRB2 polymorphisms 46A/G (rs1042713), 79C/G (rs1042714) and 523C/A (rs1042718) as the best disease predicting combination; whereas, greater power was demonstrated by ADRB2 haplotypes to predict HAPE. The genome-wide comparison corroborates difference in SNPs of genes or regions close to the above candidate genes. The participation of vascular homeostasis genes in adaptation to HA environment is perceptible. The high throughput genetic tools have laid a platform to diagnose genetic markers of predisposition to HA adaptation/mal-adaptation. SNP, measured by the odds ratio and its corresponding 95% confidence interval, was estimated using unconditional logistic regression models. At the second stage, tow-way interactions were investigated using multivariate logistic models. Genotypic and allelic frequencies of the P53BP1 Glu325Asp and of P53BP1 Gly412Ser lack association with respect to breast cancer risk when considered in overall, stratification according to menopausal status shows a modest increase of risk among homozygous carrier of P53BP1 412Ser/Ser P=0.08 (OR = 4.00, 95% CI 0.85-18.34) in post menopausal patients compared to postmenopausal control women and of Ser alleles carrier P=.0.05 (OR= 5.71 (95% CI .0.92-5.5). No significant associations were seen among homozygous carrier of P53BP1 353 Asp/Asp neither of Glu alleles versus Asp alleles in the menopausal subgroup. In the haplotype of the 2 SNPs of P53BP1, no significant associations were observed nor when the genotype investigated in overall to the breast cancer risk. Genetic epidemiology study replication and functional assay of these SNPs as well as of haplotypes should permit a better understanding of the role of these genetic variants and breast cancer risk.

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TUMOUR NECROSIS FACTOR ALPHA -308 A/G POLYMORPHISM AND THE OCCURRENCE OF PRETERM BIRTH (PTB) IN MALAYSIAN POPULATION

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Preterm birth or PTB (delivery before 37 weeks of gestation) is the major cause for neonatal mortality and morbidity worldwide. The incidence of PTB accounts for approximately 10% and this statistic has not been decreasing even with the advancement of the medical technology. PTB is multifactorial and the occurrence can vary amongst ethnicities. One of the theories, PTB may be a result of an inflammation response triggered at the genetic level. Here, one of the important polymorphism involved in preterm birth was studied, the Tumor necrosis factor alpha specifically at the 308 position of its promoter region. Objective of study: To determine the association of Tumor Necrosis Factor Alpha (TNFa) polymorphism and the occurrence of preterm birth in the Malaysian population. Peripheral blood were drawn from women of the three major ethnic of Malaysia namely the Malays, Chinese and Indians with less than 37 weeks of gestation as case (preterm) and between 37 to 42 weeks as control (term) who fits the inclusion and exclusion criteria and showing sign and symptom of spontaneous labor. RealTime-Polymerase Chain Reaction (RT-PCR) technique was use for genotyping the single nucleotide polymorphism at the position 308 of the TNFa promoter region. A total of 161 women was enrolled (116 control and 45 case) and the sample size was in Hardy-Weinberg Equilibrium (HWE). Genotyping founds that TNFa -308 A/G single nucleotide polymorphism was not associated with the occurrence of preterm birth (df=2, p-value= 0.272) in the Malaysia population. There was no significant difference between the case and control in terms of TNFa -308 A/G polymorphism with the occurrence of PTB in the Malaysian population (p-value >0.05).

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ABSENCE OF ASSOCIATION BETWEEN ACE GENE POLYMORPHISM AND PLACENTAL INSUFFICIENCY

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Placental insufficiency (PI) is one of the most common complications of pregnancy. It is the cause of intrauterine growth retardation and fetal hypoxia. Recently, great attention in the pathogenesis of PI is paid for genetic factors. The aim of the study was to evaluate the role of G2350A polymorphism of angiotensin-converting enzyme (ACE) gene in the formation of hereditary predisposition to the development of placental insufficiency in women living in Kazan, Tatarstan. The sample in this study consisted of 170 pregnant women: 90 women with PI and 70 women with a normal pregnancy. Genomic DNA was extracted from samples of whole blood in accordance with standard phenol-chloroform method. This polymorphism was genotyped using RFLP-PCR analysis. Data were analyzed using Chi-square test and 95% confidence interval (CI). Analysis of results showed that the frequency of

alleles and genotypes for tested polymorphic variant of the ACE gene did not significantly differ in groups of healthy subjects and patients with PI. Thus, G2350A polymorphism of the ACE gene is not associated with the development of the PI in women in the Tatarstan.

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LIPOPROTEIN LIPASE GENE POLYMORPHISM AND RISK OF ATHEROSCLEROSIS

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Lipoprotein lipase (LPL) plays a key role in lipid metabolism. There are several polymorphic loci in LPL gene. Among them HindIII-polymorphism takes a special place because it is associated with cardiovascular diseases and hypertrygliceridemia in some populations. So the aim of this study was to investigate the association between the HindIII-polymorphism gene LPL and susceptibility to atherosclerosis (AT) in two populations (Tatars and Russian) of the Republic of Tatarstan (RT). We analyzed the HindIII-polymorphism of LPL gene in 148 patients with AT and 90 healthy subjects. Genotypes were determined by the PCR-RFLP method. Data were analyzed using Chi-square test and 95% confidence interval (CI). Statistical analysis showed that the genotype H+H+ is a marker of genetic predisposition to the AT in Tatars (OR=5,44 CI 4,51-6,37), moreover this genotype was associated with the increased risk for AT in men (odds ratio OR = 3,56 95% CI 2,80-4,36). No differences in genotype frequencies were observed between AT and controls for studied polymorphism in Russian population of the RT. Thus, this study confirmed an association between HindIII-polymorphism of LPL and risk of development of AT.

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PERSONALIZED AND HOLISTIC MEDICINE: INTEGRATION OF GENETICS AND INFORMATICS

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Clinical diagnosis and healthcare management combined with modern medicines save millions of lives every day. It focuses on the individual patient's phenotypes like clinical signs and symptoms, combined with metatypes like medical and family history, and data from laboratory and imaging evaluation to diagnose and treat illnesses. This is a reactive approach, where the treatment or medication starts after the signs and symptoms appear; and, treated with generic or blockbuster drugs. Some of these drugs work well for many people but do not work for many others. Or, it might cause severe side effects for many. Why do medicines act differently on different individuals? Because, individual‘s genes, lifestyle, age, environment, microbes, and overall health influence response to medicines, science is maturing and we are at a point where we can look into personalized medicine and holistic wellbeing instead of just reactive healthcare. In holistic wellbeing we will look at specific gene variations and the genotypes (genotyping and genetic signatures like eSNP, eQTL derived from GWAS, CNV, LD, Population genetics, Expression profile, Imputation analysis etc) of individuals alongside the phenotypes with responses to particular medications. Also, in holistic wellbeing we will look at individual‘s participatory role in diagnosis where individuals use their mobile device and communication networks to record clinical events at the individual‘s end; these events combined with patient‘s history at the clinician‘s end will help understand the lifestyle and environmental factors in illness. In addition, in holistic wellbeing we will look into metagenomics to determine the microbe population and their equilibrium within and around the individual. With this information, doctors would be better equipped to tailor treatments to individuals. A marriage between genetics, epigenetics, metagenetics, statistical bioinformatics, and informatics opens up the opportunity for personalized medicine and pharmacogenomics that offers the promise of predicting an illness before they happen and whether a medication is likely to help or hurt the individual. Pharmacogenetics (also termed pharmacogenomics) is aimed at tailoring drug discovery to identify the molecules that are most appropriate for an individual or his metabolic properties or determine the therapy and a dosage appropriate for an individual. Gene-centered pharmacogenetics will also speed the development of novel therapeutics and has the potential to reduce the cost of treatment. This talk will articulate integration of all the above technologies and the path to Personalized and Holistic medicine.

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GENOME-WIDE ASSOCIATION STUDY OF BMI AND WAIST CIRCUMFERENCE WITH TYPE 2 DIABETES IN LARGE ARAB FAMILY FROM UNITED ARAB EMIRATES

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Overweight and obesity are major risk factors for a number of chronic diseases, including Type 2 Diabetes (T2D), cardiovascular disease and cancer. In the United Arab Emirates (UAE), it has been estimated that some twenty percent of adults suffer from obesity. The incidence of T2D in the UAE population is also among the highest in the world. To identify factors that result in obesity, and its association with T2D, we conducted a Genome-Wide Association Study (GWAS) and specifically assessed genetic associations with 'Body Mass Index' (BMI) and 'Waist Circumference' (WC). GWAS analysis of 178 individuals in an extended family of

Arab descent revealed four loci that reached genome-wide significance, two of which were found in previous studies. The previously described association between the Single Nucleotide Polymorphism (SNP) at position rs2793823 within the ADAM30 locus (identified through meta-analysis of a GWAS study of subjects of Caucasian descent) was also shown to be associated with the disease in Arabs (p = 1.86E-8). Our study also confirmed the association between SNPs within the JAZF1 loci and BMI, WC and T2D as reported in other studies. Two novel associations were noted in our study: (1) a novel locus on chromosome 16 within the FBXO31 locus (rs9308437, p = 7.5E-7) was shown to be associated with the WC phenotype, and (2) the SNP (rs7120774) in GALNTL4 of chromosome 11 was found to be associated with BMI (p =1.82E-10). FBX031 is a candidate gene for breast cancer, whereas GALNTL4 plays a role in insulin stimulated glucose transport in muscle. Work continues to replicate the two latter findings in independent cohorts to confirm the involvement of FBXO31 and GALNTL4.

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MOLECULAR CYTOGENETIC IDENTIFICATION OF A DICENTRIC Y;22 TRANSLOCATION IN A BOY WITH DELAYED MILESTONES

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Chromosomal rearrangements involving chromosome Y and 22 are very rare and may result in a number of phenotypes. Here we report a 1 year 5 month old boy who was referred to our Institute with delayed milestones. The cytogenetic analysis revealed a karyotype of 45,X, 22p+. NOR staining was done to rule out the presence of double satellites on 22p+. The negative results of NOR indicated that it is a euchromatic region. There was no evidence of Y chromosome material on any of the chromosomes analyzed by Q banding and DAPI staining, which highlights the heterochromatic region. Hence we concluded that the additional material on chromosome 22 is likely to be of Y origin. Further molecular cytogenetic analysis with Fluorescence in situ hybridization (FISH) was performed to identify the rearranged chromosome. Whole chromosome paint (WCP) with chromosome 22 probe also showed that the p region is from a different chromosome. FISH with alphoid repeat DYZ3 showed signal almost at the terminal region of the rearranged chromosome indicating that the Y chromosome is translocated on to chromosome 22. Subsequently WCP for Y chromosome was also performed to confirm the translocation. FISH with Alphoid 22 probe was done to confirm the dicentric status of the rearranged chromosome. Both the father and sibling‘s karyotype showed normal Y chromosome. In our case the heterochromatin region of Y chromosome is not seen and also the very small size of the p+ region indicated that the Y chromosome is partly deleted. To find the extent of deletion, FISH with three BAC clones was performed RP11-375P13 on Yp11.2 region, RP11-71 M 14 on Yq11.221 and RP11-20 H 21 on Yq11.222. There were no signals observed which indicated the deletion of those regions. Further investigation to find the extent of deletion and also the presence of SRY region is underway. Our investigations help in identifying the cryptic rearrangements of involving chromosome Y and 22 and its correlation with the phenotype.

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DISTAL GENE REGULATORY ELEMENTS HAVE AN AVERAGE SIZE OF A NUCLEOSOME

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The genome is packaged in nucleosomes comprising 147 bp of DNA wrapped around 8 histone proteins with a normal distance of 20-30 bp between the end of one nucleosome and the beginning of the next. Transcription factors (TFs) bind to promoters and distal regulatory elements in regions free of nucleosomes and regulate the activity of nearby genes. Promoters located upstream of genes are well known but distal regulatory elements are at present poorly defined as to location and size. We used chromatin immunoprecipitation and large scale sequencing (ChIP-seq) in the liver derived cell line HepG2 to map several TFs that bind to distal gene regulatory elements and RNA Pol II, which binds to promoters. In addition, we treated chromatin with MNase I to create mononucleosomes that were subject to large scale sequencing (MNase-seq). To apply the strategy to a gene of medical interest, we studied SNPs associated with dose requirement of the drug warfarin, which is commonly used to prevent thrombosis. GWAS studies have identified many SNPs in high linkage disequilibrium in and around the VKORC1 gene associated with dose of warfarin, but the functional one has not been identified. At these SNPs we also performed qPCR of DNA isolated using formaldehyde assisted isolation of regulatory elements (FAIRE) to detect nucleosome-free regions i.e. sequences with regulatory potential. We found 18783 sites bound by the TF HNF4a, 7266 sites bound by FOXA2 and 3564 bound by both of them, the great majority located far from annotated transcription start sites. With MNase-seq we obtained 200 million aligned reads and used them to generate footprints around binding sites for individual and pairs of TFs. In all cases, the pattern of nucleosomes suggests that one nucleosome is displaced at regulatory elements. Since the studied TFs bind to distal elements, this suggests that the pattern is present at most enhancers and silencers. To validate the findings, we generated footprints of nucleosomes around public ENCODE data of DNase I hypersensitivity sites located more than 5 kb from promoters. Also in these regions the data suggests that a single nucleosome has been removed. Out of 22 tested VKORC1 SNPs, 7 are located in nucleosome-free regions as determined by MNase-seq and qPCR of FAIRE DNA, which indicates that they may be functional. Our results indicate that most distal regulatory elements are generated through the removal of one nucleosome, which is replaced by TFs binding to those sequences. We used several chromatin signals to prioritize among VKORC1 SNPs associated with dose of warfarin and found that most of them are located in chromatin without

regulatory potential. Some SNPs are, however, located in nucleosome-free regions and are subject to further analysis.

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A HIGH-DENSITY ASSOCIATION MAPPING OF A CANDIDATE REGION FOR YOUNG-ONSET TUBERCULOSIS IDENTIFIED A NEW SUSCEPTIBILITY GENE

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We have previously performed a genome-wide linkage study in Thai using high-throughput microarray-based SNP genotyping platform (Mahasirimongkol et al., 2009) and reported that chromosome 20p13-12.3 showed a significant linkage with young-onset tuberculosis (TB) after applying ordered-subset analysis based on age at onset (LOD=3.33, p=0.0183, marker= rs750702). In order to narrow down the candidate region, a high density association mapping of 1 Mbp region around the SNP marker was performed in the present study using 160 tag SNPs of Han Chinese in Beijing (CHB) Hapmap phase II data with 275 cases and 250 controls of Indonesian. 130 SNPs passed the quality control and were used for further analyses. The results showed that SNP-a has significant association with TB, even after applying Bonferroni correction (pallele=7.14×10-5, pc=0.009, OR=1.67 (1.30-2.15). After ordered-subset analysis for case-control study was applied, lower p-value was obtained for the SNP-a in the case samples with age 45 years old and younger. In young-onset group, three SNPs showed the lowest p-value (SNP-a, p=7.19×10-6, pc=9.35×10-4; SNP-b, p=4.58×10-5, pc=5.95×10-3 and SNP-c, p=6×10-4, pc=ns). For further high density mapping, five additional SNPs reported in CHB Hapmap phase III and NCBI dbSNP were genotyped. None of the additional SNPs showed significant association in young- and late-onset groups. SNP-b and SNP-c were in strong linkage disequilibrium (LD) (r2=0.71), however those two SNPs were in low LD with SNP-a (r2=0.12 (SNP-a – SNP-b) and r2=0.10 (SNP-a –SNP-c)). The logistic regression analyses in young-onset group showed that SNP-c remained significant after controlling SNP-a and SNP-b, however when all SNPs were adjusted by SNP-a and SNP-c, no SNPs remained significant. All significant SNPs were located at the region containing two neighboring genes (Gene-X and gene-Y). These results suggested that the association between the region and young-onset TB observed in this study could be explained by the combination effect between SNP-a and SNP-c. In the late-onset group, no significant results were observed. SNP-a was located at 5‘ region of gene-X and at 3‘ region of gene-Y. The gene expression database of CHB population (Barrett et al., 2009) revealed that allele T of SNP-a had significantly higher expression of gene-X than allele C (p-value=0.02, 1-tail Mann-Whitney U test). The SNP-a did not affect the expression of gene-Y. These results suggested that SNP-a was a causative and functional SNP for young-onset TB in Indonesian. However the possibility of the presence of other primary SNP(s) in strong LD still remains. Gene-X is involved in the regulation of immune balance mechanism. It was hypothesized that the individuals carrying the risk allele may have lower immune response to mycobacterium invasion, accordingly increase susceptibility to develop young-onset TB. Further confirmatory association studies in other populations are needed.

GENOMICS AND THE BIOECONOMY

P298
ECONOMIC VIABILITY OUTCOME OF ASSISTED REPRODUCTION TECHNOLOGY SETUP: MATHEMATICAL MODEL

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Objective: To develop an evaluation method measuring the economic viability outcome of ART setup in a concerted fashion. Design: Cross-sectional study. Setting: Banoon Assisted Reproductive Technology (ART) Centre, Military Hospital, Bahrain. Subjects and Methods: All patients who underwent assisted reproductive treatment cycles in the centre during the period September 2004 to September 2006 were included in this study. A mathematical model namely; economic viability outcome (EVO) value has been purposely constructed and was put to the test. The model consists of three important domains: 1. Economic performance outcome of the setup; 2. Sustainability outcome; and 3. Control outcome. Main Outcome measures: Economic viability outcome of ART setup. Results: Application of the model at the said centre resulted in an increase of EVO value by 32% from 0.56 to 0.82 within 12 months of rectifications which started Sep 2005. Even though the economic performance has dropped by approximately 22%, due to extra spending towards assets and lower utilization of treatment cycles, the centre showed improvements at various levels as evident from the resulting higher EVO value. Conclusions: EVO value, as a model, provides a mechanism by which ART setup can be economically evaluated and self-assessed. It can also generate a method of measuring the safety and efficacy of the treating centre.

GENOMICS AND THE DEVELOPING WORLD

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TELOMERE LENGTH IN NEWBORNS AND ADULT HUMAN POPULATIONS FROM HIGH LEVEL NATURAL RADIATION AREAS OF KERALA COAST IN SOUTH WEST INDIA

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Telomeres are specialized nucleo-protein complexes consisting of tandem repeats of the DNA sequence (TTAGGG)n at the end of the eukaryotic chromosomes. It protects the coding parts of the DNA for recombination, degradation and replication damage and thus play an important role in maintaining chromosome stability. Telomere length has been determined by using techniques like southern blot, fluorescence in situ hybridization (FISH), Flow-FISH and most recently, by quantitative real time PCR. Quantitative real time PCR method provides relative results about telomere length by calculating the ratio of a PCR reaction product from the same sample using specific primers for telomeres and single copy gene (T/S ratio). Shortening of telomere length has been reported to be associated with aging, stress, diabetes, hypertension, many other age related diseases and cancer. Data on telomere length variation in response ionizing radiation is very limited. However, till date, no in vivo data on telomere length in response elevated level of back ground radiation is available. In the present study, we have determined telomere length in normal newborns and their parents residing in high level natural radiation areas (HLNRA) and adjoining normal level radiation areas (NLNRA) of Kerala coast to assess whether the elevated level of background radiation has any significant effect on telomere length. Methods: We have analysed a total of 197 adults (75 from NLNRA and 122 from HLNRA) and 132 newborns (43 from NLNRA and 89 from HLNRA) using SYBR green based real time PCR assay. These samples included 81 mother-child pairs and 63 father-child pairs. Genomic DNA was amplified using telomere (T) and single gene copy primers(S) and relative T/S ratio was calculated. Results: Our data did not reveal dose related loss of telomere length in both newborns and adults. The mean telomere length in adults and newborns were 1.16 ± 0.12 and 1.03 ± 0.10. No significant difference was observed among male and female newborns and adults. No significant change in the telomere length was observed in high level natural background radiation area as compared to normal back ground radiation area.

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STRATEGY FOR EARLY DIAGNOSIS OF MYOTONIC DYSTROPHY IN THE MALAYSIAN POPULATION

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Myotonic dystrophy (DM1) is an autosomal dominant multiorgan disorder characterized by progressive muscle weakness and myotonia. The congenital form leads to neonatal death. It is considered the most prevalent inherited neuromuscular disease in adults with an incidence in 5.5/100000 in Japanese. Individuals affected with DM1 have an unstable expansion of a CTG trinucleotide repeat array in the untranslated region (UTR) of the Myotonic Protein Kinase (DMPK) gene on chromosome 19q13.3. The age of onset and phenotypic severity correlates with the CTG expansion size. DM1 patients have 50 to 1000 CTG repeats in mild and classic form and up to several thousand repeats in severe congenital form. Healthy individuals have highly polymorphic alleles between 5 and 35 repeat. In developing countries like Malaysia, the molecular diagnosis of DM1 is not available. This had hampered early diagnosis, genetic counseling and management of the condition. The objective of this study is to develop a polymerase chain reaction (PCR) analysis and Southern transfer approach to diagnose DM1 and the secondary aim is to determine the prevalence of DM1 among Malay by investigating the CTG repeat size. When an individual demonstrates two different normal size alleles on PCR, DM1 is excluded. The presence of a single band may indicate CTG expansion or an unaffected individual homozygous for a given normal allele. Therefore, Southern blotting test is performed. We determined the heterozygosity of DM1 alleles and the frequency distribution of various CTG repeats in normal Malays and optimized Southern blotting to determine the CTG repeats in affected families. Blood samples were collected from normal adult population as well as affected individuals with DM1. Ethical approval was obtained for this study. The peripheral blood DNA was extracted and the PCR reaction was carried out followed by usual get electrophoresis. The purified PCR products were send for DNA sequencing and the data were analyzed to determine the size of CTG repeat. Samples which were suspected to have expanded allele were subjected to Southern blot analysis which included gel electrophoresis, blotting, labeling, hybridization, stringency washing and autoradiography exposure. Based on autoradiography film signal, the sizes of the expanded alleles were calculated. In 120 normal Malays, 58% were heterozygous while 42% were homozygous for the DM1 alleles. Amongst 240 normal chromosomes, a total of 14 alleles with different CTG lengths from 5 to 28 were found. The frequency of CTG > 18 alleles was 3.3%. We successfully determined the number of CTG repeats in two families who had several affected individuals. We developed an effective strategy to screen Malaysian patients for DM1 using PCR analysis. Based on the CTG allele frequency in the Malaysian Malay population, we predicted a low incidence of DM1 among the Malay population. These findings have clinical and population genetic implications for the South-east Asia region. Individuals with DM1 homozygous alleles were subjected to Southern transfer for ascertainment of CTG repeats. Genetic counseling was provided for affected families.

GLOBAL AND REGIONAL INITIATIVES

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NO ASSOCIATION EXISTS BETWEEN CYP3A4 POLYMORPHISMS WITH ANTI-HEPATITIS A VIRUS SEROPREVALENCE AMONG CHRONIC VIRAL HEPATITIS B AND C LIVER DISEASE PATIENTS

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Review of epidemiology for hepatitis A infection indicates a shifting pattern in the prevalence of anti-HAV to lower endemicity in South-East Asia. As a result, vaccination against hepatitis A virus is recommended in chronic liver disease patients to prevent liver decompensation due to superinfection. CYP3A4 is the major cytochrome in humans which shows reduced activity in chronic liver disease (CLD) as well as in hepatic cirrhosis. It is postulated that the detection of this polymorphism may give an indication on the prognosis of patients having chronic viral hepatitis with superimposed Hepatitis A infection. The aim of this study is to correlate the seroprevalence of anti-HAV antibodies in patients with CLD with CYP3A4 polymorphism. The diagnosis of CLD was based on the presence of viral markers of more than 6 months. The diagnosis of liver cirrhosis was based on clinical, biochemical, radiological profiles. Patients' (n=119) serums were tested for anti-HAVIgG and CYP3A4*18 polymorphism. The overall anti-HAV seroprevalence was 88.2%. The etiology of CLD was hepatitis B in 96 patients (80.7%) and hepatitis C in 23 patients (19.3%). Patients were grouped according to age: 24 (20.2%) patients in the 21-30 age group, 22(18.5%) in the 31-40 age group, 31 (26.1%) in the 41-50 age group, 23 (19.3%) in the 51-60 age group and 19 (16.0%) patients aged more than 60 years with the seroprevalence reported at 66.7%, 95.5%, 93.5%, 91.3% and 94.7% respectively. The mean age was 44.4 ±14 years. There was a marked increase in the age of the prevalence of this disease after 30 years of age (p=0.008). All patients with the CYP3A4*18 mutations were found to be heterozygous. CYP3A4*18 polymorphism was detected in 3 (2.5%) of the patients with CLD. Our study demonstrated that age was the most important factor in determining anti-HAV positivity and with most patients ageing more than 30 likely to have developed natural immunities. There was no significant association between CP3A4*18 mutation and anti-HAV serology (p=0.221). It is concluded that CYP3A4 genetic polymorphism does not play a role in influencing the seroprevalence of Anti-hepatitis A among chronic viral hepatitis B and C liver disease patients.

P302

NUCLEOSIDES 71: SYNTHESIS, STRUCTURE AND BIOLOGICAL ACTIVITY OF NEW 6-ARY-LIDENAMINO-2-THIO-AND 2-BENZYLTHI-OPYRIMIDINE N-NUCLEOSIDES

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The condensation of 6-amino-2-thioxo-2,3-dihydro-1H-pyrimidine-4-one (1) with aromatic aldehydes 2 afforded azomethine derivatives 3. The formed azomethines underwent glycosidation with ?-acetobromoglucose 4 to form the corresponding pyrimidine N-glycosides 6 and not S-glycosides 5. The interaction of 3 with 1-O-acetyl-2, 3, 5-tri-O-benzoyl-?-D-ribofuranose 8, afforded the corresponding pyrimidine N-riboside10 and not S-riboside 9. Deacetylation and debenzoylation of each of 6 and 10 by using methanolic sodium methoxide afforded the corresponding free N-nucleosides 7 and 11, respectively. Next, the reaction of 2-benzylthio-6-benzylidenaminouracil 13 with 4 and 8 did not yield the corresponding protected N-nucleosides 14 and 17, while it afforded 15 and 18, respectively. The latter compounds 15 and 18 were stirred in methanolic sodium methoxide to yield the corresponding free N-nucleosides 16 and 19, respectively. The structures of products have been elucidated and reported and also some of the products were screened for their antimicrobial activity.

P303

PORTRAIT OF SCHIZOPHRENIA IN PSYCHIATRIC PATIENTS IN THE CITY OF MANAUS

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Schizophrenia (ESQ) is an intriguing psychiatric illness, which has a prevalence of about 1% and generally affects people during the height of their production processes. The ESQ, as well as other complex diseases, seems to be caused by a number of factors, including environmental and multifactorial inheritance. According to the multifactor model, there are several genes involved in this disorder that may act additively and suffer environmental influences, increasing susceptibility to this disease and/or worsening the patient's condition is a threshold genetic influenced by the environment. Our research tried to overview Manaus, the largest city in northern Brazil, with approximately 2 million habitants. This research is the first held in the Amazon that aims to study the genetic patterns of this disease. Investigations were carried out in cases of ESQ in the family of 10 diagnosed patients from the Eduardo Ribeiro Psychiatric Center, through interviews with them, relatives or guardians, which served as information for the pedigrees‘ construction for each family of the patients who agreed to participate. From the data analysis we made 10 families‘ pedigrees, containing 3-5 generations each, with 15-47 individuals in a total universe of 285 people, 26 (16 men and 10 women) of those diagnosed with schizophrenia. The

risk of developing schizophrenia was increased in relatives of probands, and more pronounced for 1st degree and lower in the 2nd. Depression appears as one of the most frequent phenotype in affected and their relatives in Manaus, followed by bipolar disorder.

P304

ALU-RECOMBINATION MEDIATED DELETIONS CONTRIBUTE TO GENOMIC DIVERSITY BETWEEN HUMAN POPULATIONS

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Alu elements comprise more than 10% of the human genome. These elements are prone to non-allelic homologous recombination that creates genomic deletions which have previously been associated with a variety of human diseases. The role of this ectopic recombination process in creating human genomic variation between individuals remains unknown. Here, we addressed this question by comparing two fully sequenced human genomes [Public Human Genome (PHG) and Celera Human Genome (CHG)] to generate a snapshot view of Alu recombination-mediated deletions (ARMDs) during recent human genome evolution. Combining computational data mining and wet-bench verification techniques, we identified 54 individual-specific deletions (of 144 computationally predicted deletions) attributable to this process, which removed ~70 kb of sequence from both Public and Celera human genomes. Approximately 54% of ARMDs events were located within known or predicted genes. Polymorphic assessment at the population level were done by amplifying these loci on a panel of human genomic DNA samples from 80 unrelated individuals from four geographically separated human populations: African-American, Caucasian, South American and Asian. Structure analysis of the 54 ARMDs revealed a distinct population structure in the 80 human individuals we genotyped. This study presents a comprehensive analysis of ARMDs in two different assemblies of the human genome and demonstrates that ARMDs plays an important role in generating inter-individual structural variations, and that these deletions may contribute to phenotypic variation between humans.

P305

GENOTYPE AND ALLELE FREQUENCIES OF THE INTESTINAL FATTY ACID BINDING PROTEIN-2 GENE POLYMORPHISM AMONG ARABS

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Intestinal fatty acid binding protein (IFAPB) participates in the uptake, intracellular metabolism and/or transport of long chain fatty acids. A polymorphism at codon 54 in exon 2 of the FABP2 gene, which encodes for the IFAPB, exchanges an Alanine for Threonine. The aim of this study was to determine the frequency of the Ala54Thr FABP2 polymorphism in three Arab populations. Genotyping was investigated in 182, 120 and 180 unrelated healthy subjects from Bahrain, Jordan, and Egypt, respectively. A PCR-RFLP assay was applied for the determination of Ala54Thr FABP2 polymorphism. Allele frequencies were calculated by direct counting. Hardy Weinberg Equilibrium was evaluated using a Chi-square goodness of fit test. Results showed that 52.7% of the studied Bahraini subjects were homozygous for the Ala54/Ala54 genotype, 35.7% were heterozygous for the Ala54/Thr54 genotype and 11.5% were homozygous for the Thr54/Thr54 genotype. The gene frequencies obtained in Jordanians were: 48.3%, 43.3% and 8.3% for Ala54/Ala54; Ala54/Thr54 and Thr54/Thr54 genotypes, respectively. For Egyptians, 56.7% were homozygous for the Ala54/Ala54 genotype, 33.3% were heterozygous for the Ala54/Thr54 genotype and 10% were homozygous for the Thr54/Thr54 genotype. The frequencies of the Ala54 allele and the Thr54 allele of the FABP2 gene were found to be 0.706 and 0.294 for Bahrainis, 0.700 and 0.300 for Jordanians and 0.733 and 0.267 for Egyptians, respectively. The frequencies of the Thr54 allele in the studied Arab populations does not differ from previously reported frequencies among European populations. In conclusion, this is the first study to investigate the population frequency of the Thr54 allele in Bahraini, Jordanian and Egyptian populations.

P306

TOLL-LIKE RECEPTOR 4 POLYMORPHISMS IN DENGUE VIRUS INFECTED CHILDREN

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Differential viral recognition by cells bearing the TLR4 polymorphisms Asp299Gly and Thr399Ile may influence susceptibility and severity of dengue virus infection (DVI). In Central Java, Indonesia, we investigated 201 children with dengue hemorrhagic fever (DHF), either with stage I or II, or with stage III or IV, and 179 healthy controls. Patients and controls were mostly ethnic Javanese. TLR4 Asp299Gly and Thr399Ile polymorphisms were determined in patients and controls, and in the patients also plasma leakage. No significant difference in prevalence of TLR4 Asp299Gly and/or Thr339Ile genotype between controls and patients was apparent. Interestingly, an almost complete cosegregation of the two mutations was observed. Similarly, no difference in

TLR4 polymorphisms within different stages of DHF was found. Also, vascular leakage in patients with different TLR4 genotypes did not differ. In conclusion, the 299/399 TLR4 haplotype does not influence susceptibility and severity of complicated DVI.

P307

DIFFERENCE IN MTDNA WHOLE SEQUENCE BETWEEN TIBETAN AND HAN POPULATIONS INDICATED CLUES OF ADAPTIVE SELECTION

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Human mitochondrial DNA (mtDNA) is the extra-nuclear circular molecule and spans 16,569 base pairs including the encoded genes of 13 peptides, 2 rRNA, 22 tRNA and 1,121 nucleotide pairs of control region (D-loop). The function of mtDNA oxidative phosphorylation (OXPHOS) were determined by the encoded genes of the 13 peptides, the expressions of the genes of rRNA and tRNA and the modulation of D-loop in transcription and replication. The mtDNA has a lot of characteristics which differ from nuclear genome, such as lack of recombination, frequent mutations, high copy number and maternal inheritance. All of these characteristics offer the potentials of investigating the human evolution and origin. Previous studies indicated that mtDNA sequences harbor geographic variation traditionally due to genetic drift. However, the effects of natural selection on characteristic variations in mtDNA remain unclear. To clarify this, we conducted the study of whole mtDNA genome comparison in 90 pooled subjects between Tibetan and Han population in China. In this study, whole mtDNA sequencing was performed using ABI 3730 sequencer. Data were analyzed using software phredPhrap 16.0, Network, DnaSP 4.20.2, SSPro, 3Dpro, MaxSprout, Rasmol, Swiss-pdbviewer, and RNAfold. We found all the subjects were classified into 13 haplogroups pertained to the Macrohaplogroup M and N, and there no difference was observed among all haplogroups between Tibetan and Han populations except M9. Principal component analysis indicated that the Tibetan and Han populations pitched different quadrants. Between the two populations, 18 variations detected by comparing mtDNA whole sequences were significant difference; 5 variations were first identified and 8 variations were defined at the internal branch. Predicting of structure changes in protein and RNA was conferred by using the 7 dominated variations in Tibetans. We found that the structure stability of ND2, COX2, tRNA alanine and 12S rRNA was increased. Comparing the base substitutions of nonsynonumous (N) versus synonymous (S) in 13 protein-encoded genes between the Tibetan and Han, we found N/S values of ATP6, ATP8, and Cyt b genes were higher (>1) in Tibetan than that of in Han. The analysis of whole mtDNA sequence provided clues that the existence of adaptive selection for ATP6, ATP8, Cyt b, ND2, COX2, tRNA alanine and 12S rRNA genes in Tibetans attributed to the adaptation in the special geographic environment.

P308

PREVALENCE OF SICKLING IN A SELECTED SPOT OF RAJNANDGAON DISTRICT (CHHATTISARH, INDIA) AND ITS ASSOCIATION WITH PREVALENCE OF PLASMODIUM FALCIPARUM

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Sickle cell disease is a blood disorder resulting from inheritance of abnormal gene from parents. It is caused due to mutation in the □-globin gene. Sickle cell disease is wide spread in Central India. Present study was under taken to study the prevalence of the disorder in Rajnandgaon district of Central India. A random sampling of 1749 people, was done to test sickling problem. By slide test method 71 people were found sickled positive. Further electrophoresis test was performed for all 71 of which 24 were found homozygous (HbSS) and 47 were found heterozygous (HbAS) positive. Beside above analysis, chloroquine prophylaxis associated with high prevalence of Plasmodium falciparum Pfcrt K76T mutation in people (n=26) with sickle cell disease was also analyzed. The genotype of the subject was screened using hemoglobin electrophoresis system and the P. falciparum Pfcrt genotyping was carried out using PCR- restriction fragment length polymorphism (RFLP). The prevalence rate of Pfcrt K76T mutant gene was proportionately found higher in the hemoglobin SS (n=9, m=6, r=0.66) genotype individuals than the hemoglobin AS (n=17, m= 9, r=0.52) and AA (n=32, m= 12, r= 0.37).

P309

BONE HEALTH AND COMMON DISEASE IN THE KOREAN AND KAZAKH DIASPORA IN CENTRAL ASIA: A NATURAL EXPERIMENT TO STUDY GENE BY ENVIRONMENT INTERACTION

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It is widely accepted that genetic and environmental factors and interactions among them have a significant role in the etiology of common disease. In agricultural studies, one popular study design to separate these effects by growing plants from the same set of strains in a variety of soil/fertilizer/climactic conditions. Humans, unlike plants, choose their environments, and humans that are genetically similar to one another often have similar culture and environment, even when living in different parts of the world due to recent emigration. In the last century, however, the

establishment of borders and Cold War politics in Central Asia together have led to cultural isolation of ethnic Kazakhs in Kazakhstan from ethnic Kazakhs in China. Similarly, ethnic Koreans in Kazakhstan have been separated from ethnic Koreans in China and Korea. We are taking advantage of these unique opportunities to examine what happens when humans from similar genetic populations live under radically different cultural and environmental conditions as a human analogue of the agricultural study design. In addition, we ascertain available 2- or 3-generation families to better understand segregation of traits in families for subsequent genetic studies. Ethnic Kazakhs in Kazakhstan have lost much of their traditional lifestyle over the years from Stalinist collectivization and Russification of their culture. On the other hand, ethnic Kazakhs in China still live a largely nomadic existence herding sheep in the Altay and Tian Shan mountains. Ethnic Koreans ended up in Kazakhstan after Stalin deported them from the Russian Far East in the 1930s, and had their culture and traditional diet stripped from them as they moved to the Central Asian steppes. Because of Cold War isolation, rapid cultural evolution has led to the same genetic populations existing today with uniquely disparate culture and lifestyle, we have a natural experiment to examine gene-environment interaction as in agricultural studies. We have been investigating traits related to bone health and metabolic syndrome in Kazakhs and Koreans in Kazakhstan, China, and Korea, and here we specifically focus on the work we conducted in Almaty, Kazakhstan. We compared bone stiffness values for randomly selected non-diseased ethnic Kazakhs vs. ethnic Koreans living in Kazakhstan. For both sexes, ethnic Kazakhs had a higher bone stiffness value than ethnic Koreans (males: 105.4 vs. 94.8, respectively; females: 90.4 vs. 83.9, respectively). Ethnic Russians, another comparison group, had the highest mean bone stiffness value. We computed heritability for multiple quantitative traits, such as bone stiffness index, anthropometry, clinical chemistry, etc, using ethnic Korean families in Kazakhstan. The heritability estimate for bone stiffness index was high (h2=0.86). Some of the anthropometric measures, such as arm length and sitting height, had high heritability (>0.55), while others (biiliocristal diameter and transverse chest) yielded low heritability estimates. In addition, a substantial genetic contribution was observed for liver functions, where the heritability estimates ranged from 0.64-0.88. Additional results will be discussed. Here we present a natural experiment involving ethnic Kazakh and Korean populations in Central Asia to understand the role of gene-environment interaction in common disease.

P310

STUDY OF GENE-ENVIRONMENT INTERACTIONS IN MARACAIBO-VENEZUELA

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Age-related dementia disrupts normal functioning of afflicted individuals and their families, imposing significant social, economic, and public health burdens. Prevalence of dementia is increasing in both developed and developing countries, including Venezuela, but many of the underlying causes remain to be identified and understood. Ischemic small vessel disease (SVD) is a leading cause of vascular dementia and a major contributor to Alzheimer's disease. White matter hyperintensities (WMH) evident in neuroimages can be used to evaluate subclinical and clinical SVD. The WMH phenotype is complex, and its causes are not well known. WMH is highly heritable (55-83%); however, previous studies have not identified genes that contribute to the WMH phenotype, probably because WMH is affected by multiple genetic variants with small effect sizes, by multiple environmental risk factors, or by gene-environment interactions. To examine the contribution of genetic and environmental factors in the expression of WMH and to circumvent some of the aforementioned problems, we are studying individuals over 40 y of age, who are members of a large (n=1900), highly inbred, extended family, residing in Lake Maracaibo, Venezuela. Similar families have previously been useful in the discovery of the gene for Huntington's disease. We have taken advantage of information and methodology developed by the Maracaibo Aging Studying (MAS) to implement standardized assessment procedures, including full neuropsychiatric examination, cardiovascular evaluation, nutritional and anthropological assessment, neuropsychological testing, brain magnetic resonance imaging and routine laboratory tests for all participants. Ethical, legal, and social challenges encountered during the population-based phase of the MAS were identified, and a strategy was developed to engage the community, advocacy groups, journalists, educators and librarians, and to enhance their understanding of the aims, risks, and benefits of the study, through community assemblies, symposia, conference, media appearances and workshops. Cooperative efforts among researchers, patients, caregivers, and the community also address challenges in enrollment, retention, intervention adherence, and development of services. Overall, the research program demonstrates the feasibility of modern genetic studies for brain disorders that incorporate a consortium of expertise in human biology, molecular genetics, statistical genetics, neuropsychology, and neuroimaging maintaining sensitivity to cultural demands of the research setting, and respecting the international ethical standards of collaborative research.

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COMPETENCE CENTER TECHNOLOGY TRANSFER AND GENOME MARKETPLACE - TWO INITIATIVES IN THE NATIONAL GENOME RESEARCH NETWORK (NGFN) AND THE PROGRAM OF MEDICAL GENOME RESEARCH IN GERMANY

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Genome Research is not only a basic research source but also a platform for creating and developing new health products and

services. The number of innovations in genetics/genomics leading to applications in the health sector is steadily growing. The results from the genome research programs are early stage in terms of applicability, and it is important to develop strategies to ensure that these advances are progressed suitably to benefit people and their health. It is required to consider the entire process, from discovery, research and development, commercialization and finally up to application. To integrate genome technologies into health systems in an affordable, sustainable, and in a socially appropriate fashion, the Competence Center Technology Transfer (KTT) has been established in 2005 coordinating and supporting invention management and intellectual property asset management activities from NGFN. The KTT Office links the many different scientific groups and parties involved. The internet market platform Genome Marketplace (www.genome-marketplace.de) gives industry centralized access to commercially valuable results from NGFN. To achieve this, we implement our principle of 'One Face to the Client'. Furthermore, most technologies based on NGFN funding are presented to companies at various partnering meetings and show case exhibitions. In addition, Genome Marketplace is the information and communication platform for scientists involved and allows easy communication within the NGFN network. The KTT supports and consults all researchers and associated technology transfer managers regarding all issues of technology transfer (invention - patenting - marketing). Tools like publication screen, reports and round table meetings are organized regularly and assure training of researchers and transfer managers. Through these means we aim to achieve sustainable and effective mechanisms to realize the potential of new technologies for the full benefits of human health. The Genome Marketplace concept of KTT is a key factor on the road to success to combine health and science needs and economic and socio-ecological value. It is this mix of economic and societal benefit that helps to earn proof-of-concept grants and licensing expertise for NGFN inventions and projects. KTT helps industry and society to access efficiently the results from genome research in Germany through sharing knowledge and experience.

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PROTEOMIC STUDY OF THE EFFECTS OF SATURATED FREE FATTY ACID ON SKELETAL MUSCLE CELL LINE C2C12

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Insulin resistance plays a central role in the development of type 2 diabetes mellitus (T2DM). Increased plasma free fatty acid (FFA) levels are observed in T2DM and may be related to the pathophysiology of insulin resistance. Skeletal muscle is one of the most important insulin target tissue and has been the focus of insulin resistance studies. Insulin resistance is often observed in skeletal muscle of T2D patient. In fact, prolonged exposure to high FFA levels could result insulin resistance in skeletal muscle, but the detailed molecular mechanisms involved are not clear. In this study, the protein expression profiles of FFA treated mouse skeletal muscle cell line C2C12 and control were investigated. Total protein extracts from the muscle cell lines were separated via 2D gel electrophoresis and mass spectrometry analysis was followed. We attempt to study the effects of elevated FFA on the cell line by correlating the proteins involved in the energy metabolism, and a shift in energy metabolism from using glucose to FFA as energy source was identified. Insulin sensitivity between the FFA treated and control cell were tested and a decrease was found in the FFA treated cells. Through western analysis, alteration in abundance of proteins involved in insulin signaling was detected; IRS-1 content was decreased while serine 612 phosphorylation in IRS-1 was increased in FFA treated cells.

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MORPHOMETRIC AND ANCIENT DNA STUDY OF HUMAN SKELETAL REMANANTS IN INDIAN SUBCONTINENT

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Studies on the origins of modern humans in Indian subcontinent has taken two different approaches â€—one, focusing on the archaeological record of the initial settlement of our species in South Asia, the other, pinpointing on the genetic diversity and evolutionary history of Indian populations. Our work aims at bridging these two approaches by investigating ancient DNA and human skulls using 3-Dimensional morphometric analysis. We recovered, amplified and sequenced the mitochondrial DNA of 40 hominid remains (20 from Burma, 15 from Nicobar Island and 6 from Andaman Island) and the same Skulls were studied for their morphology, using novel 3D morphometric techniques. To compare the extent of admixture, we also sequenced and analyzed the modern DNA samples from neighboring populations. Results showed the predominant frequency of F1a1 haplogroup and complete absence of 9bp deletion in ancient Nicobarese. Our study on Burmese population is the first genetic study done elsewhere. We find Burmese are much closer to East Asian rather than South East Asian populations and also found significant admixture of Burmese with South Asian and West Eurasian populations, which clearly suggest the late admixture with the neighbouring populations. To rule out the chance of contamination in ancient DNA, we repeated and reproduced our results in two different labs. Three studied populations are quite different in their genetic structure but 3D morphometric study using 128 cranial landmarks explains a close homology among these populations and this can be explained by the role of climatic signature on these populations.

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EASTERN MEDITERRANEAN HEALTH GENOMICS AND BIOTECHNOLOGY NETWORK, TOWARDS REGIONAL INITIATIVE NETWORKING

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To induce collaboration in production, training, research and development to help EMRO countries to be self reliant in health genomics and biotechnology as well facilitate cooperation between developed and developing countries to upgrade health standards, Eastern Mediterranean Health Genomics and Biotechnology Network (EMGEN) was created in 2004 with collaboration of representatives of selected centers of excellence in (health related) molecular biology, biotechnology & genomics in the Eastern Mediterranean region by recommendation of WHO/EMRO efforts. The EMGEN visions generally involve creating and sustaining value by being recognized as a player in the international biopharmaceutical, genomics and biotechnological industry aiming at promoting health in the region, parallel to sustainable developing health genomics and biotechnology through facilitation of high quality R&D training and sharing information, experience distribution and technology transfer in order to meet common and regional health needs of member countries. In this abstract, the latest progress of this network is discussed. Headlines of main performed EMGEN activities: Establishing short term trainings and research exchanging program in EMRO countries in collaboration with TWAS as UNESCO-TWAS-EMGEN Associateship. Organizing EMGEN Grant 2009 involved EMRO countries. Establishing several international workshops and meetings. Holding the 1st International Congress on Health Genomics and Biotechnology proudly took place during 24-26 Nov., 2007 in Tehran, Islamic Republic of Iran successfully by cooperation of EMGEN & Pasteur Institute of Iran. Publishing electronic more than 36 regular issues of EMGEN newsletters during 2007-2010 in genomics and biotechnology areas accessible via www.EMGEN.net and www.EMGEN.net. Also it has been sent to academic and industrial databases (more than 28000 entries) by EMGEN staffs. Managing and updating of EMGEN.NET and EMHGBN.NET websites. Making and growing EMGEN colleagues database (more than 28000 academics and industrial entries). Making bioinformatics information services. Designing respected scientific subjects of training media. Advertising and sharing facilities, services, request distribution related to several fields of health genomics and biotechnology in EMRO countries.

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RARE POLYMORPHISM GLN3405GLU OF APOLIPOPROTEIN B IN POPULATIONS OF NORTH ASIA AND ITS ASSOCIATION WITH PLASMA LIPIDS LEVELS

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The study was aimed at the analysis of the rare polymorphism Gln3405Glu of apolipoprotein B (APOB) in different ethnic groups of North Asia and in patients with low and high total cholesterol level. Polymorphism Gln3405Glu is located in the putative receptor- binding domain of APOB. Few papers report the low population frequency of this variant in Caucasian population (< 1%) and provide controversial data on its phenotypic expression (Pullinger CR et al., 1996; Ludwig EH et al., 1997; Gaffney D et al., 1998). In present study we analyzed this polymorphism in Caucasian and Non-Caucasian population of North Asia and its association with total cholesterol level in these ethnic groups. The rare allele 3405Glu frequency was analyzed in Caucasian (Russians) and in number of Non-Caucasian North Asia populations living in different parts of Siberia and Russian Far East. The phenotype expression of this allele in Non-Caucasians was studied in population sample of native inhabitants of Chukotka Peninsula (Chukchis and Asian Eskimos). The Caucasian patients included in the analyses were selected based on total cholesterol (TC) level from population sample surveyed in frame of HAPIEE project (~9000 participants, aged 45-69, men/women – 50/50%). Totally 98 patients with highest total cholesterol level (TC>300mg/dl), 94 patients with low total cholesterol level (TC<200mg/dl) and 102 randomly selected patients (mean TC level - 233.6±47,7mg/dl) were included in the analyses. The plasma lipids levels were determined by standard enzymatic assays. Gln3405Glu polymorphism of APOB (Gln3405Glu) gene was analyzed by original method. The allele 3405Glu was absent in the majority of studied Non-Caucasian populations of North Asia except native inhabitants of Chukotka Peninsula (Chukchis and Asian Eskimos) were its frequency was as high as ~15%. The frequency in Russian population was close to previously reported data for other Caucasian population (~0.5%). 3405Glu allele was significantly associated with elevated TC level in population of Arctic Asians. The frequency of 3405Glu allele was 0.49%, 0.53%, and 4.1% in HAPIEE population, low and highest TC level groups, respectively ($p<0.05$). Two homozygous genotypes were detected in group with highest TC level. The frequency of 3405Glu allele is low in majority of Caucasian and Non-Caucasian populations of North Asia except Arctic Mongoloids of Chukotka Peninsula were it is as high as 15%. This study is the first that demonstrated the association of this allele with elevated total cholesterol level at population level both in Arctic natives and in Caucasians of North Asia. This work was supported in part by Grant of President of Russian Federation MK-2666.2009.7.

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SNP POLYMORPHISM OF COLD AND MENTHOL RECEPTOR 1 (CMR1, TRPM8) IN NATIVE AND CAUCASIAN POPULATIONS OF NORTH ASIA

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The study was aimed at the analysis of SNP polymorphism of TRPM8 receptor in native and Caucasian populations of North Asia living in contrast climate conditions. TRPM8 (2q37.1) gene, coding for cold and menthol receptor of primary afferent sensory neurons of afferent nerve fibers, mediates the detection of cold thermal stimuli. Potentially it may play important role in human adaptation to cold climate and susceptibility to chronic inflammatory and metabolic diseases. Limited data on its polymorphism are currently available. Thus, analysis of SNP polymorphism of this gene in populations living in contrast climate conditions including most severe in respect of low temperature is an important step to systematic analysis of its clinical and adaptive importance. In present study following SNPs localized in coding part of TRPM8 gene were analyzed; rs13004520 (R247T), rs 28901637 (P249P), rs17868387 (Y251C), rs11562975 (L250L), rs7593557 (S419N), rs11563071 (V1058V). Studied populations included Caucasian (Russians, Novosibirsk, n=170), Chukchis (Chukotka Peninsula, n=80) and Kazakhs (Republic of Altai, n=117). Chukchis live in one of most severe Arctic Region and Kazakhs live in most South part of Russian Central Asia. Allele frequency differences were estimated by $\chi 2$. Haplotype and linkage analyses were performed by Arlequin program. It was shown that polymorphic sites R247T and Y251C have close population frequencies and were in linkage disequilibrium. Minor alleles of these sites (247T, 251C) are in cis-state. In all studied populations allele 247T (SNP R247T) was found only in combination with alleles 251C (SNP Y251C) and 419N (SNP S419N). Significant population differentiation was found for frequencies of SNP P249P, L250L, S419N and V1058V), their corresponding haplotypes and linkage pattern. The genetic differentiation was highest between Russians and Chukchis Fst=0,214 (P 0,000). Kazakhs of Republic of Altai had intermediate position Fst=0,050, P 0,000 (relative to Russians) and Fst=0,055, P 0,000 (relative to Chukchis). TRPM8 receptor gene is highly variable in North Asia populations and its polymorphism is characterized by significant between population heterogeneity. The genetic distances correlate with geographic distances and possible ethno-historical relationship. SNP polymorphism of this gene may be informative for further studying of genetic background of human adaptation and predisposition to common diseases.

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GENOMEWIDE STRUCTURE OF THE CAUCASUS POPULATIONS

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The Caucasus, inhabited by modern humans since the Early Upper Paleolithic and known for its linguistic diversity, is considered to be important for understanding human dispersals and genetic diversity in Eurasia. We report a synthesis of autosomal (610 00 SNPs from 214 samples), Y chromosome (51 Y chromosome SNP markers genotyped on 1952 samples) and mtDNA (HVSI and coding region markers done on 2262 samples) variation in populations from all major subregions and linguistic phyla of the area. Signals of regional patrilineal founder effects distinguish the eastern from western North Caucasians. Variation within the autosomal genome is consistent with predominantly Near/Middle Eastern origin of Caucasians, with minor external impacts. Genetic discontinuity between North Caucasus and the East European Plain contrasts with continuity through Anatolia and Balkans, suggesting major routes of ancient gene flows and admixture.

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THE MALAYSIAN HUMAN GENOME VARIATION PROJECT

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Malaysia is a multi cultural, multi religious and multi ethnic country comprising of numerous ethnic groups. Malays form the major ethnic group and can be further subdivided into various sub-groups. The genome wide mapping of these ethnic groups for the creation of genetic database will provide the genetic map of the country migration history and uncover the extent of genetic similarity between the various populations along with the study of common diseases in the Malaysian populations. The SNP multilocus genotype data of the Malay subethnic groups were obtained through the use of the Affymetrix 50K microarray chips and were analyzed together with those of 12 other populations from Thailand, Indonesia, China, India, Africa and Orang Asli sub groups in Peninsula Malaysia obtained from the Pan-Asian SNP (PASNP) database. Phylogenetic analyses of all 54,794 autosomal SNPs were implemented by maximum likelihood algorithm. Bayesian clustering procedure using STRUCTURAL algorithm was performed to examine the ancestry of all 472 individuals. The phylogenetic analyses showed the Malay sub ethnic groups are separated into at least 2 different clusters. The Jawa, Bugis and Minang have a very close genetic relationship with Indonesian populations indicating a common ancestral origin, while the Kelantan and Kedah formed a distinct group on the tree indicating that they are genetically different from the other Malay sub ethnic groups. From our results, we could also conclude that while the Malays belong to the Southern Mongoloid group of races, there are evidence of gene flow from the Indians to Malays. Our results have provided information on the genetic differentiation between the sub ethnic groups and valuable insight into the origin of the Malay sub ethnic groups in peninsula Malaysia. The created database on these populations will complement the HapMap database and contribute valuable information on the genetic background of the South-East Asian population.

GLOBAL ETHICAL AND LEGAL CHALLENGES

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HUMAN GENOME SEQUENCING FOR WHOM? A STUDY OF ETHICAL AND MORAL ISSUES THAT PEOPLE RAISE

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With the unfolding of human genome, the genomic mapping of normal and abnormal genes of populations has become a regular affair globally. Every society, whether primitive or modern, has ethical yardsticks to judge the moral strength of all actions. The genome study on man is no exception to that, and in fact, it has generated worldwide intense debate on how the fruits of human genome studies can be reconciled with certain core ethical and social norms without compromising with human dignity and human rights- that the declaration of the ―Humane Genome and Human rights" under the auspices of UNESCO strongly advocates. The publication of ethical guidelines for biomedical research on human subject brought out by ICMR, Govt. of India is indeed a laudable endeavor in our commitments to human rights obligations and social issues. However, when we critically make analysis of several social and ethical implications of human genome studies, it is the general opinion that the people who have donated their body parts for research and study are least benefited, and apprehensions are in circulation that the outcome of human genome research may trigger infringement of human rights and human dignity. Against the backdrop of conceptual framework stated above, the present study was carried out among (i) individuals/families, who have donated their blood/tissues for human genome (diversity and disease) studies and (ii) among the scientists/scholars, who have undertaken such projects, with an aim to assess the emerging issues namely: human rights and ownership issues such as rights of the people over their genome, promises made and fulfilled at the beginning and at the end of the study, sharing the benefit of the project with the people, dividing the people of the community as ―normal" and ―abnormal" categories or as vulnerable/susceptible group, issue of individual/community consent, the issue of confidentiality of results of genetic testing, the question of authorship and right to information and the issue of commercial interest versus people's interest. People are never given opportunity to know the implication of their genome sequencing. The identification of some groups of people or individuals who are likely to become vulnerable to certain genetic diseases or even tracing the ancestry of people to specific ethnic stain on the basis of genome data has resulted in serious social and ethical fallout. The paper pleads for restructuring the policy of social and ethical guide lines prescribed for human genomic studies keeping in view emerging social, ethical repercussions and moral landscape of the people.

HOST RESPONSE IN INFECTIOUS DISEASES

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HLA-C -35C/T VARIANT IS ASSOCIATED WITH NON-PROGRESSOR PHENOTYPE IN HIV-1 INFECTED PATIENTS DUE TO HIGHER HLA-C EXPRESSION AND REACTIVITY

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Genome-wide association studies have identified several host genetic variants within or near genes encoding adaptive or innate immune responses molecules, affecting human immunodeficiency virus (HIV) infection course. A variant 35kb upstream of the HLA-C gene (-35 C/T) has been implicated as a major determinant in early phase and late outcomes of HIV infection, influencing steady-state viral load and time to death. However, little is known regarding the functional effects of such increase in vivo, in terms of enhancement of T cell responses. A group of 639 HIV+ patients (304 progressors and 155 long-term non-progressors, LTNP) and 180 uninfected individuals were selected and genotyped for the -35C/T SNP using Taqman SNP genotyping assay. HLA-B*57 was typed by PCR amplification followed by oligonucleotide specific array hybridization. In a subgroup of 31 controls and LTNP patients, HLA-C mRNA levels were determined by quantitative RT-PCR. Responses to peptides containing optimally defined HLA-C restricted CTL epitopes were determined by Elispot. Genotyping of the -35C/T variant in 639 subjects confirmed the association of the -35C/T variant with a LTNP phenotype in Spanish HIV+ subjects (p-value=1x10-5), also when considering the protective HLA-B*57 allele as a covariate. Measurement of HLA-C mRNA levels showed a 1.7 fold increase in those with the -35CC genotype compared to -35TT genotype. When assessing responses to peptides containing HLA-C restricted epitopes, HIV+ subjects with the -35CC genotype mounted broader responses than those with -35TT or -35TC genotype (median 1.5 in -35CC versus median 0 in -35CT and -35TT). The -35CC genotype is associated to slow disease progression in

Spanish HIV-1 infected patients. The higher HLA-C expression associated with -35C protective allele may lead to a condition where there is more effective antigen presentation, providing new insights on the functional correlates that explain the effect on disease progression of the HLA-C -35C/T genetic variant.

P321
KINETIC OF EPSTEIN-BARR VIRUS DNA LOAD IN TUNISIAN NASOPHARYNGEAL CARCINOMA PATIENTS

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We studied the kinetics of Epstein-Barr virus (EBV) deoxyribonucleic acid (DNA) in sera of nasopharyngeal carcinoma (NPC) patients to determine the correlation with tumor load and response to treatment. Quantitative real-time polymerase chain reaction (PCR) using SYBR Green I fluorescent dye was used to detect the EBV DNA copy number. We showed that EBV DNA load was similar between males and females NPC patients. Respecting the bimodal age distribution in intermediate risk region, we showed no difference in the amount sera EBV DNA load between young and adult NPC patients. Furthermore, EBV DNA load was correlated with advanced NPC stage. This suggests that EBV DNA load depend only of tumor status. After treatment, the EBV DNA concentration decline significantly in NPC patients. In consequence, patient with sera EBV DNA load less than 1000 copies showed a better overall free survival. With a mean of three months before radiological assessment, EBV DNA load quantification showed that plasma EBV DNA level reached a maximum in relapsed patients. These results suggest that the quantification of the EBV DNA fluctuation is an important tool to predict potential relapse.

P322
A WORLDWIDE ANALYSIS OF BETA-DEFENSIN COPY NUMBER VARIATION SUGGESTS RECENT SELECTION OF A HIGH-EXPRESSING DEFB103 GENE COPY IN EAST ASIA

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Beta-defensins are a family of multifunctional genes with roles in defence against pathogens, reproduction and pigmentation. In humans, six beta-defensin genes are clustered in a repeated region which is copy-number variable as a block, with a diploid copy number between 1 and 12. The role in host defence makes the evolutionary history of this CNV particularly interesting, because morbidity due to infectious disease is likely to have been an important selective force in human evolution, and to have varied between geographical locations. Here, we show CNV of the beta-defensin region in chimpanzees, and identify a beta-defensin block in the human lineage that contains rapidly-evolving non-coding regulatory sequences. We also show that variation at one of these rapidly-evolving sequences affects expression levels and cytokine responsiveness of DEFB103, a key inhibitor of influenza virus fusion at the cell surface. A worldwide analysis of beta-defensin CNV in 67 populations shows an unusually high frequency of high-DEFB103-expressing copies in East Asia, the geographical origin of historical and modern influenza epidemics, possibly as a result of selection for increased resistance to influenza in this region.

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EPIDEMIOLOGY AND MOLECULAR TYPING OF CANDIDA SPP IN MOROCCO

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Candida albicans is a facultative commensal yeast of the human gastrointestinal and genital mucosa. Medical progress in developing countries has been accompanied by an increase in opportunistic candidiasis. In the present study, we have investigated the prevalence of Candida commensal carriage in 697 asymptomatic Moroccan women between 2006 and 2008. Aims of the study: Assess through sampling the prevalence of vaginal colonization by Candida species in asymptomatic healthy women living in Morocco. Evaluate the species distribution from this collection of Candida isolates Determine the genetic diversity of C. albicans strains isolated from vaginal samples in Morocco. Examine genetic relationships among C. albicans recovered during vaginal colonization from healthy women from 3 countries representing 3 continents: Morocco (North Africa), France (Western Europe) and Brazil (South America). 144 out of 697 vaginal cultures from asymptomatic women examined at the consultation of Institut Pasteur Casablanca from 2006 to 2008. Identification of Candida species was performed using: API 20C galleries, CHROMAgar Candida identification and PCR ITS with sequencing of ITS1&2 regions. All C. albicans isolates obtained were typed by MLST. We found 144 clinical isolations of Candida spp. indicating a prevalence of 20.7% for genital carriage in the investigated population. Phenotyping and PCR analysis showed that 68 were C. albicans (47%) and 76 were other species (C. glabrata, 34%; C. tropicalis, 4.1%; C. parapsilosis, 4.1%; C. dubliniensis, 2.0%). This confirmed the predominance of C. albicans in genital specimen. Molecular typing of Candida spp. was done by MLST and indicated that C. albicans isolates had a phylogenetic distribution mostly similar to that observed in developed countries. MLST of C. albicans isolates originated from

Morocco revealed an extensive diversity. MLST showed that the distribution in clades of C. albicans vaginal isolates sampled in Morocco, France and Brazil did not differ significantly.

P324
IL-10 LOW PRODUCERS AND RISK OF GASTRIC AND DUODENAL LESIONS DEVELOPMENT

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Gastric cancer (GC) remains as one of the major causes of cancer death in developing countries such as Iran. GC is a multi-factorial disease in which host genetic susceptibility particularly pro and anti inflammatory cytokines, H. pylori infection and environmental factors are involved. We have, therefore, investigated the role of IL-10 polymorphisms which lead to its down regulation yielding a pro-inflammatory state causing susceptibility to gastrointestinal mucosal damages. Dyspeptic patients (158 NUD and 32 DUD) who underwent upper GI endoscopy were included in the study following provision of informed consent. Hp infection was identified by biopsy based methods including RUT, culture and histopathology as well as serology. IL-10 single nucleotide polymorphisms in three loci (-1082, -819 and -592) were investigated individually by our newly developed PCR-two confronting pairs of primers (PCR-CTPP) approach instead of the routine PCR-RFLP method. Our newly designed PCR-CTPP method was confirmed by random sequencing of PCR products. IL-10 polymorphisms at the three mentioned loci (GCC>ATA, low IL-10 producers) plus Hp infection increased the risk of premalignant lesion development by nearly three folds, following adjustment for age, gender and ethnicity (OR=3.3, 95%CI=1.35-7.97). Hp infection was considered as a strong independent risk factor for duodenal ulcer development (OR= 2.82, 95%CI=1.5-5.23), but triple IL-10 polymorphisms (GCC>ATA, low IL-10 producers) further enhanced the risk of DU development in Hp infected patients (OR=3.73, 95%CI=1.28-10.9). Profiling anti-inflammatory IL-10 gene polymorphisms demonstrated a significantly enhanced risk of developing gastric premalignant lesions as well as duodenal ulcers among patients with ATA (low IL-10 producers) genotype, which lends support to the role of inflammation in development of these lesions.

INBORN ERRORS OF METABOLISM

P325
CLINICAL, BIOCHEMICAL AND GENETIC ANALYSES OF ALKAPTONURIA IN JORDAN

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Alkapotonuria (AKU) is one of the four initially identified inborn errors of metabolism. It is an autosomal recessive disorder characterized by excretion of large quantities of homogentisic acid (HGA) in urine and a slowly progressive deposition of HGA in connective tissues. Clinical features of AKU are darkening of urine, dark pigmentation of connective tissues (ochronosis) and arthritis. AKU affects 1 in 250,000 people worldwide; however, the prevalence is unknown in Jordan. Objectives: A research project was launched recently in Jordan. The aims of the project were to determine the prevalence of AKU in Jordan, raise the awareness about AKU among health care providers and the community, screen all family members with history of AKU, and to identify mutations in the HGD gene in affected individuals. The preliminary results of screening all family members with history of AKU have identified 40 cases of AKU (age range, 1-60 years). The clinical, biochemical and genetic findings will be presented. Five novel mutations have been identified in Jordanian population. The prevalence of AKU among Jordanian is likely to be greater than prevalence rates worldwide due to the high rate of consanguineous marriages. Therefore, awareness campaigns are needed to explain the deleterious impact of consanguinity on health, and specially increased the probability of expression of autosomal disorders, and ultimately to decrease the incidence of genetic diseases.

P326
MOLECULAR SCREENING AND MODELING ANALYSIS OF TWO INBORN ERRORS OF METABOLISM IN THE UNITED ARAB EMIRATES POPULATION

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Inborn errors of metabolism (IEM) disorders are a group of rare genetic conditions that result from abnormalities in the synthesis or catabolism of proteins, carbohydrates, fats or complex molecules. Most metabolic disorders are mostly recessive and present in neonatal or early infancy period but some could present in childhood or even adulthood. Due to high rates of consanguinity in the United Arab Emirates and other Arab and Middle Eastern countries, IEM disorders are

encountered more frequently than in the rest of the world. In UAE population, more than 30 metabolic disorders have been reported. However, the molecular underlying causes have not been established for the majority of those disorders. DNA samples from 4 unrelated Isovaleric academia (IVA) patients and 11 unrelated phenylketonuria (PKU) patients were evaluated for defects in isovaleryl-CoA dehydrogenase (IVD) and hyperphenylalaninemia (PAH) genes respectively using direct genomic sequencing. To assess the severity of a mutation‘s impact, the exploration of the structural properties and potential modulation of these mutant proteins was carried out using Deep-View version 3.5.1 program. In the PAH gene, a total of 11 different mutations were identified, including 7 missense and 4 splice mutations. Only one splice mutation was novel. Whereas in the case of IVD gene, three novel mutations were detected. One of them has been reported to be the most frequent mutation found in UAE-IVA patients, based on the identification of this mutation in two unrelated UAE families. Mutation analysis of IEM in UAE populations could, therefore, be helpful for further understanding of the correlation between the genotype and phenotype, and for genetic counseling and prognostic evaluation of future cases of IEM in the region.

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HEMOCHROMATOSIS GENE (HFE) POLY-MORPHISMS IN SLOVAK MAJORITY AND ROMANY POPULATION

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Hereditary hemochromatosis is a genetic disease characterized by excessive iron overload. Three mutations in the HFE gene are associated with the disease: C282Y, H63D and S65C. The aim of this study was to determine frequency of HFE mutations in Slovak majority and Romany population and to compare two high-throughput real-time PCR methods of detection of these mutations. The analyzed sample consisted of unrelated individuals from eastern Slovakia, selected randomly, regardless of their health status. Buccal swabs were collected 737 individuals, genotyping all three mutations were successful in 396 subjects, the majority of Slovakia's population (215 men and 181 women) and 341 Roma minority individuals (151 men and 190 women). Genomic DNA was extracted from buccal swabs by standard extraction procedures using JETQUICK (Genomed). Genotypic analysis of single nucleotide polymorphisms of the HFE gene were performed on high-performance device Rotor Gene 6000 (Corbett research). From a wide variety of detection methods, we decided on two alternatives, which we then compared and evaluated their usefulness for further practice. Commercial kits Hemochromatosis HFE-C282Y and Hemochromatosis HFE-H63D, S65C (Nuclear Laser Medicine, Italy) allow seamless rapid detection of three mutations in the HFE gene. Genotype of analyzed samples was determined from the melting curve graph generated by software RotorGene. Our aim was also to optimize the protocol for high-performance method for real-time PCR detection hemochromatosis mutations based on TaqMan probes and compared this method with a standardized kit for detection HFE-mutations in terms of efficiency, financial and time demands. The reaction was optimized separately for each mutation, varying the concentration of labeled probes, and change in conditions of PCR reactions. During optimization, we used samples of known genotype, previously had been genotyped using commercial kits FRET method - melting curve analysis. Course of the PCR reaction was evaluated by analysis, scatter plot and, allelic discrimination' the carrying device software RotorGene. The observed allele frequencies were 3.9% (C282Y), 13.2% (H63D) and 0.8% (S65C) in the majority and 3.8% (C282Y), 4.5% (H63D) and 0.0% (S65C) in the Romany population. Occurrence of mutations in the majority population correlated with the reported occurrence in the Central Europe. Prevalence of H63D mutation in the Romany population was significantly lower than in the majority population and it was also lower than the prevalence in the Northern India, where Romany originate. Probable reason of this result is a founder effect and a high degree of inbreeding among Romanys in Slovakia. Both detection methods, FRET-melting curve analysis and TaqMan probes, were accurate and fast. Despite the fact that it demanded extensive optimization, the TaqMan assay proved to be more cost-effective for analyzing large amount of samples.

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THE BIOCHEMICAL DIAGNOSIS OF MUCO-POLYSACCHARIDOSIS OVER 11 YEARS: THE EGYPTIAN EXPERIENCE

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The laboratory diagnosis of mucopolysaccharidosis (MPS) and related disorders among clinically suspected cases referred to the Biochemical Genetics Department, National Research Centre, to find out the distribution and the frequency of each type among the Egyptian population. Among 1041 patients screened for MPS, 540 (51.9%) cases had elevated GAGS in urine. Two dimensional electrophoretic separation of GAGS for this 540 cases revealed, 239 MPS patients (44.3% out of the 540 and 22.9% out of the 1041). Another 31 cases (2.97% from the 1041) were diagnosed as having Mucolipidosis. The specific enzyme assay for the 239 cases confirmed the diagnosis and revealed the following results: MPS I H (Hurler disease) n= 79 (33% out of the 239). MPS II (Hunter disease) n=46 (19.3% out of the 239), MPS III (Sanfilippo Syndrome) n= 43 (18% out of the 239) and MPS VI (Maroteaux Lamy) n=71 (29.7%). Another 39 patients were diagnosed by the specific enzyme assay to have MPS type IV A. Accordingly the total number of MPS patients diagnosed during the last 11 years is 278 cases with the following distribution. 79 MPS type I (28.5% out of the 278), 46 MPS type II (16.5% out of the 278), 43 MPS type III (15.5% out of the 278), 71 MPS type VI (25.5% out of the 278) and 39 MPS IV (14%). Quantitative determination of GAGS in urine is a simple procedure to select cases for electrophoretic separation of GAGS. However, enzymatic assay is mandatory to confirm the MPS type, especially with the presence of enzyme replacement therapy

for type I, II VI and for prenatal diagnosis in future pregnancies. The commonest MPS disorders among the diagnosed cases in this study were MPS type I (33%) and type VI (29.7%) followed by type II (19.3%).

P329
TAG SEQUENCING BASED TRANSCRIPTOME ANALYSIS OF WHITE AND BROWN ADIPOSE TISSUES DURING COLD ADAPTATION

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Adipose tissue can be divided in two major types, white and brown. Whereas white adipocytes store excess energy as fat, brown adipocytes are able to dissipate energy as heat. Understanding differences between these two types at the genomic and transcriptomic levels is helpful in the eventual aim of addressing obesity. The white adipocytes and the classic brown adipocytes originate from distinct cellular lineages. However, adipocytes in several white adipose depots can in a beta-adrenergic-dependent manner transform into brown-like thermogenic adipocytes expressing many, but not all characteristic brown adipocyte markers. In this study, we performed a transcriptome analysis of inguinal WAT (iWAT), epididymal WAT (eWAT) and interscapular BAT (iBAT) from cold-exposed mice to elucidate similarities and differences in gene expression of these adipose tissues. The transcriptome analysis was based on the Differential Gene Expression Tag-Profiling (DGEP) protocol using Illumina sequencing technology. Prior to cold exposure, iBAT exhibited a relatively high expression of genes involved in metabolic pathways such as fatty acid biosynthesis and oxidative phosphorylation, while iWAT and eWAT exhibited a high basal expression of genes involved in other non-metabolic pathways. Cold induction led to a shift in iWAT gene expression, so that metabolic genes were expressed at a higher level. Our results provide information that will help understand differences in the signaling pathways involved in regulation of the induction and/or acquisition of thermogenic functions in brown and white adipose tissues.

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MOLECULAR, PHENOTYPICAL AND THERAPEUTIC CHARACTERISTICS IN A GROUP OF ROMANIAN PATIENTS WITH PHENYLKETONURIA

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The study of the relationship between the genetic background and the influence of the environment in the characteristics of human genetic disorders remain of great importance; in this view, the genotype-phenotype correlations in phenylketonuria (PKU) is a possible way to look for these relationships. PKU is an autosomal recessive disease that, if is untreated, will impair postnatal cognitive development resulting from a neurotoxic effect of hyperphenylalaninemia (HPA); the associated clinical phenotype varies considerably. Its metabolic phenotype is accountable to multifactorial origins both in nurture, where the normal nutrition introduces L-phenylalanilne (Phe), and in nature, where mutations (>520 alleles) occur in the PAH gene. The allelic variation at the PAH locus yield greater or lesser risk of impaired cognitive development according to the degree of HPA that is linked to the therapeutic characteristics. The clinical evaluation of a group of 20 PKU patients (with different stage of treatment) from clinical sections of Cluj Children Hospital, Romania, was done according to The Munchen development scale for the children with mental age below 3 years, with The Simon-Binet test for children with mental age between 3-7 years and with The Raven's Progressive Matrices for those above 7 years. Biochemical phenotypes associated were included in severe (classic PKU) when the level of Phe is above 1200 □mol/l, moderate PKU (Phe: 600-1200 µmol/l) or mild HPA for Phe: 120-600 µmol/l. The leukocyte DNA was isolated using classical method (phenol and chloroform) followed by polymerase chain reaction (PCR) with subsequent restriction analysis. In this group we identified patients homozygous for mutation R408W (for more than 50%), patients compound heterozygotes for R408W/L48S or R408W/R261Q mutations. Our data provide that the highest degree of concordance was found in patients with null/null genotypes.

NEW STRATEGIES IN QUANTITATIVE PHENOTYPING

P331
HERITABILITY OF ADIPOCYTOKINE LEVELS AND THEIR ASSOCIATIONS WITH METABOLIC TRAITS IN AN ARAB COHORT

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Adipose tissue secreted cytokines (adipocytokines) have significant effects in the physiology and pathology of human metabolism relevant to diabetes and cardiovascular disease. We determined the relationship of the pattern of these circulating hormones with obesity-related phenotypes and whether such pattern is transmitted from parent to offspring. A combined total of 403 individuals from 156 consenting Saudi families divided into initial [119 families (123 adults and 131 children) and replication cohort of 37 families (58 adults and 91 children)] were randomly selected from the RIYADH Cohort study. Anthropometrics were evaluated and metabolic measures such as fasting serum glucose, lipid profiles, insulin, leptin, adiponectin, resistin, tumor necrosis factor alpha, activated plasminogen activator inhibitor 1, C-reactive protein and angiotensin II were also assessed. Parent-offspring regressions revealed that with the exception of hsCRP, all hormones measured showed evidence for significant inheritance. Principal component (PC) analysis of standardized hormone levels demonstrated surprising heritability of the three most common axes of variation. PC1, which explained 21% of the variation, was most strongly loaded on levels of leptin, TNFÎ±, insulin, and aPAI1, and inversely with adiponectin. It was significantly associated with body mass index (BMI) which was stronger in children and showed a heritability of ~50%, after adjustment for age, gender and generational effects. Adipocytokines are highly heritable and their pattern of co-variation significantly influences BMI as early as pre-teens. Investigation at the genomic scale is required to determine the variants affecting the regulation of the hormones studied.

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ANTI-CANCER INITIATION ACTIVITY OF A NEWLY INTRODUCED POLYSACCHARIDE DRUG

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The aim of this study was to examine the anti-initiation effect of a bacterial polysaccharide drug* (Bacillus subtilis sulphated Levan BSL) relevant for prevention of tumor development during initiation stage. The initiation is the first stage of carcinogenesis and the activity of BSL can be tested via a series of assays; its effect on CYP 450 (Carcinogen activator Cytochrome P450 enzyme; which are carcinogen activator enzymes); its effect on GSTs (glutathione S-transferase enzymes responsible for the removing of carcinogens i.e., detoxification enzymes); and its scavenging capacity towards DPPH radicals. Experiment was performed using Hep-G2 cells .It was cultured in tissue culture flasks and maintained in RPMI medium. Results showed that (BSL)resulted in a significant increase in (GST) activity and GSH (glutathione) level .BSL decreased GST-P expression in hepatocytes.BSL possessed anti inflammatory activity through its capacity to enhance macrophages proliferation rate and its ability to inhibit stimulated nitrous oxide, TNF-α and Cox-2 levels by its high SC50 value (half maximal scavenging capacity). In addition significant CYP 1A inhibition resulted. In conclusion, BSL was represented as promising cancer chemopreventive agent against initiation of hepatocarcinogenesis). *The drug was purchased by Dr. Amira M. Gamal-Eldeen.

REGULATION OF GENOMIC SERVICES AND PRODUCTS

P333

DIRECT-TO-CONSUMER GENETIC TESTING: USERS' PERCEPTIONS

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This presentation will deal with direct-to-consumer genetic tests (DTCGT) that represent a new online market since the early 2000s. These devices aim at screening the purchaser's genome for manifold diseases and traits as well as at providing information about ancestry. Thus, one can consider DTCGT as new tools of ―personalized genomics". Public health authorities and bioethics committees worldwide question the uses of DTCGT: health care systems have to face a novel situation, since they are currently regulating general use of genetic tests, but the DTCGT e-economy challenges national as well as regional attempts of control. Beyond debates between professionals, it is relevant to explore the wider context of appearance of this new e-economy. Thus, the study aims at investigating users' motives for purchasing such devices online, as well as their perceptions of DTCGT and the way they integrate (or not) these tests in their itineraries of health management and identity quest. Given the increased importance of informed consent and the growing tendency of health practitioners to encourage patients to rationalize their health decisions, individuals are more and more empowered. The study also explores the dialectic links between autonomy of choice and access to genetic knowledge, consumerism and ―healthism", personal risk management behaviors and institutional public health messages. Method: This study has been conducted through qualitative sociological methods, based on a grounded-theory approach. Data were collected on one hand through interviews (N=30) with users and on the other hand through analysis of relevant websites and forums. Based on the users' words and views, the study shows: 1/ DTCGT results, stating individual genetic susceptibilities, can be experienced as a medical diagnosis. Statistical risk indeed tends to be framed individually (for example as a validation of

one's family medical history, and not as a neutral figure); 2/ Even minor deviations from the mean figures can lead to prevention behaviors. This shows the users' perception of health as an acceptable deviation from a population genomics standard profile, and not as a complex frame taking individual specificities into account; 3/ The sharing of DTCGT users' experiences has resulted in the appearance of virtual bio-communities, where one searches for fellow creatures with similar genetic profile, without ―real life" interactions.

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DIRECT TO CONSUMER GENETIC TESTING: A REGULATOR'S DILEMMA. ARE WE READY TO LET THE GENIE OUT OF THE BOTTLE?

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The proliferation of Direct to Consumer (DTC) genetic testing services poses many challenges to regulatory agencies as it is now marketed as a means to determine an individual's susceptibility to disease or alternatively as a precursor to one's innate abilities. This presents a unique conundrum for both scientific and government agencies to determine how we validate these tests and are present day genomic platforms really predictive for such phenotypes or are they used as clever marketing tools to promote personal genomic services? It is imperative that a regulatory framework has to be developed to achieve some consensus as to how regulatory authorities can validate upstream scientific genomic tools used for genetic tests as well as downstream governance of personal genomic information. The upstream validation of any single nucleotide polymorphisms (SNPs) which may have a high degree of association with disease or phenotype, has to be predicated on unequivocal scientific evidence and not loose associations. The regulator's perspective is not clouded by a single dimension of just scientific proof but the ripple effect of such genetic test results on society. For as and when a true genetic map can accurately predict an individual's susceptibility to a disease phenotype, we have to be prepared to concurrently address a host of bioethical issues which may not have been adequately considered. The old adage that prevention is better than cure resonates with proponents of DTC genetic testing. For an individual to recognize that he is predisposed to greater cardiovascular or cancer risks may encourage the adoption of healthier lifestyle habits, however the converse is also true whereby riskier behaviors may arise if one is found to be free of such disease risks. Any regulation of DTC genetic testing has to be objective to embrace the true scientific merits that this new frontier of scientific technology may bring. But the cautionary tales of evaluating risk versus benefit will apply with respect to the utility of such genetic tests. It cannot be viewed as an innocuous commercial service open to the lay public without oversight, for the wrong information may have devastating consequences especially if an individual's life decisions are influenced by unsubstantiated scientific evidence. Our discussion of any future proposed regulatory frameworks for DTC genetic testing has to consider the pace of scientific discovery in determining the true relationship between genotype and phenotype and how will health authorities manage the introduction of such tools in clinical practice. A collaborative partnership has to be fostered between academia and government agencies to determine what will be acceptable genetic testing methods used and standards applied in interpreting these results. The graduated approach to embracing such testing may have to be initially managed as a clinical service rendered only by trained healthcare professionals. Until such time when genomic sciences has established its unequivocal validity in determining health outcomes, the debate of nature versus nurture will continue and the value of present day DTC genetic testing has to be challenged.

RNA AND EPIGENETICS

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GENETIC AND EPIGENETIC VARIATION: IMPACT ON HEPATIC CYP2A6 LEVELS AND NICOTINE METABOLIZING ACTIVITY

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Smoking's addictive properties are largely due to the psychoactive effects of nicotine. Due to the relatively short half-life of nicotine (~2 hrs) dependent smokers smoke regularly to maintain desired nicotine plasma levels. Therefore, factors that alter the intake or removal (e.g. metabolism) of nicotine can affect smoking behaviors (e.g. number of cigarettes smoked and cessation). In humans, the majority (70-80%) of nicotine is metabolically inactivated to cotinine via a pathway that is principally (~90%) catalyzed by the hepatic enzyme Cytochrome P450 2A6 (CYP2A6). Substantial interethnic and interindividual variability is observed in CYP2A6 activity and nicotine metabolism. Objective: Investigate the role of genetic and epigenetic factors in regulating CYP2A6 expression and nicotine metabolism. Human liver samples (n=67) were assessed for nicotine metabolism and CYP2A6 expression (mRNA and protein). DNA from liver samples (n=67) was isolated and genotyped for major CYP2A6 alleles. In addition, a subset of livers (n=18), human cryopreserved hepatocytes (n=2), and HepG2 cells were used for DNA methylation analyses. DNA methylation status was evaluated by DNA sodium bisulphite treatment followed by PCR and sequencing. CYP2A6 protein and mRNA levels correlated significantly (rs2=0.45, p<0.001). In addition, CYP2A6 protein levels and the metabolism of nicotine to cotinine correlated significantly (rs2=0.37,

p<0.001). Compared to wild-type livers (n=48), liver samples with variant CYP2A6 alleles (n=17) had significantly lower CYP2A6 protein expression (0.40±0.40 vs. 0.90±0.90, p=0.006), nicotine metabolizing activity (26±27 vs. 30±23 nmol mg protein-1 h-1, p=0.03), and affinity for nicotine (56±26 vs. 80±29 µM, p=0.001). The CYP2A6 mRNA levels were similar between the two groups (variant (n=8): 368±431 vs. wild-type (n = 30): 291±298, (p=0.8)). DNA methylation status was not associated with altered CYP2A6 expression and nicotine metabolism among the human livers. However, HepG2 cells which express very low levels of CYP2A6 compared to human livers had an opposite DNA methylation profile compared to human livers. We have identified genetic variation as an important factor in regulating hepatic nicotine metabolism and CYP2A6 expression. Moreover, our data suggest that the lower nicotine metabolizing activity associated with the CYP2A6 alleles is likely mediated by CYP2A6's lower protein expression and affinity toward nicotine. Understanding sources and mechanisms of variability in CYP2A6 and nicotine metabolism is important to improve future association studies between CYP2A6 genotype, nicotine metabolism, and smoking behaviors. Supported by: Centre for Addiction and Mental Health, Canadian Institutes for Health Research (CIHR) MOP86471, CIHR-Strategic Training Program in Tobacco Use in Special Populations (TUSP), and Ontario Graduate Scholarship program (OGS). Dr. Rachel Tyndale holds a Canada Research Chair in Pharmacogenetics.

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IDENTIFICATION AND CHARACTERIZATION OF A NOVEL CENTROMERE AUTOANTIGEN

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Problems of chromosome missegregation can result in aneuploid cells with gained or lost chromosomes. In humans, aneuploidy is often associated with cancer due to the loss of tumour-suppressor genes or gain of oncogenes. As the centromere is a key structure that underpins chromosome stability and faithful segregation, a sound knowledge on the organisational and functional properties of this structure would lead to a better understanding and management of the associated conditions. In this study we pre-screened patient sera for the presence of additional non CENP-A, B and C bands using immunoblotting, which were subsequently used to probe a HeLa cDNA phage expression library. Two novel centromere autoantigens have been identified, one included the recently characterized SCAN-zinc finger protein, ZNF397, and the other, FAM44A, a large protein, approximately 330 kD, containing domains with hallmarks of chromatin regulation. Using RNAi knockdown in human cells we show that this protein plays an important role in the correct segregation of chromosomes during mitosis. Mitotic defects include, poor chromosome alignment during metaphase, lagging anaphases and chromatin bridges. These results suggest that FAM44A may have a role in the regulation of other chromosome segregation protein/s.

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INCREASED FREQUENCY OF MULTILOCUS LOSS OF METHYLATION IN BECKWITH WIEDEMANN SYNDROME CASES CONCEIVED USING ASSISTED REPRODUCTIVE TECHNOLOGIES

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Beckwith Wiedemann syndrome (BWS) is an overgrowth syndrome that is associated with epigenetic and /or genetic alterations of chromosome 11p15. The most common epimutation, present in 50% of BWS cases, is a loss of methylation (LOM) at imprinting center 2 (IC2, also known as KvDMR1). Further, recent reports show that imprint deregulation in approximately 23% of BWS cases with LOM at IC2 were also described to have multilocus loss of methylation (MLOM) at targeted maternal differentially methylated regions (DMRs) associated with imprinted genes such as PLAGL1 and GNAS on chromosomes 6 and 20, respectively. The incidence of BWS patients born following infertility/assisted reproductive technologies (ART) is increased 4 -9X.The vast majority of these cases demonstrate IC2 LOM. Thus, the genomic imprint at IC2 is vulnerable to environmental insults. We undertook a study to compare the rates of MLOM in BWS cases with and without a history of exposure to ART. We hypothesized that post- ART BWS cases with LOM at IC2 would have more genome-wide imprint instability than cases with the same BWS-associated epigenetic alteration without a history of ART. To significantly increase the number of imprinted targets available to assess MLOM, we undertook a genome-wide approach to analyze DNA methylation in BWS patients with LOM at IC2. We used bisulfite modified genomic DNA from 27 BWS patients and 66 controls hybridized to the Illumina methylation 27 array. This array covers ~27,600 CpG sites (promoter of ~14000 genes). We performed a detailed analysis of all CpG sites that overlap 22 known imprinted DMRs. Cases with MLOM showed CpG methylation alterations at most imprinted DMRs with the highest frequencies at DIRAS3 (26%), GNAS(26%) and PLAGL1(19%). An increased frequency of MLOM was seen in BWS cases post-ART with 60% of these cases having MLOM while only 34% of BWS in the no-ART group had MLOM. There were also differences in the spectrum of deregulated imprinted DMRs seen in these 2 groups. Our approach provides the most comprehensive analysis to date for characterizing genome wide deregulation of imprinted loci in BWS. Furthermore, we report here an association between subfertility/ART and increased frequency of MLOM in BWS. The underlying mechanisms associating ART with aberrant imprinting are unclear. However, it is thought that the procedures involved in ART may impact imprinting by altering the maintenance of germ cell imprints. Therefore are screening for mutations in ZFP57 (DNA methylation maintenance gene) in BWS patients with identified MLOM. We are also investigating the impact of MLOM on the clinical manifestations of BWS and other human disorders caused by imprinted gene deregulation.

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CHARACTERIZATION OF 5'CAP STRUCTURE OF SHORT RNA

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PolII transcribed RNAs typically have a cap at their 5' end that is added very early after initiation of RNA transcription and is required for protein translation and RNA stability. Transcription initiation per se might generate the capped (promoter associated short RNAs; PASR). However, this does not seem to be typical because, capped ncRNAs are produced not only by primary transcription but also by capping events that are independent from primary transcription. This is the case of at least a large part of PASRs as well as other truncated and secondarily capped RNA that map on exons. The reason for PASR capping is unknown, but perhaps PASRs are involved in cell compartment localization and RNA stability. Some of the PASRs negatively regulate gene transcription by mechanisms yet to be discovered. Immununoprecipitation using anticap antibodies has confirmed the capping of PASRs, (termini associated short RNAs TASRs and other RNAs that have 5'end sites that map on exons. However, neither CAGE nor immunoprecipitation using currently available antibodies can properly distinguish between different cap structures. Chemical characterizations of those caps will be instrumental for annotating those ncRNA and shed light on their biological meaning.

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OPTIMIZING MIR-21'S DETECTION, AS A GENERAL TUMOR MARKER, IN SERUM, URINE AND BIOPSY SAMPLES OF BLADDER CANCER PATIENTS

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MicroRNAs (miRNA, mir) are small endogenously-produced, non-coding RNAs with an important role in regulating gene expression. Based on recent studies miRNAs' expression profiles represent significant tumor-specific changes that are unique for most cancers. Over-expression of mir-21 has been reported in a variety of solid tumors, where it functions to make cells resilient to apoptosis, stimulates invasion, metastasis and chemo-resistance. The aim of this study was to evaluate the expression of miR-21 in a wide variety of biological samples (serum, urine, fresh and frozen biopsies) of patients with bladder cancer in comparison to their normal counterpart samples. 4 ml of urine samples from patients as well as age-matched bladder cancer free volunteers (control group) were aliquoted in Eppendorf tubes and stored in -80ºC. Fresh surgical tumor/non-tumor samples of bladder samples were obtained. RNA extraction was carried out using Trizol solution. RNA concentration and optical absorption in 260 and 280 nanometers were measured by Nanodrop instrument. Presence of mir-21 was quantified in the samples by means of LNA primers and real-time RT-PCR. Presence of mir-21 was detected in the urine and serum of control and patient groups as samples of bladder. Expression level of mir-21 was significantly higher in tumor samples in comparison to their normal counterparts. In case of urine of patients with bladder cancer, there was significant difference in miRNA levels between patients (17 samples) and normal (12 samples) urines. Mir-21 was upregulated in sample group in comparison to control group by the mean factor of 5.39. P value was 0.017. MiR-21 seems to be a suitable and reliable diagnostic/prognostic tumor marker in bladder cancer. It is also easily detectable in a variety of biological materials, where other tumor markers (mRNA and proteins) are hard to detect.

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A MICRORNA SIGNATURE IN THE HUMAN PRION DISEASE BRAIN NEURODEGENERATION

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Prion diseases are a related group of rare, fatal brain diseases (progressive conditions that affect the nervous system) in humans and animals, also known as transmissible spongiform encephalopathies (TSE). Prion protein (PrP) is the cause of TSE. PrPC refers to the endogenous form of prion protein (PrP), which is found in a multitude of tissues, while PrPSc refers to the misfolded form of PrP, that is responsible for the formation of amyloid plaques and neurodegeneration. This altered structure is extremely stable and accumulates in infected tissue, causing tissue damage and cell death. The exact molecular mechanism underlying prion induced neurodegeneration and neuronal death is still largely unknown. The most common human prion disease is the sporadic form of Creutzfeldt-Jakob disease (CJD), which accounts for about 85% of all cases. MicroRNAs (miRNAs) are small, noncoding RNAs acting as post-transcriptional regulators of gene expression. MiRNAs are effectors of brain function with roles in ischemia and injury, neuroprotection, and neurodegeneration They are included in physiological and pathological processes as well as in development. Compelling evidence links miRNAs also to the control of neuronal development and differentiation, however, very little is known about their role in human prion disease. We used coordinated approach to integrate miRNA and mRNA profiling and bioinformatic predictions to profile miRNA expression changes in the human brains of sporadic CJD. Total RNA was isolated from brain tissue of 5 patients with diagnosed CJD and brain tissue of 5 healthy individuals. Expression analysis was performed using hybridization to µParaflo microfluidics micorarrays in the version of the Sanger miRBase database

Release 10.1 (each of the microarrays held all 719 predicted mature human miRNA probes). Our analysis revealed over hundred of differentially expressed (up- or down-regulated) miRNAs. 16 of them showed similar dysregulation in experimental animals, in brains of mice infected with mouse-adapted scarpie, and in the brains of BSE-infected cynomolgus macaques as a model for CJD. Further, we selected 15 miRNAs for microarray validation using real-time PCR. MiRNA miR-342-3p, which showed up-regulation in our microarray experiment, has been also up-regulated in brains of BSE-infected macaques. Neuronal-specific miRNA, miR-124a, was also up-regulated in our experiment; this miRNA is believed to have constant expression in adult neurons. Therefore, neuronal death should have some impact on miR-124a expression. Another up-regulated miRNAs, miR-16 and miR-98, are involved in apoptosis as being pro-apoptotic miRNAs, with miR-16 believed to be involved in apotosis of developing neurons. Neuronal autophagy and apoptosis are the mechanisms of programmed cell death. Since there are some informations that autophagy and apoptosis are processes naturally occurring in experimentally induced scrapie and CJD, we believed that miRNAs regulating apoptosis may also play a role in transmissible spongiform encephalopathies. Computational analysis predicted numerous potential gene targets of these miRNAs, including some genes previously determined to be also de-regulated in mouse scrapie. In conclusion, we have detected several novel miRNAs and confirmed their down-regulation in prion disease human brains.

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MEASUREMENT OF GLOBAL METHYLATION AND GENE SPECIFIC METHYLATION IN COLORECTAL CANCER PATIENTS

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Epigenetic alterations occur during the adenoma-carcinoma sequence of colon cancer formation and play important role in initiation and progression of colon cancer formation. Global methylation may play role in the instability occurring in cancer cells and aberrant methylation of genes promoters is epigenetic mechanism for silencing genes and may affect tumor suppressor genes in colon cancer. The aim of this study was to determine CpG island methylation and gene specific methylation in a group of samples from Sudanese colorectal cancer patient. Global methylation level and gene-specific methylation was measured in both tumor and control tissue from Sudanese colorectal patients. Global methylation was measured in genomic DNA using LUMA (LUminometric Methylation Assay) method and Gene specific promoter methylation (GSPM) was measured in 3 selected tumors suppressor genes (APC, MLH, and MCC) related to initiation of colorectal cancer. Gene specific promoter methylation was measured, in Bisulphite treated DNA, using Real time PCR and bisulphite pyrosequencing Our result indicate that tumor tend to be hypomethylated compared to control tissue, When looking at gene specific methylation for APC gene it was found to be hypermethylated in less than 50% of tumor tissue while control tissue tend to be hypomethylated, for MCC and MLH, % of hypermethylation is higher than hypomethylation in tumor tissue while control tissue tend to be hypomethylated.

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IDENTIFICATION AND CHARACTERIZATION OF THE MICRO-RNAS AND THEIR TARGETS IN THE AQUATIC ENVIRONMENTAL MONITORING FISH (SALMO SALAR)

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Micro-RNAs (miRNAs) are small, non-coding and regulatory RNAs about 20 to 24 nucleotides long. Their conserved nature among the various organisms makes them a good source of new miRNAs discovery by comparative genomics approach. The study resulted in novel 46 precursor miRNAs containing 67 mature sequences belonging to 34 families in an important aquatic environmental monitoring fish (Salmo salar). All the miRNA families (let-7, miR-9, 21, 92, 96, 122, 126, 129, 130, 142, 144, 147, 148, 187, 196, 202, 212, 220, 223, 375, 429, 451, 466, 682, 700, 1935, 2132, 2133, 2135, 2140, 2141, 2145, 2146 and 2182) are found for the first time in S. salar. All 46 miRNA precursors form stable minimum free energy stem loop and the mature miRNAs reside in the stem portion of the stem loop structure. Their target proteins are involved in development and differentiation (21%), cell signaling (18%), transcription factors (17%), tumor associated (13%) and miscellaneous (31%) functions.

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ELUCIDATION OF MOLECULAR PATHOGENESIS AND CLASSIFICATION OF BREAST CANCERS BASED ON GENE-EXPRESSION AND PROMOTER METHYLATION PATTERNS TO INDIVIDUALIZE THERAPY IN SAUDI PATIENTS

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Breast cancer is the most common malignancy among women with an annual worldwide incidence of about 1.2 million. It is the leading malignancy, comprising about 25% of all malignancies and leading cause of cancer related death in Saudi women. Human breast tumor is a heterogeneous disease with involvement of different cell types and molecular alterations. Variation in transcriptional programs accounts for much of the biological diversity of human cells and tumors. The current clinico-pathological strategy to classify breast cancer is suboptimal as patients with similar grade and stage of the disease exhibit grossly different response to therapy. Hence, there is an urgent need to accurately classify these tumors for better patient management. Recent advances in cDNA microarray technology have made it possible to classify breast cancers in western women based on the gene-expression

patterns. However, this molecular classification may not be applicable for Saudi Arabian patients due to ethnic differences clearly demonstrated by different median age of onset of breast cancers between the two ethnic groups (46 years for Saudi patients Vs 62 years for US patients). We have initiated a study to classify breast cancers arising in Saudi patient cohort into categories based on shared gene-expression profile utilizing Illumina‘s mRNA-Seq technology. Besides relative abundance of transcripts, mRNA-Seq will aid in discovering transcript isoforms as well as annotate coding SNPs. Additionally, we will study whole-genome promoter methylation which is a well known mechanism to silence tumor suppressor genes and has been shown to have clear implications in the pathogenesis of breast cancers. Our goal will be to obtain a ―Methylation Signature" for the breast cancers in Saudi Population and secondly, to correlate promoter methylation with the gene expression pattern. Genome-wide screening of DNA methylation patterns will be conducted using Illumina‘s Infinium BeadArray platform. Finally, results obtained from gene-expression and methylation studies with the normal and breast tumor tissues will assist us to further dissect the pathways and gain insights into the mechanisms involved in driving the progression of breast cancers. These analyses will pave the way for further investigations in breast cancer/normal cell culture models to activate/inhibit the pathways involved in the tumors by gene manipulation and the phenotype studied. Overall, our research will help in the detailed analysis of breast cancer providing a guideline to accurately classify these tumors resulting in improved therapeutic design and better patient management.

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THERAPEUTIC RELEVANCE OF NOVEL EPIGENETIC DRUGS ON ABDOMINAL AORTIC ANEURYSM

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Abdominal aortic aneurysm (AAA) is an abnormal dilatation in a weakened region of the main abdominal blood vessel. Currently it is estimated that ~5% of men over 65 years of age have an AAA, and the disease is becoming increasingly common in women. Expansion of AAA is usually progressive and the risk of aortic rupture and fatal bleeding increases with an increase in AAA diameter. Patients with AAA present an increased risk of major cardiovascular events such as stroke and myocardial infarction, and AAA is amongst the leading 15 causes of death for people aged more than 60 year. Despite the importance of AAA, there is still a need of improved patient management strategies. At present the only treatments for AAA are surgical, which are not beneficial for smaller aneurysms. Surgical intervention is currently the gold-standard method for AAA correction but is associated with significant peri-operative mortality and morbidity. This warrants the identification of new effective drug therapies to manage AAA at an early stage. Epigenetic mechanisms play a crucial role in regulation of gene expression by affecting chromatin accessibility. Due to the reversibility of epigenetic events, drugs that inhibit DNA methyltranferase (DNMT) or histone deacetylases (HDAC) can synergistically reactivate epigenetically silenced genes. A number of epigenetic drugs are currently being evaluated and many of them have been approved for clinical therapies for various diseases. Till date, there is no study assessing the epigenetic state of various genes involved in AAA development. Several lines of evidences suggest an important role of altered epigenetic status in inflammation, proliferation and remodeling processes which are also associated with the development of AAA indicating that epigenetic changes are crucial in the development and progression of AAA. We hypothesis that many crucial regulatory genes may be silenced in VSMCs which may lead to AAA development and epigenetic drugs will induce reactivation of those silenced genes in vascular smooth muscle cells (VSMCs) leading to identification of new therapeutic targets. Preliminary studies conducted by our group shows promising results using epigenetic drugs to reactivate certain genes silenced in AAA. Microarray studies conducted by our group and others identified a set of genes down regulated in AAA. Our in vitro studies in VSMCs indicate that the set of epigenetically silenced genes can be reactivated by DNA-demethylating drugs or HDACi's, indicating that epigenetic drug therapy modulates gene expression in VSMCs. In the present study two novel HDACi's synthesized by us (MCT-2 & MCT-4) are also evaluated for their efficacy. We present novel data of the possibility of epigenetic therapies is managing AAA.

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SYSTEMATIC ANALYSIS OF GENOMIC VARIATIONS IN HUMAN MICRORNAS

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MicroRNAs are 19-22 nt-long RNAs and well studied class of small non-coding RNAs which regulate gene expression. The regulatory role of microRNAs (miRNAs) has been well studied in a wide variety of biological processes yet there have been no systematic effort to analyze and understand the role of genetic variations in miRNA loci and study its possible functional consequences. Recent evidence suggests an increasing role of genomic variations in modulating miRNA function and regulation. Thus, it is imperative to catalogue the genome wide variations in miRNAs and analyze the results to infer biological significance. We have comprehensively collected and curated genetic variations in miRNA loci in the human genome (hg18) and established a computational pipeline to assess potential functional consequences of these variants along with methods for systematic curation and reporting of variations in these loci. We have mapped validated SNPs from dbSNP (build 130) on human precursor miRNAs (miRBase Release 13) and 85 miRNAs were found to harbor 106 SNPs. Analysis of positions of SNPs on the total 108 miRNAs (from dbSNP mapping and also literature

surveys) revealed 6 SNPs mapped to terminal loop, 67 to Stem and Secondary Loop (excluding mature region) , 10 to Overhang (5` or 3`) and 23 to mature miRNAs with 5 in seed region. To study the effect of variations on biogenesis and functioning of miRNAs, we checked alteration in dicer cleavage sites using PHDcleav and alteration in selection of miRNA guide strand using RISCbinder. PHDcleav predicted hsa-mir-449b and hsa-mir-1324 to have altered dicer cleavage sites on the incorporation of SNP and RISCbinder predicted hsa-mir-608 to have altered mature miRNA incorporation in RISC. To understand the penetrance of these SNPs in the population, we have analyzed the allele frequencies of 41 SNPs from the HapMap populations and found the median allele frequency to be less than 0.1. In addition, for 23 SNPs the minor allele was absent in at least one of the populations. Both these facts point towards a possible negative selection for the minor allele implicating that there might be functional consequences for the variant allele. The consolidated data has been uploaded on miRvar (http://genome.igib.res.in/mirlovd), a community curation resource for genomic variation in miRNA loci. miRvar provides a user friendly interface to search variants in different miRNAs and has information about the variant position and the allele change in the respective miRNA, diseases association, in addition to making it easy to browse for information through linkouts like miRBase, UCSC Genome Browser, miR2Disease, 1000 Genomes Project and miRecords. The strategy has been applied onto personal genomes and small RNA sequencing data from Short Read Archive (SRA, NCBI) to map all variations in non-coding RNAs. Since the understanding of miRNAs and their effects in biological processes, including diseases are just emerging and so is the understanding on the potential functional role of the genomic variations in these loci, we foresee this database to be enriched with new variations and information on disease associations with community efforts.

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MRNA-SEQ ANALYSIS OF MONOZYGOTIC TWINS DISCORDANT FOR TRISOMY 21 REVEALS LARGE CHROMOSOMAL DOMAINS OF GENE EXPRESSION DYSREGULATION

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Trisomy 21 (T21) is the most widely studied model phenotype of whole chromosome aneuploidy. It is likely that the majority of the T21 phenotypes are related to alterations of gene expression. Entire transcriptome sequencing now provides the opportunity to investigate in detail the perturbations of gene expression in T21 cells and tissues. In this study we used fibroblasts derived from a pair of monozygotic twins discordant for T21 (Dahoun et al. 2008). For the first time, the use of these samples eliminates the bias of genome variability and thus most of transcriptome differences observed are likely to be related to the supernumerary chromosome 21. The transcriptome (polyA+ mRNA) was studied by RNA-Seq; more than 200 million 76 bp paired-end reads were generated from each sample and mapped using both MAQ (Li et al. 2008) and GEM (Ribeca et al, unpublished method). The expression level of about 15â€™000 protein-coding genes were compared between the samples. The differences of gene expression level, spliced isoform utilization and allelic expression were studied. In average, we found that 4% of the genes are differentially expressed between the two samples. As expected, the majority (93%) of differentially expressed genes on chromosome 21 are upregulated in the trisomic twin. Amazingly, for most of the chromosomes, we could also identify large chromosomal regions that are either up- or downregulated in the trisomic twin. This raised the hypothesis that differential expression may be organized in domains throughout the genome. The same domains have also been found when we compared the gene expression between induced pluripotent stem cells derived from the same twins fibroblasts. In addition, we identified 58 genes that differentially utilized alternative spliced isoforms between the two samples and 8 genes that show differential allele specific expression. Our study shows that RNA-Seq in monozygotic discordant twins provides the opportunity to identify biologically relevant transcriptome differences without the bias of the genetic variation among the samples.

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ROLE OF POLYCOMB REPRESSION COMPLEX 2 IN THE REGULATION OF MICRORNA EXPRESSION

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Enhancer of zeste homolog 2 (EZH2), the catalytic subunit in polycomb repressive complex 2 (PRC2), is responsible for histone H3K27 trimethylation (H3K27me3). EZH2 is over-expressed in diverse malignancies including pancreatic ductal adenocarcinoma (PDAC). While protein coding genes repressed by EZH2 have been widely studied, the miRNAs repressed during EZH2 over-expression is largely unexplored. Here, our objectives are to identify miRNAs that are regulated by EZH2. A lentiviral vector containing full-length EZH2 was transduction into normal human pancreatic ductal epithelial cells (HPDE) for ectopic EZH2 expression. In addition, PDAC cell line sw1990 was treated with a small molecule EZH2 inhibitor deazanoplasnocin A (DZNep) which caused the cellular depletion of PRC2 proteins EZH2, EED, SUZ12 and H3K27me3. In turn, LNA-mediated qRT-PCR miRNA profiling was performed in both the HPDE and sw1990 cells. The changes of miRNA expression level were determined via comparison with appropriate controls. In silico analysis including miRNA target prediction and targets functional analysis were performed in order to determine potential tumor suppressing effects for the miRNAs regulated directly by EZH2. Among 742 human miRNAs measured, 231 miRNAs

were downregulated and 79 miRNAs were upregulated in EZH2-overexpressing HPDE cells. For DZNep-treated sw1990 cells, 96 miRNAs were upregulated and 406 miRNAs were downregulated. Functional similarity analysis which based on the miRNA-disease association showed that EZH2 aberration altered miRNAs with similar biological function. For EZH2-overexpressing HPDE, several downregulated miRNAs have been implicated in breast cancer and ovarian cancer. On the other hand, DZNep treatment upregulated miRNAs that has reduced level in pancreatic cancer. Together, 23 miRNAs were concurrently reduced in EZH2-overexpressed HPDE cells and increased in DZNep-treated sw1990 cells, which showed great potential to be the candidate miRNAs aberrantly suppressed by EZH2 in PDAC. A few of them such as miR-7 and miR-218 were previously shown to associate with cancer development. Gene ontology analysis on the targets of the candidates showed that these miRNAs regulated different set of genes important during tumorigenesis. For instances, targets of miR-218 and miR-421 involved in cell-cell or homophilic cell adhesion; targets of miR-7, miR-188-3p, miR-513a-5p and miR-520h regulated transcription and gene expression; and targets of miR-513a, miR-520h and miR-602 participated in developmental process. Our results demonstrated an important role for EZH2 in the regulation of miRNA and identified miRNAs with tumor suppressing potential. It also suggested a possible linkage between EZH2 over-expression and PDAC development which is mediated by miRNAs repression. While new therapeutic strategies based on miRNA technologies in PDAC are warranted, the framework of this study is worthy of applying to other malignancies with EZH2 aberration for identification of novel tumor suppressor miRNA. Acknowledgement: This work was supported by Hong Kong Research Grants Council GRF grant (CUHK462109) and Direct Grant from The Chinese University of Hong Kong to Y.C.

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METHYLATION PROFILE OF CANCER RELATED GENES IN TUNISIAN PATIENTS WITH BREAST, GASTROINTESTINAL AND NASOPHARYNGEAL CARCINOMAS

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Epigenetic modification is one of the mechanisms leading to gene silencing in neoplastic cells. By methylation-specific PCR, we analyzed the promoter methylation profile of cancer-related genes in Tunisian patients with breast, gastrointestinal and nasopharyngeal carcinomas. These genes are involved in crucial cellular functions such as the tumor suppressor (RASSF1A), cell cycle control (P16INK4a), DNA repair (hMLH1), cell signaling (RARb2) and apoptosis (DAPKinase). The MSPCR was performed on tumor DNA as well as normal tissues. We showed that RASSF1A gene promoter is highly methylated in breast and nasopharyngeal carcinoma. However, the percentage of methylated RASSF1A is lower in colorectal (35%) and gastric (45%) adenocarcinomas. Moreover, we showed that aberrant methylation of p16INK4a and hMLH1 promoters occur more frequently in colorectal than in breast carcinoma (47% vs 19 % for p16INK4a and 53% vs 24% for hMLH1). Significant associations were revealed between aberrant methylation status and clinico-pathological parameters. In fact, hypermethylation of hMLH1 is predictive of poor prognosis in breast and colorectal carcinomas while the methylated RASSF1A correlated with advanced TNM in nasopharyngeal carcinoma of Tunisian patients. Altogether, our data supports that the methylation profiles of CpG-island hypermethylation vary with tumor types.

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CHIP-CHIP INVESTIGATION OF EPIGENETIC CHANGES IN RESPONSE TO VARIOUS GLUCOSE ENVIRONMENTS

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With the rise in incidences of Diabetes within the Middle East, it will be important to understand the environmental and genetic components of the disease. Epigenetic changes, including DNA methylation and histone modifications, can be a response to environmental signals resulting in stable gene expression changes. To begin understanding the epigenetic effects of glucose in the diet we conducted chromatin immunoprecipitation followed by tiling array (ChIP-chip) analysis on in vitro cultures of cells grown in varying amounts of glucose. We have investigated the effects on DNA methylation and various histone methylation levels. Results from this study are presented. Initial results from this study will guide more detailed analysis of the progress of epigenetic changes, their stability, and their possible transmission to future generations.

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RECOVERED MICROGRAVITY-EXPOSED NORMAL HUMAN OSTEOBLAST CELLS HAVE AN EXTENDED LIFE SPAN

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The theory that microgravity causes accelerated aging was dismissed because astronauts and bed-rest patients recover swiftly after the period of muscular-skeletal up-loading. Concerns however remained because microgravity caused bone loss was replaced without achieving the initial bone density. While exposed to microgravity, osteoblast cells undergo a variety of morphological and transcriptional

changes leading to cell senescence and bone loss. So far no gene expression profiling has been done on microgravity-exposed osteoblast cells after they have been recultured at 1G. Therefore the objective of this study was to compare physiological changes with gene expression data from microgravity recovered osteoblast (MRO) cells. Normal Human osteoblast cells, purchased from LONZA (USA) were sent with Soyuz TMA-11 to the International Space Station where they were cultured at 37C for 10 days. After landing the cells were collected and recultured under 1G standard cell culture conditions for 3 weeks before they were cryo-preserved for further experiments. For the microarray experiments the Affymetrix GeneChip Human Gene 1.0 ST were used and Microarray data analysis was done using GeneSpring GX11.0 analysis software (Agilent Technologies Inc, Santa Clara, CA). Significant up- and down-regulated genes were determined using ANOVA with p-value <0.01 and fold change≥ 2.0for each gene. The Integrated Discovery (DAVID; http://niaid.abcc.ncifcrf.gov/) and Panther Classification system (http://www.pantherdb.org) were used for annotation and visualization of pathways of significant regulated transcripts. Microarray results of selected genes were validated using real-time PCR. The microarray results showed that 786 genes mapping to 95 pathways were significantly different expressed in the MRO cells. The pathways with the most differently expressed genes were the Wnt signaling pathway (19 genes), cell cycle regulation (19 genes), ubiquitin mediated proteolysis (12 genes) and inflammation pathway (12 genes). Interestingly the highly significant different genes mapped to the Wnt and the Cytoskeletal regulation by Rho GTPase pathyway. Both pathways are very important for osteoblast proliferation, differentiation, function and cell death. Changes in the Rho GTPase pathway may explain the cytoskeletal changes observed in the MRO cells. Increased ubiquitination is associated with increased protein degradation while decreased ubiquitination is observed in aging. In the MRO cells however the expression of UBE3B, HERC4 and DDB1 were increased which would counter indicate pre-maturely aged cells. New research indicates that ubiquitination is also involved in transcriptional regulation and DNA repair. Conclusion Together with the observed changes in the cell cycle regulation and apoptosis pathway this may indicate a reduced ability of MRO cells to undergo apoptosis. It also may explain to why MRO cells are able to proliferate longer, although slower than the normal, non-microgravity exposed osteoblast cells.

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EFFECT OF MATERNAL MICRONUTRIENT DEFICIENCY IN OFFSPRING: AN EPIGENETIC PERSPECTIVE

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Various environmental influences in-utero are known to predict risk of complex disorders like cardiovascular disease and diabetes. In spite of previous epidemiological studies demonstrating the above mentioned fact, the precise mechanism for this deregulation remains elusive. DNA methylation (the methylome) is particularly vulnerable to nutritional perturbations during embryogenesis, as nutrients like vitamin B6, B12, folate and methionine are the primary source of methyl groups for all biological methylation reactions. Some studies have provided evidence for a role of epigenetic mechanisms in exerting these long term changes but this has not been explicitly demonstrated. The objective of our study was to ascertain whether maternal micronutrient (Vitamin B12) deficiency affects developmental epigenetic reprogramming and thus could form a basis of complex diseases in adults. We had earlier observed an increased risk of various intermediate traits such as obesity etc. that are related to risk of diabetes and cardiovascular disorders in pups born to female rats fed vitamin B12 deficient diet. We used liver tissue of rat pups born to Vitamin B12 restricted mothers and the control mothers as the model system to identify the differentially methylated regions (DMRs). We were able to generate a high resolution map of the rat liver methylome using methylated DNA immunoprecipitation (MeDIP) assay, followed by high throughput sequencing (MeDIP-Seq) on Illumina‘s Solexa platform. We parallely employed quantitative proteomic approaches using differential in gel electrophoresis to generate the differential proteome profile of liver tissue. At the proteome level, several proteins were found to be differentially expressed between the control and vitamin B12 deficient pups. This study is first of its kind as it compares the global methylation profiles with the differential protein expression profiles, which will enable us to understand the effect of micronutrients during fetal life. We found a few DMRs and are further analyzing the data to ascertain the differentially methylated regions throughout the genome. Correlation of the effects of maternal nutrition on genome methylation and the corresponding proteome profile of the offspring would help us understand the potential mechanisms by which nutritional deficiency during early developmental stages, leads to changes in methylome and manifest diseases in adults.

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INVESTIGATING AND VISUALIZING VARIOUS LEVELS OF GENETIC VARIATIONS FOR UNDERSTANDING THE MOLECULAR CAUSES OF BREAST CANCER

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Next-generation sequencing (NGS) allows the characterization of cells at the genomic, transcriptomic and epigenetic levels. For a normal cell to become a cancer cell changes on all these levels accumulate over many years. Hence, to understand a certain type of cancer on the molecular level a comprehensive analysis based on all these levels is needed. In this work, we investigate seven different breast cancer cell lines by analyzing

and integrating various types of NGS datasets, these are: DNA-seq, RNA-seq, small RNA-seq, DNA and methylation sequencing datasets. In the first level of analysis, all these datasets are analyzed individually to generate a compendium of genomic, transcriptomic and epigenetic alterations for each breast cancer cell line. This compendium includes gene fusions, SNPs, copy number variations (CNVs), alternative splicing, methylation sites in regulatory regions and small-RNA expression. In the second level of analysis, the various alterations are combined to generate a comprehensive picture of cellular misregulation in cancer. Regulatory networks are generated that combine transcriptomic changes with CNVs, methylation alterations and expert-curated annotations. By linking different lines of evidence, the results of this work allow to unravel and underpin genetic alterations in cancer. To present these results visually we developed a network and transcriptome viewer. The network viewer allows to depict gene expression, methylation and additional expert curated information in a network view for all breast cancer cell lines. The transcriptome viewer, in addition, allows viewing changes in transcript expression and novel splice-junctions for all cell lines. Overall, this study pinpoints and visualizes many genomic, transcriptomic and epigenetic alterations that are potential causes for the different types of breast cancer under investigation.

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DIFFERENTIAL GENE EXPRESSION PROFILING OF CD14+ CELLS DIFFERENTIATED FROM CD34+ UMBILICAL CORD BLOOD HAEMATOPOIETIC PROGENITOR CELLS

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Hematopoietic stem cell (HSC) derived from cord blood has many advantages for blood transplantation and gene therapy especially in hematologically and immuno-compromised diseases, but the recipient is restricted to pediatric patients because of the small volume inherent from cord blood. These inconveniences have been considered to be resolved if ex vivo expansion and differentiation of HSC to matured blood cells would turn out to be a reality. To date, there is no report on transcriptomic profiling carried out on HSC derived monocyte, therefore this study is conducted to determine the differential profiling of differentiated CD34+ hematopoietic progenitor cells (HPCs) monocytes compared to the monocytic cells isolated from peripheral blood (PB) of normal individuals. Normal CD34+ HPCs isolated from umbilical cord blood (UCB), purchased from LONZA (USA) were expanded and differentiated using specific cytokines cocktails at 37°C and 5% CO2 in 6-well plates. Monocytes expressing CD14+ were isolated from PB using Ficol-Hypaque (1.077 g/ml) gradient density method. Pure cell populations of CD34+ HPCs, CD34+ derived monocytes and monocytes from PB were enriched using CD34+ and CD14+ MACS magnetic beads isolation kits (Miltenyi, German) and validate using FACScan (Beckman Coulter). Total RNA isolation was carried out by the use of Trizol (Qiagen). To understand the differential gene expression profiling pattern showed by both cell populations, we carried out microarray analysis by using Affymetrix GeneChip® Human Gene 1.0 ST (Affymetrix, USA). Data analysis was done using Gene Spring GX11.0 (Agilent Technologies Inc, Santa Clara, CA). Significant genes expression changes were validated using ANOVA with a p-value <0.01 and fold-change ≥ 2.0 for each gene. The Integrated Discovery DAVID software; (http://niaid.abcc.ncifcrf.gov/) and the Panther Classification system (http://www.pantherdb.org) were used for annotation and visualization of differentially expressed pathways of statistical significance. Microarray data of selected genes were validated using SYBR Green qRT-PCR. From the analyses, gene profiling of ex vivo CD34+ differentiated monocyte cells showed marked differences compared to the monocyte cells isolated from peripheral blood as demonstrated by Stec et al. (2007). The microarray results showed that 187 genes were significantly different in the HPC derived CD14 cells with 114 genes were upregulated and 73 were downregulated compared to PB derived CD14 cells. From the KEGG pathway, the most differently expressed genes were the cancer cell pathway (11 genes), lysosome pathway (9 genes), regulation of actin cytoskeleton (8 genes), ribosome pathway (8 genes), haematopoietic cell lineage pathway (6 genes) and leukocytes transendothelial migration pathway (6 genes). From this preliminary data, the demonstrated changes in the oncogene pathway and hematopoietic cell lineage pathway may indicate a higher ability of HPC derived CD14 cells to maintain cell proliferation. It may also indicate that differentiated cells are able to expressed stemness characteristic compared to the normal monocyte cells which are isolated from peripheral blood.

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ALTERATION IN THE EXPRESSION OF MIR-21 AND MIR17-92 IN SKIN BIOPSIES OF WAR VETERANS WITH SULFUR MUSTARD EXPOSURE

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Sulfur mustard (SM), a chemical warfare agent, interferes with fundamental cellular processes such as DNA replication, transcription and translation. It also affects divergent cellular responses/pathways including cell cycle control, apoptosis/necrosis, electron transport, cell adhesion, inflammatory response, and morphogenesis and repair. However, its affects on human cells and tissues are poorly understood. MicroRNAs (miRNAs) are a novel post-transcriptional gene regulators, each targeting several (even >100) mRNAs. They are being indicated in an increasing

number of cellular abnormalities, so holding promise as possible therapeutics or therapeutic targets through the use of miRNA mimics or antagomirs, respectively. However, to date, the role of miRNAs in the cellular response to sulfur mustard has remained entirely unnoticed. Aberrant expression of miR-21 and miR17-92 has been associated with various cellular abnormalities. These miRNAs are validated to control targets in P53, NFkB, apoptosis, JAK-STAT, TGF-β and AKT pathways. As these pathways are already shown to - through microarray studies- contribute to SM pathogenesis, it would be interesting to assess the effects of SM exposure on these miRNAs. Methods: Normal human fibroblasts were maintained in RPMI (37°C, 5% CO2). Near-confluent cell cultures were exposed to 50, 150, and 300 micromoles of SM for different time pointss (.5, 1, 10 hrs) and were used along with skin biopsies obtained from Iranian veterans to determine changes in mir-21 and mir-17-92 cluster. After RNA extraction and cDNA synthesis the expression of candidate miRNAs were assayed using real time PCR. Results and Discussion: Using LNA specific primers, we were able to detect and quantify the expression of mir-21 and mir-20a in exposed cells, and skin biopsies. Our preliminary data suggest that mir-21 and mir-20a are downregulated in biopsies obtained from lesion areas of skin, in comparison to the normal skin tissue from the same patient. SM exposure on fibroblast cells also altered the expression of mir-21 and mir-20a, in a dose-dependent manner. Our data suggest that SM exposure could cause expression alteration in miRNAs, and that this alteration might contribute to the pathogenesis of the exposed tissues.

STATISTICAL GENETICS

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INVOLVEMENT OF TP53 G/C CODON 72 POLYMORPHISM IN PREDISPOSITION TO CERVICAL CANCER IN SAUDI PATIENTS

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Carcinoma of the uterine cervix is one of the most common neoplasia among women worldwide, second only to breast cancer. However, it ranks number 8 in Saudi Arabian women. The actual causes of this relatively low incidence are unknown but it could be related to the susceptibility to infection with human papilloma viruses (HPV) and genetic predisposing factors. In fact, individuals differ in their inherent tendency to develop cancer. This has been suggested to be related to polymorphic variations between individuals. Single nucleotide polymorphisms (SNPs) are the most common form of genetic variations found in the human population. SNPs in genes involved in pathways related to cell-cycle control, DNA repair and apoptosis are likely to affect cancer susceptibility due to inability to accurately repair DNA damage and halt the division of injured cells. A strong candidate is the tumor suppressor gene TP53-mediated pathway. A common G/C polymorphism at codon 72 of TP53 that results in a proline to arginine change in the amino acid sequence of the encoded p53 protein has been proposed to influence individual susceptibility to cancer. It has been suggested that the arginine form is more susceptible to HPV E6 mediated degradation and therefore, it could predispose to cervical cancer development. The aim of this study was to investigate the association between the SNP TP53 codon 72 G/C (Arg/Pro) and the risk to develop cervical cancer in Saudi women. A cohort of 339 females was studied (including 133 cervical cancer patients and 206 controls). DNA was extracted from 5 ml whole blood and the relevant DNA segment was PCR-amplified, sequenced and TP53 G72C genotyped. Results showed statistically significant associations (P = 0.03) between the TP53 G72C and cervical cancer occurrence. The variant C/C genotype showed increased risk to develop cervical cancer (Odds Ratio = 2.08, confidence interval: 1.07-4.07). Interestingly, at 5% significance level for 1 degree of freedom, the genotype frequencies of the control group were out of the Hardy-Weinberg equilibrium (x^2 = 9.6), while that of the patients were in the Hardy-Weinberg equilibrium (x^2= 0.41). We conclude that TP53 G72C polymorphism is associated with cancer predisposition and the variant C/C genotype increases 2-fold the risk of developing cervical cancer in Saudi females. Larger studies are required to confirm these results and to uncover more polymorphic variations that can be used as biomarkers to identify women at high risk of cervical cancer. Supported by KACST grant # ARP-27-12 and # LGP-12-4 (KFSH&RC ORA # 2060 029 and # 2060 027).

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ASSOCIATION STUDY OF CARD-8 (C10X) AND NLRP3 (Q705K) VARIANTS WITH RHEUMATOID ARTHRITIS IN TUNISIAN POPULATION

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The inflammasomes are essential regulators of cytokine production. We investigated whether two polymorphisms in the genes encoding TUCAN (CARD8) and cryopyrin (NLRP3) influence susceptibility in RA in Tunisian population. CARD-8 (rs2043211) and NLRP3 (rs35829419) single nucleotide polymorphisms (SNPs) were genotyped in

141 Tunisian RA patients, 191 unrelated healthy controls, using TaqMan 5' allelic discrimination assay. Data were analyzed by x^2-test, Genotype Relative Risk (GRR) and Odds Ratio (OR). No significant difference in allele and genotype frequencies was detected between RA patients and controls either with CARD-8 or NLRP3 genes (p=0.42, p=0.155 and p=0.28, p=0.34; respectively). Stratifying patients according to the presence of rheumatoid factor (RF), anti-cyclic peptides antibodies (ACPA), erosion, nodules, another autoimmune disease or in HLA-DRB1*04 and HLA-DRB1*0404 positive subgroups did not show any significant association with CARD-8 or NLRP3 (p>0.007). Our data suggest that CARD-8 (C10X) and NLRP3 (Q705K) single nucleotide polymorphisms have no effect on RA susceptibility in the Tunisian population.

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GENOME-WIDE ASSOCIATION STUDY OF ANTERIOR CHAMBER DEPTH (ACD) IN TWO ASIAN POPULATIONS

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The aim of this study was to discover genetic variants associated with anterior chamber depth (ACD) in an urban Singaporean population. We conducted a population-based genome-wide association study (GWAS) of ACD in Singaporean Malays and in Singaporean Indians aged between 40-80 years from two well characterized population-based studies: the Singapore Malay Eye Study (SiMES) and the Singapore Indian Eye Study (SINDI), respectively. A non-contact partial coherence laser interferometry (IOLMaster V3.01, Carl Zeiss; Meditec AG Jena, Germany) was used to measure ACD in the horizontal and vertical meridian. ACD measurements were available for 2862 participants in SiMES and 3373 in SINDI. Of these, 2209 and 2521 had DNA available and were genotyped using the Illumina Human610-Quad BeadChips. Pseudo-phakic or aphakic individuals were excluded. For those individuals who have had cataract surgery, only the phakic eye ACD measurements were used. For those individuals with two phakic eyes, individuals were excluded when ACD measurements between the two eyes differed more than 0.2mm (top 20 percentile), which gave both a high phenotypic and high GWAS p-value correlation between the left and right eye (>0.95 and >0.85, respectively). In the final GWAS, the mean measurement of ACD was used. Final samples yielded a total of 1752 Malays and 1860 Indians who had both phenotypic and genotypic data. Separate association analysis in either cohort did not yield in any results reaching genome-wide significance (p-value <5x10-8). However, upon pooling data from both SiMES and SINDI, a promising locus on chromosome 3 (meta p-value ~7x 10-7, just below GWAS significance) was identified for which replication is pending. We discovered a potential gene influencing ACD in two ethnic Singaporean populations. Further investigation is warranted as to the nature of this locus and its relationship to ACD and/or PACG.

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FMO3 ALLELIC VARIANTS IN A MEDITERRANEAN POLULATION: FREQUENCY AND LINKAGE ANALYSIS

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Trimethylaminuria (TMAU) is a metabolic disorder that produces pronounced body odors resulting from the systemic accumulation of an excessive amount of unoxidized trimethylamine that is then excreted in the breath, sweat, and urine. The biochemical deficit causing this condition is the inability to completely metabolize trimethylamine (TMA) to TMA-oxide (TMAO) in the liver. There are several types of TMAU caused by a 'spectrum' of changes in the gene which controls the formation of the flavin-containing monooxygenase 3 (FMO3) enzyme. In humans, this is an important liver enzyme that controls the metabolism of substances such as TMA. The most severe form of TMAU appears to be caused by mutations in the FMO3 gene; these mutations appear inherited in an autosomal recessive fashion, but the less severe forms of TMAU are caused by several genetic polymorphisms in the FMO3 gene. It is estimated that as much as one percent of the population may suffer from TMAU (but its true incidence is not yet known) and that the condition affects people of both sexes and of all ages and races from around the world. Three coding region variants g.15167G>A c.472 G>A, p.E158 K (exon 4), g.18281 G>A c.769 G>A, p.V257M (exon 6), g.21443A>G c. 923 A>G, p.E308G, (exon 7) have been identified in all population examined so far with considerable frequency differences between the major ethnicities. A fourth polymorphism, the g.26990 G>A, p.G475D, c.475 G>A (exon 9), is less common in the general population so far screened. Variable extent of decreased FMO3 enzyme activity has been characterized as the functional impact of the four variants in vitro. We report the distribution of four variants in 573 healthy individual sampled from several geographical sites: 105 samples for the North Africa (Morocco, Algeria, and Tunisia), 318 for the south of Italy, 150 for eastern Mediterranean (Greece and Albania). Genotypic frequencies were determined by PCR-RFLP method and allele frequencies were estimated by the gene counting method. Table: Exons/Variant/Allelic frequency (Nord Africa/South Italy/East Mediterranean), Ex4/E158K/0.32/0.36/0.40, Ex6/V257M/0.50/0.50 /0.50, Ex7/E308G/0/0.08/0.16, Ex 9/G475D/0.50/0.50/0.50.

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ALLELE FREQUENCY DISTRIBUTION BASED ON 10 STR MARKERS IN THE CENTRAL REGION OF IRAN

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The aim of this study was to investigation of Allele frequency and distribution of 10 STRs marker (TPOX; vWA; D7S820; D8S1179; D13S317; D16S539; D18S51; D5S818; THO1; D21S311). Whole blood samples was collected from 100 unrelated individuals (man and woman) living in the central region of Iran. PCR amplifications of the 10 STR loci were performed by ABI PRISM® 3130xl DNA Genetic Analyzer. The PopGen32 and Power Stats v.1.2 software was used for investigation of population and forensic parameters. Allelic frequencies and gene diversities for locus was calculated from the numbers of each genotype in the sample set. The most and least alleles were observed in D21S311 (12 alleles) and TPOX markers (6 alleles) respectively. The expected heterozygosity (unbiased estimate) ranges from 0.66 (TPOX) to 0.88 (D8S1179). The D18S51, D8S1179 and D21S311 loci had a high power of discrimination (PD) with values of 0.962, 0.944 and 0.94, respectively. The probability of excluding paternity (PE) varies between 0.369 (TPOX) and 0.755 (D18S51). The Polymorphic Index Content were variable from 0.55 (TPOX) to 0.87 (D18S51), Paternity Index from 1.47 (TPOX) to 4.17 (D8S1179) which is indicative good information for all of the STRs. Results indicated that usefulness of studied STRs loci in paternity testing and personal identification in Iranian population.

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GENETIC DIVERSITY AND PHYLOGENETIC RELATIONSHIPS INVESTIGATION IN 6 IRANIAN ETHNIC GROUPS BY 10 STR LOCI

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Population genetics and forensic biology are inextricably linked together. The STRs are hyper variable markers that can propose the better understanding needed to distinguish relationships among closely related populations at the same time. The objective of this study was to investigate genetic diversity and estimated phylogenetic distance in 6 Iranian populations. For this propose, ten STR loci (D21S311, D18S51, D16S539, D13S317, D8S1179, D7S820, D5S818, TPOX, THO1 & vWA) were selected. Blood samples were obtained from 550 Iranian unrelated healthy donors (woman and man) living in different regions of Guilan, Fars, Kordestan, Khouzestan, Azarbayjan and Sistan & Baluchestan province. The PCR amplification was carried out in final volume of 25µl with the special annealing temperature for a pair of primer without the extension time. The PCR products were separated by electrophoresis on denaturing 8% polyacrylamide gel, using the Gel Sequencing System of the Bio-RAD company. The PopGen32 and Power Stats v.1.2 software was used for investigation of population and forensic parameters. The most and least alleles were observed in D21S311 (21 alleles) and TPOX markers (6 alleles). The heterozygote content was from 0.699±0.0491 (TPOX) to 0.903±0.0491 (D21S311) respectively. Deviation from Hardy Weinberg equilibrium was seen in the locus of D7S820 (P=0.0405) and D8S1179 (P= 0.0387). This decrease in equilibrium was eliminated under the Bonfferroni correction (P<0.05). Based upon the allelic frequencies, several important forensic parameters were calculated. The PIC was variable from 0.65 (TPOX) to 0.88 (D21S311), Power of Discrimination from 0.860 (TPOX) to 0.974 (D21S311), Power of Exclusion from 0.427 (TPOX) to 0.802 (D21S311). The Paternity Index was variable from 1.66 (TPOX) to 5.16 (D21S311), that is indicative good information for all of the STRs. The Fis, Fit and Fst was 0.0196, 0.0327 and 0.0134 respectively. Increasing of Fst was indicated that there is partial segregation between populations. The gene flow between populations was estimated 18.4408. Correlation content of STR loci within and between populations was evaluated 0.6839 and 0.99999999 respectively. Comparison between ethnics and drawing phylogenetic tree with UPGMA phylogram and calculation genetic genuineness and distance represented that genetic genuineness and distance of Guilak and Fars populations are closed to each other and have most genetic interval with other ethnic groups (P<0.05). Also, the results indicated that the integrative relationship between population genetics and forensic science parameters can be useful for thorough genetic characterization of extant human ethnic populations, but D18S51 locus was very effective marker in investigated populations.

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IMPACT OF COMMON VARIANTS OF IGF2BP2, CDKAL1 AND KCNJ11 GENES ON THE RISK OF TYPE II DIABETES (T2D) IN WEST ALGERIAN POPULATION

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Diabetes mellitus type 2 (T2D) is a common metabolic disorder resulting from complex interactions between environment and human genetic factors. It now affects 171 million people worldwide and its prevalence is increasing at a global level with large variations from one population to another, depending on the ethnic origin and life style. In Algeria, the prevalence of type 2 diabetes is 12.29% (www.ands.dz/insp/synthese-mortalite-finalpdf1.pdf). This

high prevalence is explained by the epidemiological transition (change of lifestyle and eating habits). In this context, the NEPAD/NABNet set up a North African network that aims to identify the genetic basis of type II diabetes and its complications among North African populations, thus providing tools for early genetic testing for better prevention and care. Population study and Methods: A total of 528 individuals old > 45 years, comprising 269 type 2 diabetes patients (122 men and 147 women) and 259 controls (115 men and 144 woman), were included in the present study. For each subject, anthropometric variables including height, weight, waist and hip circumferences were measured; medical background was investigated, looking for familial history of diabetes, personal history of malnutrition or obesity, alcohol and smoking habits. Biochemical Measures: Blood samples were collected from subjects after an overnight fast for 12 h. The plasma was separated by centrifugation and frozen until determinations. The plasma glucose, total cholesterol, HDL and LDL cholesterol concentrations were measured by the enzymatic method using commercial kits (Biomaghreb). Determination of genetic admixture: Five ml of blood was collected for each subject. Genomic DNA was extracted from buffy coats, using the QIAmp DNA isolation kit (QIAGEN), according to the standard protocol. Genotyping by Real-Time Assay: The rs4402960 G/T intron 2 polymorphism of IGF2BP2, rs7756992 in CDKAL1 CDK5 regulatory subunit associated protein 1-like 1, and rs5219 in KCNJ11 Glu23Lys (E23K) was genotyping using a TaqMan assay (Applied Biosystems). Statistical analysis: Means and standard deviations (SD) were compared by ANOVA test using SPSS software (version 11.5). Genotype distributions between cases and controls were compared using the Pearson‘s chi-square test. The genotype distributions for both single nucleotide polymorphisms (rs4402960 and rs5219) were in accordance with the Hardy-Weinberg equilibrium (p=0.079 and p=0.196, respectively), but not the polymorphism rs 7756992 (p=0.013).Nominally significant associations were observed between type 2 diabetes and the rs4402960 SNP in test Heterozygous (ORGGvsGT=1.562 C.I95%[1.075-2.268], p=0.019), and test allele positivity (ORGGvsGT+TT=1.530 C.I95%[1.077-2.172], p=0.017). However, the two markers rs7756992 (ORrs7756992=1.017, p=0.776) and rs5219 (ORrs5219=1.087, p=0.943) were not associated with T2D in west Algerian population. Variant located within the gene IGF2BP2 is strongly associated with T2D, providing support to previous evidence indicating that polymorphisms at the IGF2BP2 gene increase T2D risk. In contrast, the CDKAL1 and KCNJ11 polymorphisms are not associated with T2D in Algerian population. Genes expressed in the pancreas interact together and their combined effect dramatically increases the risk for T2D, opening avenues for the development of genetic prediction tests.

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GENETIC ANALYSIS OF ALZHEIMER'S DISEASE ASSOCIATED GENES-A PERSPECTIVE FROM ABNORMAL CHOLESTEROL METABOLISM

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The physiopathology of Alzheimer's disease (AD) is complex and multifactorial. Abnormal cholesterol metabolism has been found to be implicated in the disease pathogenesis process. Thus, cholesterol metabolism genes could be plausible candidate genes in predisposing to Alzheimer's disease. The apolipoprotein E (APOE), ATP-binding cassette, subfamily A, member 1 (ABCA1), and cholesterol 24S-hydroxylase (CYP46A1) genes are all key factors in cholesterol transportation and metabolism pathways, and have been associated with the risk of AD. Genetic associations of the genes APOE ABCA1 and CYP46A1 with AD have been analyzed by different groups and across multiple populations. However, due to heterogeneity in genetic constitutions and other confounding risk factors, the research outcome of association studies has always been controversial and inconclusive. To clarify the association of APOE ABCA1 and CYP46A1 with AD in the Chinese population, case-control association studies, bioinformatics data mining, and statistical analyses were performed. Hong Kong sporadic and late-onset AD subjects (n=290, 79.3±6.5 years; 73.0% females and 27.0% males) and age-matched healthy controls (n=384, 72.0±5.5 years; 72.7% females and 27.3% males) were recruited in this study. Sequenom platform was used for genotyping most genetic variants. Furthermore, restriction fragment length polymorphism (RFLP) was used for genotype APOE gene and CYP46A1 intron 2 polymorphism. Statistical genetics analyses were then performed through standard statistical tests (Chi square, Fisher's exact, etc.) and haplotype analysis software programs (Haploview, Gevalt). Consistent with previous genetic studies, the APOE E4 allele was significantly associated with AD in the Hong Kong AD data set. Moreover, significant associations of ABCA1 and CYP46A1 with AD were observed in both single gene analysis and haplotypic association. The most important findings of this project were the discovery of a possible functional polymorphism (rs2297404) in ABCA1 gene and new regulatory promoter single nucleotide polymorphisms (SNPs) in CYP46A1. Furthermore, functional study on CYP46A1 promoter SNPs showed that different promoter haplotypes contributed differently to reporter genes expression, thus linking genetic difference with the underlying patho-physiological mechanism. In addition, investigation of cholesterol pathway genes (APOE, CYP46A1, and ABCA1) via logistic regression model revealed that these genetic risk factors, as a whole, interacted with one another and mediated the risk of disease predisposition. Conclusions Genetic analyses and association studies provided evidence that cholesterol pathway genes (APOE, CYP46A1, and ABCA1) were significantly associated with AD in the Chinese population, and the effect was in combination with the APOE E4 allele. Considering the biological significance of cholesterol metabolism, this study was not only a mere genetic analysis but it could also offer significant implications for therapeutic strategies in disease treatment.

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A DETAILED VIEW ON MODEL-BASED MULTIFACTOR DIMENSIONALITY REDUCTION

WITH QUANTITATIVE TRAITS FOR DETECTING GENE-GENE INTERACTIONS: DIFFERENT WAYS OF ADJUSTING FOR LOWER-ORDER EFFECTS

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Understanding the effects of genes on the development of complex diseases and traits in humans is a major aim of genetic epidemiology. In particular, if there exist significant main effects unaccounted for during epistasis screening, false positives arise and therefore epistasis results reported might not be genuine. Using Model-Based Multifactor Dimensionality Reduction (MB-MDR) method, a power study for quantitative traits has been performed by Mahachie John et al., 2010 and on family data by Cattaert et al., 2010, with and without correction of functional SNPs main effects. Their results emphasized the importance of lower-order effects adjustment when searching for epistasis in order to keep the number of spurious findings under control. However, a thorough investigation of the power of MB-MDR to identify gene-gene interactions with different strategies to adjust for lower-order effects, whether or not being part of a functional interaction has not yet been performed. In this study, we use simulation to assess the effect of implementing different corrective measures for lower-order effects in an MB-MDR context of two-locus detection, on both power and family-wise error rate. The implemented MB-MDR strategy reduces the multi-locus genotype dimension to one with three possible outcomes, while pooling multi-locus genotypes into three groups of risk (High, Low and No Evidence) based on the liberal p-value threshold 0.1. When no correction for main effects is performed, the original trait is used as the outcome. Adjusting for main effects is performed in two categories: 1); main effects screening prior to MB-MDR and 2; main effect adjustment during MB-MDR run. For the first category, significant SNPs are first regressed out, corresponding residuals are derived from the appropriate regression model, and are subsequently analyzed as new outcomes for MB-MDR analysis whereas the second category involves main effects adjustment _on the fly', i.e., regardless of significance, we always adjust for main effects of the pair we are looking at when running MB-MDR. Two extreme ways of correcting for main effects are implemented, referring to an additive or genotype genetic model. In addition, MB-MDR order-1 is performed to identify significant SNPs and these SNPs are adjusted for in the way their risk cells would have been identified. Data are simulated according to two quantitative trait models (M27 and M170) of Evans et al. 2006 that incorporate varying degrees of epistasis, and include a range of allele frequencies p, p ε {0.1, 0.25, 0.5}, at the predetermined functional SNPs. The total genetic variance for the two-locus model is varied as an element of {0.01, 0.02, 0.03, 0.05, 0.1}. For each parameter setting, we consider 500 simulation replicates, involving 2000 unrelated individuals. MB-MDR screening is performed on 100 SNPs which are assumed to be in Hardy-Weinberg Equilibrium. No linkage disequilibrium exists between the SNPs. In conclusion, preliminary results showed that indeed uncorrected for main effects results have false positives amounting to as high as 100%. Also, additive modeling, the mainly used first strategy in the context of main effects GWAS may not be sufficient for epistasis screening.

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EFFECT OF AGE SUBSET ON GENOME-WIDE ASSOCIATION ANALYSIS OF TUBERCULOSIS IN THAIS

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Conventional candidate gene approach has been applied in search for genetic risks for tuberculosis (TB), 160 candidate genes were reported in HuGE database. Unfortunately, majority of the proposed genetic risks are not replicated in second population except the variations within IL12-IFNG axis and HLA class II. Linkage analyses identified a genome-wide significance on 8p and suggestive evidences on 5q, 6p, 7p, 10q, 11q, 15q, 20p, 20q, Xq. We did ordered subset analysis of TB sibpairs and identified an effect of age at onset on linkage analysis of TB on chromosome 20p and 17p (Mahasirimongkol et al. 2009). Recently, a genome-wide association study (GWAS) of two African TB populations identified gene desert on 18q11.2 as novel candidate locus for TB caused by Mycobacterium tuberculosis, but TB GWAS was not successful in identifying genetic factors with moderate to large effect sizes (Thye et al. 2010). This is a striking contrast for a related disease caused by Mycobacterium Leprae. Linkage analyses (Mira et al. 2003) and GWAS in leprosy (Zhang et al. 2009) identified multiple genetic factors with moderate effect sizes in biologically relevant genes such as LTA, PARK2, HLA-DR-DQ, C13orf31, CCDC122 and RIPK2. For several common infectious diseases, susceptibility loci with moderate to large effect sizes (at risk odds ratio > 1.5) were identified by GWAS (Davila et al. 2010) We aimed to determine the effect of subset analysis based on age of TB cases on Thai TB GWAS and the effect of age stratification on 3315 SNPs in 160 reported candidate genes of tuberculosis. Thai samples for genome-wide genotyping comprised of 433 TB patients and 295 healthy control samples. TB patients were recruited from TB clinics in ChiangRai province. The control samples were recruited from blood donors in the province. All cases were HIV seronegative when TB was diagnosed by identification of mycobacterium. GWAS was done on subsets of cases stratified based on age of TB patients. Age cut off at 25 to 60 by 5 years intervals were used to divide subsets of cases, in total 16 subsets were analyzed. The rank of statistical evidence of variations in candidate genes for TB including MHC class II region were presented and discussed. For GWAS in Thai TB, the exploration of age cut off and the effect of this stratification on the deviation of the chi-square statistics in the

GWAS analysis of cases based on age strata suggested that the young TB and old TB patients have non-overalapping rank of top single nucleotide polymorphisms (SNPs). SNPs within HLA-Class II region provided stronger associations in young TB population compared to old TB patients. The top SNPs in young TB patients have moderate to large effect sizes, however, this initial analysis has not yet provided the genome-wide significant evidence and we need replication studies to confirm this finding. Some candidate genes showed evidence of subset in TB. Subset analysis of GWAS by age at onset in TB might provide consistent replication evidences for genetic risks of TB.

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DO POLYMORPHISMS AFFECTING GENES OF THE RENIN-ANGIOTENSIN SYSTEM AFFECT MYOCARDIAL INFARCTION RISK AND BLOOD PRESSURE IN THE ALGERIAN POPULATION?

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Molecular variants of individual components of the renin-angiotensin system (RAS) are reported to participate to the inherited predisposition to cardiovascular diseases, e.g. essential hypertension or myocardial infarction. Polymorphisms within the genes encoding for angiotensinogen (AGT), angiotensin II type 1 receptor (AT1R), and angiotensin-converting enzyme (ACE), which have been widely investigated in population-based samples as well as in case-control studies, have been proposed as risk factors for coronary heart disease (CHD). However, considering the relatively large discrepancy in frequency and impact of these variants between ethnic groups and populations, similar data from Arab populations are needful but limited in number. In such context, our purpose was to evaluate the association between the AGT M235T, AT1R +1166A/C, and ACE I/D polymorphisms and (i) the risk of myocardial infarction (MI), and (ii) variations in systolic (SBP), diastolic (DBP) and pulse (PP) blood pressure values. Concerning MI, the polymorphisms were characterized in a case-control study (69 cases vs 67 age-matched controls) based on the male population originating from Oran, Algeria. The allele-specific oligonucleotide (ASO) method was used to identify the AGT M235T and AT1R +1166A/C polymorphisms. The ACE I/D polymorphism was determined by Polymerase chain reaction (PCR). The associations with blood pressure were assessed in an enlarged control group including 115 male subjects. The frequencies of the rare AGT 235T, AT11166C and ACE I alleles were estimated to 48%, 19% and 28% respectively. The allele frequencies of the three polymorphisms in the Algerian population were similar to these reported in other Arab populations. However, we neither showed associations of the ANG M235T and AT1R +1166A/C polymorphisms with variations in blood pressure values. The ACE I/D polymorphism needs further investigations in a larger study, especially concerning its putative impact on SBP and pulse pressure.

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DETAILED GENETIC ANALYSIS OF KIR2DL4 GENE AND ITS ASSOCIATION WITH RECURRENT MISCARRIAGES AMONG NORTH INDIAN WOMEN

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Decidual natural killer (NK) cells play key developmental roles at the feto-maternal interface. NK cells have a series of receptors including the KIRs, the ligands for which include HLA-C, HLA-E and HLA-G, which are expressed on the trophoblast cells. Individual differences in KIR repertoire can result in varied NK cell effector functions, and KIR-HLA diversity has been shown to be associated with the disorders of placentation like pre-eclampsia and recurrent miscarriage. Among the members of KIR gene family, KIR2DL4 is unique in its genomic organization, expression, and function. KIR2DL4 is considered a framework KIR gene, being present in almost all genomes. Functionally, KIR2DL4 has been reported to be an inhibitory receptor but ligation of KIR2DL4 with mAb results in activation of IFN-γ secretion and cytotoxicity in peripheral NK cells. These different functional activities of KIR2DL4 are consistent with the fact that KIR2DL4 has both an ITIM in its cytoplasmic domain and a charged residue in the transmembrane domain, suggesting KIR2DL4 may mediate different functions under different circumstances. Two common alleles of the transmembrane domain of KIR2DL4 exist. The 10A allele with 10 adenines at the end of the transmembrane exon encodes a full length receptor, whereas the 9A allele has only 9 adenines resulting in a frame shift which in turn generates a stop codon early in the first cytoplasmic exon. It has been shown that the KIR2DL4 genotype influences expression and function in NK cells. Evidences suggest that HLA-G is the ligand for KIR2DL4 and since IFN-γ is an important mediator of vascular changes associated with placentation, interaction between KIR2DL4 on dNK cells and HLA-G on trophoblast cells may be important for placental development. The aims of this study were to characterize the distribution of KIR2DL4 alleles among recurrent miscarriage (RM) patients and healthy parous controls from North India. Detailed analysis of KIR2DL4 gene was carried out by direct sequencing of the PCR amplified products. Sequencing analysis of the gene included exons 3, 5, 6, 7 and a fragment containing exons 8 and 9. Oligonucleotide primers flanking these exons were obtained so as to cover the coding regions as well as the exon-intron boundaries. KIR2DL4 allele distribution among North Indian women experiencing RM was characterized and was compared with that of controls. There was no significant different in allele frequencies of RM patients and controls. Analysis of 10A and 9A alleles also revealed fairly uniform distribution among individuals of both groups. The frequencies of 10A and 9A alleles respectively was 0.66 and 0.34 in RM patients and 0.65 and 0.35 in controls. Our results did not find any association of KIR2DL4 variants with RM. The high prevalence of 9A in this

population support the view that the maintenance of this non-expressed genotype is not selected against in humans. However, it must be considered that a beneficial role for KIR2DL4 in pregnancy is still possible under certain conditions. The distribution of KIR2DL4 alleles in this population is reported for the first time in this study.

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THE EFFECT OF PHENOTYPE DEFINITION ON IDENTIFYING KNEE OSTEOARTHRITIS RISK LOCI: THE ARCOGEN GENOME-WIDE ASSOCIATION STUDY

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The genetic architecture of osteoarthritis (OA) has not as yet been fully characterized. To date only two loci have been reproducibly associated with knee OA in Europeans at genome-wide significance levels: rs143383 in the GDF5 gene and rs3815148 on chr7q22. Phenotype definition has been proposed as a likely factor for the paucity of robust findings. Here, we use arcOGEN genome-wide association scan (GWAS) data comprising 3,498 knee OA cases to explore the effect of different phenotype definitions on signal detection. OA cases were ascertained based on X-ray evidence of disease (Kellgren-Lawrence grade≥ 2) or clinical evidence of disease to a level requiring total joint replacement (TJR) and were genotyped on the Illumina Human610 platform. We performed analyses using two types of controls: population-based controls (n=11,009, female n=5,515) and OA-free controls (females only, n=1,828). To enable direct comparison, we focused on the female subsets of cases and controls. We find that evidence for association with the GDF5 proxy SNP, rs4911494, (r squared=0.93 with rs143383), was stronger when female knee OA cases (n=2,135) were analyzed using OA-free (OR=1.10 [1.01-1.21], p=0.03861) compared to population-based (OR=1.04 [0.97-1.12], p=0.2883) controls. The same pattern was observed for the chr7 locus (OR=1.19 [1.07-1.32], p=0.0015 for OA-free controls, compared to OR=1.10 [1.01-1.20], p=0.0225 for population-based controls). Notably, when the full set of 3,498 knee OA cases and 11,009 population-based controls were analysed, the signal at chr7 became stronger (OR=1.12 [1.05-1.19], p=0.00065). We also investigated the effect of case phenotype definition by comparing the results of analyses using knee TJR-only cases (severe endpoint of disease, n=2,164) and all knee OA cases combined (TJR and X-ray, n=3,498) versus the full set of 11,009 population-based controls. We observe similar patterns of a lack of association in the signal for the GDF5 locus (OR=0.98 [0.92-1.05], p=0.5661 for TJR-only; OR=1.01 [0.96-1.07], p=0.7256 for all knee OA cases). Focusing the phenotype on TJR did not decrease the strength of association with the chr7 SNP despite the smaller sample size (OR=1.14 [1.06-1.23], p=0.00087, for TJR-only versus OR=1.12 [1.05-1.19], p=0.00065 for all knee OA cases). We conclude that for a highly prevalent and heterogeneous disorder like OA, where multiple loci conferring small effects appear to contribute to overall susceptibility, improved definition of phenotype appears to be important for both cases and controls. However, the approach of maximizing sample size to balance misclassification in controls is effective when very large case/control sample sizes are employed.

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POPULATION GENETIC DATA ANALYSIS AND ALLELE FREQUENCIES FOR TEN STR LOCI (D21S311, D18S51, D16S539, D13S317, D8S1179, D7S820, D5S818, TPOX , THO1 & VWA) IN IRANIAN TURK AND SISTANI ETHNICS

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Population genetics and forensic biology are linked together inextricably. Autosomal short tandem repeats (STRs) are hyper variable markers that can provide the better understanding needed to determine relationships among closely related populations in evolutionary history and provide the allelic distributions used in forensic calculations at the same time. The objective of this study was investigated genetically characterize and distribute the ten STRs allele frequencies (D21S311, D18S51, D16S539, D13S317, D8S1179, D7S820, D5S818, TPOX , THO1 & vWA) of 150 Iranian unrelated healthy donors (woman and man) living in different regions of Azarbayjan and Sistan & Baluchestan province. The PCR amplification was carried out in final volume of 25µl with the special annealing temperature for a pair of primer without the extension time. The PCR products were separated by electrophoresis on denaturing 8% polyacrylamide gel, using the Gel Sequencing System of the Bio-RAD company. The PopGen32 and Power Stats v.1.2 software was used for investigation of population and forensic parameters. The most and least alleles were observed in D21S311 (13 alleles) and TPOX markers (6 alleles) and D21S311 (17 alleles) and TPOX markers (6 alleles) at the Turk and Sistan population respectively. The heterozygote content was different from 0.6414 ± 0.0469 (THO1) to 0.9179 ± 0.0469 (D5S818) and 0.6234 ± 0.0469 (TPOX) to 0.9519 ± 0.0469 (D21S311) for Turk and Sistan population respectively. Deviation from Hardy Weinberg equilibrium was seen in the locus of vWA (P=0.0425) and TPOX (P= 0.0347). This decrease in equilibrium was eliminated under the Bonfferroni correction (P<0.05). Based upon the allelic frequencies, several important forensic parameters were calculated. The Polymorphic Index Content were variable from 0.58 (TPOX) to 0.84 (D21S311) and 0.62 (TPOX) to 0.95 (D21S311), Power of Discrimination from 0.781 (TPOX) to 0.947 (D21S311) and 0.879 (TPOX) to 0.966 (D21S311), Power of Exclusion from 0.3519 (THO1) to 0.826 (D5S818) and 0.327 (TPOX) to 0.909 (D21S311) at the Turk and Sistan population respectively. The Paternity Index from were variable from 1.42 (THO1) to 5.88 (D5S818) and 1.35 (TPOX) to 11.13 (D21S311) at the Turk and Sistan population respectively, that is indicative good information for all of the STRs. The results showed that the D18S51 locus was

more effective marker to investigate Iranian Turk and Sistan ethnics population and microsatellite markers are useful for identification, paternal traits test and population genetic studies. Also, the results indicated that the integrative relationship between population genetics and forensic science parameters can be useful for a thorough genetic characterization of extant human ethnic populations.

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WORLDWIDE MHC CLASS I AND II DIVERSITY

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In my study, I tried to increase the understanding in the maintenance of the Major Histocompatibility Complex (MHC), also called the Human Leukocyte Antigen (HLA), diversity and possibly more importantly in variation thereof in various human populations. The MHC is a key component of the immune system of vertebrate as it is responsible for the recognition and presentation of antigens and comprises the most polymorphic genes in vertebrates. Numerous hypotheses have been proposed to explain how this extraordinary diversity could be maintained. While there is no consensus on the exact mechanisms behind this extraordinary polymorphism, there are several lines of evidence suggesting that the genetic diversity at this gene complex might be driven and maintained by Pathogen-Driven Balancing Selection. A prediction under this hypothesis is that populations exposed to a wider variety of diseases should be characterized by higher diversity at their MHC genes. My project begins by investigating the geographic apportionment of the MHC class I and class II genetic diversity in relation to both demography and selection. It also involves searching for individual geographic associations between specific alleles and single pathogens to show that certain MHC alleles provide increased resistance against single pathogens. My study indicates that the geographic apportionment of MHC diversity is the product of both past demography and complex selective pressures. My work highlights the complexity of the selective process, with the likely involvement of coevolution with KIR genes and marked differences between different classes of genes. It also confirms that the dominant localized pathogens determine the frequencies of the alleles in their regions, and thus, the frequencies of alleles vary between different geographical regions, with certain MHC alleles providing increased resistance against single pathogens. Finally, it provides a first list of all candidate associations when looking for functional links between immune genes and specific pathogens.

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INVESTIGATION ON MITOCHONDRIAL DNA MUTATIONS IN FIRST REPORTED PROGERIA CASE OF BANGLADESH

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According to the mitochondrial theory of aging, accumulation of mutations in mitochondrial DNA (mtDNA) plays the paramount function in the cellular pathology of aging and in development of age-related degenerative ailments, suggesting that mitochondria might be the biological clock in aging. Mitochondrial DNA alterations have been suggested as a potentially sensitive and specific biomarker for premature aging in progeria. To determine the somatic mitochondrial DNA mutations as well as rare polymorphisms in progeria, we examined first reported progeria case of Bangladesh by direct partial sequencing of mtDNA which cover both noncoding D-loop and coding regions of mt-DNA. Objectives: 1. Study the whole mitochondrial DNA of first reported progeria case of Bangladesh. 2. Construct pre-mature aging marker. 3. Find-out the connection of progeria to common heart diseases & aging. Methods: Samples were collected from progeria patient as well as from his family members after receiving the informed written consent in a prescribed form. Short family history was also collected. The sample types were considered 2-3 ml of blood. PCR amplification of mtDNA D-loop was performed; direct sequencing was carried out with ABI3130 Genetic Analyzer and the sequences were edited as required using the Sequence Analysis software v5.2. The edited sequences were aligned with the revised Cambridge Reference Sequence (rCRS) using Autoassembler software for identification of the mutations/polymorphisms. The variants were checked further in the world population from the mitochondrial genome database, Mitomap (www.mitomap.org). The functional implications were examined using Mitoanalyzer (www.genpat.uu.se/mtDB). We identified that the progeroid patient and his family members (maternal lineage) beared haplotype M37e (Motif- 16111 16189 16223 16295). Overall 12 mutations at non-coding region were identified. Of the 12 mutations, 6 single-base substitution (16111 C > T, 16184 C > T, 16223 C > T, 16294 C > T, 16295 C > T, and 16399 A > G), 1 novel insertions (16185 T ins) and 1 deletion (16189 T del) were observed in progeria and also in his family members. Four other novel insertions (16475 G ins, 16488 A ins, 16496 C ins, and 16505 G ins) were identified only in non-coding region of pogeria case. Our ultimate goal is to study mitochondrial DNA mutations believed to be associated with genetic disorder like progeria. First progeria reported case in Bangladesh: Tuhin Islam Raju - 12 years old is our subject of study. This research study on first progeria reported case will be the first genetic study in Bangladesh on progeria syndrome.

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ALLELIC AND HAPLOTYPIC DIVERSITY OF MICROSOMAL EPOXIDE HYDROLASE (EPHX1) GENE POLYMORPHISM IN SOUTH INDIAN POPULATION

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The microsomal epoxide hydrolase is a phase I enzyme of the biotransformation. That human EPHX1 gene lies on Chromosome 1q42.1 and exhibits Polymorphism. Two single nucleotide polymorphisms (SNPs) have been described in the coding region of the EPHX1 gene that produces two protein variants. This study thus sought to investigate the distribution of the rs1051740, rs2292566 and rs2234922 polymorphisms of EPHX1 in 5 south Indian populations. A total of 230 samples belongs to 5 different populations were screened for the genotypes using TaqMan allelic discrimination. All the three SNPs were polymorphic with minor allele frequency of 0.368, 0.249 and 0.232 respectively for rs1051740, rs2292566 and rs2234922. None of the polymorphic site deviated from Hardy Weinberg equilibrium. From the three polymorphisms studied, two were in strong linkage disequilibrium and form 1 haplotype block. Greater allelic diversity leading to weak LD between the markers across the EPHX1 region and provide the greatest possible advantage to the organism. This is the first report from India that will serve as a template for future investigations of the prevalence of EPHX alleles in association with various clinical entities.

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TRANSFORMING GROWTH FACTOR GENES IN PATIENTS WITH LUNG INJURIES DUE TO SULFUR MUSTARD

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There are approximately 30,000 survivors that were exposed to toxic inhalants during the Iraq- Iran war (1981–1989). These survivors suffer from late effect of this warfare, including ophthalmic, cutaneous, and respiratory sequels. Recent surveys have indicated that bronchiolitis obliterans (BO) is the main late respiratory complaint of these patients, but the BO observed in these patients is somehow different from BO resulted from other causes. Transforming growth factor beta (TGF-β) is a multifunctional cytokine that controls different sets of processes, including tissue remodeling and repair, cell apoptosis and survival, extracellular matrix production, and inflammation .Three structurally similar isoforms of TGF-β (TGF-β1, -β2, and -β3), encoded by 3 distinct genes, have been identified in mammalian species. TGF-β is produced by lung epithelium, fibroblasts, and smooth muscle cells, and contributes to airway remodeling in chronic lung diseases .In view of TGF-β properties, we assumed that TGF-β might be responsible for airway remodeling, homeostasis, and slow progression of respiratory disease in chemical-injured patients. Fourteen healthy volunteers and 20 patients suffering from late effects of exposure to chemical gases were included in the study. Patients group had shown symptoms of BO and biopsy samples taken by bronchoscopy. All patients were male with the age range of 38 to 56 years. The biopsies were snap-frozen in liquid nitrogen and stored at −80◦C until RNA extraction. Total RNA was isolated from frozen specimens using the high pure RNA tissue kit (Roche, Germany), according to the manufacturer‘s instructions. Briefly, lung biopsies were homogenized, lysis buffer was added, and centrifuged; total RNA was precipitated by absolute ethanol, incubated with DNase, and centrifuged; finally total RNA was washed by wash buffer, and was eluted by distilled water. The purified RNA was used for first-strand cDNA synthesis, using first-strand cDNA synthesis kit (Cinnagene Iran) by oligo (dT)18 primer (MWG, Germany) in a 20-μL reaction according to the manufacturer‘s instructions. The amplification of the genes of interest was performed in 25-μL reaction mixture containing 10mM Tris-HCl (pH 8.3), 50 mM KCl, 1.5 mM MgCl2, 0.5 μL of first-strand cDNA, 0.5 U of recombinant Taq DNA polymerase (Cinagene), 200 μM of each deoxynucleoside triphosphate, and 4 μM of each primer .PCR was performed under similar conditions for selected genes and the internal control. The expression level of gene was quantified according to the band intensity on agarose gel stained with ethidium bromide was measured using UVItec software. The identity of PCR products were confirmed by restriction enzyme digestion and also by sequencing. RESULTS: The results indicated that that levels of TGF-β1 and TGF-β3 mRNAs were significantly higher in chemical gas–injured patients than noninjured group ($P < .05$). Therefore, the authors speculate that TGF-β1 and TGFβ3, but not TGF-β2, secretion is a result of efficient efferocytosis in chemically injured patients, playing a protective role by improving airway remodeling and lung homeostasis in this group. These properties of TGF-β are consistent with long-time survival of chemical-injured people suffering from BO.

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GALLBLADDER CANCER PREDISPOSITION: A MULTIGENIC APPROACH TO INFLAMMATORY AND CHOLESTEROL METABOLIZING PATHWAY GENES

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Being relatively rare worldwide, gallbladder cancer (GBC) shows highest incidence and mortality rates in parts of Northern India. Apart from gallstones being the predominant risk factor, the precise etiology of GBC is poorly understood. Since a complex disease like cancer typically occurs through a multifactorial interplay between many genetic and environmental factors, the effect of each individual SNP is unlikely to be substantial. Identification of risk sets of polymorphisms contributing to the disease will assist in determining individuals at risk for the disease. Previous studies have highlighted the biological relevance of inflammatory and cholesterol metabolizing pathway to GBC risk. In this study, we applied a pathway-based genotyping approach to assess the combined effects of a panel of polymorphisms in inflammatory pathway and cholesterol metabolizing genes with GBC risk. Methods: In the present case-control study with 185 GBC patients and 185 controls, we applied a multigenic approach to examine the association of a comprehensive panel of 12

selected polymorphisms in inflammatory pathway [PTGS2 (-1195G>A), (-765G>C) and (Ex10+837T>C); TLR2 -196 to -174del; TLR4 Thr399Ile; CR1 (Exon 22 (A>G) and Intron 27 (T>C)]; and CCR5 □32] and cholesterol metabolizing pathway genes [CYP7A1 (-204A>C) and (-469T>C); HMGCR (8302A>C); ABCG8 Asp19His] with GBC risk. Odds ratio (OR) and 95% confidence interval (CI) were calculated in multivariable logistic regression analysis for the association of individual SNPs with GBC. We performed an exploratory correlation and regression tree analysis (CART) and grade-of-membership analysis (GoM) analysis to elucidate high-order gene-gene interactions among the inflammatory and cholesterol metabolizing pathway gene polymorphisms in modifying the risk for GBC. Results: Individually, most of the studied polymorphisms exhibited statistically significant main effects. We found a significant gene-dosage effect for increasing numbers of potential high-risk alleles in inflammatory pathway and both pathways combined. For the inflammatory pathway, compared with the referent group (≤2 adverse alleles), individuals with >2 variant alleles [OR=1.25, CI=1.10-2.02) had increasingly elevated risks of GBC (Ptrend=0.005). Each additional adverse allele was associated with a 1.04-fold increase in risk (CI=1.01-1.10). For the combined analysis of inflammatory pathway and cholesterol metabolizing pathway SNPs, compared with the referent group (0-10 adverse alleles), the ORs for individuals with >10 adverse alleles was 2.29 (CI=1.67-3.10; Ptrend<0.001). The CART analysis revealed PTGS2 -1195G>A and ABCG8 Asp19His polymorphisms as the best polymorphic signature for discriminating between cases and controls. In the GoM analysis, the data was categorized into six sets representing risk for GBC with respect to the investigated polymorphisms. Sets I, II and III described low intrinsic risk characterized by multiple protective alleles while sets IV, V and VI represented high intrinsic risk groups characterized by the presence of multiple risk alleles. This is the first comprehensive study to use a multigenic analysis for GBC, and the data suggest that individuals with a higher number of genetic variations in inflammatory and cholesterol metabolizing pathway genes are at an increased risk for GBC. The study highlights the value of using multiple complementary analytic approaches to identify multi-factor interactions in GBC risk assessment.

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DETAILED LIPOPROTEIN SUBCLASS PROFILING VIA HIGH-THROUGHPUT NMR METABONOMICS TO REVEAL THE HETEROGENEITY OF KNOWN LIPID LOCI

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A recent genome-wide scan of over 100,000 individuals of European ancestry identified 95 genetic loci to associate with plasma levels of cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) or triglycerides (TG), thus providing broader biological understanding of lipid and lipoprotein metabolism and the potential pathways leading to the development of coronary artery disease. However, these lipid measures are heterogeneous being composites of subclass particles that vary in size, lipid composition and metabolic interactions. As concentrations of lipoprotein subclasses are likely to reflect more accurately the various metabolic phenomena and the risk for various vascular outcomes, we characterized the metabolic pathways underlying the 95 known plasma lipid loci at the lipoprotein subclass level. Applying the latest high-throughput NMR metabonomics platform the serum metabonomes comprising of a broad quantitative lipoprotein subclass profile, complemented with tens of other metabolic measures, were determined for over 9000 individuals from five population-based Finnish cohorts. Combined with the genome-wide profiles of genetic variation in the same individuals, this information represents a powerful resource for large-scale investigation of the molecular level variability of the gene functions. Many of the lipid genes had unique effects on the lipoprotein subclasses. For example, three newly verified HDL genes (PPP1R3B, GALNT2 and TTC39B) all show remarkable differences in their associations to HDL subclasses. The functionality of PLTP in modulating HDL size is clearly shown in its association profile to HDL particles as its effects to large and small particles are reversed (p = 3.16*10-19 for mean diameter for HDL particles). Our results also highlight other lipid and - somewhat unexpectedly - some low-molecular-weight molecules associated with the lipid loci. GCKR associates with the concentration of alanine (p = 1.41*10-17) and branched-chain amino acids (p = 2.93*10-14 for isoleucine), which suggest its involvement in energy metabolism beyond glucose and lipids. Suggestive evidence arises for an association between PPP1R3B and GALNT2 and ketone bodies (p = 6.99*10-7 and p = 3.97*10-5 for acetoacetate, respectively). These results also suggest that detailed phenotyping will help to indentify functions of new, yet uncharacterized genes. All in all, this study underlines the value of deeper and more comprehensive metabolic profiling enabled by the cost-effective NMR metabonomics platform as a means to provide additional insight into lipoprotein metabolism.

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GOT GENETIC HERITABILITY LOST IN A WORLD OF INTERACTIONS?

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Over the last few years it has become clear that the output potential arising from main effect genetic association analyses is reaching a plateau. In the quest for genetic susceptibility factors and the search for _the missing heritability‘,

supplementary and complementary efforts have been undertaken. These include the inclusion of several genetic inheritance assumptions in model development, the consideration of different sources of information, and the acknowledgement of disease underlying pathways of networks. The search for epistasis or gene-gene interaction effects on traits of interest is marked by an exponential growth, not only in terms of methodological development, but also in terms of practical applications, translation of statistical epistasis to biological relevance, and integration of omics information sources. The current popularity of the field, as well as its attraction to interdisciplinary teams, each making valuable contributions with sometimes rather unique viewpoints, renders it impossible to give an exhaustive review of to-date available approaches for epistasis screening. The purpose of this work is to give a perspective view on currently active analysis strategies and concerns in the context of epistasis detection, and to provide an eye to the future of gene-gene interaction analysis. Although there is no single best analysis strategy in the search for epistasis effects, there is a clear trend towards the development of data reduction techniques and merging evidence from _ensembles‘ of techniques. Therefore, special emphasis will be given to a relatively new, yet promising, dimensionality reduction technique, MB-MDR, which is short for Model-Based Multifactor-Dimensionality Reduction (Calle et al., 2008). The approach taken in MB-MDR builds upon the widely used Multifactor Dimensionality Reduction technique of Ritchie et al. (2001) for epistasis detection. The latter, referred to as MDR, suffers from some major drawbacks including that important interactions could be missed due to pooling too many multi-locus genotype cells together. Pros and cons of MB-MDR will be discussed, whether in the context of family-based or population-based designs, or whether handling univariate categorical, continuous, and survival-type of data, or multivariate correlated traits.

THERAPY OF GENETIC DISORDERS

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QUERCETIN INCREASES SURVIVAL MOTOR NEURON MRNA EXPRESSION

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Quercetin is a natural polyphenolic compound, which is an important constituent of various plants and has widespread biological activities. Recent reports have highlighted the antioxidant and neuroprotective properties of polyphenols and their therapeutic potentials for various diseases such as spinal muscular atrophy (SMA). SMA is neurodegenerative disorder, which is characterized by degeneration of motor neurons of the spinal cord and caused by mutations of the SMN1 gene. Increasing SMN2 expression is an important approach to attenuate disease severity. Therefore, we investigated the effects of quercetin on SMN2 mRNA and protein expressions in two different SMA type I fibroblast cell lines (GM03813, GM09677). Quercetin was applied at 20, 50 and 100 uM concentrations and incubated for 24 hours. We detected 3.1 (GM03813) and 4.4 (GM09677) fold increase on SMN2 mRNA expression, after treatment with 20uM quercetin, by RT-PCR. In order to analyze the effects of quercetin on protein level, 20 uM quercetin was applied to GM09677 cell line and incubated for 24, 48 and 72 hours. Western blot results showed that there was no change in the protein level at any time point. According to our results quercetin significantly increases SMN2 mRNA but not protein. It may indicate that quercetin plays a role at the level of transcription but new transcripts fail to proceed translation. Further studies are being planned to explain the possible reasons why quercetin affects only on SMN2 mRNA but not protein level.

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ISOLATION AND CHARACTERIZATION OF RAT PANCREATIC STROMAL CELLS: THEIR APPLICATION IN REPAIRING INJURED PANCREATIC ISLETS

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Stem cell therapy is one of the most promising treatments for the near future. Curative therapy for diabetes mellitus mainly implies replacement of functional insulin-producing pancreatic Î² cells, with pancreas or islet-cell transplants. Because donors are in short supply, only a minority of patients benefit from this procedure. Pancreatic progenitor cells are a promising resource for regeneration of new islets. Therefore, the aim of our study was to isolate and characterize rat pancreatic stromal cells, and using them for in vitro repairing of injured pancreatic islets. Male adult Wistar strain rats (200-250g) were randomly divided into two groups and maintained on a free access to food and water throughout the experiment. Diabetes was induced in group II rats by injecting alloxan after keeping the animals in fasting conditions for 24 hours. Diabetic condition was confirmed 24 hours after alloxan injection. Not all the rats were diabetic at this time, but they were all found to

be diabetic after 72 hours. In group I rats, pancreases were exposed with PBS, and then were digested by collagenase P. The cells were sub-cultured after 5 days, and RT-PCR was performed for the following genes: Nanog, Vimentin, Nucleostemin, CyclinD1, Oct4, and Sox2. Our data revealed that the isolated cells from group I rats expressed Vimentin, Nucleostemin and Cyclin D1 markers, which are related to the mesenchymal cells. However, they didn't express markers associated with embryonic stem cells (ESCs), including Oct4 and Sox2. After characterizing the isolated stromal cells, they were labeled with DiI dye and considered for transplantation. We expect that the in vitro propagated stromal cells could repair the damaged islets of an alloxan-induced diabetic model of rat.

EXPEDITED ABSTRACTS

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MUTATION HOTSPOT - A WEB APPLICATION FOR MUTATION MINING IN PUBLICLY AVAILABLE EXOME SEQUENCES

Rudd Stephen, Chung Tay Liang, Mui Lee Chiew, Yiew Hwah Shih, Fong Ho Kim, Meng Ching Soo, Kumar Manish, Ibrahim Maarif, Hercus Robert
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Genome and exome sequencing has become affordable and, within clinical research projects, it is now reasonable to perform whole genome or exome sequencing for moderately sized cohorts of individuals. Sequence reads from a variety of sequencing technologies are mapped to a reference genome and the analysis of the systematic differences relative to the reference and those shared by different project subjects may be used to identify rare novel gene variants, genes associated with disease or to characterize finer patterns of genomic context. Exome sequencing has been applied for oncology, rare Mendelian disease research and within population genomics. The assignment of meaning and the identification of patterns within the data are complicated by the large volumes of complex data. To simplify the process of identifying different classes of variation, we have implemented a web-accessible database system for the mining of sequence variation. Starting with primary sequence read data from publicly available exomes, we mapped the reads to a reference human genome. Scoring algorithms have been applied to the sequence variations characterized within individual exomes. Mutations can thus be filtered on the basis of confidence scores. The total variation has been loaded into a relational database. Simple user interfaces provide functionality to identify the patterns of variation, namely, those that are common to groups of individuals, those that contrast groups of individuals, and can be used further to identify the polymorphisms that appear unique within individuals. Genes containing variations, genes enriched for multiple variations and genes belonging to functionally related gene sets are linked to external databases so that the meaning and relevance of specific variations can be assessed.

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GENOME SIMULATION FOR EVALUATION OF SENSITIVITY AND SELECTIVITY OF SNV RECALL USING ILLUMINA AND COMPLETE GENOMICS HUMAN GENOMES

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Human genome and exome sequencing has become a mainstay of contemporary genetics research. Our ability to sequence a genome and to investigate complex patterns of single nucleotide variations, larger insertion / deletion events and complex segmental rearrangements is of great relevance in the understanding of both complex diseases and in more general human evolution. A number of proprietary and open-source software solutions are available for the mapping of sequence reads from different sequencing technologies to a reference genome. These software solutions can be used to characterize the apparent variation relative to the reference. An objective comparison of these software tools is complicated by a lack of information as to which of the identified differences really exist and which are statistical anomalies. We present MGRC's genome simulation software that has been developed to produce Illumina, 454, SOLiD base-space and Complete Genomics DNA sequence reads. The software simulates reads of varying quality where SNVs, INDELs and gross chromosomal rearrangements are included. This allows for an empirical assessment of sensitivity and selectivity of variation recall within both idealized genome sequences and across data that is close to real-life data. Simulated data is used to compare and contrast different genome mapping software pipelines. Different mapping software shows varying degrees of run-time, sensitivity and selectivity. A more objective comparison of sequencing technology, mapping software and genome context may be used to refine an ideal strategy for genomics based research. Our poster provides a link through which the software may be downloaded.

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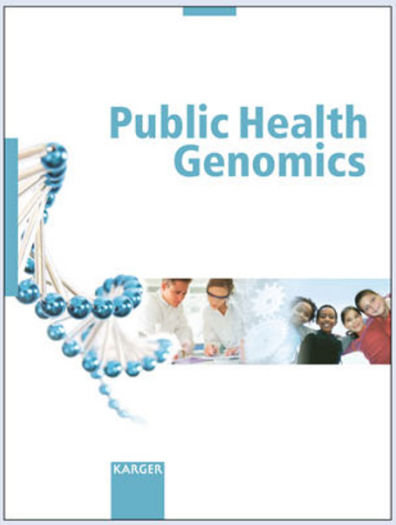

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