ORIGINAL ARTICLE

Multi-phenotype analyses of hemostatic traits with cardiovascular events reveal novel genetic associations

Gerard Temprano-Sagrera[1] | Colleen M. Sitlani[2] | William P. Bone[3] |
Miguel Martin-Bornez[1] | Benjamin F. Voight[4,5] | Alanna C. Morrison[6] |
Scott M. Damrauer[7,8] | Paul S. de Vries[6] | Nicholas L. Smith[9,10,11] |
Maria Sabater-Lleal[1,12]

[1]Genomics of Complex Disease Unit, Sant Pau Biomedical Research Institute. IIB-Sant Pau, Barcelona, Spain

[2]Cardiovascular Health Research Unit, Department of Medicine, University of Washington, Seattle, Washington, USA

[3]Genomics and Computational Biology Graduate Group, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

[4]Department of Systems Pharmacology and Translational Therapeutics and Department of Genetics, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA

[5]Institute of Translational Medicine and Therapeutics, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA

[6]Human Genetics Center, Department of Epidemiology, Human Genetics, and Environmental Sciences, School of Public Health, The University of Texas Health Science Center at Houston, Houston, Texas, USA

[7]Department of Surgery and Department of Genetics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

[8]Corporal Michael Crescenz VA Medical Center, Philadelphia, Pennsylvania, USA

[9]Department of Epidemiology, University of Washington, Seattle, Washington, USA

[10]Kaiser Permanente Washington Health Research Institute, Kaiser Permanente, Seattle, Washington, USA

[11]Seattle Epidemiologic Research and Information Center, Department of Veterans Affairs Office of Research and Development, Seattle, Washington, USA

[12]Cardiovascular Medicine Unit, Department of Medicine, Center for Molecular Medicine, Karolinska Institutet, Stockholm, Sweden

Correspondence
Maria Sabater-Lleal, Genomics of Complex Disease Unit, Sant Pau Biomedical Research Institute (IIB Sant Pau), St. Quintí 77-79, P3-002, 08041-Barcelona, Spain.
Email: msabater@santpau.cat

Funding information
National Heart, Lung, and Blood Institute, Grant/Award Number: HL134894, HL139553 and HL141291; European Social Fund

Abstract

Background: Multi-phenotype analysis of genetically correlated phenotypes can increase the statistical power to detect loci associated with multiple traits, leading to the discovery of novel loci. This is the first study to date to comprehensively analyze the shared genetic effects within different hemostatic traits, and between these and their associated disease outcomes.

Objectives: To discover novel genetic associations by combining summary data of correlated hemostatic traits and disease events.

Methods: Summary statistics from genome wide-association studies (GWAS) from seven hemostatic traits (factor VII [FVII], factor VIII [FVIII], von Willebrand factor [VWF] factor XI [FXI], fibrinogen, tissue plasminogen activator [tPA], plasminogen activator inhibitor 1 [PAI-1]) and three major cardiovascular (CV) events (venous thromboembolism [VTE], coronary artery disease [CAD], ischemic stroke [IS]), were

combined in 27 multi-trait combinations using metaUSAT. Genetic correlations between phenotypes were calculated using Linkage Disequilibrium Score Regression (LDSC). Newly associated loci were investigated for colocalization. We considered a significance threshold of 1.85×10^{-9} obtained after applying Bonferroni correction for the number of multi-trait combinations performed ($n = 27$).

Results: Across the 27 multi-trait analyses, we found 4 novel pleiotropic loci (*XXYLT1*, *KNG1*, *SUGP1/MAU2*, *TBL2/MLXIPL*) that were not significant in the original individual datasets, were not described in previous GWAS for the individual traits, and that presented a common associated variant between the studied phenotypes.

Conclusions: The discovery of four novel loci contributes to the understanding of the relationship between hemostasis and CV events and elucidate common genetic factors between these traits.

KEYWORDS

blood coagulation, cardiovascular diseases, genetic pleiotropy, genome-wide association study, hemostasis

1 | INTRODUCTION

Genome-wide association studies (GWAS) have identified dozens of loci underlying the variability of plasma levels for individual hemostatic traits.[1-8] Further, GWAS for venous thromboembolism (VTE),[9,10] coronary artery disease (CAD)[11-13] and ischemic stroke (IS),[11,14] have discovered 34, 169, and 20 genetic risk loci associated with these cardiovascular (CV) events, respectively.

Results from GWAS indicate that several of these hemostatic traits are genetically correlated with each other, sharing genetic loci that regulate their plasma levels.[1,4-8] There are also shared genetic loci between hemostatic traits and CV events, again suggesting common regulators and possibly a causal pathway between the hemostatic trait and the CV event.[4,7-9,12,14] The common regulatory loci between traits—even if the traits are not causally associated with each other—can be used to advance discovery of novel genetic loci common to the traits. This discovery can be accomplished with multi-phenotype methods that incorporate summary statistics from several GWAS, increasing the statistical power to detect loci affecting two or more phenotypes by increasing the effective sample size.[15-17]

In the present study, we used summary statistics of published GWAS from 7 hemostatic traits (FVII, FVIII, VWF, FXI, fibrinogen, PAI-1, tPA), and 3 CV events (VTE, CAD, IS) to calculate their genetic correlations and to conduct multi-phenotype meta-analyses to detect new genetic loci not previously known to be associated with these phenotypes.

2 | METHODS

2.1 | Study design and resources

The setting of the project is the Cohorts of Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium

---

Essentials

- Multi-phenotype analysis of genetically correlated phenotypes may lead to novel discoveries.
- Summary statistics of hemostatic traits and cardiovascular events were combined with metaUSAT.
- We identified four novel associations with a shared variant between the studied phenotypes.
- Our results shed light on the relationship between hemostatic traits and cardiovascular events.

Hemostasis Working Group.[18] We used GWAS summary statistics from seven hemostatic traits (FVII ($N = 27\,495$), FVIII ($N = 32\,610$), VWF ($N = 46\,354$), FXI ($N = 16\,169$), fibrinogen ($N = 120\,246$), PAI-1 ($N = 19\,599$), tPA ($N = 26\,929$)), and three CV events (VTE (N cases $= 30\,234$, N controls $= 172\,122$), CAD (N cases $= 172\,122$, N controls $= 566\,864$), IS (N cases $= 60\,341$, N controls $= 454\,450$)) to perform multi-phenotype analyses. Summary statistics of FVII,[1] FVIII,[4] VWF,[4] VTE,[9] CAD[12,13,19] and IS,[14] come from trans-ethnic analyses, while summary statistics of FXI,[6] fibrinogen,[5] tPA[8] and PAI-1[7] are European ancestry only (additional information, including the sample sizes, detailed ancestry groups, confounders considered and data access URLs, of the phenotypes that have been used, is available in Supplementary Table S1). Summary statistics for FVII, FVIII, VWF, FXI, fibrinogen, tPA, PAI-1, were obtained from the most recent CHARGE meta-analysis data[18] and are available on dbGaP[20] (Appendix A). Data for VTE was obtained from INVENT[9] consortium and is available on request from corresponding authors (Appendix B). Data from IS were obtained from the MEGASTROKE Consortium,[14] and is available at https://www.megastroke.org/ (Appendix C). For CAD, we used METAL to perform an inverse variance weighted meta-analysis between previously combined data

from CARDIoGRAMplusC4D Consortium[19] and UK Biobank datasets[12] (available at https://data.mendeley.com/datasets/2zdd47c94h/1), and the Biobank Japan dataset available at https://humandbs.biosciencedbc.jp/en/hum0014-v21 using METAL. All the included data have been published between December 2012 and October 2020. The overlap of individuals observed in our combinations of phenotypes ranges between 0 and 0.58. The overlap between the CARDIoGRAMplusC4D Consortium and UK Biobank datasets that were combined by other authors, and used in this project, was estimated to be <0.1 %.[12]

2.2 | Study of heritability and genetic correlation

We determined the heritability of each phenotype and genetic correlations (r_g) between all pairs of hemostatic traits, between each hemostatic factor and the CV events and between all pairs of CV events, using linkage disequilibrium (LD) score regression (LDSC).[21] LDSC uses a regression analysis between LD scores and the summary statistics of GWAS to provide an estimate of the shared heritability between phenotypes.[22] We used pre-computed LD scores from the European population of 1000G project.[23] A subset of the European-ancestry summary statistics was used in this step for each trait except for CAD where the European-only meta-analysis was not available. Alleles were merged with the HapMap3 single nucleotide polymorphisms (SNPs) list,[24] to avoid incompatibilities between phenotypes, as recommended by the authors, and missing variants were removed.

For the threshold of statistical significance for each genetic correlation, we applied a Bonferroni correction for multiple comparisons, considering all pairwise genetic correlations calculated ($p < .05/45 = .001$).

2.3 | Multi-phenotype analysis

We performed multi-phenotype analyses using GWAS summary statistics from different combinations of traits using the metaUSAT R package.[17] metaUSAT is a statistical approach for testing genetic association with one or more phenotypes simultaneously, using only common variants between the phenotypes. metaUSAT allows summary data as input that includes overlapping samples, which can be a source of bias with other methods; further, it does not assume homogeneity of trait effects across studies.[17] Compared to similar methods, metaUSAT performs similarly while requiring less computational time.[25]

In total, we performed 27 multi-phenotype analyses, considering all pairs of hemostatic traits that showed significant genetic correlations ($p < .001$) (Supplementary Table S2), pairs of combinations between each hemostatic trait and each of the three CV events, and other combinations included based on biological aspects of the analyzed proteins: Fibrinogen-FVII-FXI-tPA were analyzed because all of them are synthesized in the liver —although tPA is mostly produced by endothelial cells, recent studies that focused on the basal plasma tPA activity have also demonstrated the effects of hepatic produced tPA in fibrinolysis—.[26] Secondly, tPA was combined with FVIII and VWF, that are highly correlated, because it is known that these three phenotypes share loci like *STXBP5* that are involved in endothelial exocytosis.[4,8] Finally, the combination of fibrinogen and FVII was included to potentially discover genetic insights to the antithrombin (AT) pathway. It is known that AT deficiency is a strong risk factor for VTE, and that AT inhibits the FVIIa-tissue factor complex's activation of FX.[27,28] Moreover, AT modifies prothrombin's conversion of fibrinogen to fibrin.[29] Given this evidence, we hypothesize that potential common loci that regulate AT, FVII and fibrinogen might arise from this combination. Figure 1 shows all combinations that were analyzed.

For a metaUSAT p-value ($pvalue_{multivariate}$) to be declared statistically significant, it needed to exceed a Bonferroni correction of the traditional GWAS statistical significance threshold to account for multiple testing for 27 multi-trait combinations: $5 \times 10^{-8}/27 = 1.85 \times 10^{-9}$. For those variants with statistically significant metaUSAT p-values, we defined a locus as the genomic region $+/- 500$ kb around the variant with the lowest p-value and any other variants that were in LD of $r^2 > 0.2$. We used HaploR R package to
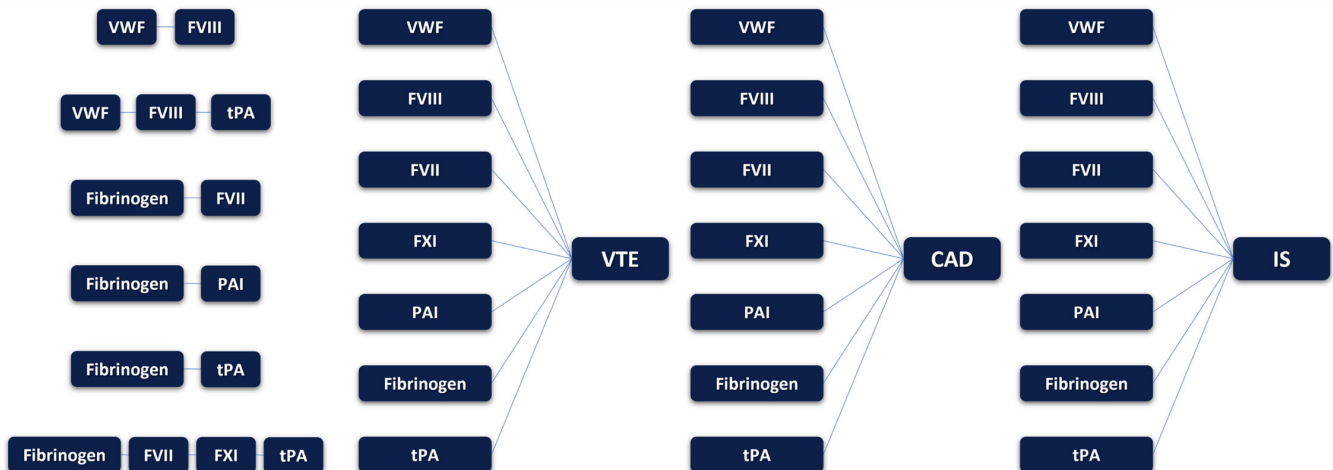

FIGURE 1 Schematic representation of the 27 multi-phenotype combinations

retrieve variants in LD with the lead variant in each locus (the variant with the lowest *p*-value).

In order to identify novel associated loci, we considered the following steps (Figure 2): (1) we identified all loci that were statistically significant in the multi-phenotype analysis ($p\text{-value}_{multivariate} < 1.85 \times 10^{-9}$) (significant loci); (2) among these, we identified all loci with a lead variant that was at least nominally significant for two of the individual datasets used in each combination of phenotypes (lead variant $p\text{-value}_{univariate} < .005$)[30–32] (significant loci driven by more than one phenotype); (3) among the loci from step 2, we then narrowed it down to loci that were new for at least one of the phenotypes used in the combination, defined as loci where no other variant in the locus had a *p*-value lower than 5×10^{-8} ($p\text{-value}_{univariate} < 5 \times 10^{-8}$) in the GWAS we used, and the locus had not been previously detected in another GWAS for the same phenotypes (new loci for one of the phenotypes used in the combination); and (4) among the loci from step 3, we identified loci that were new for all the phenotypes used in the combination (new loci for all the phenotypes used in the combination). We used the GWAS catalog database,[33] (available at https://www.ebi.ac.uk/gwas/docs/file-downloads) to detect loci that were published in previous GWAS. We used HaploReg v4[34] to retrieve previous results and biological annotations from the lead variants.

2.4 | Trait-trait colocalization

For novel loci that were new for all traits, we then performed additional colocalization analysis to look for the existence of common
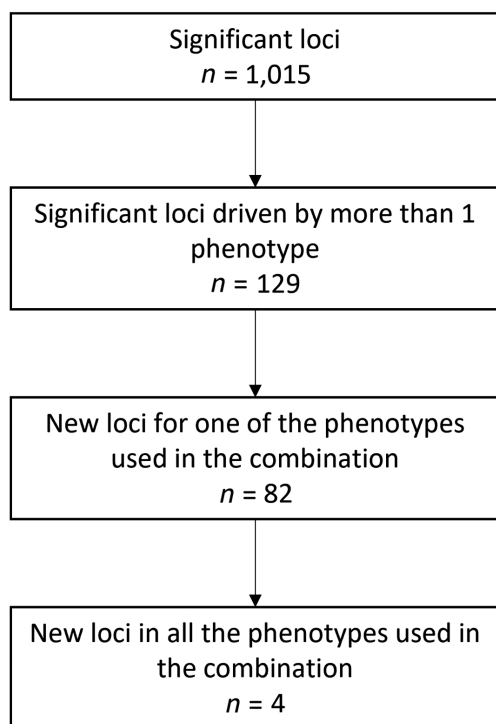

FIGURE 2 Schematic representation of the analysis plan for multi-phenotype analyses

associated variants across multiple traits. We used COLOC[35] for loci associated with pairs of traits, and the R package HyPrColoc[36] for loci associated with more than two traits. We considered windows of +/− 500 kb around the lead variant to define loci. For each locus, COLOC returns posterior probabilities (PP) for 4 different hypotheses (H_n): PP_{H0} (the locus is not associated with any of the traits), PP_{H1}/PP_{H2} (the locus is only associated with one of the traits), PP_{H3} (the locus is associated with both traits but there is no evidence of them sharing a causal variant), PP_{H4} (the locus is associated with both traits and LD patterns suggest the existence of a causal variant). We considered pleiotropic loci those that reached a conditional probability of colocalization (CPC) (PP_{H4} / (PP_{H4} + PP_{H3})) > 0.8, which is defined as the conditional probability of colocalization with one causal variant, assuming the existence of a signal in both traits. To consider pleiotropic loci in multiple traits, we performed colocalization using HyPrColoc, where posterior probabilities of colocalization > 0.7 were required. Regional plots for significant colocalizing loci were done using LocusCompare R package.

2.5 | Trait-tissues colocalization

In order to prioritize candidate causal genes, we used novel pleiotropic loci identified in previous steps and performed an additional trait-expression colocalization analysis using RNAseq data from the Genotype-Tissue Expression (GTEx) project.[37] First, we identified the lead variants that were significant expression quantitative trait loci (eQTL) and splicing quantitative trait loci (sQTL) for all tissues in GTEx V8 (available at https://www.gtexportal.org/home/datasets). Then, we performed colocalization with HyPrColoc,[36] between the two or more phenotypes and the GTEx eQTL and sQTL results, using the complete GTEx V8 files (available at https://console.cloud.google.com/storage/browser/gtex-resources), in order to identify the functional tissue and elucidate on the biological mechanism causing the associations. We required a probability of colocalization > 0.7 to consider significant colocalization between traits and tissue expression.

We restricted eQTL and sQTL analyses to a subset of GTEx tissues that could be of interest in relation to CV events and hemostatic traits: vascular tissues (artery aorta, artery coronary, artery tibial) lipid metabolism related tissues (adipose subcutaneous, adipose visceral omentum), blood (whole blood) and liver. All loci that showed significant colocalization between at least two traits were analyzed for colocalization with tissue expression in those tissues.

3 | RESULTS

3.1 | Linkage disequilibrium score regression (LDSC)

Genetic correlations were calculated for every pair of phenotypes used, including hemostatic traits and CV events. In total, 45 genetic correlations were calculated, 24 of which presented nominal

significant p-values (p <.05) and seven were significant after applying multiple testing correction (p <.001). Among the seven genetic correlations that were significant, three were between hemostatic traits (VWF-FVIII ($r_g = 0.86$, $p = 1.25 \times 10^{-15}$), fibrinogen-PAI-1 ($r_g = 0.4$, $p = 9.29 \times 10^{-5}$), fibrinogen-tPA ($r_g = 0.28$, $p = 0.001$)) and were used for multi-phenotype analyses, 3 were between a CV event and a hemostatic trait (CAD-fibrinogen ($r_g = 0.19$, $p = 6.6 \times 10^{-6}$), CAD-tPA ($r_g = 0.48$, $p = 4.9 \times 10^{-7}$), CAD-PAI-1 ($r_g = 0.52$, $p = 4.55 \times 10^{-6}$)) and one was between two CV events (CAD-IS ($r_g = 0.5$, $p = 2.23 \times 10^{-22}$)). All genetic correlations are shown in a heatmap in Figure 3 and are available at Supplementary Table S2.

3.2 | Multi-phenotype analysis results

Overall, we performed 27 multi-phenotype analyses: three (FVIII-VWF, fibrinogen-tPA and fibrinogen-PAI-1) based on significant genetic correlations between pairs of phenotypes, three (fibrinogen-FVII-tPA-FXI, fibrinogen-FVII and VWF-FVIII-tPA) due to previously known common regulatory biological pathways, and 21 between combinations of each of the seven hemostatic traits (FVII, FVIII, VWF, FXI, fibrinogen, tPA, PAI-1) and each of the three CV events (VTE, CAD, IS).

The number of significant loci remaining in each step is represented in Figure 2. In total, we found 1 015 significant loci across the 27 multi-phenotype combinations (Supplementary Table S3). Among them, 129 loci were driven by more than one of the phenotypes used in the combination (Supplementary Table S4), and 82 of them were new associations for one of phenotypes of the combination (Supplementary Table S5).

We found four novel associations that were not significant in the original individual datasets and had not been described in previous GWAS of the same traits (Table 1). Additional information on these loci, including the complete COLOC and HyPrColoc results are available at Supplementary Table S6. Figure 4 contains graphic representations of the p-values and regional plots for each of these 4 loci.

3.3 | XXYLT1

We detected a newly associated locus, with lead variant rs3796159, a 3' UTR variant in *XXYLT1* gene, in the multi-phenotype analysis between VTE and FVII. Significant colocalization analysis (CPC > 0.8) (Figure 4A) in this locus suggested the existence of a common variant as a regulator of both phenotypes, VTE and FVII. Colocalization analysis in tissues indicated that rs3796159 is a significant eQTL for *XXYLT1* in five different tissues (adipose subcutaneous, adipose visceral omentum, artery aorta, artery coronary, artery tibial) and HyPrColoc results (Supplementary Table S7) showed a triple significant colocalization (Posterior probability > 0.7) in adipose subcutaneous, adipose visceral omentum, artery aorta and artery tibial tissues in the *XXLYT1* gene.

3.4 | KNG1

Although previously identified in a candidate gene experiment as a risk factor for thrombosis[38] and suggestively associated in other GWAS for VTE,[39] this work represents the first time that the *KNG1* locus, with lead variant rs710446, has been significantly associated to risk of VTE and FVIII in GWAS. rs710446 is a missense variant in the *KNG1* gene that causes an amino acid change at the position 581 (Ile581Thr).[40] Colocalization results between VTE and FVIII (CPC > 0.8) suggest that rs710446 in *KNG1* gene is associated both with FVIII and VTE (Figure 4B). Our results could not provide evidence for this variant being a significant eQTL or sQTL in any of the analyzed tissues which suggest an effect through protein function.

3.5 | SUGP1/MAU2

CAD and fibrinogen multi-trait analysis resulted in the identification of a novel association on *SUGP1* gene (lead variant rs10401969, intronic). Colocalization analysis between CAD and fibrinogen (Figure 4C) implicated that there is a shared associated variant at this locus (CPC > 0.8), while the analysis in GTEx tissues (Supplementary Table S7) and colocalization using HyPrColoc indicated a significant triple colocalization between CAD, fibrinogen and the GTEx dataset in blood in *MAU2* gene (Posterior probability > 0.7).

3.6 | TBL2/MLXIPL

The multi-phenotype combination of hemostatic proteins that are synthesized in the liver (fibrinogen-FVII-FXI-tPA), revealed a new association on *TBL2* gene (lead variant rs11974409, intronic). Although not reaching the significance threshold for the 4 phenotypes (Posterior probability > 0.8), significant colocalization results (Figure 4D) between FVII and tPA suggest that a shared causal variant regulates both phenotypes in this locus.

rs11974409 variant is an eQTL in adipose subcutaneous, adipose visceral omentum, artery aorta, and whole blood, and an sQTL in adipose subcutaneous and adipose visceral omentum tissues. HyPrColoc analysis results suggested the existence of a common causal variant that regulates FVII, tPA and the expression of three different genes (*AC005089.1*, *MLXIPL*, *BCL7B*) in adipose subcutaneous, adipose visceral omentum and blood tissues (Posterior probability > 0.7) (Supplementary Table S7), and a common causal variant that regulates FVII, tPA and the splicing of *MLXIPL* gene in adipose subcutaneous and adipose visceral omentum tissues (Posterior probability > 0.7) (Supplementary Table S8).

3.7 | MYRF/TEMEM258/FADS1/FADS2

Additionally, a novel association on *MYRF/TMEM258/FADS1/FADS2* locus was detected in the multi-phenotype analysis

between IS-VWF. Although just below the limit of significance (p-value$_{multivariate}$ = 1.64 × 10^{-8}) (Supplementary Table S6), *MYRF/TMEM8*/FADS1/*FADS2* locus has also been identified in the combinations between VWF and the other two CV events (VTE and CAD), (lead variant rs174528, intronic in *MYRF* gene). This association was reported for VTE in a previous European GWAS[10] and also for CAD,[13] but has not been associated with VWF or IS before. The three colocalization analyses between VWF and the CV events (Supplementary Table S6) in this locus suggest the existence of a variant regulating all traits (CPC > 0.8). HyPrColoc analysis revealed significant colocalization (Posterior probability > 0.7) between VWF, VTE and *FADS1* gene expression in artery tibial and liver tissues (Supplementary Table S7), while also suggested —not significantly— (0.7 > Posterior probability > 0.5) an effect in splicing regulation in adipose visceral omentum in *FADS2* and *FEN1* genes with VTE and CAD (Supplementary Table S8). We were unable to identify triple colocalizations between VWF, IS and gene regulation.
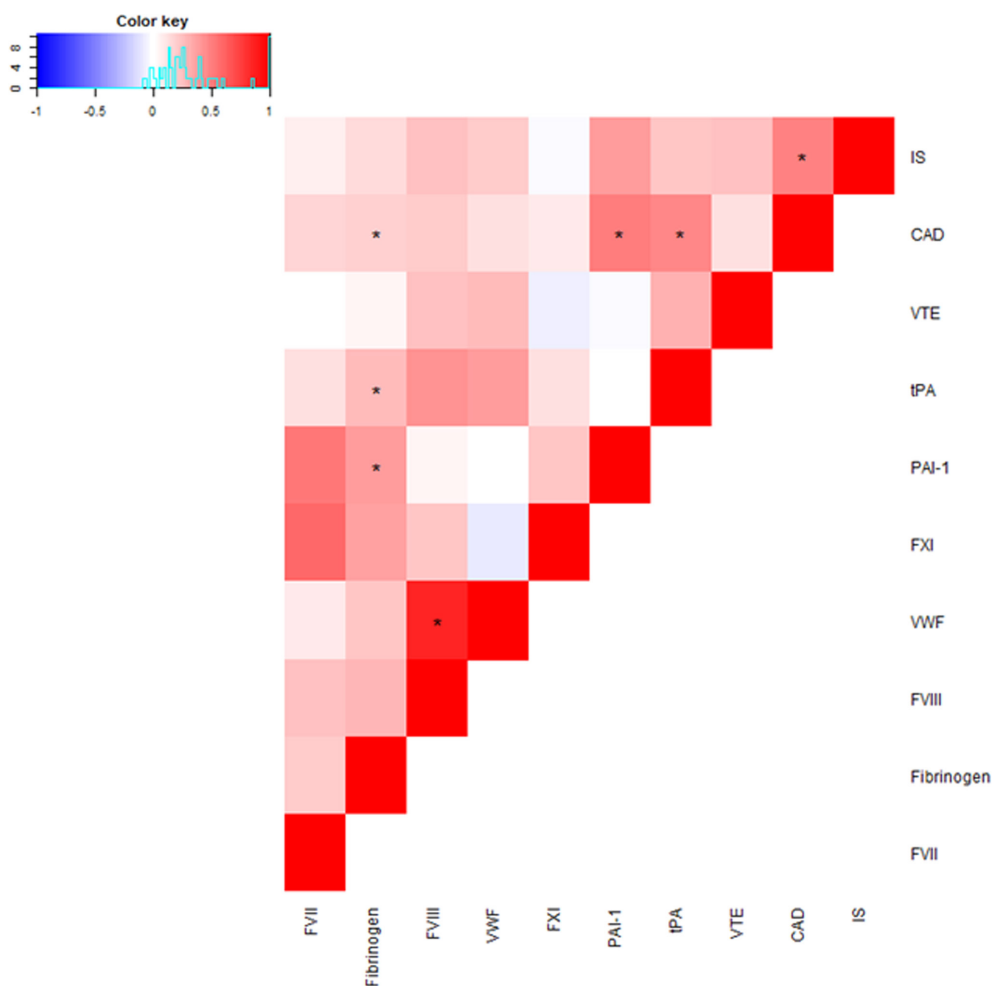

FIGURE 3 Heatmap of the genetic correlations between the two traits used in the multi-phenotype analyses. * Indicates traits are significantly correlated with a *p*-value <.001.

TABLE 1 Summary of the four novel associations identified in the 27 multi-phenotype analyses that were not significant in the individual datasets and previous GWAS

Marker Name	Traits	Variant	Effect Allele	MAF	Effect 1	Effect 2	Effect 3	Effect 4
3:194790434	VTE-FVII	rs3796159	C	0.2684	0.0605	−0.0112	-	-
3:186459927	VTE-FVIII	rs710446	T	0.4136	−0.0601	−0.012	-	-
19:19407718	CAD-FIBR	rs10401969	T	0.0768	0.0386	−0.0089	-	-
7:72989390	FIBR-FVII-FXI-TPA	rs11974409	A	0.1816	0.0035	0.0154	0.0079	0.023

[a]Posterior probability FVII-tPA.

[b]Conditional probability of colocalization.

4 | DISCUSSION

We performed a multi-phenotype approach using correlated hemostatic traits and three CV events and detected four novel pleiotropic loci that had not been previously described in association with these hemostatic traits or CV events.

Given a common locus between two or more phenotypes, three scenarios are possible: (1) there are different causal variants associated with the different traits, (2) the same variant associates with the different traits separately (horizontal pleiotropy), or (3) the variant associates with one trait, which in turn causes association with another trait (vertical pleiotropy).[41] While our analyses did not allow to differentiate between horizontal and vertical pleiotropy, we have found evidence of common variants in the four new pleiotropic loci, which agrees with the previous notion that pleiotropy is common between variants associated with correlated disease traits.[42] Common genetic regulators, however, do not mean that the associated phenotypes are causally associated. Causal associations between related phenotypes can be explored through Mendelian randomization (MR) methods.

We found a total of 1015 significant loci across all the multi-phenotype combinations. Among these, 129 were driven by more than one phenotype, of which 46 were found in combinations with CAD, 38 with VTE, 28 in combinations between hemostatic traits, and 16 with IS. Finally, among the 82 loci that were new for at least one of the phenotypes used in the combination, 30 were identified in combinations with CAD, 23 with VTE, 15 between hemostatic traits, and 13 with IS.

4.1 | *XXYLT1* and regulation of FVII

XXYLT1 codes for xyloside xylotransferase 1, an enzyme that elongates O-linked glycans in the epidermal growth factor (EGF) repeats of O-linked glycosylated proteins like FVII.[43] However, the direction of the effect of this variant suggests a decrease in FVII levels for allele C and an increase in the risk of VTE. In addition, MR analyses previously performed between VTE and FVII did not conclusively identify FVII as a cause of VTE,[1] which suggests that the common variant at this locus on xyloside xylotransferase 1 enzyme could be affecting both phenotypes independently, through expression of *XXYLT1* in adipose subcutaneous, adipose visceral omentum, artery

aorta or artery tibial tissues. In this direction, it is known that other coagulation factors, like factor IX, are also glycosylated in the EGF repeats.[44] It would be plausible to speculate that *XXYLT1* could affect FVII levels and also other EGF-glycosylated proteins that would eventually modify VTE risk. Therefore, further research in this locus is recommended to fully understand the possible relationship between *XXYLT1*, FVII and VTE, and the possible effect that other hemostatic proteins could have in this association.

4.2 | *KNG1* and risk of VTE through FVIII levels

The protein encoded by this gene, Kininogen-1 (KNG1), is the precursor of two other proteins, obtained through alternative splicing: high-molecular-weight kininogen (HMWK) and low-molecular-weight kininogen (LMWK). Through a process facilitated by Factor XII (FXII), the peptide bradykinin is cleaved from HMWK by the enzyme kallikrein.[45]

There is strong biological evidence that associate *KNG1* gene with the coagulation system.[40,46,47] HMWK, along with FXII and prekallikrein (PK) complex, conform the plasma kallikrein-kinin system (KKS), that plays an important role in human physiology. The activation of KKS components results in the induction of genes and biomolecules that participate in blood coagulation, among other processes.[48,49] Bradykinin, on its turn, is an important molecule involved in vascular permeability and also in mechanism of pain.[45]

We have previously shown[6,50,51] that the lead variant on *KNG1* (rs710446) is also strongly associated to activated partial thromboplastin time (aPTT), prekallirein, FXI and coagulation activity of FVIII in a candidate gene experiment, indicating a pleiotropic effect of this gene on regulating the intrinsic pathway of coagulation,[52] resulting in modified risk of VTE.

Although the association with VTE has been demonstrated in candidate-gene studies,[38] the combination between VTE-FVIII, enhanced the association, suggesting a plausible functional relationship between KNG1 and FVIII that had never been reported in GWAS. This association could be explained by a putative regulation of KNG1 also on FVIII, which would imply an effect of KNG1 on the common pathway of coagulation. Associations of *KNG1* with the entire coagulation cascade, and not just the intrinsic pathway, have been proposed by others.[72] The significant colocalization analysis between VTE and FVIII in this locus aligns with previous evidence

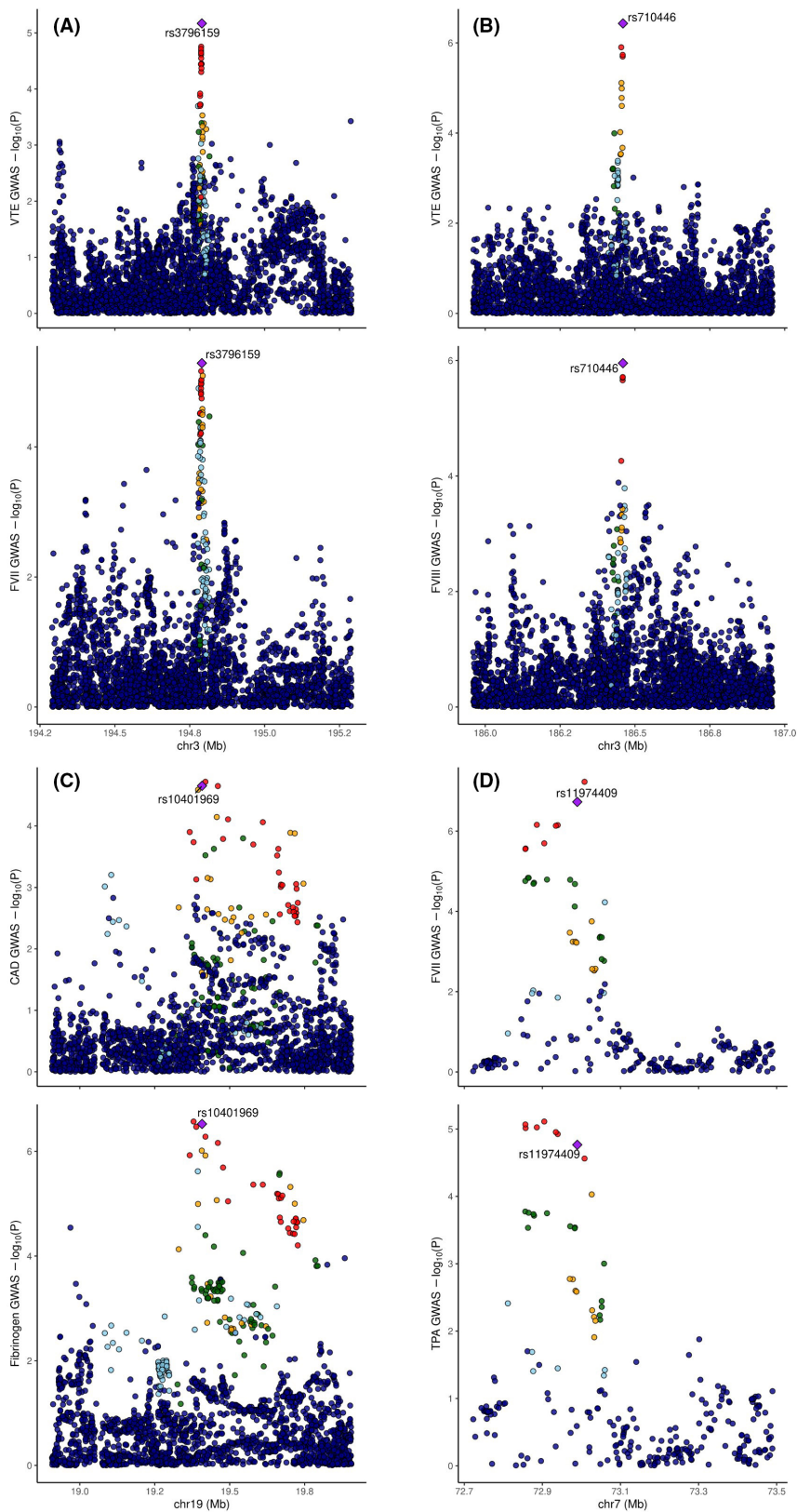| Locus Name	p-value$_{multivariate}$	p-value$_{univariate}$ 1	p-value$_{univariate}$ 2	p-value$_{univariate}$ 3	p-value$_{univariate}$ 4	CPC[b]
XXYLT1	1.78×10^{-9}	6.77×10^{-6}	5.15×10^{-6}	-	-	0.9727
KNG1	4.12×10^{-11}	3.71×10^{-7}	1.1×10^{-6}	-	-	0.9962
SUGP1/MAU2	8×10^{-11}	2.22×10^{-5}	2.99×10^{-7}	-	-	0.9827
TBL2/MLXIPL	3.22×10^{-11}	.0019	1.87×10^{-7}	0.014737	1.71×10^{-5}	0.9896[a]

FIGURE 4 A: Regional plots for rs3796159 variant on *XXYLT1* gene on VTE (top) and FVII (bottom). B: Regional plots for rs710446 variant on *KNG1* gene on VTE (top) and FVIII (bottom). C: Regional plots for rs10401969 on *SUGP1* gene on CAD (top) and fibrinogen (bottom). D: Regional plots for rs11974409 on *TBL2* gene on FVII (top) and TPA (bottom).

and suggests that rs710446 affects the regulation of both phenotypes along with other related hemostatic phenotypes.

4.3 | *SUGP1/MAU2* and CAD risk through fibrinogen levels

CAD and fibrinogen multi-trait analysis resulted in the identification of a new pleiotropic locus on *SUGP1/MAU2* genes, with lead variant rs10401969. *SUGP1/MAU2* is a pleiotropic locus that has been associated to lipid's metabolism traits levels (total cholesterol, apolipoprotein B, triglycerides), liver related proteins levels (alanine transaminase, asparatate aminotransferase, alanine aminotransferase), blood-related phenotypes (red cell distribution width, mean reticulocyte volume), type 2 diabetes and cirrhosis.[33] This locus has also been associated to CAD in candidate gene studies in Chinese and Caucasian populations but never in GWAS studies.[53,54] *SUGP1* codes for a protein called SURP and G patch domains-containing protein 1 (SUGP1), that it is believed to function in pre-mRNA splicing mechanisms.[55] This is the first time that *SUGP1* is associated with coagulation factors and colocalization results suggest that the common variant at this locus is regulating both, CAD and fibrinogen. The identification of our lead variant, rs10401969, as a significant eQTL for *MAU2* gene in blood, and the identification of this locus in a significant colocalization between CAD, fibrinogen and eQTL data in blood, also suggests the existence of a variant regulating both phenotypes that would take place through the *MAU2* gene expression. *MAU2* codes for MAU2 chromatid cohesion factor homolog and has an important role in loading the cohesion complex to DNA.[56,57] *MAU2* has never been associated to coagulation factor levels.

Fibrinogen levels have been found significantly higher in cases of CAD in epidemiological studies,[58,59] although MR studies have only been able to demonstrate a small causal effect using multi-variant MR approaches.[60,61] Further evidence is needed to clearly elucidate if the effect of this variant on *SUGP1/MAU2* locus on CAD is through fibrinogen levels or if this locus influences both phenotypes in parallel.

4.4 | Liver produced proteins and the *TBL2/MLXIPL* locus

The *TBL2/MLXIPL* locus has been associated with other phenotypes of interest related to lipids metabolism levels (triglycerides, high density lipoprotein, low density lipoprotein) and other liver related proteins levels (alkaline phosphatase, C-reactive protein, gamma glutamyl transferase or alanine aminotransferase),[33] but this is the first time that a variant located on *TBL2* reaches the significance threshold in a GWAS involving hemostatic factors. Also, in a previous candidate gene study for FVII levels, the variant rs7777102, located upstream the *MLXIPL* gene and ~70 kb away rs11974409 ($D' = 0.85$, $R^2 = 0.44$, in 1000G project European population[51]), was found associated to FVII.[51] *TBL2* codes for an endoplasmic reticulum

transmembrane protein called transducin (β)-like 2 (TBL2) that, upon ER stress, interacts with PERK (PKR-like ER-resident kinase) and is able to regulate *ATF4* (activation transcription factor 4) translation. It has also been demonstrated that TBL2 has a WD40 (beta-transducin repeat) domain that is essential for the association with mRNA of *ATF4*.[62,63] *MLXIPL* codes for Carbohydrate response element binding protein (ChREBP), a transcription factor highly enriched in the liver with a key role in lipids metabolism. ChREBP has also shown a response for glucose metabolites that change its cellular location and stability and also imply post-translational modifications. ChREBP binds to several proteins that are crucial to induce its nuclear translocation or biding to nuclear receptors.[64] Considering the previous results obtained in a candidate gene studies in FVII,[51] that associated this locus to FVII levels, together with the significant colocalization results between FVII and tPA, and the significant results also of HyPrColoc with several tissues, all suggest that the *TBL2/MLXIPL* locus has a pleiotropic effect on the expression of several hemostatic traits. The colocalization results in tissues suggest *MLXIPL* gene as a good candidate gene, with a common variant in this locus regulating *MLXIPL* expression and splicing in adipose visceral and adipose visceral omentum tissues, FVII levels, and TPA levels at the same time.

4.5 | *MYRF/TMEM258/FADS1/FADS2* and its effect on CV events

MYRF codes for a membrane-associated transcription factor, that participates in the activation of myelin genes and that has been associated to brain development issues.[65,66] Previous GWAS have also associated the genomic region of *MYRF* and *TMEM258* genes to hematologic and lipid metabolism traits.[33] *TMEM258* codes for a protein with two predicted transmembrane domains, with no clear function *in vivo*, that has been associated with endoplasmic reticulum stress when knocked out and as an important regulator of intestinal hemostasis. *TMEM258* has also been described as a potential causal gene of cardiovascular traits and as a regulatory site of abdominal visceral fat.[67,68]

Although not new for VTE and CAD, the identification of the same locus in the multi-phenotype analyses with all 3 CV events and a hemostatic trait supports the idea that the *MYRF/TMEM258/FADS1/FADS2* locus is common regulator. Significant colocalization results between VWF and the cardiovascular outcomes, also support this idea. Our effort to prioritize a causal gene through the colocalization analysis in different tissues, revealed that a common variant at this locus regulates expression of *FADS1* gene in artery tibial and liver and the splicing regulation of *FADS2*, although the colocalization was not significant. *FADS1* and *FADS2* code for members of the fatty acid desaturase gene family that catalyze several steps in the formation of omega-3 and omega-6 fatty acids.[69] The rs174547 variant located on *FADS1*, in high LD with our lead variant rs174528 ($D' = 1$, $R^2 = 0.84$) in the European population of 1000 Genomes project,[70] has been implicated in the risk of suffering multiple CV events, including VTE, CAD and IS,

in a previous MR study.[71] Our results clearly support a regulatory role of this locus on several CV events and suggest the involvement of VWF in the association between *FADS1*/*FADS2* and CV events.

4.6 | Strengths and limitations

This is the first systematic multi-phenotype analysis using summary data for hemostatic traits related to CV events to increase power to detect loci associated with more than one related phenotype. We have leveraged data from the leading consortia worldwide analyzing genetics of hemostatic traits, VTE, CAD, and IS, often providing the largest datasets currently available. We consider this, one of the most major strengths of this work. Moreover, most phenotypes included trans-ethnic population, which give a broader transferability of the results.

We are aware of the existence of several limitations in this work. First, there are notable differences between the sample sizes of the hemostatic traits used, the largest one being fibrinogen (N = 120 246 cases) and the smallest one PAI-1 (N = 19 599), which leads to differences in statistical power between multi-phenotype analyses. Second, we were limited to use summary statistics of mostly European origin to calculate genetic correlations, given the lack of good references in other populations to generate the LD scores, which implies that these results cannot be applied to global populations. LDSC filters out variants with low sample size. For some phenotypes this information was not available, and we used the maximum sample size of the phenotype. This could have created some error. Third, we are also aware that there are limitations associated with the use of GTEx data. This data has limited sample sizes that vary greatly from tissue to tissue. For example, the number of liver samples (N = 208) is considerably lower than the samples of tissues such as artery tibial (N = 584) or adipose subcutaneous (N = 581), which may end up in differences in power to detect associations. The lower numbers of liver samples may have affected our power to detect some of the identified variants as significant eQTL in the liver, and therefore the implication of causal tissues should be interpreted with caution. Finally, we are not providing functional validation of these results. Therefore, further experiments are needed to confirm the implication of the novel suggested loci in disease.

5 | CONCLUSIONS

We have shown that the multi-phenotype analysis of biologically related phenotypes expands discovery of newly associated loci. Using summary GWAS data from hemostasis and CV events, we identified four colocalizing novel loci that were not identified as statistically significant in the source datasets and have not been described in other GWAS of the phenotypes involved. Although our strategy does not allow to unequivocally identify the causal variant or variants at each locus, the colocalization results suggest the existence of common regulatory variants at the newly identified loci.

Some of these loci appear to represent genes that may simultaneously regulate more than one hemostatic trait (horizontal pleiotropy), and some seem to reflect the risk mechanism from a gene to one or more CV events through regulation of a hemostatic factor (vertical pleiotropy),[41] therefore revealing novel biological mechanisms. Both cases of pleiotropy are novel interesting insights that will help understand the pathophysiology of clinical CV events.

CONFLICT OF INTEREST
S.M. Damrauer is named as a co-inventor on a government-owned US Patent application related to the use of genetic risk prediction for venous thromboembolic disease filed by the US Department of Veterans Affairs in accordance with Federal regulatory requirements. All other authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

M. Sabater-Lleal, N.L Smith and P.S. de Vries conceived and designed the study and provided access to the data. G. Temprano-Sagrera performed, analyzed, and interpreted the data and drafted the manuscript. C. M. Sitlani, W. P. Bone, and M. Martin-Bornez, analyzed data and contributed to method selection and interpretation. B. F. Voight, A. C. Morrison, S. M. Damrauer, P. S. de Vries N. L. Smith and M. Sabater-Lleal contributed to writing and editing the manuscript. All the authors revised and approved the final version of the manuscript.

ORCID

Gerard Temprano-Sagrera https://orcid.org/0000-0001-6136-8915

Colleen M. Sitlani https://orcid.org/0000-0001-7656-7482

William P. Bone https://orcid.org/0000-0002-9617-4624

Miguel Martin-Bornez https://orcid.org/0000-0001-8221-3816

Benjamin F. Voight https://orcid.org/0000-0002-6205-9994

Alanna C. Morrison https://orcid.org/0000-0001-6381-4296

Scott M. Damrauer https://orcid.org/0000-0001-8009-1632

Paul S. de Vries https://orcid.org/0000-0003-0964-0111

Nicholas L. Smith https://orcid.org/0000-0003-3483-353X

Maria Sabater-Lleal https://orcid.org/0000-0002-0128-379X

REFERENCES

1. de Vries PS, Sabater-Lleal M, Huffman JE, et al. A genome-wide association study identifies new loci for factor VII and implicates factor VII in ischemic stroke etiology. *Blood*. 2019;133:967-977.
2. Junker R, Heinrich J, Schulte H, van de Loo J, Assmann G. Coagulation factor VII and the risk of coronary heart disease in healthy men. *Arterioscler Thromb Vasc Biol*. 1997;17:1539-1544.
3. Olson NC, Raffield LM, Lange LA, et al. Associations of activated coagulation factor VII and factor VIIa-antithrombin levels with genome-wide polymorphisms and cardiovascular disease risk. *J Thromb Haemost*. 2018;16:19-30.
4. Sabater-Lleal M, Huffman JE, de Vries PS, et al. Genome-wide association transethnic meta-analyses identifies novel associations regulating coagulation factor VIII and von Willebrand factor plasma levels. *Circulation*. 2019;139:620-635.
5. de Vries PS, Chasman DI, Sabater-Lleal M, et al. A meta-analysis of 120 246 individuals identifies 18 new loci for fibrinogen concentration. *Hum Mol Genet*. 2016;25:358-370.
6. Sennblad B, Basu S, Mazur J, et al. Genome-wide association study with additional genetic and post-transcriptional analyses reveals novel regulators of plasma factor XI levels. *Hum Mol Genet*. 2017;26:637-649.
7. Huang J, Sabater-Lleal M, Asselbergs FW, et al. Genome-wide association study for circulating levels of PAI-1 provides novel insights into its regulation. *Blood*. 2012;120:4873-4881.
8. Huang J, Huffman JE, Yamkauchi M, et al. Genome-wide association study for circulating tissue plasminogen activator (tPA) levels and functional follow-up implicates endothelial STXBP5 and STX2. *Arterioscler Thromb Vasc Biol*. 2014;34:1093-1101.
9. Lindström S, Wang L, Smith EN, et al. Genomic and transcriptomic association studies identify 16 novel susceptibility loci for venous thromboembolism. *Blood*. 2019;134:1645-1657.
10. Klarin D, Busenkell E, Judy R, et al. Genome-wide association analysis of venous thromboembolism identifies new risk loci and genetic overlap with arterial vascular disease. *Nat Genet*. 2019;51:1574-1579.
11. Ishigaki K, Akiyama M, Kanai M, et al. Large scale genome-wide association study in a Japanese population identifies novel susceptibility loci across different diseases. *Nat Genet*. 2020;52:669-679.
12. van der Harst P, Verweij N. Identification of 64 novel genetic loci provides an expanded view on the genetic architecture of coronary artery disease. *Circ Res*. 2018;122:433-443.
13. Koyama S, Ito K, Terao C, et al. Population-specific and trans-ancestry genome-wide analyses identify distinct and shared genetic risk loci for coronary artery disease. *Nat Genet*. 2020;52:1169-1177.
14. Malik R, Chauhan G, Traylor M, et al. Multiancestry genome-wide association study of 520,000 subjects identifies 32 loci associated with stroke and stroke subtypes. *Nat Genet*. 2018;50:524-537.
15. Diggle P, Heagerty P, Liang K-Y, Zeger S. *Analysis of Longitudinal Data*. OUP; 2013.
16. Turley P, Walters RK, Maghzian O, et al. Multi-trait analysis of genome-wide association summary statistics using MTAG. *Nat Genet*. 2018;50:229-237.
17. Ray D, Boehnke M. Methods for meta-analysis of multiple traits using GWAS summary statistics. *Genet Epidemiol*. 2018;42:134-145.
18. Psaty BM, O'Donnell CJ, Gudnason V, et al. Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium: design of prospective meta-analyses of genome-wide association studies from five cohorts. *Circ Cardiovasc Genet*. 2009;2:73-80.
19. Nikpay M, Goel A, Won H-H, et al. A comprehensive 1000 Genomes–based genome-wide association meta-analysis of coronary artery disease. *Nat Genet*. 2015;47:1121-1130.
20. Rich SS, Wang ZY, Sturke A, et al. Rapid evaluation of phenotype, SNP and summary results through the dbGaP Charge Summary site. *Nat Genet*. 2016;48:702-703.
21. Bulik-Sullivan B, Finucane HK, Anttila V, et al. An atlas of genetic correlations across human diseases and traits. *Nat Genet*. 2015;47:1236-1241.
22. Bulik-Sullivan BK, Loh P-R, Finucane H, et al. LD score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nat Genet*. 2015;47:291-295.
23. Auton A, Abecasis GR, Altshuler DM, et al. A global reference for human genetic variation. *Nature*. 2015;526:68-74.
24. Altshuler DM, Gibbs RA, Peltonen L, et al. Integrating common and rare genetic variation in diverse human populations. *Nature*. 2010;467:52-58.
25. Sitlani CM, Baldassari AR, Highland HM, Hodonsky CJ, McKnight B, Avery CL. Comparison of adaptive multiple phenotype association tests using summary statistics in genome-wide association studies. *Hum Mol Genet*. 2021;30:1371-1383.
26. Zheng Z, Nayak L, Wang W, et al. An ATF6-tPA pathway in hepatocytes contributes to systemic fibrinolysis and is repressed by DACH1. *Blood*. 2019;133:743-753.
27. Spiezia L, Rossetto V, Campello E, et al. Factor VIIa-antithrombin complexes in patients with arterial and venous thrombosis. *Thromb Haemost*. 2010;103:1188-1192.
28. Spiezia L, Campello E, Valle FD, Woodhams B, Simioni P. Factor VIIa-antithrombin complex: a possible new biomarker for activated coagulation. *Clin Chem Lab Med*. 2017;55:484-488.
29. Patnaik MM, Moll S. Inherited antithrombin deficiency: a review. *Haemophilia*. 2008;14:1229-1239.
30. Greenwald AG, Gonzalez R, Harris RJ, Guthrie D. Effect sizes and p values: what should be reported and what should be replicated? *Psychophysiology*. 1996;33:175-183.
31. Johnson VE. Revised standards for statistical evidence. *Proc Natl Acad Sci USA*. 2013;110:19313-19317.
32. Benjamin DJ, Berger JO, Johannesson M, et al. Redefine statistical significance. *Nat Hum Behav*. 2018;2:6-10.

33. Buniello A, MacArthur JAL, Cerezo M, et al. The NHGRI-EBI GWAS Catalog of published genome-wide association studies, targeted arrays and summary statistics 2019. *Nucleic Acids Res*. 2019;47:D1005-D1012.

34. Ward LD, Kellis M. HaploReg v4: systematic mining of putative causal variants, cell types, regulators and target genes for human complex traits and disease. *Nucleic Acids Res*. 2016;44:D877-D881.

35. Giambartolomei C, Vukcevic D, Schadt EE, et al. Bayesian test for colocalisation between pairs of genetic association studies using summary statistics. *PLoS Genet*. 2014;10:e1004383.

36. Foley CN, Staley JR, Breen PG, et al. A fast and efficient colocalization algorithm for identifying shared genetic risk factors across multiple traits. *Nat Commun*. 2021;12:764.

37. Lonsdale J, Thomas J, Salvatore M, et al. The Genotype-Tissue Expression (GTEx) project. *Nat Genet*. 2013;45:580-585.

38. Morange P-E, Oudot-Mellakh T, Cohen W, et al. KNG1 Ile581Thr and susceptibility to venous thrombosis. *Blood*. 2011;117:3692-3694.

39. Hinds DA, Buil A, Ziemek D, et al. Genome-wide association analysis of self-reported events in 6135 individuals and 252 827 controls identifies 8 loci associated with thrombosis. *Hum Mol Genet*. 2016;25:1867-1874.

40. Wang Q, Cheng G, Wang X, et al. Genetic effects of BDKRB2 and KNG1 on deep venous thrombosis after orthopedic surgery and the potential mediator. *Sci Rep*. 2018;8:17332.

41. Hemani G, Bowden J, Davey Smith G. Evaluating the potential role of pleiotropy in Mendelian randomization studies. *Hum Mol Genet*. 2018;27:R195-R208.

42. Sivakumaran S, Agakov F, Theodoratou E, et al. Abundant pleiotropy in human complex diseases and traits. *Am J Hum Genet*. 2011;89:607-618.

43. Sethi MK, Buettner FFR, Krylov VB, et al. Identification of glycosyltransferase 8 family members as xylosyltransferases acting on O-glucosylated notch epidermal growth factor repeats. *J Biol Chem*. 2010;285:1582-1586.

44. Spiro RG. Protein glycosylation: nature, distribution, enzymatic formation, and disease implications of glycopeptide bonds. *Glycobiology*. 2002;12:43R-56R.

45. Golias C, Charalabopoulos A, Stagikas D, Charalabopoulos K, Batistatou A. The kinin system - bradykinin: biological effects and clinical implications. Multiple role of the kinin system - bradykinin. *Hippokratia*. 2007;11:124-128.

46. Houlihan LM, Davies G, Tenesa A, et al. Common variants of large effect in F12, KNG1, and HRG are associated with activated partial thromboplastin time. *Am J Hum Genet*. 2010;86:626-631.

47. Hu Z, Liu J, Song Z, Hou Q, Fan X, Hou D. Variants in the Atherogenic ALOX5AP, THBD, and KNG1 genes potentiate the risk of ischemic stroke via a genetic main effect and epistatic interactions in a Chinese population. *J Stroke Cerebrovasc Dis*. 2015;24:2060-2068.

48. Bryant JW, Shariat-Madar Z Human plasma kallikrein-kinin system: physiological and biochemical parameters. *Cardiovasc Hematol Agents Med Chem*. 2009;7:234-250.

49. Madeddu P, Emanueli C, El-Dahr S. Mechanisms of Disease: the tissue kallikrein–kinin system in hypertension and vascular remodeling. *Nat Rev Nephrol*. 2007;3:208-221.

50. Sabater-Lleal M, Martinez-Perez A, Buil A, et al. A genome-wide association study identifies KNG1 as a genetic determinant of plasma factor XI level and activated partial thromboplastin time. *Arterioscler Thromb Vasc Biol*. 2012;32:2008-2016.

51. Taylor KC, Lange LA, Zabaneh D, et al. A gene-centric association scan for coagulation factor VII levels in European and African Americans: the Candidate Gene Association Resource (CARe) Consortium. *Hum Mol Genet*. 2011;20:3525-3534.

52. Chaudhry R, Usama SM, Physiology BHM. *Coagulation Pathways* [Internet]. En: StatPearls. StatPearls Publishing; 2021 [citado 2021 oct 18]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK482253/

53. Zhou L, Ding H, Zhang X, et al. Genetic variants at newly identified lipid loci are associated with coronary heart disease in a Chinese Han population. *PLoS One*. 2011;6:e27481.

54. Zhuang K, Zhang W, Zhang X, Wu F, Cheng L. Effects of SNPs at newly identified lipids loci on blood lipid levels and risk of coronary heart disease in Chinese Han population: a case control study. *J Huazhong Univ Sci Technolog Med Sci*. 2011;31:452.

55. Sampson ND, Hewitt JE. SF4 and SFRS14, two related putative splicing factors on human chromosome 19p13.11. *Gene*. 2003;305:91-100.

56. Bot C, Pfeiffer A, Giordano F, Edara DM, Dantuma NP, Ström L. Independent mechanisms recruit the cohesin loader protein NIPBL to sites of DNA damage. *J Cell Sci*. 2017;130:1134-1146.

57. Bermudez VP, Farina A, Higashi TL, et al. In vitro loading of human cohesin on DNA by the human Scc2-Scc4 loader complex. *Proc Natl Acad Sci USA*. 2012;109:9366-9371.

58. Kannel WB, Wolf PA, Castelli WP, D'Agostino RB. Fibrinogen and risk of cardiovascular disease: the Framingham study. *JAMA*. 1987;258:1183-1186.

59. Stec JJ, Silbershatz H, Tofler GH, et al. Association of fibrinogen with cardiovascular risk factors and cardiovascular disease in the Framingham offspring population. *Circulation*. 2000;102:1634-1638.

60. Ward-Caviness CK, de Vries PS, Wiggins KL, et al. Mendelian randomization evaluation of causal effects of fibrinogen on incident coronary heart disease. *PLoS One*. 2019;14:e0216222.

61. Keavney B, Danesh J, Parish S, et al. Fibrinogen and coronary heart disease: test of causality by 'Mendelian randomization'. *Int J Epidemiol*. 2006;35:935-943.

62. Tsukumo Y, Tsukahara S, Furuno A, Iemura S, Natsume T, Tomida A. TBL2 associates With ATF4 mRNA via its WD40 domain and regulates its translation during ER stress. *J Cell Biochem*. 2016;117:500-509.

63. Tsukumo Y, Tsukahara S, Furuno A, Iemura S, Natsume T, Tomida A. The endoplasmic reticulum-localized protein TBL2 interacts with the 60S ribosomal subunit. *Biochem Biophys Res Comm*. 2015;462:383-388.

64. Ortega-Prieto P, Postic C. Carbohydrate sensing through the transcription factor ChREBP. *Front Genet*. 2019;10:472.

65. Kurahashi H, Azuma Y, Masuda A, et al. MYRF is associated with encephalopathy with reversible myelin vacuolization. *Ann Neurol*. 2018;83:98-106.

66. An H, Fan C, Sharif M, Kim D, Poitelon Y, Park Y. Functional mechanism and pathogenic potential of MYRF ICA domain mutations implicated in birth defects. *Sci Rep*. 2020;10:814.

67. Graham DB, Lefkovith A, Deelen P, et al. TMEM258 is a component of the oligosaccharyltransferase complex controlling ER stress and intestinal inflammation. *Cell Rep*. 2016;17:2955-2965.

68. Taylor K, Davey Smith G, Relton CL, Gaunt TR, Richardson TG. Prioritizing putative influential genes in cardiovascular disease susceptibility by applying tissue-specific Mendelian randomization. *Genome Med*. 2019;11:6.

69. Park WJ, Kothapalli KSD, Lawrence P, Tyburczy C, Brenna JT. An alternate pathway to long-chain polyunsaturates: the FADS2 gene product Δ8-desaturates 20:2n−6 and 20:3n−3. *J Lipid Res*. 2009;50:1195-1202.

70. Machiela MJ, Chanock SJ. LDlink: a web-based application for exploring population-specific haplotype structure and linking correlated alleles of possible functional variants. *Bioinformatics*. 2015;31:3555-3557.

71. Yuan S, Bäck M, Bruzelius M, Mason AM, Burgess S, Larsson S. Plasma phospholipid fatty acids, FADS1 and risk of 15 cardiovascular diseases: a Mendelian randomisation study. *Nutrients*. 2019;11:3001.

72. Brunel H, Massanet R, Martinez-Perez A, Ziyatdinov A, Martin-Fernandez L, Souto JC, Perera A, Soria JM. The Central Role

of KNG1 Gene as a Genetic Determinant of Coagulation Pathway-Related Traits: Exploring Metaphenotypes. *PLOS ONE.* 2016;11(12):e0167187.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

APPENDIX A

Abbas Dehghan[1], Adam SHeath[2], Alanna CMorrison[2], Alex PReiner[3], Andrew Johnson[4], Anne Richmond[5], Annette Peters[6], Astrid van Hylckama Vlieg[7] Barbara McKnight[8], Bruce MPsaty[9], Caroline Hayward[5], Cavin Ward-Caviness[10], Christopher O'Donnell[11], Daniel Chasman[12], David PStrachan[13], David ATregouet[14], Dennis Mook-Kanamori[7], Dipender Gill[1], Florian Thibord[4], Folkert WAsselbergs[15], Frank W.G. Leebeek[16], Frits RRosendaal[7], Gail Davies[17], Georg Homuth[18], Gerard Temprano[19], Harry Campbell[20], Herman ATaylor[21], Jan Bressler[2], Jennifer EHuffman[22], Jerome IRotter[21], Jie Yao[21], James FWilson[5], Joshua CBis[23], Julie MHahn[2], Karl CDesch[24], Kerri LWiggins[23], Laura MRaffield[25], Lawrence FBielak[26], Lisa RYanek[27], Marcus EKleber[28], Maria Sabater-Lleal[19], Martina Mueller[6], Maryam Kavousi[29], Massimo Mangino[30], Melissa Liu[4], Michael RBrown[2], Matthew PConomos[8], Min-A Jhun[26], Ming-Huei Chen[4], Moniek P.M. de Maat[16], Nathan Pankratz[31], Nicholas LSmith[3], Patricia APeyser[26], Paul Elliot[1], Paul Sde Vries[2], Peng Wei[32], Philipp SWild[33], Pierre EMorange[34], Pim van der Harst[35], Qiong Yang[36], Ngoc-Quynh Le[19], Riccardo Marioni[37], Ruifang Li[7], Scott MDamrauer[38], Simon RCox[17], Stella Trompet[39], Stephan BFelix[40], Uwe Völker[18], Weihong Tang[41], Wolfgang Koenig[42], J. Wouter Jukema[43], Xiuqing Guo[21].

[1]Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, UK. [2]Human Genetics Center, Department of Epidemiology, Human Genetics, and Environmental Sciences; School of Public Health, The University of Texas Health Science Center at Houston, Houston, Texas, USA. [3]Department of Epidemiology, University of Washington, Seattle, WA, USA. [4]National Heart Lung and Blood Institute, Division of Intramural Research, Population Sciences Branch, The Framingham Heart Study, Framingham, MA, USA. [5]MRC Human Genetics Unit, Institute of Genetics and Molecular Medicine, University of Edinburgh, Western General Hospital, Edinburgh, Scotland. [6]Research Unit Molecular Epidemiology, Helmholtz Zentrum München, München, Germany. [7]Department of Clinical Epidemiology, Leiden University Medical Center, the Netherlands. [8]Department of Biostatistics, University of Washington, Seattle, WA. [9]Cardiovascular Health Research Unit, Department of Medicine, University of Washington, Seattle, WA, United States. [10]Office of Research and Development, U.S. Environmental Protection Agency, Chapel Hill, NC, USA. [11]Cardiology, VA Boston Healthcare System, Boston, MA, USA. [12]Division of Preventive Medicine, Brigham and Women's Hospital, Boston, MA, USA. [13]Population Health Research Institute, St George's University of London, London, UK. [14]Bordeaux Population Health Research Center, University of Bordeaux, Bordeaux, France. [15]Department of Cardiology, Division Heart & Lungs, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands. [16]Department of Hematology, Erasmus Medical Center, Rotterdam, the Netherlands. [17]Lothian Birth Cohorts, Department of Psychology, University of Edinburgh, Edinburgh, UK. [18]Department of Functional Genomics, Interfaculty Institute for Genetics and Functional Genomics, University Medicine Greifswald, Greifswald, Germany. [19]Unit of Genomics of Complex Diseases. Sant Pau Biomedical Research Institute (IIB-Sant Pau), Barcelona, Spain. [20]Global Health Research, Usher Institute for Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, Scotland, UK. [21]The Institute for Translational Genomics and Population Sciences, Department of Pediatrcs, The Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center, Torrance, CA USA. [22]Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC), VA Boston Healthcare System, Boston, MA, USA. [23]Cardiovascular Health Research Unit Department of Medicine University of Washington Seattle Washington USA. [24]Department of Pediatrics, University of Michigan, C.S. Mott Children's Hospital, Ann Arbor, MI, USA. [25]Department of Genetics, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA. [26]Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, MI. [27]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA. [28]SYNLAB MVZ für Humangenetik Mannheim, Mannheim, Germany. [29]Department of Epidemiology, Erasmus Medical Center, University Medical Center Rotterdam, Rotterdam, Netherlands. [30]Department of Twin Research and Genetic Epidemiology, Kings College London, London, UK. [31]Department of Laboratory Medicine and Pathology, University of Minnesota Medical School, Minneapolis, MN, USA. [32]Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston. [33]Department of Cardiology, Cardiology I, University Medical Center, Johannes Gutenberg University Mainz, Mainz, Germany. [34]Hematology Laboratory, La Timone University Hospital of Marseille, Marseille, France. [35]Department of Cardiology, University Medical Center Utrecht, Utrecht, Netherlands. [36]Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA. [37]Centre for Genomic and Experimental Medicine, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, UK. [38]Department of Surgery, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA. [39]Section of Gerontology and Geriatrics, Department of Internal Medicine, Leiden University Medical Center, Leiden, The Netherlands. [40]Department of Internal Medicine B, University Medicine Greifswald, Greifswald, Germany. [41]School of Public Health, University of Minnesota, Minneapolis, MN, USA. [42]DZHK (German Centre for Cardiovascular Research), partner site Munich

Heart Alliance, Munich, Germany. [43]Department of Cardiology, Leiden University Medical Center, The Netherlands.

APPENDIX B

Sara Lindstrom, PhD[1], Lu Wang, PhD[2], Erin NSmith, PhD[3], William Gordon, MS[4], Astrid van Hylckama Vlieg, PhD[5], Mariza de Andrade, PhD[6], Jennifer ABrody, BA[7], Jack WPattee, BA[8], Jeffrey Haessler, MS[9], Ben MBrumpton, PhD, MPH[10], Daniel IChasman, PhD[11], Pierre Suchon, MD-PhD[12], Ming-Huei Chen, PhD[13], Constance Turman, MS[14], Marine Germain[15], Kerri LWiggins, MS, RD[16], James MacDonald, MS[17], Sigrid KBraekkan, PhD[18], Sebastian MArmasu, MS[19], Nathan Pankratz, PhD[20], Rebecca DJackson, MD[21], Jonas BNielsen, MD, PhD[22], Franco Giulianini, PhD[23], Marja KPuurunen, MD, PhD[24], Manal Ibrahim, MD[25], Susan RHeckbert, MD, PhD[26], Theo KBammler, PhD[27], Kelly AFrazer, PhD[28], Bryan MMcCauley, MS[29], Kent Taylor, PhD[30], James SPankow, PhD, MPH[31], Alexander PReiner, MD, MPH[32], Maiken EGabrielsen, PhD[33], Jean-François Deleuze, PhD[34], Chris JO'Donnell, MD[35], Jihye Kim, PhD, MPH[36], Barbara McKnight, PhD[37], Peter Kraft, PhD[38], John-Bjarne Hansen, MD, PhD[39], Frits RRosendaal, MD, PhD[40], John AHeit, MD[41], Bruce MPsaty, MD, PhD[42], Weihong Tang, MD, PhD[43], Charles Kooperberg, PhD[44], Kristian Hveem, MD, PhD[45], Paul MRidker, MD, MPH[46], Pierre-Emmanuel Morange, MD-PhD[47], Andrew DJohnson, PhD[48], Christopher Kabrhel, MD MPH[49], David-Alexandre Trégouët, PhD[50], Nicholas LSmith, PhD[51].

Author Affiliations: [1]Department of Epidemiology, University of Washington, Seattle, Washington, USA; Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA. [2]Department of Environmental and Occupational Health Sciences, University of Washington, Seattle, Washington, USA. [3]Department of Pediatrics and Rady Children's Hospital, University of California San Diego, La Jolla, USA; K.G. Jebsen Thrombosis Research and Expertise Center, Department of Clinical Medicine, UiT – The Arctic University of Norway, Tromsø, Norway. [4]Department of Epidemiology, University of Washington, Seattle, WA, USA. [5]Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands. [6]Department of Health Sciences Research, Mayo Clinic, Rochester, MN USA. [7]Cardiovascular Health Research Unit, Department of Medicine, University of Washington, Seattle WA USA. [8]Division of Biostatistics, School of Public Health, University of Minnesota, Minneapolis, MN USA. [9]Division of Public Health, Fred Hutchinson Cancer Research Center, Seattle WA, USA. [10]K.G. Jebsen Center for Genetic Epidemiology, Department of Public Health and Nursing, NTNU, Norwegian University of Science and Technology, Trondheim, Norway; MRC Integrative Epidemiology Unit, University of Bristol, Bristol, UK; Clinic of Thoracic and Occupational Medicine, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway. [11]Division of Preventive Medicine, Brigham and Women's Hospital, Boston, USA; Harvard Medical School, Boston, USA. [12]Laboratory of Haematology, La Timone Hospital, Marseille, France; C2VN, Aix Marseille University, INSERM, INRA, C2VN, Marseille, France. [13]Population Sciences Branch, Division of Intramural Research, National Heart, Lung and Blood Institute, Bethesda, MD, USA; NHLBI and Boston University's The Framingham Heart Study, Framingham, MA, USA. [14]Program in Genetic Epidemiology and Statistical Genetics, Harvard T.H. Chan School of Public Health, Boston, MA, USA. [15]INSERM UMR_S 1219, Bordeaux Population Health Research Center, University of Bordeaux, France. [16]Cardiovascular Health Research Unit, Department of Medicine, University of Washington, Seattle WA USA. [17]Department of Environmental and Occupational Health Sciences, University of Washington, Seattle, Washington, USA. [18]K.G. Jebsen Thrombosis Research and Expertise Center, Department of Clinical Medicine, UiT – The Arctic University of Norway, Tromsø, Norway; Division of Internal Medicine, University Hospital of North Norway, Tromsø, Norway. [19]Health Sciences Research, Mayo Clinic, Rochester, MN USA. [20]Department of Laboratory Medicine and Pathology, School of Medicine, University of Minnesota, Minneapolis, MN, USA. [21]Division of Endocrinology, Diabetes and Metabolism, The Ohio State University, Columbus OH, USA. [22]Department of Internal Medicine, Division of Cardiology, University of Michigan Medical School, Ann Arbor, Michigan, USA. [23]Division of Preventive Medicine, Brigham and Women's Hospital, Boston, USA. [24]NHLBI and Boston University's The Framingham Heart Study, Framingham, MA, USA. [25]Laboratory of Haematology, La Timone Hospital, Marseille, France.; C2VN, Aix Marseille University, INSERM, INRA, C2VN, Marseille, France. [26]Department of Epidemiology, University of Washington, Seattle, Washington, USA; Kaiser Permanente Washington Health Research Institute, Kaiser Permanente Washington, Seattle WA USA. [27]Department of Environmental and Occupational Health Sciences, University of Washington, Seattle, Washington, USA. [28]Department of Pediatrics and Rady Children's Hospital, University of California San Diego, La Jolla, USA; K.G. Jebsen Thrombosis Research and Expertise Center, Department of Clinical Medicine, UiT – The Arctic University of Norway, Tromsø, Norway; Institute of Genomic Medicine, University of California San Diego, La Jolla, California, USA. [29]Health Sciences Research, Mayo Clinic, Rochester, MN USA. [30]Los Angeles Biomedical Research Institute and Department of Pediatrics, Harbor-UCLA Medical Center, Torrence CA 90502, USA. [31]Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, Minnesota, USA. [32]Department of Epidemiology, University of Washington, Seattle WA, United States; Division of Public Health, Fred Hutchinson Cancer Research Center, Seattle WA, United States. [33]K.G. Jebsen Center for Genetic Epidemiology, Department of Public Health and Nursing, NTNU, Norwegian University of Science and Technology, Trondheim, Norway. [34]Centre National de Recherche en Génomique Humaine, Direction de la Recherche Fondamentale, CEA, 91057 Evry, France; CEPH, Fondation Jean Dausset, Paris, France. [35]Million Veteran's Program, Veteran's Administration, Boston, MA; Population Sciences Branch, Division of Intramural Research, National Heart, Lung and Blood Institute, Bethesda, MD, USA; NHLBI and Boston University's

The Framingham Heart Study, Framingham, MA, USA. [36]Program in Genetic Epidemiology and Statistical Genetics, Harvard T.H. Chan School of Public Health, Boston, MA, USA. [37]Department of Biostatistics, University of Washington, Seattle WA USA; Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, USA. [38]Program in Genetic Epidemiology and Statistical Genetics, Harvard T.H. Chan School of Public Health, Boston, MA, USA. [39]K.G. Jebsen Thrombosis Research and Expertise Center, Department of Clinical Medicine, UiT – The Arctic University of Norway, Tromsø, Norway; Division of Internal Medicine, University Hospital of North Norway, Tromsø, Norway. [40]Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands. [41]Health Sciences Research, Mayo Clinic, Rochester, MN USA. [42]Cardiovascular Health Research Unit, Departments of Medicine, Epidemiology, and Health Services, University of Washington, Seattle WA USA; Kaiser Permanente Washington Health Research Institute, Kaiser Permanente Washington, Seattle WA USA. [43]Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, Minnesota, USA. [44]Division of Public Health, Fred Hutchinson Cancer Research Center, Seattle WA, United States. [45]K.G. Jebsen Center for Genetic Epidemiology, Department of Public Health and Nursing, NTNU, Norwegian University of Science and Technology, Trondheim, Norway. [46]Division of Preventive Medicine, Brigham and Women's Hospital, Boston, USA; Harvard Medical School, Boston, USA. [47]C2VN, Aix Marseille Univ, INSERM, INRA, C2VN, Marseille, France; Laboratory of Haematology, La Timone Hospital, Marseille, France; CRB Assistance Publique - Hôpitaux de Marseille, HemoVasc (CRB AP-HM HemoVasc), Marseille, France. [48]Population Sciences Branch, Division of Intramural Research, National Heart, Lung and Blood Institute, Bethesda, MD, USA; NHLBI and Boston University's The Framingham Heart Study, Framingham, MA, USA. [49]Center for Vascular Emergencies, Department of Emergency Medicine, Massachusetts General Hospital; Channing Division of Network Medicine, Brigham and Women's Hospital; Harvard Medical School. [50]INSERM UMR_S 1219, Bordeaux Population Health Research Center, University of Bordeaux, France. [51]Department of Epidemiology, University of Washington, Seattle, Washington, USA; Kaiser Permanente Washington Health Research Institute, Kaiser Permanente Washington, Seattle WA USA; Seattle Epidemiologic Research and Information Center, Department of Veterans Affairs Office of Research and Development, Seattle WA USA.

APPENDIX C

Rainer Malik[1], Ganesh Chauhan[2], Matthew Traylor[3], Muralidharan Sargurupremraj[4,5], Yukinori Okada[6,7,8], Aniket Mishra[4,5], Loes Rutten-Jacobs[3], Anne-Katrin Giese[9], Sander W van der Laan[10], Solveig Gretarsdottir[11], Christopher D Anderson[12,13,14,14], Michael Chong[15], Hieab HH Adams[16,17], Tetsuro Ago[18], Peter Almgren[19], Philippe Amouyel[20,21], Hakan Ay[22,13], Traci M Bartz[23], Oscar R Benavente[24], Steve Bevan[25], Giorgio B Boncoraglio[26], Robert D Brown, Jr.[27], Adam S Butterworth[28,29], Caty Carrera[30,31], Cara L Carty[32,33], Daniel I Chasman[34,35], Wei-Min Chen[36], John W Cole[37], Adolfo Correa[38], Ioana Cotlarciuc[39], Carlos Cruchaga[40,41], John Danesh[28,42,43,44], Paul IW de Bakker[45,46], Anita L DeStefano[47,48], Marcel den Hoed[49], Qing Duan[50], Stefan T Engelter[51,52], Guido J Falcone[53,54], Rebecca F Gottesman[55], Raji P Grewal[56], Vilmundur Gudnason[57,58], Stefan Gustafsson[59], Jeffrey Haessler[60], Tamara B Harris[61], Ahamad Hassan[62], Aki S Havulinna[63,64], Susan R Heckbert[65], Elizabeth G Holliday[66,67], George Howard[68], Fang-Chi Hsu[69], Hyacinth I Hyacinth[70], M Arfan Ikram[16], Erik Ingelsson[71,72], Marguerite R Irvin[73], Xueqiu Jian[74], Jordi Jiménez-Conde[75], Julie A Johnson[76,77], J Wouter Jukema[78], Masahiro Kanai[6,7,79], Keith L Keene[80,81], Brett M Kissela[82], Dawn O Kleindorfer[82], Charles Kooperberg[60], Michiaki Kubo[83], Leslie A Lange[84], Carl D Langefeld[85], Claudia Langenberg[86], Lenore J Launer[87], Jin-Moo Lee[88], Robin Lemmens[89,90], Didier Leys[91], Cathryn M Lewis[92,93], Wei-Yu Lin[28,94], Arne G Lindgren[95,96], Erik Lorentzen[97], Patrik K Magnusson[98], Jane Maguire[99], Ani Manichaikul[36], Patrick F McArdle[100], James F Meschia[101], Braxton D Mitchell[100,102], Thomas H Mosley[103,104], Michael A Nalls[105,106], Toshiharu Ninomiya[107], Martin J O'Donnell[15,108], Bruce M Psaty[109,110,111,112], Sara L Pulit[113,45], Kristiina Rannikmäe[114,115], Alexander P Reiner[65,116], Kathryn M Rexrode[117], Kenneth Rice[118], Stephen S Rich[36], Paul M Ridker[34,35], Natalia S Rost[9,13], Peter M Rothwell[119], Jerome I Rotter[120,121], Tatjana Rundek[122], Ralph L Sacco[122], Saori Sakaue[7,123], Michele M Sale[124], Veikko Salomaa[63], Bishwa R Sapkota[125], Reinhold Schmidt[126], Carsten O Schmidt[127], Ulf Schminke[128], Pankaj Sharma[39], Agnieszka Slowik[129], Cathie LM Sudlow[114,115], Christian Tanislav[130], Turgut Tatlisumak[131,132], Kent D Taylor[120,121], Vincent NS Thijs[133,134], Gudmar Thorleifsson[11], Unnur Thorsteinsdottir[11], Steffen Tiedt[1], Stella Trompet[135], Christophe Tzourio[5,136,137], Cornelia M van Duijn[138,139], Matthew Walters[140], Nicholas J Wareham[86], Sylvia Wassertheil-Smoller[141], James G Wilson[142], Kerri L Wiggins[109], Qiong Yang[47], Salim Yusuf[15], Najaf Amin[16], Hugo S Aparicio[185,48], Donna K Arnett[186], John Attia[187], Alexa S Beiser[47,48], Claudine Berr[188], Julie E Buring[34,35], Mariana Bustamante[189], Valeria Caso[190], Yu-Ching Cheng[191], Seung Hoan Choi[192,48], Ayesha Chowhan[185,48], Natalia Cullell[31], Jean-François Dartigues[193,194], Hossein Delavaran[95,96], Pilar Delgado[195], Marcus Dörr[196,197], Gunnar Engström[19], Ian Ford[198], Wander S Gurpreet[199], Anders Hamsten[200,201], Laura Heitsch[202], Atsushi Hozawa[203], Laura Ibanez[204], Andreea Ilinca[95,96], Martin Ingelsson[205], Motoki Iwasaki[206], Rebecca D Jackson[207], Katarina Jood[208], Pekka Jousilahti[63], Sara Kaffashian[4,5], Lalit Kalra[209], Masahiro Kamouchi[210], Takanari Kitazono[211], Olafur Kjartansson[212], Manja Kloss[213], Peter J Koudstaal[214], Jerzy Krupinski[215], Daniel L Labovitz[216], Cathy C Laurie[118], Christopher R Levi[217], Linxin Li[218], Lars Lind[219], Cecilia M Lindgren[220,221], Vasileios Lioutas[222,48], Yong Mei Liu[223], Oscar L Lopez[224], Hirata Makoto[225], Nicolas Martinez-Majander[172], Koichi Matsuda[225], Naoko Minegishi[203], Joan Montaner[226], Andrew P Morris[227,228], Elena Muiño[31], Martina Müller-Nurasyid[229,230,231], Bo Norrving[95,96], Soichi Ogishima[203], Eugenio A Parati[232], Leema Reddy Peddareddygari[56], Nancy L

Pedersen[98,233], Joanna Pera[129], Markus Perola[63,234], Alessandro Pezzini[235], Silvana Pileggi[236], Raquel Rabionet[237], Iolanda Riba-Llena[30], Marta Ribasés[238], Jose R Romero[185,48], Jaume Roquer[239,240], Anthony G Rudd[241,242], Antti-Pekka Sarin[243,244], Ralhan Sarju[199], Chloe Sarnowski[47,48], Makoto Sasaki[245], Claudia L Satizabal[185,48], Mamoru Satoh[245], Naveed Sattar[246], Norie Sawada[206], Gerli Sibolt[172], Ásgeir Sigurdsson[247], Albert Smith[248], Kenji Sobue[245], Carolina Soriano-Tárraga[240], Tara Stanne[249], O Colin Stine[250], David J Stott[251], Konstantin Strauch[229,252], Takako Takai[203], Hideo Tanaka[253,254], Kozo Tanno[245], Alexander Teumer[255], Liisa Tomppo[172], Nuria P Torres-Aguila[31], Emmanuel Touze[256,257], Shoichiro Tsugane[206], Andre G Uitterlinden[258], Einar M Valdimarsson[259], Sven J van der Lee[16], Henry Völzke[255], Kenji Wakai[253], David Weir[260], Stephen R Williams[261], Charles DA Wolfe[241,242], Quenna Wong[118], Huichun Xu[191], Taiki Yamaji[206], Dharambir K Sanghera[125,169,170], Olle Melander[19], Christina Jern[171], Daniel Strbian[172,173], Israel Fernandez-Cadenas[31,30], W T Longstreth, Jr[174,65], Arndt Rolfs[175], Jun Hata[107], Daniel Woo[82], Jonathan Rosand[12,13,14], Guillaume Pare[15], Jemma C Hopewell[176], Danish Saleheen[177], Kari Stefansson[11,178], Bradford B Worrall[179], Steven J Kittner[37], Sudha Seshadri[180,48], Myriam Fornage[74,181], Hugh S Markus[3], Joanna MM Howson[28], Yoichiro Kamatani[6,182], Stephanie Debette[4,5], Martin Dichgans[1,183,184].

[1]Institute for Stroke and Dementia Research (ISD), University Hospital, LMU Munich, Munich, Germany. [2]Centre for Brain Research, Indian Institute of Science, Bangalore, India. [3]Stroke Research Group, Division of Clinical Neurosciences, University of Cambridge, UK. [4]INSERM U1219 Bordeaux Population Health Research Center, Bordeaux, France. [5]University of Bordeaux, Bordeaux, France. [6]Laboratory for Statistical Analysis, RIKEN Center for Integrative Medical Sciences, Yokohama, Japan. [7]Department of Statistical Genetics, Osaka University Graduate School of Medicine, Osaka, Japan. [8]Laboratory of Statistical Immunology, Immunology Frontier Research Center (WPI-IFReC), Osaka University, Suita, Japan. [9]Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA. [10]Laboratory of Experimental Cardiology, Division of Heart and Lungs, University Medical Center Utrecht, University of Utrecht, Utrecht, Netherlands. [11]deCODE genetics/AMGEN inc, Reykjavik, Iceland. [12]Center for Genomic Medicine, Massachusetts General Hospital (MGH), Boston, MA, USA. [13]J. Philip Kistler Stroke Research Center, Department of Neurology, MGH, Boston, MA, USA. [14]Program in Medical and Population Genetics, Broad Institute, Cambridge, MA, USA. [15]Population Health Research Institute, McMaster University, Hamilton, Canada. [16]Department of Epidemiology, Erasmus University Medical Center, Rotterdam, Netherlands. [17]Department of Radiology and Nuclear Medicine, Erasmus University Medical Center, Rotterdam, Netherlands. [18]Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan. [19]Department of Clinical Sciences, Lund University, Malmö, Sweden. [20]Univ. Lille, Inserm, Institut Pasteur de Lille, LabEx DISTALZ-UMR1167, Risk factors and molecular determinants of aging-related diseases, F-59000 Lille, France. [21]Centre Hosp. Univ Lille, Epidemiology and Public Health Department, F-59000 Lille, France. [22]AA Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA. [23]Cardiovascular Health Research Unit, Departments of Biostatistics and Medicine, University of Washington, Seattle, WA, USA. [24]Division of Neurology, Faculty of Medicine, Brain Research Center, University of British Columbia, Vancouver, Canada. [25]School of Life Science, University of Lincoln, Lincoln, UK. [26]Department of Cerebrovascular Diseases, Fondazione IRCCS Istituto Neurologico "Carlo Besta", Milano, Italy. [27]Department of Neurology, Mayo Clinic Rochester, Rochester, MN, USA. [28]MRC/BHF Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK. [29]The National Institute for Health Research Blood and Transplant Research Unit in Donor Health and Genomics, University of Cambridge, UK. [30]Neurovascular Research Laboratory, Vall d'Hebron Institut of Research, Neurology and Medicine Departments-Universitat Autònoma de Barcelona, Vall d'Hebrón Hospital, Barcelona, Spain. [31]Stroke Pharmacogenomics and Genetics, Fundacio Docència i Recerca MutuaTerrassa, Terrassa, Spain. [32]Children's Research Institute, Children's National Medical Center, Washington, DC, USA. [33]Center for Translational Science, George Washington University, Washington, DC, USA. [34]Division of Preventive Medicine, Brigham and Women's Hospital, Boston, MA, USA. [35]Harvard Medical School, Boston, MA, USA. [36]Center for Public Health Genomics, Department of Public Health Sciences, University of Virginia, Charlottesville, VA, USA. [37]Department of Neurology, University of Maryland School of Medicine and Baltimore VAMC, Baltimore, MD, USA. [38]Departments of Medicine, Pediatrics and Population Health Science, University of Mississippi Medical Center, Jackson, MS, USA. [39]Institute of Cardiovascular Research, Royal Holloway University of London, UK & Ashford and St Peters Hospital, Surrey UK. [40]Department of Psychiatry, The Hope Center Program on Protein Aggregation and Neurodegeneration (HPAN), Washington University, School of Medicine, St. Louis, MO, USA. [41]Department of Developmental Biology, Washington University School of Medicine, St. Louis, MO, USA. [42]NIHR Blood and Transplant Research Unit in Donor Health and Genomics, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK. [43]Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge, UK. [44]British Heart Foundation, Cambridge Centre of Excellence, Department of Medicine, University of Cambridge, Cambridge, UK. [45]Department of Medical Genetics, University Medical Center Utrecht, Utrecht, Netherlands. [46]Department of Epidemiology, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, Netherlands. [47]Boston University School of Public Health, Boston, MA, USA. [48]Framingham Heart Study, Framingham, MA, USA. [49]Department of Immunology, Genetics and Pathology and Science for Life Laboratory, Uppsala University, Uppsala, Sweden. [50]Department of Genetics, University of North Carolina, Chapel Hill, NC, USA. [51]Department of Neurology and Stroke Center, Basel

University Hospital, Switzerland. [52]Neurorehabilitation Unit, University and University Center for Medicine of Aging and Rehabilitation Basel, Felix Platter Hospital, Basel, Switzerland. [53]Department of Neurology, Yale University School of Medicine, New Haven, CT, USA. [54]Program in Medical and Population Genetics, The Broad Institute of Harvard and MIT, Cambridge, MA, USA. [55]Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA. [56]Neuroscience Institute, SF Medical Center, Trenton, NJ, USA. [57]Icelandic Heart Association Research Institute, Kopavogur, Iceland. [58]University of Iceland, Faculty of Medicine, Reykjavik, Iceland. [59]Department of Medical Sciences, Molecular Epidemiology and Science for Life Laboratory, Uppsala University, Uppsala, Sweden. [60]Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, USA. [61]Laboratory of Epidemiology and Population Science, National Institute on Aging, National Institutes of Health, Bethesda, MD, USA. [62]Department of Neurology, Leeds General Infirmary, Leeds Teaching Hospitals NHS Trust, Leeds, UK. [63]National Institute for Health and Welfare, Helsinki, Finland. [64]FIMM - Institute for Molecular Medicine Finland, Helsinki, Finland. [65]Department of Epidemiology, University of Washington, Seattle, WA, USA. [66]Public Health Stream, Hunter Medical Research Institute, New Lambton, Australia. [67]Faculty of Health and Medicine, University of Newcastle, Newcastle, Australia. [68]School of Public Health, University of Alabama at Birmingham, Birmingham, AL, USA. [69]Department of Biostatistical Sciences, Wake Forest School of Medicine, Winston-Salem, NC, USA. [70]Aflac Cancer and Blood Disorder Center, Department of Pediatrics, Emory University School of Medicine, Atlanta, GA, USA. [71]Department of Medicine, Division of Cardiovascular Medicine, Stanford University School of Medicine, CA, USA. [72]Department of Medical Sciences, Molecular Epidemiology and Science for Life Laboratory, Uppsala University, Uppsala, Sweden. [73]Epidemiology, School of Public Health, University of Alabama at Birmingham, USA. [74]Brown Foundation Institute of Molecular Medicine, University of Texas Health Science Center at Houston, Houston, TX, USA. [75]Neurovascular Research Group (NEUVAS), Neurology Department, Institut Hospital del Mar d'Investigació Mèdica, Universitat Autònoma de Barcelona, Barcelona, Spain. [76]Department of Pharmacotherapy and Translational Research and Center for Pharmacogenomics, University of Florida, College of Pharmacy, Gainesville, FL, USA. [77]Division of Cardiovascular Medicine, College of Medicine, University of Florida, Gainesville, FL, USA. [78]Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands. [79]Program in Bioinformatics and Integrative Genomics, Harvard Medical School, Boston, MA, USA. [80]Department of Biology, East Carolina University, Greenville, NC, USA. [81]Center for Health Disparities, East Carolina University, Greenville, NC, USA. [82]University of Cincinnati College of Medicine, Cincinnati, OH, USA. [83]RIKEN Center for Integrative Medical Sciences, Yokohama, Japan. [84]Department of Medicine, University of Colorado Denver, Anschutz Medical Campus, Aurora, CO, USA. [85]Center for Public Health Genomics and Department of Biostatistical Sciences, Wake Forest School of Medicine, Winston-Salem, NC, USA. [86]MRC Epidemiology Unit, University of Cambridge School of Clinical Medicine, Institute of Metabolic Science, Cambridge Biomedical Campus, Cambridge, UK. [87]Intramural Research Program, National Institute on Aging, National Institutes of Health, Bethesda, MD, USA. [88]Department of Neurology, Radiology, and Biomedical Engineering, Washington University School of Medicine, St. Louis, MO, USA. [89]KU Leuven – University of Leuven, Department of Neurosciences, Experimental Neurology, Leuven, Belgium. [90]VIB Center for Brain & Disease Research, University Hospitals Leuven, Department of Neurology, Leuven, Belgium. [91]Univ.-Lille, INSERM U 1171. CHU Lille, Lille, France. [92]Department of Medical and Molecular Genetics, King's College London, London, UK. [93]SGDP Centre, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK. [94]Northern Institute for Cancer Research, Paul O'Gorman Building, Newcastle University, Newcastle, UK. [95]Department of Clinical Sciences Lund, Neurology, Lund University, Lund, Sweden. [96]Department of Neurology and Rehabilitation Medicine, Skåne University Hospital, Lund, Sweden. [97]Bioinformatics Core Facility, University of Gothenburg, Gothenburg, Sweden. [98]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden. [99]University of Technology Sydney, Faculty of Health, Ultimo, Australia. [100]Department of Medicine, University of Maryland School of Medicine, MD, USA. [101]Department of Neurology, Mayo Clinic, Jacksonville, FL, USA. [102]Geriatrics Research and Education Clinical Center, Baltimore Veterans Administration Medical Center, Baltimore, MD, USA. [103]Division of Geriatrics, School of Medicine, University of Mississippi Medical Center, Jackson, MS, USA. [104]Memory Impairment and Neurodegenerative Dementia Center, University of Mississippi Medical Center, Jackson, MS, USA. [105]Laboratory of Neurogenetics, National Institute on Aging, National institutes of Health, Bethesda, MD, USA. [106]Data Tecnica International, Glen Echo MD, USA. [107]Department of Epidemiology and Public Health, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan. [108]Clinical Research Facility, Department of Medicine, NUI Galway, Galway, Ireland. [109]Cardiovascular Health Research Unit, Department of Medicine, University of Washington, Seattle, WA, USA. [110]Department of Epidemiology, University of Washington, Seattle, WA. [111]Department of Health Services, University of Washington, Seattle, WA, USA. [112]Kaiser Permanente Washington Health Research Institute, Seattle, WA, USA. [113]Brain Center Rudolf Magnus, Department of Neurology, University Medical Center Utrecht, Utrecht, The Netherlands. [114]Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, UK. [115]Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK. [116]Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, USA. [117]Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA. [118]Department of Biostatistics, University of Washington, Seattle, WA, USA. [119]Nuffield Department of Clinical Neurosciences, University of Oxford, UK. [120]Institute for Translational Genomics and Population Sciences, Los Angeles Biomedical Research Institute

at Harbor-UCLA Medical Center, Torrance, CA, USA. [121]Division of Genomic Outcomes, Department of Pediatrics, Harbor-UCLA Medical Center, Torrance, CA, USA. [122]Department of Neurology, Miller School of Medicine, University of Miami, Miami, FL, USA. [123]Department of Allergy and Rheumatology, Graduate School of Medicine, the University of Tokyo, Tokyo, Japan. [124]Center for Public Health Genomics, University of Virginia, Charlottesville, VA, USA. [125]Department of Pediatrics, College of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA. [126]Department of Neurology, Medical University of Graz, Graz, Austria. [127]University Medicine Greifswald, Institute for Community Medicine, SHIP-KEF, Greifswald, Germany. [128]University Medicine Greifswald, Department of Neurology, Greifswald, Germany. [129]Department of Neurology, Jagiellonian University, Krakow, Poland. [130]Department of Neurology, Justus Liebig University, Giessen, Germany. [131]Department of Clinical Neurosciences/ Neurology, Institute of Neuroscience and Physiology, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden. [132]Sahlgrenska University Hospital, Gothenburg, Sweden. [133]Stroke Division, Florey Institute of Neuroscience and Mental Health, University of Melbourne, Heidelberg, Australia. [134]Austin Health, Department of Neurology, Heidelberg, Australia. [135]Department of Internal Medicine, Section Gerontology and Geriatrics, Leiden University Medical Center, Leiden, the Netherlands. [136]INSERM U1219, Bordeaux, France. [137]Department of Public Health, Bordeaux University Hospital, Bordeaux, France. [138]Genetic Epidemiology Unit, Department of Epidemiology, Erasmus University Medical Center Rotterdam, Netherlands. [139]Center for Medical Systems Biology, Leiden, Netherlands. [140]School of Medicine, Dentistry and Nursing at the University of Glasgow, Glasgow, UK. [141]Department of Epidemiology and Population Health, Albert Einstein College of Medicine, NY, USA. [142]Department of Physiology and Biophysics, University of Mississippi Medical Center, Jackson, MS, USA. [143]A full list of members and affiliations appears in the Supplementary Note. [144]Department of Human Genetics, McGill University, Montreal, Canada. [145]Department of Pathophysiology, Institute of Biomedicine and Translation Medicine, University of Tartu, Tartu, Estonia. [146]Department of Cardiac Surgery, Tartu University Hospital, Tartu, Estonia. [147]Clinical Gene Networks AB, Stockholm, Sweden. [148]Department of Genetics and Genomic Sciences, The Icahn Institute for Genomics and Multiscale Biology Icahn School of Medicine at Mount Sinai, New York, NY, USA. [149]Department of Pathophysiology, Institute of Biomedicine and Translation Medicine, University of Tartu, Biomeedikum, Tartu, Estonia. [150]Integrated Cardio Metabolic Centre, Department of Medicine, Karolinska Institutet, Karolinska Universitetssjukhuset, Huddinge, Sweden. [151]Clinical Gene Networks AB, Stockholm, Sweden. [152]Sorbonne Universités, UPMC Univ. Paris 06, INSERM, UMR_S 1166, Team Genomics & Pathophysiology of Cardiovascular Diseases, Paris, France. [153]ICAN Institute for Cardiometabolism and Nutrition, Paris, France. [154]Department of Biomedical Engineering, University of Virginia, Charlottesville, VA, USA. [155]Group Health Research Institute, Group Health Cooperative, Seattle, WA. USA. [156]Seattle Epidemiologic Research and Information Center, VA Office of Research and Development, Seattle, WA, USA. [157]Cardiovascular Research Center, Massachusetts General Hospital, Boston, MA, USA. [158]Department of Medical Research, Bærum Hospital, Vestre Viken Hospital Trust, Gjettum, Norway. [159]Saw Swee Hock School of Public Health, National University of Singapore and National University Health System, Singapore. [160]National Heart and Lung Institute, Imperial College London, London, UK. [161]Department of Gene Diagnostics and Therapeutics, Research Institute, National Center for Global Health and Medicine, Tokyo, Japan. [162]Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine, New Orleans, LA, USA. [163]Department of Cardiology, University Medical Center Groningen, University of Groningen, Netherlands. [164]MRC-PHE Centre for Environment and Health, School of Public Health, Department of Epidemiology and Biostatistics, Imperial College London, London, UK. [165]Department of Epidemiology and Biostatistics, Imperial College London, London, UK. [166]Department of Cardiology, Ealing Hospital NHS Trust, Southall, UK. [167]National Heart, Lung and Blood Research Institute, Division of Intramural Research, Population Sciences Branch, Framingham, MA, USA. [169]Department of Phamaceutical Sciences, Collge of Pharmacy, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA. [170]Oklahoma Center for Neuroscience, Oklahoma City, OK, USA. [171]Department of Pathology and Genetics, Institute of Biomedicine, The Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden. [172]Department of Neurology, Helsinki University Hospital, Helsinki, Finland. [173]Clinical Neurosciences, Neurology, University of Helsinki, Helsinki, Finland. [174]Department of Neurology, University of Washington, Seattle, WA, USA. [175]Albrecht Kossel Institute, University Clinic of Rostock, Rostock, Germany. [176]Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK. [177]Department of Genetics, Perelman School of Medicine, University of Pennsylvania, PA, USA. [178]Faculty of Medicine, University of Iceland, Reykjavik, Iceland. [179]Departments of Neurology and Public Health Sciences, University of Virginia School of Medicine, Charlottesville, VA, USA. [180]Department of Neurology, Boston University School of Medicine, Boston, MA, USA. [181]Human Genetics Center, University of Texas Health Science Center at Houston, Houston, TX, USA. [182]Center for Genomic Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan. [183]Munich Cluster for Systems Neurology (SyNergy), Munich, Germany. [184]German Center for Neurodegenerative Diseases (DZNE), Munich, Germany. [185]Boston University School of Medicine, Boston, MA, USA. [186]University of Kentucky College of Public Health, Lexington, KY, USA. [187]University of Newcastle and Hunter Medical Research Institute, New Lambton, Australia. [188]Univ. Montpellier, Inserm, U1061, Montpellier, France. [189]Centre for Research in Environmental Epidemiology, Barcelona, Spain. [190]Department of Neurology, Università degli Studi di Perugia, Umbria, Italy. [191]Department of Medicine, University of Maryland School of Medicine, Baltimore, MD, USA. [192]Broad Institute, Cambridge, MA, USA. [193]Univ. Bordeaux, Inserm, Bordeaux

Population Health Research Center, UMR 1219, Bordeaux, France. [194]Bordeaux University Hospital, Department of Neurology, Memory Clinic, Bordeaux, France. [195]Neurovascular Research Laboratory. Vall d'Hebron Institut of Research, Neurology and Medicine Departments-Universitat Autònoma de Barcelona. Vall d'Hebrón Hospital, Barcelona, Spain. [196]University Medicine Greifswald, Department of Internal Medicine B, Greifswald, Germany. [197]DZHK, Greifswald, Germany. [198]Robertson Center for Biostatistics, University of Glasgow, Glasgow, UK. [199]Hero DMC Heart Institute, Dayanand Medical College & Hospital, Ludhiana, India. [200]Atherosclerosis Research Unit, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden. [201]Karolinska Institutet, Stockholm, Sweden. [202]Division of Emergency Medicine, and Department of Neurology, Washington University School of Medicine, St. Louis, MO, USA. [203]Tohoku Medical Megabank Organization, Sendai, Japan. [204]Department of Psychiatry, Washington University School of Medicine, St. Louis, MO, USA. [205]Department of Public Health and Caring Sciences / Geriatrics, Uppsala University, Uppsala, Sweden. [206]Epidemiology and Prevention Group, Center for Public Health Sciences, National Cancer Center, Tokyo, Japan. [207]Department of Internal Medicine and the Center for Clinical and Translational Science, The Ohio State University, Columbus, OH, USA. [208]Institute of Neuroscience and Physiology, the Sahlgrenska Academy at University of Gothenburg, Goteborg, Sweden. [209]Department of Basic and Clinical Neurosciences, King's College London, London, UK. [210]Department of Health Care Administration and Management, Graduate School of Medical Sciences, Kyushu University, Japan. [211]Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Japan. [212]Landspitali National University Hospital, Departments of Neurology & Radiology, Reykjavik, Iceland. [213]Department of Neurology, Heidelberg University Hospital, Germany. [214]Department of Neurology, Erasmus University Medical Center. [215]Hospital Universitari Mutua Terrassa, Terrassa (Barcelona), Spain. [216]Albert Einstein College of Medicine, Montefiore Medical Center, New York, NY, USA. [217]John Hunter Hospital, Hunter Medical Research Institute and University of Newcastle, Newcastle, NSW, Australia. [218]Centre for Prevention of Stroke and Dementia, Nuffield Department of Clinical Neurosciences, University of Oxford, UK. [219]Department of Medical Sciences, Uppsala University, Uppsala, Sweden. [220]Genetic and Genomic Epidemiology Unit, Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK. [221]The Wellcome Trust Centre for Human Genetics, Oxford, UK. [222]Beth Israel Deaconess Medical Center, Boston, MA, USA. [223]Wake Forest School of Medicine, Wake Forest, NC, USA. [224]Department of Neurology, University of Pittsburgh, Pittsburgh, PA, USA. [225]BioBank Japan, Laboratory of Clinical Sequencing, Department of Computational biology and medical Sciences, Graduate school of Frontier Sciences, The University of Tokyo, Tokyo, Japan [226]Neurovascular Research Laboratory, Vall d'Hebron Institut of Research, Neurology and Medicine Departments-Universitat Autònoma de Barcelona. Vall d'Hebrón Hospital, Barcelona, Spain. [227]Department of Biostatistics, University of Liverpool, Liverpool, UK. [228]Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK. [229]Institute of Genetic Epidemiology, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany. [230]Department of Medicine I, Ludwig-Maximilians-Universität, Munich, Germany. [231]DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany. [232]Department of Cerebrovascular Diseases, Fondazione IRCCS Istituto Neurologico "Carlo Besta", Milano, Italy. [233]Karolinska Institutet, MEB, Stockholm, Sweden. [234]University of Tartu, Estonian Genome Center, Tartu, Estonia, Tartu, Estonia. [235]Department of Clinical and Experimental Sciences, Neurology Clinic, University of Brescia, Italy. [236]Translational Genomics Unit, Department of Oncology, IRCCS Istituto di Ricerche Farmacologiche Mario Negri, Milano, Italy. [237]Department of Genetics, Microbiology and Statistics, University of Barcelona, Barcelona, Spain. [238]Psychiatric Genetics Unit, Group of Psychiatry, Mental Health and Addictions, Vall d'Hebron Research Institute (VHIR), Universitat Autònoma de Barcelona, Biomedical Network Research Centre on Mental Health (CIBERSAM), Barcelona, Spain. [239]Department of Neurology, IMIM-Hospital del Mar, and Universitat Autònoma de Barcelona, Spain. [240]IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain. [241]National Institute for Health Research Comprehensive Biomedical Research Centre, Guy's & St. Thomas' NHS Foundation Trust and King's College London, London, UK. [242]Division of Health and Social Care Research, King's College London, London, UK. [243]FIMM-Institute for Molecular Medicine Finland, Helsinki, Finland. [244]THL-National Institute for Health and Welfare, Helsinki, Finland. [245]Iwate Tohoku Medical Megabank Organization, Iwate Medical University, Iwate, Japan. [246]BHF Glasgow Cardiovascular Research Centre, Faculty of Medicine, Glasgow, UK. [247]deCODE Genetics/Amgen, Inc., Reykjavik, Iceland. [248]Icelandic Heart Association, Reykjavik, Iceland. [249]Institute of Biomedicine, the Sahlgrenska Academy at University of Gothenburg, Goteborg, Sweden. [250]Department of Epidemiology, University of Maryland School of Medicine, Baltimore, MD, USA. [251]Institute of Cardiovascular and Medical Sciences, Faculty of Medicine, University of Glasgow, Glasgow, UK. [252]Chair of Genetic Epidemiology, IBE, Faculty of Medicine, LMU Munich, Germany. [253]Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute, Nagoya, Japan. [254]Department of Epidemiology, Nagoya University Graduate School of Medicine, Nagoya, Japan. [255]University Medicine Greifswald, Institute for Community Medicine, SHIP-KEF, Greifswald, Germany. [256]Department of Neurology, Caen University Hospital, Caen, France. [257]University of Caen Normandy, Caen, France. [258]Department of Internal Medicine, Erasmus University Medical Center, Rotterdam, Netherlands. [259]Landspitali University Hospital, Reykjavik, Iceland. [260]Survey Research Center, University of Michigan, Ann Arbor, MI, USA. [261]University of Virginia Department of Neurology, Charlottesville, VA, USA.