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ABSTRACTS

Single gene disorders

008: Study of the gene causing congenital insensitivity to pain among Israeli-Beduins

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Background: Congenital insensitivity to pain (CIP) syndrome is one of the rare hereditary sensory autonomic neuropathies. We characterized a Beduin family from the Negev, in which three individuals suffer from this disease.
Aim: To identify the mutation which causes the disease.
Methods: A SNP genotyping using the GeneChip mapping 250 K array was performed with samples from the three affected individuals and one unaffected parent in the family. Homozygosity mapping and sorting of genomic regions were performed with software specially programmed for this purpose. Several regions were selected upon their physical size and number of SNPs they contain. These regions were genotyped for all members of the family with microsatellite markers and linkage was found to one region. Sequencing of the genes in the interval was done to identify the mutation causing the disease.
Results and Conclusions: We have mapped the locus to a 14.2 Mb region on chromosome 2q. Screening of candidate genes in this region identified a protein-damaging mutation in SCN9A gene, which encodes for the voltage-gated sodium channel Nav1.7. This mutation was not found in 130 healthy Beduins.

009: Novel CUL7 mutation in 49 Yakut patients with short stature syndrome

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Yakuts have a high frequency of some hereditary diseases, because they have experienced a serious bottleneck effect. Hereditary short stature syndrome is one of the major concerns in Yakuts. We have identified 49 patients with short stature syndrome in 43 Yakut families with pre- and post-natal non-progressive growth failure, facial dysmorphism and normal intelligence. The average of birth length was 42.0 cm $\pm$ 6.2 standard deviation score (SDS), and that of weight was 2.330 kg. A genome-wide linkage analysis for these families revealed linkage to region 6p21.1 with the highest multipoint LOD score of 24.6 at D6S282. We applied a homozygosity mapping approach and narrowed the causative gene to the same locus of the 3-M syndrome and the gloomy face syndrome (Huber et al. 2005). We found a novel homozygous 4582insT mutation in CUL7, which resulted in a frameshift and subsequent premature stop codon at 1,553 (Q1553X). The clinical presentations of 49 patients with short stature syndrome (from birth to 45 years) in Yakut were similar to those of 3-M syndrome. However, they have a high frequency of neonatal respiratory distress (41.98%) and a low frequency of X-ray abnormalities. These findings may provide better understanding of the clinical diversity of short stature syndrome with the CUL7 mutation.

010: Molecular genetics of primary microcephaly in Indian families

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Microcephaly (small head) is defined as a condition in which the head circumference of an affected individual is >3 SD below the population age and sex related mean. The small cranial capacity results from underlying hypoplasia of the cerebral cortex rather than abnormal development of the overlying skull. Primary microcephaly (MCPH; OMIM 251200) is a distinct subtype that is defined by the absence of associated malformations and of secondary or environmental causes. It is inherited as an autosomal recessive trait. Patients with MCPH have mild to severe mental retardation but without any other neurological deficits. It has an incidence of 1/30,000–1/250,000 live births in western populations. The actual incidence of MCPH is not known

in India, but it could be higher in south Indian states of Karnataka, Andhra Pradesh, Kerala and Tamil Nadu where ~33% of marriages are consanguineous. It is a genetically heterogeneous disorder with six known loci: MCPH1–MCPH6. So far, genes for MCPH1 (MCPH1), MCPH3 (CDK5RAP2), MCPH5 (ASPM) and MCPH 6 (CENPJ) loci have been identified. We have ascertained a total of 42 families with MCPH from the states of Karnataka, Andhra Pradesh and Tamil Nadu. We have carried out linkage analysis of a majority of these families using PCR-based microsatellite markers from the candidate regions of six known MCPH loci. Our analysis showed that the ASPM gene is a major cause of MCPH in Indian families. The presence of unlinked families to any of the known MCPH loci in our dataset suggested the involvement of a seventh locus for this disorder. We are performing a genome-wide screening of unlinked families to identify a novel MCPH locus. DNA sequence analysis in MCPH5-linked families has identified one known and four novel mutations in the ASPM gene in a homozygous state.

011: CC2D1A is involved in autosomal recessive non-syndromic mental retardation in a Pakistani family

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Mental retardation is the most frequent handicap among children and young adults affecting 1-3% of the general population. To date of 11 loci, with linkage to nonsyndromic autosomal recessive mental retardation (NSARMR), only four genes have been found with associated mutations. The MRT3 locus was initially mapped in families with NSARMR to an interval of 2.4 Mb and is caused by deletion of CC2D1A gene. We have studied a three generation Pakistani family with three affected individuals. The affected individuals of the family segregate NSMR and have psychomotor developmental delay in childhood. None of the diseased individual reveals the presence of autism spectrum disorders or seizures. The DNA samples from five family members, including three affected females were used for genotyping of microsatellite markers linked to known MRT (MRT1-11) loci. Analysis of the results indicates linkage of the studied family to MRT3 (19p13.12) locus with a maximum two-point LOD score of 2.08 at markers D19S892 and D19S556. The same markers yielded multipoint LOD score of 2.64. Sequencing of CC2D1A gene is in progress to identify the mutation responsible for NSARMR in Pakistani family.

012: Origin of Friedreich's ataxia (FRDA) mutation predates divergence of Indian and Caucasian populations

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Friedreich's ataxia (FRDA) is an autosomal inherited recessive ataxia caused by expansion of GAA repeats in the intron 1 of frataxin gene. The GAA repeats polymorphic in the normal individuals are restricted to a threshold which varies in length from 7 to 16. Once unstable these repeats expand from 120 to over thousand repeats in the affected individuals. Haplotype analysis has revealed that expanded alleles arise through an intermediate premutation stage from large normal alleles (LNs) of GAA repeat (>12) and the frequency of the LNs determine prevalence of FRDA in a population. In this study, we have undertaken a detailed haplotype analysis of 23 FRDA families which had tested positive for homozygous GAA expansion and 200 ethnically matched normal individuals of Indian origin. The families though inhabitants of diverse geographical regions were all of Indo-European (I.E) origin. An earlier study by the Indian Genome Variation Consortium has revealed that I.E populations are genetically closer to CEU in HAPMAP. Therefore, we undertook this analysis using tag SNPs derived from CEU population. These SNPs span a 200 kb region encompassing the GAA repeat and also include two SNPs (ITR3-rs3829062; FAD1-rs11145465) which have earlier been associated with GAA expanded alleles in the French population as well as few Indian families of eastern India. We observed a significant association ($p < 10–6$) of four SNPs rs3829062 (93%), rs11145326 (93%), rs7861997 (79%) and rs11145465 (73%) with the expanded alleles. The SNPs rs3829062 and rs11145465 have been significantly associated with expanded alleles in French population with frequencies of 100 and 90%, respectively. These results suggest that Indian and French population share a common founder which predates divergence of these populations. Compared to 17% frequency of LNs in French population we observed its frequency to be 4.8% in the Indian population. This correlates with differences in FRDA prevalence between the two populations. The haplotype associated with the LNs in Indian population is also shared with the expanded alleles. It would be interesting to determine whether the expanded alleles have arisen from de novo recurrent mutations of LNs in the Indian population or through admixture with the CEU population.

013: Mitochondrial gene mutations as a cause of non-syndromic hearing impairment among probands from Andhra Pradesh

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Hearing impairment affecting 1 in 1,000 newborns is a highly heterogeneous disorder with majority of the cases being non-syndromic (NSHI). It can result from a mutation in a single gene or from a combination of mutations in different genes or by environmental factors and also by interaction between genetic and environmental factors. Mitochondrial DNA mutations have been found to be associated with both aminoglycoside induced hearing impairment and NSHI. The common mtDNA mutations causing NSHI include A7445G, T7510C, T7511C in tRNA Ser (UCN) gene and A1555G in 12S rRNA gene. This mutation is more frequent in many populations and is considered as a primary factor underlying the development of deafness. However, the expression of the deafness phenotype associated with this mutation requires contributions of nuclear modifier genes or aminoglycoside antibiotics which affect the phenotypic manifestation by enhancing or suppressing the biochemical effect of the mutation. A nuclear modifier gene on chromosome 8 is thought to account for deafness in those individuals who do not have aminoglycoside exposure. 484 probands with profound bilateral sensorineural hearing impairment were ascertained for various

epidemiological parameters and 303 DNA samples of patients including 25 families and 200 control samples were screened for mitochondrial mutations by PCR–RFLP followed by genotyping on 2% agarose gels stained with ethidium bromide. The epidemiological results revealed: preponderance of males (58.7%) as compared to females (41.3%) indicating high risk for hearing impairment in males. High incidence of positive family history (59.9%), parental consanguinity (58.0%) and delayed milestones (59.5%) was recorded in males as compared to females. 32.6% of the cases with delayed milestones were considered as due to vestibular dysfunction. Screening for mutations revealed absence of A7445G, T7510C and T7511C in tRNA Ser (UCN) gene. Three homozygous mutants were found for A1555G mutation in 12S rRNA gene. All the three probands had profound non-syndromic hearing impairment and had no history of exposure to aminoglycoside antibiotics suggesting the possible involvement of nuclear modifier gene that might interact with the mutated 12SrRNA and affect the phenotypic manifestation by enhancing or suppressing the biochemical effect of the mutation. None of the controls showed the mutation. This is the first study from India showing the prevalence of A1555G mutation among non-syndromic hearing impaired patients.