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## ORIGINAL RESEARCH ARTICLE

## Cross-Ancestry Investigation of Venous Thromboembolism Genomic Predictors

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**BACKGROUND:** Venous thromboembolism (VTE) is a life-threatening vascular event with environmental and genetic determinants. Recent VTE genome-wide association studies (GWAS) meta-analyses involved nearly 30 000 VTE cases and identified up to 40 genetic loci associated with VTE risk, including loci not previously suspected to play a role in hemostasis. The aim of our research was to expand discovery of new genetic loci associated with VTE by using cross-ancestry genomic resources.

**METHODS:** We present new cross-ancestry meta-analyzed GWAS results involving up to 81 669 VTE cases from 30 studies, with replication of novel loci in independent populations and loci characterization through in silico genomic interrogations.

**RESULTS:** In our genetic discovery effort that included 55 330 participants with VTE (47 822 European, 6320 African, and 1188 Hispanic ancestry), we identified 48 novel associations, of which 34 were replicated after correction for multiple testing. In our combined discovery-replication analysis (81 669 VTE participants) and ancestry-stratified meta-analyses (European, African, and Hispanic), we identified another 44 novel associations, which are new candidate VTE-associated loci requiring replication. In total, across all GWAS meta-analyses, we identified 135 independent genomic loci significantly associated with VTE risk. A genetic risk score of the significantly associated loci in Europeans identified a 6-fold increase in risk for those in the top 1% of scores compared with those with average scores. We also identified 31 novel transcript

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associations in transcriptome-wide association studies and 8 novel candidate genes with protein quantitative-trait locus Mendelian randomization analyses. In silico interrogations of hemostasis and hematology traits and a large phenome-wide association analysis of the 135 GWAS loci provided insights to biological pathways contributing to VTE, with some loci contributing to VTE through well-characterized coagulation pathways and others providing new data on the role of hematology traits, particularly platelet function. Many of the replicated loci are outside of known or currently hypothesized pathways to thrombosis.

**CONCLUSIONS:** Our cross-ancestry GWAS meta-analyses identified new loci associated with VTE. These findings highlight new pathways to thrombosis and provide novel molecules that may be useful in the development of improved antithrombosis treatments.

**Key Words:** genetics ■ genome-wide association study ■ meta-analysis ■ venous thromboembolism ■ venous thrombosis

## Clinical Perspective

### What Is New?

- Our venous thromboembolism (VTE) genetic analyses revealed 135 loci associated with VTE, of which 92 were novel. Although novel VTE-associated variants were typically noncoding and displayed small odds ratios, they point at novel biological pathways involved in VTE.
- In particular, a large number of novel VTE variants are shared with platelet traits and located in loci with known roles in hematopoiesis or megakaryocyte development, which suggests that platelet generation, turnover, or reactivity may be a feature of VTE pathogenesis.

### What Are the Clinical Implications?

- These results constitute a valuable resource for thrombosis researchers and for the discovery of new VTE therapeutic targets.
- A genetic risk score constructed from the European-specific results and applied to the UK Biobank participants of European ancestry explained ~5% of the phenotypic variance, and displayed a strong predictive ability with an area under the curve equal to 0.62.

**V**enous thrombosis is a vascular event resulting from an imbalance in the regulation of hemostasis, with subsequent pathologic coagulation and vascular thrombosis formation. Clinically, venous thrombosis can manifest as deep vein thrombosis, when occurring in the deep veins primarily of the legs and trunk, or as a pulmonary embolism, when the thrombus embolizes and obstructs the pulmonary arteries. Collectively, these events are known as venous thromboembolism (VTE), a life-threatening condition with an incidence of 1 to 2 events per 1000 person-years.<sup>1–3</sup> VTE is a complex disease with both environmental and genetic determinants. Family studies, candidate-gene approaches, and early genome-wide association studies (GWAS) primarily identified genetic risk factors in loci with well characterized effects on coagulation (*F2*, *F5*, *F11*, *FGG*, *ABO*,

## Nonstandard Abbreviations and Acronyms

<b>AA</b>	African ancestry
<b>AUC</b>	area under the curve
<b>CBC</b>	complete blood count
<b>EA</b>	European ancestry
<b>GRS</b>	genetic risk score
<b>GWAS</b>	genome-wide association study
<b>HIS</b>	Hispanic ancestry
<b>LD</b>	linkage disequilibrium
<b>MAF</b>	minor allele frequency
<b>MR</b>	Mendelian randomization
<b>OR</b>	odds ratio
<b>PAI-1</b>	plasminogen activator inhibitor 1
<b>PheWAS</b>	phenome-wide association study
<b>pQTL</b>	protein quantitative trait loci
<b>QTL</b>	quantitative trait loci
<b>TWAS</b>	transcriptome-wide association study
<b>VTE</b>	venous thromboembolism
<b>VWF</b>	von Willebrand factor

*SERPINC1*, *PROCR*, *PROC*, *PROS1*), supporting current therapeutic strategies that mainly target the coagulation cascade.<sup>4–8</sup> In recent years, larger GWAS meta-analyses revealed unanticipated loci, such as *SLC44A2*,<sup>9</sup> which was later characterized as a choline transporter involved in platelet activation,<sup>10</sup> and in the adhesion and activation of neutrophils.<sup>11,12</sup> Thus, genetic associations with VTE in larger and more diverse populations may uncover new biological pathways and molecular events contributing to the disease and potentially help identify novel targets for treatment. Most recently, 2 large efforts involving up to 30 000 VTE cases, led by the INVENT (International Network Against Venous Thrombosis) consortium<sup>13</sup> and the MVP (Million Veteran Program),<sup>14</sup> identified up to 43 genetic loci associated with VTE. To expand discovery of novel VTE risk loci, we conducted a large, cross-ancestry GWAS meta-analysis involving >80 000 VTE cases, along with a replication of novel loci and their characterization through downstream analyses.

## METHODS

The data that support the findings of this study will be available through dbGaP (database of Genotypes and Phenotypes).

### Design and Study Participants

The study design (Figure 1) included a cross-ancestry discovery meta-analysis of GWAS summary data from 4 consortia/studies (INVENT-2019, MVP, FinnGen, Estonian Genome Project) followed by a replication of discovery loci that exceeded the genome-wide significance threshold ( $P < 5.0 \times 10^{-8}$ ). The replication population involved 12 studies, limiting data to nonoverlapping studies with our discovery.<sup>15</sup> The combined discovery and replication data (when available) were then meta-analyzed, and ancestry-stratified meta-analyses were performed for African-ancestry (AA), European-ancestry (EA), and Hispanic-ancestry (HIS) participants to enable further downstream ancestry-specific analyses, such as fine mapping. Participants from studies provided written informed consent for use of their genetic and health information for analysis, and the studies were individually approved by the appropriate institutional review boards (Supplemental Material).

### Study-Specific GWAS

Each study performed association analyses and provided summary data for meta-analysis. Genotyping arrays, imputation panels, and analyses performed by each participating study are detailed in Table S1. Additional study specifics are available as Supplemental Material.

### Discovery, Replication, and Combined GWAS Meta-Analyses

All GWAS meta-analyses were conducted with METAL,<sup>16</sup> using a fixed-effects inverse-variance weighted model. All variants were included and there was no lower minor allele frequency (MAF) limit beyond study-specific minor allele count. Genome-wide significant variants ( $P < 5.00 \times 10^{-8}$ ) were kept if a concordant effect direction was observed in 2 or more studies and

grouped into the same locus if they were within 1 Mb. We used the closest gene to the lead variant to refer to each locus, except at known loci where the causal gene has been previously identified and is different from the closest gene (such as *PROCR* or *PROS1*). We defined a locus as novel if a genetic association with VTE has not been previously observed in the region according to our review of peer-reviewed published reports.

### Discovery Meta-Analysis

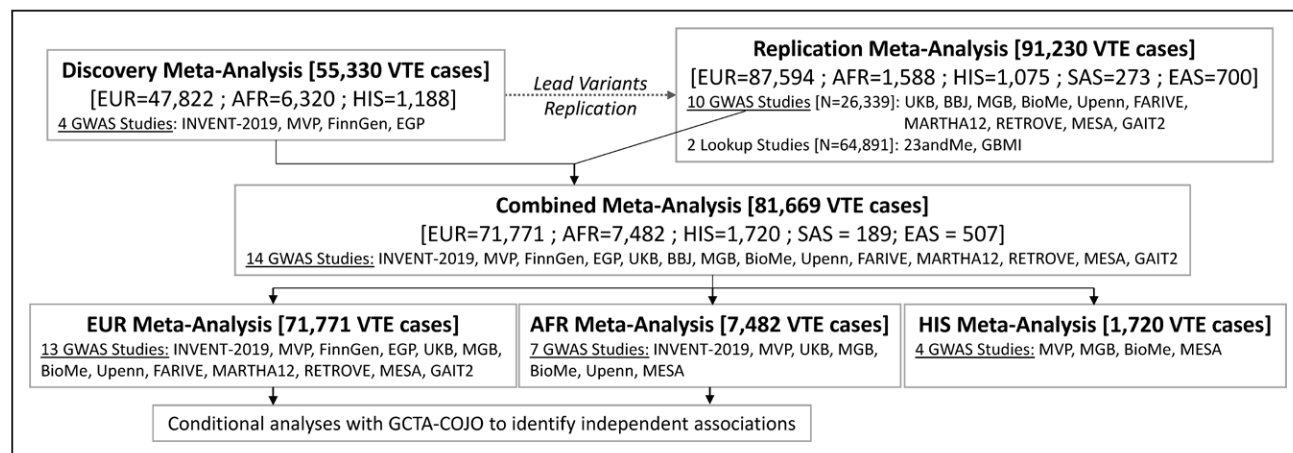
For the discovery cross-ancestry GWAS meta-analysis, we meta-analyzed data from 4 consortia/studies: INVENT-2019, MVP, FinnGen, and EGP. Participants were EA, AA, and HIS adult men and women with VTE (either deep vein thrombosis or pulmonary embolism cases) and controls. At each locus with a genome-wide significant signal, the lead variant was extracted and tested in an independent replication meta-analysis.

### Replication

The replication GWAS meta-analysis consisted of the remaining 10 participating studies, as well as 2 external collaborators (GBMI<sup>15</sup> and 23andMe<sup>17</sup>). Replicating variants from the discovery were defined as those that had concordant effect direction in the discovery and the replication, and reached a Bonferroni-corrected  $P$  value threshold in the replication population corresponding to the number of variants tested for replication with a 1-sided hypothesis:  $P$  value threshold =  $[(0.05 \cdot 2) / \text{number of variants tested for replication}]$  in the replication analysis.

### Combined GWAS Meta-Analysis and Stratification by Ancestry

We performed a combined, cross-ancestry GWAS meta-analysis of discovery and replication data (when available) using participating studies with genome-wide summary data. We included variants with  $\text{MAF} \geq 0.01$  to maintain adequate statistical power by reducing the number of low-powered tests because replication was not available. We estimated the heterogeneity associated with each variant using the Cochran Q test and the corresponding  $I^2$  statistic. We assessed the genomic inflation with the lambda genomic control.<sup>18</sup> We report on variants exceeding the genome-wide



**Figure 1. Analyses workflow.**

Workflow of genetic analyses conducted for this study. AFR indicates African ancestry; BBJ, Biobank Japan; EAS, East Asian ancestry; EUR, European ancestry; GAIT2, Genetic Analysis of Idiopathic Thrombophilia; GBMI, Global Biobank Meta-Analysis Initiative; HIS, Hispanic ancestry; INVENT-2019, International Network Against Venous Thrombosis (2019 meta-analysis); MARTHA12, Marseille Thrombosis Association study of 2010-2012; MESA, Multi-Ethnic Study of Atherosclerosis; MGB, Mass General Brigham Biobank; MVP, Million Veteran Program; RETROVE, Riesgo de Enfermedad Tromboembólica Venosa study; SAS, South Asian ancestry; UKB, UK Biobank; Upenn, Penn Medicine Biobank; and VTE, venous thromboembolism.

threshold ( $P < 5.00 \times 10^{-8}$ ) and view these as candidate novel loci associated with VTE and needing future replication.

We then stratified the analyses by ancestry and limited strata to EA, AA, and HIS because the remaining ancestries had too few VTE events to be informative. We estimated heterogeneity and genomic inflation; the linkage disequilibrium (LD) score intercept was computed for EA analysis, using the recommended Hapmap3 variants.<sup>19</sup> We report all additional ancestry-specific variants exceeding the genome-wide threshold ( $P < 5.00 \times 10^{-8}$ ) and view these as ancestry-specific candidate loci associated with VTE and needing future replication.

### Ancestry-Stratified Analyses: Conditional Analyses and Fine-Mapping

To estimate the presence of independent signals, we performed conditional analyses with GCTA-COJO<sup>20</sup> at each locus with significant signals in EA, AA, and HIS GWAS meta-analyses. The TOPMed (Trans-Omics for Precision Medicine) ancestry-specific sequence data were used as reference panels.<sup>21</sup> Conditional analyses were performed at each locus, using a window that encompassed at least the genome-wide significant variants present in the locus with an additional buffer of  $\pm 100$  kb. A stepwise joint regression model was used to identify secondary signals with joint  $P$  values  $< 5.00 \times 10^{-8}$  and a LD  $r^2 < 0.2$  with selected variants. In addition, for each locus and for each ancestry-specific GWAS meta-analysis, we produced forest plots, Manhattan plots, and regional association plots to visually inspect the local genetic architecture (Figures S1–S9).<sup>22,23</sup> Additional information is found in the Supplemental Material.

### Genetic Risk Score

We constructed an ancestry-specific genetic risk score (GRS) derived from the genome-wide significant lead variants observed in the EA meta-analysis and evaluated it for UK Biobank EA participants. The GRS for AA and HIS were not constructed because of a lack of availability of a large-scale dataset with accessible genotype data for other ancestries. The EA GRS was calculated for each individual as a summation of log(odds ratio [OR])-weighted genotypes. We then performed logistic regression to measure the association of the GRS with VTE status, while correcting for age, sex, and the top 10 genetic principal components. The predictive ability of the score was estimated by calculating the area under the curve (AUC), using the *pROC*R library.<sup>24</sup> Additional information is available in the Supplemental Material.

### Transcriptome-Wide Association Studies

We performed a transcriptome-wide association study (TWAS) with the FUSION pipeline<sup>25</sup> using the EA meta-analysis results. We first performed a series of single-tissue TWAS using gene expression from expression quantitative trait loci (eQTL) datasets relevant to blood and thrombosis disorders: whole blood, peripheral blood, liver, lung, and spleen.<sup>26–28</sup> All associations reaching a Bonferroni-corrected significance threshold corresponding to the number of genes tested ( $N = 14\,219$ ,  $P < 3.52 \times 10^{-6}$ ) were deemed statistically significant. Additional details are available in the Supplemental Material.

### Protein QTL Mendelian Randomization

Using the combined, cross-ancestry VTE GWAS meta-analysis results, we performed a proteome Mendelian randomization (MR) analysis with high-confidence genomic instruments corresponding to protein QTL (pQTL) for 1216 circulating plasma proteins that passed consistency and pleiotropy filters, as previously described.<sup>29</sup> Additional information is available in the Supplemental Material. To account for multiple testing, associations passing the Bonferroni-corrected threshold ( $N = 1256$ ,  $P < 3.98 \times 10^{-5}$ ) were considered statistically significant.

### Association of VTE Loci With Hemostasis and Hematology Traits

We conducted a series of *in silico* investigations involving hemostasis and hematology traits to better characterize the VTE-associated variants from the GWAS meta-analyses. To better understand if novel VTE-associated variants operate through hemostasis pathways, we extracted associations from published GWAS of 10 hemostatic traits: fibrinogen<sup>30</sup>; fibrin D-dimer<sup>31</sup>; coagulation factors VII,<sup>32</sup> VIII,<sup>33</sup> and XI<sup>34</sup>; von Willebrand factor (VWF)<sup>33</sup>; tissue plasminogen activator<sup>35</sup>; PAI-1 (plasminogen activator inhibitor 1)<sup>36</sup>; activated partial thromboplastin time; and prothrombin time.<sup>37</sup> Because each variant association was investigated in 10 hemostasis traits, we set a  $P$  value threshold of 0.005 (0.05/10 traits tested for each lead variant of a locus) to separate associations of interest from other associations.

Similarly, we extracted associations with complete blood count (CBC) measures using summary data from nearly 750 000 individuals on 15 leukocyte, erythrocyte, and platelet traits.<sup>38</sup> Given the large sample size and high statistical power of these analyses, we used a more stringent threshold of interest that was a Bonferroni correction corresponding to the number of look-ups performed ( $P < 1.92 \times 10^{-5}$ ). We further performed colocalization analyses with the *coloc*<sup>39</sup> R library for significant associations, using the discovery, combined, EA, and AA VTE meta-analyses. Additional information is available in the Supplemental Material.

### Phenome-Wide Association Testing

To explore associations between VTE-associated variants and other traits agnostically, we performed a phenome-wide association study (PheWAS) using the Medical Research Council Integrative Epidemiology Unit infrastructure and the associated *ieugwasr* R library.<sup>40</sup> Lead variants identified in our VTE meta-analyses were queried in 2 sources of GWAS (using the PheWAS codes “ukb-a” and “ukb-d”), which correspond to 1500 UKB analyses performed by the Neale laboratory (<https://gwas.mrcieu.ac.uk/datasets/>) on 337 000 individuals of British ancestry. We then retrieved associations reaching genome-wide significance ( $P < 5.00 \times 10^{-8}$ ) for each of the 1500 traits investigated.

## RESULTS

### Discovery Cross-Ancestry Meta-Analysis and Replication

The primary cross-ancestry discovery analysis included 55 330 participants among 3 ancestry groups with VTE



(47 822 EA, 6320 AA, and 1188 HIS) and 1 081 973 participants without VTE (918 195 EA, 118 144 AA, and 45 634 HIS). Over the 22 autosomal and X chromosomes, 35.5 million variants were analyzed, and the observed lambda was 1.06. We identified 10 493 variants reaching genome-wide significance, corresponding to 85 loci, of which 48 have not been identified in previous genetic studies of VTE (Table S2).

We tested lead variants from these 85 loci for replication in 91 230 cases and 3 322 939 controls from the independent replication data. After meta-analyzing the results of these 85 tests in the replication population, we identified 83 variants with a concordant effect direction between the discovery and the replication, of which 68 were replicated at the 1-sided Bonferroni-corrected significance threshold ( $P < 0.1/83 = 0.0012$ ; Table 1, Figure 2, Table S2). The successfully replicated signals corresponded to 34 known and 34 novel loci. Among the 34 novel loci that replicated, heterogeneity was minimal (heterogeneity  $P > 0.05$ ), ORs ranged between 0.84 to 0.98 and 1.03 to 1.18, and MAFs were all  $\geq 0.021$ . The majority of variants were gene-centric (4 exonic, 16 intronic, and 3 in 3' or 5' untranslated regions or immediately downstream), 3 were linked to intronic noncoding RNA, and 8 were considered intergenic. Among the 17 variants and their associated loci that failed replication, 14 were novel and remain candidate loci that merit additional replication, whereas 3 were known loci.

## Combined Cross-Ancestry GWAS Meta-Analysis and Ancestry-Stratified Results

### Combined

The combined, cross-ancestry meta-analysis of the studies with genome-wide markers included 81 669 individuals with VTE and 1 426 717 individuals without VTE. We analyzed 19.1 million common variants ( $MAF \geq 0.01$ ) and observed a lambda of 1.16, which is slightly elevated but expected for large-scale meta-analyses of polygenic traits.<sup>41</sup> We identified 16 550 variants reaching genome-wide significance in 111 loci, of which 41 were not observed in the discovery analysis (Table S3, Figure 2). Of these 41 additional loci, 1 corresponded to a common variant at the known *SERPINC1* locus (rs6695940) which encodes antithrombin, 4 were previously identified in the INVENT-2019<sup>13</sup> or MVP<sup>14</sup> meta-analyses at the *PEPD*, *ABCA5*, *MPHOSPH9*, and *ARID4A* loci, and 1 was a known pathogenic missense variant located in *SERPINA1* (rs28929474, p.Glu366Lys).<sup>42</sup> The remaining 35 loci were novel associations and are presented in Table 2. Among these 35 candidate loci, all had ORs with ranges of 0.93 to 0.97 and 1.03 to 1.15 and had a minimum MAF of 0.021. The majority of the variants were gene-centric (18 intronic and 3 in 3' untranslated

regions), 3 were intronic in noncoding RNA, and 11 were considered intergenic.

### European Ancestry

The EA meta-analysis, which included 71 771 participants with VTE and 1 059 740 participants without VTE, had a lambda of 1.22. Because population stratification might be introduced by founder effects in Finnish participants from FinnGen, we did a sensitivity analysis by removing this cohort, and observed a similar genomic factor of 1.19. We also observed an LD score intercept of 1.07, indicating an inflation mainly caused by polygenic architecture, and possibly slight residual stratification. Of the 11.1 million variants analyzed, 16 867 were genome-wide significant and clustered into 100 regions, of which 7 did not overlap with loci identified in the discovery or combined meta-analysis (Table 2, Figure 2, Table S4). For these 7 additional candidate loci, the ORs ranged from 0.94 to 0.97 and 1.04 to 1.07, and the minimum MAF was 0.058. Conditional analyses were performed at each of the 100 significant loci and revealed a subset of 21 loci with multiple independent signals (Table S5) and included 3 of the novel loci.

### African Ancestry

The AA meta-analysis included 7482 participants with VTE and 129 975 participants without VTE from 7 cohorts and had a lambda of 1.05. Here, 17.1 million variants were analyzed, of which 752 were genome-wide significant and located within 13 loci, of which 2 corresponded to novel ancestry-specific signals at *RBFOX1* (OR=0.56; MAF=0.04) and *COL6A2* (OR=2.16; MAF=0.011; Table 2, Figure 2, Table S6). Conditional analyses were performed at each of the 13 significant loci and revealed 3 loci with additional independent signals (Table S7).

### Hispanic Ancestry

The HIS meta-analysis included 1720 participants with VTE and 57 367 participants without VTE from 4 cohorts and had a lambda of 1.02. We analyzed 11.1 million variants, of which 58 were genome-wide significant, all located at the *ABO* locus with rs2519093 as lead variant (OR=1.49, MAF=0.15,  $P=3.08 \times 10^{-15}$ ). The conditional analysis revealed a secondary signal at this locus (Table S7).

### Comparison of Ancestry-Specific and Cross-Ancestry Meta-Analysis Results

We then investigated the lead variants from the AA and EA meta-analyses at the 11 loci (all known) identified in both analyses. At 5 loci, none of the AA lead variants were available in the EA analyses, because of their low frequency in EA ( $MAF < 0.0006$  for all 5 lead variants in non-Finnish Europeans according to gnomAD<sup>43</sup>). At the remaining 6 loci, the lead variants from the AA analysis were also genome-wide significant in the EA analysis, and shared similar effect sizes.

**Table 1. Sixty-Eight Lead Variants From the Discovery That Meta-Analysis Successfully Replicated**

rsID	CHR:POS:EA:NEA	EAF.Disc	OR.Disc	P.Disc	OR.Repl	P.Repl	Locus.Context	Locus.Gene
rs9442580	1:9339467:T:C	0.1551	1.06	1.83E-08	1.03	9.70E-05	Intergenic	<i>H6PD;SPSB1*</i>
rs3767812	1:118155620:A:G	0.2437	1.05	9.64E-11	1.06	1.03E-20	Intronic	<i>TENT5C*</i>
rs6025	1:169519049:T:C	0.0259	3.02	8.40E-811	3.59	9.29E-3103	Exonic	<i>F5</i> (p.Q534Q)
rs2842700	1:207282149:A:C	0.1092	1.11	5.95E-17	1.12	1.19E-25	Intronic	<i>C4BPA</i>
rs3811444	1:248039451:T:C	0.3324	0.96	5.70E-09	0.95	1.53E-20	Exonic	<i>TRIM58*</i> (p.T374M)
rs7600986	2:68636923:A:T	0.2819	1.06	3.54E-12	1.05	9.18E-19	Intergenic	<i>PLEK;FBXO48</i>
rs182293241	2:128029746:A:G	0.0195	1.89	1.83E-27	1.55	0.0001063	Intronic	<i>ERCC3</i>
rs6719550	2:188272460:T:C	0.6639	1.04	7.56E-09	1.05	1.93E-17	Intronic	<i>CALCRL*</i>
rs715	2:211543055:T:C	0.7022	0.95	3.51E-09	0.95	1.43E-17	UTR3	<i>CPS1*</i>
rs13412535	2:224874874:A:G	0.2047	1.06	3.05E-10	1.08	1.10E-36	Intronic	<i>SERPINE2*</i>
rs13084580	3:39188182:T:C	0.1076	1.09	2.89E-15	1.08	9.10E-22	Exonic	<i>CSRNP1</i> (p.G18S)
rs562281690	3:90177913:T:G	0.0024	2.01	6.45E-15	2.40	8.68E-31	Intergenic	<i>EPHA3;NONE</i>
rs62282204	3:138584405:T:C	0.5784	0.96	1.87E-08	0.98	6.73E-05	Intergenic	<i>PIK3CB;LINC01391*</i>
rs7613621	3:169191186:A:G	0.4467	1.04	3.21E-09	1.03	5.33E-09	Intronic	<i>MECOM*</i>
rs710446	3:186459927:T:C	0.5799	0.96	5.92E-11	0.96	1.41E-16	Exonic	<i>KNG1</i> (p.I581I)
rs6797948	3:194784705:T:C	0.7983	1.06	2.99E-11	1.05	7.59E-16	Intergenic	<i>LINC01968;XXYLT1*</i>
rs6826579	4:83785031:T:C	0.7914	1.05	2.38E-08	1.03	2.44E-07	Intronic	<i>SEC31A*</i>
rs17010957	4:86719165:T:C	0.8581	1.06	3.99E-09	1.05	1.00E-11	Intronic	<i>ARHGAP24*</i>
rs2066864	4:155525695:A:G	0.2585	1.23	1.98E-172	1.23	1.94E-284	UTR3	<i>FGG</i>
rs3756011	4:187206249:A:C	0.3903	1.23	7.48E-198	1.24	9.26E-398	Intronic	<i>F11</i>
rs16867574	5:38708554:T:C	0.6673	0.95	2.78E-11	0.95	5.67E-16	ncRNA_intronic	<i>OSMR-AS1</i>
rs38032	5:96321887:T:C	0.6049	1.04	8.74E-09	1.03	1.49E-09	Intronic	<i>LNPEP*</i>
rs9268881	6:32431606:A:T	0.5727	0.96	4.17E-10	0.97	6.73E-09	Intergenic	<i>HLA-DRA;HLA-DRB5*</i>
rs145294670	6:34622561:A:AG	0.1385	1.06	6.11E-10	1.04	6.89E-06	Intronic	<i>ILRUN*</i>
rs9390460	6:147694334:T:C	0.4957	0.95	2.49E-13	0.95	1.01E-20	Intronic	<i>STXBP5</i>
rs67694436	8:6654220:T:C	0.3486	0.96	3.94E-08	0.98	0.0001105	Intergenic	<i>AGPAT5;XKR5*</i>
rs2685417	8:27807434:C:G	0.2562	1.06	1.57E-14	1.06	2.84E-25	Intronic	<i>SCARA5</i>
rs6993770	8:106581528:A:T	0.7142	1.08	4.48E-25	1.09	3.55E-48	Intronic	<i>ZFPM2</i>
rs35208412	9:99194509:A:AT	0.8298	1.09	1.56E-08	1.04	5.54E-06	Intergenic	<i>ZNF367;HABP4*</i>
rs505922	9:136149229:T:C	0.6334	0.74	1.11E-425	0.69	1.55E-1043	Intronic	<i>ABO</i>
rs1887091	10:14535113:T:C	0.4936	0.96	4.77E-08	0.98	0.001107	Intergenic	<i>MIR1265;FAM107B*</i>
rs17490626	10:71218646:C:G	0.1136	0.80	1.02E-79	0.80	3.23E-160	Intronic	<i>TSPAN15</i>
rs16937003	10:80938499:A:G	0.0287	1.15	1.07E-08	1.11	2.11E-11	Intronic	<i>ZMIZ1*</i>
rs2274224	10:96039597:C:G	0.4414	1.04	2.55E-09	1.03	1.29E-10	Exonic	<i>PLCE1*</i> (p.R1267P)
rs10886430	10:121010256:A:G	0.8897	0.89	7.34E-25	0.88	2.76E-64	Intronic	<i>GRK5</i>
rs11032074	11:32993887:A:G	0.7792	1.05	5.37E-09	1.03	3.24E-06	Intronic	<i>QSER1</i>
rs1799963	11:46761055:A:G	0.0136	2.05	2.19E-135	2.09	6.86E-420	UTR3	<i>F2</i>
rs141687379	11:56666822:A:G	0.9953	0.52	3.56E-31	0.64	1.06E-42	Intronic	<i>FADS2B</i>
rs174551	11:61573684:T:C	0.6583	1.07	1.65E-19	1.07	4.90E-35	Intronic	<i>FADS1</i>
rs35257264	11:126296816:T:C	0.0212	1.21	2.88E-14	1.18	2.28E-24	Intronic	<i>ST3GAL4*</i>
rs1558519	12:6153738:A:G	0.6175	0.93	7.73E-24	0.92	1.42E-55	Intronic	<i>VWF</i>
rs7311483	12:9053661:T:C	0.3589	0.96	2.74E-09	0.97	2.73E-07	Intergenic	<i>A2ML1;PHC1*</i>
rs6580981	12:54723028:A:G	0.5081	0.96	3.71E-09	0.95	2.26E-23	Intronic	<i>COPZ1*</i>
rs3184504	12:111884608:T:C	0.4520	1.05	1.18E-11	1.04	3.30E-12	Exonic	<i>SH2B3*</i> (p.T178T)

(Continued)

**Table 1. Continued**

rsID	CHR:POS:EA:NEA	EAF:Disc	OR:Disc	P:Disc	OR:Repl	P:Repl	Locus.Context	Locus.Gene
rs3211752	13:113787459:A:G	0.5527	0.95	1.69E-12	0.94	3.49E-25	Intronic	<i>F10</i>
rs57035593	14:92268096:T:C	0.3202	1.07	1.08E-20	1.07	2.64E-38	Intronic	<i>TC2N</i>
rs8013957	14:103140254:T:C	0.3699	1.04	5.33E-09	1.03	2.23E-07	Intronic	<i>RCOR1*</i>
rs55707100	15:43820717:T:C	0.0270	0.87	2.90E-08	0.84	2.49E-27	Exonic	<i>MAP1A*</i> (p.P2349L)
rs59442804	15:60899031:G:GAAAT	0.6438	0.96	4.67E-08	0.97	5.42E-10	ncRNA_intronic	<i>RORA-AS1*</i>
rs12443808	16:30996871:C:G	0.4668	1.06	3.89E-14	1.03	1.85E-07	UTR5	<i>HSD3B7*</i>
rs56943275	16:81898152:T:G	0.2446	1.08	4.15E-13	1.07	1.20E-26	Intronic	<i>PLCG2</i>
rs28634651	16:88553198:T:C	0.6191	1.06	9.20E-13	1.04	7.62E-14	Intronic	<i>ZFPM1*</i>
rs6503222	17:1977862:A:G	0.6188	1.05	1.59E-12	1.04	5.21E-06	Intronic	<i>SMG6</i>
rs7225756	17:6893691:A:G	0.4877	0.96	3.57E-08	0.98	1.20E-06	ncRNA_intronic	<i>ALOX12-AS1*</i>
rs62054822	17:43927708:A:G	0.8028	0.95	6.39E-09	0.95	7.11E-19	ncRNA_intronic	<i>MAPT-AS1*</i>
rs142140545	17:64191540:CTATT:C	0.1169	0.93	2.27E-08	0.95	7.83E-07	Intergenic	<i>CEP112;APOH*</i>
rs59277920	19:6077231:A:G	0.8210	0.94	1.47E-09	0.96	8.52E-06	Intronic	<i>RFX2*</i>
rs8110055	19:10739143:A:C	0.2000	0.89	5.36E-44	0.89	6.50E-70	Intronic	<i>SLC44A2</i>
rs34783010	19:46180414:T:G	0.2132	0.95	3.25E-09	0.96	4.87E-10	Intronic	<i>GIPR*</i>
rs1688264	19:49209560:T:G	0.5341	0.96	2.07E-10	0.96	3.02E-15	downstream	<i>FUT2*</i>
rs1654425	19:55538980:T:C	0.1468	0.91	2.65E-18	0.94	4.21E-14	Exonic	<i>GP6</i> (p.S192S)
rs79388863	20:23168500:A:G	0.1521	0.92	1.74E-18	0.92	4.48E-27	Intergenic	<i>LINC00656;NXT1</i>
rs6060288	20:33772243:A:G	0.3417	1.12	8.19E-54	1.13	1.52E-102	Intronic	<i>MMP24-AS1-EDEM2</i>
rs4820093	22:33160208:T:C	0.2693	1.05	1.04E-08	1.04	5.39E-14	Intronic	<i>SYN3*</i>
rs9611844	22:43115776:C:G	0.1286	1.10	2.09E-21	1.07	7.54E-20	Intronic	<i>A4GALT</i>
rs3002416	23:39710195:T:C	0.3638	0.95	2.20E-18	0.93	2.23E-23	Intergenic	<i>MIR1587;BCOR</i>
rs6048	23:138633280:A:G	0.7215	1.07	1.09E-25	1.08	1.59E-46	Exonic	<i>F9</i> (p.T156T)
rs2084408	23:154346709:T:G	0.3764	0.94	5.36E-19	0.94	6.27E-09	Intronic	<i>BRCC3</i>

Results from the discovery are in presented in columns suffixed with "Disc," whereas results from the replication are in columns suffixed with "Repl." CHR indicates chromosome; EA, effect allele; EAF, effect allele frequency; NEA, noneffect allele; OR, odds ratio; P, P value; and POS, position (hg19 build). \*Indicates novel genetic associations.

Across the discovery, combined, EA, AA, and HIS meta-analyses, we identified 135 distinct loci (Figure 2). A summary of each locus, including LD patterns between lead variants from each meta-analysis as well as independent signals and association test results across all meta-analyses, is available in Table S8.

## Genetic Risk Score

Using the 100 lead variants identified in the EA meta-analysis, we developed a GRS that was applied to independent UKB EA participants, which included 18 516 cases and 92 929 controls (Figure 3A and 3B). The GRS was significantly associated with VTE status (OR, 1.55 [95% CI, 1.53–1.58]), and the phenotypic variance explained by the score was estimated at 0.051. To assess the predictive ability of the score, we first calculated the AUC of the base model, which included the age, sex, and 10 genetic principal components, and obtained

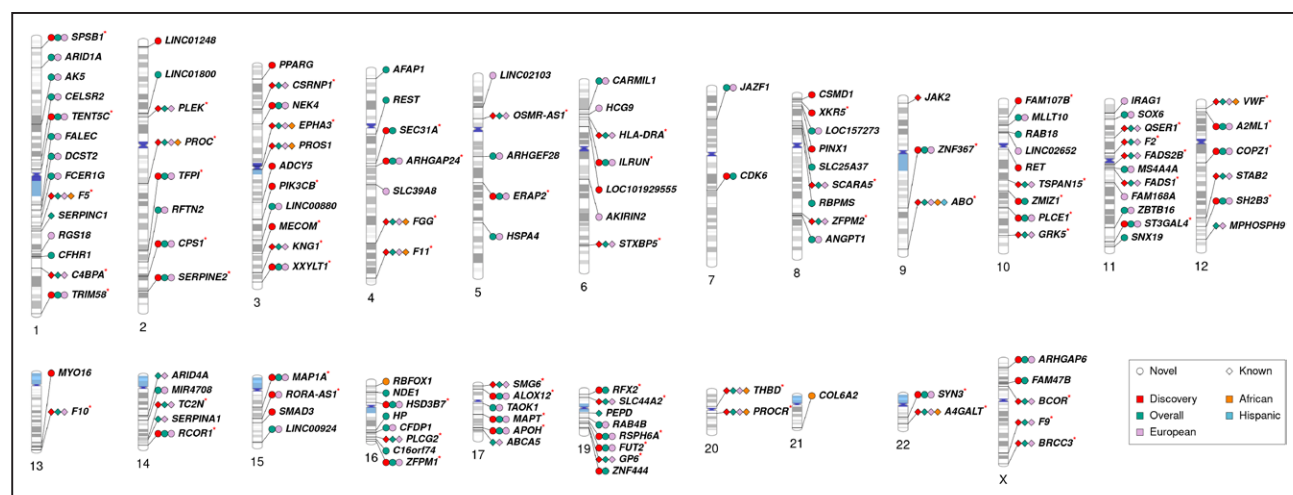
$AUC_{base} = 0.516$  (95% CI, 0.511–0.520). After adding the GRS to the model, the AUC reached  $AUC_{GRS} = 0.620$  (95% CI, 0.616–0.625), an increase of  $\Delta AUC = 0.104$  over the base model. Compared with individuals with a score in the middle stratum (45%–55%), participants with a GRS in the top 1% had a significantly higher risk (OR, 6.07 [95% CI, 5.33–6.91]), whereas individuals in the bottom 1% had a significant risk reduction (OR, 0.52 [95% CI, 0.42–0.65]; Figure 3, Table S9).

## Gene Prioritization With TWAS and pQTL MR

### Transcriptome-Wide Association Study

Across the 6 single-tissue and 3 cross-tissues datasets analyzed, we identified 166 significant ( $P < 3.52 \times 10^{-6}$ ) and conditionally independent associations with a high posterior probability of colocalization ( $> 0.75$ ) between gene expression and VTE risk (Table S10). These associations involved 108 genes, of which 77 were mapped





**Figure 2. Genetic loci associated with VTE.**

This figure presents the 135 loci significantly associated with VTE identified across all 5 meta-analyses: the discovery (in red), the overall meta-analysis (in green), and the analysis restricted to individuals of European ancestry (in purple), African ancestry (in orange), and Hispanic ancestry (in blue). Novel loci are represented with circles and known loci with diamonds. Loci with replication evidence are indicated with a red asterisk. VTE indicates venous thromboembolism.

to 46 genome-wide significant GWAS loci, leaving an additional 31 novel candidate genes that mapped outside of genome-wide significant GWAS loci (Table S11). At 33 GWAS loci, an associated gene matched the gene closest to the lead variant, supporting a role as a causal gene, whereas associated genes at the remaining 13 GWAS loci indicate genes for further investigation.

### Protein QTL MR

We performed agnostic MR of 1216 plasma circulating pQTL using the combined VTE meta-analysis results and identified 23 proteins with a significant association ( $P < 3.98 \times 10^{-5}$ , Figure 4, Table S12). For 13 proteins, the gene coordinates matched a genome-wide significant GWAS locus and included 5 of the novel GWAS loci.

### Association of VTE-Associated Variants With Hemostasis and Hematology Traits

The association of any lead or conditionally independent variant at the 135 GWAS loci with hemostasis traits is presented in Figure 5A and Table S13. Across the 10 traits, we observed 83 signals shared with VTE. Among the 92 novel (replicated and candidate) loci reported above (see “Discovery Cross-Ancestry Meta-Analysis and Replication” and “Combined Cross-Ancestry GWAS Meta-Analysis and Ancestry-Stratified Results”), 18 (19%) had a variant associated with 1 or more of the 10 hemostasis traits (Figure S10A).

Next, we investigated associations of the 135 GWAS loci with hematology traits, presented in Figure 5B and Table S14. Across all 15 CBC measures, we identified 375 shared signals, and among the 92 novel loci, we observed at least 1 association at 55 (59%) novel (replicated and candidate) loci (Figure S10B).

Rates of colocalization with VTE signals (colocalized signals/total shared signals) were similar for hemostatic factors (48/83=58%, Figure S11A) and hematology traits (214/375=57%, Figure S11B). At shared loci, we also examined the effect directions of both VTE risk and the studied trait levels. For each hemostatic factor, the observed directions of effect were mostly consistent and agreed with our current biological knowledge, with the exception of factor VII, which shared 4 loci with the same effect direction than VTE, 4 with an opposite direction, and 1 with 2 independent variants that displayed the same direction for the first and an opposite direction for the second. Hematology traits displayed less consistent directions of effect with VTE across shared loci.

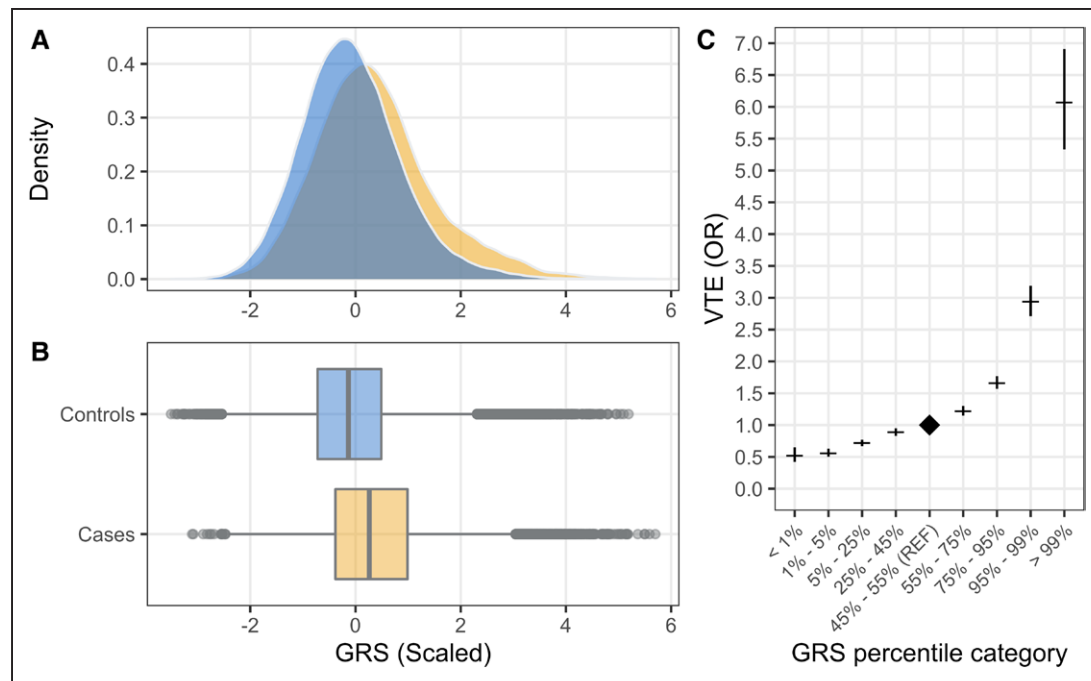
### Phenome-Wide Association Studies

We performed a PheWAS of lead and conditionally independent variants at the 135 significantly associated loci across 1500 publicly available phenotypes involving EA UKB participants (Table S15). For each trait, only genome-wide significant variants were retrieved, and we restricted our analyses on traits sharing at least 10 loci with VTE (Figure 6, Table S16), which might indicate common biological pathways. Hematology traits, in particular platelet traits, shared the most loci with VTE (for example, 33 for platelet count), consistent with our observations from the larger CBC GWAS (N~750 000) sample (Figure 5B). Several traits correspond to height and weight measurements, as well as enzymes mainly produced by the liver (such as albumin, sex hormone-binding globulin, or insulin growth factor-1), and plasma lipid-related traits (apoA and apoB, high-density lipoprotein cholesterol, or triglycerides). Blood pressure (systolic and diastolic), glycosylated hemoglobin, calcium, cystatin C,

**Table 2. Additional 44 Candidate Novel Loci Identified in the Overall, European, and African Ancestry Meta-Analyses**

rsID	CHR:POS:EA:NEA	EAF	EFFECT	SE	OR	P value	Locus.Context	Locus.Gene
Novel loci identified in the overall meta-analysis								
rs551176418	1:27107263:T:TC	0.9248	0.0759	0.0132	1.08	9.61E-09	UTR3	ARID1A
rs6695572	1:77945635:A:G	0.1938	0.0424	0.0072	1.04	4.28E-09	Intronic	AK5
rs3832016	1:109818158:CT:C	0.7627	-0.0449	0.0066	0.96	8.95E-12	UTR3	CELSR2
rs1267881263	1:150496127:CA:C	0.5468	0.0426	0.0076	1.04	2.36E-08	Intergenic	FALEC;ADAMTSL4
rs905938	1:154991389:T:C	0.7448	-0.0346	0.0063	0.97	3.70E-08	Intronic	DCST2
rs3557	1:161188893:T:G	0.9182	0.0654	0.0106	1.07	7.70E-10	UTR3	FCER1G
rs143410348	1:196809316:T:TAA	0.5434	0.0415	0.0074	1.04	2.44E-08	Intergenic	CFHR1;CFHR4
rs78475244	2:65086804:T:C	0.0542	-0.0713	0.0128	0.93	2.52E-08	ncRNA_intronic	LINC01800
rs78872368	2:198545250:C:G	0.1919	-0.0412	0.0071	0.96	7.27E-09	Intergenic	RFTN2;MARS2
rs900399	3:156798732:A:G	0.6205	0.0382	0.0060	1.04	1.46E-10	Intergenic	LINC02029;LINC00880
rs9654093	4:7903763:C:G	0.1504	0.0492	0.0081	1.05	1.03E-09	Intronic	AFAP1
rs781656	4:57778645:A:G	0.1963	0.0389	0.0070	1.04	2.26E-08	Intronic	REST
rs7730244	5:72957088:T:C	0.5245	-0.0328	0.0057	0.97	1.04E-08	Intronic	ARHGEF28
rs147133967	5:132426851:G:GTT	0.0810	-0.0659	0.0110	0.94	2.43E-09	Intronic	HSPA4
rs214059	6:25536937:T:C	0.4331	0.0357	0.0055	1.04	1.01E-10	Intronic	CARMIL1
rs2394251	6:29943688:G:C	0.7331	-0.0405	0.0063	0.96	1.43E-10	ncRNA_intronic	HCG9
rs1513275	7:28259233:T:C	0.7453	0.0449	0.0070	1.05	1.40E-10	ncRNA_intronic	JAZF1-AS1
rs10099512	8:9178821:C:G	0.1105	0.0608	0.0105	1.06	6.98E-09	Intergenic	LOC101929128;LOC157273
rs2048528	8:23373680:A:G	0.3089	-0.0347	0.0060	0.97	5.77E-09	Intergenic	ENTPD4;SLC25A37
rs2915595	8:30402817:A:G	0.2391	0.0365	0.0065	1.04	2.52E-08	Intronic	RBPMS
rs4236786	8:108291878:C:G	0.2492	0.0353	0.0064	1.04	3.93E-08	Intronic	ANGPT1
rs1243187	10:21907016:T:C	0.6920	-0.0341	0.0061	0.97	2.53E-08	Intronic	MLLT10
rs4272700	10:27881308:A:T	0.2726	0.0395	0.0064	1.04	7.75E-10	Intergenic	RAB18;MKX
rs2030291	11:16251251:A:T	0.6077	-0.0325	0.0056	0.97	8.19E-09	Intronic	SOX6
rs4354705	11:60088159:C:G	0.3635	0.0315	0.0058	1.03	4.83E-08	Intergenic	MS4A4A;MS4A6E
rs2846027	11:114003415:T:C	0.3112	-0.0344	0.0061	0.97	1.42E-08	Intronic	ZBTB16
rs7107568	11:130779668:T:C	0.5610	-0.0303	0.0056	0.97	4.71E-08	Intronic	SNX19
rs2127869	14:65794352:T:C	0.3350	-0.0340	0.0062	0.97	4.68E-08	Intergenic	LINC02324;MIR4708
rs7183672	15:96101018:A:G	0.6432	-0.0358	0.0062	0.96	7.34E-09	Intergenic	LINC00924;LOC105369212
rs71376077	16:15738114:C:G	0.9728	0.1408	0.0249	1.15	1.57E-08	Intronic	NDE1
rs7197453	16:72079127:C:G	0.3572	0.0315	0.0057	1.03	3.19E-08	Intergenic	DHODH;HP
rs77246010	16:75429853:T:C	0.4489	0.0408	0.0069	1.04	4.12E-09	Intronic	CFDP1
rs8049403	16:85778651:A:G	0.0214	0.1365	0.0248	1.15	3.91E-08	Intronic	C16orf74
rs71138827	17:27833678:A:AGATT	0.4288	0.0336	0.0058	1.03	5.89E-09	Intronic	TAOK1
rs2545774	19:41287674:T:C	0.2528	-0.0378	0.0065	0.96	6.80E-09	Intronic	RAB4B
Additional novel loci identified in the European meta-analysis								
rs4540639	1:192104320:C:G	0.4675	0.0346	0.0060	1.04	6.88E-09	Intergenic	LINC01680;RGS18
rs35225200	4:103146888:A:C	0.9190	-0.0645	0.0115	0.94	1.89E-08	Intergenic	BANK1;SLC39A8
rs112367053	5:28379046:T:G	0.6662	0.0586	0.0107	1.06	4.07E-08	Intergenic	LINC02103;LSP1P3
rs2754251	6:88385949:A:G	0.0584	0.0715	0.0129	1.07	2.65E-08	Intronic	AKIRIN2
rs10763665	10:28771491:C:G	0.5783	-0.0342	0.0062	0.97	3.13E-08	ncRNA_intronic	LINC02652
rs7122100	11:10732560:A:C	0.2411	0.0410	0.0075	1.04	4.93E-08	Intergenic	IRAG1;CTR9
rs1145656	11:73305859:A:C	0.8171	-0.0442	0.0079	1.05	2.00E-08	upstream	FAM168A
Additional novel loci identified in the African meta-analysis								
rs76668186	16:6686083:A:T	0.9597	-0.5776	0.1056	0.56	4.52E-08	Intronic	RBFox1
rs114102448	21:47523605:A:G	0.0114	0.9527	0.1725	2.60	4.11E-08	Intronic	COL6A2

CHR indicates chromosome; EA, effect allele; EAF, effect allele frequency; NEA, noneffect allele; OR, odds ratio; POS, position (hg19 build); and SE, standard error of effect.



**Figure 3. GRS analysis.**

Distribution of the GRS in VTE cases (in green) and controls (in purple) as a density plot (A) and a boxplot (B). C, Presentation of the VTE risk as ORs and associated 95% CIs (y axis) for different percentiles ranges of the GRS score (x axis) relative to the middle range (45%–55%). GRS indicates genetic risk score; OR, odds ratio; REF, reference; and VTE, venous thromboembolism.

and C-reactive protein levels were among additional traits sharing at least 10 loci with VTE. Few traits had a consistent direction of effect with respect to VTE risk across shared loci (Figure 6). For example, out of 10 loci shared between bilirubin levels and VTE, 9 (90%) were associated with an increase of both bilirubin levels and VTE risk. For albumin levels, glycated hemoglobin, and systolic blood pressure, an opposite direction of effect between these traits and VTE risk was observed at >75% of shared loci.

## DISCUSSION

We identified 135 independent genomic loci and 39 additional genes from TWAS and pQTL associated with an increased or decreased risk of VTE. This reflects a substantial increase in the number of validated and candidate loci for VTE risk beyond past genetic mapping efforts.<sup>13,14</sup> Although the novel VTE associated variants were typically noncoding and displayed small effect sizes, they may provide valuable insights into genetic loci not previously suspected to play a role in VTE. Our results highlight genetic variation across the rare-to-common allele frequency spectrum in multiple ancestry groups and add new evidence of biologic predictors of VTE pathogenesis for further investigation. The in silico interrogations provide valuable clues about the putative causal gene at each locus and additional insights to biological pathways shared with VTE.

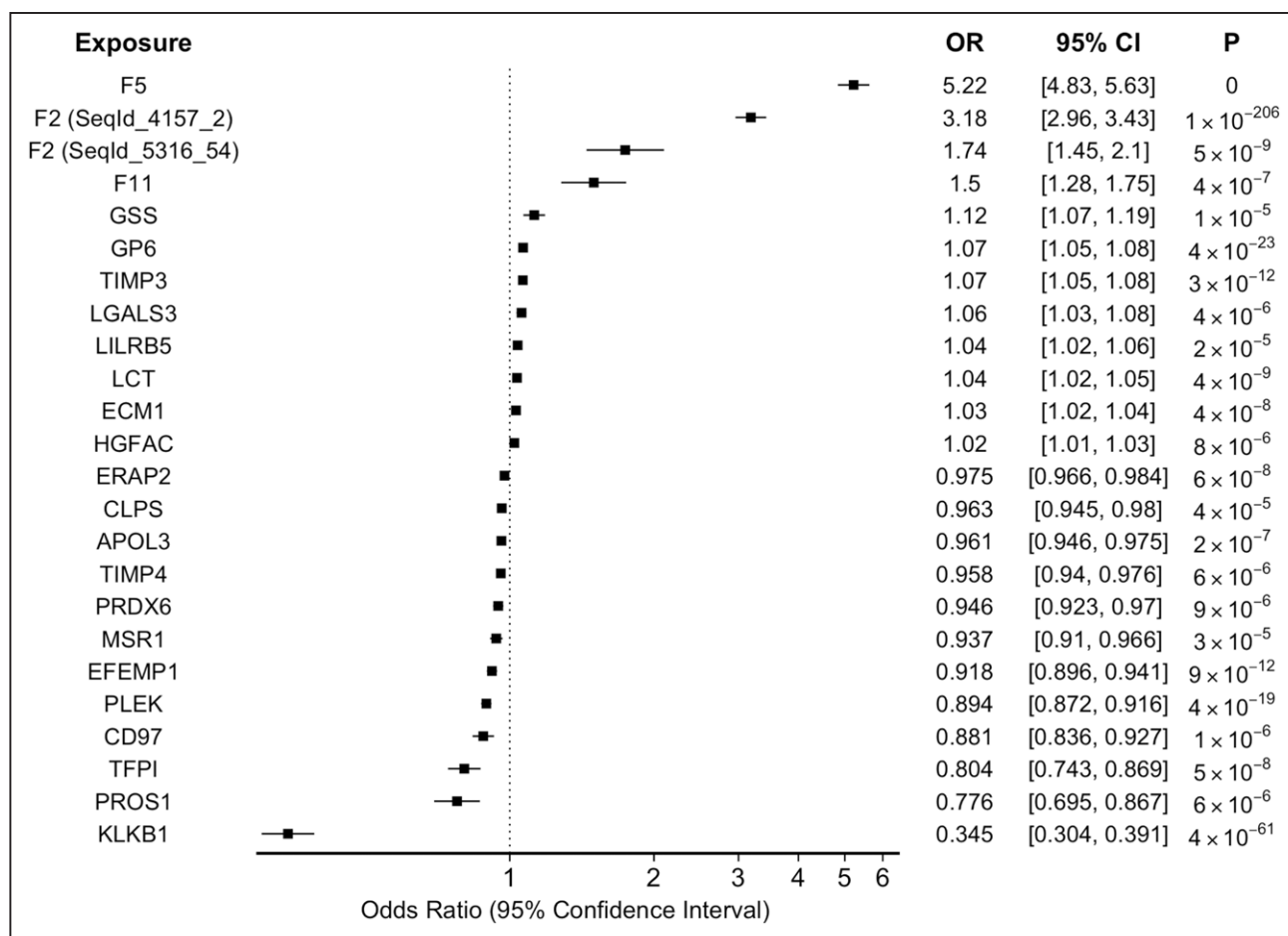
## Biological Insights

### Novel Replicated Loci

Our strongest evidence supports 34 loci with novel VTE associations. Except for *TFPI* and *SERPINE2*, the novel genetic loci were not in established VTE pathophysiology pathways. A subset of these 34 loci (12 loci, 35%) was associated with plasma levels of the hemostasis traits interrogated, and most (26 loci, 76%) were associated with a hematology trait. This contrast should be interpreted with caution because statistical power for the hemostasis traits was much smaller than for the hematology traits.

Although most of the novel associations reported had an OR in the range of 0.90 to 0.98 and 1.03 to 1.10, we were able to identify and replicate 3 uncommon variants with larger estimated effects: an intronic variant (MAF=0.021) in the glycosyltransferase *ST3GAL4* (OR<sub>discovery</sub> OR=1.21, OR<sub>replication</sub>=1.18), which was also associated with increased VWF and factor VIII levels; an intronic variant (MAF=0.029) in the transcriptional coactivator *ZMIZ1* (OR<sub>discovery</sub>=1.15, OR<sub>replication</sub>=1.11); and an exonic variant (MAF=0.027) in *MAP1A* (p.Pro2349Leu, OR<sub>discovery</sub>=0.87, OR<sub>replication</sub>=0.84), which was also associated with decreased levels of VWF and fibrinogen, and had a protective effect against VTE.

Variants associated with hemostasis traits provide clues that the causal gene at these loci might directly or indirectly perturb the coagulation cascade. For instance, *XXYL1* encodes a xylosyltransferase



**Figure 4. Significant associations of protein quantitative trait loci Mendelian randomization.**

Twenty-three proteins significantly associated with venous thromboembolism, of 1216 plasma protein analyzed, using the combined venous thromboembolism summary statistics. OR indicates odds ratio.

known to interact with coagulation factors<sup>44</sup> and had a nearby variant ( $OR_{\text{discovery}}=1.06$ ,  $OR_{\text{replication}}=1.06$ ) also associated with decreased factor VII levels. Another example is *FUT2*, a fucosyltransferase gene with a downstream variant ( $OR_{\text{discovery}}=0.96$ ,  $OR_{\text{replication}}=0.96$ ) that was also associated with decreased VWF levels. In addition, some variants were associated with several hematology traits, suggesting common genetic regulatory pathways affecting hematopoiesis, such as the replicated *RCOR1* signal on chromosome 14, and the candidate gene *REST* on chromosome 4 identified in the combined meta-analysis, 2 genes that form the transcriptional repressor CoREST, known to mediate hematopoiesis.<sup>45</sup>

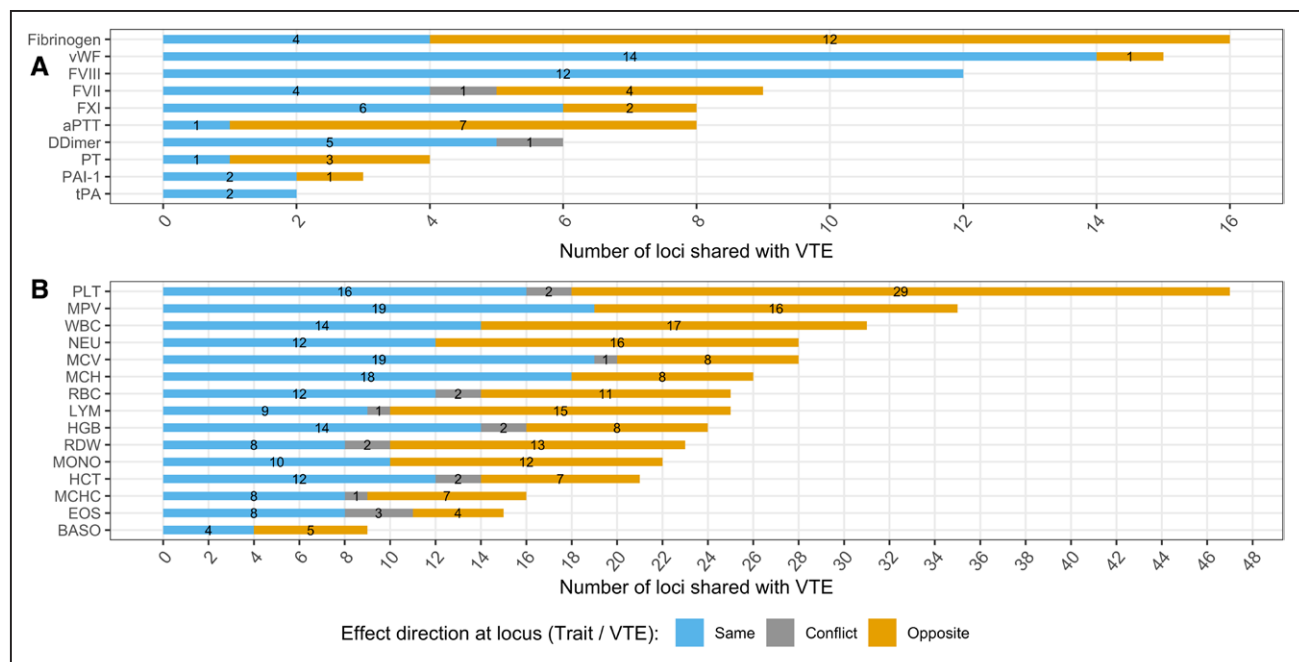
Among the 34 loci, 17 (50%) had TWAS evidence linking transcript expression with a gene in the locus, and 3 were linked to protein measures. These results may help to prioritize biologically relevant genes for further investigations. At the *COPZ1* locus, the lead variant was associated with several CBC measures, including platelet count and red blood cell count, and the TWAS revealed an association with *NFE2*, known to regulate erythroid and megakaryocyte maturation.<sup>46</sup>

### Other Replicated and Nonreplicated Loci

Replicated variants included 2 rare variants at the known *EPHA3* (intergenic,  $MAF=0.0024$ ,  $OR=2.40$ ) and *FADS2B* (intronic,  $MAF=0.0047$ ,  $OR=0.64$ ) loci. Among the 17 failed replications, 7 reached nominal significance ( $P<0.05$ ), suggesting that these variants might need a larger replication sample to be validated. See the [Supplemental Material](#) for more details.

### Novel Candidate Loci

Across the multiple interrogation approaches, we identified several scores of candidate loci with evidence to support their association with VTE, although not yet replicated. This included 35 candidates from the combined GWAS, 7 candidates from the EA GWAS, and 2 candidates from the AA GWAS. Interestingly, the 2 variants ( $MAF$  0.04 and 0.011) in the AA population were not present in EA participants and were associated with nearly 2-fold changes in risk of VTE. However, these 2 variants were detected in only a subset of studies, which included only 882 AA VTE cases out of 7482, warranting additional investigations to confirm these 2 signals in *RBFOX1* (an RNA-binding protein)



**Figure 5. VTE genetic loci shared with hemostatic factors and blood traits.**

**A**, Number of VTE loci shared with each of the 10 hemostatic factors investigated. Loci with shared variants that had an opposite effect direction between the trait and VTE are indicated in orange, whereas those that had the same effect direction are presented in blue. Loci with multiple independent shared variants and conflictual effect directions are indicated in gray. **B**, The same analysis with complete blood count traits: platelet count (PLT), mean platelet volume (MPV), red blood cell count (RBC), mean corpuscular volume (MCV), hematocrit (HCT), mean corpuscular hemoglobin (MCH), MCH concentration (MCHC), hemoglobin concentration (HGB), red cell distribution width (RDW), white blood cell count (WBC), monocyte count (MONO), neutrophil count (NEU), eosinophil count (EOS), basophil count (BASO), and lymphocyte count (LYM). aPTT indicates activated partial thromboplastin time; PT, prothrombin time; and VTE, venous thromboembolism.

and *COL6A2* (a collagen-generating gene that contains several domains similar to *VWF* type A domains). For the remaining candidate GWAS loci, we saw attributes and associations similar to those with the replicated loci. With additional replication resources in the future, these candidates may become fully replicated genetic associations.

In addition, the conditional analyses revealed independently associated variants mapping to distinct genes that may be of interest for further investigations, such as *BRD3* at the *ABO* locus, a chromatin reader known to associate with the hematopoietic transcription factor *GATA1*.<sup>47</sup> At the *EPHA3* locus, we also noted that the lead GWAS variant and the conditionally independent variant mapped upstream and downstream of *PROS2P*, a protein S pseudogene that might be of interest.

At these candidate loci, genes prioritized by the TWAS may also provide putative genes at these loci. For example, *ZBTB7B*, a zinc-finger protein that represses the expression of extracellular matrix genes such as fibronectin and collagen,<sup>48</sup> was identified by TWAS at the GWAS candidate locus *DCST2*. The 31 candidate genes identified in the TWAS as well as the additional 8 from the pQTL MR analyses, although lacking a significant genetic association at these loci, might indicate relevant genes for future investigations. For instance, SYK is a critical platelet-activation protein, and tyrosine

kinase inhibitors of SYK have been explored for platelet inhibition.<sup>49,50</sup>

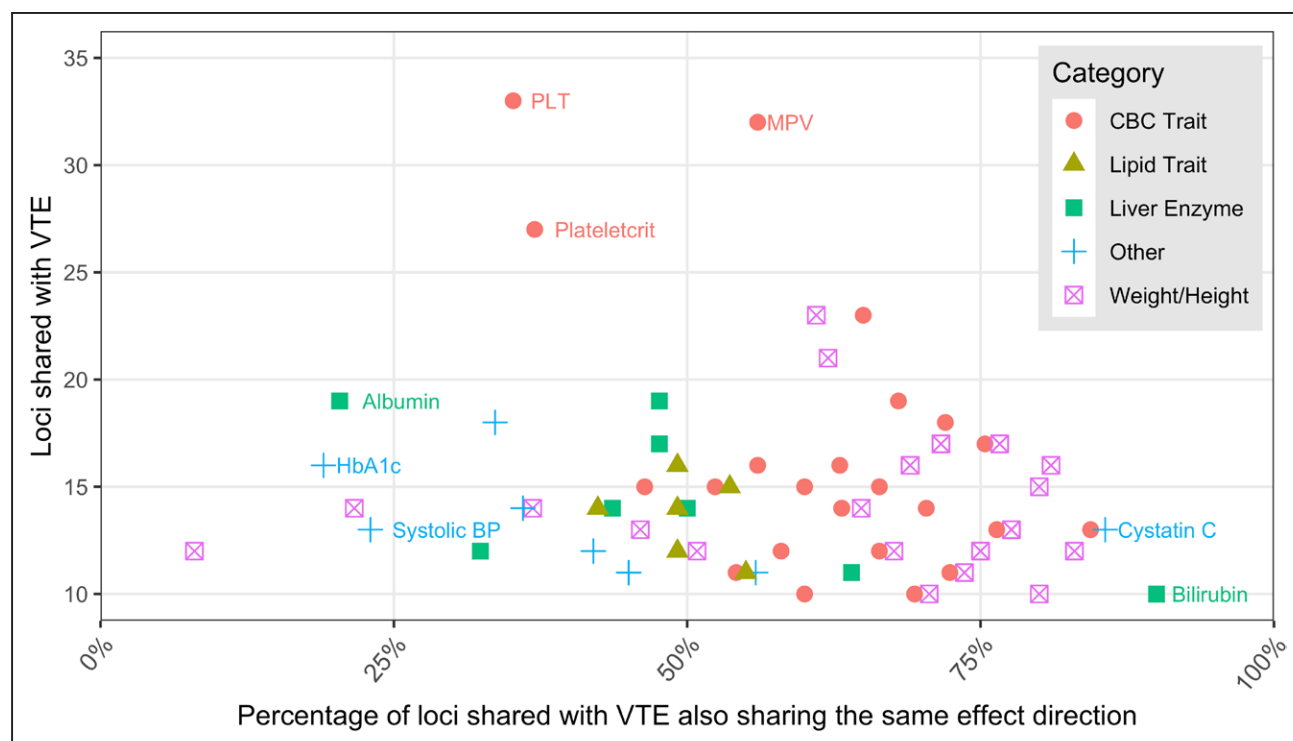
## Clinical Implications

The GRS provided VTE risk discrimination in our EA population, and those at the extremes of the score distribution experienced multifold risk differences. We were not able to integrate or to compare nongenetic risk factors with the GRS.

Current anticoagulation therapy to prevent or treat VTE operates through the modulation of proteins produced in the liver (coumarin-based therapies) or through direct inhibition of coagulation factors IIa (thrombin) and Xa. Although the safety profile of anticoagulation treatments has evolved, bleeding remains a life-threatening off-target outcome. New approaches to preventing thrombosis while minimizing bleeds are in development, including a focus on contact (intrinsic) pathway proteins factor XI, factor XII, prekallikrein, and high-molecular-weight kininogen.<sup>51</sup> Agnostic interrogations such as these may lead to discovery of novel proteins that “break the inexorable link between antithrombotic therapy and bleeding risk.”<sup>52</sup>

The hematology traits investigations and the PheWAS established that CBC measures share a large number of loci with VTE, and platelet phenotypes in particular are





**Figure 6. PheWAS traits sharing at least 10 loci with VTE.**

The PheWAS traits sharing at least 10 loci with VTE. Shape and color represent 1 of 5 categories: complete blood count (CBC) traits, lipid traits, liver enzyme, height and weight traits, or other (if the trait did not fit in one of the aforementioned categories). The x axis indicates the number of loci shared between VTE and the PheWAS trait, whereas the y axis indicates the proportion of loci where the direction of effect was the same between the PheWAS trait and VTE. As a result, traits close to 100% have the same direction of effect as VTE at most shared loci, whereas traits close to 0% have an opposite direction than VTE at most shared loci. BP indicates blood pressure; HbA1c, glycated hemoglobin; MPV, mean platelet volume; PheWAS, genome-wide association study; PLT, platelet count; and VTE, venous thromboembolism.

the most frequent traits shared with VTE variants: 51 loci were associated with platelet count, mean platelet volume, plateletcrit, or platelet distribution width in the PheWAS, and 35 of these loci are novel, which represents more than a third of all novel genetic associations. Several loci associated with VTE harbor genes with known roles in hematopoiesis and megakaryocyte development, or platelet turnover,<sup>45,46,53–60</sup> or platelet aggregation (Supplemental Material).<sup>10,61–71</sup> Altered platelet generation, turnover, or reactivity may be a feature of VTE pathogenesis. For one, past prospective studies<sup>72</sup> and case-control studies<sup>73,74</sup> suggest that enlarged platelets, as measured by mean platelet volume, are associated with VTE and VTE outcomes. Studies of platelet function measures with VTE have been less conclusive, which may relate to the limitations of these studies in assessing comprehensive and standardized platelet reactivity mechanisms.<sup>75–77</sup> Collectively, these results suggest that treatments inhibiting platelet activation such as aspirin might be beneficial in the prevention of VTE, although previous studies and trials on aspirin and combinations with anticoagulants offered mixed results.<sup>78</sup> Different antiplatelets, such as more targeted thrombin, PAR1 or PAR4 inhibitors, or intracellular PDE platelet signaling inhibitors like cilostazol, could be worthwhile for further study in VTE prevention.

## Strengths and Limitations

The major strength of this genetic discovery effort is the large sample size of the populations contributing to the genetic variation interrogations. We increased statistical power compared with previous VTE GWAS meta-analysis efforts and increased our ability to detect new associations, many of which were replicated, and less common genetic variations. The cross-ancestry meta-analyses also increased discovery potential where allele frequencies were more common in some populations compared with others.

Several limitations deserve mention. Case ascertainment varied by study, and some studies provided validated VTE events whereas others relied on information from electronic health records. Further, some studies included only hospitalized VTE events and did not capture events in the outpatient setting. These differences may have introduced some bias if case ascertainment and hospitalization status have genetic determinants. We included all VTE cases and did not stratify by provoked status to increase statistical power. Many of the studies had not classified the VTE events as provoked and unprovoked. In addition, although the cross-ancestry approach provided benefits, the numbers of VTE cases were not evenly distributed by ancestry, thus reducing

our ability to detect ancestry-specific VTE variants in the underrepresented ancestry groups with more modest case counts. Because of the diversity of imputation panels used by the participating studies, genetic variants had variable coverage across studies, which weakened our power to detect associations. Another limitation of our approach that used summary GWAS statistics from meta-analyses is the absence of participant-specific genotype-level information. This required us to rely on LD information extracted from external datasets, which can result in variants being missed and LD patterns not accurately captured. This may have introduced some bias in analyses that relied on LD, such as the conditional analyses and the TWAS. Further, *in silico* work was performed using external datasets such as the hemostatic factors and hematology traits summary statistics, where the size (and statistical power) of the datasets varied greatly. Although different significance thresholds were used for significance, this may have biased the detection of significant associations to those traits that had large sample sizes. In addition, the pQTL MR analyses relied in some cases on a single genetic instrument, such as the *KLKB1* analysis, and these results should be considered hypothesis-generating.

## Conclusions

These cross-ancestry GWAS meta-analyses identified 34 loci that replicated discovery findings. Some of the novel loci may contribute to VTE through well-characterized coagulation pathways, whereas others provide new data on the role of hematology traits, particularly platelet function. Many of the replicated loci are outside of known or currently hypothesized pathways to thrombosis. We also provided a list of 44 new candidate loci including candidates from the combined cross-ancestry GWAS, from the EA GWAS, from the AA GWAS, and also 39 candidate genes from the TWAS and pQTL MR. These findings highlight new pathways to thrombosis and provide novel molecules that may be useful in the development of antithrombotic treatment that reduces bleeding adverse occurrences.

## ARTICLE INFORMATION

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## Supplemental Material

Supplemental Methods  
Supplemental Discussion  
Figures S1–S13  
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