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GENOMICS NEWS

Genome Mirror-2006

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The human variome project

Well before the completion of the Human Genome Project in 2003, geneticists had already known about errors in the human genetic code and their role in hereditary single-gene disorders. Apart from uncommon Mendelian diseases, hundreds of common and rare alleles of several genes had been associated with susceptibility to a whole range of common but complex medical diseases, notably cancers, coronary heart disease, stroke, diabetes, hypertension, neurodegenerative disorders and psychiatric illnesses like bipolar disorder and schizophrenia. The completion of Human Genome Project and the availability of this information to the entire scientific and genetics community have now offered a unique opportunity to move forward. However, most of this information in the public domains is recorded randomly and in a somewhat idiosyncratic style. It seems as if developers failed to visualise a much broader picture emerging on the horizon. There are several technical hiccups, for example lack of universal gateways, limited interoperability and no standardised template for researchers and clinicians to record or annotate their findings.

Among many frustrated scientists, Prof. Dick Cotton, founder and director of the Australian 'Genomics Disorders Research Centre' [GRDC] in Melbourne, has taken the lead in attempting to resolve this matter. He also happens to be the founder of the journal *Human Mutation.* He has galvanised the momentum in organising the First International Meeting to discuss the feasibility of launching a major global initiative—recording all human genetic variation including both mutations and gene polymorphisms.

Several eminent geneticists and researchers visited Australia in August 2006 to participate in the 11th International Congress of Human Genetics held in Brisbane (10–14 August 2006). This occasion was capitalised upon by Dick Cotton who organised the first international planning meeting for a major initiative called the 'Human Variome Project', a logical and essential sequel to the Human Genome Project. Fifty-five eminent researchers from all over the world attended the meeting. Cotton expressed his satisfaction—''It was a wonderful meeting that produced amazing consensus. Everyone agreed on the need for a Human Variome Project and that it was timely. All the central database developers were excited about being included. We've had great enthusiasm from organisations interested in funding the database, like the March of Dimes in the US, and the European Commission.''

Professor Richard Gibbs of the Baylor College of Medicine in the US, said: ''I don't know why this project wasn't considered as a component of the Human Genome Project—it was a natural successor to it.'' People at the meeting agreed that it was a natural name and endorsed the meeting as the 'Human Variome Project' meeting. Dick Cotton predicted that it would be another five years before all the required components of the HVP are organised and operating efficiently and gathering information about all known human variation. It would become fairly automated and template-driven. The ultimate aim of the project is to study all human genome variation including that associated with human disease, a task already being undertaken by the Human Gene Mutation Database (http://www.hgmd.org). The project is likely to run for several years, or at least until

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all variation has been described in all human genes, and in intergenic DNA.

The future for the Human Variome Project [HVP] looks bright. It is envisaged that the HVP database will be a powerful resource for the coming revolution of personalised medicine. It would also be a powerful resource for studying human evolution from prehistoric times to the present age. Already some nations have begun their own projects, for example, Arab states have recently launched the Arab Variome Project and the Government of India has commissioned the 'Indian Genome Variation Database Project'*(Human Genetics* doi 10:1007/s00439-005-0009-9). It is important that the HVP takes the lead and establishes itself as the focal point for all these small projects organised and funded at regional levels. The HVP would be coordinated from GRDC in Melbourne.

The nobel worthiness of RNA interference

For the second time in five years, the Nobel prize for Physiology or Medicine has gone to researchers working with one of molecular biology's favourite laboratory animals: the nematode *Caenorhabditis elegans*. Even more striking is the short interval (eight years) since Andrew Fire and Craig Mello began publishing the work on RNA interference that has now won them the 2006 award. Their findings have already proved valuable in the laboratory and may yet do so in the clinic. Both in their mid-40s, Professor Fire, working at Stanford University in California, and Professor Mello, of the University of Massachusetts Medical School, had set out to tackle what seemed to be an esoteric problem. They wanted to find out why and how the artificial introduction of RNA into a cell interfered with the function of its genes.

Fig. 1 Nobel prize winners Andrew Fire (left) and Craig Mello said 1998: ''The mechanisms underlying RNA interference probably exist for a biological purpose''

RNA is one of the key elements of what Francis Crick dubbed the ''central dogma of molecular biology''—in essence, that DNA makes RNA makes protein, although this has been widely misinterpreted to mean that most genes encode proteins through the intermediate of RNA—may be true in microorganisms, but is increasingly appearing not be true in complex organisms. In the years since Crick and Watson unwound the double helix, scientists have picked over the detail of the process by which genetic information is transcribed as proteins. In the first phase of the process, the transcription mechanism of the cell uses a section of DNA as a template on which to construct a complementary, single stranded length of RNA. It is this ''messenger'' RNA that delivers the information required by the cell's synthetic machinery to churn out a protein of the appropriate composition. What Fire and Mello found, to their surprise, was that introducing a length of double stranded RNA into a cell interfered with the normal function of the length of DNA—the gene—of which it was the counterpart. Further work by them and later work by others showed that they had inadvertently stumbled on a previously unsuspected piece of biochemical machinery.

It is believed that RNA interference serves several purposes. It helps to regulate the expression of genes and stabilises the genome against promiscuous transposon activity. By degrading the double stranded RNA that certain viruses use to store their genetic information, it also acts as a cellular defence mechanism. Biologists have been quick to exploit RNA interference. By choosing the sequence of a length of double stranded RNA they can use it to close down the activity of specific genes in cells they want to study. It has given them, in effect, a molecular switch. Findings in molecular biology do not always meet with speedy recognition. In this case Fire and Mello realised that they had hit on something important. As they say in their 1998 Nature paper, ''The mechanisms underlying RNA interference probably exist for a biological purpose'' (*Nature 1998; 391:806–811*).

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Metabolomics and beyond

The suffix '*omics*' is fast becoming fashionable. Well before the completion of the Human Genome Project in 2003, some new scientific '-OMIC' fields emerged within cell and molecular biology. Apart from genomics, we now have a plethora of fields ending with *omics*. Examples

include transcriptomics, functional genomics, proteomics, pathogenomics, toxicogenomics, nutrigenomics, pharmacogenomics and the list is expanding rapidly. However, perhaps only three of these would matter at present to most human geneticists—genomics, proteomics and metabolomics. Genomics is about studying all genes in their entirety including all related non-coding sequences and polymorphisms. Proteomics is the study of all proteins, and metabolomics is the study of all molecules derived from metabolism (metabolites) in any living organism. However, given the increasing evidence that most of the human genome is transcribed, mainly into RNAs that do not encode proteins, and that increasing numbers of these transcripts (or their derived products such as miRNAs) are being shown to be functional, it is likely that transcriptomics will assume increasing importance.

So far human and medical genetics has largely concentrated on well-defined genetic diseases and some complex medical diseases with possible genetic bases. Apart from some diagnostic applications, there have been extremely limited therapeutic benefits. The ultimate goal of clinical medicine is to offer treatment based on individuals' genetic make-up or genomic profile. This is what is meant by *personalized medicine.* Development of new drugs based up on individuals' favourable or unfavourable drug responses would become the gold standard. The FDA, academic and medical institutions and pharmaceutical companies worldwide are all working to learn more about fundamental cellular components, which can lead to more effective treatments for people based on their genetic structures and acquired differences. Yvonne Dragon, a research biologist and director of the Division of Systems Toxicology within the FDA's National Center for Toxicological Research (NCTR) believes that ''new biological understanding to help us to combat common diseases will come from knowledge of genes, proteins and metabolites. The long-goal is to be able to personalize medicine. Metabolomics is one of many tools to achieve this.'' The National Human Genome Research Institute (NHGRI) defines metabolomics as the evaluation of tissues and body fluids, such as urine, plasma, blood, saliva and cerebrospinal fluid, for metabolite changes that may result from physiological responses or pathological changes. The term is interchangeably used with ''metabonomics'', which is an older term that usually refers to principles or rules that govern the generation and regulation of metabolites. However, increasingly the latter term ''metabolomics'' is accepted as this encompasses both theoretical and practical aspects.

While genomics researchers are searching for variations in genes that cause disease and proteomics researchers are seeking out abnormal protein patterns in different pathological conditions, metabolomic researchers focus on studying abnormal metabolite patterns. Numerous metabolites are generated through different chemical reactions in several metabolic pathways that are essential in maintaining *homeostasis* and regulate various body functions. It is estimated that there are probably 3,000 metabolites that are essential for normal growth and development (primary metabolites) and thousands more unidentified ones that are not essential for growth and development (secondary metabolites) but may help to fight off infection and other forms of physiological stresses. Among these, very small metabolites, known as low-molecular-weight metabolites, are of major importance. These include amino acids, sugars and lipids.

The metabolomic studies are conducted using predominantly two methods—nuclear magnetic resonance (NMR) and mass spectrometry (MS). NMR can identify and quantify hundreds of metabolites in a sample of body fluid. MS complements NMR in that it can display quantity and generate profiles of thousands of metabolites with more sensitivity than NMR. The profiles are then run through powerful computers that process, store, and generate data in a form for scientists and clinicians to visualize and interpret.

Researchers and potential future users are both optimistic and cautious about predicting the potential of metabolomics. Dr. Richard Beger, Director of the Center of Metabolomics at NCTR acknowledges that the field of metabolomics is still in its infancy. However, it is probably cheaper and faster than applying proteomics or other -omic technologies. More importantly, the sample for metabolomics is obtained routinely through a relatively non-invasive procedure. Any abnormal result can then be confirmed with genomics- or proteomics-based tests, which would require highly sophisticated equipments and expertise.

Metabolomics is a relatively new field with tremendous potential. It will help in profiling the chemical phenotype of the individual or organism under study. In a crude way, this is part of clinical medicine in the form of several routine or specialised biochemical tests. However, these often have limited power in predicting the current disease state and therapeutic outcomes. Metabolomics is essentially combining this approach with genomics or proteomics.

Researchers and scientists working in the field of metabolomics believe that the field has enormous potential to improve human health in a number of ways:

1. To make safer drugs by predicting the potential for adverse effects (or toxicity) earlier
2. To target specific groups of people most likely to benefit from a drug, while excluding its use by those who may be harmed by it

3. To speed the discovery and development of drugs
4. To diagnose disease and predict the risk of disease
5. To determine whether a given drug treatment is working or not
6. To monitor healthy people to detect early signs of disease

In brief, metabolomics is ''a molecular way to do what physicians have done for thousands of years'', which is to diagnose and treat patients based on a combination of symptoms and signs aided by a battery of tests. The same thing is done at the molecular level. The challenge of metabolomics is to identify molecules or patterns of molecules, out of tens of thousands of metabolites that are specific enough to be used as disease markers.

On-line information on metabolomics is available: http://www.metabolomicssociety.org or http://www.fda.gov/nctr/science/centers/metabolomics/