Genetic variation associated with plasma von Willebrand factor levels and the risk of incident venous thrombosis

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In a recent genome-wide association study, variants in 8 genes were associated with VWF level, a risk factor for venous thrombosis (VT). In an independent, population-based, case-control study of incident VT, we tested hypotheses that variants in these genes would be associated with risk. Cases were 656 women who experienced an incident VT, and controls comprised 710 women without a history of VT. DNA was obtained from whole blood. Logistic regression was used to test associations between incident VT and single nucleotide polymorphisms (SNPs) in 7 genes not previously shown to be associated with VT. Associations with \( P < .05 \) were candidates for replication in an independent case-control study of VT in both sexes. Two of the 7 SNPs tested yielded \( P < .05 \): rs1039084 (\( P = .005 \)) in \( STXB5 \), a novel candidate gene for VT, and rs1063856 (\( P = .04 \)) in VWF, a gene whose protein level is associated with VT risk. Association results for the remaining 5 variants in \( SCAR5, STAB2, STXB, TC2N, \) and \( CLEC4M \) were not significant. Both \( STXB5 \) and VWF findings were replicated successfully. Variation in genes associated with VWF levels in the genome-wide association study was found to be independently associated with incident VT. (Blood. 2011;117(22):6007-6011)

Introduction

Elevated plasma levels of factor VIII (FVIII) and von Willebrand factor (VWF) are risk factors for venous thrombosis (VT).1,2 Genome-wide association studies of intermediate phenotypes such as FVIII and VWF may also identify genetic predictors of clinical events such as VT. The Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium recently identified 8 genes in which nucleotide variation was associated with VWF antigen (VWF:Ag) levels and 5 genes in which variation was associated with FVIII activity (FVIIIc) levels among ~23,000 European-ancestry participants in 5 studies: (1) the Atherosclerosis Risk in Communities Study, (2) the Cardiovascular Health Study, (3) the Framingham Heart Study, (4) the Rotterdam Study, and (5) the British 1958 Birth Cohort.3-12 For VWF:Ag levels, 2 of the 8 associations were among genes known to be associated with plasma levels of VWF:Ag, \( ABO \) and VWF, the VWF gene. Among the 6 genes not known to be associated with VWF levels, syntaxin-binding protein 5 (\( STXB5 \)), scavenger receptor class A member 5 (\( SCAR5 \)), stabilin 2 (\( STAB2 \)), syntaxin 2 (\( STX2 \)), tandem C2 domains nuclear (\( TC2N \)), and C-type lectin domain family 4 member M (\( CLEC4M \)), associations with VWF:Ag levels were replicated for 5 genes (all except \( STX2 \)) in independent populations.3 For FVIIIc levels, all 5 genes were a subset of the VWF:Ag level genes: \( STBP5, SCAR5, ABO, VWF, \) and \( STAB2 \). Among the 8 genes, only variation in \( ABO \) has been shown previously to be associated with the risk of VT. We hypothesized that variation in the other 7 genes associated with VWF:Ag levels would also be associated with VT. We tested these hypotheses in a population-based, case-control study of incident VT and attempted replication of the significant associations in an independent case-control study of VT.

Methods

Setting and design

The setting for this observational study was Group Health, a large, integrated health-care system in western Washington state. These analyses were part of a series of ongoing, population-based, case-control studies known as the Heart and Vascular Health (HVH) studies, which include outcomes of myocardial infarction, stroke, VT, and atrial fibrillation.13-17 For these analyses, we included women who had experienced an incident VT and matched controls. This study was approved by the Group Health Human Subjects Review Committee, and all study participants provided written informed consent in accordance with the Declaration of Helsinki.


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Study population

Subjects were women 40–89 years of age who were Group Health members. Case subjects suffered an incident VT—either a deep vein thrombosis (DVT) or pulmonary embolism (PE)—between January 1, 1995, and December 31, 2006, and were alive at the time of study recruitment. The date of the event served as the index date. Control subjects were a random sample of Group Health members who comprised a pool of control subjects shared by several case-control studies of cardiovascular disease conducted at Group Health. Control subjects were frequency matched by age (within a decade), treated hypertension status, menopausal status, and index year of identification. The index date for control subjects was a randomly chosen date within the calendar year from which they were selected as a control. For these analyses, which used genotype data collected from genome-wide markers (see “Genetic variation and genotyping”), we matched controls to cases approximately 1 to 1.

Case subjects were identified using ICD-9 codes from Group Health and non-Group Health hospitalizations for VT. For nonhospitalized VT events, we screened Group Health pharmacy records to identify women who were dispensed a prescription for a low-molecular weight heparin, the required drug in the clinical pathway established for outpatient treatment of DVT at Group Health. Trained medical record abstractors reviewed the medical records of all potential cases to verify the event. Records of imaging tests were used to confirm the presence of a DVT or a PE.

Measures

Demographic and clinical measures and blood collection. Demographic and health-status information was obtained by review of the entire Group Health ambulatory medical record up to the index date. Medical records included notes from primary care and specialty physician visits, emergency department visit notes, discharge summaries, and laboratory and diagnostic test reports. Information was collected on treated hypertension and menopausal status. Menopause was defined by the cessation of ovarian function that occurred naturally or through a bilateral oophorectomy. If menopausal status was not explicitly stated in the record, women 55 years of age and older were considered postmenopausal. Information was collected on most recent weight and height and comorbid conditions before age 100. Menopausal status was not explicitly stated in the record, women 55 years of age and older were considered postmenopausal. Information was collected on most recent weight and height and comorbid conditions before the index date. A telephone interview collected self-reported race information. A blood sample was collected from each consenting subject and DNA extracted from white blood cells using standard procedures.

Genetic variation and genotyping. In the CHARGE consortium plasma VWF:Ag levels analyses, the single nucleotide polymorphism (SNP) that yielded the smallest P value for a particular genetic locus was selected as the marker variant. For the VWF phenotype, all of the locus markers were within genes: rs9390459 in ABO markers were within genes: rs9390459 in selected as the marker variant. For the VWF phenotype, all of the locus (SNP) that yielded the smallest

Table 1. Characteristics of participants in the HVH study

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Case</th>
<th>Control</th>
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<tbody>
<tr>
<td>Participants, n</td>
<td>656</td>
<td>710</td>
</tr>
<tr>
<td>Mean age, y (SD)</td>
<td>64.7 (12.1)</td>
<td>67.7 (9.3)</td>
</tr>
<tr>
<td>Female sex, %</td>
<td>100</td>
<td>100</td>
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<tr>
<td>European ancestry, %</td>
<td>100</td>
<td>100</td>
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<tr>
<td>BMI, kg/m² (SD)</td>
<td>31.8 (9.4)</td>
<td>29.0 (6.6)</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>7.8</td>
<td>10.7</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>7.8</td>
<td>7.0</td>
</tr>
<tr>
<td>Current estrogen use, %</td>
<td>30.2</td>
<td>31.4</td>
</tr>
<tr>
<td>Factor V Leiden carriers, %</td>
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<td>4.1</td>
</tr>
<tr>
<td>Incident VT events, %</td>
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<td></td>
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<tr>
<td>PE with or without DVT</td>
<td>48</td>
<td>0</td>
</tr>
<tr>
<td>DVT only</td>
<td>52</td>
<td>0</td>
</tr>
</tbody>
</table>

BMI indicates body mass index.

Analyses

Hypothesis testing. Logistic regression was used to test the association between the number of copies of each SNP variant (an additive genetic model) and incident VT, adjusting for the study design variables of age (both indicators by decade and continuous), hypertension status, menopausal status, and index year. The relative risk associated with each additional copy of the minor allele was estimated using the odds ratio (OR) approximation, and 95% confidence intervals (CIs) around these estimates were also calculated. Analyses were restricted to subjects who self-reported white race.

Replication. Variants associated with incident VT in the Group Health study (P < .05) were examined for replication in the Leiden Multiple Environmental and Genetic Assessment (MEGA) study. Briefly, MEGA recruited consecutive patients 18–70 years of age with a first diagnosis of DVT or PE from 6 anticoagulation clinics in The Netherlands between March 1999 and September 2004. Participants of participating patients were invited to part as control participants. Additional control participants were recruited from the same geographic region by a random-digit dialing method, and were frequency matched to patients by age and sex. All participants completed a questionnaire on risk factors for VT, provided a blood or buccal swab sample for DNA extraction, and provided written informed consent. The MEGA study was approved by the Medical Ethics Committee of the Leiden University Medical Center, Leiden, The Netherlands. A candidate variant was considered replicated if the direction of the association in logistic-regression additive genetic models was the same and the P values were imputed: rs2726953 (imputation quality score of 0.89), rs4981022 (0.40), rs7978987 (0.82), rs10133762 (1.00), and rs868875 (0.17).

Secondary analyses were performed on associated SNPs that replicated. We meta-analyzed relative risk estimates from the 2 populations using inverse-variance weighted meta-analysis. For the additive genetic models, standard meta-analysis methods were applied. For the models in which the risk was estimated separately for heterozygous and homozygous carriers of the minor allele, the vector of regression coefficients was meta-analyzed using multivariate inverse-variance weighted analysis, which takes into account the correlation between the individual regression coefficient estimates. We also calculated the population-attributable risk percentage of each variant, using the prevalence of genetic variants in the combined control populations and the relative-risk estimate from the meta-analysis.

Results

Genome-wide markers were available for 710 controls and 656 nonfatal incident VT cases in the HVH study. Characteristics of the cases and controls are provided in Table 1.

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Among the 7 variants tested for associations with VT, 2 yielded \( P < .05 \) (Table 2). The rs1039084 SNP (A → G) that produces a nonsynonymous substitution (N436S) in exon 23 of \( STXBP5 \) was associated with a decreased risk of VT (OR: 0.78 per allele; 95% CI: 0.65-0.93; \( P = .005 \)), which is in agreement with the CHARGE VWF phenotype findings that the variant was associated with lower plasma VWF:Ag levels. The minor allele frequency for this variant, G, was 0.46, with 48% of the population carrying 1 copy and 21% carrying 2 copies. The rs1063856 SNP (A → G) that produces a nonsynonymous substitution (T789A) in exon 18 of VWF was associated with an increased risk of VT (OR: 1.20 per allele; 95% CI: 1.01-1.42; \( P = .04 \)), which is in agreement with the CHARGE VWF phenotype findings that this variant was associated with elevated plasma VWF:Ag levels. The minor allele frequency for the variant was 0.37, with 47% of the population carrying 1 copy and 14% carrying 2 copies. The synonymous variants in both the VWF and \( STXBP5 \) genes were also associated with VT (OR: 0.79; 95% CI: 0.67-0.93; and OR: 1.20; 95% CI: 1.01-1.42, respectively). For both nonsynonymous variants, \( ABO \) O/non-O genotype (rs687621) did not modify the association with VT risk. The remaining 5 variants in \( SCARA5, STAB2, STX2, TC2N, \) and \( CLEC4M \) were not significantly associated with risk of VT. ORs were close to 1.0, and only variants in \( STAB2, STX2, \) and \( TC2N \) had estimates with a direction in agreement with the differences seen with plasma VWF:Ag levels.

Replication in the MEGA sample

Using the 4467 case and 4859 control subjects in MEGA, we attempted replication of the HVH findings by testing the association between the 2 SNPs that produce nonsynonymous substitutions in \( STXBP5 \) and VWF and incident VT. Both replications were successful: rs1039084 in \( STXBP5 \) (OR: 0.91 per allele; 95% CI: 0.85-0.97; 1-sided \( P \) value = .001); and rs1063856 in VWF (OR: 1.15 per allele; 95% CI: 1.08-1.23; 1-sided \( P \) value < .001).

Combined hypothesis testing and replication samples

Table 3 presents the additive and allele-specific risk associations for both variants in each study individually and from the meta-analysis. The meta-analyzed OR estimate under an additive model was 0.90 per allele (95% CI: 0.82-0.98) for the \( STXBP5 \) rs1039084 variant; 70% of the control population carried 1 or 2 copies. The relative-risk estimates for heterozygous and homozygous carriers of rs1039084 were of similar magnitudes, so a dominant model of risk was fit: OR = 0.82 for carriers versus noncarriers (95% CI: 0.72-0.93). Because this variant was protective against VT, we calculated a population-attributable risk among noncarriers of the variant (30%) and used the inverse of the relative risk estimate (1/0.82 = 1.22); the estimated population-attributable risk for noncarriers of \( STXBP5 \) rs1039084 G-allele was 6.1%. For the VWF rs1063856 variant, the meta-analyzed OR estimate was 1.16 per allele (95% CI: 1.06-1.26); 56% of the control population carried 1 or 2 copies. The estimated population-attributable risk was 8.1% under the additive model. When a dominant model was fit, the OR was 1.24 for carriers versus noncarriers of the G allele (95% CI: 1.10-1.40) and the estimated population-attributable risk was 11.7%.

Discussion

We have demonstrated in the present study that genetic variants associated with the intermediate phenotype of plasma VWF:Ag levels are also associated with the risk of incident VT. Specifically, variants producing nonsynonymous amino acid substitutions in \( STXBP5 \) and VWF, which were among those most strongly associated with VWF:Ag levels in a previous report, were also risk factors for incident VT risk in women 40-89 years of age. These associations were replicated in a large, case-control study of VT in men and women 30-70 years of age.

For both the \( STXBP5 \) and VWF variants, the direction of the association with VT, either an increase or decrease in VT risk, reflected the observed difference in VWF:Ag levels seen in the previous report. The magnitudes of the genetic associations were modest in both the additive and dominant models, but the prevalences of the variant alleles were high enough that population-attributable risk estimates were not negligible. For example, the population-attributable risk for the VWF rs1063856 variant (11%) was approximately three-fourths of the estimated population attributable risk of 15% for the factor V Leiden variant (G → A at position 1691; rs6025), which has a 4.5-fold increase in risk and a population prevalence of 0.05 for carriers of the A allele.

\( STXBP5 \) and VT risk

Apart from the initial discovery of the association of \( STXBP5 \) with plasma levels of VWF:Ag, this protein has no known relationship with the coagulation system. The gene product has not been described, and little is known about the potential protein structural or functional changes at amino acid 436 when N is substituted for S.
Weibel-Palade body exocytosis. We are not aware of any previous tally, murine knock-down of syntaxin 4 resulted in inhibition of which, when secreted, increases plasma VWF levels. Experimen-
tally, murine knock-down of syntaxin 4 resulted in inhibition of VWF the VWF molecule transports or releases FVIII into circula-
tion.

VWF and VT risk

Increased levels of plasma VWF, the carrier of coagulation FVIII, is a known risk factor for VT.1,2 In the present study, we have identified the first variant in VWF that is associated with both VWF:Ag levels and higher risk of VT. The candidate variant (rs1063856) in exon 18 changes the amino acid from T to A at position 789. This variant was associated with higher levels of plasma VWF and an increase in VT risk. This site encodes for the characteristic of von Willebrand disease type 2N.24,25 It is possible or how this substitution decreases levels of plasma VWF, a risk factor for VT. In these analyses, we also investigated a variant in STX2, the binding substrate for STXB5, which was not significantly associated with VT. STXB4, another soluble NSF attachment protein receptor (SNARE) protein in the same family as STXB5, plays an intermediary role in the exocytosis of Weibel-Palade bodies from endothelial cells by docking intercellular Weibel-Palade bodies to the plasma membrane and facilitating extracellular release.22 VWF is the main constituent of the bodies, which, when secreted, increases plasma VWF levels. Experimentally, murine knock-down of syntaxin 4 resulted in inhibition of Weibel-Palade body exocytosis.23 We are not aware of any previous studies showing that STXB5 is involved in Weibel-Palade body exocytosis or VWF secretion.

Limitations

Although we detected statistically significant signals in the STXB5 and VWF genes, our power to do so was small; we estimated that it was no more than 25% for either gene association based on meta-analyzed, relative-risk estimates. If the magnitude of a variant’s association with VT is proportional to its effect on plasma VWF:Ag levels, our power to detect VT associations in the other 5 genes considered would be poor.3 Further, compared with variation in the STXB5 and VWF genes, the SNPs in the other 5 genes were intronic and may be weaker proxies for causal variants lying in exons or regulatory regions.3 The poor imputation quality of the STAB2 and CLEC4M variants further diluted statistical power. The discovery and the replication case-control studies were retrospective designs, so fatal cases of PE were not included. In addition, discovery and replication work was conducted in subjects of European ancestry and may not generalize to other ancestries.

Summary

We have shown that 2 nonsynonymous amino acid substitutions in STXB5 and VWF that were previously shown to be associated with plasma VWF were associated with VT incidence in 2 large, population-based, case-control studies. Although plasma levels of VWF are associated with VT risk, this is the first variant in VWF shown to be associated with VT risk. STXB5 is a novel candidate gene for VT and further study of the biology of its protein product is warranted.

Table 3. Replicated variants and their association with incident VT in the HVH and MEGA studies and in a meta-analysis

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<th>SNP</th>
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<th>Model</th>
<th>HVH</th>
<th>MEGA</th>
<th>Meta-analysis</th>
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<tbody>
<tr>
<td>rs1039084</td>
<td>STXB5 (N436S)</td>
<td>Additive</td>
<td>0.78 (0.65-0.93)</td>
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<td></td>
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<td>Noncarriers</td>
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<td></td>
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<td></td>
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<td>Homozygotes</td>
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<td></td>
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<td>1.23 (1.13-1.34)</td>
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<td></td>
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<td>Homozygotes</td>
<td>1.45 (1.00-2.07)</td>
<td>1.25 (1.10-1.43)</td>
<td>1.28 (1.12-1.45)</td>
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VT indicates venous thrombosis; HVH, Heart and Vascular Health; MEGA, Multiple Environmental and Genetic Assessment; and OR, odds ratio.

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Acknowledgments

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Authorship

Contribution: N.L.S., S.R.H., B.M.P., and F.R.R. designed re-

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References


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