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ABSTRACTS

Genomics of complex disorders II

070: Neural tube defects in India occur despite normal maternal folate status and low frequency of T allele at C677T polymorphism in the MTHFR gene

[1]**Koumudi Godbole**, [2]Gayathri Panjalingam, [2]Smitha Parameswaran, [1]Smita Ghule, [1]Nilam Memane, [1]Pornima Deshpande, [3]Krupa Shah, [2]Giriraj Chandak, [3]Jayesh Sheth, [4]S Suresh, [1]Chittaranjan Yajnik

[1]Diabetes Unit, KEM Hospital Research Center, Rasta Peth, Pune, MH, PIN 411011, India, [2]Centre for Cellular and Molecular Biology, Uppal Road, Hyderabad, AP, PIN 500007, India, [3]Foundation for Research in Genetics and Endocrinology, 20/1, Bimannagar, Opp Umiyavijay, Satellite Road, Ahmedabad, Gujarat, PIN 380015, India, [4]Fetal Care Research Foundation, 203 Avvai Shanmugam Road, Royapettah, Chennai, TN, PIN 600014, India

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-center case-control study funded by the Department of Biotechnology to investigate the genetic susceptibility to neural tube defects and its association with maternal vitamin B12 and folate status involving subjects from four cities in four different states.

During the period of January 2007–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 B12 concentration and 45.6% had hyperhomocysteinemia (more than 10 mmol/l). Folate deficiency contributed only 4.6% to the risk of hyperhomocysteinemia while vitamin B12 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 cases 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 B12 deficiency contributes to this problem and also to study the role of gene–gene and gene–nutritional interaction.

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

[1]**Anastasiya Kazantseva**, [2]Daria Gaysina, [1]Elza Khusnutdinova

[1]Institute of Biochemistry and Genetics, Ufa Scientific Center, Russian Academy of Sciences, 71, Prospekt Oktyabrya, Ufa 450054, Russia, [2]MRC SGDP Centre, Institute of Psychiatry, King's College London, De Crespigny Park, London SE5 8AF, United Kingdom

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, 08-06-00579a) and Russian Science Support Foundation (to A.Kazantseva, D.Gaysina).

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

[1]**Jharna Ray**, [1]Arindam Biswas, [1]Gautami Das, [2]Shyamal K. Das, [3]Kunal Ray

[1]S. N. Pradhan Centre for Neurosciences, University of Calcutta, Kolkata, India, [2]Bangur Institute of Neuroscience and Psychiatry, Institute of Postgraduate Medical Education and Research, Kolkata, India, [3]Indian Institute of Chemical Biology, Council of Scientific and Industrial Research, Kolkata, India

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 ± 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.

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

[1]**Ratnakar Tripathi**, [1]Rajnikant Mishra

[1]Banaras Hindu University, Varanasi, India

The PAX6 is one of the critical transcriptional regulators 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.

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

[1]**Inderjeet Kaur**, [1]Saritha Katta, [1]Avid Hussain, [2]Retina Research Group, [1]Subhabrata Chakrabarti

[1]Kallam Anji Molecular Genetics Laboratory, HERF, L V Prasad Eye Institute, Road# 2 Banjara Hills, AP, India, [2]Smt Kanuri Retina Vitreous Centre, HEI, L V Prasad Eye Institute, Road# 2 Banjara Hills, AP, India

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.

075: In Silico analysis reveals Pyrroloquinoline quinine is an effective ligand for α-synuclein: a key player in Parkinson's disease

[1]**Sayak Ganguli**, [1]Sangeeta Mondal, [1]Abhijit Datta

[1]Bioinformatics Infrastructure Facility, Presidency College, 86/1 College Street, Kolkata 700073, India

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 mis-sense 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.