

THE COMPLEX INTERACTION BETWEEN THE SECRETOR AND ABO BLOOD GROUP GENOTYPES DETERMINES LARGE DIFFERENCES IN FACTOR VIII LEVELS AMONG SEVERE AORTIC STENOSIS PATIENTS

B. Lunghi¹, A. Castagna², M. Baroni¹, G. Marchetti³, M. Spizzo², G. Mango², S. Friso², N. Martinelli², F. Bernardi¹

¹Dept. of Life Sciences and Biotechnology, University of Ferrara, Italy; ²Dept. of Medicine, University of Verona, Italy; ³Dept. of Neuroscience and Rehabilitation, University of Ferrara, Italy

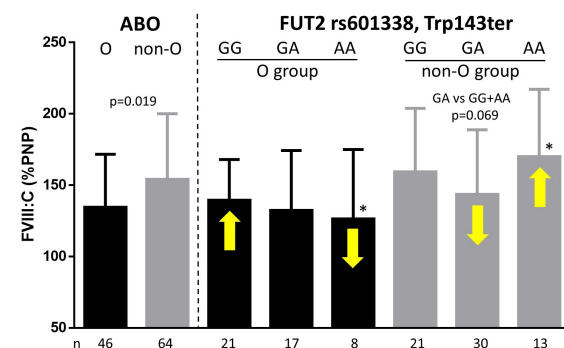
Background and Aims. More than 100 SNPs across dozens of loci have been reported to influence plasma factor VIII (FVIII) and/or von Willebrand factor (VWF) levels. Among these, several FVIII/VWF clearance receptor genes display a role in combination with the ABO locus, a main determinant of these plasma phenotypes. We reported that selected lectin (ASGR2 and CLEC4M) and low-density lipoprotein receptor (LDLR) cell receptor genotypes differentially modulate the ABO blood group influence on FVIII levels in severe aortic stenosis (SAS), which alters VWF conformation through turbulent blood flow. We aimed at investigating the impact on FVIII levels of the interaction between genotypes encoding the ABO blood groups and genotypes responsible for ABO(H) glycan secretion in plasma (α 1,2 fucosyltransferase, FUT2/Secretor gene).

Methods. This observational study was performed within the angiographically-controlled cardiovascular cohort of Verona Heart Study. SAS patients (n=110, 59±12 years) undergoing angiography before heart valve surgery were selected. All the patients had the aortic valve area < 1.0 cm² or the trans-valvular pressure mean gradient ≥ 40 mm Hg or peak aortic jet velocity ≥ 4 m/s by transthoracic echocardiography. SAS patients were genotyped and categorized for O and non-O blood groups (ABO), and for a frequent FUT2 SNP (rs601338G/A, MAF=0.48) that abolishes (Trp143ter) secretion (non-secretor blood group status). The association of combined genotypes with FVIII activity levels (% PNP) was investigated by t-test. Results (figure 1): FVIII levels (mean±SD), which showed high intragroup variability, were 20% lower (p=0.019) in patients with the O (n=46, 134.5±37.1) than non-O (n=64, 154.1±45.9) blood groups. Whereas in the O group the highest FVIII levels were observed among the Secretor homozygotes (O FUT2 GG, n=21, 139.4±28.6), in the non-O group were observed in the non-Secretor homozygotes (non-O FUT2 AA, n=13, 170.0±47.1). Differently, the O FUT2 AA genotype was associated to the lowest levels (n=8, 126.4±48.5, range 75-219). Consequently, the non-Secretor FUT2 AA genotype increases intragroup FVIII level variance by predicting the highest FVIII levels in the non-O and the lowest in the O group,

with 43% mean differences (p=0.061, Mann Whitney test). Among non-O patients, the FUT2 GA heterozygotes, predicting a Secretor phenotype, displayed the lowest levels (n=30, 143.5±45.3), which produced a trend for significant intragroup differences (GA vs GG+AA, p=0.069, Mann Whitney test) and similar FVIII levels in non-O FUT2 GA and O FUT2 GG (139.4±28.6) subgroups. This suggests that ABO/Secretor genotype combinations contribute to abolish the expected ABO effects. The unexpected FVIII-lowering effect of ABO/FUT2 GA was similar to that previously observed for the non-lectin LDLR r688C/T genotypes (CT n=32, 147.3±41.3).

Conclusions. The interaction between the FUT2 Trp143ter null genotypes and ABO groups profoundly influences FVIII activity levels, potentially by clearance mechanisms. The genotype-driven large differences among groups i) may have clinical implication for SAS, characterized by either pro-thrombotic or bleeding diathesis, the latter also favored by the often concomitant anticoagulant therapies and ii) contribute to interpret the high inter-patient level variability. These observations deserve investigation in larger cohorts of patients, to confirm and better quantify the size of potentially remarkable effects.

FVIII activity levels (mean±SD) in severe aortic stenosis patients grouped for ABO and α 1,2 fucosyltransferase (FUT2/Secretor) genotypes.



FVIII-increasing/lowering effects in genotype combinations are indicated by the arrows. *Comparison between O FUT2 AA and non-O FUT2 AA groups, p=0.061