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 STXBPS5, 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, STX2, T2CN, and CLEC4M were not significant. Both STXBPS5 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.1-12 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 (STXBPS5), scavenger receptor class A member 5 (SCAR5), stabilin 2 (STAB2), syntaxin 2 (STX2), tandem C2 domains nuclear (T2CN), 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.
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 calendar 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 as 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 the index date. A telephone interview collected self-reported race information, completed a questionnaire on risk factors for VT, and were frequency matched to patients by age and sex. All participants were also calculated. Analyses were restricted to subjects who self-reported white race.

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 variants were within genes: rs9390459 in STXB5, rs2726953 in SCARAT, rs687621 in ABO, rs1063857 in VWF, rs4981022 in STAB2, rs7978987 in STX2, rs10133762 in TC2N, and rs868875 in CLEC4M. Because the STXB5 and VWF variants were exonic and associated with synonymous substitutions, we also identified and prioritized for testing in this study a non-synonymous variant in high linkage disequilibrium with the candidate SNP. For rs9390459 in STXB5, we identified rs1039084 (r² = 0.91 with rs9390459; N (Asn) to S (Ser) at amino acid position 436. For rs1063857 in VWF, we identified rs1063856 (r² = 1.0 with rs1063857). T (Thr) to A (Ala) at amino acid position 789. Both variants were strongly associated with VWF:Ag levels in the CHARGE discovery sample (P = 6.9 × 10⁻²² and 3.4 × 10⁻²², respectively). The rs687621 variant in ABO distinguished O blood groups from non-O groups, and its association with VT has been shown previously.

Genotyping was performed using the Illumina 370CNV BeadChip system at the Genomics Resource Laboratory of Fred Hutchinson Cancer Research Center and at the General Clinical Research Center’s Phenotyping/Genotyping Laboratory at Cedars-Sinai. Genotypes were called using Illumina BeadStudio software, Version 3.3. Imputation was performed using BIMBAM with reference to HapMap CEU using release 22, build 36. An imputation quality score, the ratio of the observed to the expected variance of the genotype, was calculated for each SNP, and scores ranged from 1 (excellent) to 0 (poor). For this analysis, 5 of the 7 candidate SNPs were imputed: rs2726953 (imputation quality score of 0.89), rs4981022 (0.40), rs7978987 (0.82), rs10133762 (1.00), and rs868875 (0.17).

Table 1. Characteristics of participants in the HVH study

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Case</th>
<th>Control</th>
</tr>
</thead>
<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>
</tr>
<tr>
<td>European ancestry, %</td>
<td>100</td>
<td>100</td>
</tr>
<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>
<td>14.3</td>
<td>4.1</td>
</tr>
<tr>
<td>Incident VT events, %</td>
<td></td>
<td></td>
</tr>
<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. Partners of participating patients were invited to take 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 1-sided P value was < .05.

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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Table 2. Candidate variants and their association with incident VT in the HVH study

<table>
<thead>
<tr>
<th>CHR</th>
<th>SNP</th>
<th>Gene</th>
<th>Variant†</th>
<th>Substitution</th>
<th>P</th>
<th>MAF</th>
<th>OR† (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>rs1039084</td>
<td>STXB5 (exon)</td>
<td>A → G</td>
<td>N → S</td>
<td>0.052</td>
<td>0.46</td>
<td>0.78 (0.65-0.93)</td>
</tr>
<tr>
<td>8</td>
<td>rs7226953</td>
<td>SCARA5 (intron)</td>
<td>C → T</td>
<td>0.81</td>
<td>0.31</td>
<td>0.98 (0.81-1.18)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>rs687621</td>
<td>ABO (intron)</td>
<td>T → C</td>
<td>0.000024</td>
<td>0.34</td>
<td>1.52 (1.28-1.80)</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>rs1063856</td>
<td>VWF (exon)</td>
<td>A → G</td>
<td>T → A</td>
<td>0.36</td>
<td>0.37</td>
<td>1.20 (1.01-1.42)</td>
</tr>
<tr>
<td>12</td>
<td>rs4981022</td>
<td>STAB2 (intron)</td>
<td>T → C</td>
<td>.83</td>
<td>0.37</td>
<td>0.97 (0.74-1.27)</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>rs7978987</td>
<td>STX2 (intron)</td>
<td>G → A</td>
<td>.94</td>
<td>0.32</td>
<td>1.01 (0.83-1.22)</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>rs10133762</td>
<td>TC2N (intron)</td>
<td>G → T</td>
<td>.81</td>
<td>0.43</td>
<td>1.02 (0.87-1.20)</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>rs688787</td>
<td>CLEC4M (3’ UTR)</td>
<td>A → G</td>
<td>.77</td>
<td>0.23</td>
<td>1.07 (0.67-1.72)</td>
<td></td>
</tr>
</tbody>
</table>

VT indicates venous thrombosis; HVH, Heart and Vascular Health; CHR, chromosome; MAF, minor allele frequency; OR, odds ratio; and CI, confidence interval.
†Relative risk associated with each additional copy of the variant allele.

Hypothesis testing in the HVH study

Among the 7 variants tested for associations with VT, 2 yielded

\[ P < 0.05 \] (Table 2). The rs1039084 SNP (A → G) that produces a
nonsynonymous substitution (N343S) in exon 23 of STXB5 was

associated with a decreased risk of VT (OR: 0.79 per allele; 95% CI:
0.72-0.93; \( P = 0.005 \)), which is in agreement with the CHARGE

VWF phenotype findings that that variant was associated with

lower plasma VWF:Ag levels. The minor allele frequency for this

variant 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; \( P = 0.04 \)), which is in agreement with the

CHARGE VWF phenotype findings that this variant was associ-

ated 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 STXB5 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 associa-
tion between the 2 SNPs that produce nonsynonymous substitu-
tions in STXB5 and VWF and incident VT. Both replications

were successful: rs1039084 in STXB5 (OR: 0.91 per allele; 95% CI:
0.85-0.97; 1-sided \( P = 0.001 \)); and rs1063856 in VWF (OR:
1.15 per allele; 95% CI: 1.08-1.23; 1-sided \( P < 0.001 \)).

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 STXB5 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 STXB5 rs1039084 was 0.05 for carriers versus noncarriers (95% CI: 0.85-0.97 (0.74-1.27); 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

STXB5 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 STXB5 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 attribut-

able 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.

STXB5 and VT risk

Apart from the initial discovery of the association of STXB5 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

or functional changes at amino acid 436 when N is substituted for S

or functional changes at amino acid 436 when N is substituted for S

or functional changes at amino acid 436 when N is substituted for S
or how this substitution decreases levels of plasma VWF, a risk factor for VT. In these analyses, we also investigated a variant in \( \text{STX}2 \), the binding substrate for \( \text{STXBP5} \), which was not significantly associated with VT. \( \text{STXBP4} \), another soluble NSF attachment protein receptor (SNARE) protein in the same family as \( \text{STXBP5} \), 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. VWF is the main constituent of the bodies, which, when secreted, increases plasma VWF levels. Experimentally, murine knock-down of \( \text{STXBP5} \) demonstrated that the mutation at amino acid 789 increases the efficiency with which the VWF molecule transports or releases \( \text{FVIII} \) into circulation, thereby increasing the risk of VT. In these analyses, we have identified the first variant in \( \text{STXBP5} \) that is associated with both plasma 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 \( \text{C}^\text{D} \) domain, which is involved in binding of \( \text{FVIII} \). Rare missense mutations in the \( \text{C}^\text{D} \) part of \( \text{VWF} \) have been associated with normal or reduced levels of plasma VWF and low levels of \( \text{VWF} \) III, which is characteristic of von Willebrand disease type 2N. It is possible that the mutation at amino acid 789 increases the efficiency with which the VWF molecule transports or releases \( \text{FVIII} \) into circulation, thereby increasing the risk of VT.

**VWF and VT risk**

Increased levels of plasma VWF, the carrier of coagulation \( \text{FVIII} \), is a known risk factor for VT. In the present study, we have identified the first variant in \( \text{VWF} \) 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 \( \text{C}^\text{D} \) domain, which is involved in binding of \( \text{FVIII} \). Rare missense mutations in the \( \text{C}^\text{D} \) part of \( \text{VWF} \) have been associated with normal or reduced levels of plasma VWF and low levels of \( \text{VWF} \) III, which is characteristic of von Willebrand disease type 2N. It is possible that the mutation at amino acid 789 increases the efficiency with which the VWF molecule transports or releases \( \text{FVIII} \) into circulation, thereby increasing the risk of VT.

**Limitations**

Although we detected statistically significant signals in the \( \text{STXBP5} \) and \( \text{VWF} \) 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. Further, compared with variation in the \( \text{STXBP5} \) and \( \text{VWF} \) genes, the SNPs in the other 5 genes were intronic and may be weaker proxies for causal variants lying in exons or regulatory regions. The poor imputation quality of the \( \text{STAB2} \) and \( \text{CLEC4M} \) 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 \( \text{STXBP5} \) and \( \text{VWF} \) 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 \( \text{VWF} \) shown to be associated with VT risk. \( \text{STXBP5} \) is a novel candidate gene for VT and further study of the biology of its protein product is warranted.

**Acknowledgments**

The Heart and Vascular Health Study is supported by National Heart, Lung, and Blood Institute (National Institutes of Health, Bethesda, MD) grants HL43201, HL60739, HL68986, HL73410, HL74745, HL85251, and HL95080, and by a grant from the Leducq Foundation (Paris, France) for the development of Transatlantic Networks of Excellence in Cardiovascular Research. The Multiple Environmental and Genetic Assessment (MEGA) study is funded by the Netherlands Heart Foundation (NHS 98.113), the Dutch Cancer Foundation (RUL 99/1992), and the Netherlands Organization for Scientific Research (912-03-033/2003). DNA handling and genotyping was supported in part by National Center for Research Resources grant M01-RR00425 to the Cedars-Sinai General Clinical Research Center Genotyping core and National Institute of Diabetes and Digestive and Kidney Diseases grant DK063491 to the Southern California Diabetes Endocrinology Research Center. A.v.H.V. is a recipient of a Leducq Transatlantic Networks of Excellence in Cardiovascular Research. The Heart and Vascular Health Study is supported by National Heart, Lung, and Blood Institute (National Institutes of Health, Bethesda, MD) grants HL43201, HL60739, HL68986, HL73410, HL74745, HL85251, and HL95080, and by a grant from the Leducq Foundation (Paris, France) for the development of Transatlantic Networks of Excellence in Cardiovascular Research. The Multiple Environmental and Genetic Assessment (MEGA) study is funded by the Netherlands Heart Foundation (NHS 98.113), the Dutch Cancer Foundation (RUL 99/1992), and the Netherlands Organization for Scientific Research (912-03-033/2003). DNA handling and genotyping was supported in part by National Center for Research Resources grant M01-RR00425 to the Cedars-Sinai General Clinical Research Center Genotyping core and National Institute of Diabetes and Digestive and Kidney Diseases grant DK063491 to the Southern California Diabetes Endocrinology Research Center. A.v.H.V. is a recipient of a Leducq Transatlantic Fellowship from the Leducq Foundation. The funding agencies had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. N.L.S. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Authorship**


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

<table>
<thead>
<tr>
<th>SNP</th>
<th>Gene</th>
<th>Model</th>
<th>HVH</th>
<th>MEGA</th>
<th>Meta-analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs1039084</td>
<td>STXBP5 (N436S)</td>
<td>Additive</td>
<td>0.78 (0.65-0.93)</td>
<td>0.91 (0.86-0.97)</td>
<td>0.90 (0.82-0.98)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Noncarriers</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Heterozygotes</td>
<td>0.73 (0.56-0.95)</td>
<td>0.82 (0.75-0.90)</td>
<td>0.81 (0.74-0.88)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Homozygotes</td>
<td>0.66 (0.48-0.92)</td>
<td>0.86 (0.76-0.97)</td>
<td>0.83 (0.74-0.93)</td>
</tr>
<tr>
<td>rs1063856</td>
<td>VWF (T789A)</td>
<td>Additive</td>
<td>1.20 (1.01-1.42)</td>
<td>1.15 (1.08-1.23)</td>
<td>1.16 (1.06-1.26)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Noncarriers</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Heterozygotes</td>
<td>1.18 (0.92-1.51)</td>
<td>1.24 (1.14-1.36)</td>
<td>1.23 (1.13-1.34)</td>
</tr>
<tr>
<td></td>
<td></td>
<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>
</tr>
</tbody>
</table>

VT indicates venous thrombosis; HVH, Heart and Vascular Health; MEGA, Multiple Environmental and Genetic Assessment; and OR, odds ratio.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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

Nicholas L. Smith, Kenneth M. Rice, Edwin G. Bovill, Mary Cushman, Joshua C. Bis, Barbara McKnight, Thomas Lumley, Nicole L. Glazer, Astrid van Hylckama Vlieg, Weihong Tang, Abbas Dehghan, David P. Strachan, Christopher J. O'Donnell, Jerome I. Rotter, Susan R. Heckbert, Bruce M. Psaty and Frits R. Rosendaal

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