

Venue: PYRAMID 1  
 23rd August 2007  
 1100-1215 hr

### **Symposium 5B: Molecular genetics**

#### **S5B-1. Between genotype and phenotype: genetic modifiers in beta Thalassemia**

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Although the defective genes for many genetic diseases become is not known, it is clear that patients with apparently identical genotypes may have many different clinical presentations. Beta thalassemia is a very heterogeneous disorder due to variations in inactivation mechanism of the  $\beta$ -globin genes. Point mutations and small deletions or insertions in the nucleotide are the main molecular defects for most  $\beta$ -thalassemia. In spite of seemingly identical genotypes, severity of  $\beta$ -thalassemic patients can vary greatly. Heterogeneity in the clinical manifestation of  $\beta$ -thalassemia may occur from the nature of  $\beta$ -globin gene mutation,  $\beta$ -thalassemia gene interaction and difference in the amount of Hb F production. We identify disease modifier genes among  $\beta^0$ -thalassemia/Hb E patients by genome-wide association study involving 110,000 gene-based single nucleotide polymorphisms (SNPs). The sample derives from 1,200 subjects. DNAs from approximately 200 matched patients representing the extremes of disease severity (mildest vs. severest) were included in each DNA pool. Allele frequencies for all SNPs were estimated in both pools, and those showing significant differences (p values <0.02) were selected for verification by repeated pooled DNA analysis. Approximately 800 SNPs were selected for individual genotyping to determine precise allele and genotype frequencies. The most strongly associated SNPs were within chromosome 11 distinct from the  $\beta$ -globin gene cluster. A number of SNPs have evidence for association with disease severity, including several in reported quantitative trait loci (QTLs) associated with fetal hemoglobin Hb F levels. Moreover 210 SNPs on 160 genes confirmed to have statistically significant differences between mild and severe patients (P<0.05). Additional support for these findings will come from replication in independent patient collections and functional analyses.

#### **S5B-2. Polymorphisms in hepatic lipase – a new biomarker?**

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Abstract not available at time of printing.

**S5B-3. Genetic polymorphism of warfarin resistance**

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Warfarin is the most widely prescribed anticoagulant for thromboembolic therapy. It has a 20 fold interindividual difference in dose requirement and a narrow therapeutic range and therefore bleeding complications particularly in the initiation phase of treatment are a major risk. Though it is known that demographic and environmental factors contribute to this interindividual variability to some extent, recent studies have thrown more light on the influence of genetic factors. Interethnic differences in warfarin requirement have been reported between African Americans, European Americans and Asians and between different Asian ethnic groups. Warfarin is metabolized to inactive form by cytochrome P450 enzymes (CYP2C9) and attention was focused on this gene for CYP2C9). It was shown that genetic alterations (polymorphisms) of this gene could significantly impact warfarin therapy. Genetic analysis found three major alleles CYP2C9\*1 (wild type), CYP2C9\*2 and CYP2C9\*3 and these 2 variants were associated with reduced warfarin requirements. However, these variants could account for about 10% of the interindividual variability. Warfarin inhibit the action of vitamin K epoxide reductase whose gene (VKORCI) has been recently discovered. This complex recycles, reduced vitamin K which is essential for the post-translational gamma-carboxylation of vitamin K dependant clotting factors. It was shown that some patients with warfarin resistance had unique missense single nucleotide polymorphisms (SNP) in the new gene. Researches have recently identified informative SNPs in VKORCI. They identified ten common non-coding VKORCI SNPs and inferred five major haplotypes. About 25% of the variance in warfarin dose could be explained by these haplotypes alone. They identified a low dose haplotype group (A) and a high dose haplotype group (B). They found that the mean maintenance dose of warfarin differed significantly among the three haplotype combinations. Asian Americans had a higher proportion of group A haplotypes whereas the African Americans had a higher proportion of group B haplotype. It is also likely that interindividual variability is due at least in part to additional genetic factors including genes encoding vitamin K dependant clotting factors and gamma-glutamyl carboxylase. By providing an estimate of the therapeutic warfarin dose, pharmacogenetics-based therapy may improve the safety and effectiveness of warfarin therapy but this depends on the methods that are available for rapid and easy genotyping in the clinical setting.