Genomic Landscape of Thrombosis Recurrence Risk Across Venous Thromboembolism Subtypes.

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KEY POINTS

- 29 loci/proteins associated with VT recurrence risk.
- The genomic architecture of VT recurrence risk varies based on the initial clinical presentation.

ABSTRACT

Venous thromboembolism (VT) is a frequent (annual incidence of 1 to 2 per 1,000) and potentially life-threatening (case-fatality rate up to 10%) disease. VT is associated with serious short-term and long-term complications including a recurrence rate of approximately 20% within five years. Anticoagulant therapy, the mainstay of VT treatment, drastically reduces the risk of early VT recurrence, but it exposes patients to a substantial risk of bleeding. We analysed the genomic architecture of VT recurrence using data from 6,571 patients across eight cohorts, 1,816 of whom experienced recurrence, with a particular focus on the clinical manifestation of the type of first VT event. Through genome-wide association studies (GWAS), we identified three loci significantly associated ($P<5\times10^{-8}$) with VT recurrence in the general VT population: *GPR149/MME*, *L3MBTL4*, and *THSD7B*. Protein Quantitative Trait Locus and Mendelian Randomization analyses further identified elevated plasma levels of coagulation factor XI and GOLM2 as risk factors for recurrence, while decreased levels of PCSK9 and pro-IL16 were linked to reduced VT recurrence risk.

Subgroup analyses revealed 18 loci associated with VT recurrence, with notable differences between pulmonary embolism (PE) and deep vein thrombosis (DVT). For example, the exonic variant *SLC4A1* p.Glu40Lys was significantly associated with recurrence in PE patients (Hazard Ratio (HR)=3.23, $P=9.7\times10^{-12}$) but showed no effect in DVT (HR=1.00, P=0.98).

These findings emphasize the role of specific genetic loci and protein pathways in influencing VT recurrence and provide valuable insights into potential therapeutic targets. Further research is needed to clarify the biological mechanisms driving these associations.

Key-words: genetics; genome-wide association study; meta-analysis; venous thromboembolism recurrence

INTRODUCTION

Venous thromboembolism (VT) encompasses deep vein thrombosis (DVT) and pulmonary embolism (PE). With an incidence of 1 to 2 per 1,000 adults annually and a mortality of about 10%, VT is the third most common cause of cardiovascular death worldwide[1,2]. The mainstay of treatment is anticoagulant therapy, which should be administered for a minimum of three months to prevent early recurrence and death[3]. After discontinuation, the risk of recurrent VT is variable, depending on the presence of major factors at the time of VT. When VT is provoked by a major transient risk factor (*e.g.*, surgery, immobilisation), the risk of recurrent VT is low (<2% at one year) and anticoagulation should not be continued[3]. For VT diagnosed in the context of cancer, therapeutic anticoagulation is needed for as long as the cancer is considered active[3]. However, in more than 50% of cases, VT occurs in absence of any major risk factors (termed unprovoked VT)[4]. In these cases, more than 35% will develop recurrent VT if anticoagulation is stopped, with a case-fatality rate of about 10% [3,5–7]. Consequently, international guidelines recommend to treat patients with a first episode of unprovoked VT "indefinitely" [3]. However, such practice exposes patients to a substantial linear increase in the risk of bleeding[5,7] and proposing indefinite anticoagulation in all patients with unprovoked VT exposes 65% of patients, who would never have recurrence after anticoagulation discontinuation, to an unjustified risk of bleeding. Hence, determining the optimal duration of anticoagulant treatment for VT is a major public health issue[8]. For this purpose, a better understanding of the mechanisms involved in VT recurrence is crucial for improving prevention and identifying patients who may not require extended anticoagulation.

Established risk factors for VT recurrence currently established are: unprovoked first VT, elevated D-dimer levels and male sex[9]. Several biological clinical scores have been developed in order to predict the risk of VT recurrence and to identify who should stop or continue anticoagulants (*i.e.*, HERDOO2, DASH, VIENNA, L-TRRiP, and VTE-PREDICT scorers)[10–14]. However, the discriminant power of these scores is moderate and their use in current practice is limited. While several scores consider D-dimers levels as a predictor of VT recurrence, other biological candidate risk factors such as coagulation factor XI (FXI), coagulation factor VIII (FVIII), von Willebrand factor (vWF) and tissue factor pathway Inhibitor (TFPI) have been identified but reproducibility issues limit their use and they may not be independent[15–19].

The observations that, in patients with unprovoked VT, the risk of recurrent VT is high and the risk of VT in their first degree relatives is high whether an inherited thrombophilia is detected, suggest that genetic factors may be underpinning VT recurrence in these patients[20–24]. However, among the aforementioned prediction scores, only L-TRRiP includes genetic predictors, the FV Leiden and non-O blood groups, both well known to associate with first VT[12]. Unfortunately, knowledge of the genetic factors for VT recurrence is currently scarce. Indeed, while over 100 genetic loci associated for first VT have been identified[25,26], only few studies have thoroughly investigated the genetic factors of VT

recurrence. To date, only one genome wide association study (GWAS) has been performed on VT recurrence (totalling 1,279 patients including 447 VT recurrences)[27]. This GWAS identified the *F5* locus as the only genome-wide significant ($P<5\times10^{-8}$) locus. Genotype analysis in replication cohorts suggested the existence of another susceptibility locus in the 18q22 region. However, in the combined meta-analysis, this association ($P=5.8\times10^{-6}$) did not reach genome-wide significance. Finally, it is worth noting that the *ABO* locus, and more precisely A1 and A2 haplotypes, has recently been observed to be associated with VT recurrence ($P=4.2\times10^{-3}$)[28].

We sought to identify new susceptibility loci for VT recurrence in the largest GWAS meta-analysis encompassing 6,571 patients, including 1,816 VT recurrences. We conducted downstream analyses to investigate the identified loci, followed by the same strategy stratified by sex, provoked/unprovoked status of the initial VT and the type of first VT (*i.e.*, PE/DVT).

METHODS

Studies

The recurrent VT GWAS meta-analysis included eight studies with confirmed unrelated VT cases of European ancestry free of cancer history: EDITH, FHS, HVH (HVH1 and HVH23), MARTHA, MEGA, PADIS-PE and REVERSE-I (**Supplementary Material**).

GWAS analysis and meta-analysis

In each study, all variants with a minor allele frequency (MAF) higher than 0.01 and an imputation quality score (INFO) higher than 0.3 were considered. Each study implemented a Cox model to analyse VT recurrence considering the delay since the first VT as time scale and adjusting for age at the first VT, sex, the presence of provoking factors and location of the first VT (if relevant) and the first principal components of the population stratification. Detailed information on genotyping arrays is provided in **Supplementary Table S1**.

In the primary analysis, only SNPs present in at least seven out of the eight participating cohorts were included in the meta-analysis conducted with the GWAMA software, using a fixed-effects inverse-variance weighted (IVW) model[29].

Testing of genetic variants associated with first VT

In a secondary analysis, we assessed whether the 100 genetic loci associated at $P<5\times10^{-8}$ with first VT in the European ancestry meta-analysis were also associated with recurrent VT in the current GWAS meta-analysis[26].

Transcriptome-wide association studies

From GWAS meta-analysis of VT recurrence, transcriptome-wide association study (TWAS) complemented by conditional and colocalization analyses, were performed with FUSION pipeline[30,31]. Tissues considered are in **Supplementary Table S2**. Associations were considered significant if they

reached the corrected threshold corresponding to the average number of genes tested in each tissue (N=6,528, $P<7.7\times10^{-6}$). Results with a posterior probability of sharing a single causal variant (PP4) from the colocalization analysis higher than 0.75 were considered[31].

Mendelian Randomization with haemostatic phenotypes

From GWAS summary statistics of VT recurrence, we performed Mendelian randomization (MR) analyses with 29 haemostatic traits (**Supplementary Table S3**) using publicly available summary statistics from GWAS catalog (https://www.ebi.ac.uk/gwas/downloads/summary-statistics) and resources from the CHARGE hemostasis working group.

For each trait, we identified *cis* and *trans* independent genetic instruments ($P<5\times10^{-8}$) after clumping for linkage disequilibrium (LD) at $r^2<0.01$ for a distance of 10Mb (based on European 1000 Genomes phase 3 reference panel). For phenotypes with less than two instruments, the selection threshold was lowered to $P<1\times10^{-6}$. We applied the recommended IVW MR method and to assess robustness of the findings, we further applied alternative MR methods that are more robust for the presence of pleiotropic or outlier instruments (Weighted Median method, MR-Egger)[32]. MR analyses were performed in R v.4.1.0 using the TwoSampleMR R package[33].

Mendelian Randomization with proteins

We performed a proteome MR analysis using publicly available GWAS results on 4,907 and 4,979 blood proteins measured with the Somalogic platform from the deCODE project (N=35,559) and the Fenland study (N=10,708)[34,35]; and 2,940 proteins measured with the antibody-based Olink Explore 3072 PEA in UK Biobank study (N=34,557)[36]. In each proteogenomics resource, we selected proteins influenced by more than two independent *cis* or *trans* genetic instruments ($P<5\times10^{-8}$). This led to the selection of 4,677 unique proteins present in deCODE (N=3,469), Fenland (N=2,706) or UK Biobank (N=2,217). We applied IVW method on each protein as well as the different aforementioned MR methodologies for sensitivity analyses. To account for multiple testing, we used a proteome-wide significance level of $P<1.07\times10^{-5}$ (~0.05/4677) with IVW method.

Mendelian Randomization with metabolites

We used GWAS summary statistics from 1,091 blood metabolites and 309 metabolite ratios to perform MR on VT recurrence with a similar approach as described above[37]. We identified 459 metabolites with more than two genetic instruments ($P<5\times10^{-8}$) which led to a statistically significant threshold of $P<1.09\times10^{-4}$ (~0.05/459).

Subgroup analyses

To better characterize heterogeneity of VT recurrence, a similar framework was applied to six subgroups: male/female sex; first VT provoked/first VT unprovoked; DVT only as first VT/PE±DVT as first VT. To account for multiple testing, additional correction for six phenotypes was applied for GWAS meta-analyses and downstream analyses. Because of lower sample sizes, we retained only

variants with low heterogeneity across studies (I2<50%) and present in at least N-1 studies, with N the number of studies contributing to the dedicated subgroup analysis.

RESULTS

Population characteristics

A brief description of the eight participating cohorts totalling 6,571 patients among which 1,816 experienced VT recurrences is presented in **Table 1**. Some differences were observed: *e.g.*, DVT represented approximately 80% of first VT in MARTHA whereas PADIS-PE was fully composed of PE patients; first VT was unprovoked in 32% of MEGA patients and was an inclusion criterion in PADIS-PE and REVERSE-I. A detailed description according to the incidence of VT recurrence is presented in **Supplementary Table S4**.

GWAS meta-analysis of VT recurrence

In the GWAS meta-analysis, 8,194,239 autosomal SNPs were tested with VT recurrence. The genomic inflation factor (lambda) was 1.04 and the associated Manhattan plot is presented in **Figure 1**. Three independent genetic loci were significantly ($P<5\times10^{-8}$) associated with VT recurrence (**Table 2, Supplementary Table S5**):

-rs34097149 variant mapping to the *GPR149/MME* locus on 3q25.2 (**Figure 2A**) where the C allele (2.4%) was associated with an increasing risk of VT recurrence (hazard ratio (HR)=1.84 [1.49-2.29], $P=2.65\times10^{-8}$). Of note, *GPR149* was previously associated with coronary artery disease and with haemostatic traits (FXI, FVII, Fibrinogen, vWF)[38,39].

-rs144475075, intronic to *L3MBTL4* at the 18p11.31 locus where the T allele (1.6%) was associated with HR=2.16 [1.65-2.83] ($P=2.82\times10^{-8}$) (**Figure 2B**). *L3MBTL4* is a coding gene mainly expressed in vascular smooth muscle cells that may trigger vascular remodeling[40,41]. Little is known about its association with thrombotic disorders, except a potential link with hypertension[41] and FVII activity[42].

-rs72844599, downstream to *THSD7B* on chromosome 2q22.1 with T allele (1.4%) associated with HR=1.98 [1.55-2.52] ($P=3.83\times10^{-8}$) (**Figure 2C**). *THSD7B* belongs to the thrombospondin family, an inhibitor of angiogenesis that has been identified to associate with paediatric VT[43,44]. Of note, there was a trend for a stronger effect of this variant in younger patients (**Supplementary Table S6**). Thrombospondin is also known to be involved in platelet aggregation and has been proposed to interact with fibrinogen on the surface of activated platelets[45].

For these three loci, the genetic effects were homogeneous across studies (**Supplementary Figure 1A-C**) as well as between subgroups (**Supplementary Figure 2A-C**). None of these lead SNPs were reported in GTEx portal as influencing gene expressions. They were however reported in the JASPAR database[46] to be located in binding domains of a few transcription factors: *CDX1*, *CDX2*, *CDX4*, *HOXA10*, *HOXB13*, and *HOXD9* for rs34097149, *STAT4* for rs144475075 and *BCL6* for rs72844599.

Noteworthy, only the rs34097149 was reported to possibly act as a plasma protein quantitative trait locus (pQTL) (for *PDCD1LG2* and *SORBS3* at $P<10^{-4}$) in Fenland (**Supplementary Table S7**).

In addition to these three significant loci, there was a variant that nearly reached ($P<5\times10^{-7}$) genome wide significance: rs73149254 in the 3'UTR of *GATA5* (HR=1.75 [1.42-2.16], $P=1.68\times10^{-7}$) (**Supplementary Table S8**, **Figure 2D, Supplementary Figure 1D-2D**). *GATA5* is a transcription factor that influences angiogenesis, endothelial cells function, platelets production and megakaryocyte development[47,48]. Rs73149254 influenced plasma levels of *ROBO2* in UK Biobank (**Supplementary Table S7**) and it was predicted to map to a binding site for hsa-miR-4737 [49] as well as for transcription factors *ZNF257* and *ZKSCAN5* [46].

Effects of the variants associated with first VT on VT recurrence

Due to low frequency or imputation quality, only 88 first VT-associated SNPs[26], could be tested for association with VT recurrence (**Supplementary Table S9**). Two associations passed the corrected threshold ($P<5.7\times10^{-4}$), *i.e.,* rs2066864-A in the 3'UTR of *FGG* (HR=1.14, $P=2.3\times10^{-4}$) and the *KNG1* exonic rs710446-C (HR=1.13, $P=5.0\times10^{-4}$). For these two variants, the observed genetic effects were in the same direction as that observed for first VT (**Table 3**).

TWAS on VT recurrence

The main results ($P<1\times10^{-5}$) of the TWAS on VT recurrence are provided in **Supplementary Table S11**. No new loci were identified using the pre-specified statistical threshold of $P<7.7\times10^{-6}$.

Mendelian randomization with haemostatic phenotypes

Results of MR on 29 haemostatic phenotypes are presented in **Table 4**. At the Bonferroni corrected threshold for multiple testing ($P<1.7\times10^{-3}$), only higher levels of FXI were significantly associated with a greater risk of VT recurrence (HR=1.21 [1.09-1.35], $P=4.76\times10^{-4}$).

Protein QTL Mendelian Randomization on VT recurrence

MR analysis on 4,677 human plasma circulating proteins (all results in **Supplementary Table S11**) identified three significant ($P<1.07\times10^{-5}$) associations (**Table 5**) which were consistent across the three used MR methods (**Supplementary Figure S3**). Effects of the genetic instruments for the three proteins identified are presented in **Supplementary Table S12**.

From deCODE, MR results showed that one unit increase of genetically-determined levels of protein GOLM2 was significantly associated with an increasing risk of VT recurrence (HR=1.35 [1.18-1.55], $P=4.36\times10^{-6}$). In both Fenland and UK Biobank, the *ABO* rs550057-C was the strongest genetic instrument for GOLM2 while it was rs687289-A in deCODE. Interestingly, rs550057-C tagged *ABO* A1 and A2 haplotypes while rs687289-A tagged non-O *ABO* haplotypes (**Supplementary Figure S4**). Using raw proteogenomic data from the 3C-study (**Supplementary Materials**)[50] we confirmed that GOLM2 plasma levels were increased in A1 carriers (**Supplementary Table S13**). Associations of ABO blood group tagging SNPs with VT recurrence are shown in **Supplementary Table S14**.

Secondly, we observed that one unit increase of genetically-determined plasma levels of pro-Interleukin-16 (*IL16*) was significantly associated with a decreased risk of VT recurrence (HR=0.81 [0.78-0.95], $P=7.77\times10^{-6}$) in deCODE. Similar trends were observed in UKBiobank (HR=0.86, P=0.011) and Fenland studies (HR=0.88, P=0.045). The strongest genetic instrument for pro-IL16 in deCODE (**Supplementary Table S12**) was the intronic *IL16* rs17875523 variant, which was in complete LD ($r^2=1$ according to HaploReg v4.2)[51] with the missense rs11556218 (p.Asn1147Lys). The rs11556218-G allele was associated with decreased pro-IL16 levels and slightly with increased risk of VT recurrence (HR=1.18, $P=4.5\times10^{-3}$). Of note, MR association observed in deCODE remained unchanged after removing rs11556218 (or any SNP in strong LD) from the genetic instruments (HR=0.70, $P=8.9\times10^{-5}$).

Finally, we observed that increase of genetically-determined plasma levels of proprotein convertase subtilisin/kexin type 9 (*PCSK9*) was significantly associated with a lower risk of VT recurrence (HR=0.68 [0.58-0.80], $P=4.70\times10^{-6}$) from UK Biobank. Similar associations were observed in deCODE (HR=0.73, P=0.06) and Fenland (HR=0.63, $P=1.04\times10^{-3}$). The strongest genetic instrument of PCSK9 in UK Biobank was the missense *PCSK9* rs11591147-T (p.Arg46Leu) variant associated with decreased PCSK9 levels ($\beta=-1.06$, $P<1\times10^{-200}$) and increasing risk of VT recurrence (HR=1.76, $P=4.28\times10^{-6}$). After removing this variant from the MR analysis, no association remained (UK Biobank: HR=0.81, P=0.11; Fenland: HR=0.89, P=0.55; deCODE: HR=0.96, P=0.86).

Mendelian randomization with metabolites on VT recurrence

Results of MR with 459 metabolites on the risk of VT recurrence are presented in **Supplementary Table S15**. No significant association was identified at the predefined threshold of $P<1.09\times10^{-4}$.

Subgroup analysis

The same GWAS workflow, together with downstream analyses, were deployed in specific subgroups of VT patients. All results are provided in **Supplementary Table S16-20 and Supplementary Figures S5-22**.

By conducting subgroup specific GWAS meta-analyses, we identified 25 SNPs, mapping to 18 independent loci, which reached the predefined statistical threshold of $P<8.3\times10^{-9}$ (**Supplementary Table S16**). All the identified SNPs were low-frequency variants (about 2%) and showed concordant directions of effect across the contributing studies. Among these results, the most significant finding was the *SLC4A1* rs45562031-T missense variant (p.Glu40Lys) identified in the PE subgroup (HR=3.23 [2.30-4.52], $P=9.7\times10^{-12}$). Interestingly, this variant had no effect (HR=1.00, P=0.98) in the DVT subgroup (**Supplementary Figure S4B**).

TWAS results that passed the corrected threshold used for the main analysis ($P<7.7\times10^{-6}$) are presented in **Supplementary Table S17**. After correction, only two associations remained significant ($P<1.3\times10^{-6}$) but there was no evidence of colocalization.

For pQTL-MR, MR analyses with metabolites and haemostatics phenotypes, no significant association remained after correction for multiple phenotypes ($P<1.78\times10^{-6}$, $P<1.82\times10^{-5}$ and $P<2.87\times10^{-4}$, respectively). Results are presented in **Supplementary Table S18** for MR with haemostatics phenotypes and nominal associations in **Supplementary Table S19-20** for pQTL-MR and metabolites MR, respectively.

DISCUSSION

The current study, representing the largest effort to identify molecular risk factors for VT recurrence, identified 29 significant molecular markers (summarized in **Figure 3**). Consistent with the hypothesis that VT recurrence is a complex trait, we observed that 9 of these markers (*FGG*, *KNG1*, *GPR149*, *L3MBTL4* and *THSD7B* loci; GOLM2, FXI, IL16 and PCSK9 plasma levels) pertained to VT recurrence in the general populations of VT patients while the remaining 20 were more specific to subgroups of VT patients based on sex, type of first event (PE/DVT), or provoked/unprovoked status of the first VT. Furthermore, we demonstrated that the genetics of VT recurrence differed from that of the first VT as only three markers (*FGG*, *KNG1* loci and genetically-determined FXI plasma levels) were shared. Sensitivity analyses addressing the possible impact of the collider bias phenomenon due to case-only design did not modify these findings (**Supplementary Note**).

MR analyses supported the causal association between the plasma levels of 4 proteins (GOLM2, FXI, IL16 and PCSK9) and the risk of recurrence. Increasing genetically-determined FXI levels associated with increased risk of recurrence, which was in line with the use of FXI inhibitors to prevent VT recurrence[52] and consistent with previously reported results[15]. In the same study, lower plasma levels of free TFPI[16] and high plasma levels of FVIII[17] were associated with a higher risk of VT recurrence. Results of our MR analyses showed consistent suggestive evidence for both haemostatic traits on the risk of VT recurrence, HR=0.77 ($P=3.91\times10^{-3}$) and HR=1.14 ($P=6.95\times10^{-3}$) for TFPI and FVIII plasma levels, respectively (**Table 4**). Of note, the association between FXI and recurrent VT remained unchanged when excluding from the MR analysis the *KNG1* rs710446 variant (HR=1.18, P=0.03), which is known to influence plasma FXI levels[53].

By contrast, MR results observed for GOLM2, IL16 and PCSK9 were novel.

The GOLM2 protein is involved in cellular processes related to cancer development and progression. While its precise functions are not fully understood, GOLM2 is believed to be involved in cell proliferation, apoptosis, contributing to tumorigenesis when dysregulated[54]. The association between GOLM2 and recurrent VT was consistent across subgroups, including provoked and unprovoked VT patients (**Supplementary Table S19**), suggesting that the biological impact of GOLM2 extends beyond cancer related mechanisms. The most consistent pQTLs for GOLM2 were located in the *ABO* (9q34.2), *SIK3* (11q23.3) and *POC1B* (12q21.33) loci, among which *ABO* was the most strongly

associated with VT recurrence (**Supplementary Table S21**). However, ABO blood groups only contributed to 2.5% of GOLM2 plasma levels variability in the 3C study.

We also identified that higher levels of pro-IL16 were protective against VT recurrence. Interestingly, the missense *IL16* rs11556218-G variant has recently been reported to associate with VT in leukemia patients[55]. However, no trend for association was observed in the GWAS on first VT (OR=1.01, P=0.56)[26]. Pro-IL16 has been described to act as a transcriptional repressor in lymphocytes cells[56] which regulates cell proliferation[57]. While high levels of the mature form of pro-IL16 are associated with a poorer cancer prognosis[56], there is growing evidence supporting a protective role of pro-IL16 in cardiovascular diseases. Indeed, several studies demonstrated a protective role of IL16 in atherosclerotic plaque stabilization and a reduced incidence of cardiovascular events[58–60]. By facilitating plaque stabilization, pro-IL16 may attenuate tissue factor activation, fibrin formation and platelet recruitment[61] thereby contributing to protection against VT recurrence.

The third protein identified was PCSK9, a protein well known for its role in lipid metabolism by its ability to enhance the degradation of low-density lipoprotein (LDL) receptors[62]. However, our results identifying a lower VT recurrence risk with increased PCSK9 levels were counterintuitive and seemed to contradict previous studies showing that PCSK9 inhibitors, prescribed to lower LDL cholesterol, were associated with a reduced risk of cardiovascular diseases, including the risk of VT[63–65]. Given that the association with PCSK9 levels disappeared after removing the effect of the missense variant *PCSK9* p.Arg46Leu, it is possible that this variant qualitatively impacts the ability of the proteomic technique used to measure PCSK9 plasma levels. However, this could not explain why we observed a deleterious effect of the Leu46 variant on the risk of VT recurrence, while it has a protective effect on coronary artery disease[66,67]. Conversely, this variant did not show any association with VT incidence[26] nor with stroke[68]. MR analysis with LDL cholesterol levels[69] on VT recurrence did not support a causal association (HR=0.97, P=0.59). This suggests that the PCSK9 association identified may reflect mechanisms outside the LDL-pathway. In line with this hypothesis is the observation that statin therapy, which has been proposed to prevent VT recurrence[70–72], can also increase PCSK9 levels[65]. Of note, in the EDITH study, the *PCSK9* Leu46 variant tended to associate with VT recurrence more strongly in patients under statins therapy (HR=14.40, $P=2.0\times10^{-3}$) than in the group of non-statins users (HR=1.45, P=0.13) (**Supplementary Table S22**). Altogether, these findings suggest either the presence of an unmeasured confounder and/or more complex interactions between the underlying mechanisms. Further works are needed to better clarify the association of PCSK9 and the risk of VT recurrence.

Beyond these MR findings, we identified 3 novel loci (*GPR149*, *L3MBTL4* and *THSD7B*) harbouring SNPs associated with VT recurrence in the general population of VT patients. None of the lead SNPs demonstrated strong statistical association with gene expression or plasma protein levels, highlighting

the need for further characterization of their functional impact. In our meta-GWAS analysis, we did not replicate the previously reported association of the rs9946608-C (HR=1.13, P=0.28, I^2=21%, **Supplementary Figure S24**) and observed a strong heterogeneity in the association of FV Leiden with VT recurrence (HR=1.14, P=0.04, I^2=74%, **Supplementary Figure S23**).

In subgroups analyses, attention was drawn to the missense *SLC4A1* p.Glu40Lys (rs45562031) variant associated with a three-fold increased risk of recurrence in PE patients (**Supplementary Figure S10**). Interestingly, a rare missense variant in exon 6 of *SLC4A1* (p.Gly130Arg, rs121912749) was identified in an Asian pedigree with unexplained venous and arterial thrombi[73]. The band 3 protein encoded by *SLC4A1* is a chloride/bicarbonate exchanger lying in the red blood cell (RBC) membrane and involved in carbon dioxide transport from tissues to lungs. It is also found in the kidney, where it is involved in acid secretion. Rare coding mutations in *SLC4A1* are responsible for new blood group antigens belonging to the Diego blood group system. These mutations can also alter the RBC membrane and kidney functions. Whether the *SLC4A1* p.Glu40Lys variant has similar functional impacts on RBC or on kidney remains to be elucidated. The broad biological implications of the band 3 protein in functions of the respiratory system[74] may explain why this gene was identified only in the PE subgroup. Of note, no criteria on the localisation was applied to qualify a recurrent VT, as in approximately 80% of cases, the clinical manifestation of a VT recurrence is the same as the initial VT presentation[75].

Despite being the largest GWAS on VT recurrence, the moderate size of our study may have hampered our power to detect additional significant findings. Some borderline findings would require further investigations such as the association of the *GATA5* 3'UTR rs73149254 or the association of the *PLXNA4* locus with VT recurrence in PE patients (**Supplementary Table S16**), a locus identified with the risk of PE in a plasma proteomic study[76].

By bringing together almost all known existing cohorts with data on recurrent VT, we were unable to identify a substantial sample to replicate the associations identified. To support our findings and go further to decipher the mechanisms involved, we have extensively leveraged publicly available genomic data.

Another limitation of this work is its focus exclusively on populations of European ancestry. It is now widely acknowledged that incorporating cross-ancestry populations can improve the power of GWAS to identify genetic loci. However, it is important to note that the MAF of the identified variants is often lower in non-European ancestry populations (**Supplementary Table S23**), which will substantially reduce the power to replicate these findings in other ancestral groups.

In conclusion, we described 25 loci and 4 proteins significantly associated with VT recurrence. Some of these associations pertained to the risk of recurrence in the general population of VT patients of

European ancestry and some were restricted to specific subgroups. Our findings provided novel insights into the genomic architecture of VT recurrence, and highlighted potential targets for developing or repositioning drugs. The newly identified markers now need to be integrated into prediction tools to evaluate their clinical relevance for more personalized anticoagulation therapy.

STATEMENTS AND DECLARATIONS

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Authorship Contributions

GM, NLS, FC, PEM and DAT participated in study concept and design. GM, JAB, AvHV, PS, KLW, L.Goumidi, LBH, MAR, FG, FRR, ADJ, NLS, FC, PEM and DAT participated in phenotype data acquisition or control quality. MHC, AvHV, L.Gourhant, MG, IC, RO, NS, CB, DB, AB, S.Debette, JFD, FG, FRR, ADJ, NLS, FC, PEM and DAT participated in genotype or biological data acquisition or control quality. GM, MHC, OCB, JAB, FT, LBH, CAL, S.Danckwardt, HJG, ADJ, NLS, FC, PEM and DAT participated in data analysis and interpretation. GM and DAT wrote the initial draft of the manuscript which was reviewed and approved by all co-authors.

Disclosures

The authors have no conflict of interest to declare.

Ethics approval

Research have been performed in accordance with the Declaration of Helsinki.

All experimental protocols to study the genetics of VT recurrence were approved by the local ethic committee "Mediterranean I Committee for the Protection of Individuals" (reference: 12 61) for MARTHA study.

The MEGA study was approved by the local ethic committee "Medical Ethics Committee of the Leiden University Medical Center".

The HVH study was approved by the institutional review board of the Kaiser Permanente Washington Health Research Institute.

The EDITH study was approved by Brest University Hospital scientific and ethics board, in accordance with the Declaration of Helsinki.

The Institutional Review Board of Boston University Medical Center approved the study protocol for FHS study.

PADIS-PE study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki, Good Clinical Practice, and relevant French regulations regarding ethics and data protection. The protocol and amendments were approved by a central independent ethics committee and written informed consent was obtained from all participants.

Protocols to study genetics in REVERSE I was approved by the University of Toronto Research Ethics Board. Institutional research ethics board approvals were obtained by all participating centers (Ottawa Hospital Research Ethics Board).

Consent to participate

Written informed consent to participate was obtained from all participants.

Data sharing statement

Summary statistics from the main analysis will be uploaded on GWAS catalog.

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TABLES

Table 1: Description of the main population characteristics of the studies part of the meta-analysis.

Variables	EDITH	FHS	HVH (HVH1+HVH23)	MARTHA	MEGA	PADIS-PE	REVERSE-I
	N=1,646	N=224	N=1,323	N=1,518	N=1,254	N=155	N=451
	N (Freq)	N (Freq)	N (Freq)	N (Freq)	N (Freq)	N (Freq)	N (Freq)
Sex							
Men	736 (44.7%)	113 (50.4%)	552 (41.7%)	512 (33.7%)	615 (49.0%)	77 (49.7%)	232 (51.4%)
Age at the first VT *(mean ± SD)*	57.2 ± 19.7	70.1 ± 15.0	63.3 ± 14.2	41.0 ± 15.7	48.1 ± 12.8	57.2 ± 17.8	53.3 ± 17.6
Type of the first VT							
DVT only	681 (41.4%)	141 (62.9%)	624 (47.2%)	1,200 (79.1%)	765 (61.0%)	-	230 (51.0%)
Characteristic of the first VT							
Provoked	544 (33.1%)	137 (61.2%)	546 (41.3%)	1,004 (66.1%)	849 (67.7%)	-	-
Family history of VT	*(N=1,627)*		*(N=1,055)*	*(N=1,473)*	*(N=1,111)*		
Yes	414 (25.5%)	112 (50.0%)	188 (17.8%)	750 (50.9%)	361 (32.5%)	NA	104 (23.0%)
Delay of follow-up in years *(mean ± SD)*	6.4 ± 4.5	10.0 ± 6.4	4.7 ± 2.5	9.7 ± 9.6	5.2 ± 2.9	3.7 ± 0.9	5.2 ± 3.2

Table 2: Genome wide significant loci associated with VT recurrence in the GWAS meta-analysis.

					Meta-analysis for VT recurrence								
CHR:POS:NEA:EA	**rsid**	**Cytoband**	**Location**	**Gene**	**EAF**	**Effects***	**HR**	**HR_L95**	**HR_U95**	**I2**	**N_samples**	**N_Recurrences**	**Pvalue**
3:154545386:T:C	rs34097149	3q25.2	intergenic	GPR149;MME	0,024	++-+++?+	1,84	1,49	2,29	46	6416	1790	2,65E-08
18:6214286:C:T	rs144475075	18p11.31	intronic	L3MBTL4	0,016	++++++?+	2,16	1,65	2,83	0	6416	1790	2,82E-08
2:137678403:G:T	rs72844599	2q22.1	downstream	THSD7B	0,015	++++++?+	1,98	1,55	2,52	36	6416	1790	3,83E-08

** effects are presented in the following order: EDITH, FHS, HVH1, HVH23, MARTHA, MEGA, PADIS-PE, REVERSE-I*

Table 3: Nominal effects on VT recurrence of SNPs previously identified to associate with first VT.

					European meta-analysis for VT (Thibord et al. 2022)						Meta-analysis for VT recurrence						
CHR:POS:NEA:EA	**rsid**	**Cytoband**	**Location**	**Gene**	**EAF**	**OR**	**OR_L95**	**OR_U95**	**I2**	**Pvalue**	**EAF**	**HR**	**HR_L95**	**HR_U95**	**I2**	**N_samples**	**Pvalue**
4:154604543:G:A	rs2066864	4q32.1	UTR3	FGG	0,25	1,23	1,22	1,25	53	8,63E-218	0,29	1,14	1,07	1,23	57	6571	2,32E-04
3:186742138:T:C	rs710446	3q27.3	exonic	KNG1	0,41	1,05	1,03	1,06	11	2,12E-14	0,43	1,13	1,05	1,21	38	6571	4,96E-04
10:94263320:T:C	rs57866767	10q23.33	intronic	PLCE1	0,43	1,04	1,03	1,05	0	4,64E-11	0,46	1,12	1,05	1,19	10	6571	9,36E-04
3:90388838:A:G	rs9866664	3p11.1	intergenic	EPHA3;NONE	0,49	0,95	0,94	0,97	0	1,38E-13	0,45	0,88	0,81	0,95	50	6571	1,68E-03
9:133261703:G:A	rs687289	9q34.2	intronic	ABO	0,36	1,34	1,32	1,35	86	7.25e-507	0,44	1,11	1,04	1,19	0	6571	2,19E-03
1:109272258:C:T	rs4970834	1p13.3	intronic	CELSR2	0,19	1,05	1,03	1,06	4	6,92E-10	0,19	0,88	0,80	0,95	20	6571	2,51E-03
11:46739505:G:A	rs1799963	11p11.2	UTR3	F2	0,01	1,99	1,90	2,09	74	8,44E-170	0,03	1,43	1,12	1,81	19	5317	3,40E-03
17:2075894:T:C	rs4790311	17p13.3	intronic	SMG6	0,60	1,05	1,04	1,06	0	3,19E-15	0,62	0,91	0,85	0,98	0	6571	8,69E-03
4:186285095:C:A	rs3756011	4q35.2	intronic	F11	0,40	1,22	1,21	1,23	66	1,15E-238	0,47	1,09	1,02	1,17	5	6571	1,31E-02
12:54336088:T:C	rs4759076	12q13.13	intronic	COPZ1	0,47	0,95	0,94	0,96	0	6,35E-17	0,42	0,92	0,85	0,98	0	6571	1,64E-02
8:105569300:A:T	rs6993770	8q23.1	intronic	ZFPM2	0,28	0,93	0,92	0,94	0	4,61E-29	0,27	0,91	0,84	0,99	0	6571	2,11E-02
12:8901065:T:C	rs7311483	12p13.31	intergenic	A2ML1;PHC1	0,68	1,04	1,02	1,05	0	3,63E-08	0,65	1,08	1,01	1,16	31	6571	2,61E-02
1:207108804:C:A	rs2842700	1q32.2	intronic	C4BPA	0,06	1,12	1,10	1,15	26	2,50E-19	0,07	1,14	1,01	1,29	0	6571	3,49E-02
10:119250744:A:G	rs10886430	10q26.11	intronic	GRK5	0,12	1,12	1,10	1,14	0	3,59E-34	0,14	1,10	1,01	1,21	0	6571	3,64E-02
1:169549811:T:C	rs6025	1q24.2	exonic	F5	0,97	0,34	0,33	0,35	84	1.57e-1028	0,92	0,87	0,77	0,99	74	6571	3,83E-02
19:10628160:A:G	rs8109681	19p13.2	intronic	SLC44A2	0,79	1,12	1,10	1,14	14	9,19E-55	0,78	1,10	1,00	1,20	10	6571	4,47E-02
22:42719770:G:C	rs9611844	22q13.2	intronic	A4GALT	0,12	1,08	1,06	1,10	48	7,94E-17	0,13	1,10	1,00	1,21	0	6571	4,54E-02
12:6051448:C:T	rs7135039	12p13.31	intronic	VWF	0,36	1,07	1,06	1,09	11	1,20E-31	0,39	1,07	1,00	1,15	45	6571	4,76E-02

Table 4: Results of MR analyses with 29 haemostatic phenotypes on the risk of VT recurrence.

Exposure	PUBMED ID	Sample size	Threshold_instrument	NbSNPS	Beta_IVW	SE_IVW	P_IVW	Heterogeneity	P_Heterogeneity	Beta_Egger	SE_Egger	P_Egger	Egger_Intercept	P_Intercept	Beta_Wmedian	SE_Wmedian	P_Wmedian
Coagulation Factor XI	33328453	10,708	**$5x10^{-8}$**	**13**	**0,19**	**0,06**	**4,76E-04**	**41,26**	**0,10**	**0,31**	**0,12**	**3,08E-02**	**-0,05**	**0,33**	**0,21**	**0,05**	**3,18E-05**
Tissue_factor_pathway_inhibitor	29875488	3,301	$5x10^{-8}$	4	-0,26	0,09	3,91E-03	0,00	0,87	-0,35	0,19	2,15E-01	0,03	0,66	-0,26	0,11	1,53E-02
Coagulation Factor VIII	33328453	10,708	$5x10^{-8}$	17	0,13	0,05	6,95E-03	15,31	0,34	0,07	0,07	3,52E-01	0,03	0,22	0,16	0,06	7,00E-03
Platelets	29892013	600,968	$5x10^{-8}$	1320	0,10	0,05	5,33E-02	4,61	0,11	0,15	0,09	1,10E-01	0,00	0,53	0,12	0,09	2,05E-01
vonWillebrandFactor	33328453	10,708	$5x10^{-8}$	6	0,30	0,18	9,65E-02	66,29	0,04	-0,10	0,39	8,17E-01	0,07	0,33	0,38	0,17	2,91E-02
Prothrombin_time	33441150	34,919	$5x10^{-8}$	4	0,31	0,21	1,32E-01	5,56	0,55	0,44	0,72	6,06E-01	-0,02	0,87	0,22	0,24	3,75E-01
Coagulation Factor IX	33328453	10,708	$1x10^{-6}$	7	0,32	0,23	1,56E-01	52,21	0,11	0,13	1,32	9,25E-01	0,02	0,89	0,44	0,25	7,69E-02
Protein_S_free	37128921	4,113	$1x10^{-6}$	5	-0,01	0,01	1,83E-01	0,00	0,94	-0,01	0,01	4,76E-01	0,02	0,78	-0,01	0,01	1,47E-01
Neutrophil	32888493	519,288	$5x10^{-8}$	748	-0,09	0,07	2,07E-01	2,09	0,34	-0,28	0,15	6,87E-02	0,00	0,17	-0,17	0,15	2,56E-01
Tissue_plasminogen_activator	33067605	21,758	$1x10^{-6}$	5	-0,31	0,27	2,53E-01	23,95	0,41	-0,45	0,90	6,55E-01	0,01	0,88	-0,36	0,36	3,25E-01
Lymphocytes	32888493	524,923	$5x10^{-8}$	962	0,07	0,07	2,92E-01	6,92	0,06	-0,03	0,14	8,33E-01	0,00	0,42	-0,03	0,11	7,94E-01
Protein_S_total	37128921	6,409	$1x10^{-5}$	21	0,00	0,01	3,47E-01	46,45	0,02	-0,01	0,01	6,83E-01	0,00	0,99	0,00	0,01	9,68E-01
Fibrinogen	33328453	10,708	$1x10^{-6}$	5	0,22	0,24	3,57E-01	55,74	0,15	0,13	0,74	8,70E-01	0,02	0,91	0,08	0,22	7,13E-01
Antithrombin	37128921	25,243	$5x10^{-8}$	4	-0,02	0,02	3,60E-01	29,02	0,42	0,10	0,08	3,24E-01	-0,15	0,25	-0,03	0,03	2,30E-01
Coagulation Factor VII	33328453	10,708	$5x10^{-8}$	9	-0,03	0,04	3,73E-01	0,00	0,89	-0,01	0,05	9,11E-01	-0,02	0,44	-0,03	0,04	4,98E-01
Monocytes	29892013	545,193	$5x10^{-8}$	893	-0,04	0,06	5,00E-01	3,35	0,24	0,06	0,11	5,56E-01	0,00	0,24	0,03	0,10	7,94E-01
Coagulation Factor Xa	33328453	10,708	$5x10^{-8}$	8	-0,08	0,12	5,10E-01	56,51	0,05	0,03	0,25	9,15E-01	-0,02	0,63	-0,01	0,13	9,23E-01
Plasminogen_activator_inhibitor	34187551	34,448	$5x10^{-8}$	5	0,00	0,00	5,19E-01	65,32	0,07	0,00	0,00	7,24E-01	-0,18	0,77	0,00	0,00	4,21E-01
Eosinophil	29892013	513,859	$5x10^{-8}$	811	0,04	0,07	5,33E-01	4,53	0,18	-0,02	0,14	8,72E-01	0,00	0,58	0,01	0,12	9,09E-01
Leukocytes	29892013	503,19	$5x10^{-8}$	734	-0,04	0,08	5,73E-01	0,69	0,45	-0,19	0,18	2,97E-01	0,00	0,37	-0,13	0,14	3,61E-01
Coagulation Factor X	33328453	10,708	$5x10^{-8}$	10	-0,05	0,10	5,95E-01	41,02	0,14	-0,01	0,20	9,55E-01	-0,01	0,82	0,00	0,11	9,91E-01
Basophil	32888493	474,001	$5x10^{-8}$	270	0,06	0,12	6,17E-01	0,00	0,55	-0,24	0,25	3,37E-01	0,01	0,17	-0,23	0,20	2,51E-01
Neutrophil_Extracellular_Traps	37388819	657	$1x10^{-6}$	3	-0,02	0,05	6,44E-01	63,97	0,25	0,46	0,31	3,76E-01	-0,45	0,36	-0,06	0,05	2,31E-01
Coagulation Factor XIII	33328453	10,708	$5x10^{-8}$	13	0,02	0,06	7,58E-01	0,00	0,84	0,08	0,10	4,01E-01	-0,03	0,41	0,02	0,07	7,65E-01
Protein_C	37128921	16,597	$5x10^{-8}$	14	-0,02	0,07	8,02E-01	44,47	0,06	-0,06	0,10	5,99E-01	0,01	0,61	-0,04	0,07	5,82E-01
Coagulation Factor V	33328453	10,708	$5x10^{-8}$	10	-0,01	0,08	8,99E-01	46,85	0,09	-0,11	0,14	4,54E-01	0,03	0,40	-0,12	0,08	1,59E-01
Erythrocyte	29892013	526,54	$5x10^{-8}$	947	-0,01	0,06	9,13E-01	2,76	0,27	-0,07	0,12	5,71E-01	0,00	0,55	-0,12	0,13	3,42E-01
Thrombomoduline	33067605	21,758	$5x10^{-8}$	9	0,00	0,11	9,64E-01	43,68	0,13	0,16	0,18	4,07E-01	-0,04	0,30	0,01	0,10	8,97E-01
Fibrin_Ddimeres	29875488	3,301	$1x10^{-5}$	12	0,00	0,10	9,91E-01	23,65	0,29	-0,18	0,33	5,94E-01	0,03	0,57	0,04	0,12	7,20E-01

Table 5: Significant results of pQTL MR on VT recurrence.

STUDY	UniProt_ID	FULLNAME	GENE_NAME	GENE_ID	NbSNPS	Beta_IVW	SE_IVW	P_IVW	Heterogeneity	P_Heterogeneity	Beta_Egger	SE_Egger	P_Egger	Egger_Intercept	P_Intercept	Beta_Wmedian	SE_Wmedian	P_Wmedian
DECODE	Q6P4E1	Protein GOLM2	GOLM2	ENSG00000166734	34	0,30	0,07	4,36E-06	11,45	0,32	0,25	0,10	1,39E-02	0,01	0,49	0,26	0,08	8,36E-04
UK Biobank	Q6P4E1	Protein GOLM2	GOLM2	ENSG00000166734	21	0,34	0,08	2,73E-05	2,97	0,48	0,40	0,13	7,16E-03	-0,01	0,58	0,44	0,11	5,95E-05
FENLAND	Q6P4E1	Protein GOLM2	GOLM2	ENSG00000166734	6	0,27	0,08	4,37E-04	0,00	0,76	0,35	0,13	5,32E-02	-0,02	0,50	0,29	0,08	3,62E-04
DECODE	Q14005	Pro-interleukin-16 [Cleaved into: Interleukin-16	IL16	ENSG00000172349	36	-0,21	0,05	7,77E-06	0,00	0,81	-0,16	0,06	1,00E-02	-0,02	0,13	-0,16	0,05	2,87E-03
UK Biobank	Q14005	Pro-interleukin-16 [Cleaved into: Interleukin-16	IL16	ENSG00000172349	19	-0,15	0,06	1,06E-02	0,00	0,62	-0,16	0,07	2,61E-02	0,01	0,63	-0,16	0,06	6,82E-03
FENLAND	Q14005	Pro-interleukin-16 [Cleaved into: Interleukin-16	IL16	ENSG00000172349	5	-0,13	0,07	4,54E-02	51,96	0,18	-0,21	0,07	5,33E-02	0,05	0,16	-0,14	0,05	1,20E-02
UK Biobank	Q8NBP7	Proprotein convertase subtilisin/kexin type 9	PCSK9	ENSG00000169174	21	-0,38	0,08	4,70E-06	0,00	0,57	-0,46	0,11	3,44E-04	0,02	0,23	-0,47	0,10	9,94E-07
FENLAND	Q8NBP7	Proprotein convertase subtilisin/kexin type 9	PCSK9	ENSG00000169174	5	-0,47	0,14	1,04E-03	52,71	0,17	-0,73	0,16	1,99E-02	0,08	0,11	-0,60	0,14	1,68E-05
DECODE	Q8NBP7	Proprotein convertase subtilisin/kexin type 9	PCSK9	ENSG00000169174	17	-0,31	0,16	6,07E-02	70,08	2,18E-05	-0,51	0,23	4,17E-02	0,04	0,23	-0,52	0,13	4,86E-05

SUPPLEMENTARY TABLE TITLES

Supplementary Table S1: Design and genetic/phenotypic details of studies that contributed to the meta-analysis on VT recurrence.

Supplementary Table S2: List of the tissues from GTEx v8 analyzed in TWAS.

Supplementary Table S3: Description of the 29 haemostatic phenotypes from GWAS catalog used to perform targeted MR with VT recurrence.

Supplementary Table S4: Description of the clinical characteristics of the patients from the studies part of the meta-analysis according to the incidence of VT recurrence.

Supplementary Table S5: Study specific effects of the three genome-wide significant loci associated with VT recurrence in the GWAS meta-analysis.

Supplementary Table S6: Effect of rs72844599 (*THSD7B*) on VT recurrence in younger patients in EDITH, MARTHA and MEGA.

Supplementary Table S7: Lead variants identified in GWAS for VT recurrence (in global and in subgroups) and their impact in proteogenomic resources.

Supplementary Table S8: Additional *GATA5* locus strongly associated with VT recurrence in the GWAS meta-analysis.

Supplementary Table S9: Association with VT recurrence of 88 SNPs previously identified to associate with first VT.

Supplementary Table S10: Main results of TWAS performed on the summary statistics of the GWAS meta-analysis on VT recurrence.

Supplementary Table S11: All results of pQTL MR with IVW method on VT recurrence

Supplementary Table S12: Instruments used for MR analyses on GOLM2, IL16 (from deCODE) and PCSK9 (from UK Biobank) and their association with first VT and VT recurrence.

Supplementary Table S13: Association of ABO haplotypes with GOLM2 plasma levels in the 3C-study (N=1,087).

Supplementary Table S14: Effect of ABO variants on VT recurrence in the GWAS meta-analysis (N=6,571).

Supplementary Table S15: Results of MR analyses with 459 metabolites from *Chen et al. (2022)* on the risk of VT recurrence.

Supplementary Table S16: Genome wide significant variant ($P<5\times10^{-8}$) associated with VT recurrence in the GWAS meta-analysis for the 6 subgroups.

Supplementary Table S17: Results of TWAS on VT recurrence in the 6 subgroups that passed the statistical threshold used for the main analysis ($P<7.7\times10^{-6}$).

Supplementary Table S18: Results of MR analyses with 29 haemostatic phenotypes on the risk of VT recurrence in 6 subgroups.

Supplementary Table S19: Nominal results of pQTL MR analyses with IVW method on the risk of VT recurrence in 6 subgroups.

Supplementary Table S20: Nominal associations of MR analyses with 459 metabolites on the risk of VT recurrence in the 6 subgroups.

Supplementary Table S21: Effect of GOLM2 pQTLs identified in the three proteogenomic resources on the risk of VT recurrence in the GWAS meta-analysis.

Supplementary Table S22: Effects of the missense variant PCSK9 p.Arg46Leu (rs11591147-T) on the risk of VT recurrence in EDITH patients with available information on treatment.

Supplementary Table S23: Effects of the variants identified with VT recurrence on the risk of first VT in *Thibord et al. (2022)* and their frequencies in ethnic groups.

FIGURE LEGENDS

Figure 1: Manhattan plot representing GWAS results from the meta-analysis on VT recurrence. Horizontal red line represents the genome wide threshold ($P<5\times10^{-8}$). The three significant loci are annotated on this plot with their nearest gene.

Figure 2: Regional association plot of the three significant loci and the suggestive locus identified in the main GWAS meta-analysis on VT recurrence. A) rs34097149 (3q25.2 *GPR149;MME*). B) rs144475075 (18p11.31 *L3MBTL4*). C) rs72844599 (2q22.1 *THSD7B*). D) rs73149254 (20q13.33 *GATA5*). This plot was generated with *locuszoom* software.

Figure 3: Representation of all loci identified to significantly associate with VT recurrence. Shapes are specific to the analysis: round for GWAS, diamond for pQTL-MR, circle for look-up of first VT SNPs, square for TWAS and triangle for MR on haemostasis phenotypes. Different colours are used to differentiate the groups: blue for the global analysis, dark green for unprovoked, yellow for provoked, light green for PE, red for DVT, dark for females and pink for males. This plot was generated with *PhenoGram* web tool (http://visualization.ritchielab.org/).

SUPPLEMENTARY FIGURE LEGENDS

Supplementary Figure S1: Study-specific effect of the 4 loci identified in the GWAS meta-analysis for VT recurrence. Figure A corresponds to rs34097149-C (*GPR149;MME*), B to rs144475075-T (*L3MBTL4*), C to rs72844599-T (*THSD7B*) and D to rs73149254-A (*GATA5*). N: Total sample size / NREC: Number of VT recurrences / EAF: Effect Allele Frequency / HR: Hazard Ratio for VT recurrence.

Supplementary Figure S2: Subgroup-specific effect of the 4 loci identified in the GWAS meta-analysis for VT recurrence. Figure A corresponds to rs34097149-C (*GPR149;MME*), B to

rs144475075-T (*L3MBTL4*), C to rs72844599-T (*THSD7B*) and D to rs73149254-A (*GATA5*). N: Total sample size / NREC: Number of VT recurrences / EAF: Effect Allele Frequency / HR: Hazard Ratio for VT recurrence.

Supplementary Figure S3: Representation of the associations with VT recurrence in the three proteogenomics resources and according to the MR sensitivity methods, for the three proteins identified in the pQTL-MR analysis.

Supplementary Figure S4: Construction of haplotypes with LD Link tool[77] (https://ldlink.nih.gov/) using the 5 variants identified by *Goumidi et al. (2021)*[78] to tag ABO haplotypes and 2 pQTLs of GOLM2 located in the *ABO* locus (rs550057 by Fenland and UK Biobank ; rs687289 by deCODE).

Supplementary Figure S5: Associations of rs145765113-T identified in the female subgroup. A) Forest plot representing the hazard ratio for VT recurrence of the SNP-effects across the subgroups and in the main analysis. B) Forest plot representing the hazard ratio for VT recurrence of the SNP in the female subgroup for all studies that contributed to this subgroup analysis. C) Regional association plot around the SNP in the female subgroup analysis. N: sample size / NREC: number of VT recurrences / EAF: effect allele frequency / INFO: imputation quality score / HR: Hazard ratio.

Supplementary Figure S6: Associations of rs185486549-A identified in the female subgroup. A) Forest plot representing the hazard ratio for VT recurrence of the SNP-effects across the subgroups and in the main analysis. B) Forest plot representing the hazard ratio for VT recurrence of the SNP in the female subgroup for all studies that contributed to this subgroup analysis. C) Regional association plot around the SNP in the female subgroup analysis. N: sample size / NREC: number of VT recurrences / EAF: effect allele frequency / INFO: imputation quality score / HR: Hazard ratio.

Supplementary Figure S7: Associations of rs115157965-T identified in the male subgroup. A) Forest plot representing the hazard ratio for VT recurrence of the SNP-effects across the subgroups and in the main analysis. B) Forest plot representing the hazard ratio for VT recurrence of the SNP in the male subgroup for all studies that contributed to this subgroup analysis. C) Regional association plot around the SNP in the male subgroup analysis. N: sample size / NREC: number of VT recurrences / EAF: effect allele frequency / INFO: imputation quality score / HR: Hazard ratio.

Supplementary Figure S8: Associations of rs116666788-A identified in the DVT only as first VT subgroup. A) Forest plot representing the hazard ratio for VT recurrence of the SNP-effects across the subgroups and in the main analysis. B) Forest plot representing the hazard ratio for VT recurrence of the SNP in the DVT subgroup for all studies that contributed to this subgroup analysis. C) Regional association plot around the SNP in the DVT subgroup analysis. N: sample size / NREC: number of VT recurrences / EAF: effect allele frequency / INFO: imputation quality score / HR: Hazard ratio.

Supplementary Figure S9: Associations of rs117366080-A identified in the DVT only as first VT subgroup. A) Forest plot representing the hazard ratio for VT recurrence of the SNP-effects across the subgroups and in the main analysis. B) Forest plot representing the hazard ratio for VT recurrence of

the SNP in the DVT subgroup for all studies that contributed to this subgroup analysis. C) Regional association plot around the SNP in the DVT subgroup analysis. N: sample size / NREC: number of VT recurrences / EAF: effect allele frequency / INFO: imputation quality score / HR: Hazard ratio.

Supplementary Figure S10: Associations of rs45562031-T identified in the PE as first VT subgroup. A) Forest plot representing the hazard ratio for VT recurrence of the SNP-effects across the subgroups and in the main analysis. B) Forest plot representing the hazard ratio for VT recurrence of the SNP in the PE subgroup for all studies that contributed to this subgroup analysis. C) Regional association plot around the SNP in the PE subgroup analysis. N: sample size / NREC: number of VT recurrences / EAF: effect allele frequency / INFO: imputation quality score / HR: Hazard ratio.

Supplementary Figure S11: Associations of rs140802879-G identified in the PE as first VT subgroup. A) Forest plot representing the hazard ratio for VT recurrence of the SNP-effects across the subgroups and in the main analysis. B) Forest plot representing the hazard ratio for VT recurrence of the SNP in the PE subgroup for all studies that contributed to this subgroup analysis. C) Regional association plot around the SNP in the PE subgroup analysis. N: sample size / NREC: number of VT recurrences / EAF: effect allele frequency / INFO: imputation quality score / HR: Hazard ratio.

Supplementary Figure S12: Associations of rs34475559-A identified in the PE as first VT subgroup. A) Forest plot representing the hazard ratio for VT recurrence of the SNP-effects across the subgroups and in the main analysis. B) Forest plot representing the hazard ratio for VT recurrence of the SNP in the PE subgroup for all studies that contributed to this subgroup analysis. C) Regional association plot around the SNP in the PE subgroup analysis. N: sample size / NREC: number of VT recurrences / EAF: effect allele frequency / INFO: imputation quality score / HR: Hazard ratio.

Supplementary Figure S13: Associations of rs6474692-A identified in the PE as first VT subgroup. A) Forest plot representing the hazard ratio for VT recurrence of the SNP-effects across the subgroups and in the main analysis. B) Forest plot representing the hazard ratio for VT recurrence of the SNP in the PE subgroup for all studies that contributed to this subgroup analysis. C) Regional association plot around the SNP in the PE subgroup analysis. N: sample size / NREC: number of VT recurrences / EAF: effect allele frequency / INFO: imputation quality score / HR: Hazard ratio.

Supplementary Figure S14: Associations of rs148611543-A identified in the unprovoked first VT subgroup. A) Forest plot representing the hazard ratio for VT recurrence of the SNP-effects across the subgroups and in the main analysis. B) Forest plot representing the hazard ratio for VT recurrence of the SNP in the unprovoked subgroup for all studies that contributed to this subgroup analysis. C) Regional association plot around the SNP in the unprovoked subgroup analysis. N: sample size / NREC: number of VT recurrences / EAF: effect allele frequency / INFO: imputation quality score / HR: Hazard ratio.

Supplementary Figure S15: Associations of rs117509298-C identified in the unprovoked first VT subgroup. A) Forest plot representing the hazard ratio for VT recurrence of the SNP-effects across the

subgroups and in the main analysis. B) Forest plot representing the hazard ratio for VT recurrence of the SNP in the unprovoked subgroup for all studies that contributed to this subgroup analysis. C) Regional association plot around the SNP in the unprovoked subgroup analysis. N: sample size / NREC: number of VT recurrences / EAF: effect allele frequency / INFO: imputation quality score / HR: Hazard ratio.

Supplementary Figure S16: Associations of rs148811092-A identified in the provoked first VT subgroup. A) Forest plot representing the hazard ratio for VT recurrence of the SNP-effects across the subgroups and in the main analysis. B) Forest plot representing the hazard ratio for VT recurrence of the SNP in the provoked subgroup for all studies that contributed to this subgroup analysis. C) Regional association plot around the SNP in the provoked subgroup analysis. N: sample size / NREC: number of VT recurrences / EAF: effect allele frequency / INFO: imputation quality score / HR: Hazard ratio.

Supplementary Figure S17: Associations of rs3744462-G identified in the provoked first VT subgroup. A) Forest plot representing the hazard ratio for VT recurrence of the SNP-effects across the subgroups and in the main analysis. B) Forest plot representing the hazard ratio for VT recurrence of the SNP in the provoked subgroup for all studies that contributed to this subgroup analysis. C) Regional association plot around the SNP in the provoked subgroup analysis. N: sample size / NREC: number of VT recurrences / EAF: effect allele frequency / INFO: imputation quality score / HR: Hazard ratio.

Supplementary Figure S18: Associations of rs112440311-T identified in the provoked first VT subgroup. A) Forest plot representing the hazard ratio for VT recurrence of the SNP-effects across the subgroups and in the main analysis. B) Forest plot representing the hazard ratio for VT recurrence of the SNP in the provoked subgroup for all studies that contributed to this subgroup analysis. C) Regional association plot around the SNP in the provoked subgroup analysis. N: sample size / NREC: number of VT recurrences / EAF: effect allele frequency / INFO: imputation quality score / HR: Hazard ratio.

Supplementary Figure S19: Associations of rs111665167-A identified in the provoked first VT subgroup. A) Forest plot representing the hazard ratio for VT recurrence of the SNP-effects across the subgroups and in the main analysis. B) Forest plot representing the hazard ratio for VT recurrence of the SNP in the provoked subgroup for all studies that contributed to this subgroup analysis. C) Regional association plot around the SNP in the provoked subgroup analysis. N: sample size / NREC: number of VT recurrences / EAF: effect allele frequency / INFO: imputation quality score / HR: Hazard ratio.

Supplementary Figure S20: Associations of rs6475173-A identified in the provoked first VT subgroup. A) Forest plot representing the hazard ratio for VT recurrence of the SNP-effects across the subgroups and in the main analysis. B) Forest plot representing the hazard ratio for VT recurrence of

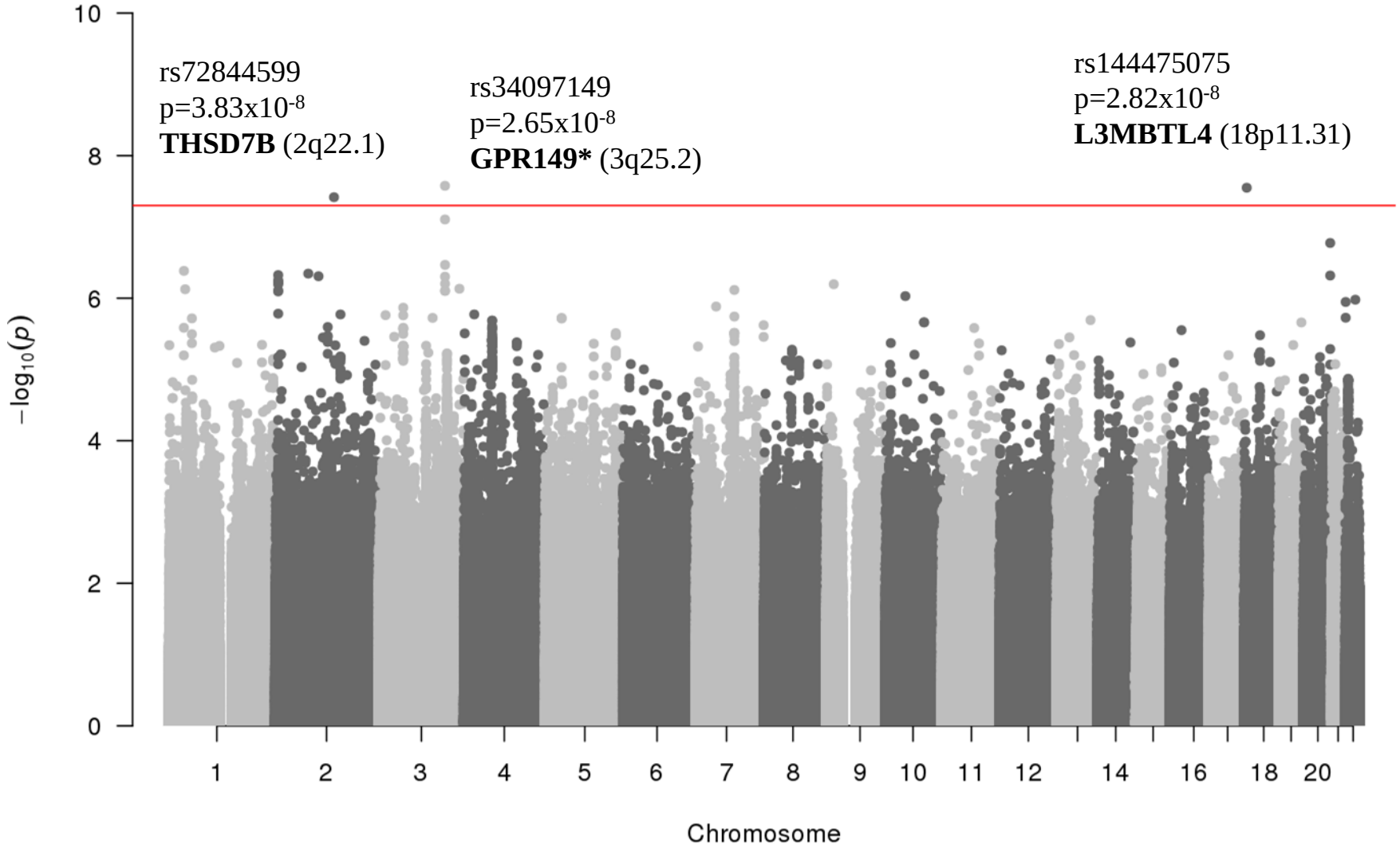
the SNP in the provoked subgroup for all studies that contributed to this subgroup analysis. C) Regional association plot around the SNP in the provoked subgroup analysis. N: sample size / NREC: number of VT recurrences / EAF: effect allele frequency / INFO: imputation quality score / HR: Hazard ratio.

Supplementary Figure S21: Associations of rs62174841-T identified in the provoked first VT subgroup. A) Forest plot representing the hazard ratio for VT recurrence of the SNP-effects across the subgroups and in the main analysis. B) Forest plot representing the hazard ratio for VT recurrence of the SNP in the provoked subgroup for all studies that contributed to this subgroup analysis. C) Regional association plot around the SNP in the provoked subgroup analysis. N: sample size / NREC: number of VT recurrences / EAF: effect allele frequency / INFO: imputation quality score / HR: Hazard ratio.

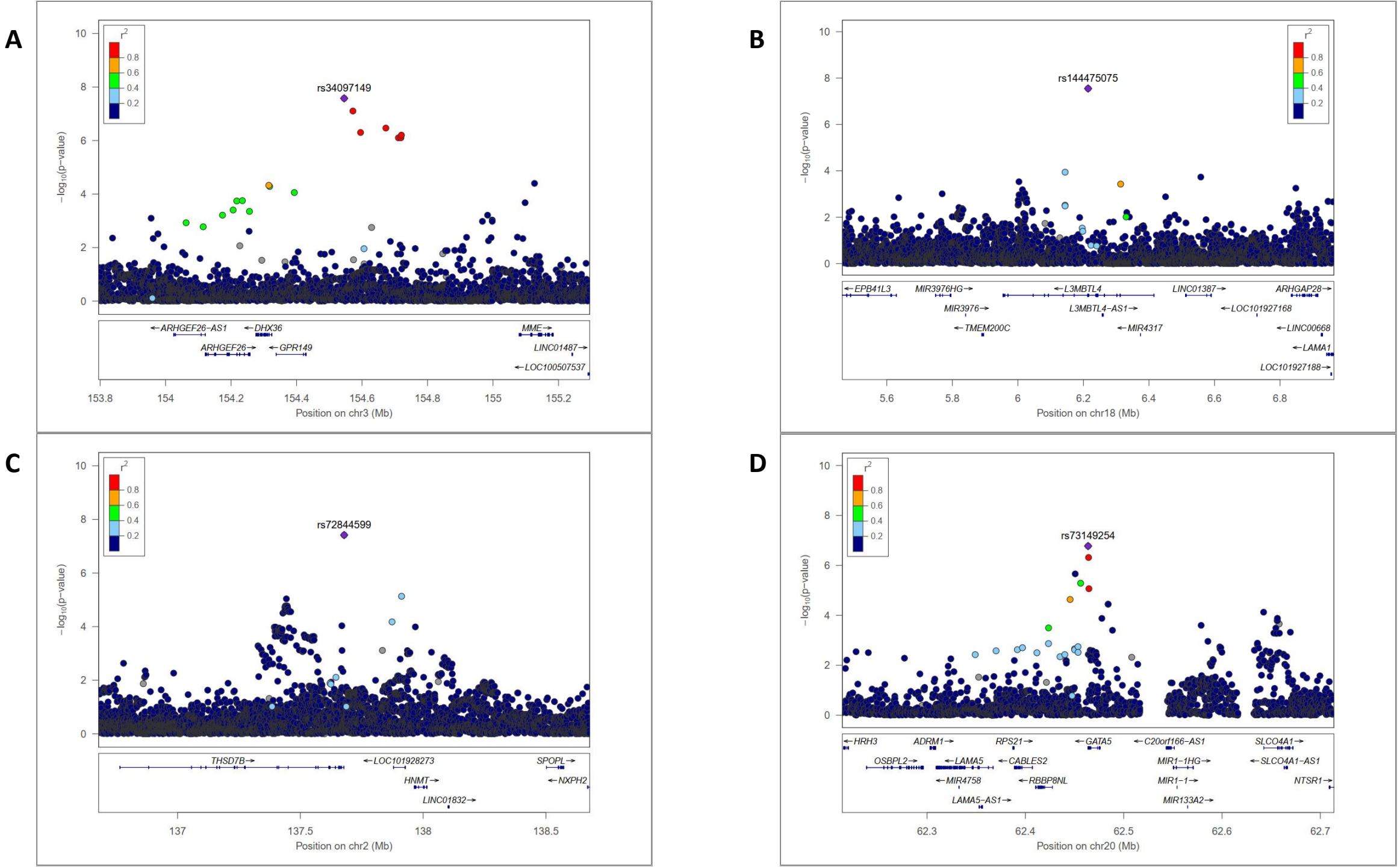
Supplementary Figure S22: Associations of rs180737225-G identified in the provoked first VT subgroup. A) Forest plot representing the hazard ratio for VT recurrence of the SNP-effects across the subgroups and in the main analysis. B) Forest plot representing the hazard ratio for VT recurrence of the SNP in the provoked subgroup for all studies that contributed to this subgroup analysis. C) Regional association plot around the SNP in the provoked subgroup analysis. N: sample size / NREC: number of VT recurrences / EAF: effect allele frequency / INFO: imputation quality score / HR: Hazard ratio.

Supplementary Figure S23: Forest plot representing the associations of rs6035-T in the studies and the whole meta-analysis on VT recurrence. N: sample size / NREC: number of VT recurrences / EAF: effect allele frequency / INFO: imputation quality score / HR: Hazard ratio.

Supplementary Figure S24: Forest plot representing the associations of rs9946608-C in the studies and the whole meta-analysis on VT recurrence. N: sample size / NREC: number of VT recurrences / EAF: effect allele frequency / INFO: imputation quality score / HR: Hazard ratio.



**nearest gene*


A
rs34097149
r²
0.8
0.6
0.4
0.2
−log10(p−value)
ARHGEF26−AS1
DHX36
MME
ARHGEF26
GPR149
LINC01487
LOC100507537
153.8
154
154.2
154.4
154.6
154.8
155
155.2
Position on chr3 (Mb)
B
rs144475075
EPB41L3
MIR3976HG
L3MBTL4
LINC01387
ARHGAP28
MIR3976
L3MBTL4−AS1
LOC101927168
TMEM200C
MIR4317
LINC00668
LAMA1
LOC101927188
5.6
5.8
6
6.2
6.4
6.6
6.8
Position on chr18 (Mb)
C
rs72844599
THSD7B
LOC101928273
SPOPL
HNMT
NXPH2
LINC01832
137
137.5
138
138.5
Position on chr2 (Mb)
D
rs73149254
HRH3
ADRM1
RPS21
GATA5
C20orf166−AS1
SLCO4A1
OSBPL2
LAMA5
CABLES2
MIR1−1HG
SLCO4A1−AS1
MIR4758
RBBP8NL
MIR1−1
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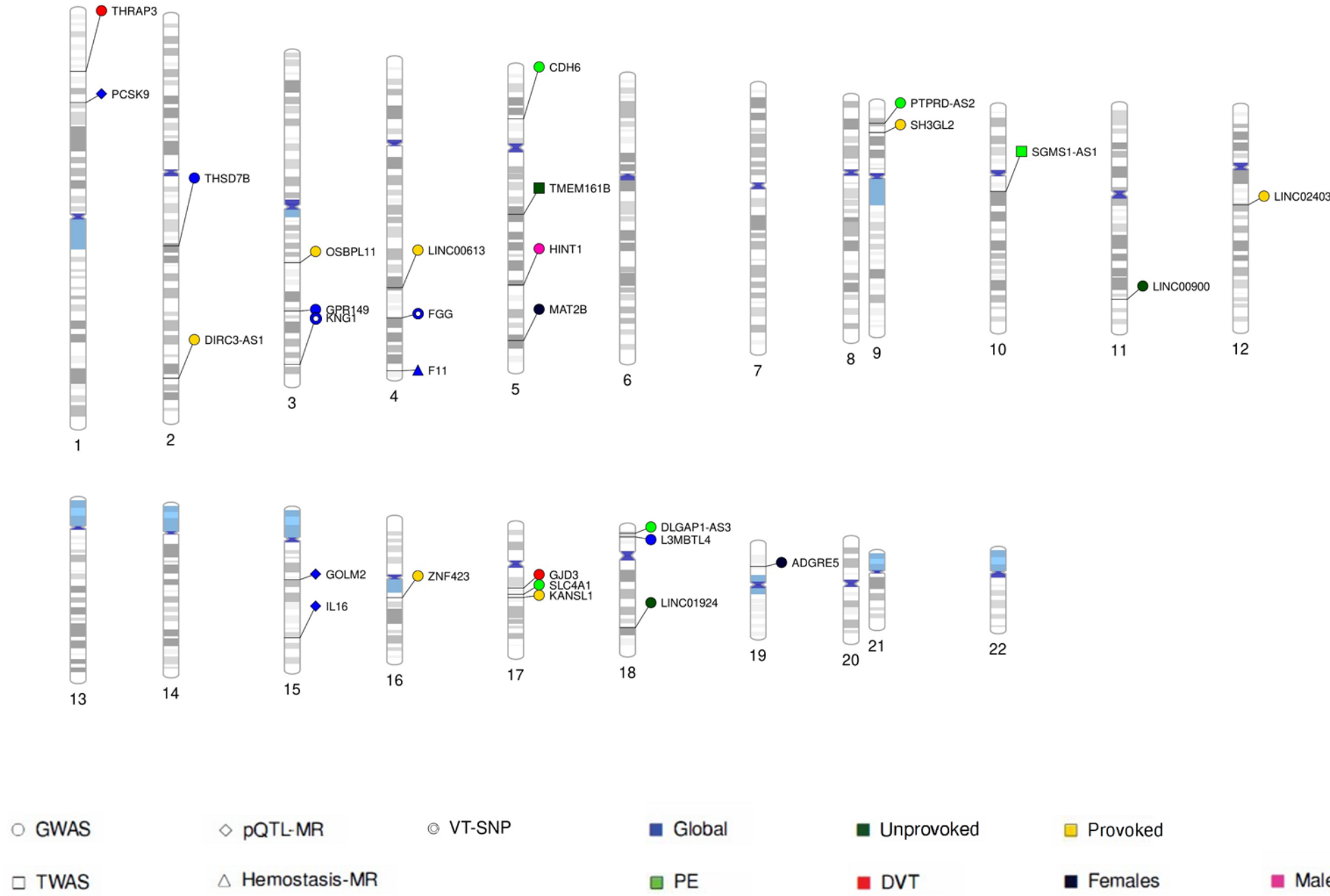
LAMA5−AS1
MIR133A2
62.3
62.4
62.5
62.6
62.7
Position on chr20 (Mb)


THRAP3
PCSK9
THSD7B
DIRC3-AS1
OSBPL11
GPR149
KNG1
LINC00613
FGG
F11
CDH6
TMEM161B
HINT1
MAT2B
PTPRD-AS2
SH3GL2
SGMS1-AS1
LINC00900
LINC02403
GOLM2
IL16
ZNF423
GJD3
SLC4A1
KANSL1
DLGAP1-AS3
L3MBTL4
LINC01924
ADGRE5
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
GWAS
pQTL-MR
VT-SNP
Global
Unprovoked
Provoked
TWAS
Hemostasis-MR
PE
DVT
Females
Males