Common single nucleotide variants in the stabilin-2 *(STAB2)* gene influence von Willebrand Factor levels in type 1 von Willebrand disease patients

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Background: Type 1 von Willebrand disease (VWD) is an inherited bleeding disorder that involves partial quantitative deficiency of the glycoprotein coagulation factor von Willebrand factor (VWF). Type 1 VWD is characterized by incomplete penetrance and variable expressivity, and 35% of patients are "mutation negative" after Sanger sequencing the VWF coding region. This suggests that loci external to the *VWF* gene might modify the type 1 VWD phenotype. Stabilin-2 is a VWF clearance receptor expressed on the sinusoidal endothelial cells of the liver and spleen. Common single nucleotide variants (SNVs) in the *STAB2* gene associate with VWF (rs4981022, c.6987+378G>A) or FVIII (rs12229292, c.7248+582G>T) levels in normal individuals. We hypothesized that SNVs in the *STAB2* gene can influence plasma VWF levels in type 1 VWD patients.

Methods/Patients: 165 type 1 VWD patients from the Canadian and Milwaukee populations were genotyped for SNVs in *STAB2* using Taqman analysis. Inclusion criteria included a bleeding diathesis and plasma levels of VWF:Ag and VWF:RCo between 0.05 and 0.50 U/mL, VWF:RCo/VWF:Ag ratio >0.6 U/mL and normal VWF multimers. Patient characteristics are as follows: Median patient age= 17 (range 1-65); VWF:Ag IU/dL= 0.36 (IQR: 0.27-0.42); VWF:RCo= 0.34 IU/dl (IQR: 0.22-0.4); FVIII:C= 0.51 (IQR: 0.41-0.6); female sex= 45%; blood group O= 71.6%. Mutation status was as follows: unknown= 5.3%; mutation negative= 53.8%, mutation positive (1 or more)= 40.9%. Using each SNV genotype as a continuous variable we performed linear regression analysis to quantify differences in VWF:Ag, VWF:RCo, and FVIII:C. All models were adjusted for age and ABO blood group. The study was approved by the Research Ethics Board of participating institutions.

Results: Genotype analysis of rs4981022 showed an association with lower mean VWF:Ag (TT: 0.345 IU/dL, TC: 0.321 IU/dL, CC: 0.294 IU/dL) and FVIII:C (TT: 52.86%, TC: 50.02%, CC: 29.3%). Linear regression confirmed the *STAB2* SNV rs4981022 association with lower VWF:Ag (β:-2.8%; CI:-5.5, -0.1; p=0.041) and FVIII:C (β:-1.4%; CI:-6.5, 3.6; p=0.58). Genotype analysis of rs12229292 showed an association with higher mean VWF:Ag (GG: 0.314 IU/dL, GT: 0.343 IU/dL, TT: 0.388 IU/dL) and FVIII:C (GG: 50.18%, GT: 52.51%, TT: 55.28%). Linear regression confirmed the *STAB2* SNV rs12229292 associated with elevated VWF:Ag (β:3.8%; CI:0.8, 6.8; p=0.014) and FVIII:C (β:1.9%; CI:-3.8, 7.6; p=0.51). Chi-square analysis demonstrated an increased association of rs12229292 with mutation negative cases (p=0.015) which was confirmed by logistic regression (odds ratio: 0.464, CI: 0.262, 0.823; p=0.009).

Conclusions: We observed that *STAB2* SNVs associated with VWF:Ag levels in type 1 VWD with a magnitude of effect and direction of association consistent with results observed in normal individuals. Variants in *STAB2* can thus modify the type 1 VWD phenotype through regulation of VWF clearance from the plasma. Understanding the influence of external genetic loci in the type 1 VWD phenotype may improve molecular diagnostics for this inherited bleeding disorder.