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ABSTRACTS

Genomics of complex disorders II

482: A nonsynonymous SNP in CYP1B1 is associated with primary open angle glaucoma

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Primary open angle glaucoma (POAG) is the most prevalent of the glaucoma subtypes. The disease is known to be transmitted mostly as a complex disease. Though CYP1B1 is primarily known to cause primary congenital glaucoma, defects in the gene have also been reported to cause POAG by either serving as a modifier locus and on rare occasions as a primary locus. POAG primarily being a complex disease, we speculate that CYP1B1 might have a wider role in its pathogenesis, which prompted us to examine the potential for association of single nucleotide variations in the gene with the disease. Towards this goal we examined a few cSNPs in the gene for their potential role in POAG. Comparison of the allele frequencies of such SNPs among patients and controls revealed that for the Leu432Val polymorphism Val432 (c.1666G) allele is significantly over represented among POAG patients (p value: 0.0001. Odds ratio: 6.027, 95% CI: 3.863–9.401) suggesting it to be a potential risk allele towards disease predisposition. Analysis of genotype frequencies of the polymorphism between the two groups demonstrated GG as a potential risk haplotype (p value: 0.0001, Odds ratio = 15.505, 95% CI: 5.529–43.474) for the disease. CYP1B1 Val432 was estimated to generate higher reactive super oxides (ROS) in RPE cells compared to its allelic variant (Leu432). It has been reported that the allele resulting Val432 isoform has higher ability for 4-hydroxylation of 17 beta estradiol which generates higher ROS in cells. Oxidative stress generated by ROS can lead to the damage of the retinal ganglion cells leading to glaucoma. Therefore, inter-individual differences in estrogen metabolism resulting from the Leu432Val variant in CYP1B1 may lead to differences in susceptibility to complex diseases like POAG. Moreover, the prevalent haplotype CGGTA for CYP1B1 locus among POAG patients was found to be the same as that reported in PCG patients harboring CYP1B1 mutations (p value: 0.0001, by Fisher's exact test). Studies are in progress to measure enzymatic activity and protein expression of CYP1B1 in the background of major haplotypes to elicit more complete information on molecular basis of POAG pathogenesis led by CYP1B1. The study is supported by funds provided by council of scientific and industrial research (CSIR), Govt. of India.

483: Involvement of IL1 gene cluster in glaucoma pathogenesis

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Glaucoma is a group of neurodegenerative disorder of eye and the second leading cause of blindness worldwide after cataract. Recent evidences suggest a possible role of immune system in glaucoma pathogenesis. Studies indicate that several SNPs in the interleukin 1 gene have either protective or adverse effect on primary open angle glaucoma (POAG)—the major subtype of glaucoma across globe. So we intended to investigate the role of these SNPs in a group of eastern Indian POAG patients. Towards this goal we genotyped three SNPs in IL1 gene cluster (rs1800587, rs16944 and rs1143634) consisting of two promoter SNPs (IL1A −889C/T, IL1B −511T/C) and a coding SNP (IL1B + 3953C/T) in 332 unrelated POAG patients and 111 controls by PCR–RFLP analysis. The allele and genotype frequencies were determined for comparison between the cases and controls; similarly distribution of haplotypes (consisting of these three SNPs) was estimated between the two groups using HaploView 3.32. Since POAG consists of high tension glaucoma (HTG) and normal tension glaucoma (NTG), which is distinguished by the intra-ocular pressure, we conducted similar exercise for HTG (n = 124) and NTG (n = 208) patients in our POAG cohort. Significant difference was observed in the genotype and allele frequency distribution between NTG patients and control group for IL1A (−889C/T) SNP. Thus, IL1A −889C allele was significantly over represented in NTG patient cohort [p value = 0.031, OR (95% CI) = 1.496 (1.052–2.126)] and the patients carrying the CC genotype were in greater risk for having NTG [p value = 0.019, OR (95% CI) = 1.790 (1.125–2.847)]. Also, haplotype analyses revealed a statistically significant biased distribution of

CTC haplotype in the NTG patients, which pose a risk for the disease. Thus our study suggests that IL1 gene cluster is possibly involved in normo-tensive glaucoma pathogenesis in eastern Indian patients, which need to be further vindicated by similar studies using larger and additional cohort of POAG patients. This study is supported by funds from council of scientific and industrial research (CSIR), Govt. of India.

484: Association of MAPT haplotype-tagging SNPs with Parkinson's disease among Indians

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Parkinson's disease (PD) is a progressive neurodegenerative disorder of the central nervous system characterized clinically by a movement disorder manifesting as rest tremor, bradykinesia, rigidity and postural instability. Significant differences in the reported prevalence of PD in different countries worldwide suggest ethnic and/or environmental-associated multigenic contributions to this disease. Microtubule associated protein tau (MAPT) gene encodes for a phosphorylated protein, tau that regulates neuronal microtubule dynamics and assembly. Tau has been reported to co-aggregate with α-synuclein in Lewy bodies (LB) in post mortem brain of PD patients indicating its role in the disease process. Association of MAPT with PD among Caucasians has been extensively studied but till date no such study has been done among Indian PD patients. Here we have examined the possible genetic role of MAPT with PD using haplotype-tagging SNPs (rs1467967, rs242557, rs2471738 and rs7521) and the 238 bp deletion–insertion polymorphism, del-In9 of MAPT in 213 clinically confirmed PD patients and 209 healthy controls of India. In the single-locus association analysis, we did not find any significant difference in genotype or allele distribution between cases and controls. However, on comparing the allele frequencies of the del/In9 between late onset PD patients (age at onset $\geq$50 years) and early-onset PD (age at onset <50 years) a marginal significance was observed ($p = 0.035$; Odds ratio = 2.451; 95% CI: 0.996–6.03) implying that this deletion is a risk in late onset PD. Comparison of the haplotype diversities revealed a single risk haplotype (GAC + G) among Indian PD patients ($p = 0.042$; Odds ratio = 1.577; 95% CI: 1.03–2.42). Our study supports the role of genetic variability in MAPT in the etiology of PD among Indians which requires to be further explored by replicating the study in larger and additional cohort. This study is supported by CSIR, Govt. of India.

485: Analysis of association between genetic polymorphisms and aggressive traits in intellectually disabled individuals from eastern India

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Intellectual and developmental disabilities are the most common neurological problem affecting 1–3% of the world population. Cognitive impairment along with neuromotor dysfunction is also frequently observed in Down syndrome patients. Influence of dopaminergic and serotoninergic neurotransmission on cognition is well known and monoamine oxidase A (MAOA) plays an important regulatory role in maintaining the level of these neurotransmitters. In the present investigation, three variable number of tandem repeats (VNTR) in the dopamine receptor D4 (DRD4 exon3 48 bp VNTR), serotonin transporter (SLC6A4-5HTTLPR) and MAOA (MAOA-uVNTR) have been analyzed in subjects suffering from various levels of intellectual disability. Intellectually challenged individuals were recruited following the criteria mentioned by diagnostic and statistical manual of mental disorders (DSM-IV) and classified based on the intelligent quotient (IQ). Control individuals belonging to the same ethnic group were also recruited after evaluation. Peripheral blood was collected, after obtaining informed written consent, for isolation of genomic DNA to be used for PCR-based amplification of target sites and analysis. By both case–control and family-based association methods, no significant contribution of the DRD4 ex3 VNTR was observed ($p > 0.1$). The 5HTTLPR and MAOA-uVNTR also failed to show any significant difference between control and intellectually challenged subjects ($p > 0.4$ and 0.3 for 5HTTLPR and MAOA-uVNTR, respectively). However, a trend towards association with the shorter repeats of the MAOA-uVNTR was noticed in a sub-group of intellectually disabled people with aggressive behavior ($p < 0.05$). For the first time, association of these polymorphisms in individuals with intellectual disability have been explored and the data obtained revealed significant contribution of the MAOA-uVNTR in the behavioral attributes of intellectually challenged individuals while no significant correlation was noticed with the level of IQ.
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486: In silico analysis reveals pyrroloquinoline quinine is an effective ligand for α—synuclein—a key player in Parkinson's disease

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Alpha-synuclein is a member of the synuclein family, which also includes beta- and gamma-synuclein. Synucleins are abundantly expressed in the brain and alpha- and beta-synuclein inhibit phospholipase D2 selectively. SNCA may serve to integrate presynaptic signaling and membrane trafficking. Three novel missense mutations as well as gene triplication genetically link the 140-residue protein — synuclein at A30P (VAR_007957), E46K (VAR_022703) and A53T (VAR_007454) believed to cause Familial Early-Onset Parkinson's Disease. Analysis of the SNCA exon showed a GCA to CCA nucleotide substitution in codon 134, GAG to AAG nucleotide substitution in codon 182 and GCA to ACA, nucleotide substitution in codon 203 of the SNCA gene, causing amino acid substitutions of Ala to Pro (A30P), Glu to Lys (E46K), and Ala to Thr (A53). These point mutations show heterozygosity and have definite roles in determining protein secondary structure conformation and abnormal folding of non-beta amyloid protein, whose function is unclear but thought to be involved in neuronal degeneration causing a loss of dopamine synthesis. Homology modeling of three variants shows slight difference in Ramachandran plot values at corresponding mutated residues which provide valuable information about their structural backbone orientation. It was shown that neither the A53T nor the A30P

mutation has a significant effect on the structure of the folded protein, although the A30P mutation may cause a minor perturbation in the helical structure around the site of the mutation. α-Synuclein is a Parkinson's disease-related protein. It forms aggregates in vivo, and these aggregates cause cell cytotoxicity. Aggregation inhibitors are expected to reduce α-synuclein cytotoxicity, and an aggregation accelerator has recently been reported to reduce α-synuclein cytotoxicity. Agents that prevent the formation of amyloid fibrils might allow a novel therapeutic approach to PD. The results of the current study indicate that Pyrroloquinoline quinine and its derivatives might serve as effective ligands for alpha—synuclein thus reducing its cytotoxic effects.

487: A study of GRIK1 gene polymorphism in mental retardation related to Down syndrome

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Background: Down syndrome (DS) is the most common genetic cause of mental retardation (MR). The inheritance of a risk allele by non-disjunction from a heterozygous parent results in the DS offspring being homozygous for the risk allele. This increases susceptibility to mental retardation. The kainate subtype glutamate receptor subunit GluR5, encoded by the GRIK1 gene on chromosome 21q22.1, is a candidate gene for MR in DS and is expressed in brain regions responsible for learning and memory. Single nucleotide polymorphisms in GRIK1 could increase susceptibility to DS related MR. Aim: We wished to identify non-disjoining/risk allele(s) of GRIK1 in Down syndrome individuals and the parent/stage of origin of non-disjunction in patient families.
Methods: Three single nucleotide polymorphisms [522(A/C), 1173(C/T) and 2705(T/C)] in GRIK1 were genotyped by PCR–RFLP assay in 255 healthy individuals and 61 DS patient families (trios). Of the polymorphisms studied, 1173(C/T) is the most informative marker due to its heterozygosity (0.341) and population specific difference in major allele frequency. Out of 61 families, 40 families were genotyped for 1173(C/T) where at least one parent is heterozygous and parent to offspring allelic transmission could be studied. In 40 families, 19 families with homozygous probands were informative where non-disjoining allele and parent/stage of origin could be determined. The study was further extended by including the other two markers that were significantly in linkage disequilibrium with 1173(C/T) polymorphism.
Results: 'C-1173' is non-disjoining allele in 18/20 cases whereas 'T-1173' is non-disjoining allele in 1/20 cases. So, 'C-1173' is the risk allele. Out of 18 cases, the risk allele arises from maternal meiosis I (10/18), paternal meiosis I (5/18) and meiosis II (3/18) with parent of origin unknown. For all three markers, most (8/11) of the non-disjunction error occurred in meiosis I in mothers aged between 25.5 and 35.5 years.
Conclusion: The non-disjoining C-1173 risk allele shows biparental mode of origin with errors occurring in meiosis I and II. Maternal age between 25.5 and 35.5 years is risk for meiotic non-disjunction error.
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488: Neural tube defects in India occur despite normal maternal folate status and low frequency of T allele at C677T polymorphism in the MTHFR gene

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India has a high projected burden of neural tube defects (NTDs) and incidence in some states is reported to be as high as 11.4/1,000 births. Despite this, no study has systematically probed into the nutritional or genetic etiology of NTDs. We present an interim report of our 3-year, multi-centre case–control study funded by the Department of Biotechnology to investigate the genetic susceptibility to neural tube defects and its association with maternal vitamin B_{12} and folate status involving subjects from four cities in four different states. During the period of January 2007 to May 2008, 132 NTD case trios (offspring and both parents) were enrolled. Plasma folate concentrations were normal (more than 7 nmol/l) in 93.5% mothers, while 36.7% had low (less than 150 pmol/l) plasma vitamin B_{12} concentration and 45.6% had hyperhomocysteinemia (more than 10 mmol/l). Folate deficiency contributed only 4.6% to the risk of hyperhomocysteinemia while vitamin B_{12} deficiency contributed 29.73% (population attributable risk). Frequency of the risk allele 'T' at the C677T polymorphism was 13.3% in mothers with NTD fetuses and 13.4% in control mothers. The homozygous TT genotype was present in two case and control fetuses each but in none of the mothers in the study. No evidence of preferential transmission of the T allele to the affected fetus from mothers was noted. Our results suggest for the first time that folate deficiency and the predisposing MTHFR C677T polymorphism has a limited contribution to the etiology of NTDs in India. Thus, it may be important to look beyond folate and MTHFR C677T polymorphism for exploring the etiology of NTDs in India. We will have an opportunity to study whether vitamin B_{12} deficiency contributes to this problem and also to study the role of gene–gene and gene–nutritional interaction.

489: Preliminary analysis of SLC6A4 gene polymorphisms indicates the possibility of a positive association of the gene with autism in Indian population

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Dysfunction of serotoninergic neurotransmission has long been implicated in autism. The presence of platelet hyperserotoninemia in 25–30% of the autistic children, the role of serotonin transporter

(SERT) in the regulation of serotonin uptake, betterment of ritualistic behavioral symptoms in autism by selective serotonin reuptake inhibitors (SSRI) and location of SLC6A4, the gene that codes for SERT to autism critical region on chromosome 17q11 put forth the notion that SLC6A4 can be a potential candidate gene for autism. However, in the present scenario, we have only very little information available on the association of this gene with autism in the Indian population. Therefore, in the present study we investigate the possible genetic association of two markers of SLC6A4 gene [a 17 bp VNTR at intron2 (STin2) and an G/T SNP at 3′UTR (HTT-3′UTR-SNP)] with autism in the Indian population employing family and population-based approaches. Study subjects were recruited after a detailed psychometric evaluation following the criteria of DSM-IV by a panel of psychiatrist, clinical psychologist and pediatrician. On the basis of assessment using CARS, 93 autistic subjects with their parents and 104 controls were selected for the genotyping analysis. The genotypic and allelic frequencies of all the groups conformed to Hardy–Weinberg Equilibrium. The family-based association studies using the two markers (STin2 and HTT-3′UTR-SNP) did not show any preferential transmission of alleles and specific haplotypes from parents to the affected children. Interestingly from our analysis using the cases and control subjects from West Bengal state in India, we observed a contrasting linkage disequilibrium (LD) pattern showing strong LD (D′ value = 0.82, r2 = 0.34) in the autistic group compared to the control individuals (D′ value = 0.27, r2 = 0.05) along with a disease-specific distortion of specific haplotypes formed between the two markers (LRS = 11.85, p = 0.02). These findings indicate suggestive evidence towards association of these markers of SLC6A4 or any other nearby markers with autism in the Indian population. The replication of the study in other populations and using wider sample size is warranted to corroborate our present preliminary finding of positive allelic association.

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490: Contributions of the ARMS2 (LOC387715) and HTRA1 variants in the risk of age-related macular degeneration among Indian patients

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Objectives: Single nucleotide polymorphisms (SNPs) in the *ARMS (LOC387715)* (rs10490924), *HTRA1* (rs11200638) and *CFH* (rs1061170) genes have been implicated in age-related macular degeneration (AMD). The present study was undertaken to understand the involvement of the *ARMS2* and *HTRA1* in an AMD cohort from India.
Methods: The coding region of *ARMS2* (exon I) and the promoter of *HTRA1*were screened by resequencing in AMD cases (n = 250) and normal controls (n = 250). Odds ratios were calculated to assess the risk of individual genotypes. Linkage disequilibrium (LD) and haplotype frequencies were estimated with Haploview software. Population attributable risk (PAR%) for the associated SNPs and their combined effects were calculated. Meta analysis of the associated SNPs was done across different studies.
Results: Significant associations were noted with the risk alleles of rs10490924 ('T' allele; $p = 5.34 \times 10^{-12}$) in *ARMS2*, and rs11200638 ('A' allele; $p = 4.32 \times 10^{-12}$) and rs2672598 ('C' allele; $p = 3.39 \times 10^{-11}$) in *HTRA1* amongst the cases. Correspondingly, the homozygous risk genotypes 'TT', 'AA' and 'CC' in these SNPs exhibited higher disease odds and PAR%. The rs10490924 and rs11200638 were in tight LD (D′ = 0.90, 95%CI 0.84–0.93). The 'G-C-T-A-C' was the risk haplotype ($p = 8.04 \times 10^{-15}$), while the 'G-C-G-G-T' haplotype was protective ($p = 2.01 \times 10^{-4}$). The combined effect of *CFH* (CC) and *ARMS2* (TT) risk genotypes exhibited a PAR of 93.7% (OR = 73.89, 95%CI, 8.69–628.13). Meta analysis reinforced the earlier findings that the rs10490924 (*ARMS2*) risk genotype TT contributed to an increased risk of AMD (pooled OR = 8.13, 95%CI, 6.82–9.68) compared to a single copy (pooled OR = 2.47, 95%CI, 2.23–2.74) of the risk (T) allele.
Conclusions: The *ARMS2* (rs10490924) SNP conferred a higher susceptibility to AMD than the *HTRA1* SNPs, as evident from genotype, haplotype and Meta analysis. Overall, these results underscore the functional importance of these SNPs in AMD pathogenesis and provide their risk estimates in the Indian cohort that may be useful for predictive testing.

491: The influence of SLC6A3 and DRD2 genes variation on personality traits modified by gender—ethnicity confounding

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Individual differences in personality were reported to be influenced by both environmental and genetic factors. Psychobiological model proposed by Cloninger supposes that sociability related personality traits are mediated by dopaminergic system functioning. It has been accepted now that complex phenotypes, such as personality traits, are presumably affected by the interaction of multiple genes of small effect. Such factors as age, ethnicity and gender, cultural and environmental conditions could also contribute into variation of personality. We aimed to define a possible epistasis of DRD2 TaqIA and SLC6A3 MspI polymorphisms, considering gender and ethnicity as confounding factors, on personality traits (assessed with the EPI and TCI questionnaires) via linear regression analyses. We recruited 602 healthy individuals (men-206, women-396) of Caucasian origin (Russians-214, Tatars-388) from Russia (mean age ± SD, 19.85 ± 2.43 years). In the present study gender and ethnicity differences in personality were observed: women scored significantly higher on Neuroticism, Novelty Seeking (NS), Harm Avoidance (HA) and Reward Dependence compared to men; Russians reported higher scores on Extraversion and NS scale, while Tatars revealed higher HA. Although both DRD2 TaqIA and SLC6A3 MspI polymorphisms might be involved in dopaminergic activity regulation, gene–gene interaction has not been demonstrated. However, DRD2 and SLC6A3 gene effects were revealed in relation to neuroticism (F = 19.10; P < 0.0001) and NS (F = 13.97; P < 0.0001) correspondingly, while adjusting for such confounding factors as gender and ethnicity, explaining 8.5 and 6.6% of variation in these personality traits. On the other hand, we observed SLC6A3 main effect on NS (F = 4.15; P = 0.042) and persistence (F = 5.40; P = 0.020) contributing to 0.5 and 0.7% of variation, correspondingly. Since DRD2 TaqIA A1-allele has been reported to result in decreased dopaminergic activity, our findings allow supposing that dopamine excess in synapse could predispose to enhanced anxiety-related traits. Since regression models involving DRD2 and SLC6A3 genes were demonstrated to influence different personality traits, polygenic cause of personality was approved indicating that a single neurotransmitter in a some extent can influence multiple personality traits. This work was supported by Russian foundation for humanities grants (06-06-00163a,

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492: High prevalence of infantile encephalitic beriberi with overlapping features of Leigh's disease

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Infantile encephalitic beriberi (IEBB), a rare form of thiamine deficiency is poorly described. The clinical picture and the imageological findings of IEBB are known to overlap with Leigh's disease (LD), which is a progressive neurometabolic disorder usually presenting in the infancy. Similar to a dramatic response to thiamine supplementation in beriberi, a type of LD due to pyruvate dehydrogenase deficiency responds equally well to treatment with thiamine. Due to these overlapping features, the two conditions are commonly misdiagnosed unless one has good clinical acumen and shows high index of suspicion. Thiamine deficiency has been a problem of developing countries but as per reports from nutritional foundation of India in 2004 and 2007, India has eliminated it through programmes such as under milling of rice. Similarly, there are few cases of LD that have been explored in India. Thus, data on both IEBB and LD is scarce and status of thiamine deficiency in India is controversial.

We report 165 infants with life-threatening respiratory and central nervous system symptoms who were remarkably responsive towards large dose of thiamine. All the patients underwent detailed clinical, biochemical and imageological investigations. Thiamine status was analyzed by estimating erythrocyte transketolase (TK) levels. Common clinical manifestations included altered sensorium, external ophthalmoplegia, seizures, hypotonia, irregular sighing or sobbing respiration, which are common in IEBB and LD. Serum and CSF lactate levels were high and TK levels were less in most of the infants. CT scan/MRI/MRS together showed abnormal brain imaging and lesion in basal ganglia. Imageological observations were also common in both the phenotypes. Several patients were followed up at different time intervals with specific stress on clinical evaluation and neuro-imageological investigations were repeated on few of them. On follow-up, majority of them had complete resolution of the brain lesions, corroborated by clinical improvement; however, many had persistent neurological and imageological abnormalities. It suggested that these patients may be of LD patients where other than thiamine deficiency, genetic factors were also playing role in disease manifestation. Our study highlights the importance of thiamine deficiency in India, especially in the breast-feds and its overlapping features with LD. Awareness of this common mode of presentation may save patients' lives by early diagnosis and timely thiamine supplementation.

493: *PDCD1* and SLE in Malaysian cohort

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Systemic lupus erythematosus (SLE) is an autoimmune disease, characterized by the production of antinuclear antibody or ANA due to abnormalities of the immune system. SLE is not only a multifactorial disorder but also a polygenic and complex disease. SLE can cause renal failure, vasculitis, arthritis, thrombosis, seizures, and other neurological complications. The disease is believed to be triggered by genetic defects, environment, viral and bacterial infection.

In this study we characterized *PDCD1* polymorphic genes and investigated their association in a cohort of Malaysian (Malays and Chinese) SLE patients. The most common *PDCD1* genotypes found in SLE patients were PD-1.1 (G/G), PD-1.2 (A/G), PD-1.3 (G/G), PD-1.4 (A/G), PD-1.5 (C/T) and PD-1.6 (A/G), with frequencies ranging from 40 to 100%. However, PD-1.3 (G/G), PD-1.4 (A/G) and PD-1.6 (A/G) were also commonly found in control individuals with frequency distributions ranging from 60 to 97%. Positive associations with the SLE phenotype were found for PD-1.9 (C/T), PD-1.5 (C/T) and PD-1.6 (A/A), while negative associations of PD-1.2 (G/G) (39 vs. 53.4%), PD-1.3 (A/G) (0 vs. 3.4%), PD-1.9 (C/C) (23.5 vs. 48.3%) and PD-1.5 (C/C) (41 vs. 62.4%) were observed. The contradictory result from the previous study probably reflects population differences in the haplotype structure of the PDCD1 locus.

494: Functional implication of CYP1B1 in primary open angle glaucoma

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Primary open angle glaucoma (POAG) is the most prevalent of the glaucoma subtypes and is transmitted mostly as a complex disease. Though CYP1B1 gene has been implicated in primary congenital glaucoma with autosomal recessive mode of inheritance, genetic studies suggests a role of this gene in primary open angle glaucoma (POAG) as a modifier along with Myocilin (MYOC), one of the well-characterized candidate for POAG. Recent evidences also suggest on rare occasions defects in CYP1B1 alone can cause POAG in autosomal recessive mode. However, functional assessment of its involvement in POAG has not yet been investigated. We sought to investigate the role of this gene in primary open angle glaucoma. Myocilin promoter region containing ERE (estrogen responsive element) and AP1 sites were cloned into promoterless pGL3 vector containing luciferase reporter gene. The constructs were transfected in RPE (retinal pigment epithelium) cells followed by treatment with 17β estradiol in a dose and time dependent manner. Consistent estradiol mediated induction was observed in the largest 'MYOC promoter—pGL3 construct' containing all three EREs as measured by luciferase assay. We propose that 17β estradiol can induce MYOC expression through the putative EREs located in its promoter and CYP1B1 could manipulate MYOC expression by converting 17β estradiol into 4-hydroxy estradiol, thus preventing it from binding to MYOC promoter. Hence any mutation in CYP1B1 that reduces its enzymatic activity can induce glaucoma pathogenesis by over expression of MYOC. The mutant CYP1B1 clones were generated and the enzymatic activity of each mutant was measured. The expression of endogenous MYOC was analyzed in the background of the CYP1B1 mutants in trabecular meshwork cell line. It was found that indeed CYP1B1 mutant is responsible for over expression of endogenous MYOC. Thus our experimental observation is consistent with our proposed hypothesis that mutant CYP1B1, which lacks the 17β estradiol metabolizing activity can induce, glaucoma by over expression of MYOC. (This study is supported by Council of Scientific and Industrial Research, Govt. of India).

495: A putative genetic locus for bipolar affective disorder at chromosome 6pter-p24.3

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Bipolar affective disorder (BPAD) is a common psychiatric disorder characterized by episodes of mania and depression with worldwide prevalence of 1%. To identify a genetic locus for BPAD we have studied a family of 19 individuals, of which nine were affected with the disorder. We examined 381 microsatellite markers, spaced at an average resolution of 10 cM in the family members. For the dominant model of inheritance, three regions provided two-point LOD scores of $\geq$1.2. These were, D6S1574 on 6p25.1 (LOD score 1.23, $\theta = 0.1$); D6S462 on 6q15 (LOD score 1.26, $\theta = 0.0$) and D11S1338 on 11p15.4 (LOD score 1.4, $\theta = 0.1$). These three sub-genomic regions were followed up using 38 additional markers located at $\leq$2 cM resolution. Manual haplotype analysis showed a 10-marker haplotype shared among eight affected individuals of the family which extends from 6pter to 6p24.3 (D6S1640) and comprises of 7.35 mega bases of DNA. Multipoint analysis of the markers in the region provided highest NPL of 3.007 ($p = 0.017$). Analysis of these additional informative markers ruled out possibility of linkage to the regions 6q and 11p. We also examined 11 families with similar BPAD phenotype for markers from the haplotype on 6p. Haplotype analysis in the additional families showed haplotype sharing in two families, with all four affected individuals sharing in one family and three among four affected individuals in other family. Two-point LOD score of 2.15 was obtained for D6S1591 ($\theta = 0.1$) at 6p25.1 in the combined analysis of the three families. When Psychosis NOS was included in the phenotype classification, two-point LOD score of 2.51 was obtained for D6S1591 ($\theta = 0.1$). Involvement of the 6pter-p24.3 region has previously been shown in bipolar and schizophrenia cohorts from European, Irish, Old Older Amish, Austria, Caucasian, Swedish and Eastern Quebec populations. Our results suggest existence of a genetic locus for BPAD at the same region on chromosome 6pter-p24.3. In search of causative mutations, analysis of candidate genes, *NRN1, SLC22A23, NQO2, TUBB2A and TUBB2B* is being taken up.

496: Association studies of neurotransmitter receptor and transporter genes in the theranostics of schizophrenia in a South Indian population

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Schizophrenia is a debilitating psychiatric disorder with a prevalence of 2.2 per 1,000 adults in India. Disturbances in dopamine and serotonin neurotransmitter is hypothesized to cause schizophrenia. Polymorphisms in these genes can affect individuals response to therapeutic agents. Understanding the pharmacogenetics of these genes have implications for therapeutic effects, abusepotential and side effects of these drugs. In this study we examined the role of 19SNPs in Dopamine receptor D3 (DRD3), Dopamine receptor D4 (DRD4), Dopamine transporter (SLC6A3), Serotonin receptor 1B (HTR1B), Serotonin receptor 6 (HTR6), Serotonin receptor 2A (HTR2A), Serotonin receptor 3B (HTR3B) and Serotonin transporter (SLC6A4) genes in schizophrenia; in the presentation of symptom and antipsychotic treatment response in South Indian population. Subjects included 243 schizophrenic patients and 243 ethnically and age-matched controls. Patients were assessed using BPRS. Clinical improvement was assessed by percent impovement after 1 year follow-up. H–WE allele and genotype frequency was calculated with COCAPHASE and LD pattern with Haploview. DRD4rs936461 is associated with of disorganized behavior ($p = 0.0153$), conceptual disorganization (0.134), motor retardation (0.012), tension ($p = 0.022$) and uncooperativeness ($p = 0.01$). Association was observed with DRD4rs936460 with somatic concern ($p = 0.05$) and DATrs2652510 with motor retardation. 5HT2AS1438 and 102T/C polymorphism influenced self neglect ($p = 0.02$), blunted effect (0.05) and motor retardation ($p = 0.04$). SLC6A4 polymorphism was significantly associated with schizophrenia. 12rpt allele and 12/12 genotype was over represented in cases when compared to controls ($p = 0.002$). DRD4rs936460 T allele was over represented in cases ($p = 0.07$). A significant difference in haplotype frequency was noted in the serotonin transporter gene with C-12 haplotype over represented in cases ($p = 0.009$). No significant association of the polymorphisms with antipsychotic treatment response was observed. This suggests that neurotransmitter receptor and transporter gene polymorphisms screened alone is not involved in complex antipsychotic drug response profile in this population. The study reports significant association with SLC6A4. The difference in the presentation of symptoms in schizophrenic patients throughout the world, influenced by the sociocultural factors like ethnicity could prove vital in solving the present chaos in the field of psychiatric genetics.

497: Molecular correlates of extreme human constitution types defined in Ayurveda: the Indian traditional system of medicine

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Genome wide expression as well as nucleotide variation studies reveals that most genetic variation is due to inter-individual differences at genetic loci even within populations. The enormous heterogeneity within population is largely responsible for the limited success and replication of genome wide association studies towards capturing markers associated with complex diseases, even when applied on large sample sizes. Key to this is to capture phenotypic uniformity with greater precision to get more uniform genetic background. This study is a step towards the same. In the Ayurveda system of medicine, method for phenotypic assessment of a person, which includes one's body constitution, has been described. In the present study only extreme constitution types from Indian populations of Indo-European origin, are considered. The peripheral blood samples were analyzed for genome wide expression and nucleotide variations in genes involved in phenotypic variability and complex diseases.

Significant differences at genome wide expression levels in 251 annotated genes (159 in males and 92 in females) and in allele frequencies of 661 of the 2,800 nucleotide polymorphisms tested, were observed. Differentially expressed genes from each constitution types was found to be significantly enriched in core biological processes like transport and regulation of cyclin dependent protein kinase activity/immune response/regulation of blood coagulation. A significant number of differentially expressed housekeeping, disease associated and hub genes were observed in these extreme constitution types which can have enormous systemic consequences. This suggests that Ayurveda based method of phenotypic classification of extreme constitutional types allows us to uncover genes that may contribute to system level differences in normal individuals which could lead to differential disease predisposition. This is a first attempt towards unraveling the clinical phenotyping principle of a traditional system of medicine in terms of modern biology. An integration of Ayurveda with genomics holds potential and promise for future predictive medicine.

498: Role of alcohol metabolizing genes in alcohol induced pancreatitis

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Oxidant stress caused by alcohol metabolism is a common element causing cellular injury in liver, pancreas, lung and brain. In order to clarify the role of genetic factors in alcohol-related chronic pancreatitis among Indians, we determined single nucleotide polymorphisms (SNPs) in the alcohol metabolizing genes prevalent in alcoholics and control subjects. A total of 183 individuals were screened for Arg47His in ADH1B, Ile349Val in ADH1C, Glu50Lys in ALDH2 gene and G1259C in CYP2E1 gene. Genotyping involved PCR–RFLP based analysis. The control population satisfies the Hardy–Weinberg equilibrium proportions ($p < 0.9$). A significant association was seen between 2-1/2-2 (Glu50Lys) allele of ALDH2 gene and alcohol use (Fisher exact p value = 0.021). A significant association was also seen between 2-2/2-2 (Glu50Glu) versus 2-1/2-2 (Glu50Lys) genotypes of ALDH2 gene in alcoholic pancreatitis patients when compared with unrelated controls (Odds Ratio (OR) = 10.5, CI = 1.645–64.650, X2 = 4.546, $p > 0.03$). The presence of ALDH2 2-2/2-2 genotype impacted the mean age of patients, $p = 0.047$, $t = 1.702$ for 2-1/2-1 vs. 2-2/2-2. On the other hand ADH1B (Arg47His) was found to be completely mono-morphic showing only Arg47 as the prevalent allele (ADH 2-1/2-1). No difference was seen in the prevalent alleles for ADH1B and ALDH2 genes among alcoholics consuming nicotine along with alcohol or not. All the cases of alcohol induced Pancreatitis were found to have the ancestral valine allele for ADH1C. Three patients of alcoholic pancreatitis and one with non-alcoholic pancreatitis were heterozygous for the G1259C mutation in CYP2E1 gene, while none of the controls was found to carry the mutated allele. The allele frequencies did not show any clear trend with the clinical traits associated with alcohol induced pancreatitis, chronic pancreatitis and pancreatitis of unknown origin except for ALDH2 gene polymorphism, which showed a significant reduction in the age of disease presentation in patients of alcoholic pancreatitis.

499: Mitochondrial dysfunction: a major cause for neuromuscular diseases

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Impairment of oxidative phosphorylation and normal physiology of mitochondria leads to a number of mitochondrial disorders. The phenotypic consequences caused by the mitochondrial DNA variations are manifested primarily in the major organs that require high-energy, important one being the neuromuscular system. Indian population has a very complex genetic architecture, which makes it suitable to study the genetic diseases. Our study includes a total of 246 clinically diagnosed individuals, having definite neuromuscular symptoms, and 300 age and ethnically matched controls. Mitochondrial myopathies form the major group of the patients consisting of 59 patients. 32 patients had multiple system involvement; such as, cardiac, ophthalmic and gastrointestinal symptoms. Complete mitochondrial DNA sequencing revealed a total of 217 novel variants, distributed all along the mitochondrial genes, however, majority of the mutations were found in ND5 gene. Interestingly, none of the mutations was found in 300 controls. These mutations were analyzed in the light of evolution and found that there is no specific mitochondrial haplogroup associated with specific mitochondrial diseases with neuromuscular symptoms. Tissue samples of 42 patients were processed for histopathology and electron microscopy. Structural and numerical abnormalities of the mitochondria were observed at least 50% of the cases. Modified Gomori Trichrome staining showed red ragged fibers (RRF), a typical feature of mitochondrial diseases in 12 cases and some showed features of the denervation and RRF. This is the first comprehensive study on the mitochondrial disorders in Indian populations and a detailed clinical, histological, biochemical and genetic data would be presented in detail during the meeting.

500: A study of A3243G mutation in mitochondrial tRNALeu among Vietnamese MELAS patients

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In this work, some results of study on the A3243G mutation in MT-TL1 mitochondrial leucine tRNA gene from total blood DNA of Vietnamese MELAS (Mitochondrial Encephalomyopathy with Lactic Acidosis and Stroke) patients and its' frequency are presented. Using a pair of specific primers, the fragment gene with 400 bp in length (from 3,095 nucleotide to nucleotide 3,494 in the mitochondrial genome) was amplified and sequenced. The presence of A3243G mutant was found by treatment of PCR product with ApaI restriction enzyme and confirmed by both direct and indirect sequencing of the

PCR products. The received sequences were aligned, analyzed, compared with sequence NC_001907.3 in NCBI by BioEdit and ClustalX (1.81) softwares. It was found also that this mutant was in the heteroplasmy form with the frequency of about five percent. We have also analyzed the serum proteome of the patients using combination of 2DE and nano liquid chromatography coupled on-line with tandem mass spectrometry (nanoLC-ESI-MS/MS) to understand the changes related to this type of mitochondrial disorder. More than ten differently expressed proteins in the serum of the patients that might be related to mitochondrial diseases were identified and need to be further characterized. The results might enable us to a strategy to discover new signs of mitochondrial diseases and identification of novel biomarkers for MELAS disease.

501: Molecular pathogenesis of Parkin gene related Parkinson's disease in Indian population

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Parkinson's disease (PD), the second most common neurodegenerative disorder, affecting at least 1% of the population over the age of 60 years. A total of 10 loci and eight causal genes have been identified for PD. Among the identified genes largest number of mutations has been detected in Parkin gene. In this study, a total of 384 PD patients, with the mean age of onset being 48 $\pm$ 13 (age range, 5–78 years), and 105 controls were recruited for the study from eastern India. Mutations were screened in Parkin by amplification of exons along with the flanking splice junctions by polymerase chain reaction, single stranded conformation polymorphism and DNA sequencing. A total of 21 nucleotide variants were detected in Parkin gene of PD patients; these include six nonsynonymous changes (Gln34Arg, Arg42Cys, Arg42His, Tyr143Cys, Arg334Cys and Gly359Asp) in heterozygous condition and two homozygous deletions encompassing exons 3 and 4, and exons 8 and 9, in two unrelated families. Mutation in Parkin was identified in 7.55% cases. Two Parkin coding polymorphisms, Ser167Asn (rs1801474) and Val380Leu (rs1801582), reported to be associated with PD in different populations but with variable results, were found to be significantly associated with PD cases in our cohort independent of age of onset and sex. This study is supported by a grant from Council and Scientific Research (CSIR), Govt. of India.

502: Integrin Beta 3 gene (ITGB3) polymorphisms and autism spectrum disorder: an association study in the Indian population from West Bengal

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Autism is a neurodevelopmental disorder, characterized by impairments in social interaction, communication and behavioral domains. Family and twin studies indicate high heritability for autism with involvement of more than 15 genes in an epistatic manner with non-genetic factors. Among the various chromosomal regions identified as autism susceptibility loci, chromosome 17q21 remains as one of them. Disturbances of serotonin system and effectiveness of selective serotonin reuptake inhibitors in treating behavioral deficits in autism has led to the concept that genes that influence serotonin system are potential risk loci for the disorder. At this juncture, ITGB3, the gene that codes for integrin beta 3 and located on chromosome 17q21.32 can be regarded as a candidate gene for the disorder as it is identified as quantitative trait locus (QTL) for the whole blood serotonin level. Various polymorphisms have been reported for ITGB3, of which T/C single nucleotide polymorphism (SNP) in the exon 3 (rs5918) that alters the 33rd leucine to proline of the protein and a A/C SNP (rs15908) in the exon 9 gained maximum attention because of their functional importance. Despite its importance, only one association study is available on this gene with autism. So in the present study, we have investigated genetic association of ITGB3 with autism spectrum disorder (ASD) in the Indian population using population and family-based studies. The probands were recruited through out patients department (OPD) of Manovikas Kendra, Kolkata after psychometric evaluation using DSM-IV criteria and assessment following CARS. Genotyping analysis was carried out for two SNPs, rs5918 and rs15908 in 84 ASD patients, 148 parents and 88 controls and genotypes showed conformation to Hardy–Weinberg equilibrium. Case–control association study on subjects from West Bengal based on allelic and genotypic frequencies did not demonstrate any significant overrepresentation in either the controls or the cases. This result was further supported by the family-based investigation, which also failed to show any preferential transmission of the alleles from parents to the affected offspring. Thus, the present preliminary study on the Indian population suggests a lack of association of the two SNP markers with ASD. In order to justify our present result, it warrants further studies involving more sample size and markers.

503: Polymorphisms analysis in the leptin gene promoter and the leptin receptor gene in a sample of Mexican obesity patients

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Introduction: Brain-derived neurotrophic factor (BDNF) is expressed predominantly in the ventromedial hypothalamus and its expression is nutritionally regulated by leptin at least in the dorsomedial hypothalamus. Recently, original studies in murine and non-human primates models have shown that mutations in neurotrophin brain-derived neurotrophic factor (BDNF) inhibits food intake, and BDNF disruption exhibit increased food intake and obesity. Furthermore, mutations and polimorphisms Iin BDNF has been linked to neurological, psychiatric, anorexia and cachexia. Those finding and linkage studies suggest that BDNF could be a susceptibility gene to obesity. Objective: Investigated the relationship of polymorphism localized in BDNF gene with body mass index (BMI), in a sample of obesity Mexican patiens.

Methods: We perfomed a case–control association study in 280 obese cases with a BMI >30 and 275 controls with a BMI <25. We analyzed rs6265, rs1519480, rs7934165, rs11030102, rs7124442, rs7124442 and rs104822. Genotyping was carried out by 5′ exonuclease assay (TaqMan).The association test, Hardy–Weinberg equilibrium (H–WE) and haplotypes were determined using EPIDAT, FINETTI and Haploview softwares, respectively.
Results: The allelic and genotype frequencies in cases and controls were in H–WE. In this study we only observed a significantly association of the K109R polymorphism from the LEPR with BMI ($P = 0.01$, OR = 0.1.67; 95% CI: 1.089–2.492).
Conclusion: Our preliminary results suggests that the polymorphism K109R in the LEPR gene could be a susceptibility factor risk to development obesity in Mexican population.

504: Role of SNAP25 genetic polymorphisms in the etiology of attention deficit hyperactivity disorder in eastern Indian subjects

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ADHD is a highly heritable childhood onset neuropsychiatric disorder characterized by inattention, hyperactivity, impulsivity and distractibility. Accordingly, the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [APA, 1994] describes three subtypes of ADHD: inattentive, hyperactive-impulsive and combined. Imaging studies have confirmed reduction in the prefrontal cortical region of ADHD patients. This area is rich in dopaminergic innervations and therefore, candidate gene search for ADHD is mainly targeted at the dopaminergic system. Dopamine is produced in several areas of the brain including substantia nigra and hypothalamus and acts on the sympathetic nervous system. Release of dopamine is controlled by presynaptic fusion of vesicles, which is governed by Ca2+/Calmodulin dependent exocytosis. Synaptosomal-associated protein-25 (SNAP-25), synaptobrevin and syntaxin have function in vesicle docking and fusion. Several SNPs in the SNAP25 gene have been reported to be associated with ADHD in different ethnic groups worldwide. A homozygous deletion in the murine SNAP25 gene was reported to be lethal and hemizygous deletion resulted in hyperactive phenotype similar to ADHD. However, till date SNAP25 gene polymorphisms have not been studied in Indian ADHD patients. In the present investigation two SNPs in the SNAP25, rs362988 and rs8636, were studied in eastern Indian children/adolescents suffering from ADHD (n = 98). Patients were recruited based on the DSM-IV criteria. Genomic DNA was isolated from peripheral blood collected after obtaining informed written consent. The SNP at exon 6, rs362988, was genotyped by PCR amplification followed by sequence analysis. The SNP rs8636 at the exon 8 was analyzed by PCR amplification followed by restriction digestion with HpyCH4IV. Case–control analysis revealed lack of significant difference between the two groups ($p > 0.05$) for both the polymorphisms. Family-based association analysis also failed to show any significant association of these polymorphic alleles with the disorder. It can be concluded from the present study, that the rs362988 and rs8636 are not contributing to the etiology of ADHD in the studied population.
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505: T-47C variation in CRYGB gene: protection against steroid induced pediatric cataract?

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Aim: Sex steroid receptors have been reported in ocular tissues. However, their clear role in eye development or ocular disorders has yet to be elucidated. Many studies have shown that glucocorticoids can lower lens glutathione (reduced) content, which has been demonstrated to be associated with various forms of cataract. Progesterone is indirectly involved in synthesis of glucocorticoids. Thus progesterone may play an indirect role in development of steroid induced cataract. The present study is an attempt to associate variations with the incidence and progression of cataract. The particular mutation under study lies in the promoter region of CRYGB gene and is predicted to impact the binding of progesterone receptor.
Methods: Total of 137 healthy volunteers and 272 (113 pediatric and 79 senile) cataract cases from western India were studied. Examination was performed so as to include volunteers with no ocular defects as controls and cases less than 12 and greater than 45 years of age diagnosed with cataract (excluding metabolic and traumatic cataract cases). PCR–RFLP based method was employed for genotyping of G198A (Intron A), T196C (Exon 3) of CRYGA and C-47T (Promoter), G449T (Exon 2) of CRYGB genes.
Results: Allele frequency of -47T of CRYGB varied significantly ($\chi 2 = 5.66$, $P = 0.02$) among different age groups and also in cases verses controls (OR: 2.9; CI = 1.24–6.47, $P = 0.01$). An in silico analysis reveals that the mutation in CRYGB promoter impacts the binding of transcription factor, PR (Progestrone Receptor) that may lead to altered expression of CRYGB. Stratification of samples according to gender also showed males and females below 12 years of age having a natural protection against cataract in the presence of mutated allele.
Conclusions: This study provides the first report of a SNP affecting the role of progesterone receptor and its protective role in cataract. The data provides strong basis for further studies on role of sex steroid hormones effecting γ-crystallin locus in ocular defects and may shed more light on a natural basis for genetic protection from pediatric cataract in population from India.

506: Lack of association of three SNP markers (A-1438G, T102C and C1354T) of serotonin receptor 2A gene (HTR2A) with autism spectrum disorder (ASD): a genetic study on Indian population

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Abnormality in serorotoninergic neurotransmission is one of the most consistant findings in autism and serotonin receptors act as mediators

for this process. Biochemical studies using 3H-Lysergic Acid Diethylamide(3H-LSD) provides substantial evidences for the involvement of 5-HT2A receptor in autism. Therefore, HTR2A, the gene that codes for serotonin receptor2A (5-HT2A) is considered as a candidate gene for autism. The location of the gene near to a suggestive autism linkage region on chromosome 13q further supports this hypothesis. Three polymorphisms i.e., A/G single nucleotide polymorphysm at 1438 bp upstream of transcription start site (A-1438G), T/C SNP in exon 1 (T102C) and C/T SNP in exon 3 (C1354T) are given much attention in various neuropsychiatric disorders. However, apart from two studies on American and Korean populations, no further reports are available on association of this gene with autism. Therefore, the present study investigates the association of HTR2A gene with autism spectrum disorders in the Indian population following population and family-based analyses. Autistic children were recruited through out patients department of the institute after psychometric evaluations using the DSM-IV criteria and the CARS is used as the assessment tool. Genotyping was carried out for 115 probands, 206 parents and 102 control subjects after PCR and RFLP analysis using the genomic DNA isolated from the white blood cells. The genotypes of all the groups conformed to Hardy–Weinberg Equilibrium. The population-based analysis did not show any bias in the genotypic or allelic distribution between the cases and the controls from West Bengal region. The family-based investigation failed to show any preferential transmission of the alleles from parents to affected offspring supporting the case–control finding. Thus, the present study suggests that the HTR2A markers are unlikely to be associated with the disorder in the Indian population.

507: Epistatic interactions in psychiatric disorders

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Genetic correlates of disease of complex inheritance may include variations in several genes lying within a network of linked biological processes. Synaptic mechanisms such as serotonin neurotransmission, and second (third) messengers (e.g., GSK) have both been implicated in susceptibility to mood disorder, the actions of drugs used to treat the syndrome, and manipulation of the circadian rhythms. To study association between these systems and BPAD, we analyzed two single nucleotide polymorphisms (SNPs) in HTR2A gene (T102C (rs6313), His452Tyr (rs6314)), one SNP in SLC6A4 (5HTTLPR promoter region)), and a promoter SNP in GSK3B gene, -50T/C (rs334558), in 186 BPAD individuals (M:F = 1:1; mean age at onset 18.38 ± 5.43) and matched controls (M:F = 1:1). We examined the epistatic interactions between the SNPs, using MDR (multifactor dimensionality reduction) method. The results suggested modestly synergistic interactions between the loci. MDR detected a two locus model involving 5HTTLPR and rs334558 (GSK3B) with maximum cross validation consistency and minimum prediction error (Monte Carlo $p = 0.008$). LL/TT and SS/TC genotype combinations were observed to possibly confer significant risk towards BPAD. The heterozygous loci, on the other hand seemed to modestly protect, suggesting a heterozygote advantage. Our results suggested an interplay between the synaptic transmission pathway involving serotonin and the post synaptic sequestration of the neurotransmitter, and the second messenger system involving GSK. This could have an important implication in the biology of complex disorders, like mood disorders.

508: Is C-A substitution in exon-2 of CRYAA gene (F71L) causally related to age-related cataracts?

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The aim of the study is to investigate the molecular variation in the exon-2 of alpha crystallin (CRYAA) among the patients of age-related cataracts.

A total of 452 age-related cataract patients with different types of cataracts (nuclear (NC)-108; cortical (CC)-105; posterior subcapsular (PSC)-95; mixed type (MT)-144 cataracts) and 148-healthy normal age-matched controls were screened for mutations in Ex-2 of CRYAA gene. The genomic DNA isolated from the blood samples of patients and controls were amplified using specific primers of Ex-2 of CRYAA gene. The resulting PCR product (223 bp) was checked for amplification on 1% agarose gel and subjected to SSCP analysis. The samples showing mobility shift were recorded.

Of the different types of age-related cataracts studied three patients, two with NC and one with MT showed mobility shift pattern by the SSCP analysis. On sequencing, substitution of C-A at position 213 (counting the A of the start codon as number-1) in Ex-2 of CRYAA gene was detected in all the three cases while among controls none of the samples showed the mutation. This nucleotide change resulted in the substitution of phenylalanine (TTC) to leucine (TTA) at amino acid position 71 (F71L) probably altering the protein structure.

The pathogenicity of this putative mutation leading to cataract formation has to be explored. It is likely that this mutation may be altering the molecular chaperon activity of CRYAA gene leading to protein aggregation and cataract formation. Mutations in CRYAA gene are known to be associated with phenotypically different types of congenital cataracts, with varied progression and inheritance while in age-related cataracts, mutations in the CRYAA gene are not yet reported. The mutation found in the present study could be the first one in the Indian population.

509: Exploring the molecular association of transthyretin amyloidosis with spinocerebellar ataxia and glaucoma

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Amyloidosis is a condition, which involves deposition of abnormally folded protein aggregates (amyloid) in various tissues. Transthyretin (TTR) amyloidosis, a late-onset autosomal dominant disorder is the most common form of hereditary amyloidosis characterized by amyloid deposition in peripheral nerves, heart, kidney, gastrointestinal tract and eye. TTR, a homo-tetramer in its native form is involved in the transport of thyroxine and retinol. TTR is predominantly synthesized in liver but

is also expressed in several other sites including choroid plexus of the brain, retinal pigment of the eye, pancreatic islets and pineal glands. Over 100 TTR variations have been identified and majority of these are associated with TTR amyloidosis. These amyloidogenic mutations in TTR interfere with the stability of the native tetramer by inducing conformational changes that trigger its dissociation into partially unfolded conformers that may self-associate to form amyloid fibrils. Several independent case reports suggest association of TTR mutations with many other neurodegenerative disorders including Alzheimer's, spinocerebellar ataxia (SCA), glaucoma and diabetes. To establish an association between TTR amyloidosis and other neurodegenerative disorders, we have sequenced TTR gene in 100 spino-cerebellar ataxia patients with peripheral neuropathy and 100 primary open angle glaucoma patients. So far, we have identified four variations in these sample sets. Interestingly, two of these are novel variations that are predicted to affect splicing. The reported non-synonymous c.76G > A variation (p.Gly26Ser) in exon-2 is a non-amyloidogenic variation in TTR, which affects thyroxine binding. We observed this variation in one out of 74 SCA12 samples, 3 out of 89 uncharacterized ataxia samples and 1 out of 169 control samples. We are now screening larger sample cohorts of ataxia and glaucoma as well as analyzing the variants in control samples. The findings and the role of these TTR variations in spinocerebellar ataxia and glaucoma will be discussed in the meeting.

510: PAX6 interacts with SPARC, Ras and P53 that links Akt and TGFbeta pathways and influences on neural functions in brain

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The PAX6 is one of the critical transcriptional regulator for the development of brain, eyes, islets of pancreas. The involvement of PAX6 in neural development is well known but the knowledge about its interaction with other proteins during development and disease is limited. Predicting interaction of PAX6 like any other protein with specificity is largely an unsolved problem. It is also not clear how mutation of the PAX6 gene results in various phenotypes and why the phenotypes are of variable expressivity. We explore PAX6 interactors through co-immunoprecipitation. It was interesting to observe a matricellular protein, SPARC, interacting with PAX6. Immunoreactive bands with Ras and P53 were also detected in the sample of brain immunoprecipitated with anti-PAX6. We also present models of PAX6 interacting protein through on-line servers STRING and PIP. This article elucidates putative interaction network of PAX6. It also provides insight to associated proteins in the cascade of hierarchy of PAX6 transcription factor. It is presumed that PAX6 interacts with SPARC, Ras and P53 that links Akt and TGFbeta pathways and influences on neural functions in brain.

511: A descriptive study of the prevalence of factor V (F5) 1691G > A, prothrombin (F2) 20210G > A and methylenetetrahydrofolate reductase (MTHFR) 677C > T polymorphisms among patients with thromboembolism in the Sri Lankan population

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Introduction: Three well known genetic thrombophilic polymorphisms have been described—F5 1691G > A, F2 20210G > A and the MTHFR 677C > T. The objective of this report is to the report the prevalence of the variant alleles of these polymorphisms in Sri Lankan patients with thromboembolism and their family members tested in Colombo, Sri Lanka.
Method: DNA was extracted from venous blood samples after obtaining written informed consent and genotyped using standard PCR/RFLP methods.
Results: A total of 577 people were tested. They consisted of 71 (12%) with cerebrovascular events (CVE); 22 (4%) with arterial thrombosis in other sites (ATO); 58 (10%) with venous thrombosis in other sites (VTO)); 419 (73%) with pregnancy complications (PC) 239 (57%) with recurrent spontaneous pregnancy loss, 175 (42%) with pre-eclampsia (PE); 3(1%) with intrauterine death; 1 (0.5%) each of abruptio placentae and intrauterine growth restriction, and 7 (1%) healthy family members of people with thrombophilic genetic variants tested as a part of pre-symptomatic family screening (PS). The variant allele frequencies were as follows: F5 1691A: CVE—1(1%); ATO—1(1%); VTO—2(2%); PC—11(1%); and PS—3(29%); F5 20210A: CVE—0(0%); ATO—0 (0%); VTO—1 (1%); PC—0(0%); and PS—0(0%); MTHFR 677T: CVE—17(7%); ATO—5 (14%); VTO—15 (14%); PC—91(11%); and PS—2 (14%).

The MTHFR 677TT genotype was present in 6 with CVE, 7 with PC and 2 in pre-symptomatic family members. The only F5 1691AA genotype was detected in a pre-symptomatic woman screened as part of family screening. Conclusions: The prevalence of the variant alleles of these polymorphisms in the Sri Lankan population is similar to that of other South Asian populations. This data will help plan future thrombophilia testing protocols as well as underscore the importance of including family screening as part of genetic testing protocols.

512: A susceptibility locus for juvenile absence epilepsy

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In complex disorders like epilepsy, susceptibility is a result of a combination of mutations or polymorphisms which cause small changes in the expression of certain genes or in the function of the protein. Solely the subtle changes may not lead to any disease and they may be found in unaffected individuals. Moreover, affected individuals may be carrying different susceptibility genes which cause changes in the disease phenotype and this explains the phenotypic difference within the same family. Juvenile absence epilepsy (JAE) and childhood absence epilepsy (CAE) are subtypes of Idiopathic generalized epilepsy (IGE) that show complex inheritance with incomplete penetrance. Genome-wide linkage studies resulted in strong disease locus on chromosome 5, 3q26, 8q24 and susceptibility locus on 14q23 and 2q36. Candidate gene approach resulted in

identification of mutations in GABAA receptor (5q31.1–33.1), voltage-gated Ca+ 2 channel (19p13) and CI channel (3q26) in three different families. In absence mouse models (tottering, lethargic, stargazer), mutations have been identified in three Ca++ channels genes; Cacna1a, Cacnab4 and Cacnag2 which encode α1A, β4, γ2 voltage-dependent Ca++ channel subunit isoforms, respectively. Genome-wide linkage analysis in absence rat models on the other hand, resulted in a susceptibility locus in syntenic 2q33-37 chromosomal region. The present study involves an association study carried out on 213 IAE patients and 214 healthy controls using 10 SNPs in the 2q36 susceptibility region. The SNP selection was based on a haplotype block analysis of the region in the Turkish population. The genotyping was done on Lightcycler 480 and the results were evaluated by Haploview version 4. In the analysis of subtypes, two SNPs were found to be highly associated with JAE phenotype with p-values 0.0029 and 0.0165. Future studies will focus on the search for possible causative mutations or common polymorphisms in the associated region.