SUPPLEMENTARY MATERIALS

Antithrombin, protein C and protein S: Genome and transcriptome wide association studies identify 7 novel loci regulating plasma levels

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SUPPLEMENTARY METHODS:

Discovery Analyses:

Meta-level quality control and meta-analysis

We used the EasyQC software to perform basic quality control and homogenization of the data. SE-N (standard error against sample size) plots were used to reveal inconsistencies of phenotype transformations or units between studies. Allele frequencies were plotted against ancestry-specific allele reference panels from TOPMed to uncover issues of strand and allele coding. Lambda was calculated for all studies individually to detect inflation of p-values caused by problems of stratification. All variants with inconsistencies, extreme beta, or standard error values and imputation values < 0.3 were removed prior to meta-analysis. We also excluded variants that had missing values of coefficients, frequency, and p-value.

Study-specific genome-wide association analysis

Residuals from regression were inverse-normal transformed and were re-scaled by the standard deviation (SD) of the pre-transformed values for antithrombin and PS. Because different studies had different unit measures for PC, we did not re-scale by SD, and used the inverse-normal transformed levels for the PC analyses. Associations with imputed genotypes were then tested using an additive genetic model between each imputed dosage and the residuals for each re-scaled (antithrombin, PS) or inverse-normal transformed (PC) phenotype using linear regression and adjusting for all the covariates used in the phenotype regression. The X chromosome was additionally stratified by sex where women and men were coded as 0, 1, 2 and 0, 2, respectively.

Meta-analysis

We meta-analyzed the 22 autosomal chromosomes and the X chromosome separately, using fixed-effects inverse variance or sample size methods implemented in the METAL software[87]. Meta-analyses within each phenotyping method were adjusted for the genomic control coefficients (λ_{GC}) of each individual cohort. Summarized coefficients and p-values for each phenotype were presented as the result. Genome-wide association significance level was set as $5x10^{-9}$.

Conditional analysis

Conditional analyses were performed using COJO (Conditional & Joint; gcta—cojo--slct)[88], implemented in the Genome-Wide Complex Trait Analysis (GCTA) software[89], to identify additional independent signals at the associated loci.

Replication

Replication was performed using summary data from DeCODE Genetics (available at https://www.decode.com/summarydata/)[18] used the SOMAscan multiplexed proteomics assay to obtain proteomic measurements on 35,559 individuals of Icelandic origin, for which antithrombin, PC and PS data is available. The significance threshold p-value of the replication study was set as 0.05 divided by the number of identified lead variants tested.

Calculation of the Proportion of variance explained (r^2)
The proportion of variance explained by the associated variants was calculated for each ethnicity using the variants identified in the cross-ancestry meta-analysis with the following formula: r^2 = 2*EAF(1 - EAF)*β2 / var(y); where EAF and β represent the frequency and the per-allele increment in phenotype of the effect allele, respectively, and var(y) represents the phenotypic variance. We defined var(y) as the square of the weighted mean of standard deviations across all the cohorts that contributed to each ethnic specific meta-analysis.

Transcription-wide association studies (TWAS)
We used the EA population from the 1000 Genomes project[90] for the imputation of the missing variants in our GWAS input and for linkage disequilibrium (LD) blocks definition. Data from the Genotype-Tissue Expression (GTEx)[91] V8 database was used as reference to build the prediction models for cis-eQTL sites using the mash-R method (v0.2.5)[36,92-94]. Weights computed with mash-R were then applied to the final antithrombin, PC, and PS GWAS meta-analyses summary statistics to identify gene-trait associations.

S-PrediXcan was run to identify gene-trait associations for each tissue, and then the significantly shared eQTL across the 5 chosen tissues were leveraged using S-MultiXcan analyses following the pipelines described in previous studies[37,92].

Only tissues with a potential role in the synthesis or regulation of anticoagulants proteins (artery aorta, artery coronary, artery tibial, liver and whole blood) were considered to reduce false positives from more distally related tissues. The significance threshold was established applying Bonferroni correction for the total number of genes examined for each tissue (**Supplementary Table S3**).

Multi-phenotype analyses
MetaUSAT meta-analyzes summary statistics of common variants between multiple phenotypes, returning a p-value for each variant (p-value multivariate). The alleles of all datasets were previously harmonized before running the analysis and variants with minor allele count (MAC) < 30 were removed prior to the analysis. The significance threshold used was set at 5 x 10-9 and loci were defined as +/- 1 Mb around the variants with the lowest p-value. Previous GWAS results for antithrombin, PC, PS free and total were queried using the GWAS catalog database (available at https://www.ebi.ac.uk/gwas/docs/file-downloads).

Characterization and Prioritization of Candidate Loci

Fine Mapping
We used FOCUS (fine mapping of causal gene sets)[95] to prioritize TWAS genes in each genome-wide significant locus by estimating credible gene sets, avoiding confounding caused by LD or horizontal pleiotropy between variants that normally affect TWAS. Summary data from the EA meta-analyses for antithrombin, PC and PS, and expression prediction weights from PrediXcan GTEx v8 MASH-R models were analyzed following software recommendations.

Reference LD was estimated using the PROCARDIS database, including 5,820 unrelated EA individuals with genome-wide genotyping data imputed to the TOPMed v5 panel. For fine-mapping purposes, only genes within approximately 1Mb regions (obtained from LDetect software[96] using EA 1000 Genomes - b38) that contained at least 1 variant in the GWAS summary statistics with p-value < 5 x 10−8 were considered as recommended in the software pipe-line. This strategy was used to prioritize putative causal genes by providing a posterior inclusion probability (PIP) for each gene per locus. The PIP was interpreted as the probability of a gene to be causal given the TWAS statistics.

Colocalization Analyses

Colocalization analyses were performed for all the new genome-wide significant associations detected in the GWAS (cross-ancestry and EA) analyses using the COLOC R package V5.1.0.1.[97] GWAS summary statistics in each associated locus were subjected to a colocalization analysis with RNAseq data from the Genotype-Tissue Expression (GTEx) project[92] to seek for evidence of shared variants affecting both gene expression levels of closest genes (eQTLs) and the levels of each anticoagulant protein. We used the complete GTEx V8 files (available at https://console.cloud.google.com/storage/browser/gtex-resources) and considered windows of +/- 1 Mb around the lead variants to run the colocalization. We required that the conditional probability of colocalization (CPC) for a variant, given that the 2 phenotypes showed evidence of association (PPH4 / (PPH3 + PPH4)) was higher than 0.8.

We also performed colocalization analyses in all novel loci identified in the multi-phenotype analysis. First, we performed colocalization across multiple traits using COLOC (for 2 phenotypes)[97], or HyPrColoc[98] (for more than 2 phenotypes) R-packages, to identify loci regulating more than one anticoagulant phenotype. We also required a CPC higher than 0.8 for COLOC, or a probability of colocalization higher than 0.7 for HyPrColoc. Second, to help prioritize the causal gene in each locus, we tested colocalization with expression data at the novel loci derived from the multi-phenotype analyses, using HyPrColoc and the complete GTEx V8 files. A probability of colocalization > 0.7 was also required. As in TWAS analysis, we only considered functional related tissues to reduce false positives triggered by non-related tissues.

Functional Studies

Cell Culture and Gene Silencing

HepG2 cells were obtained from the UNC Lineberger Comprehensive Cancer Center Tissue Culture Facility and cultured in Minimum Essential Media (MEM, catalog #11095-080, Gibco, Waltham, MA) supplemented with 10% FBS (VWR, Radnor, PA), 1 mM sodium pyruvate, and 0.1 mM non-essential amino acids (Gibco). Cells were passaged using 0.25% Trypsin-EDTA (catalog #25200-056, Gibco). Cells from passage 135-145 were used for transfection experiments. Small interfering RNA (siRNAs, Silencer Select siRNAs, Thermo Fisher Scientific, Waltham, MA) were complexed with Lipofectamine RNAi MAX (Thermo Fisher Scientific) in OptiMEM Reduced Serum Media (RSM, catalog #31985-070, Gibco) for 15 minutes before adding to a 24-well plate. Cells were passaged, resuspended in MEM supplemented with 10% FBS, 1 mM sodium pyruvate, 0.1 mM non-essential amino acids, and added to the transfection

complex (100,000-150,000 cells/well and 32 nM siRNA, final). After 48 hours, media was replaced with fresh OptiMEM RSM and enriched supernatants were collected 24 hours later.

RNA Extraction and Quantitative RT-PCR

Total RNA was extracted from transfected HepG2 cells using the RNeasy Mini Kit (Qiagen, German Town, MD). RNA concentration was determined using a NanoDrop 2000 (Thermo Fisher Scientific). cDNA was prepared from 1 µg RNA using the QuantiTect Reverse Transcription Kit (Qiagen). Real Time quantitative PCR (RT-qPCR) was performed using the QuantiFast SYBR Green RT-PCR kit (Qiagen) and Quant Studio 3 (Thermofisher), with activation (95°C, 5 minutes), denaturation (95°C, 10 seconds), and annealing/extension (60°C, 30 seconds) for 40 cycles. RNA18S was used as the housekeeping gene for relative expression calculations. Values from individual experiments were normalized to lipofectamine-treated cells in the same experiment and log-transformed data were compared using one-way ANOVA with Šidák's multiple comparisons test.

Cell counts

HepG2 cells were washed with phosphate-buffered saline, followed by trypsinization using 0.25% trypsin-EDTA, and resuspended in culture media. Cells were counted on the Countess II FL cells counter using cell counting chamber slides (Thermo Fisher Scientific). Counts for each siRNA-treated cell were normalized against lipofectamine-treated cells (control) within the same experiment and compared by one-way ANOVA and Šidák's multiple comparisons test.

Immunoblotting

Proteins were separated on 10% gels by reducing SDS-PAGE and transferred to PVDF membranes. Membranes were blocked for 1 hour in LICOR Odyssey Blocking Buffer (Lincoln, NE) and incubated overnight with 25 µg/mL sheep anti-human antithrombin antibody (Haematologic Technologies, Essex Junction, VT) diluted in Tris-buffered saline, 0.1% Tween 20 (TBST). Membranes were incubated in LICOR IRDye 800 CW donkey anti-goat secondary antibody (1:10,000 in TBST) for 1 hour at RT. All washes were done using TBST. Antithrombin bands were quantified by fluorescence (Biorad Chemi-Doc MP Imager). Densitometry values from individual experiments were normalized to lipofectamine-treated cells in the same experiment and log-transformed data were compared using one-way ANOVA with Šidák's multiple comparisons test.

Primers used for qPCR.

Primer	Forward Sequence	Reverse Sequence
PROC	CTTGTCAGGCTTGGAGAGTATG	GTGGTGCTCTTGCTGTAGTT
SERPINC1	GATGAGGGCTCAGAACAGAAG	TGCCAGGTGCTGATAGAAAG
SNX17	TGAGGTAGAACAGAGGAGAGAG	GACGCAGGAAACTGTTGAAAG
GCKR	GTGGAGCAGGTGAAAGAGAA	TGCTGATGATGGAGGGAAAG
NRBP1	CACAAATCCTCTCTGCCCTAAG	GTCCGTTGTGCTGGATGAA
HP	CTGTGCTGGCATGTCTAAGT	CTTAAGATCCCAGTCGCATACC

GOLM2	**TTTCACGCTCAAGGAGTCATAC**	**GGAGTAGGGAGGTGACTTTCTA**

Mendelian Randomization Analyses

Summary statistics for the outcomes were obtained from previously published, large-scale GWAS[40-44,99] .To maximize power and ensure African ancestry specific variants were included in our MR analyses for VTE, we performed an inverse variance weighted (IVW) meta-analysis on the results of the latest INVENT (30,234 cases and 172,122 controls) and Million Veteran Program (MVP) (11,844, and 251,951 controls) GWAS of VTE [40,41].

IVW was used as the primary analysis and MR-Egger[100-102], Weighted Median, and Weighted Mode served as secondary analyses. MR Presso was used to test for horizontal pleiotropy and variants showing evidence of pleiotropy were excluded. IVW excluding the ABO locus was also performed for PC despite the locus passing MR Presso because it has been previously associated with several hemostatic phenotypes and therefore fails the horizontal pleiotropy assumption of MR[45]. Genetic instruments for antithrombin and PC were chosen separately by first restricting the exposure and outcome summary statistics to variants they had in common, and then, filtering the genetic variants in the exposure GWAS for genome-wide significance (p-value $< 5 \times 10^{-9}$). Finally, the remaining genetic variants for each exposure were distance pruned to select the most significant genetic variants at each locus (+/- 10 Mb for antithrombin to account for the longer disequilibrium pattern of rare variants, and +/- 1 Mb for PC). Known pleiotropic loci would be removed during selection of genetic instruments.

We performed the main analyses using the instruments derived from the present study and aimed to validate using instruments derived from DECODE Genetics data[18] for the same proteins, using the same methods. Only one instrument was available for Antithrombin using DECODE genetics data, and then a Wald test was used for the MR analyses.

All analyses were performed using the 'TwoSampleMR' v0.4.26 and 'MRPRESSO' v1.0 R packages.

Cohort-Specific Information

The **Atherosclerosis Risk In Communities (ARIC)** study is a population-based prospective cohort study of cardiovascular disease sponsored by the National Heart, Lung, and Blood Institute (NHLBI). ARIC included 15,792 individuals, predominantly European American and African American, aged 45-64 years at baseline (1987-89), chosen by probability sampling from four US communities. Cohort members completed three additional triennial follow-up examinations, a fifth exam in 2011-2013, a sixth exam in 2016-2017, and a seventh exam in 2018-2019. The ARIC study has been described in detail previously[20].
Antithrombin was measured at baseline using an amidolytic assay using a synthetic chromogenic substrate for thrombin (CBS 34.47, Diagnostica Stago) and bovine thrombin (Kabi). Protein C was measured at baseline with a commercial ELISA kit (Asserachrom Protein C, Diagnostica Stago).

The **Cooperative Health Research In South Tyrol (CHRIS)** study[30] is a population-based study with a longitudinal lookout established in 2011 in the Val Venosta/Vinschgau district, South Tyrol, Italy, to investigate the genetic basis of common chronic conditions associated with human ageing. Recruited into the study at baseline between 2011 and 2018 were 13,393 participants from 13 municipalities, each one characterized by a central town, small villages, and scattered mountain farms. Settlements are located at an altitude of 600 to 2,000 m above sea level.

Participants were all adults aged over 18 and cover more than one-third of the target region population. More detailed information about the study design could be found in elsewhere[30]. After overnight fasting, blood samples were collected between 08:00 AM and 10:00 AM at the study center. After pre-analytical sample processing, samples were shipped to the laboratory of the Merano hospital, Italy. There, two different systems were used to assess hemostatic factors in an aliquot of citrated plasma: 1) ROCHE CA1500 system (between August 2011 and January 2014) and 2) Stago STA Compact max system (between February 2014 and December 2018). Antithrombin was measured with the use of chromogenic methods (Siemens Innovance Antithrombin in ROCHE system and STA-Stachrom AT III in Stago system).

The **Cardiovascular Health Study(CHS)[22]** is a population-based cohort study of risk factors for CHD and stroke in adults ≥65 years conducted across 4 field centers. The original predominantly Caucasian cohort of 5,201 persons was recruited in 1989-1990 from random samples of the Medicare eligibility lists; subsequently, an additional predominantly African American cohort of 687 persons was enrolled for a total sample of 5,888. DNA was extracted from blood samples drawn on all participants at their baseline examination in 1989-90 and all participants provided informed consent for the use of their genetic data in analyses. After an 8-12-h fast, CHS participants underwent phlebotomy by atraumatic venipuncture with a 21-gauge butterfly needle connected to a Vacutainer (Becton Dickinson, Rutherford, NJ) outlet via a Luer adaptor[103].Antithrombin was measured using a chromogenic assay with coefficient of variation as 7.0%. Protein C was measured by immunoassay with a coefficient of variation as 14.4%.

These measures were not abundantly available in African-American participants so analyses were restricted to those of European ancestry.

The **Genes and Blood-clotting Study (GABC)** is a cohort study of 1,150 siblings from the University of Michigan, Ann Arbor, during 2006-2009. All participants enrolled in the study were aged between 14 years to 35 years and had at least one eligible healthy sibling, and have signed an online agreement form[23]. Whole blood was obtained at a one-time sampling and rapidly processed into citrated plasma while buffy coats were preserved for DNA extraction. Multiple biochemical phenotypes have been assayed with preserved plasma from GABC participants, primarily focused on measurement of hemostasis and thrombosis related proteins. Participants were also phenotype for bleeding tendency and multiple other common human traits.

Antithrombin was measured by a commercial AlphaLISA kit. When available, plasma concentrations were determined by standard curve fitting to plasma standards provided by George King FACT plasma[32]. https://kingbiomed.com/products/fact-factor-assay-control/

The **Genetic Analysis of Idiopathic Thrombophilia (GAIT)** project is a family-based study where 935 subjects in 35 extended pedigrees were collected[24]. To be included in the study, a family was required to have at least 10 living individuals in 3 or more generations. Families were selected through a proband with idiopathic thrombophilia, which was defined as recurrent thrombotic events (at least one of which was spontaneous), a single spontaneous thrombotic episode plus a first-degree relative also affected, or onset of thrombosis before age 45. Thrombosis in these probands was considered idiopathic when biological causes as antithrombin deficiency, protein S and C deficiencies, activated protein C resistance, plasminogen deficiency, heparin cofactor II deficiency, Factor V Leiden, dysfibrinogenemia, lupus anticoagulant and antiphospholipid antibodies, were excluded. Subjects were interviewed by a physician to determine their health and reproductive history, current medications, alcohol consumption, use of sex hormones (oral contraceptives or hormonal replacement therapy) and their smoking history. The study was performed according to the Declaration of Helsinki. All procedures of the study were reviewed by the Institutional Review Board of the Hospital de la Santa Creu i Sant Pau, Barcelona, Spain. Adult subjects gave informed consent for themselves and for their minor children. Antithrombin and Protein C were measured in a biochemical analyzer (Metrolab;RAL,Barcelona, Spain) with the use of chromogenic methods from Chromogenix, an. Functional protein S was assayed with deficient plasma from Diagnostica Stago (Ansières, France) in the STA automated coagulometer (Boehringer Mannheim). Total free Protein S was measured by ELISA from Diagnostica Stago[104].

The **Heart and Vascular Health (HVH)** The Heart and Vascular Health (HVH) Study is a set of population-based, case-control studies evaluating risk factors for cardiovascular disease in the member of Group Health Cooperative, Washington[25,31].Eligible participants for this study were postmenopausal female HVH study controls, who were randomly-selected GHC enrollees between 2003 and 2010. Among the 1499 women with available blood samples, not history of VTE, and not using anticoagulation, we measured hemostatic measures on users and non-user

of hormone therapy. Two hemostatic measurements were performed: [1] antithrombin activity (ATc); and [2] total protein S antigen. For ATc, 100 µl AT was added to 100 µl plasma in a 1/20 dilution with Diluent buffer. After incubation for 60 seconds, 100 µl AT substrate was added and measurement started. All steps were automatically performed by the STA analyser; total protein S antigen levels (CV using commercial quality control: 4.2%) were measured by an enzyme-linked immunosorbent assay (Diagnostica Stago, Asnières, France). (Diagnostica Stago, Asnières, France)[105].

The **Ludwigshafen Risk and Cardiovascular Health (LURIC)** study[26] is an ongoing prospective study of more than 3,300 individuals of German ancestry in whom cardiovascular and metabolic phenotypes (coronary artery disease, myocardial infarction, dyslipidemia, hypertension, metabolic syndrome and diabetes mellitus) have been defined or ruled out using standardized methodologies in all study participants. Inclusion criteria for LURIC were: German ancestry (limitation of genetic heterogeneity), clinical stability (except for acute coronary syndromes) and availability of a coronary angiogram. Exclusion criteria were: any acute illness other than acute coronary syndromes, any chronic disease where non-cardiac disease predominated and a history of malignancy within the last five years. Genome-wide analyses using the Affymetrix 6.0 have been completed in all participants. A 10-year clinical follow-up for total and cause specific mortality has been completed.

Antithrombin was determined using STA ANTITHROMBIN III assay (Stago Diagnostica/Roche, Mannheim, Germany), Protein C was determined using the COAMATIC assay on a STA Stago analyser (Chromogenix Instrumentation, Laboratory SpA, Milan, Italy).

The **MARseille THrombosis Association (MARTHA)** project has been previously described[27]. Briefly, MARTHA consists on two independent samples of VT patients, named MARTHA08 (N=1,006) and MARTHA10 (N=586). MARTHA patients are unrelated subjects of European origin, with the majority being of French ancestry, consecutively recruited at the Thrombophilia center of La Timone hospital (Marseille, France) between January 1994 and October 2005. All patients had a documented history of VT and free of well characterized genetic risk factors including AT, PC, or PS deficiency, homozygosity for FV Leiden or FII 20210A, and lupus anticoagulant. They were interviewed by a physician on their medical history, which emphasized manifestations of deep vein thrombosis and pulmonary embolism using a standardized questionnaire. The thrombotic events were confirmed by venography, Doppler ultrasound, spiral computed tomographic scanning angiography, and/or ventilation/perfusion lung scan. Blood samples were collected by antecubital venipuncture into Vacutainer® tubes 0.105 M trisodium citrate (ratio 9:1, Becton Dickinson) for the coagulation tests. Platelet-poor plasma (PPP) was obtained after double centrifugation of citrated blood (3000 g for 10 min at 25°C) and kept frozen at -80°C until analysis.

Antithrombin activity levels were performed using an amidolytic assay (STA-Stachrom ATIII kit; Diagnostica Stago, Asnieres, France). Protein C activity was assayed using a chronometric assay (Instrumentation Laboratory, Paris, France). Quantitative determination of free PS levels

was performed by enzyme-linked immunosorbent assay using the Asserachrom f-PS assay (Diagnostica Stago).

The **Riesgo de Enfermedad TROmboembolica VEnosa Study (RETROVE)** is a prospective case‐control study that includes 400 consecutive patients with VTE (cancer associated thrombosis was excluded) and 400 healthy control volunteers[28].All individuals were ≥ 18 years. The diagnosis was confirmed with Doppler ultrasonography, tomography, magnetic resonance, arteriography, phlebography or pulmonary gammagraphy.

Blood samples from the patients were taken at least 6 months after thrombosis to minimize the influence of the acute phase. None of the participants was using oral anticoagulants, heparin, or antiplatelet therapy at the time of blood collection. Controls were selected according to the age and sex distribution of the Spanish population (2001 census). A total of 5 ml of blood was obtained in a Vacutainer tube (BD Vacutainer Becton Dickinson and Company, New Jersey, USA) containing EDTA as anticoagulant. All individuals were genotyped using Infinium Global Screening Array-24 v3.0 kit from Illumina. Written informed consent was obtained for all participants and all procedures were approved by the Institutional Review Board of the Hospital de la Santa Creu i Sant Pau (Barcelona). Antithrombin and Protein C functional levels were were measured in a biochemical analyzer (Metrolab;RAL,Barcelona, Spain) with the use of chromogenic methods from Chromogenix. Functional PS was determined with a kit from Diagnostica Stago. Total PS and free PS were assayed with the use of ELISA methods from Diagnostica Stago (Ansières, France).

The **Trinity Student Study (TSS)** is a cohort study of 2,524 healthy European individuals attending the University of Dublin, Trinity College, with ages between 18 and 28 years, recruited over one academic year in 2003-2004[29,106]. Plasma and DNA was collected from participants as well as demographic, diet and nutrition-based information. Hemostasis and thrombosis related traits were assayed by collaborators at the University of Michigan.
Antithrombin was measured by a commercial AlphaLISA assay. When available, plasma concentrations were determined by standard curve fitting to plasma standards provided by George King FACT plasma[32](https://kingbiomed.com/products/fact-factor-assay-control/).

Supplementary Table S1. Phenotype measurements and sample size in selected cohorts

Study	Measure	AN	Antithrombin			Protein C			Protein S Free			Protein S total		
			N	Mean (SD)	Unit	N	Mean (SD)	Unit	N	Mean (SD)	Unit	N	Mean (SD)	Unit
ARIC	Activity	EA	9,179	110.2(20.9)	%	/	/	/	/	/	/	/	/	/
	Antigen	EA	/	/	/	9,180	3.18(0.6)	Ug/mL	/	/	/	/	/	/
	Activity	AA	2,688	115.3(23.1)	%	/	/	/	/	/	/	/	/	/
	Antigen	AA	/	/	/	2,688	3.14(0.6)	Ug/mL	/	/	/	/	/	/
CHS	Activity	EA	681	109.4 (14.1)	%	/	/	/	/	/	/	/	/	/
	Antigen	EA	/	/	/	317/366	3.5 (0.7)/4.9(1.9)	ug/mL	288	5.02 (0.94)	Ug/dL	290	22.43 (3.09)	Ug/dL
CHRIS	Activity	EA	9,012	102.5 (11.5)	%	/	/	/	/	/	/	/	/	/
GABC	/	/	/	/	/	919	118.7(20.21)	IU/dL	/	/	/	934	83.49(26.5)	IU/mL*100
	Antigen	EA	932	36.32 (6.5)	IU/mL*100	/	/	/	/	/	/	/	/	/
GAIT	Activity	EA	890	112.1(13.5)	IU/mL*100	890	115.8(26.6)	IU/mL*100	/	/	/	911	102.7(24)	IU/mL*100
	Antigen	EA	/	/	/	/	/	/	922	94.7 (23.0)	IU/mL*100	922	96.5(20)	IU/mL*100
HVH1	Activity	EA	148	109(13.5)	%	/	/	/	/	/	/	/	/	/
	Antigen	EA	/	/	/	/	/	/	107	95(21)	IU/mL*100	151	115(18)	IU/mL*10)
LURIC	Activity	EA	2,705	97.1 (13.4)	%	1,041	110.5 (22.6)	%	1049	101 (27.4)	%	1,040	118.9 (31.6)	%
MARTHA	Activity	EA	897	102.9 (11.6)	%	949	111.6 (24.7)	%	949	90.4(21.5)	%	/	/	/

RETROVE cases	Activity	EA	399	106.9(13.4)	IU/mL*100	399	127.498 (24.67)	IU/mL*100	/	/	/	398	109.944 (20.3)	IU/mL*100
	Antigen	EA	/	/	/	/	/	/	398	100.6 (21.3)	IU/mL*100	/	/	/
RETROVE controls	Activity	EA	400	107.81(10.8)	IU/mL*100	400	120.49 (23.855)	IU/mL*100	/	/	/	400	108.3(21.3)	IU/mL*100
	Antigen	EA	/	/	/	/	/	/	400	99.6(21.3)	IU/mL*100	/	/	/
TSS	Activity	EA	/	/	/	2136	128.33 (19.55)	IU/dL	/	/	/	2272	84.44 (27.0)	IU/mL

AN: Ancestry, EA: European; AA: African.

Supplementary Table S2. Detailed Description of cohort characteristics, and methods for phenotyping, genotyping and imputation

Study	Ancestry	Phenotype	Study design	Population	Cite(s)	Time	Genotype measurement	Phenotype measurement	Imputation
Atherosclerosis Risk in Communities Study (ARIC)	European /African	AT act, PC act, PC ant	Population-based cohort study	Men and Women aged 45-65 years in the selected US communities	North Carolina, Mississippi, Minnesota, Maryland, US	1987-	Affymetrix SNP array 6.0	ELISA	TOPMed
Cardiovascular Health Study (CHS)	European /African	AT act, PST act, PSF act	Population-based cohort study	Adults aged over 65 years in the selected US communities	North Carolina, California, Maryland, Pennsylvania, US	1989-2010	Illumina 370CNV BeadChip/HumanOmnil-Quad_v1 Bead Chip	Coag-A-mate X2	TOPMed
The Cooperative Health Research in South Tyrol Study (CHRIS)	European	AT act	Population-based cohort study	Adults aged in middle and Upper Vinschgau/Val Venosta area of South Tyrol, Italy	Middle and upper Vinschgau/Val Venosta area of South Tyrol, Italy	2011-	Illumina Human OmniExpress Exome Bead Chip.		TOPMed
Genes and Blood-Clotting Study (GABC)	European	AT ant, PC act, PST act	Population-based cohort study	Healthy sibilings aged between 14 and 35 from University of Michigan	Michigan, US	2006-2009	Illumina HumanOmni1-Quad_v1-0_B array	AlphaLISA assay	TOPMed

Genetic Analysis of Idiopathic Thrombophilia project (GAIT)	European	AT act, PC act, PSF ant, PST act. PST ant	Family-based cohort study	397 individuals from 21 families selected from a proband with VTE diagnosis and pedigree size	Barcelona, Spain	1999-2000	HumanOmniExpress Exome-8v1.2 (324 individuals and coverage 964,193 variants) and HumanCoreExome-12v1.1 (610 individuals and coverage 542,585 variants)	CPA/ ELISA	TOPMed
HVH	European	PSF ant, PST ant	Population-based case control study	Perimenopausal and postmenopausal women aged 30 to 89 in Washington State, US	Washington State	1995-2002	GoldenGate custom panel using BeadArray tech	Medical record	TOPMed
Ludwigshafen Risk and Cardiovascular Health study (LURIC)	European	AT act, PC act, PSF act, PST act	Hospital-based cohort study	Patients diagnosed with coronary angiography	Southwestern Germany	1997-2000	Affymetrix SNP array 6.0		TOPMed

MARseille THrombosis Association Project (MARTHA)	European	AT act, PC act	Hospital-based cohort study	People with documented history VT and free of AT, PS, PC deficiency or other coagulation related status	La Timone hospital (Marseille, France)	1994-2012	Illumina Human610-Quad Beadchip/Illumina Human660W-Quad Beadchip	amidolytic assay (STA-Stachrom ATIII kit)/chronometci assay/Asserach rom f-PS assay	TOPMed
Riesgo de Enfermedad TROmboembolica VEnosa (RETROVE)	European	AT act, PC act, PC ant, PSF ant, PST act	Hospital-based case-control study	VTE patients and controls from the hospital	Barcelona, Spain		Illumina Infinium Global Screening Array-24 v2.0		TOPMed
Trinity Student Study (TSS)	European	PC act, PST act	Population-based cohort study	Irish individuals aged 18 to 28 years attending University of Dulbin	Trinity, Ireland	2003-2004	he Illumina HumanOmni1-Quad_v1-0_B array		TOPMed

AT: antithrombin, PC: protein C, PSF: protein S free, PST: protein S total, act: activity, ant: antigen.

Supplementary Table S3. Number of genes tested in TWAS by tissues.

Phenotype	Tissue	Nº of Genes
Antithrombin	Artery Aorta	14,116
	Artery Coronary	13,575
	Artery Tibial	14,243
	Liver	12,427
	Whole Blood	12,395
Protein C	Artery Aorta	14,120
	Artery Coronary	13,577
	Artery Tibial	14,244
	Liver	12,428
	Whole Blood	12,396
Protein S Free	Artery Aorta	14,110
	Artery Coronary	13,569
	Artery Tibial	14,233
	Liver	12,424
	Whole Blood	12,392
Protein S Total	Artery Aorta	14,118
	Artery Coronary	13,576
	Artery Tibial	14,244
	Liver	12,431
	Whole Blood	12,396

Supplementary Table S4. Functional annotations for candidate variants, derived from HaploReg v4.1

Phenotype	Chr:Pos:A1:A2	RSID	Gene	Functional annotation
AT	1:173914872:A:T	rs2227624	*SERPINC1*	MV to *SERPINC1*.Active transcription marks in liver. Estrogen receptor binding motif.
	2:27375230:T:C	rs4665972	*SNX17*	IV to *SNX17*; GWAS: Triglycerides
	7:7349751:T:C	rs13244268	*BAZ1B*	IV to *BAZ1B*; Active transcription marks in liver
	16:72054562:A:C	rs5471	*HP/TXNL4B*	IV to *HP*; 5' UTR to *TXNL4B*
	19:49513222:T:G	rs111981233	*FCGRT*	IV to *FCGRT*
PC	1:1092794968:T:G	rs12740374	*CELSR2*	3' UTR to *CELSR2*; GWAS: LDL cholesterol, phospholipase A2
	2:127418299:A:G	rs1799809	*PROC*	0.1 KB 5' to *PROC*
	2:27375230:T:C	rs4665972	*SNX17*	IV to *SNX17*; GWAS: Triglycerides
	7:73625076:C:G	rs35493868	*MLXIPL*	2KB 5' to *MLXIPL*
	15:42980693:T:C	rs529330569	*UBR1*	IV to *UBR1*
	20:35179967:T:C	rs11907011	*PROCR*	IV to *PROCR*
PSF	3:93868695:T:C	rs528128538	*PROS1*	1KB 5' to *PROS1*
	7:444568571:T:C	rs141292869	*DDX56*	IV to *DDX56*
	9:114321523:A:C	rs150611042	*ORM1*	2KB 5' to *ORM1*; GWAS: Thrombin generation potentials
PST	7:45231101:A:T	rs59569024	*MYL7*	380KB 5' to *MYL7**
	9:114321523:A:C	rs150611042	*ORM1*	2KB 5' to *ORM1*; GWAS: Thrombin generation potentials
Multi-phenotype	15:43528519:T:C	rs55707100	*MAP1A*	MV to *MAP1A*

AT: antithrombin, PC: protein C, PSF: protein S free, PST: protein S total, Chr: chromosome, Pos: position, A1: effect allele, A2: other allele, IV: intronic variant, MV: missense variant, 3'UTR: 3 prime untranslated regions; 5'UTR: 5 prime untranslated regions.

Supplementary Table S5. Genes selected through prioritization process in functional study.

Phenotype	Locus	Prioritized Genes	Expression in Liver (GTEx)	Liver Expression (>10 TPM)	Biological Viability	HepG2 Expression (>10 TPM)*	Lowers Cell Count
AT	*SERPINC1*	*GCKR*	Mainly liver (97 TPM)				
		NRBP1	Expression in liver (27 TPM)				
		SNX17	Expression in liver (47 TPM)				
		GTF3C2-AS2	No data in GTEx				
	SNX17-GCKR-NRBP1	*BAZ1B*	Low in liver (10 TPM)				
		MLXIPL	Mainly liver (413 TPM)				
		BCL7B	Expression in liver (20 TPM)				
	HP-TXNL4B	*HP*	Mainly liver (> 1000 TPM)				
		TXNL4B	Low in liver (9 TPM)				

PC	*FCGRT*	*FCGRT*	Expression in liver (111 TPM)				
	GOLM2-LCMT2-CATSPER2	*GOLM2*	Expression in liver (12 TPM)				
		LCMT2	Low in liver (1 TPM)				
		CATSPER2	Low in liver (1 TPM)				
		MAP1A (from multi-phenotype)	Extremely Low in liver (0.1 TPM)				
PS	*ORM1-ORM2*	*ORM1*	Mainly liver (> 1000 TPM)	No model			
		ORM2	Mainly liver (> 1000 TPM)	No model			
	MYL7	*MYL7*	Extremely Low in liver (0.3 TPM)	No model			

AT: antithrombin, PC: protein C, PS: protein S; TPM: Transcripts per million. * HepG2 expression from the Human Protein Atlas.

Supplementary Table S6. Participants and cohorts count of all specific meta-analyses

Phenotype	Cross-ethnic		African		European	
	Cohorts	Participants	Cohorts	Participants	Cohorts	Participants
AT/Activity	-	-	1	2,688	8	24,311
AT/Antigen	-	-	-	-	1	932
AT/All	9	27,931	1	2,688	9	25,243
PC/Activity	-	-	-	-	6	6,734
PC/Antigen	-	-	1	2,688	2	9,863
PC/All	8	19,285	1	2,688	8	16,597
PST/Activity	-	-	-	-	4	5,045
PST/Antigen	-	-	-	-	3	1,363
PST/All	-	-	-	-	7	6,408
PSF/Activity	-	-	-	-	2	1,998
PSF/Antigen	-	-	-	-	4	2,115
PSF/All	-	-	-	-	6	4,113

AT: Antithrombin, PC: Protein C, PST: Protein S Total, PSF: Protein S Free

Supplementary Table S7. Number of variants considered for each specific cohort (stratified by ancestry) before and after quality control

Study Name	Variants In	Variants Out	N	Lambda
Antithrombin Autosome				
ARIC EA	70,219,668	17,889,491	9,179	1.005
CHRIS EA	23,250,229	15,754,873	9,012	1.017
CHS EA	14,442,735	9,046,889	681	1.001
GABC EA	22,307,894	9,767,792	932	1.044
GAIT2 EA	18,771,000	9,564,407	890	1.021
LURIC EA	35,830,264	11,151,214	2,705	1.005
MARTHA EA	13,548,418	9,674,035	897	0.997
RETROVECASES EA	24,924,998	8,307,177	399	0.994
RETROVECONTROLS EA	24,963,152	8,311,223	400	0.996
ARIC AA	67,480,830	25,070,269	2,688	1.008
Antithrombin X chromosome				
ARIC XF	2,634,440	524,469	4,866	0.997
ARIC XM	2,526,220	509,663	4,313	1.008
CHS XF	520,226	267,751	514	0.994
CHS XM	520,226	205,063	167	0.975
GAIT2 XF	568,088	238,551	449	0.988
GAIT2 XM	555,598	237,844	441	1.003
MARTHA XF	387,325	257,744	643	0.988
MARTHA XM	286,764	210,053	254	0.959
retroveCASES XF	829,108	215,542	203	0.951
retroveCASES XM	742,620	214,540	196	0.955
retroveCONTROLS XF	828,855	216,582	206	0.960
retroveCONTROLS XM	739,571	211,793	194	1.034
Protein C Autosome				
ARIC EA	70,219,809	17,890,753	9,180	1.029
CHS 1 EA	14,442,735	8,183,875	366	1.008
CHS 2 EA	14,442,735	7,952,747	317	1.011

GABC EA	34,112,072	9,737,717	919	1.035
GAIT2 EA	19,894,686	9,813,030	890	1.028
LURIC EA	35,830,264	9,059,673	1,041	0.997
MARTHA EA	13,728,590	9,773,535	949	0.999
retroveCASES EA	26,496,726	8,535,945	399	1.015
retroveCONTROLS EA	26,531,578	8,539,692	400	1.010
TSS EA	28,227,516	11,107,799	2,136	1.007
ARIC AA	67,480,830	25,070,269	2,688	1.014
Protein C X Chromosome				
ARIC XF	2,634,454	524,485	4,866	1.038
ARIC XM	2,526,284	509,725	4,314	1.010
CHS 1 XM	520,226	245,952	366	1.002
CHS 2 XF	520,226	199,852	150	0.982
CHS 2 XM	520,226	205,063	167	0.980
GABC XF	1,116,585	291,773	562	1.179
GABC XM	1,059,867	247,835	357	0.767
GAIT2 XF	568,088	238,551	449	0.963
GAIT2 XM	555,598	237,844	441	1.141
MARTHA XF	390,592	260,079	677	0.988
MARTHA XM	291,911	213,324	272	1.050
retroveCASES XF	829,108	215,542	203	0.966
retroveCASES XM	742,620	214,540	196	0.950
retroveCONTROLS XF	828,855	216,582	206	0.886
retroveCONTROLS XM	739,571	211,793	194	0.992
Protein S free Autosome				
CHS	14,442,735	7,809,143	288	1.022
GAIT2	19,910,472	9,896,490	922	1.036
HVH1	15,455,952	1,902,147	107	1.013
LURIC	35,830,264	9,074,110	1,049	1.016
MARTHA	13,759,440	9,780,346	949	0.993
retroveCASES	26,492,308	8,531,798	398	1.005

retroveCONTROLS	26,531,578	8,539,692	400	1.012
Protein S free X Chromosome				
CHS XF	520,226	193,777	132	0.921
CHS XM	520,226	202,047	156	0.987
GAIT2 XF	568,380	240,782	465	0.954
GAIT2 XM	556,577	239,807	457	1.193
MARTHA XF	392,378	260,309	673	1.024
MARTHA XM	292,793	213,940	276	1.013
retroveCASES XF	828,693	215,349	202	1.006
retroveCASES XM	742,620	214,540	196	1.038
retroveCONTROLS XF	828,855	216,582	206	1.039
retroveCONTROLS XM	739,571	211,793	194	1.087
Protein S total				
CHS	14,442,735	7,818,959	290	0.997
GABC	34,112,072	9,771,502	934	1.043
GAIT2 activity	19,908,400	9,870,882	911	1.040
GAIT2 antigen	19,910,472	9,896,490	922	1.032
HVH1	15,455,952	1,902,147	151	1.002
LURIC	35,830,264	9,059,870	1,041	1.013
retroveCASES	26,492,308	8,531,798	398	1.007
retroveCONTROLS	26,531,578	8,539,692	400	1.011
TSS	28,227,516	1,121,0226	2,272	1.009
Protein S total X Chromosome				
CHS XF	520,226	193,777	132	1.043
CHS XM	520,226	202,657	158	0.984
GABC XF	1,117,388	292,736	571	0.885
GABC XM	1,062,748	251,085	363	0.890
GAIT2 activity XF	568,274	239,811	458	1.077
GAIT2 activity XM	556,390	239,427	453	1.198
GAIT2 antigen XF	568,380	240,782	465	1.012
GAIT2 antigen XM	556,577	239,807	457	1.062

LURIC XF	35,830,264	9,059,870	1,041	1.013
retroveCASES XF	828,693	215,349	202	1.050
retroveCASES XM	742,620	214,540	196	0.913
retroveCONTROLS XF	828,855	216,582	206	0.921
retroveCONTROLS XM	739,571	211,793	194	1.059

XF: X chromosome in females, XM: X chromosome in males, Lambda: genomic control coefficients. Analyses were stratified and by sex for X-chromosome

Supplementary Table S8. Additional independent variants from conditional analyses

Candidate gene in the loci	Independent Gene/Variant location	RSID	Beta	SE	Joint Effect	Joint SE	Original p-value	Joint p-value	LD R^2	Phenotype /Ancestry
SERPINC1	*RABGAP1L*/IV	rs182221508	13.40	2.14	13.51	2.14	3.91E-10	2.97E-10	0.0046	AT EA
PROC	*PROC*/IV	rs73492719	-0.25	0.05	-0.33	0.05	1.23E-06	1.29E-10	-0.0086	PC EA
PROCR	*PROCR*/IV, *MMP24-AS1-EDEM2*/IV	rs6060300	0.23	0.01	0.16	0.01	1.14E-65	5.92E-30	0.0000	PC EA

IV: Intronic Variant, AT: antithrombin, PC: protein C, EA: European, SE: standard error, LD R^2: linkage disequilibrium r^2.

Supplementary Table S9. Ancestry specific results of antithrombin and protein C meta-analyses

Ancestry	Chr:Pos:A1:A2	RSID	Closest Genes	N	EAF	Beta (SE)	p-value
			Antithrombin				
AA	16:72054562:A:C	rs5471	*HP|TXNL4B*	2688	0.866	9.77 (0.95)	1.37E-24
EA	1:173914872:A:T	rs2227624	*SERPINC1*	24414	0.994	8.11 (0.20)	3.33E-19
EA	2:27375230:T:C	rs4665972	*SNX17*	25242	0.447	1.00 (0.12)	7.87E-16
			Protein C				
AA	2:127423170:T:C	rs200045749	*PROC|MIR4783*	2688	0.014	-1.41 (0.12)	4.83E-34
AA	20:35176751:A:G	rs867186	*PROCR|MMP24-AS1-EDEM2*	2688	0.909	-0.73 (0.05)	4.96E-54
EA	1:109279544:A:G	rs599839	*PSRC1*	15556	0.773	0.09 (0.01)	4.30E-11
EA	2:127418299:A:G	rs1799809	*PROC*	16597	0.569	0.21 (0.01)	5.10E-83
EA	2:27375230:T:C	rs4665972	*SNX17*	16597	0.420	0.11 (0.01)	1.92E-23
EA	7:73562919:T:C	rs34594435	*BAZ1B | BCL7B | TBL2*	16597	0.187	-0.09 (0.01)	2.16E-10
EA	20:35179967:T:C	rs11907011	*PROCR|MMP24-AS1-EDEM2*	16597	0.094	0.75 (0.02)	5.07E-363
EA	20:34176377:T:C	rs17332951	*RPS2P1|ASIP*	16597	0.952	-0.51 (0.03)	1.05E-88
EA	20:36270102:A:G	rs117473488	*AAR2|DLGAP4*	16597	0.018	0.50 (0.04)	3.58E-33

AA: African ancestry, EA: European ancestry, Chr: chromosome, Pos: position, A1: effect allele, A2: other allele, SE: standard error, EAF: effect allele frequency.

Supplementary Table S10. Summary statistics results for the selected lead variants in DeCODE genetics dataset

Chr:Pos:A1:A2	RSID	Beta	P-value	SE	N	EAF
			Antithrombin			
1:173914872:T:A	rs2227624	-0.48	3.10E-21	0.05	35,351	0.005
2:27375230:C:T	rs4665972	-0.04	3.16E-06	0.01	35,374	0.339
7:73497513:C:T	rs13244268	-0.04	0.003	0.01	35,354	0.111
19:49513222:G:T	rs111981233	0.05	0.002	0.02	35,375	0.060
			Protein C			
1:109279544:A:G	rs599839	0.08	1.71E-17	0.01	35,344	0.208
2:127418299:A:G	rs1799809	0.14	4.90E-69	0.01	35,366	0.419
2:27375230:C:T	rs4665972	-0.06	6.93E-14	0.01	35,374	0.339
7:73625076:G:C	rs35493868	-0.03	0.004	0.01	35,354	0.199
20:35179967:T:C	rs11907011	0.55	<5E-307	0.01	35,367	0.093
			Protein S			
3:93868695:T:C	rs528128538	-0.93	1.44E-10	0.15	35,327	0.001
9:114321523:A:C	rs150611042	-0.30	7.53E-102	0.01	35,361	0.099

Chr: chromosome, Pos: position, A1: effect allele, A2: other allele, SE: standard error; EAF: effect allele frequency. Analysis population was based on Iceland (European) population.

Supplementary Table S11. Significant results from TWAS S-MultiXcan analyses

Region	Gene	Best predicted tissue	P-value
	Antithrombin		
chr1:173924653-173858808	*DARS2*	Artery Coronary	3.36E-07
chr1:173868082-173903549	*ZBTB37*	Artery Aorta	2.28E-10
chr1:173903800-173917327	*SERPINC1*	Whole Blood	8.78E-12
chr1:174159410-174995308	*RABGAP1L*	Whole Blood	1.13E-09
chr1:175067833-175148075	*TNN*	Liver	3.40E-09
chrchr2:27496839-27523684	*GCKR*	Liver	1.12E-06
chrchr7:73536356-73557960	*BCL7B*	Whole Blood	2.08E-06
chrchr7:73593194-73624543	*MLXIPL*	Artery Coronary	1.87E-06
chr19:49506816-49526428	*FCGRT*	Artery Coronary	1.12E-06
	Protein C		
chr1:109279556-109283186	*PSRC1*	Liver	3.82E-09
chr1:109399042-109426448	*PSMA5*	Liver	3.17E-09
chr2:27381195-27409591	*PPM1G*	Artery Aorta	6.28E-07
chr2:27427790-27442259	*NRBP1*	Artery Aorta	2.19E-08
chr2:27442366-27446481	*KRTCAP3*	Artery Tibial	1.34E-07
chr2:27496839-27523684	*GCKR*	Liver	3.26E-10
chr2:27537386-27582720	*C2orf16*	Liver	3.66E-07
chr2:27663471-27694976	*SLC4A1AP*	Artery Aorta	2.01E-07
chr2:127183832-127220313	*CYP27C1*	Artery Tibial	1.46E-09
chr2:127257290-127294166	*ERCC3*	Artery Tibial	1.67E-49
chr2:127298668-127388465	*MAP3K2*	Artery Coronary	2.53E-68
chr2:127388178-127406228	*AC068282.3*	Whole Blood	2.46E-07
chr2:127418427-127429242	*PROC*	Liver	6.78E-78
chr2:127436207-127526886	*IWS1*	Artery Aorta	2.02E-24
chr2:127638381-127681786	*LIMS2*	Whole Blood	6.74E-14
chr7:73593194-73624543	*MLXIPL*	Artery Coronary	2.35E-08
chr15:43323649-43330582	*LCMT2*	Artery Aorta	1.62E-06
chr15:43628503-43668118	*CATSPER2*	Whole Blood	1.27E-06
chr15:44288719-44415758	*GOLM2*	Whole Blood	3.19E-07
chr20:33490075-33650036	*CBFA2T2*	Artery Coronary	1.31E-09
chr20:33655701-33656423	*RP1-63M2.7*	Liver	4.32E-08
chr20:34088309-34112243	*EIF2S2*	Whole Blood	1.44E-53
chr20:34280268-34311802	*AHCY*	Liver	1.20E-67
chr20:34363241-34540748	*ITCH*	Artery Aorta	2.47E-10
chr20:34560542-34698790	*PIGU*	Artery Tibial	7.33E-100
chr20:34704339-34713439	*TP53INP2*	Artery Coronary	2.17E-18
chr20:34844720-34872856	*GGT7*	Artery Tibial	2.36E-49
chr20:34872146-34927962	*ACSS2*	Liver	3.79E-08
chr20:34928432-34956027	*GSS*	Artery Tibial	1.50E-241
chr20:34955810-35002437	*MYH7B*	Liver	9.83E-38
chr20:35002404-35092807	*TRPC4AP*	Whole Blood	3.82E-256
chr20:35115364-35147336	*EDEM2*	Artery Tibial	2.25E-98
chr20:35172072-35216240	*PROCR*	Liver	2.71E-239
chr20:35201745-35278131	*MMP24-AS1*	Artery Aorta	9.29E-96

chr20:35226690-35276998	*MMP24*	Artery Coronary	2.32E-43
chr20:35278907-35284985	*EIF6*	Liver	8.42E-173
chr20:35542038-35557634	*ERGIC3*	Artery Tibial	3.08E-25
chr20:35615829-35621094	*SPAG4*	Liver	8.39E-60
chr20:35648925-35664956	*RBM12*	Liver	4.60E-61
chr20:35668052-35699355	*NFS1*	Artery Tibial	3.68E-67
chr20:35701347-35742312	*RBM39*	Artery Aorta	1.63E-22
chr20:35953617-35959472	*SCAND1*	Artery Coronary	9.19E-71
chr20:35954564-36030700	*CNBD2*	Artery Aorta	1.12E-25
chr20:36045618-36051018	*NORAD*	Liver	7.27E-10
chr20:36651766-36746090	*NDRG3*	Artery Coronary	1.29E-14
chr20:33983052-33993124	*RALY-AS1*	Artery Tibial	1.08E-50
chr20:33666498-33668525	*ACTL10*	Whole Blood	2.11E-07
	Protein S		
chr3:93873051-93980003	*PROS1*	Artery Aorta	5.86E-07
chr3:93980139-94055678	*ARL13B*	Artery Aorta	8.96E-07
chr7:44138864-44141332	*MYL7*	Liver	1.98E-06
chr9:114329869-114332521	*ORM2*	Whole Blood	8.97E-08

Supplementary Table 12. Prioritized genes in fine-mapping analyses.

Region	Prioritized genes				
	Artery Aorta	**Artery Coronary**	**Artery Tibial**	**Liver**	**Whole Blood**
			Antithrombin		
chr1:173099832-175089390	*SERPINC1*	*SERPINC1*	*SERPINC1*	NA	*SERPINC1*
chr2:26896379-28598746	NA	NA	NA	*TNN/NRBP1*	NA
			Protein C		
chr1:108468105-1:110303740	NA	NA	NA	*PSRC1*	*PSRC1*
chr2:26896379-2:28598746	NRPB1	NA	NA	*NRBP1*	*NRBP1*
chr2:125841643-127372950	*ERCC3*	*ERCC3*	*ERCC3*	*ERCC3*	NA
chr2:127373815-128033703	*IWS1*	*MAP3K2*	*AC068282.3*	*MAP3K2*	*MAP3K2/PROC*
chr7:73335940-76455022	*MLXIPL*	NA	NA	NA	*TBL2*
chr15:42776816-44197582	*LCMT2*	NA	NA	*LCMT2*	NA
chr20:32813520-34959830	*AHCY*	*AHCY*	*AHCY*	*GSS*	*EIF2S2*
chr20:34961516-36909151	*MMP24-AS1/TRPC4AP/PROCR*	*MMP24-AS1/MYH7B*	*TRPC4AP EDEM2*	*MMP24-AS1/EDEM2/EIF6*	*MMP24-AS1 /TRPC4Ap/EDEM2*

Significance was based on posterior inclusion probability calculated with the FOCUS package.

Supplementary Table S13. Colocalization results in candidate novel loci

Phenotype	Chr:Pos:A1:A2	Tissue	Gene ID	Gene Name	PP.H3	PP.H4	CPC
AT	2:27375230:C:T	Artery Tibial	ENSG00000234072	*GTF3C2-AS2*	0.16	0.73	0.82
	2:27375230:C:T	Artery Tibial	ENSG00000115234	*SNX17*	1.00	6.09E-04	6.09E-04
	2:27375230:C:T	Artery Tibial	ENSG00000115216	*NRBP1*	0.99	0.01	0.01
	2:27375230:C:T	Whole Blood	ENSG00000138085	*ATRAID*	1.00	2.05E-11	2.05E-11
	2:27375230:C:T	Whole Blood	ENSG00000115216	*NRBP1*	1.00	6.30E-06	6.30E-06
	2:27375230:C:T	Whole Blood	ENSG00000157992	*KRTCAP3*	1.00	4.91E-05	4.91E-05
	16:72054562:A:C	Artery Tibial	ENSG00000257017	*HP*	0.83	0.17	0.17
	16:72054562:A:C	Artery Tibial	ENSG00000261701	*HPR*	1.00	6.94E-18	6.94E-18
	16:72054562:A:C	Liver	ENSG00000257017	*HP*	0.01	0.97	0.98
	16:72054562:A:C	Whole Blood	ENSG00000257017	*HP*	0.11	0.89	0.89
	16:72054562:A:C	Whole Blood	ENSG00000261701	*HPR*	0.72	0.28	0.28
PSF	9:114321523:A:C	Liver	ENSG00000228278	*ORM2*	0.01	0.98	0.99
	9:114321523:A:C	Whole Blood	ENSG00000229314	*ORM1*	1.00	9.77E-14	9.77E-14
	9:114321523:A:C	Whole Blood	ENSG00000228278	*ORM2*	1.00	1.25E-05	1.25E-05
PST	9:114321523:A:C	Liver	ENSG00000228278	*ORM2*	0.02	0.96	0.98
	9:114321523:A:C	Whole Blood	ENSG00000229314	*ORM1*	1.00	1.31E-10	1.31E-10
	9:114321523:A:C	Whole Blood	ENSG00000228278	*ORM2*	1.00	5.90E-06	5.90E-06

AT: antithrombin, PSF: protein S free, PST: protein S total, Chr: chromosome, Pos: position, A1: effect allele, A2: other allele, PP.H3: posterior probability under hypothesis 3, PP.H4: posterior probability under hypothesis 4, CPC: conditional probability of colocalization.

Supplementary Table S14. Selected genetic instruments for Mendelian randomization analyses

Outcome	RSID	Chr:Pos:A1:A2	Beta, Exposure	SE, Exposure	P-value, Exposure	EAF, Exposure	Beta, Outcome	SE, Outcome	P-value, Outcome	EAF, Outcome
Antithrombin										
VTE	rs142967416	1:175159627:T:C	-7.23	0.86	3.84E-17	0.007	0.26	0.09	0.004	0.004
VTE	rs5471	16:72054562:A:C	9.82	0.92	1.72E-26	0.874	-0.08	0.05	0.082	0.897
VTE	rs4665972	2:27375230:T:C	0.98	0.12	6.63E-16	0.443	-0.01	0.01	0.414	0.403
VTE	rs13244268	7:73497513:T:C	1.13	0.19	3.92E-09	0.891	-0.02	0.01	0.242	0.883
PAD	rs142967416	1:175159627:T:C	-7.23	0.86	3.84E-17	0.007	0.21	0.11	0.050	0.004
PAD	rs5471	16:72054562:A:C	9.82	0.92	1.72E-26	0.874	-0.06	0.04	0.128	0.902
PAD	rs4665972	2:27375230:T:C	0.98	0.12	6.63E-16	0.443	0.01	0.01	0.372	0.418
PAD	rs13244268	7:73497513:T:C	1.13	0.19	3.92E-09	0.891	-0.01	0.02	0.554	0.889
CAD	rs2227590	1:173916899:A:G	1.28	0.18	2.65E-13	0.149	0.01	0.01	0.498	0.145
CAD	rs4665972	2:27375230:T:C	0.98	0.12	6.63E-16	0.443	-0.01	0.01	0.481	0.401
CAD	rs13244268	7:73497513:T:C	1.13	0.19	3.92E-09	0.891	-0.01	0.02	0.737	0.885
IS	rs2227590	1:173916899:A:G	1.28	0.18	2.65E-13	0.149	-0.03	0.01	0.027	0.188
IS	rs4665972	2:27375230:T:C	0.98	0.12	6.63E-16	0.443	0.01	0.01	0.312	0.419
IS	rs13244268	7:73497513:T:C	1.13	0.19	3.92E-09	0.891	0.02	0.01	0.259	0.888
Protein C										
VTE	rs1799809	2:127418299:A:G	0.21	0.01	9.13E-90	0.540	-0.05	0.01	1.86E-06	0.558
VTE	rs4665972	2:27375230:T:C	0.11	0.01	7.09E-24	0.406	-0.01	0.01	0.414	0.403
VTE	rs35493868	7:73625076:C:G	0.08	0.01	5.87E-10	0.810	-0.01	0.01	0.223	0.807
PAD	rs1799809	2:127418299:A:G	0.21	0.01	9.13E-90	0.540	-0.02	0.01	0.010	0.539
PAD	rs4665972	2:27375230:T:C	0.11	0.01	7.09E-24	0.406	0.01	0.01	0.372	0.418
PAD	rs35493868	7:73625076:C:G	0.08	0.01	5.87E-10	0.810	-0.01	0.01	0.594	0.818
CAD	rs1799809	2:127418299:A:G	0.21	0.01	9.13E-90	0.540	-0.02	0.01	0.020	0.562
CAD	rs4665972	2:27375230:T:C	0.11	0.01	7.09E-24	0.406	-0.01	0.01	0.481	0.401
CAD	rs35493868	7:73625076:C:G	0.08	0.01	5.87E-10	0.810	0.01	0.01	0.512	0.823
IS	rs1799809	2:127418299:A:G	0.21	0.01	9.13E-90	0.540	0.003	0.01	0.731	0.583
IS	rs4665972	2:27375230:T:C	0.11	0.01	7.09E-24	0.406	0.01	0.01	0.312	0.419
IS	rs35493868	7:73625076:C:G	0.08	0.01	5.87E-10	0.810	0.01	0.01	0.328	0.822
Antithrombin – Replication in DeCODE										
VTE	rs148062101	1:173930941:C:T	-0.40	0.04	1.04E-20	0.008	0.11	0.06	0.059	0.008
PAD	rs2227624	1:173914872:T:A	-0.48	0.05	3.10E-21	0.005	0.15	0.07	0.084	0.003

CAD	rs545961389	1:173769941:C:A	-0.34	0.04	2.09E-18	0.010	-0.06	0.08	0.401	0.011
Protein C – Replication in DeCODE										
VTE	rs660240	1: 109275216:C:T	0.08	0.01	5.72E-18	0.205	-0.04	0.01	1.09E-04	0.768
VTE	rs139739100	2: 125073845 :T:C	-1.16	0.15	2.75E-15	0.002	0.16	0.18	3.92E-01	0.791
VTE	rs61185143	2:127407902:C:T	0.14	0.01	1.72E-70	0.001	-0.06	0.01	4.09E-14	0.009
VTE	rs4665972	2:27375230:C:T	-0.06	0.01	6.93E-14	0.339	0.01	0.01	4.14E-01	0.597
VTE	rs187426250	20:25575830:T:C	0.37	0.05	1.50E-11	0.005	0.14	0.17	4.10E-01	0.003
VTE	rs6093254	20:39847583:C:G	-0.05	0.01	9.24E-11	0.396	-0.01	0.01	9.43E-02	0.389
PAD	rs660240	1: 109275216:C:T	0.08	0.01	5.72E-18	0.205	0.06	0.01	4.72E-08	0.756
PAD	rs139739100	2: 125073845 :T:C	-1.16	0.15	2.75E-15	0.001	0.04	0.14	7.66E-01	0.008
PAD	rs61185143	2:127407902:C:T	0.14	0.01	1.72E-70	0.428	-0.03	0.01	3.20E-03	0.535
PAD	rs4665972	2:27375230:C:T	-0.06	0.01	6.93E-14	0.339	-0.01	0.01	3.72E-01	0.582
PAD	rs187426250	20:25575830:T:C	0.37	0.05	1.94E-12	0.005	0.15	0.11	1.88E-01	0.002
PAD	rs6093254	20:39847583:C:G	-0.05	0.01	9.24E-11	0.396	-0.01	0.01	8.83E-01	0.384
CAD	rs660240	1: 109275216:C:T	0.08	0.01	5.72E-18	0.205	0.10	0.01	8.66E-19	0.783
CAD	rs61185143	2:127407902:C:T	0.14	0.01	1.72E-70	0.428	-0.02	0.01	4.84E-02	0.573
CAD	rs4665972	2:27375230:C:T	-0.06	0.01	6.93E-14	0.339	0.01	0.01	4.81E-01	0.581
CAD	rs6093254	20:39847583:C:G	-0.05	0.01	9.24E-11	0.397	-0.02	0.01	1.47E-02	0.386
IS	rs660240	1: 109275216:C:T	0.08	0.01	5.72E-18	0.205	0.01	0.01	0.224	0.783
IS	rs61185143	2:127407902:C:T	0.14	0.01	1.72E-70	0.428	-0.01	0.01	0.942	0.573
IS	rs4665972	2:27375230:C:T	-0.06	0.01	6.93E-14	0.339	-0.01	0.01	0.312	0.581
SI	rs6093254	20:39847583:C:G	-0.05	0.01	9.24E-11	0.397	-0.01	0.01	0.841	0.386

VTE: venous thrombosis; PAD: Peripheral Artery disease; CAD: Coronary artery disease; IS: Ischemic Stroke, Chr: chromosome, Pos: position, A1: effect allele, A2: other allele, SE: standard error, EAF: effect allele frequency.

Supplementary Table S15. MR analysis results and replication in DeCODE

Method	Number of variants	OR (95% CI)	P-value
Antithrombin to VTE			
Inverse variance weighted	4	0.84 (0.72-0.97)	0.015
Weighted median	4	0.87 (0.76-1.00)	0.056
MR Egger	4	0.82 (0.65-1.04)	0.251
Weighted mode	4	0.88 (0.76-1.01)	0.171
Antithrombin to PAD			
Inverse variance weighted	4	0.91 (0.81-1.02)	0.111
Weighted median	4	0.91 (0.80-1.02)	0.101
MR Egger	4	0.87 (0.76-0.99)	0.175
Weighted mode	4	0.90 (0.80-1.02)	0.175
Antithrombin to CAD			
Inverse variance weighted	3	0.98 (0.81-1.19)	0.861
Weighted median	3	0.94 (0.75-1.18)	0.576
MR Egger	3	2.23 (0.41-12.02)	0.523
Weighted mode	3	0.91 (0.67-1.23)	0.594
Antithrombin to IS			
Inverse variance weighted	3	0.98 (0.70-1.36)	0.883
Weighted median	3	1.05 (0.83-1.34)	0.674
MR Egger	3	0.18 (0.02-1.76)	0.378
Weighted mode	3	1.19 (0.82-1.74)	0.462
Antithrombin to VTE – Replication in DeCODE			
Wald Ratio	1	0.75 (0.56-1.01)	0.059
Antithrombin to PAD – Replication in DeCODE			
Wald Ratio	1	0.73 (0.51-1.04)	0.084
Antithrombin to CAD – Replication in DeCODE			

Wald Ratio	1	1.21 (0.77-1.90)	0.401
Antithrombin to IS – Replication in DeCODE			
Not enough Instrument	NA	NA	NA
Protein C to VTE			
Inverse variance weighted	3	0.83 (0.76-0.92)	0.001
Weighted median	3	0.82 (0.75-0.90)	9.60E-06
MR Egger	3	0.73 (0.58-0.91)	0.224
Weighted mode	3	0.80 (0.73-0.88)	0.040
Protein C to PAD			
Inverse variance weighted	3	0.92 (0.84-1.02)	1
Weighted median	3	0.90 (0.83-0.98)	0.015
MR Egger	3	0.81 (0.61-1.09)	0.402
Weighted mode	3	0.89 (0.82-0.98)	0.132
Protein C to CAD			
Inverse variance weighted	3	0.92 (0.84-0.99)	0.031
Weighted median	3	0.91 (0.84-0.98)	0.017
MR Egger	3	0.81 (0.64-1.01)	0.312
Weighted mode	3	0.90 (0.82-0.99)	0.149
Protein C to IS			
Inverse variance weighted	3	1.04 (0.96-1.12)	0.320
Weighted median	3	1.04 (0.96-1.12)	0.392
MR Egger	3	0.94 (0.76-1.15)	0.642
Weighted mode	3	1.02 (0.93-1.12)	0.701
Protein C to VTE – Replication in DeCODE			
Inverse variance weighted	6	0.73 (0.61-0.88)	0.001
Weighted median	6	0.69 (0.62-0.77)	3.06E-11
MR Egger	6	0.59 (0.4-0.87)	0.056
Weighted mode	6	0.67 (0.6-0.75)	0.001

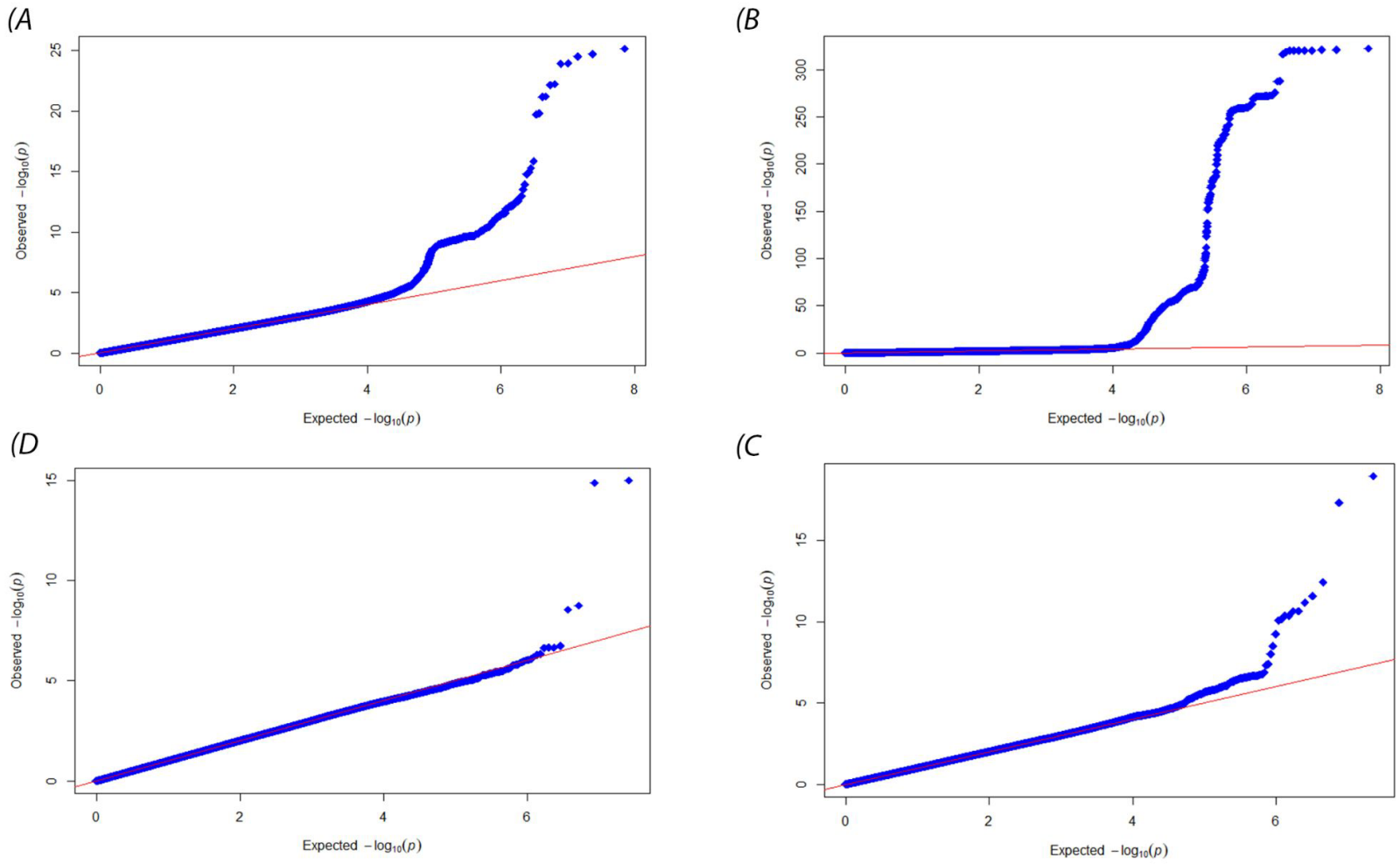
Protein C to PAD – Replication in DeCODE			
Inverse variance weighted	6	1.01 (0.78-1.32)	0.915
Weighted median	6	0.91 (0.8-1.04)	0.160
MR Egger	6	0.84 (0.49-1.43)	0.556
Weighted mode	6	0.88 (0.78-0.99)	0.088
Protein C to CAD – Replication in DeCODE			
Inverse variance weighted	4	1.15 (0.65-2.02)	0.631
Weighted median	4	0.88 (0.77-1.01)	0.063
MR Egger	4	0.69 (0.14-3.44)	0.697
Weighted mode	4	0.88 (0.77-1.00)	0.145
Protein C to IS – Replication in DeCODE			
Inverse variance weighted	4	1.04 (0.94-1.16)	0.395
Weighted median	4	1.02 (0.91-1.13)	0.791
MR Egger	4	0.94 (0.73-1.22)	0.693
Weighted mode	4	1.00 (0.89-1.13)	0.982

SE: standard error. Significance was based on inverse variance weighted method, with p-value < 0.05.

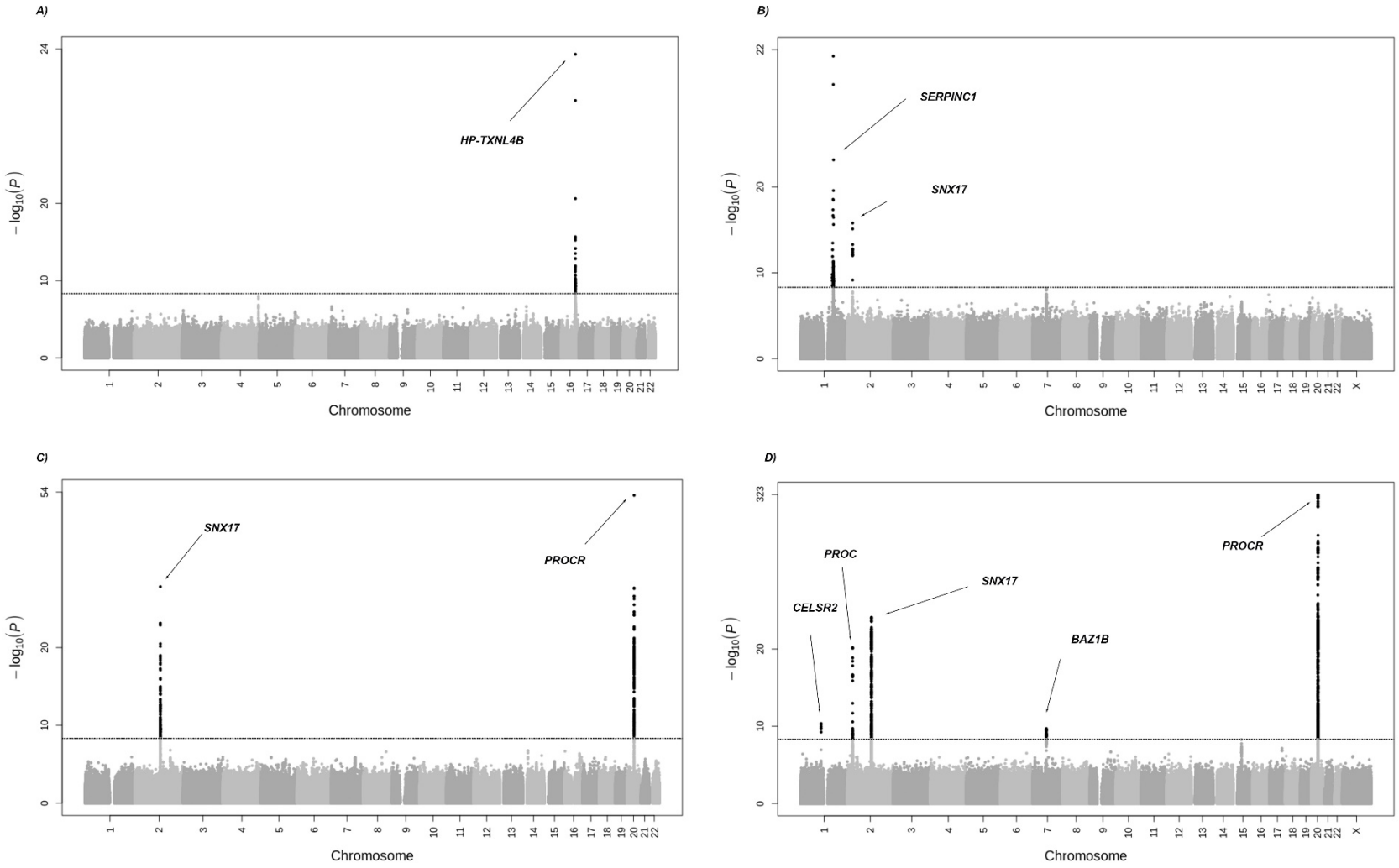
Supplementary Table S16. Associations found between cardiovascular disease phenotypes and identified loci in the analysis.

Disease Phenotype	Locus/Gene(s)	Variant (rsID)	Analysis*
VTE	*SERPINC1*[107]	rs2227624	AT GWAS
	PROC [108]	rs1799809	PC GWAS
	PROS1[109]	rs528128538	PS GWAS
	MAP1A [110]	rs55707100	Multi-phenotype
CAD	*GCKR* [111]	rs1260326, rs780094, rs780093	AT GWAS
	CELSR2-PSRC1 [112,113]	rs12740374, rs599839, rs646776	PC GWAS
	MLXIPL[114]	rs3812316	AT GWAS, PC GWAS
PAD	*CELSR2-PSRC1* [115]	rs12740374, rs599839, rs646776	PC GWAS

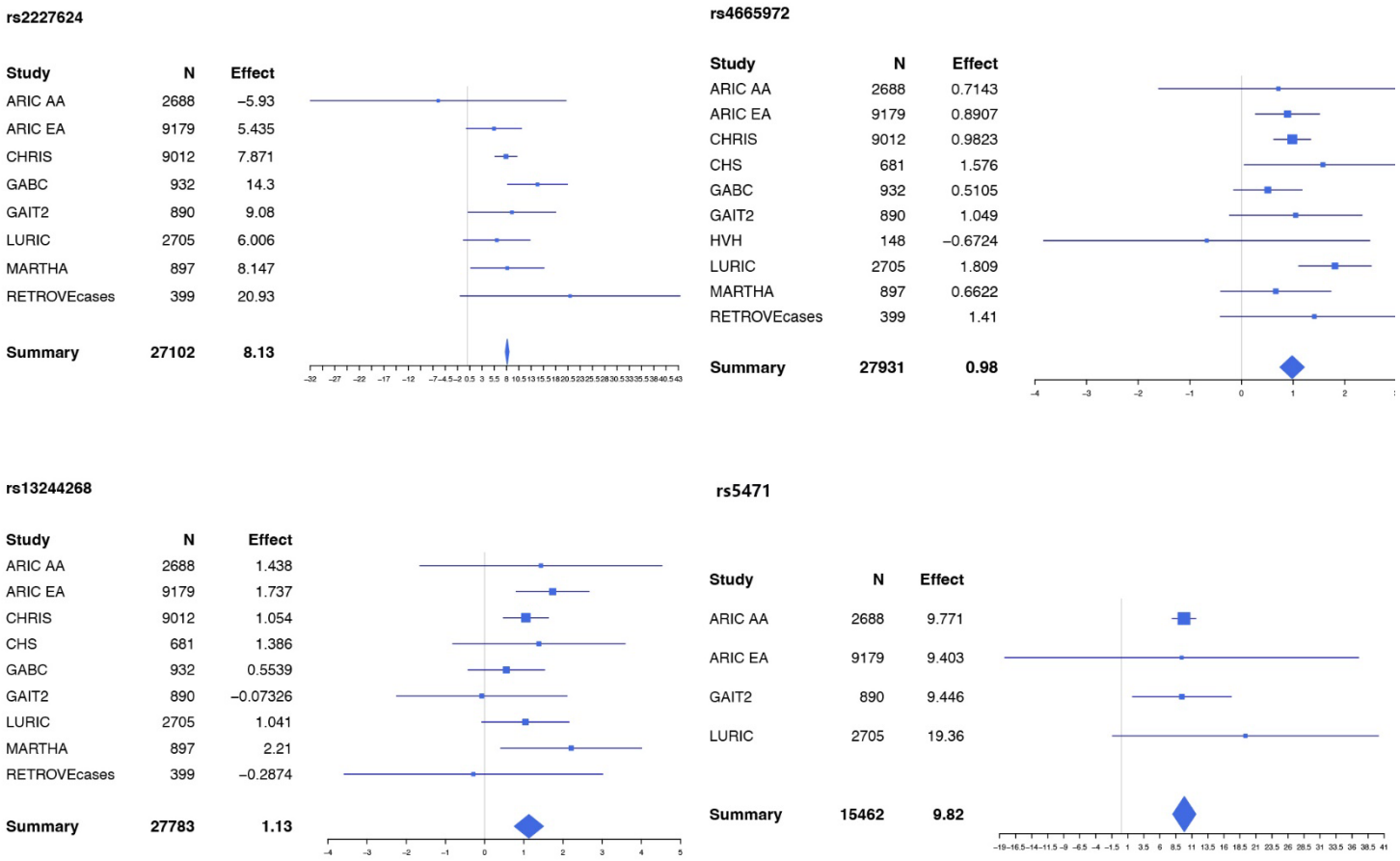
VTE: Venous thromboembolism; IS: Ischemic stroke; CAD: Coronary artery disease; PAD: Peripheral artery disease; AT: Antithrombin; PC: Protein C; PS: Protein S.
*Corresponding analysis where the loci or genes were found significantly associated with antithrombin, PC or PS in our study.



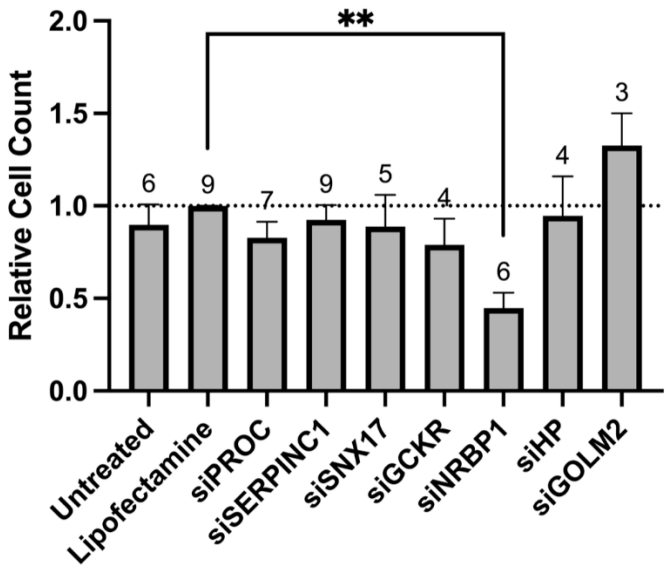
Supplementary Figure S1. Q-Q Plots of meta-analyses (A: antithrombin cross-ethnic, B: protein C cross ethnic, C: protein S free, D: protein S total).



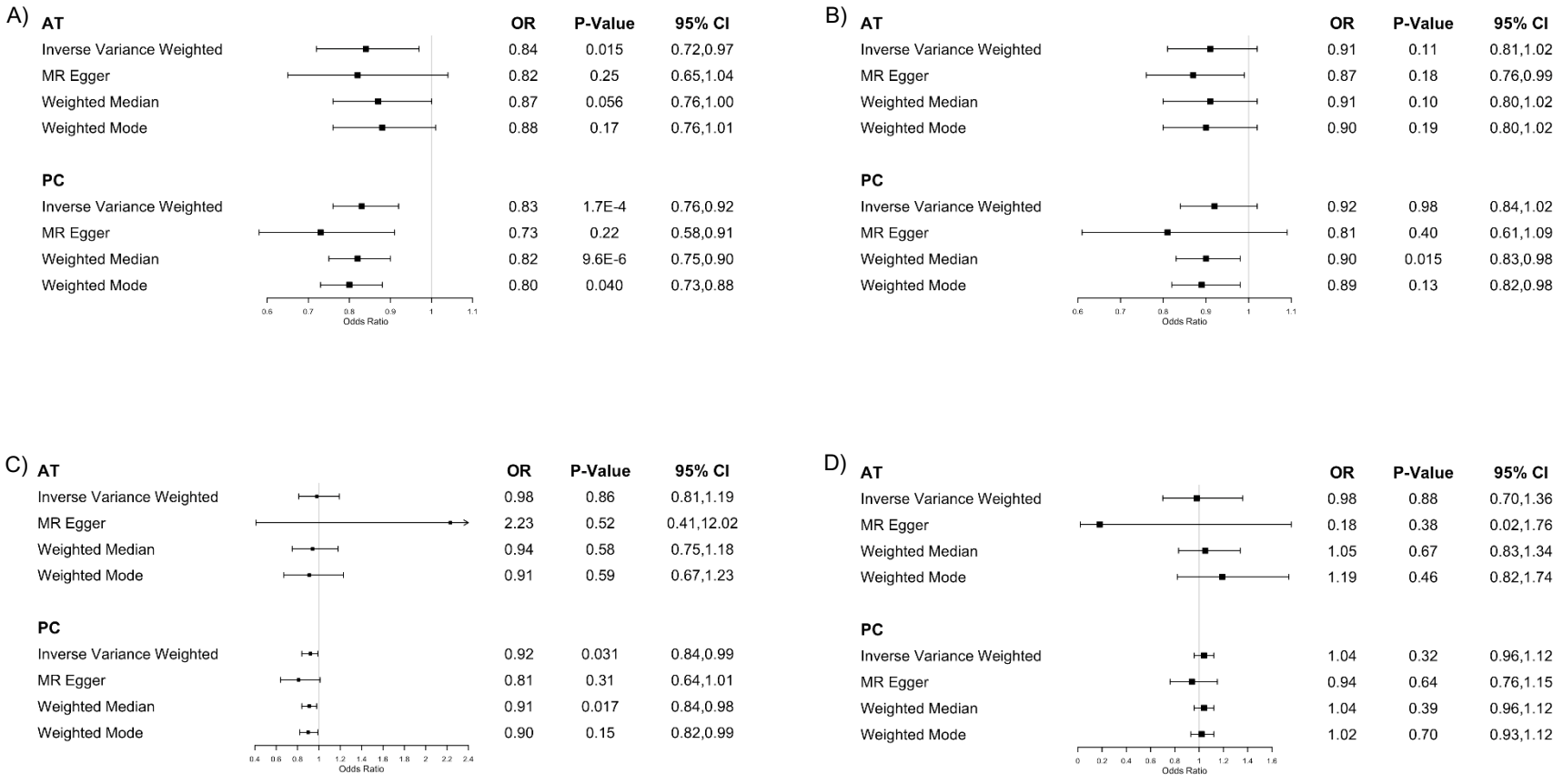
Supplementary Figure S2. Manhattan plots of population specific meta-analysis of antithrombin and protein C (A: antithrombin European, B: antithrombin African, C: protein C European, D: protein C African)



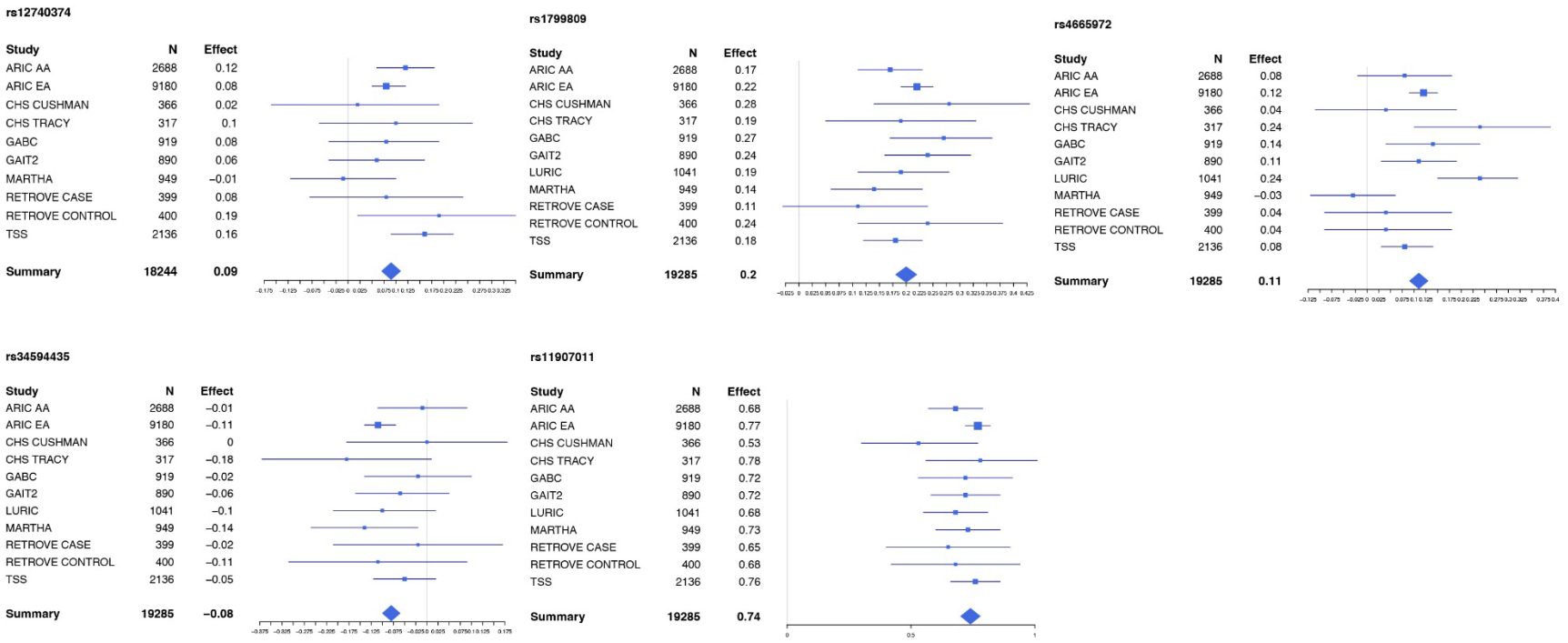
Supplementary Figure S3. Forest plots of lead variants in antithrombin cross-population meta-analysis



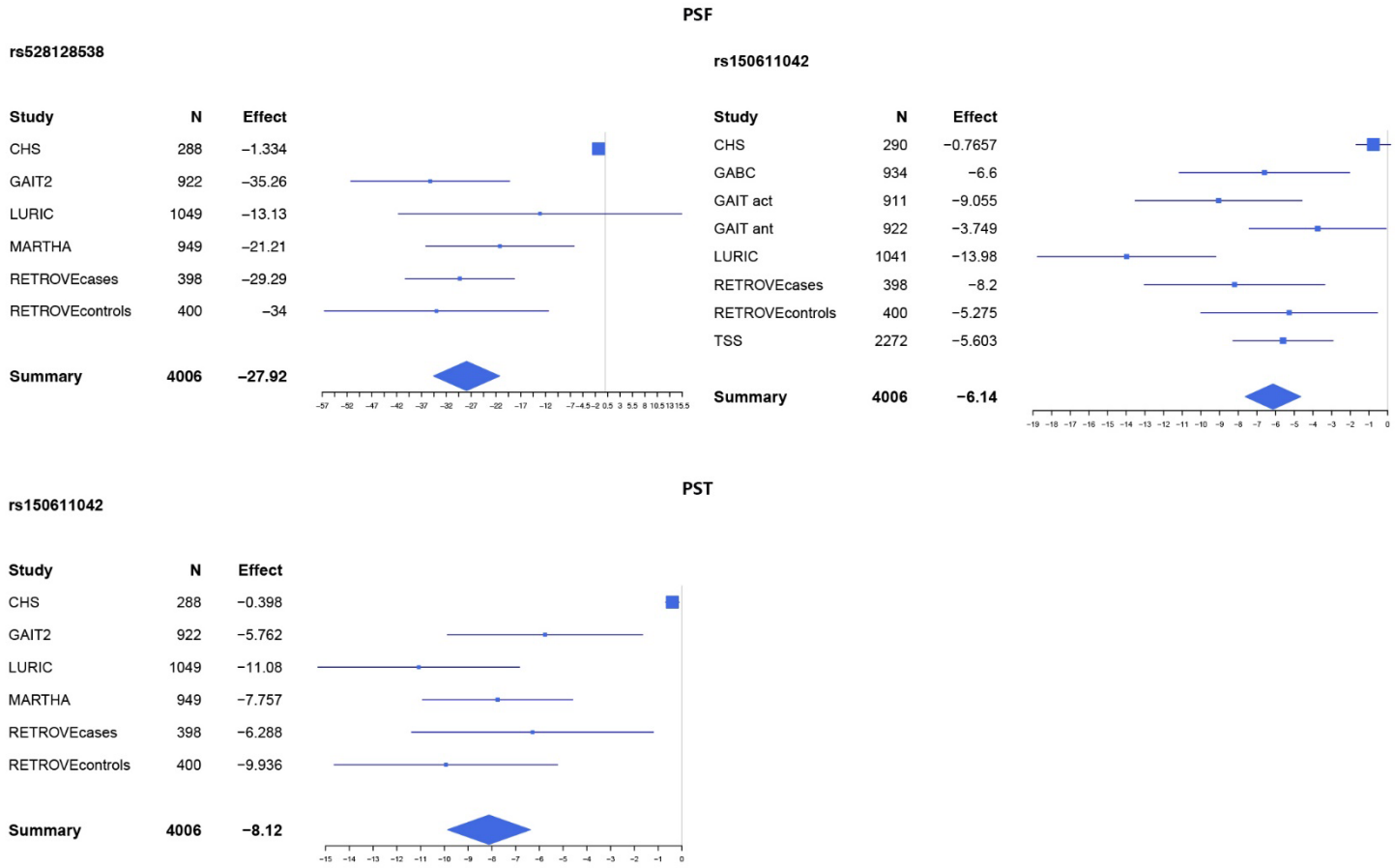
Supplementary Figure S4. Cell count of tested genes in the functional study. Knockdown of NRBP1 reduces the HepG2 cell count. Cells were counted on the Countess II FL cells counter using cell counting chamber slides. Counts for each siRNA-treated cell were normalized against lipofectamine-treated cells (control) within the same experiment and compared by one-way ANOVA and Šidák's multiple comparisons test. Bars and error bars indicate mean and standard error of the mean; Numbers indicate biological replicates; **p-value < 0.01.



Supplementary Figure S5. Forest plots of MR analysis results on selected outcomes (A: Venous thrombosis; B: Peripheral Artery disease; C: Coronary artery disease; D: Ischemic Stroke)



Supplementary Figure S6. Forest plots of significant loci in protein C cross-ancestry meta-analysis



Supplementary Figure S7. Forest plots of significant loci in Protein S free and total meta-analyses (Up: Protein S Free, down: Protein S total)

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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
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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
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228 Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK
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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

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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

Major Resources Table

In order to allow validation and replication of experiments, all essential research materials listed in the Methods should be included in the Major Resources Table below. Authors are encouraged to use public repositories for protocols, data, code, and other materials and provide persistent identifiers and/or links to repositories when available. Authors may add or delete rows as needed.

Antibodies

Target antigen	Vendor or Source	Catalog #	Working concentration	Lot # (preferred but not required)	Persistent ID / URL
Human Antithrombin III	Haemtech	PAHAT-S	2uL per 1000uL	LL0401-5MG	https://www.goprolytix.com/product/sheep-anti-human-antithrombin-iii/

Primers

Gene Name	Forward Sequence	Reverse Sequence	Company
PROC	CTTGTCAGGCTTGGAGAGTATG	GTGGTGCTCTTGCTGTAGTT	IDT
SERPINC1	GATGAGGGCTCAGAACAGAAG	TGCCAGGTGCTGATAGAAAG	IDT
SNX17	TGAGGTAGAACAGAGGAGAGAG	GACGCAGGAAACTGTTGAAAG	IDT
GCKR	GTGGAGCAGGTGAAAGAGAA	TGCTGATGATGGAGGGAAAG	IDT
NRBP1	CACAAATCCTCTCTGCCCTAAG	GTCCGTTGTGCTGGATGAA	IDT
HP	CTGTGCTGGCATGTCTAAGT	CTTAAGATCCCAGTCGCATACC	IDT
GOLM2	TTTCACGCTCAAGGAGTCATAC	GGAGTAGGGAGGTGACTTTCTA	IDT
RNA18s (Reference Gene)	Proprietary	Proprietary	Qiagen - GeneGlobe ID: QT00199367 URL: https://geneglobe.qiagen.com/us/product-groups/quantitect-primer-assays?q=QT00199367

siRNAs

Gene Name	siRNA ID	Lot Number	Catalog Number	Company
PROC	S11215	ASO2HDZI	4392420	Thermofisher
SERPINC1	S1691	ASO2HDZG	4392420	Thermofisher
SNX17	S18903	ASO2HHAP	4392420	Thermofisher
GCKR	S5651	ASO2HDZK	4392420	Thermofisher
NRBP1	S26798	ASO2HDZJ	4392420	Thermofisher
HP	S6871	ASO2HDZL	4392420	Thermofisher
GOLM2	S41443	ASO2KC33	4392420	Thermofisher

Cultured Cells

Name	Vendor or Source	Sex (F, M, or unknown)	Persistent ID / URL
Hep G2	UNC Lineberger Cancer Center Tissue Culture Facility	M	https://www.atcc.org/products/hb-8065 (ATCC Batch#: F-12883)

Data & Code Availability

Description	Source / Repository	Persistent ID / URL
Anticoagulant proteins summary statistics	dbGaP	
DeCODE genetics summary data	Webpage	https://www.decode.com/summarydata/
VTE summary statistic for MR (INVENT)	dbGaP	Upon request
VTE summary statistic for MR (MVP)	dbGaP	Upon request (Accession code: phs001672.v2.p1)
PAD summary statistics for MR (MVP)	dbGP	Upon request (Accession code: phs001672.v2.p1)

CAD summary statistics for MR (Cardiogramplusc4d)	Webpage	http://www.cardiogramplusc4d.org/data-downloads/
IS summary statistics for MR (MEGASTROKE)	Webpage	https://www.megastroke.org/download.html

Other

Description	Source / Repository	Persistent ID / URL
EasyQC software used for quality control	Webpage	https://www.uni-regensburg.de/medizin/epidemiologie-praeventivmedizin/genetische-epidemiologie/software/
METAL software used for meta-analysis	GitHub	https://github.com/statgen/METAL
COJO implemented in GCTA for conditional analysis	GitHub	https://github.com/jianyangqt/gcta
PrediXcan for TWAS	GitHub	https://github.com/hakyimlab/PrediXcan
MultiXcan for TWAS	GitHub	https://github.com/hakyimlab/MetaXcan
metaUSAT R package for multi-phenotype	GitHub	https://github.com/RayDebashree/metaUSAT
HaploR R package for functional annotations	GitHub	https://github.com/izhbannikov/haploR
FOCUS for fine-mapping	GitHub	https://github.com/bogdanlab/focus
COLOC for colocalization	GitHub	https://chr1swallace.github.io/coloc/articles/a01_intro.html
HyPrColoc for colocalization	GitHub	https://github.com/jrs95/hyprcoloc
TwoSampleMR R package for MR	GitHub	https://mrcieu.github.io/TwoSampleMR/
MRPRESSO R package for MR	GitHub	https://github.com/rondolab/MR-PRESSO