44576 - PLATELET SURFACE GENES AND THE RISK OF BLEEDING AFTER CARDIAC SURGERY

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INTRODUCTION: The risk of excessive bleeding after cardiac surgery may be influenced by genetic factors. Specific candidate genes include the GP1BA gene, encoding the glycoprotein Ib, a major component of the platelet receptor for von Willebrand factor (VWF), and the ITGA2 gene, which encodes the alpha-chain of the glycoprotein Ia/IIa, the principal platelet receptor for collagen1,2. Goals of the study were: to estimate allele frequencies of genetic variants (single nucleotide polymorphisms (SNPs) and haplotypes in ITGA2 and GP1BA in Caucasian patients undergoing cardiac surgery; to compare haplotype frequencies between Caucasian 'bleeders' and 'nonbleeders' to determine whether specific haplotype(s) confer higher risk of bleeding.

METHODS: Following REB approval, 310 Caucasian cardiac surgery patients were included in this study. Patients were stratified into two groups: 'bleeders' (n=34) with blood loss >750 ml and 'non-bleeders' (n=276) with blood loss < 750 ml during first 12 hours after cardiac surgery with CPB. Demographic and surgical characteristics were similar in the two groups. To cover genetic variation in ITGA2, we genotyped 20 SNPs, representing 202 SNPs, catalogued within the international HapMap project. In GP1BA we genotyped four SNPs representing ten common SNPs. Additionally, we genotyped three functional polymorphisms (-52)C>T, 807C>T and 1648G>A in ITGA2 and a(-5)T>C Kozak sequence polymorphism in GP1BA. SNPs were genotyped using the Sequenom MassArray platform with Iplex assay as part of a larger genotyping panel. Haplotypes were inferred with the software PHASE. Differences in allele frequencies between patient groups were compared with the chi2- test.

RESULTS: Frequencies of the genotyped SNPs were consistent with the data available from public SNP databases for Caucasian populations. Out of 23 SNPs genotyped in ITGA2, three SNPs, including the 807C>T, demonstrated significant association with bleeding (p<0.05). Comparison of ITGA2 haplotype frequencies between 'bleeders' and 'nonbleeders' showed that out of ten haplotypes carrying the 807C allele, only two haplotypes, carrying also the (-52)T and 1648A alleles, were significantly associated with bleeding (p<0.05). For GP1BA, the (-5C) allele of the (-5)T>C Kozak sequence polymorphism was found only in one out of seven common GP1BA haplotypes. This allele as well as this haplotype exhibited significantly higher frequency in the group of 'bleeders' than in 'nonbleeders' (p<0.05).

CONCLUSIONS: We identified 17 common haplotypes in the ITGA2 gene and seven common haplotypes in the GP1BA gene, of which two haplotypes in ITGA2 and one haplotype in GP1BA were associated with bleeding after cardiac surgery with CPB. These findings provide basis for

larger scale studies aimed at determining genetic variants in platelet glycoproteins conferring an increased risk of adverse outcomes after cardiac surgery.

REFERENCES:1.J Thrombosis and Haemostasis 20053:1206-1212; 2.Heart 2006 92:676-678