

Dear Readers,

It is a pleasure to bring to you through JPMA's Science Vision, the latest findings in genetic research, some of which have not yet been published. I report on the October Meeting of the American Society of Human Genetics held at the scenic Salt Lake City in Utah, USA. Many of us travel the globe to attend various international meetings where the latest breakthrough findings are presented. These findings become public knowledge and the abstracts are pub-

lished in a supplement form of a major journal. I would like to encourage everyone who has attended a recent international meeting to summarize at least few of the major findings for Science Vision for the benefit of the readership of JPMA. You may submit your piece to: editor@jpma.org.pk

Mohammad Saeed

Section Editor, Science Vision, JPMA.

Genomic Medicine

Mohammad Saeed

Department of Neurology, Northwestern University, Chicago, USA.

Multiple Sclerosis (MS)

Jonathan Haines, a world renowned Geneticist presented the findings of the International Multiple Sclerosis Consortium (IMSC) of a genome-wide linkage scan on affected relative pairs (ARP) (such as siblings with MS) to locate regions of the genome likely to harbor MS genes.¹ Previously two linkage scans had identified a region in the major histocompatibility complex (MHC) viz HLA DRB1*1501.^{2, 3} On the basis of concerns about the quality of genotyping data IMSC re-screened the largest sample of ARPs to date (n=730) with the Illumina bead array linkage mapping panel which provides 99.5% genotyping efficiency and uses a carefully selected map of single nucleotide polymorphisms (SNP) as markers.

The results were shocking. For a disease with a sibling relative risk of 15-40 this high quality, powerful linkage scan could only find a single major locus on chromosome 6p (MHC). Three other minor loci were found on chromosomes 17, 5 and 19.

Keeping this finding in view it seems that MS is predominantly modulated by the MHC.

1. Sawcer. International Multiple Sclerosis Genetics Consortium. A high-density screen for linkage in multiple sclerosis. *Am J Hum Genet.* 2005;77:454-67. Epub 2005 Jul 29.
2. Haines. A complete genomic screen for multiple sclerosis underscores a role for the major histocompatibility complex. *The Multiple Sclerosis Genetics Group. Nat Genet.* 1996;13:469-71.
3. Sawcer. A genome screen in multiple sclerosis reveals susceptibility loci on chromosome 6p21 and 17q22. *Nat Genet.* 1996;13:464-8.

Gene influencing QT interval

By an elaborate methodology and whole-genome high throughput SNP genotyping a German group has discovered that CAPON gene that functions as a regulator of neuronal nitric oxide synthase (nNOS) which plays a key role in cardiac contractility, is a susceptibility gene modulating the QT interval. They performed whole-genome association study comparing DNA variation in 100 female sub-

jects with QT interval in the lowest 10th percentile with 100 female subjects having the QT interval in the highest 10th percentile of their sample. Using this analysis they located several regions which were differentially transmitted. They performed two sets of replication studies, studying in detail 10 of the best candidate regions in 300 cases and 300 controls followed by replication of the most significantly associated SNP in CAPON gene on all ~4000 subjects. Resequencing identified a functional variant in the CAPON gene.

1. Arking. Common Variants Influencing the QT-interval by Genome-wide Association Analysis. ASHG 2005 Program number 110

LAD coronary artery MI susceptibility gene

Patients with left anterior descending coronary artery disease (LAD) have one of the worst prognoses for survival of myocardial infarction (MI). The Genecard study group identified a novel locus in the limbic system-associated membrane protein (LSAMP) gene associated with LAD risk, independent of classic MI risk factors (cholesterol, diabetes, etc!).

Using a novel DNA pooling technique to screen single nucleotide polymorphisms (SNPs) for association in MI patients (n=469) and controls (n=204) they found a 12% allele frequency difference for SNP rs1875518 which was validated by individual genotyping. Similar associations were found in additional SNPs near rs1875518. Stratifying the data by CAD index, a numerical summary of angiographic data that reflects severity of CAD revealed a strong association with LAD (p<0.001), odds ratio 2.63 (95% CI: 1.43-4.83) for the marker rs1676232 in a recessive model. The associated SNPs reside within a large intron (1.6 Mb) lying between two alternative first exons (1a and 1b) of LSAMP gene, previously only described in mouse. In silico analysis suggested a similar exon structure for the human gene. Expression of LSAMP exon 1a was studied in 37 human aortas and found to be decreased 6.5 fold (p<0.001)

in aortas with severe compared to mild atherosclerosis. In addition, the rs1676232 risk allele was associated with reduced expression of exon 1a ($p=0.05$) in the aortas. Given the pronounced risk associated with LAD, these findings could lead to a risk assessment tool facilitating early initiation of preventive and therapeutic strategies, thereby reducing CAD morbidity and mortality.

1. Wang. Identification of a novel locus for left main coronary artery disease. ASHG 2005 Program number 116.

HapMap

Inherited genetic variation has a critical but as yet largely uncharacterized role in human disease. The report by the International HapMap Consortium^{1, 2} is a major contribution to the understanding of genomics. The data is available as a public resource of common variation

in the human genome: more than one million single nucleotide polymorphisms (SNPs) for which accurate and complete genotypes have been obtained in 269 DNA samples from four populations.³

The human genome is inherited in blocks across populations. These data document the block-like structure of inheritance patterns and the correlations of markers, such as SNPs, with many of their neighbours across such regions. This correlation of markers is an important guide to the design and analysis of genetic association studies and will also shed light on structural variation and recombination as well as help to identify regions that may have been subject to natural selection during human evolution.

1. Donnelly. The International HapMap Project: A haplotype map of the human genome with 4 million SNPs. ASHG 2005 Program number 6
2. International HapMap Consortium. A haplotype map of the human genome. *Nature*. 2005;437:1299-320.