Effect of Genetic Variations in Syntaxin-Binding Protein-5 and Syntaxin-2 on von Willebrand Factor Concentration and Cardiovascular Risk

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Background—Elevated von Willebrand factor (VWF) plasma levels are associated with an increased risk of cardiovascular disease. A meta-analysis of genomewide association studies on VWF identified novel candidate genes, that is, syntaxin-binding protein 5 (STXBP5) and syntaxin 2 (STX2), which are possibly involved in the secretion of VWF. We investigated whether VWF antigen levels (VWF:Ag), VWF collagen-binding activity (VWF:CB) and the risk of arterial thrombosis are affected by common genetic variations in these genes.

Methods and Results—In 463 young white subjects (men ≤45 years of age and women ≤55 years of age), who were included 1 to 3 months after a first event of arterial thrombosis, and 406 control subjects, we measured VWF:Ag and VWF:CB. Nine haplotype tagging single-nucleotide polymorphisms of STXBP5 and STX2 were selected and subsequently analyzed using linear regression with additive genetic models adjusted for age, sex, and ABO blood group. The minor alleles of rs9399599 and rs1039084 in STXBP5 were associated with lower VWF plasma levels and activity, whereas the minor allele of rs7978987 in STX2 was associated with higher VWF plasma levels and activity. The minor alleles of the single-nucleotide polymorphisms in STX2 were associated with a reduced risk of arterial thrombosis (rs1236: odds ratio, 0.73 [95% confidence interval, 0.59, 0.89]; rs7978987: odds ratio, 0.81 [95% confidence interval, 0.65, 1.00]; rs11061158: odds ratio, 0.69 [95% confidence interval, 0.55, 0.88]).

Conclusions—Genetic variability in STXBP5 and STX2 affects both VWF concentration and activity in young individuals with premature arterial thrombosis. Furthermore, in our study, genetic variability in STX2 is associated with the risk of arterial thrombosis. However, at this point, the underlying mechanism remains unclear. (Circ Cardiovasc Genet. 2010;3:507-512.)

Key Words: von Willebrand factor ■ genetics ■ STX2 ■ STXBP5 ■ cardiovascular diseases

Because elevated von Willebrand factor (VWF) plasma levels are associated with an increased risk of cardiovascular disease (CVD), elucidating determinants of VWF plasma levels is of great interest.1,2 It is already known that VWF plasma levels can be influenced by both genetic3,4 and nongenetic factors. These factors have their effects on different stages during the lifetime of the VWF molecules, which involve many biological mechanisms. However, determinants that have been identified previously—heritability estimates for VWF levels are on average 50%—not sufficient to explain the entire variability of VWF levels.3

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VWF has a 2-fold function in primary hemostasis: It initiates adherence of platelets to the injured vessel wall and subsequent platelet aggregation, especially at sites of high shear.5,6 VWF is mainly produced by endothelial cells but also for about 5% to 10% by megakaryocytes. The majority of the newly synthesized VWF proteins is directly secreted into the circulation via the constitutive pathway.7 Large and ultralarge VWF multimers are stored in Weibel-Palade bodies (WPBs) of endothelial cells and α-granules of platelets.8,9 These
storage granules release VWF multimers upon stimulation of a variety of physiological agonists, such as hypoxia, epinephrine, histamine, thrombin, fibrin, and vasopressin.

Recently, the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium conducted a meta-analysis of genomewide association studies in 5 large population-based cohort studies to identify new genetic determinants of VWF levels. Besides confirmation of previously identified candidate genes, such as the ABO blood group gene and the VWF structural gene itself, the CHARGE consortium identified and replicated novel associations with 6 genetic loci, among which are the STXBP5 and the STX2 genes. Syntaxin 2 (STX2) is a binding substrate for syntaxin-binding protein 5 (STXBP5) and is a member of the Soluble N-ethylmaleimide-sensitive factor Attachment protein Receptor (SNARE) protein family. These proteins drive vesicle exocytosis by fusion of granules and target membranes, a process involved in the regulation of numerous secretory events, such as WPB exocytosis. WPBs and α-granules release large amounts of VWF after endothelial cell activation, for example, in atherosclerosis and subsequent arterial thrombosis. Moreover, these storage granules secrete not only VWF molecules but also other substances, including proinflammatory factors, such as P-selectin, cytokin, and interleukin-8. Hence, considering the involvement of STXBP5 and STX2 in secretion of VWF and other prothrombotic and proinflammatory factors, which may in turn lead to development of atherosclerosis, these candidate genes may have a direct effect on the risk of CVD as well.

We aimed to further expand previous findings of the CHARGE consortium in an independent case-control study. Our study population is unique because it consists of specifically young individuals with a first event of arterial thrombosis. In addition, the influence of genetics is generally more pronounced in younger individuals than in older individuals who have been exposed to potential cardiovascular risk factors for a longer period of time. Consequently, we have investigated the effect of common genetic variations in STXBP5 and STX2, including the 3′ and 5′ UTR regions, on VWF plasma concentration, VWF collagen binding activity, and the risk of arterial thrombosis.

Methods

Patients

The Genetic risk factors for Arterial Thrombosis at young age: the role of TAFI and other Coagulation factors (ATTAC) study is a single-center, case-control study, described in more detail previously. In brief, the cases (n=463) were defined as patients with a first event of arterial thrombosis, which were consecutively recruited 1 to 3 months after the event at the Departments of Cardiology, Neurology, and Vascular Surgery at the Erasmus University Medical Center. Patients were eligible for inclusion when they were 18 to 45 years of age for men and 18 to 55 years of age for women at the time of diagnosis. The cases consist of 3 subgroups: (1) patients with coronary heart disease (CHD), defined as either an acute myocardial infarction or unstable angina pectoris, (2) patients with either ischemic stroke (IS) or a transient ischemic attack (TIA), and (3) patients with peripheral arterial disease. The control group (n=409) consists of neighbors or friends of the patient, fulfilling the same age criteria and without a history of cardiovascular events. For the current study, we included white individuals only.

The study was approved by the medical research board at Erasmus University Medical Center, and written informed consent was obtained from all participants at inclusion.

Blood Sampling

Blood was drawn 1 to 3 months after the ischemic event by venipuncture in the antecubital vein using Vacutainer system (Becton-Dickinson, Plymouth, United Kingdom). Blood for coagulation measurements was collected in 3.2% trisodium citrate (9:1 vol/vol). Citrated blood was centrifuged within 1 hour at 2000g for 10 minutes at 4°C. Plasma was additionally centrifuged at 20 000g for 10 minutes at 4°C and stored in aliquots at −80°C. For DNA isolation, blood was collected in tubes containing ethylene diaminetetraacetic acid (EDTA; Beckon-Dickinson), and genomic DNA was isolated according to standard salting-out procedures and stored at 4°C for genetic analysis.

Laboratory Measurements

VWF antigen (VWF:Ag) was determined with an in-house ELISA with polyclonal rabbit antihuman VWF antibodies and horseradish peroxidase–conjugated antihuman VWF antibodies (DakoCytomation, Glostrup, Denmark) for catching and tagging, respectively. VWF collagen binding (VWF:CB) was measured with an in-house ELISA using type I collagen (Sigma, St Louis, Mo) for catching and horseradish peroxidase–conjugated antihuman VWF antibodies for tagging. The intra-assay variation coefficients of VWF:Ag and VWF:CB were 5.7% and 5.9%, respectively.

Genotyping

The STXBP5 gene spans 182 kb and is located in the q24 region of chromosome 6. The STX2 gene spans 50 kb and is located in the q24.3 region of chromosome 12. We obtained data from the International HapMap project (phase II November 2008, http://www.hapmap.org) on the linkage disequilibrium pattern and selected haplotype-tagging single-nucleotide polymorphisms (ht-SNPs) using Haplovie software (version 3.11; www.broad.mit.edu/mpg/haplovie/index.php). For both genes, blocks of haplotypes with a frequency of ≥0.03 were defined to select these ht-SNPs. We took potential functionality into consideration by preferentially selecting

| Table 1. ATTAC Population Baseline Characteristics |
|-----------------|-----------------|-----------------|-----------------|
| Demographics    | Cases (n=463)    | Control Subjects (n=409) | P Value         |
| Sex (% men)     | 188 (41%)       | 149 (36%)        | <0.0001         |
| Age, y          | 43.1±6.7        | 39.3±7.7         | <0.0001         |
| Diagnosis       |                 |                 |                 |
| UAP/AMI         | 271 (59%)       |                 |                 |
| TIA/IS          | 148 (32%)       |                 |                 |
| Peripheral arterial disease | 44 (9%) |                 |                 |
| Risk factors    |                 |                 |                 |
| Positive family history (%) | 280 (61%) | 129 (32%) | <0.0001 |
| Body mass index, kg/m² | 26.6±4.7 | 25.5±4.3 | <0.0001 |
| Hypertension (%) | 136 (29%) | 24 (6%)   | <0.0001         |
| Diabetes (%)    | 39 (8%)         | 3 (1%)          | <0.0001         |
| Statin use (%)  | 372 (81%)       | 5 (1%)          | <0.0001         |
| Current smoker (%) | 187 (41%) | 92 (23%) | <0.0001 |
| AB0 blood group |                 |                 |                 |
| O (%)           | 202 (44%)       | 186 (45%)       |                 |
| Non-O (%)       | 257 (56%)       | 123 (55%)       |                 |

Data are presented as mean±SD or percentage for categorical variables. UAP indicates unstable angina pectoris; AMI, acute myocardial infarction.
nonsynonymous ht-SNPs or SNPs that are located in known regulatory elements. In this study, we considered only SNPs that were present in a white population. We selected 6 ht-SNPs in STXBP5 and 3 ht-SNPs in STX2, which were genotyped using Custom TaqMan Genotyping Assays (Applied Biosystems, Foster City, Calif). The nucleotide sequences of the primers and probes used for the assay are available on request. End point fluorescence was measured on the ABI 7900HT instrument (Applied Biosystems). Genotyping was successful for each SNP in on average 96% of all subjects. Baseline characteristics of missing individuals were similar to those who were genotyped successfully.

Statistical Analysis
Allele frequencies were calculated by genotype counting. For each SNP, the deviation from the Hardy-Weinberg equilibrium was tested in control subjects by means of a $\chi^2$ test with 1 degree of freedom. The data of VWF:Ag and VWF:CB levels are approximately normally distributed and presented as mean and standard deviation. We used linear regression analysis with an additive genetic model, adjusted for age, sex, and ABO blood group (data are shown as unstandardized $\beta$-coefficients representing the change in VWF:Ag or VWF:CB per minor allele with a 95% confidence interval). The relative risks of arterial thrombosis for all polymorphisms were assessed by means of a logistic regression analysis using additive genetic models adjusted for age, sex, and ABO blood group (data are shown as odds ratios representing the increase in risk per minor allele with a 95% confidence interval).

Statistical analyses were performed with SPSS for Windows, version 17.0 (SPSS Inc, Chicago, Ill). A 2-sided value of $P<0.05$ was considered statistically significant.

Results

Baseline Characteristics
We included 463 cases and 406 control subjects of white origin, of which 188 (41%) in the arterial thrombosis group and 149 (36%) in the control group were men (Table 1). Mean age was 43.1±6.7 years in patients and 39.3±7.7 years in control subjects. The arterial thrombosis group consisted of 271 (59%) patients with either acute myocardial infarction or unstable angina pectoris, 148 (32%) cases with either IS or TIA, and 44 (9%) cases with peripheral arterial disease. As expected, the prevalence of known classic cardiovascular risk factors, including positive family history, high body mass index, hypertension, diabetes, statin use, and current smoking, was significantly higher in patients than in control subjects (Table 1). The distribution of ABO blood group was similar in cases and control subjects ($P$=0.66).

Mean levels of VWF:Ag and VWF:CB were significantly higher in cases (mean±SD, 1.28±0.54 IU/mL and 1.40±0.57 IU/mL, respectively) than in control subjects (1.09±0.37 IU/mL, $P<0.0001$, and 1.25±0.42 IU/mL, $P<0.0001$, respectively). The allele frequency distributions of all polymorphisms in control subjects did not deviate from Hardy-Weinberg equilibrium.

Genetic Variation and VWF Antigen Levels
In patients, 2 ht-SNPs of STXBP5 showed an association with VWF:Ag: rs9399599, which is located in intron 25, and rs1039084, which is a missense mutation that encodes an amino acid substitution of asparagine into serine at position 436 (Table 2). Both SNPs are in high linkage disequilibrium with rs9390459, which had the highest genome-wide signific-

<table>
<thead>
<tr>
<th>Gene</th>
<th>No. Allele</th>
<th>A Allele MAF</th>
<th>VWF:Ag</th>
<th>$\beta$ (95% CI)</th>
<th>P</th>
<th>VWF:CB</th>
<th>$\beta$ (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>STXBP5</td>
<td>rs9399599</td>
<td>rA &gt; A &gt; G</td>
<td>0.45</td>
<td>-0.05 [-0.08, -0.02]</td>
<td>0.06</td>
<td>-0.01 [-0.11, 0.09]</td>
<td>0.90</td>
<td>0.02 [-0.02, 0.06]</td>
</tr>
<tr>
<td></td>
<td>rs1039084</td>
<td>G-A &gt; G-T&gt; T</td>
<td>0.41</td>
<td>-0.03 [-0.09, 0.03]</td>
<td>0.55</td>
<td>0.01 [-0.04, 0.05]</td>
<td>0.66</td>
<td>0.01 [-0.01, 0.02]</td>
</tr>
<tr>
<td></td>
<td>rs9828898</td>
<td>G-A &gt; G-C &gt; C</td>
<td>0.47</td>
<td>-0.02 [-0.11, 0.07]</td>
<td>0.42</td>
<td>0.01 [-0.02, 0.04]</td>
<td>0.42</td>
<td>0.02 [-0.02, 0.05]</td>
</tr>
<tr>
<td></td>
<td>rs9828978</td>
<td>G-A &gt; G-C &gt; C</td>
<td>0.37</td>
<td>-0.02 [-0.07, 0.03]</td>
<td>0.42</td>
<td>0.01 [-0.02, 0.04]</td>
<td>0.42</td>
<td>0.02 [-0.02, 0.05]</td>
</tr>
<tr>
<td></td>
<td>rs1166115</td>
<td>G-A &gt; G-C &gt; C</td>
<td>0.28</td>
<td>0.02 [0.05, 0.09]</td>
<td>0.002</td>
<td>0.00 [-0.06, 0.08]</td>
<td>0.30</td>
<td>0.02 [-0.06, 0.11]</td>
</tr>
</tbody>
</table>

Linear regression analysis with an additive genetic model, adjusted for age, sex, and ABO blood group. $P$-value is the probability that the null hypothesis, $\beta$-coefficient is zero after adjustment, is true. Data are represented as
Table 3. Association Between STXBP5 and STX2 Polymorphisms and the Risk of Arterial Thrombosis

<table>
<thead>
<tr>
<th>Gene</th>
<th>rs No.</th>
<th>Allele</th>
<th>Total Group (OR [95% CI])</th>
<th>CHD Subgroup (OR [95% CI])</th>
<th>IS/TIA Subgroup (OR [95% CI])</th>
</tr>
</thead>
<tbody>
<tr>
<td>STXBP5</td>
<td>rs9399599</td>
<td>T&gt;A</td>
<td>1.11 [0.91, 1.34]</td>
<td>1.12 [0.88, 1.42]</td>
<td>1.04 [0.79, 1.37]</td>
</tr>
<tr>
<td></td>
<td>rs1039084</td>
<td>G&gt;A</td>
<td>0.99 [0.81, 1.21]</td>
<td>1.02 [0.80, 1.29]</td>
<td>0.87 [0.66, 1.14]</td>
</tr>
<tr>
<td></td>
<td>rs693850</td>
<td>T&gt;C</td>
<td>1.02 [0.79, 1.31]</td>
<td>0.93 [0.68, 1.26]</td>
<td>1.04 [0.74, 1.45]</td>
</tr>
<tr>
<td></td>
<td>rs497704</td>
<td>G&gt;A</td>
<td>0.88 [0.49, 1.56]</td>
<td>0.82 [0.40, 1.66]</td>
<td>0.89 [0.41, 1.96]</td>
</tr>
<tr>
<td></td>
<td>rs127173905</td>
<td>C&gt;T</td>
<td>0.99 [0.79, 1.25]</td>
<td>0.96 [0.73, 1.26]</td>
<td>1.13 [0.84, 1.54]</td>
</tr>
<tr>
<td>STX2</td>
<td>rs1236</td>
<td>T&gt;A</td>
<td>0.72 [0.59, 0.89]</td>
<td>0.64 [0.49, 0.82]</td>
<td>0.76 [0.57, 1.00]</td>
</tr>
<tr>
<td></td>
<td>rs7978987</td>
<td>G&gt;A</td>
<td>0.81 [0.65, 1.00]</td>
<td>0.70 [0.54, 0.91]</td>
<td>0.81 [0.60, 1.10]</td>
</tr>
<tr>
<td></td>
<td>rs11061158</td>
<td>G&gt;T</td>
<td>0.69 [0.55, 0.88]</td>
<td>0.67 [0.50, 0.89]</td>
<td>0.72 [0.52, 0.99]</td>
</tr>
</tbody>
</table>

Logistic regression analysis with an additive genetic model adjusted for age, sex, and blood group. Data are represented as the increase in odds ratio (OR) per minor allele with a 95% confidence interval (CI).

Risk of Arterial Thrombosis

In the total population, rs1236 and rs11061158 of STX2 had a strong and significant relationship with the risk of arterial thrombosis, independent of ABO blood group and after correction for multiple testing (Table 3). The minor alleles of rs1236 and rs11061158 had a protective effect on the occurrence of arterial thrombosis (Figure). Interestingly, in the subgroup analysis of patients with CHD, the minor alleles of the 3 polymorphisms that cover the entire genetic variation of STX2 were associated with a decreased risk of CHD. In the subgroup of patients with IS or TIA, this effect was less apparent. Genetic variants in the STXBP5 gene were not associated with the risk of arterial thrombosis.

Discussion

In the present study, we show that genetic variations in STXBP5 and STX2 affect both VWF concentration and VWF collagen-binding activity in a population of young individuals with a first event of arterial thrombosis. Whereas the minor alleles of rs9399599 and rs1039084 in STXBP5 were associated with lower VWF:Ag and VWF:CB levels, the minor allele of rs7978987 in STX2 was associated with higher VWF:Ag and VWF:CB levels. These findings are a further exploration of the results of the meta-analysis of the CHARGE consortium. Interestingly, the effects of the minor

VWF Collagen-Binding Activity

VWF collagen-binding activity (VWF:CB) levels are displayed in Table 2 for cases and control subjects, separately. Interestingly, all STXBP5 polymorphisms that were associated with VWF:Ag showed similar associations with lower VWF:CB levels in patients. None of these SNPs were associated with the VWF:CB/VWF:Ag ratio (data not shown). By contrast, rs7978987 of STX2 was associated with higher VWF:CB levels and VWF:CB/VWF:Ag ratio (β=0.18 [0.01, 0.36], P=0.03). In control subjects, VWF:CB is not influenced by genetic variability in STXBP5 and STX2.
alleles on VWF concentration are similar to those demonstrated by the CHARGE consortium (β-coefficient, −0.048 for rs9390459 and 0.033 for rs7978987 per dosage allele). As well as confirming the association with VWF plasma levels, we also found an association between these genetic variants and VWF activity. In addition, rs7978987 in STX2 was associated with a higher VWF:CB/VWF:Ag ratio, which indicates that the secreted VWF molecules are functionally more active. Because ultralarge VWF multimers, which have the most hemostatic potential, are stored in WPB and α-granules, this finding met our expectations.

It is noteworthy that the relationship between genetic variability in STXBP5 and STX2 and VWF plasma levels was seen especially in patients with arterial thrombosis and that this relationship was less clear in healthy control subjects. In healthy individuals, VWF plasma levels are determined mainly by the activity of the constitutive pathway, because the endothelium is not triggered to release the VWF molecules. Because STX2 and STXBP5 encode proteins that may be involved in the regulated secretion pathway of VWF molecules, which is only stimulated after endothelial cell activation, one would expect to find an effect of these polymorphisms not in healthy subjects, but particularly in patients who have CVD. In addition, it is known that at a higher age more atherosclerosis is present, which brings the endothelium into a mild state of activation and leads to chronic low-level stimulation of the regulatory pathway of VWF release. This may explain why a relationship between VWF:Ag levels and genetic polymorphisms in STXBP and STX2 was found in the older (mean age, 60.0 years) but relatively healthy subjects of the CHARGE cohorts.

In the CHD subgroup, the associations between polymorphisms and VWF levels seem more pronounced than in the IS/TIA subgroup. Because IS is a heterogeneous phenotype, caused by multiple and sometimes unknown underlying factors, the contribution of genetic variation is difficult to study. Although heterogeneity might be reduced by analysis of etiologic subtype, such analysis was not possible in our ATTAC study because of the limited number of patients in the subgroup of stroke.17

Unexpectedly, the minor alleles of the polymorphisms in STX2 were strongly associated with a decreased risk of arterial thrombosis. This effect appeared to be strongest in the CHD subgroup, where the minor alleles of all 3 SNPs gave a protective effect. Yet, the precise mechanisms by which these polymorphisms influence the risk of arterial thrombosis is unclear, because the minor alleles of the polymorphisms in STX2 tended to be associated with higher VWF plasma levels. As well as VWF molecules, WPBs and α-granules contain numerous other substances, such as P-selectin, angiopoietin-2, osteoprotegerin, and eotaxin.13 It has also been hypothesized that not all components of the storage granules must be present at all times per se and can even be segregated into different subgroups of substances.18 We therefore propose that the risk of CVD is reduced not by VWF itself but by other substances that are secreted by the WPBs.

In conclusion, this study shows that genetic variations in STXBP5 and STX2 affect VWF antigen plasma levels and VWF collagen binding activity in young patients with pre-mature arterial thrombosis. It remains unclear whether altered VWF levels are caused by dysfunction of the VWF secretion pathway or by another unknown mechanism. We also observed that genetic variability in STX2 is associated with the risk of arterial thrombosis in young individuals. Future research is required to study the functionality of the polymorphisms in more detail and to improve our understanding of the possible importance of the secretion pathway of VWF in the pathogenesis of arterial thrombosis.

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Disclosures

None.

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Disclosures

None.


**CLINICAL PERSPECTIVE**

It has been well established that elevated von Willebrand Factor (VWF) plasma levels are associated with an increased risk of cardiovascular disease. A meta-analysis of genomewide association studies on VWF identified novel candidate genes, that is, syntatix-binding protein 5 (STXBP5) and syntatix 2 (STX2). STX2 is a binding substrate for STXBP5 and is a member of the soluble N-ethylmaleimide-sensitive factor Attachment protein Receptor (SNARE) protein family. These proteins drive vesicle exocytosis by fusion of granules and target membranes, which may be involved in the secretion pathway of VWF multimers. We investigated whether VWF antigen levels (VWF:Ag), VWF collagen-binding activity (VWF:CB), and the risk of arterial thrombosis are affected by common genetic variations in these genes. In a case-control study 463 young white subjects (men ≤45 years of age and women ≤55 years of age), who were included 1 to 3 months after a first event of arterial thrombosis, and 406 control subjects, we showed that common genetic variations in STXBP5 and STX2 affect both VWF concentration and activity in young individuals with premature arterial thrombosis. We also demonstrated that the minor alleles of genetic polymorphisms in STX2 are associated with a decreased risk of arterial thrombosis. However, this alteration of the risk of arterial thrombosis was not explained by variation in VWF plasma levels. Our findings form a basis for future research on the role of SNARE proteins in the secretion pathway of VWF multimers and on their possible importance in the development of arterial thrombosis.
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