Supplementary Methods

Quality control

Quality control assessment of ancestry-specific results files from each study was conducted prior to meta-analysis using the EasyQC software package.[1] All quality control steps were performed in replicate by two analysts to check for consistency. Alleles were harmonized according to the 1000G phase 1 version 3 reference panel and duplicated variants or variants that had inconsistencies with the reference were excluded. Variants with betas or standard errors > 5 or imputation quality < 0.3 were excluded from the analysis. The effective minor allele count was calculated for all variants as the product of the minor allele count and the imputation quality, and variants with values < 10 were excluded from each analysis. We used the meta-analysis software METAL to apply genomic control corrections to each of the study-specific analyses in order to correct for inflation due to cryptic relatedness and population substructure.[2] Variants present in fewer than three studies were excluded from the meta-analysis.

Conditional analysis

Genotypes from 8,481 European-ancestry individuals from the Framingham Heart Study were used as the reference panel. Variants with low imputation quality ($r^2 < 0.3$) or low frequency (MAF < 0.1%) were excluded from the reference panel. A collinear parameter of 0.1 was applied, meaning that during the stepwise model selection procedure, variants correlated with any of the already selected variants at $r^2 > 0.1$ were not considered for inclusion into the model.

Proportion of variance explained

The proportion of variance in FVII activity explained by each lead variant was calculated using the formula $r^2 = beta^2/var(y) * 2*f*(1-f)$, where f is the frequency and y is log-transformed FVII activity. The beta and frequency values were taken from summary statistics and the total variance in FVII activity was calculated as the sample-size weighted mean variance across cohorts. The variance explained was first

calculated for each lead variant separately, and then summed to obtain the variance explained by all loci. For loci predicted to harbor multiple independent variants, we used the joint beta to estimate the variance explained.

Functional validation

Human liver HuH7 cells, obtained from the Health Science Research Resources Bank (cell number JCRB0403; Osaka Japan), were cultured in DMEM Glutamax 4500 glucose medium supplemented with 10% Fetal Bovine Serum (ThermoFisher Scientific) and then plated in 6 well plates. Cells were silenced at 80% confluence using Lipofectamine RNAimax (ThermoFisher Scientific) with either s37271 or s47939 to target *REEP3,* or with s225897 or s48121 to target *JAZF1*. Details on these silencers can be found in the *Silencer* Select siRNA database from ThermoFisher Scientific (https://www.thermofisher.com/order/genome-database/details/sirna/). Glucose-free medium was added 5 h after the silencer transfection, as glucose deprivation may increase the production of FVII.[3] Cells were collected 72 h after transfection and total RNA was extracted using a commercial kit (Omega-biotek). Results were compared to cells treated with a scramble siRNA (Ambion negative control #1). Relative gene expression of *REEP3*, *JAZF1*, and *F7* compared to a housekeeping gene was measured using qRT-PCR (Step One Plus Real Time PCR System, Applied Biosystems) in both groups (control and silenced cells) with TaqMan probes (ThermoFisher Scientific) and calculated using the 2-ΔΔCt method.[4] In experiments on *REEP3* the *RPLPO* housekeeping gene was used, whereas in experiments on *JAZF1* the *GAPDH* housekeeping gene was used.

To measure the amount of FVII protein released in the media, media were collected 72 h after transfection and FVII was measured using Mesoscale with the Human Factor VII MSD commercial kit (MESO SCALE DIAGNOSTICS, LLC). We repeated the experiment three times and pooled results were expressed as the significant difference between every silencer and the scramble control in a model that included the effect of experiment (FVII level ~ silencer + experiment). Analyses were performed in R.

As a positive control, we also silenced the *F7* gene itself and measured the effect on *F7* mRNA levels. We performed 2 experiments with 6 replicates each.

Mendelian randomization

Mendelian randomization based on summary statistics was performed in two steps. First, causal effect estimates are obtained separately for each of the lead genetic variant at significant loci as the ratio of the variant's association with disease to the variant's association with FVII activity, or $\beta_{\text{Variant-Disease}}/\beta_{\text{Variant-FVII}}$. The second step is to combine the causal effect estimates produced by each of the genetic variants. This is achieved using meta-analytic techniques, since each variant provides independent information on the causal effect.[5,6] We used three meta-analytic techniques: 1) inverse-variance weighted meta-analysis (primary analysis), 2) MR-Egger,[7] and 3) weighted median estimator.[8] The 95% confidence intervals for causal estimates were calculated based on the estimates (beta/log-transformed OR) and standard error (SE): estimate ± 1.96*SE. Additionally, we visually examined the causal effect estimates produced by each of the individual variants using scatter plots, funnel plots, and forest plots, and performed heterogeneity Q tests.[9,10] When there was significant heterogeneity (*P*-value <0.05) among the single variant causal effect estimates, we used scatter plots and funnel plots to identify the genetic variant with the largest outlying effect estimate. This outlier was when then removed and all analyses were repeated. In addition to the results of these three meta-analytic techniques, we also considered the causal effect estimate obtained from the lead variant at the *F7* locus, given that the lead variant at the *F7* locus is located in the gene that encodes the FVII protein, so it may be less likely to influence clinical outcomes through pathways that do not involve FVII.

There was a degree of sample overlap between our GWAS of FVII and the GWAS of IS, CAD. and VTE, which may bias the effect estimates away from the null.[11] Sample overlap between our genome-wide association study (GWAS) of FVII and the GWAS of ischemic stroke (IS), coronary artery disease (CAD), and venous thromboembolism (VTE) was evaluated on a study-by-study basis due to a lack of

access to the individual-level data used in each of these GWAS. Four studies overlapped between the MEGASTROKE GWAS of IS and our GWAS of FVII (ARIC, CHS, FHS, and RS),[12] five studies overlapped with the CARDIoGRAMplusC4D GWAS of CAD (ARIC, FHS, LURIC, PROCARDIS, and RS),[13] and three studies overlapped with the INVENT GWAS of VTE (ARIC, CHS, and MEGA).[14] While overlapping samples thus constitute a modest to large proportion of the samples in our GWAS of FVII, they only constitute a small proportion of the samples in the GWAS of these cardiovascular outcomes.

Study descriptions

The **Atherosclerosis Risk in Communities (ARIC)** study has been described in detail previously.[15] Men and women aged 45-64 years at baseline were recruited from four communities: Forsyth County, North Carolina; Jackson, Mississippi; Minneapolis, Minnesota; and Washington County, Maryland. A total of 15,792 individuals, predominantly White and African American, participated in the baseline examination in 1987-1989, with three additional triennial follow-up examinations and a fifth exam in 2011-2013, and a sixth exam in 2016-2017. Activities of FVII was measured using clotting assays (% activity) in plasma samples obtained at the baseline examination.[16,17]

The **Cardiovascular Health Study (CHS)** is a population-based cohort study of risk factors for coronary heart disease and stroke in adults ≥65 years conducted across four field centers [PMID: 1669507]. The original predominantly European ancestry 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 in 1992-1993 for a total sample of 5,888.

Blood samples were drawn from all participants at their baseline examination and DNA was subsequently extracted from available samples. Genotyping was performed at the General Clinical Research Center's Phenotyping/Genotyping Laboratory at Cedars-Sinai among CHS participants who consented to genetic testing and had DNA available using the Illumina 370CNV BeadChip system (for

European ancestry participants, in 2007) or the Illumina HumanOmni1-Quad_v1 BeadChip system (for African-American participants, in 2010).[18]

Coagulation Factor VII levels were measured on the Coag-A-Mate X2 (Organon-Teknika, Durham, NC). Factor VII activity was determined using factor VII-deficient plasma (Baxter-Dade) and Thromborel S (Behring Diagnostics, Marburg, Bermany) human placenta-derived thromboplastin. The standard was an unassayed pooled normal plasma (George King Biomedical, Overland Park, KS) that was calibrated with the World Health Organization reference plasma.

CHS was approved by institutional review committees at each field center and individuals in the present analysis had available DNA and gave informed consent including consent to use of genetic information for the study of cardiovascular disease.

The **Coronary Artery Risk Development in Young Adults (CARDIA)** study is a prospective multicenter study with 5115 Caucasian and African American participants ages 18-30 years at baseline, recruited from four centers. The recruitment was done from the total community in Birmingham, AL, from selected census tracts in Chicago, IL and Minneapolis, MN; and from the Kaiser Permanente health plan membership in Oakland, CA. The details of the study design for the CARDIA study have been published before.[19] Eight examinations have been completed since the baseline examination in 1985–1986, with follow-up examinations 2, 5, 7, 10, 15, 20, and 25 years after baseline. FVII coagulant activity was assayed at year 5 by a one-stage system with reagents from Pacific Hemostasis and George King Biomedical, Inc. The standard curve was prepared with a universal reference plasma from Curtin Matheson Scientific, and the results calculated as a percentage of the standard with a MLA-Electra 800.

The **Framingham Heart Study (FHS)** was started in 1948 with 5,209 randomly ascertained participants from Framingham, Massachusetts, US, who had undergone biannual examinations to investigate cardiovascular disease and its risk factors. In 1971, the Offspring cohort (comprising 5,124 children of the original cohort and the children's spouses) and in 2002, the Third Generation

(consisting of 4,095 children of the Offspring cohort) were recruited. FHS participants in this study are of European ancestry. The methods of recruitment and data collection for the Offspring and Third Generation cohorts have been described.[20]

Factor VII antigen levels were determined by ELISA (Diagnostica Stago) in the Offspring cohort at exam 5 (1991-1995).[21] Values were expressed as percentage of the standard. The intra-assay CV was 3.0%.

The **Genetic Analysis of Idiopathic Thrombophilia 2 (GAIT2)** project is a family based study where 935 subjects in 35 extended pedigrees were collected. 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, dysfibrogenemia, 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. By the use of the short form of the International Physical Activity Questionnaire (IPAQ, available at www.ipaq.ki.se), physical activity was also determined. Specifically, they were also questioned about previous episodes of venous and arterial thrombosis, the age at which these events occurred, and the presence of potentially correlated disorders such as diabetes, lipid disease, asthma, allergic rhinitis, atopic dermatitis, and autoimmune disease. The residence of each subject was determined to assess the contribution of shared environmental influences (such as diet) common to members of a household. 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.

The **Ludwigshafen Risk and Cardiovascular Health (LURIC)** study is a monocentric hospital based prospective study including 3,316 individuals referred for coronary angiography recruited in the Ludwigshafen Cardiac Center, southwestern Germany from 1997 – 2000 . Clinical indications for angiography were chest pain or a positive non-invasive stress test suggestive of myocardial ischemia. To limit clinical heterogeneity, individuals suffering from acute illnesses other than acute coronary syndrome, chronic non-cardiac diseases and a history of malignancy within the five past years were excluded. All participants were of European ancestry and completed a detailed questionnaire which gathered information on medical history, clinical, and lifestyle factors. Study protocols were approved by the ethics committee of the "Landesärztekammer Rheinland-Pfalz" and the study was conducted in accordance with the "Declaration of Helsinki". Informed written consent was obtained from all participants.

Coronary heart disease at baseline was defined as the presence of a visible luminal narrowing (>50% stenosis) in at least one of 15 coronary segments according to the classification of the American Heart Association. Fasting blood samples were obtained by venipuncture in the early morning and stored for later analyses. For this study a subset of 3,061 samples were used that had been genotyped on an Affymetrix 6.0 array.

The **Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis (MEGA)** study is a large population-based case-control study.[22] Data collection and ascertainment of venous thrombotic events have been previously described in detail. In short, patients with a first deep vein thrombosis or pulmonary embolism were recruited at six anticoagulation clinics in the Netherlands between 1999 and 2004. The diagnosis of a deep vein thrombosis was based on compression ultrasonography, whereas a pulmonary embolism was confirmed by perfusion and ventilation scintigraphy, helical computed tomography or pulmonary angiography. Blood samples were taken at least

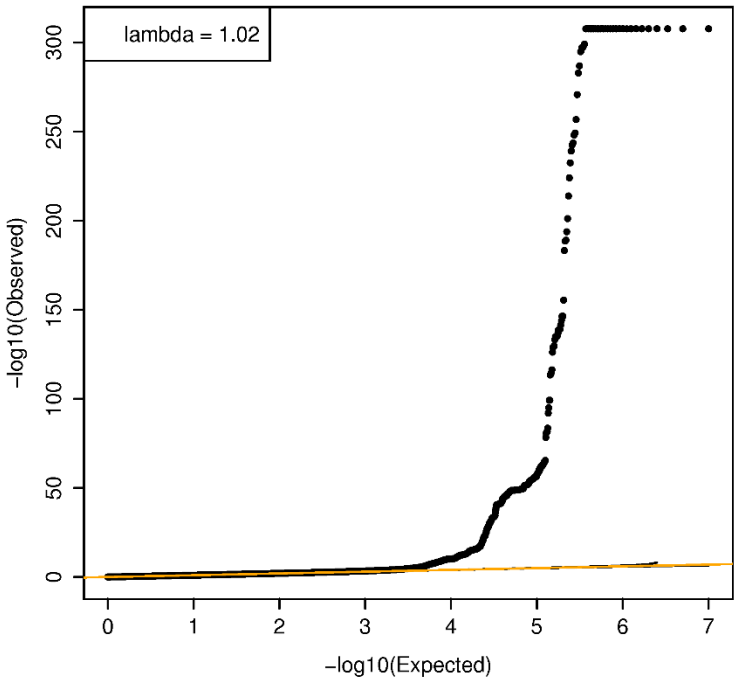
3 months after discontinuation of vitamin K antagonist treatment, unless patients were still receiving anticoagulant therapy one year after their venous thrombosis event. For the present analyses, patients who were still receiving anticoagulant treatment at the time of blood collection were excluded. Factor VII was measured with a mechanical clot detection method on an STA-R coagulation analyzer (Diagnostica Stago, Asnieres, France). For genome-wide genotyping with the Illumina Human660-Quad Beadchip, we sampled 1,499 patients with a first episode of VT. Patients with a cancer diagnosis were excluded.

The **Precocious Coronary Artery Disease Study (PROCARDIS)** consists of CAD cases and controls from four European countries (UK, Italy, Sweden and Germany). CAD (defined as myocardial infarction, acute coronary syndrome, unstable or stable angina, or need for coronary artery bypass surgery or percutaneous coronary intervention) was diagnosed before 66 years of age and 80% of cases had a sibling fulfilling the same criteria for CAD. Subjects with self-reported non-European ancestry were excluded. Among the "genetically-enriched" CAD cases, 70% had suffered myocardial infarction (MI). For this study, 1270 Swedish PROCARDIS were analyzed for FVII antigen levels in plasma using ELISA with pair antibodies from Affinity Biologicals.

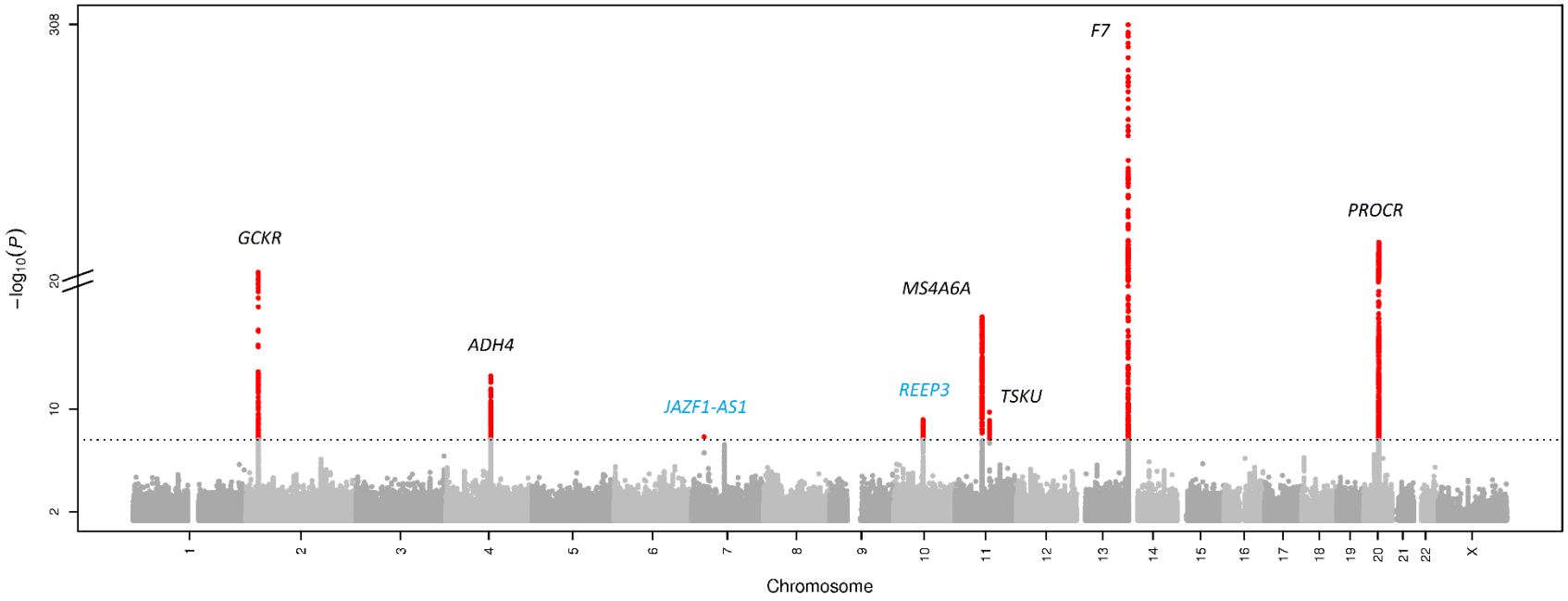
The **Rotterdam Study (RS)** is a prospective, population-based cohort study of determinants of several chronic diseases in older adults.[23] RS-I comprised 7,983 inhabitants of Ommoord, a district of Rotterdam in the Netherlands, who were 55 years or over. The baseline examination took place between 1990 and 1993.

Factor VII activity was measured with a one-stage clotting assay by using human thromboplastin (Tromborel S, Siemens) and factor VII-deficient plasma (Ortho Diagnostic System). The plasma concentrations were expressed as percentage activity by relating the clotting time to a calibration curve constructed of a standardized control plasma. As a control, the pooled plasma of 50 healthy middle-aged persons was used and three control samples were run with each batch of study samples. The intra-assay CV was 1.7%, the inter-assay CV was 3.7%, and reference range was 0.60-1.40 U/ml.

Supplementary Figure 1: QQ plot of the trans-ancestry meta-analysis of FVII activity.

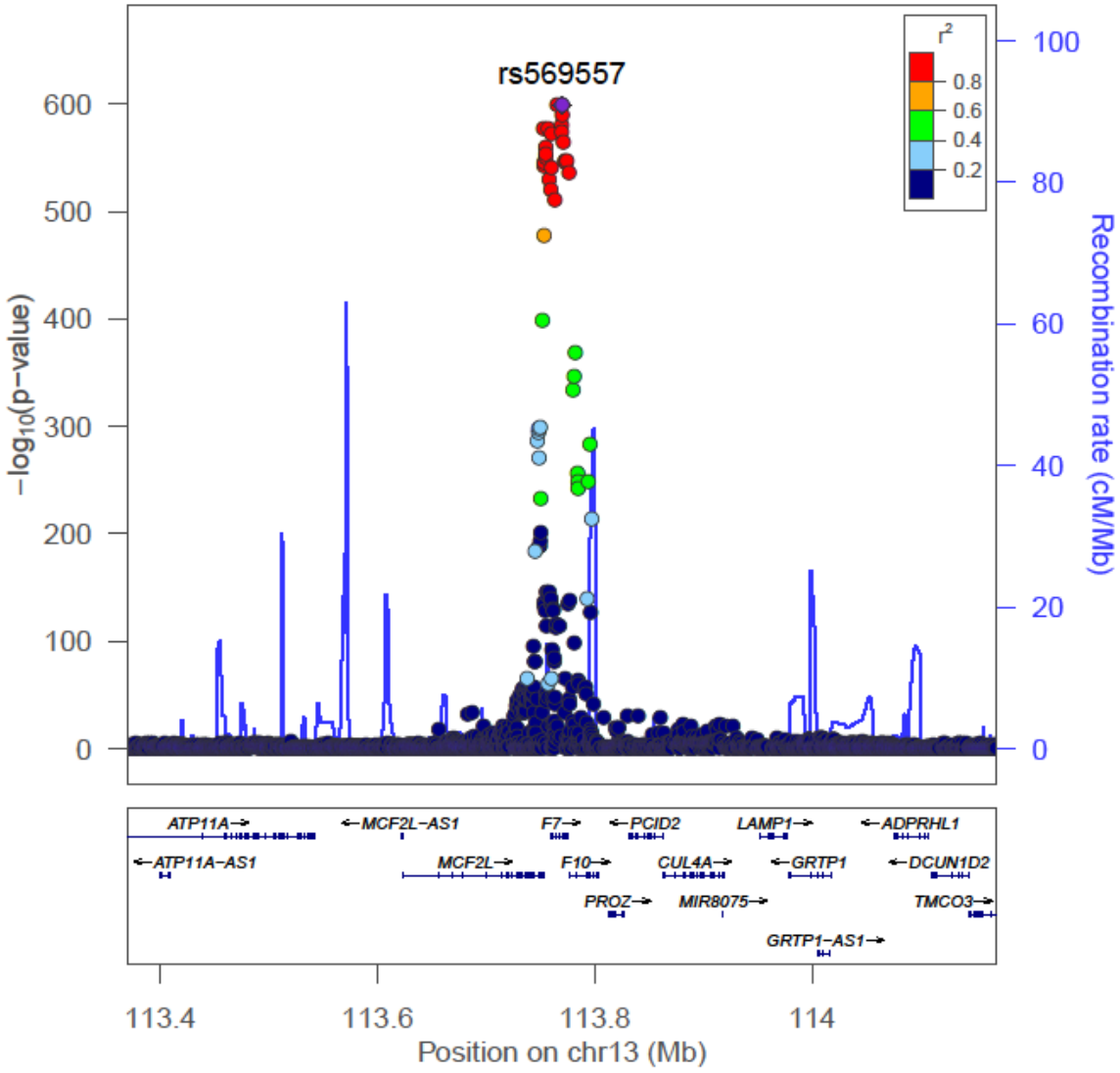


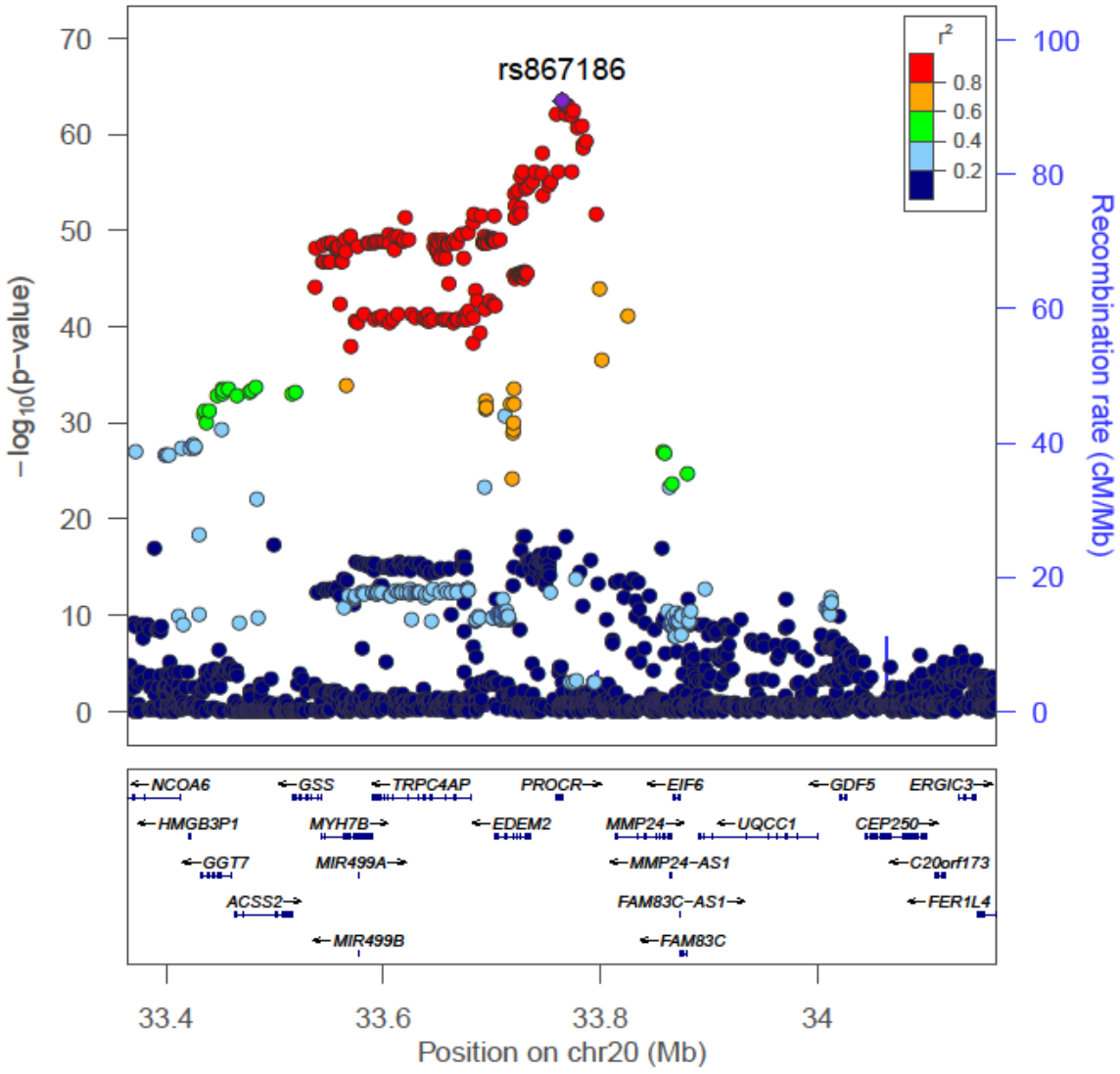
Supplementary Figure 2: Manhattan plot of the trans-ancestry meta-analysis of FVII activity.

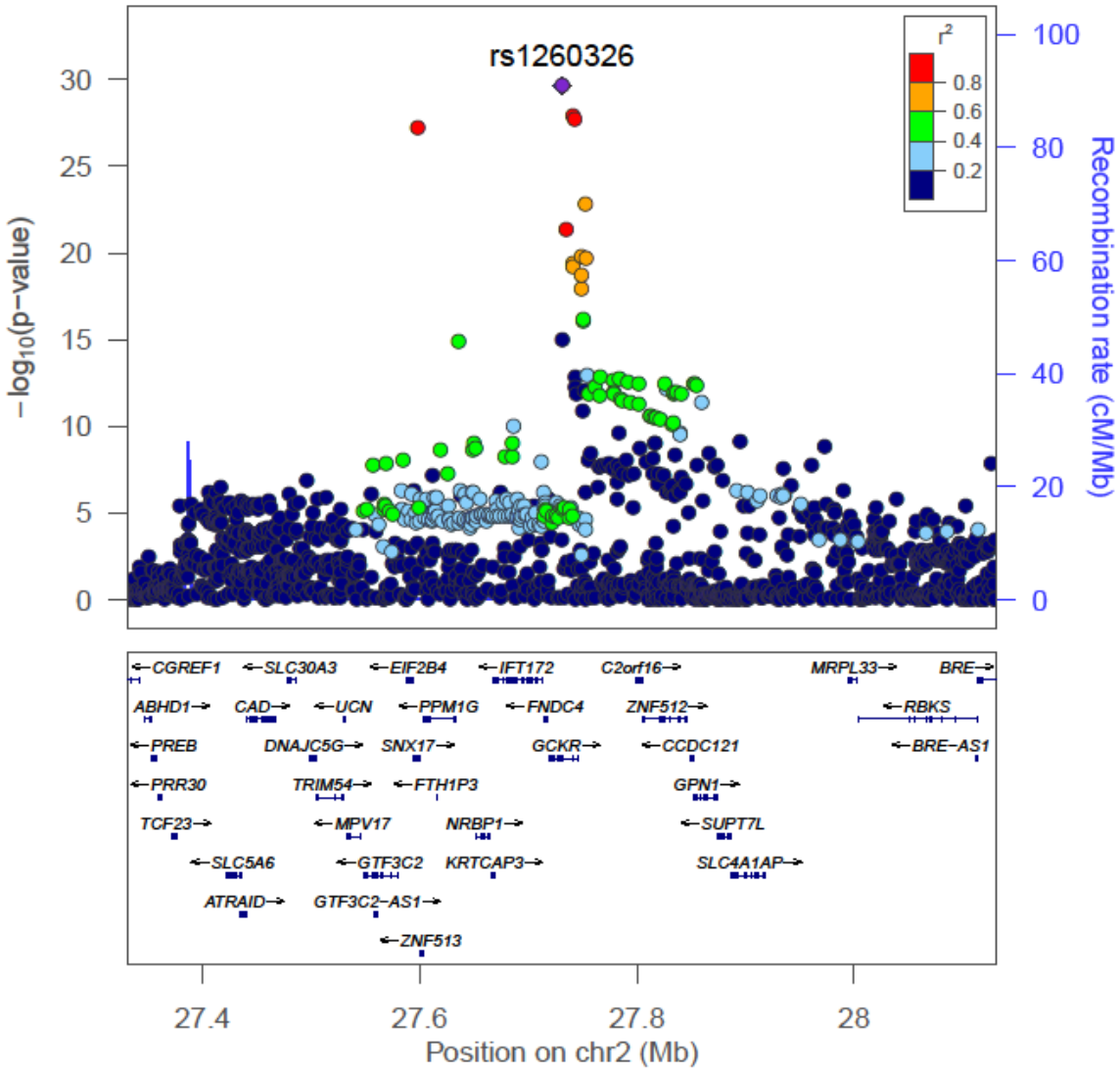


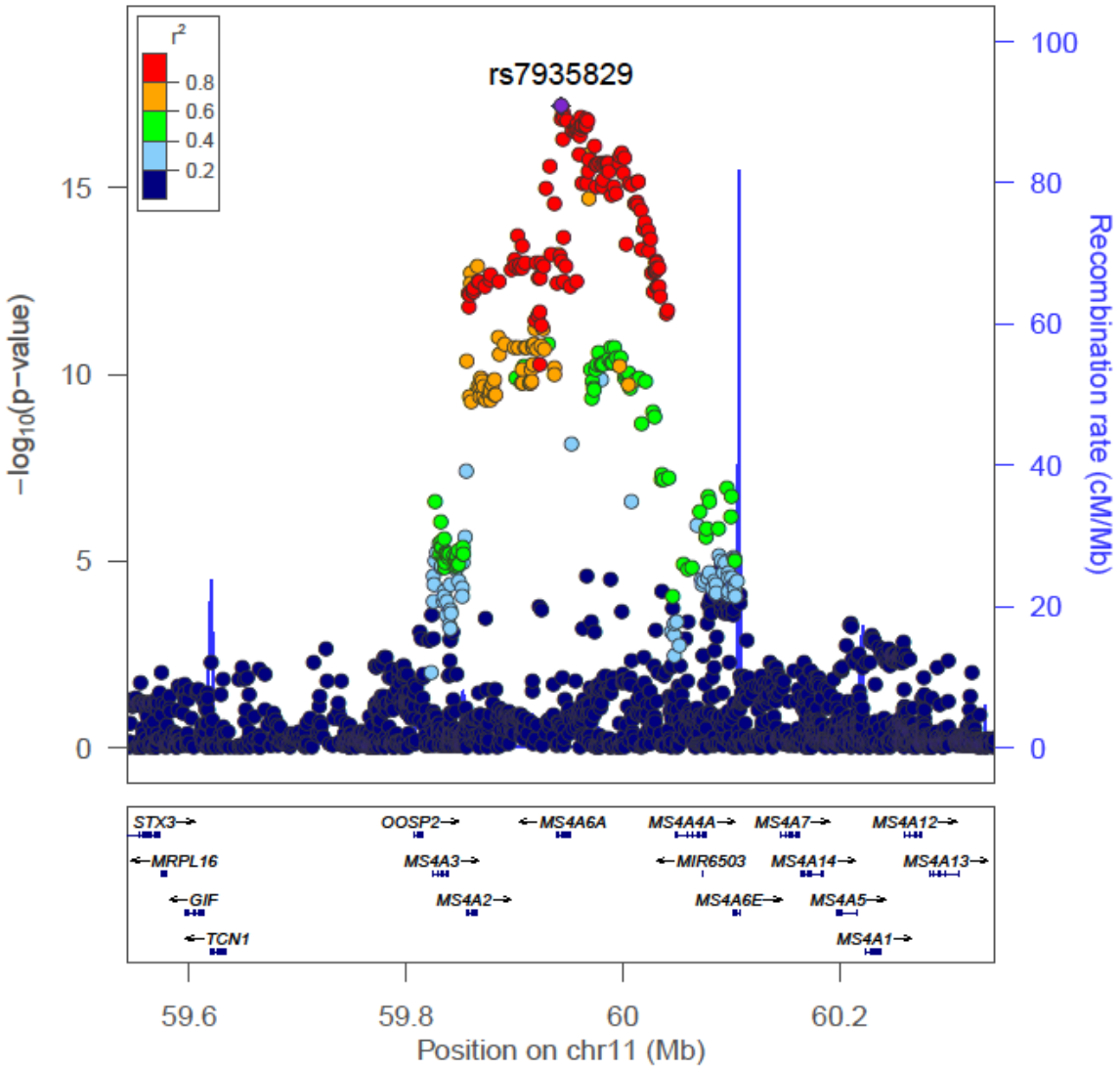
Genome-wide significant loci are annotated with the name of the closest gene. Gene names in blue indicate novel loci.

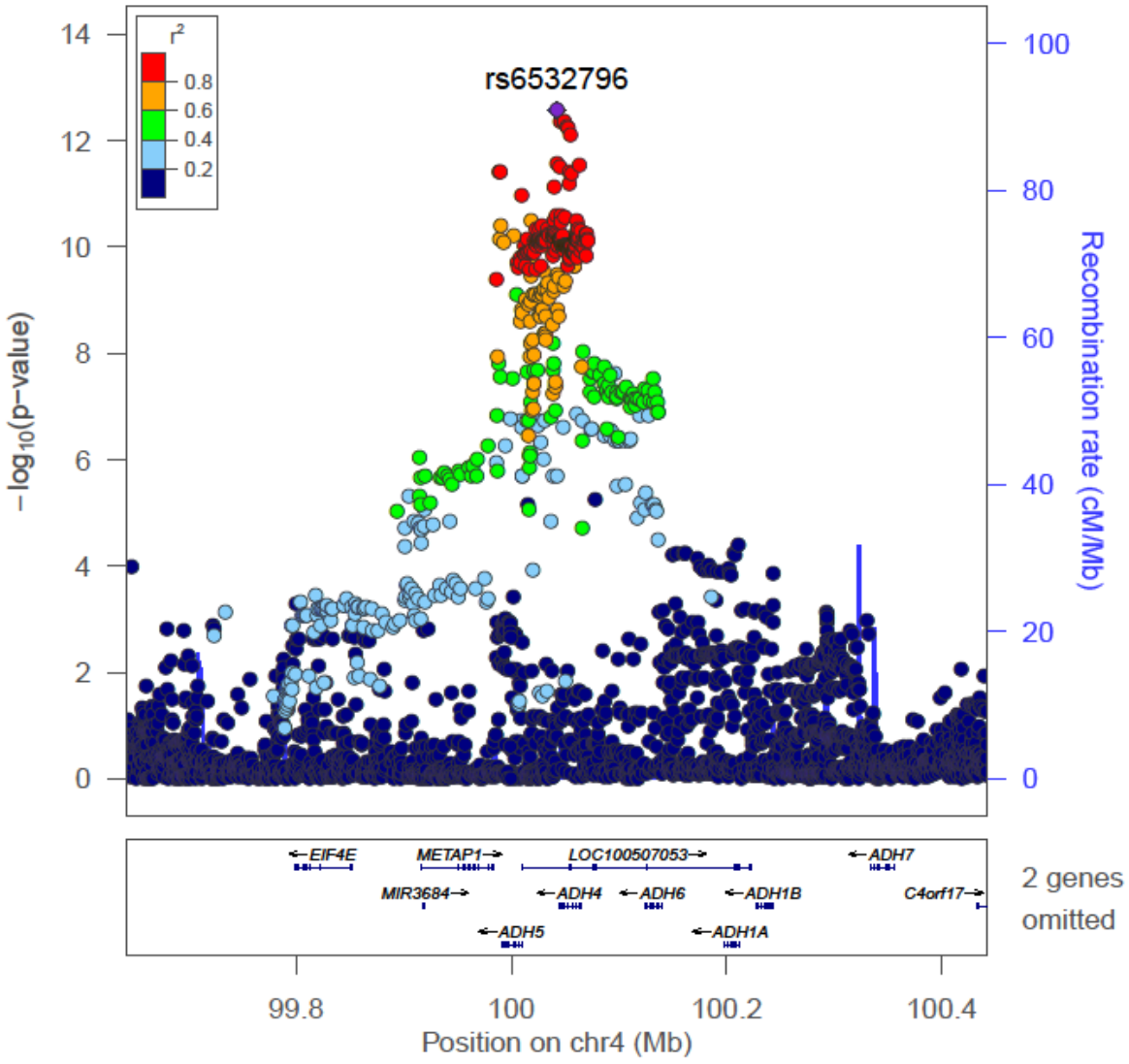
Supplementary Figure 3: Regional association plots of the known loci in the trans-ancestry meta-analysis of FVII activity. Linkage disequilibrium information based on European ancestry population.

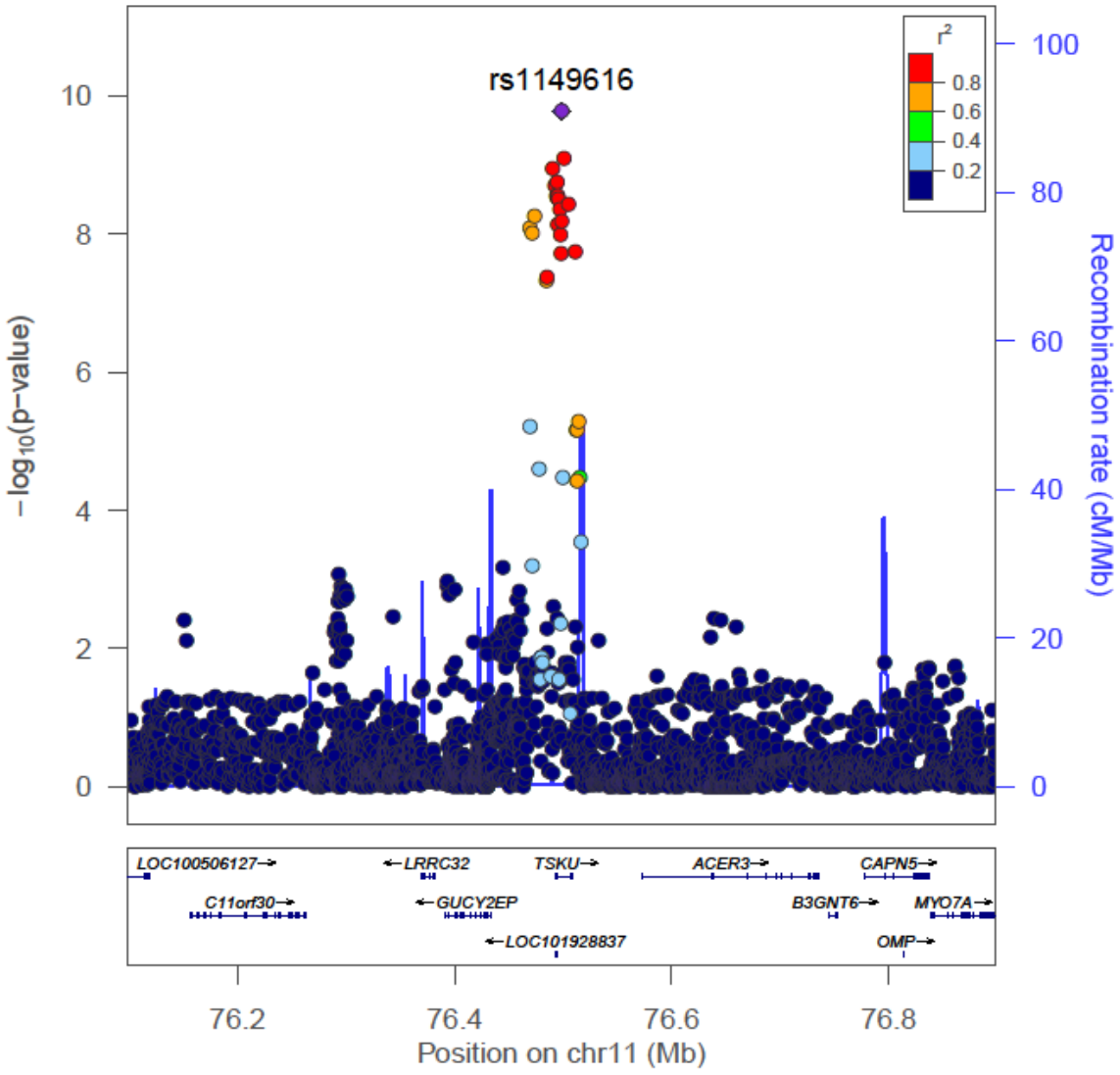



rs867186
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
70
60
50
40
30
20
10
0
100
80
60
40
20
0
NCOA6
GSS
TRPC4AP
PROCR
EIF6
GDF5
ERGIC3
HMGB3P1
MYH7B
EDEM2
MMP24
UQCC1
CEP250
GGT7
MIR499A
MMP24−AS1
C20orf173
ACSS2
FAM83C−AS1
FER1L4
MIR499B
FAM83C
33.4
33.6
33.8
34
Position on chr20 (Mb)

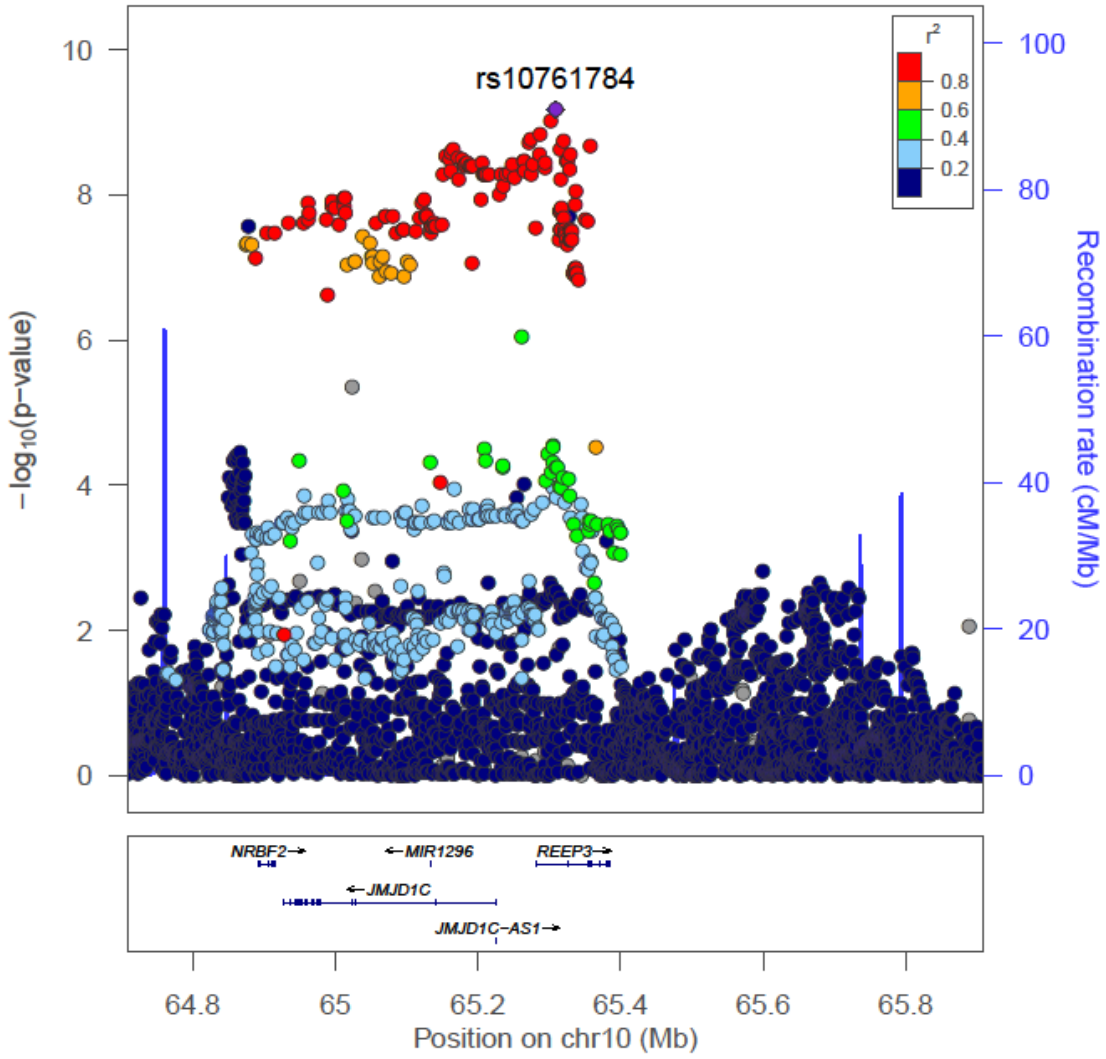

rs1260326
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
30
25
20
15
10
5
0
100
80
60
40
20
0
←CGREF1
←SLC30A3
←EIF2B4
←IFT172
C2orf16→
MRPL33→
BRE→
ABHD1→
CAD→
←UCN
←PPM1G
←FNDC4
ZNF512→
←RBKS
←PREB
DNAJC5G→
SNX17→
GCKR→
←CCDC121
←BRE−AS1
←PRR30
TRIM54→
←FTH1P3
GPN1→
TCF23→
←MPV17
NRBP1→
←SUPT7L
←SLC5A6
←GTF3C2
KRTCAP3→
SLC4A1AP→
ATRAID→
GTF3C2−AS1→
←ZNF513
27.4
27.6
27.8
28
Position on chr2 (Mb)

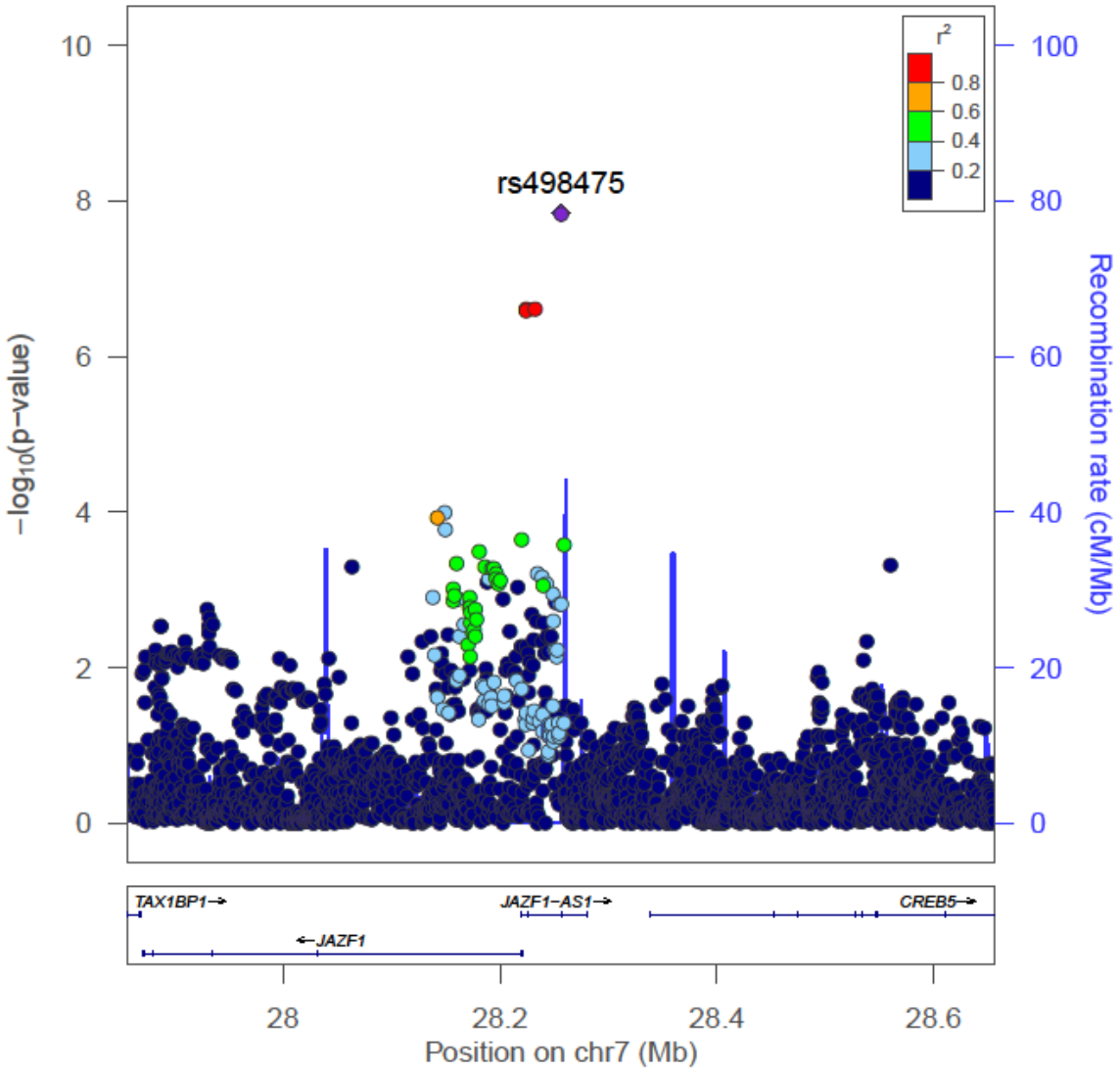

rs7935829
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
STX3
OOSP2
MS4A6A
MS4A4A
MS4A7
MS4A12
MRPL16
MS4A3
MIR6503
MS4A14
MS4A13
GIF
MS4A2
MS4A6E
MS4A5
TCN1
MS4A1
Position on chr11 (Mb)


rs6532796
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
EIF4E
METAP1
LOC100507053
ADH7
MIR3684
ADH4
ADH6
ADH1B
C4orf17
ADH5
ADH1A
2 genes omitted
99.8
100
100.2
100.4
Position on chr4 (Mb)

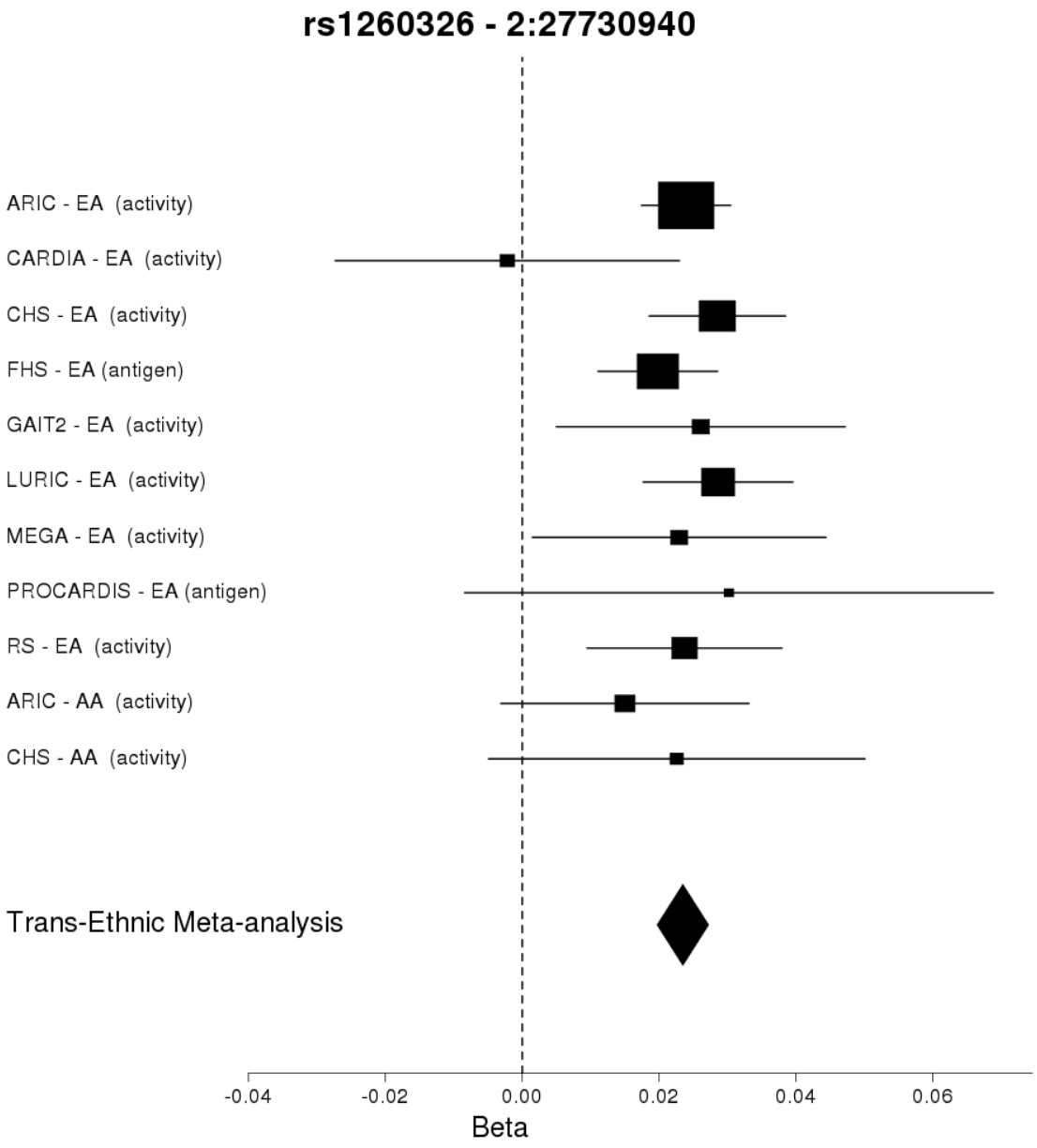

rs1149616
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
LOC100506127
LRRC32
TSKU
ACER3
CAPN5
C11orf30
GUCY2EP
B3GNT6
MYO7A
LOC101928837
OMP
Position on chr11 (Mb)

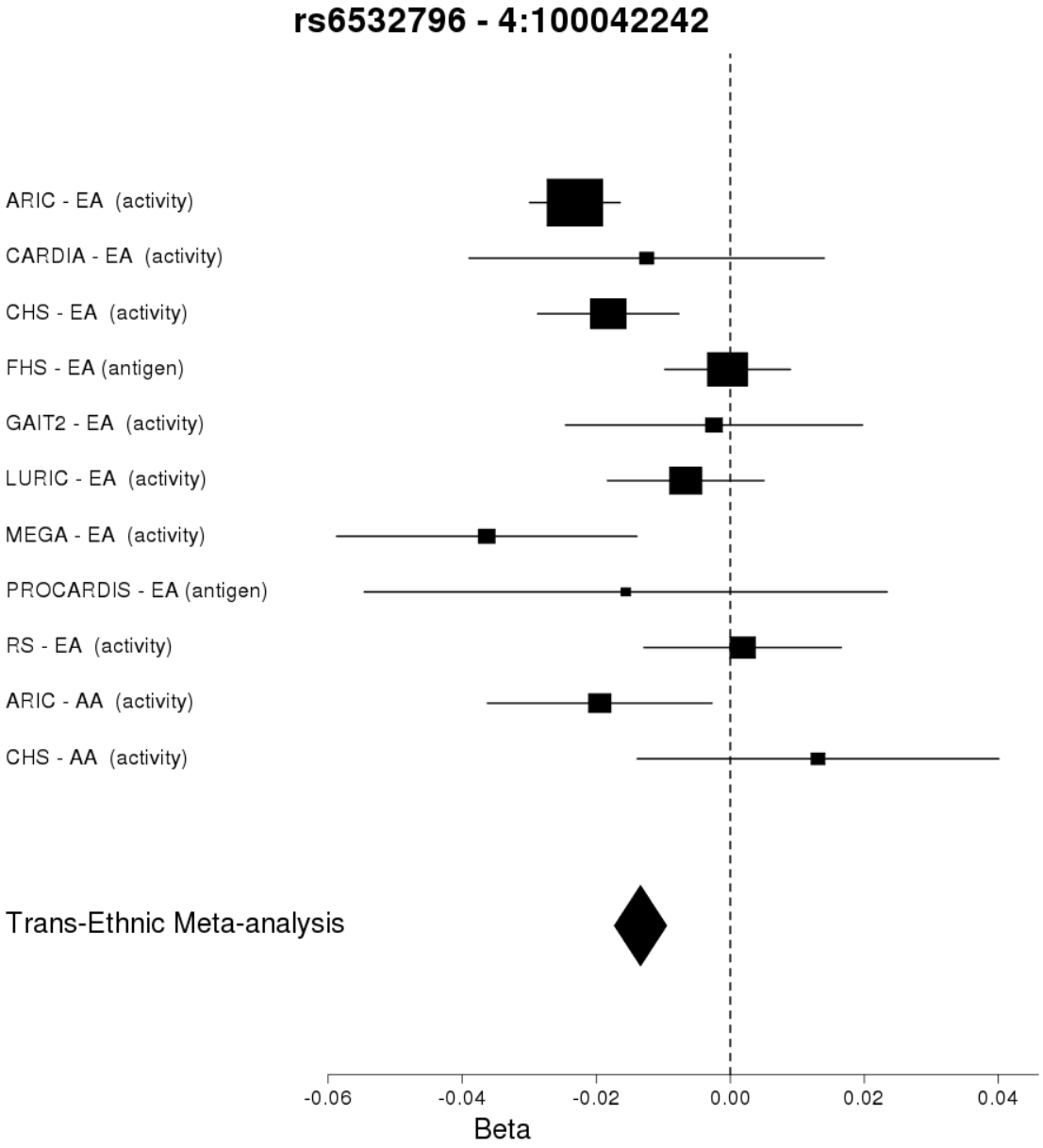
Supplementary Figure 4: Regional association plots of the novel *REEP3* and *JAZF1* loci in the trans-ancestry meta-analysis of FVII activity. Linkage disequilibrium information based on European ancestry population.

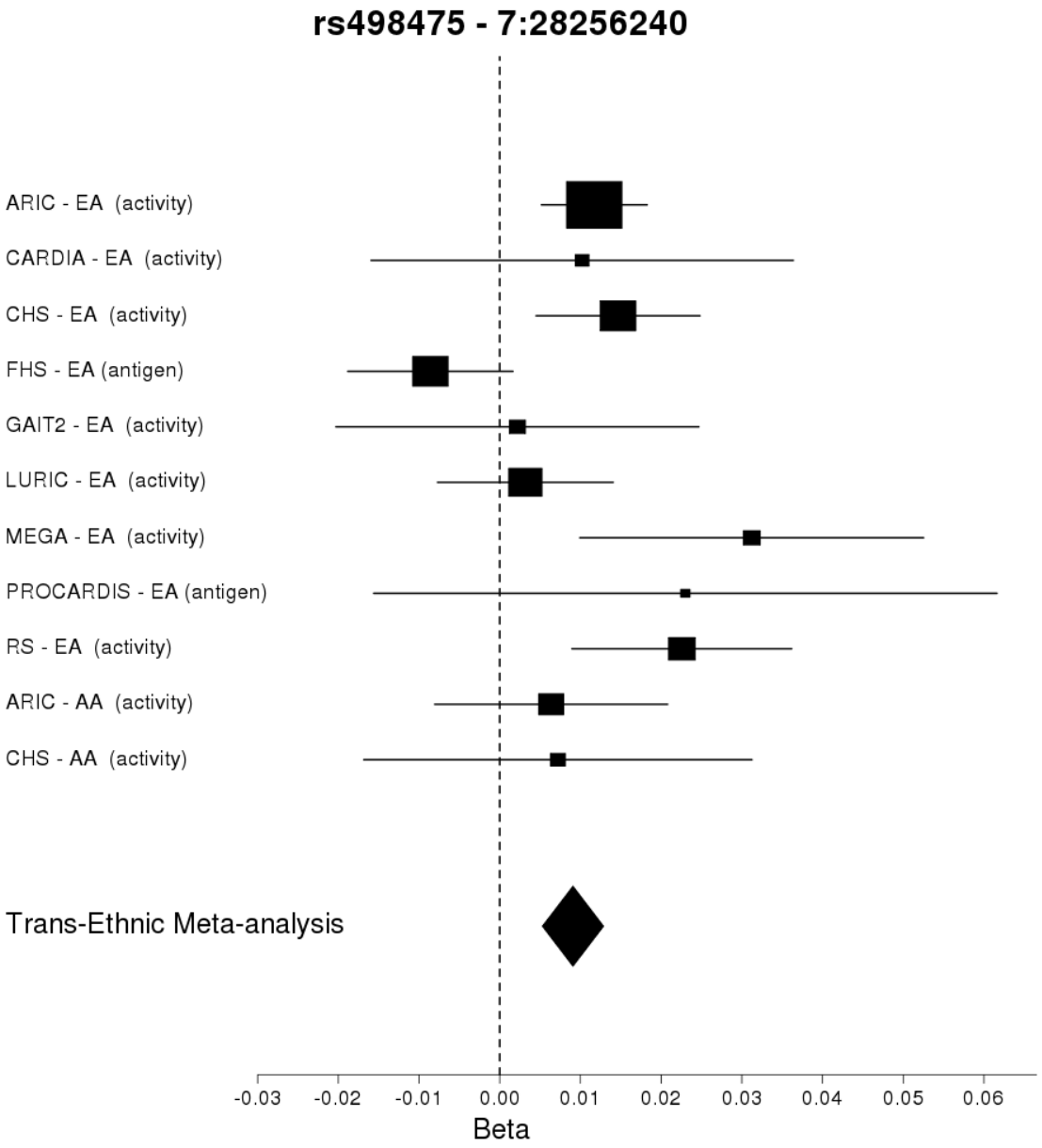


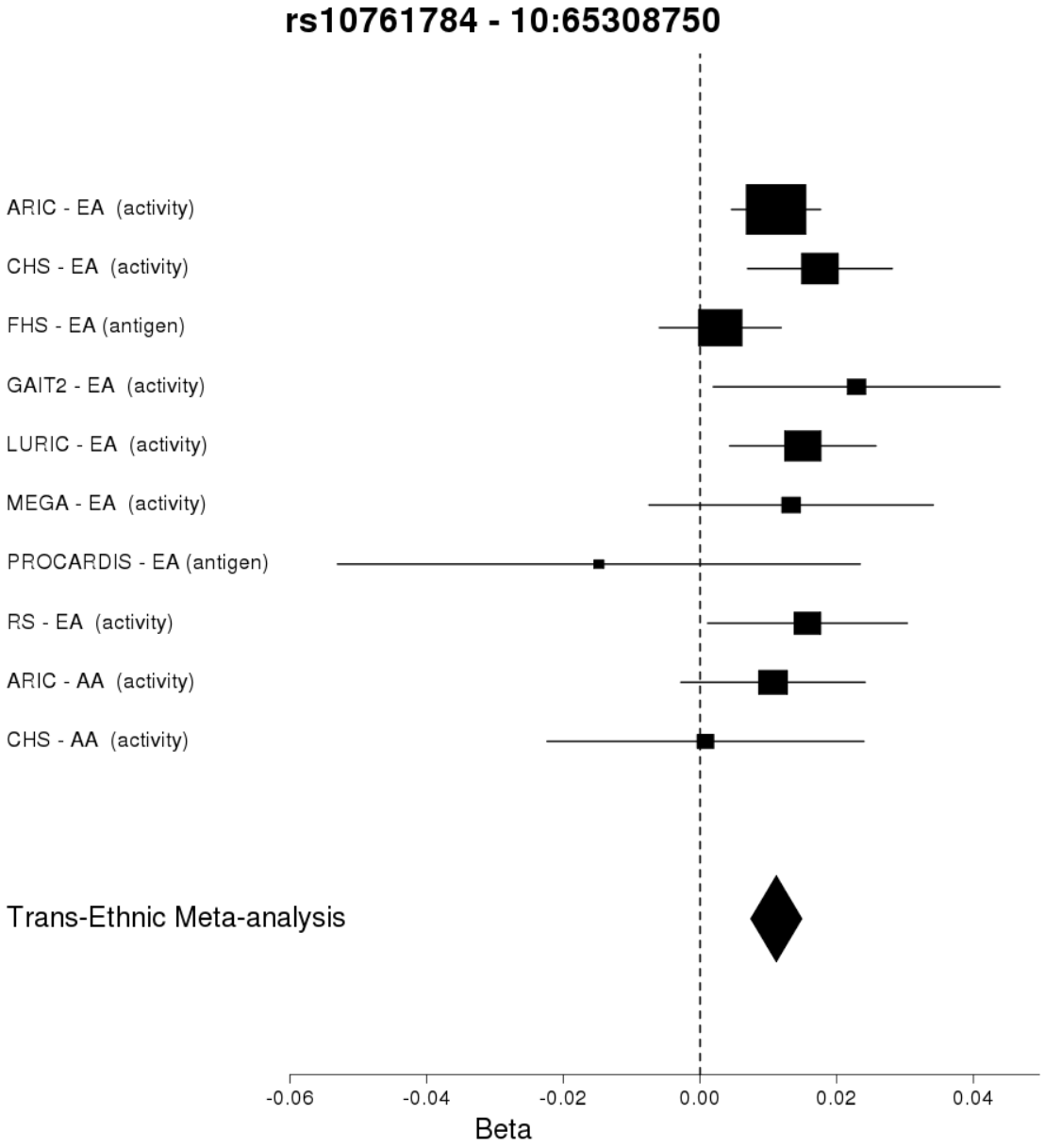

rs498475
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
10
8
6
4
2
0
100
80
60
40
20
0
TAX1BP1→
JAZF1−AS1→
CREB5→
←JAZF1
28
28.2
28.4
28.6
Position on chr7 (Mb)

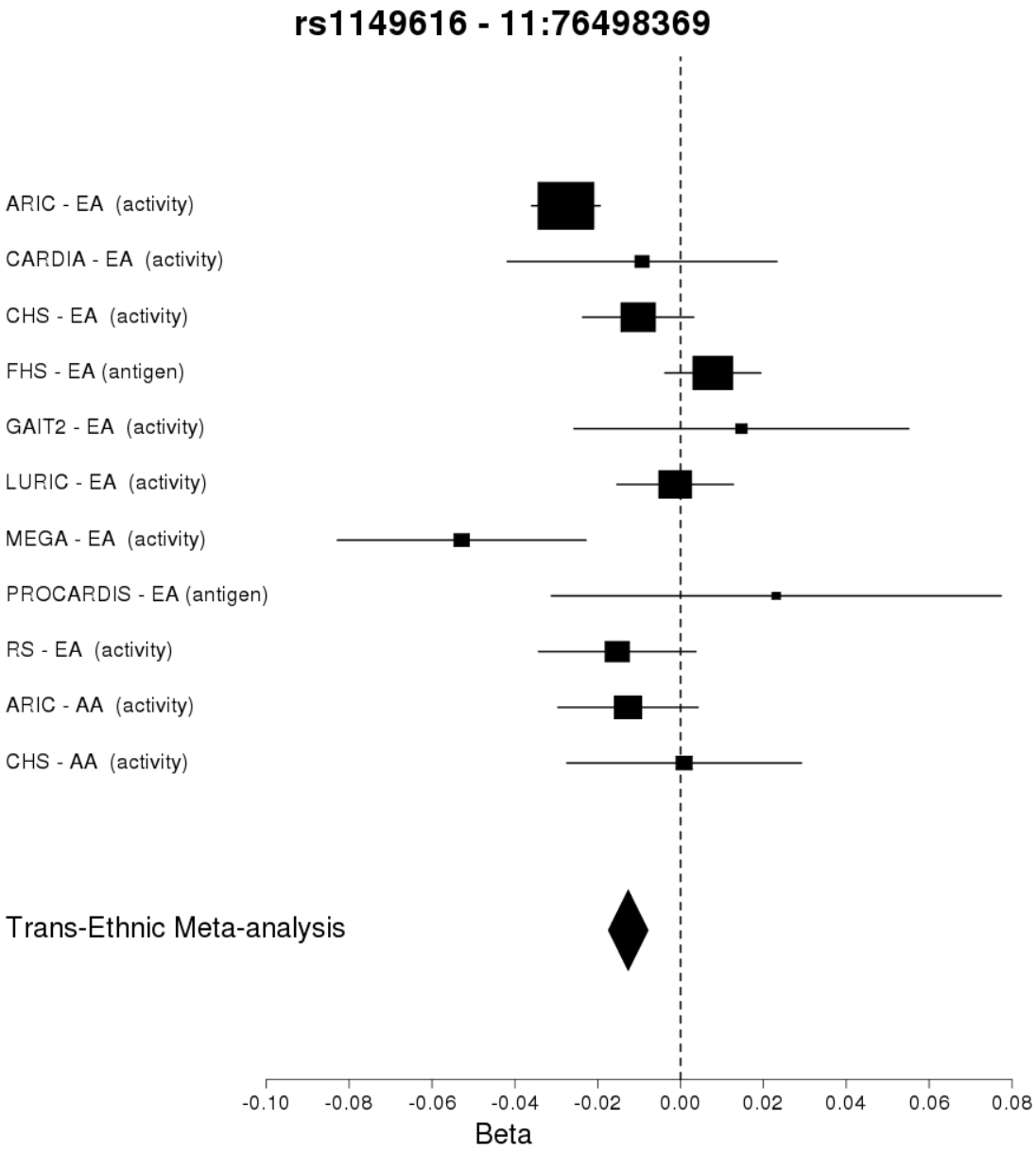
Supplementary Figure 5: Forest plots showing the study-specific associations of genetic variants with FVII activity. EA refers to European ancestry and AA refers to African American ancestry.

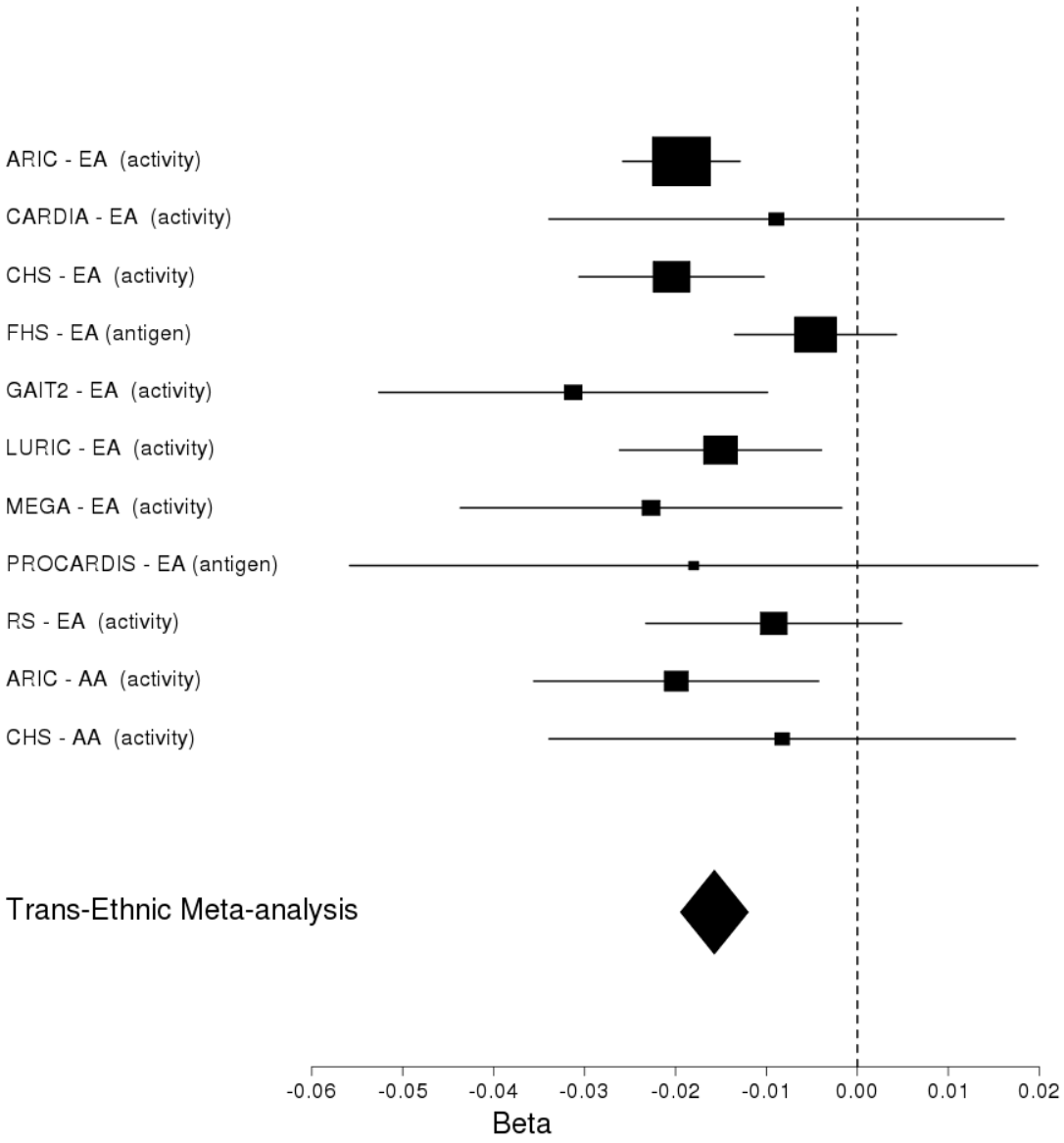


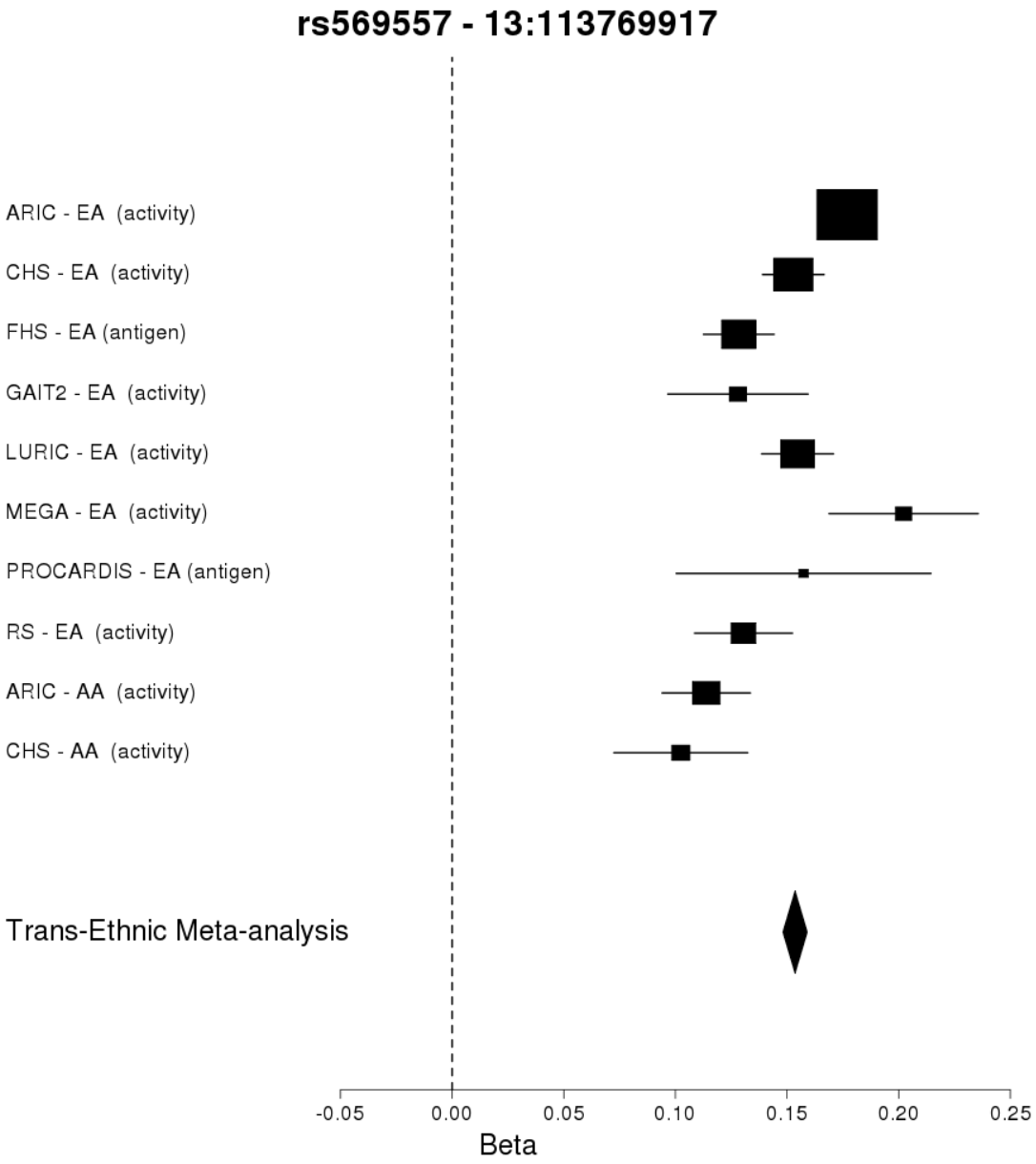

rs6532796 - 4:100042242
ARIC - EA (activity)
CARDIA - EA (activity)
CHS - EA (activity)
FHS - EA (antigen)
GAIT2 - EA (activity)
LURIC - EA (activity)
MEGA - EA (activity)
PROCARDIS - EA (antigen)
RS - EA (activity)
ARIC - AA (activity)
CHS - AA (activity)
Trans-Ethnic Meta-analysis
-0.06
-0.04
-0.02
0.00
0.02
0.04
Beta

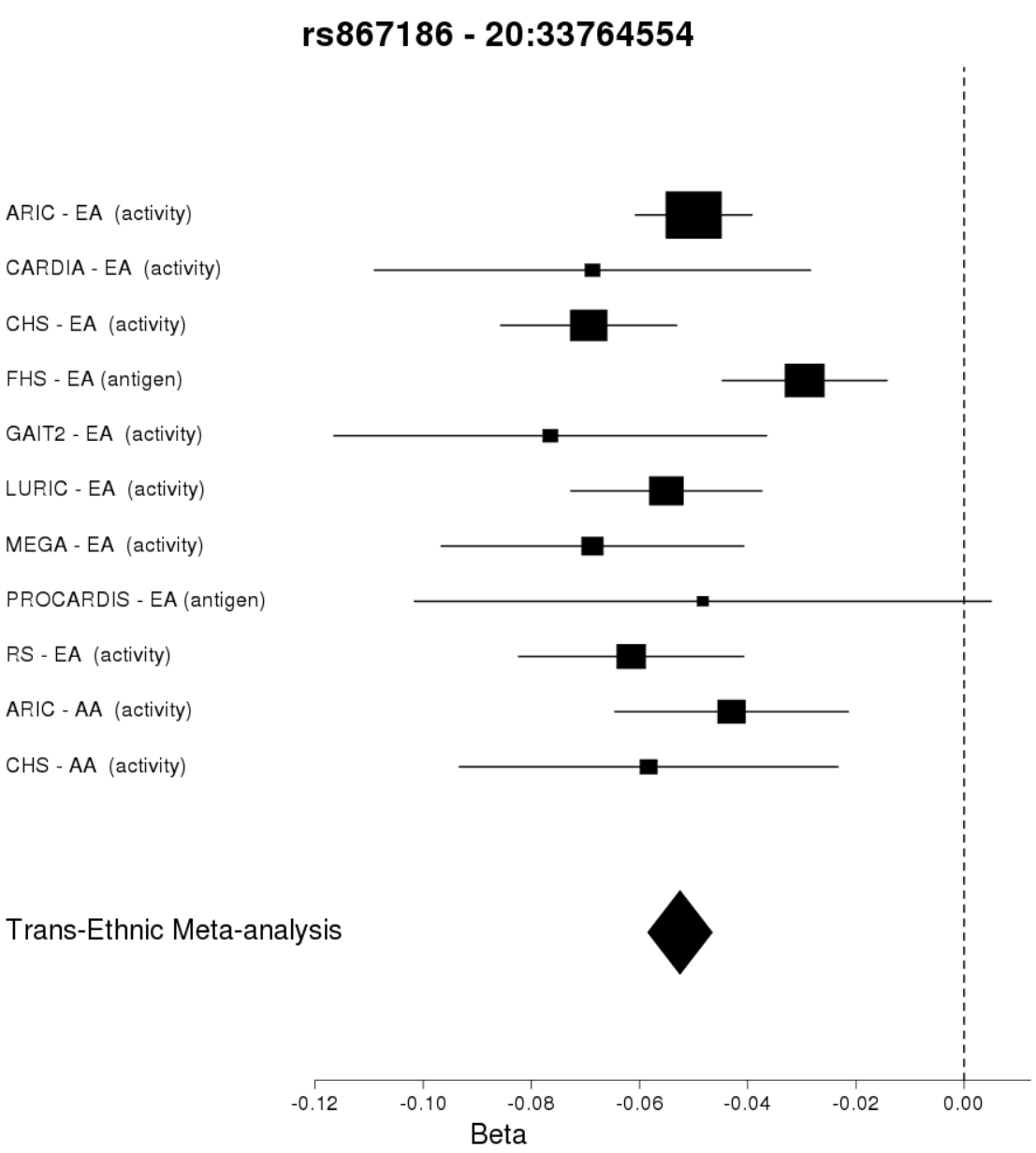

rs498475 - 7:28256240
ARIC - EA (activity)
CARDIA - EA (activity)
CHS - EA (activity)
FHS - EA (antigen)
GAIT2 - EA (activity)
LURIC - EA (activity)
MEGA - EA (activity)
PROCARDIS - EA (antigen)
RS - EA (activity)
ARIC - AA (activity)
CHS - AA (activity)
Trans-Ethnic Meta-analysis
-0.03
-0.02
-0.01
0.00
0.01
0.02
0.03
0.04
0.05
0.06
Beta


rs10761784 - 10:65308750
ARIC - EA (activity)
CHS - EA (activity)
FHS - EA (antigen)
GAIT2 - EA (activity)
LURIC - EA (activity)
MEGA - EA (activity)
PROCARDIS - EA (antigen)
RS - EA (activity)
ARIC - AA (activity)
CHS - AA (activity)
Trans-Ethnic Meta-analysis
-0.06
-0.04
-0.02
0.00
0.02
0.04
Beta

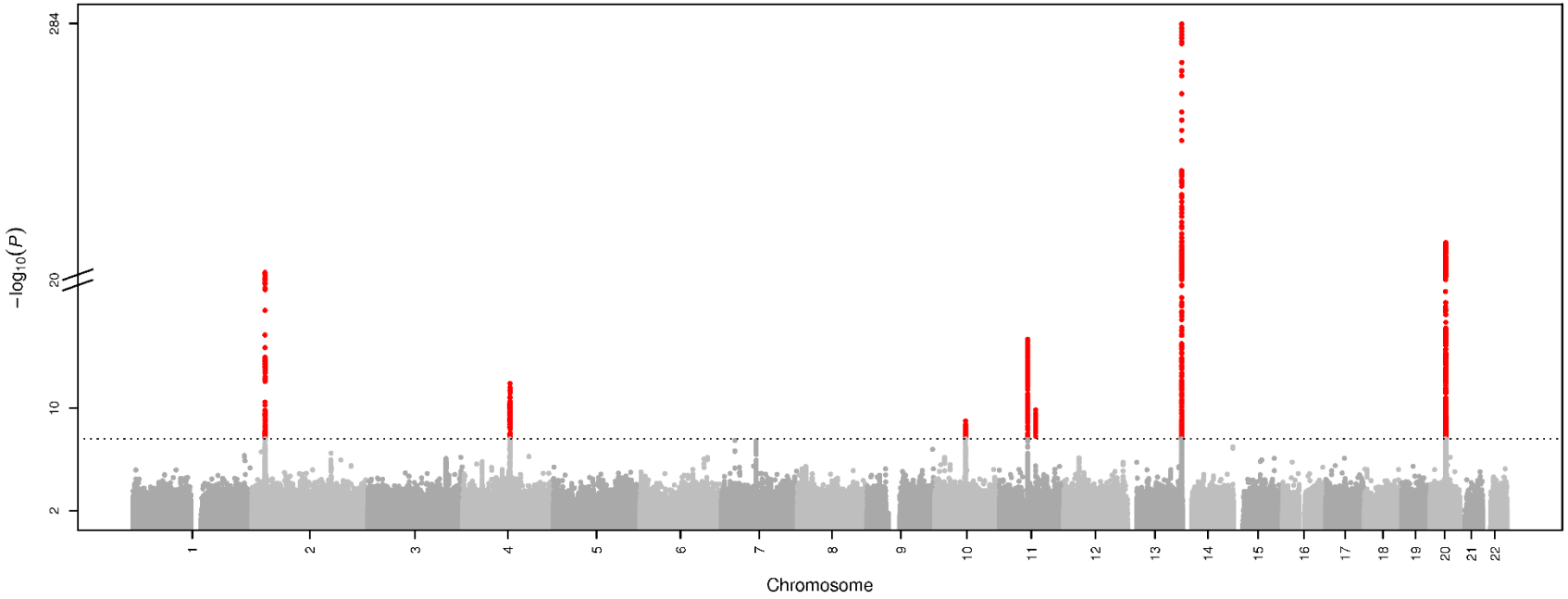

rs1149616 - 11:76498369
ARIC - EA (activity)
CARDIA - EA (activity)
CHS - EA (activity)
FHS - EA (antigen)
GAIT2 - EA (activity)
LURIC - EA (activity)
MEGA - EA (activity)
PROCARDIS - EA (antigen)
RS - EA (activity)
ARIC - AA (activity)
CHS - AA (activity)
Trans-Ethnic Meta-analysis
-0.10
-0.08
-0.06
-0.04
-0.02
0.00
0.02
0.04
0.06
0.08
Beta


rs7935829 - 11:59942815
ARIC - EA (activity)
CARDIA - EA (activity)
CHS - EA (activity)
FHS - EA (antigen)
GAIT2 - EA (activity)
LURIC - EA (activity)
MEGA - EA (activity)
PROCARDIS - EA (antigen)
RS - EA (activity)
ARIC - AA (activity)
CHS - AA (activity)
Trans-Ethnic Meta-analysis
-0.06
-0.05
-0.04
-0.03
-0.02
-0.01
0.00
0.01
0.02
Beta

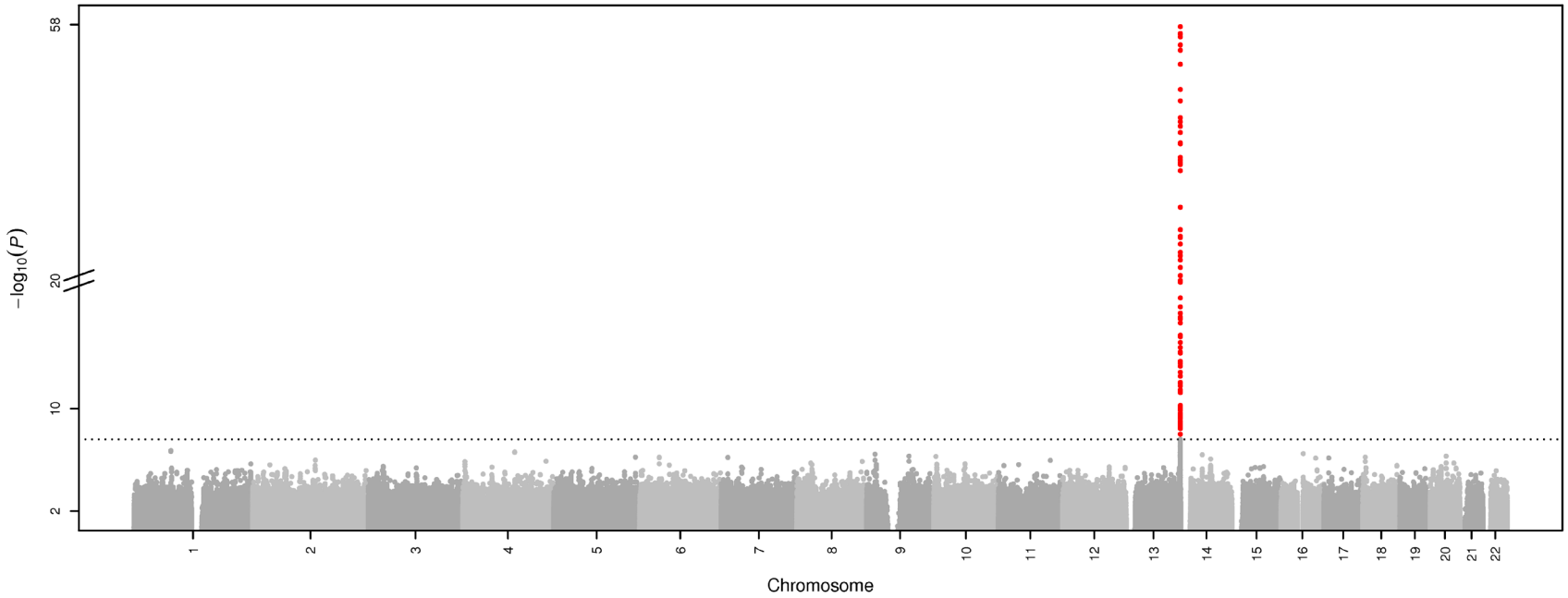

rs569557 - 13:113769917
ARIC - EA (activity)
CHS - EA (activity)
FHS - EA (antigen)
GAIT2 - EA (activity)
LURIC - EA (activity)
MEGA - EA (activity)
PROCARDIS - EA (antigen)
RS - EA (activity)
ARIC - AA (activity)
CHS - AA (activity)
Trans-Ethnic Meta-analysis
-0.05
0.00
0.05
0.10
0.15
0.20
0.25
Beta


rs867186 - 20:33764554
ARIC - EA (activity)
CARDIA - EA (activity)
CHS - EA (activity)
FHS - EA (antigen)
GAIT2 - EA (activity)
LURIC - EA (activity)
MEGA - EA (activity)
PROCARDIS - EA (antigen)
RS - EA (activity)
ARIC - AA (activity)
CHS - AA (activity)
Trans-Ethnic Meta-analysis
-0.12
-0.10
-0.08
-0.06
-0.04
-0.02
0.00
Beta

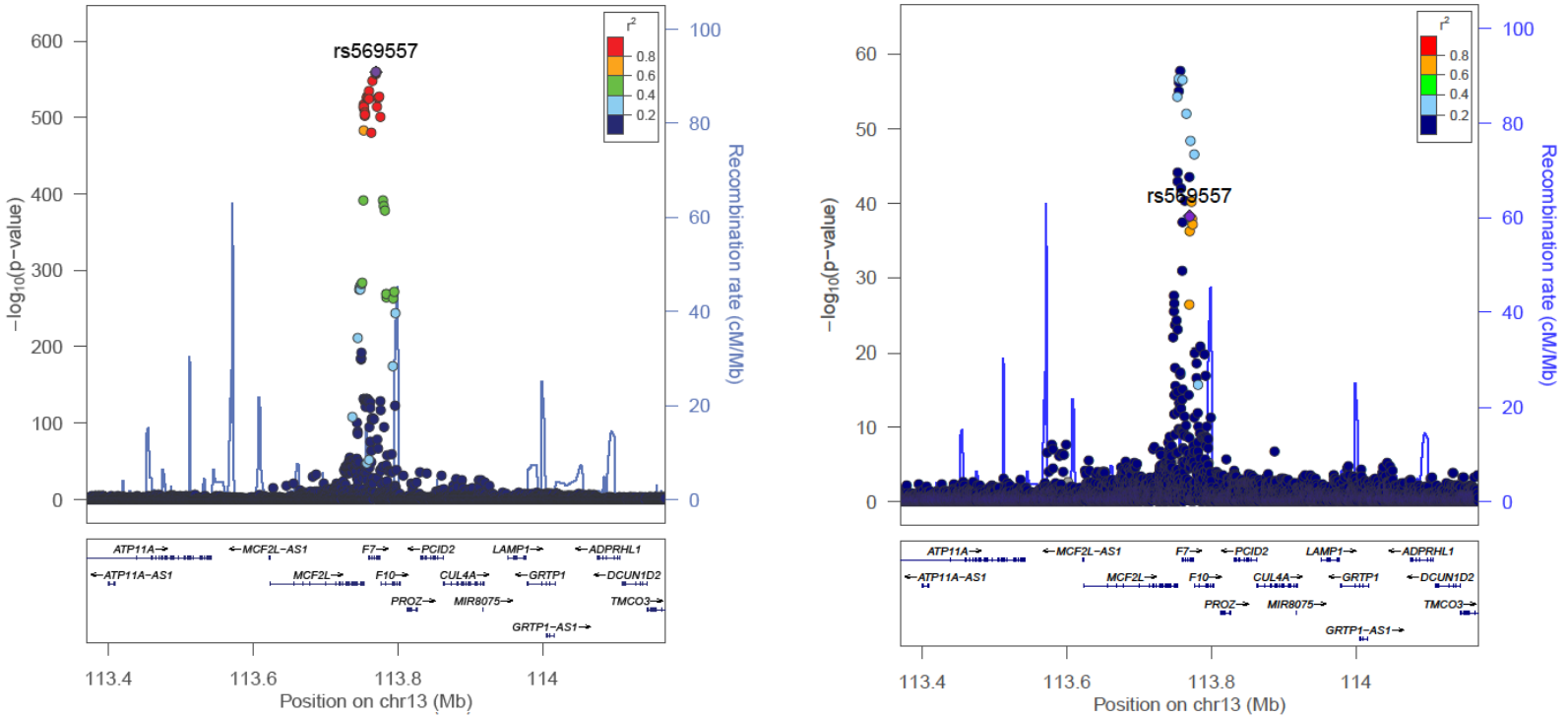
Supplementary Figure 6: Manhattan plot of the European-ancestry meta-analysis of FVII activity.

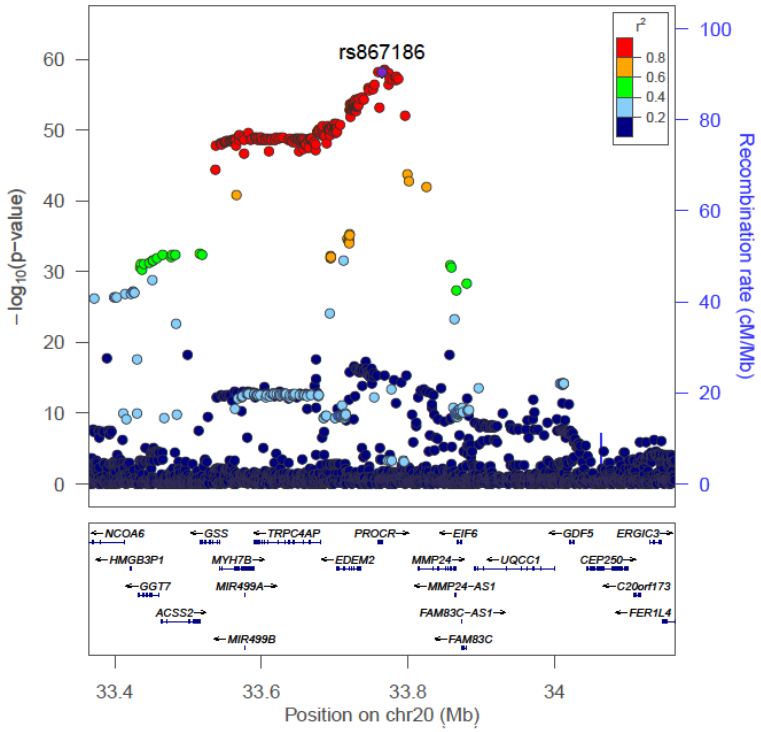


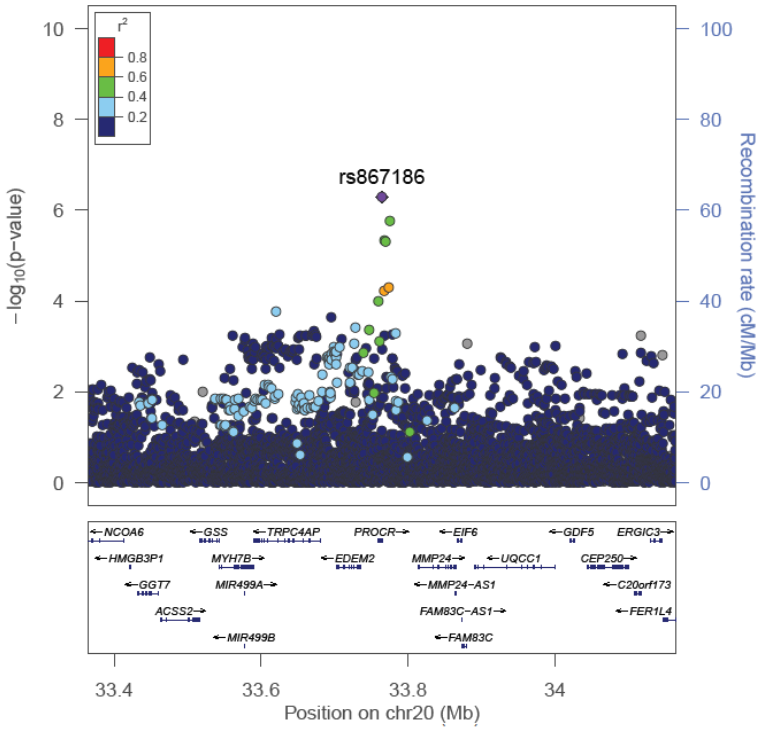
Supplementary Figure 7: Manhattan plot of the African-ancestry meta-analysis of FVII activity.

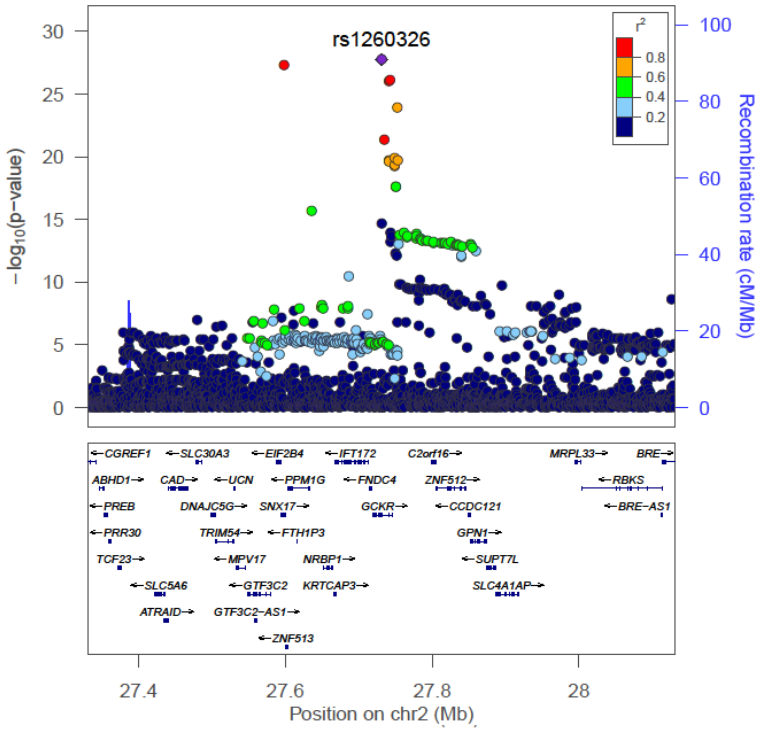


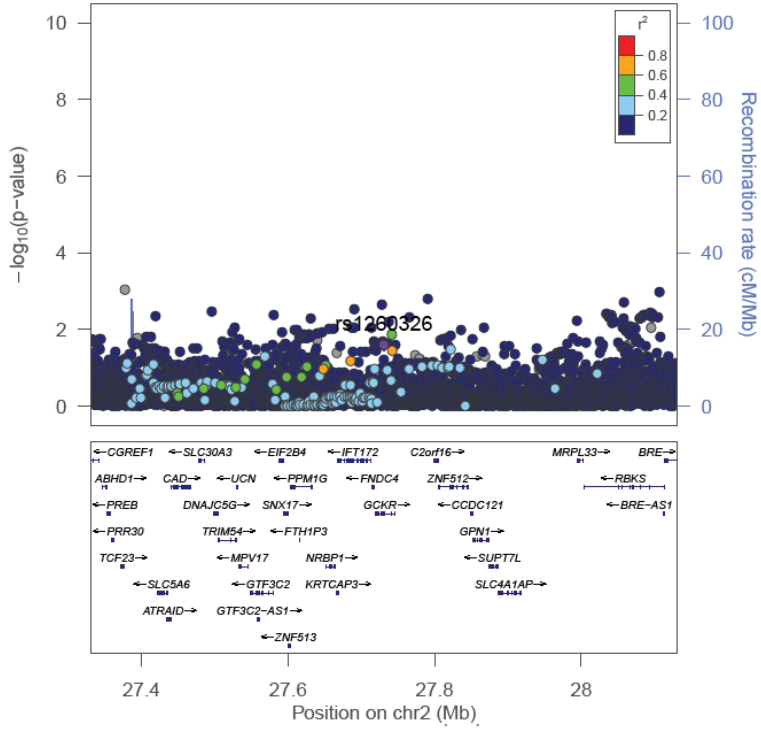
Supplementary Figure 8: Regional association plots of the ancestry-specific meta-analysis of FVII activity. European-specific results are shown on the left, with European-specific information on linkage disequilibrium, and African-specific results are shown on the right with African-specific information on linkage disequilibrium. Plots are shown for all index variants significant in the trans-ancestry meta-analysis of FVII activity.

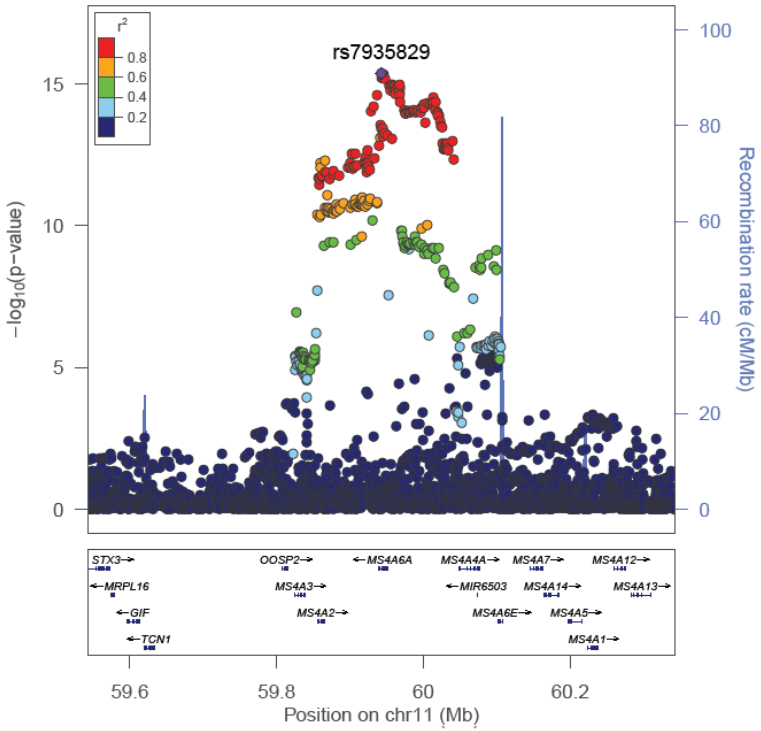


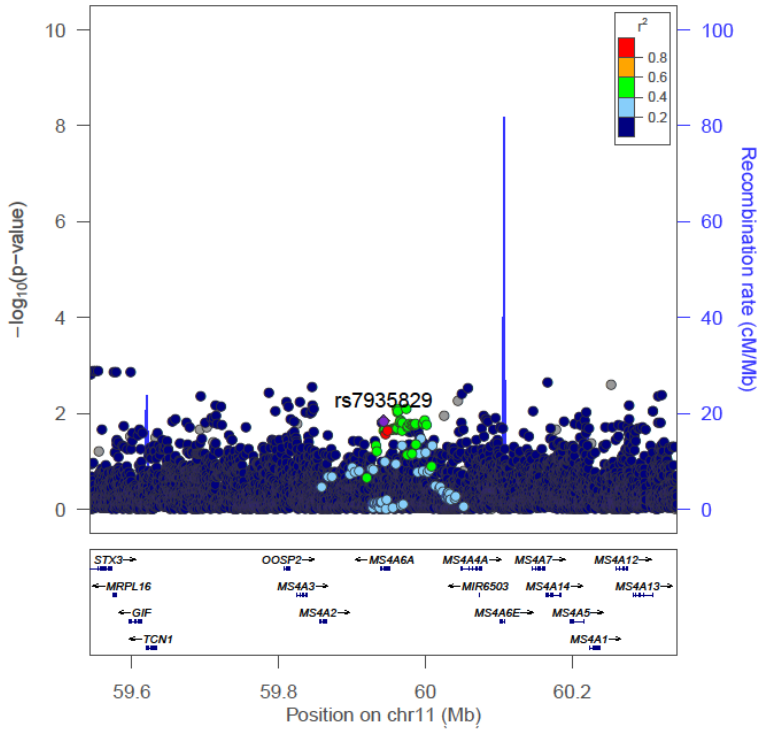

rs867186
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
NCOA6
GSS
TRPC4AP
PROCR
EIF6
GDF5
ERGIC3
HMGB3P1
MYH7B
EDEM2
MMP24
UQCC1
CEP250
GGT7
MIR499A
MMP24−AS1
C20orf173
ACSS2
FAM83C−AS1
FER1L4
MIR499B
FAM83C
Position on chr20 (Mb)

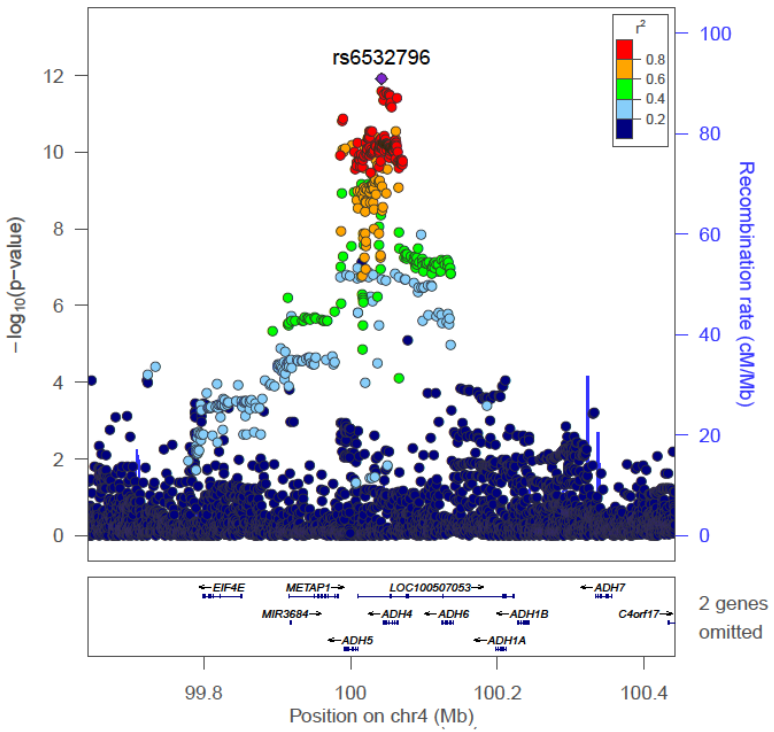

rs867186
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
NCOA6
GSS
TRPC4AP
PROCR
EIF6
GDF5
ERGIC3
HMGB3P1
MYH7B
EDEM2
MMP24
UQCC1
CEP250
GGT7
MIR499A
MMP24−AS1
C20orf173
ACSS2
FAM83C−AS1
FER1L4
MIR499B
FAM83C
Position on chr20 (Mb)

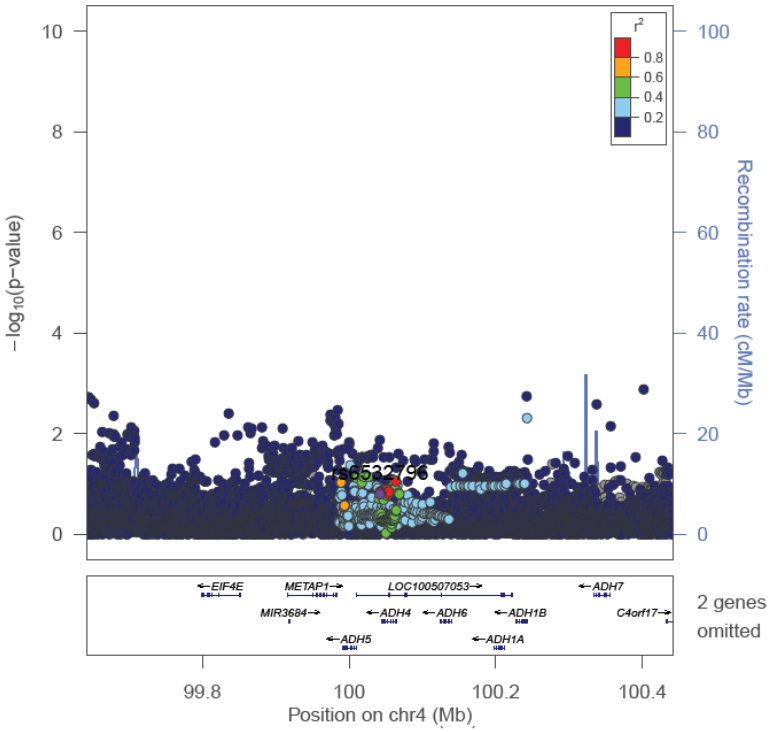

rs1260326
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
CGREF1 SLC30A3 EIF2B4 IFT172 C2orf16 MRPL33 BRE
ABHD1 CAD UCN PPM1G FNDC4 ZNF512 RBKS
PREB DNAJC5G SNX17 GCKR CCDC121 BRE-AS1
PRR30 TRIM54 FTH1P3 GPN1
TCF23 MPV17 NRBP1 SUPT7L
SLC5A6 GTF3C2 KRTCAP3 SLC4A1AP
ATRAID GTF3C2-AS1
ZNF513
Position on chr2 (Mb)

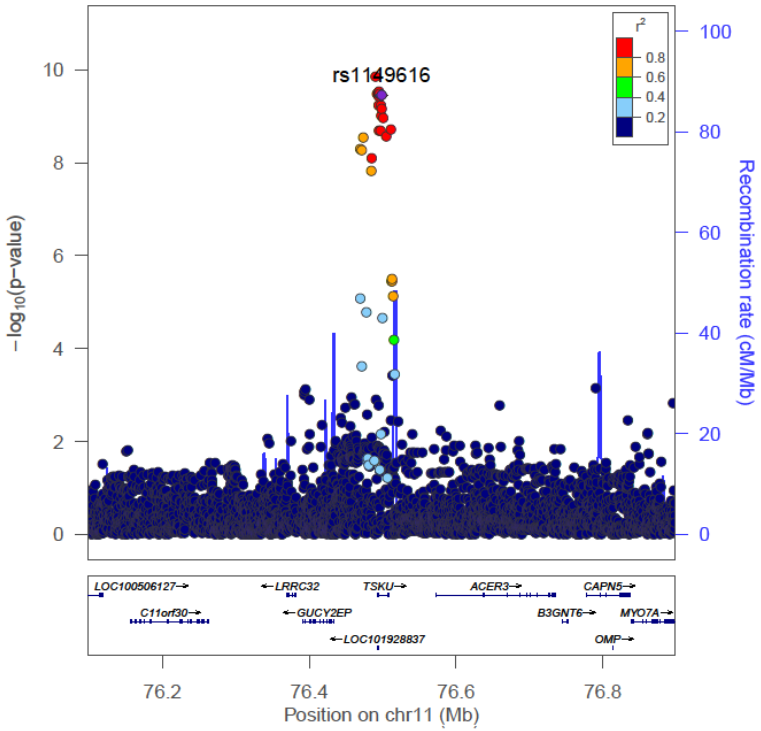

rs1260326
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
CGREF1 SLC30A3 EIF2B4 IFT172 C2orf16 MRPL33 BRE
ABHD1 CAD UCN PPM1G FNDC4 ZNF512 RBKS
PREB DNAJC5G SNX17 GCKR CCDC121 BRE-AS1
PRR30 TRIM54 FTH1P3 GPN1
TCF23 MPV17 NRBP1 SUPT7L
SLC5A6 GTF3C2 KRTCAP3 SLC4A1AP
ATRAID GTF3C2-AS1
ZNF513
Position on chr2 (Mb)

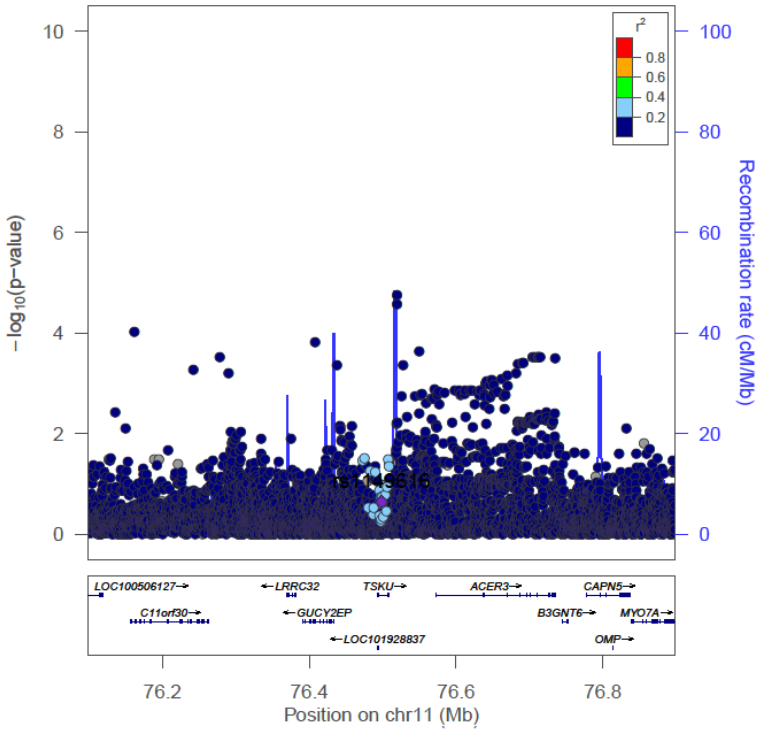

rs7935829
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
STX3
OOSP2
MS4A6A
MS4A4A
MS4A7
MS4A12
MRPL16
MS4A3
MIR6503
MS4A14
MS4A13
GIF
MS4A2
MS4A6E
MS4A5
TCN1
MS4A1
59.6
59.8
60
60.2
Position on chr11 (Mb)

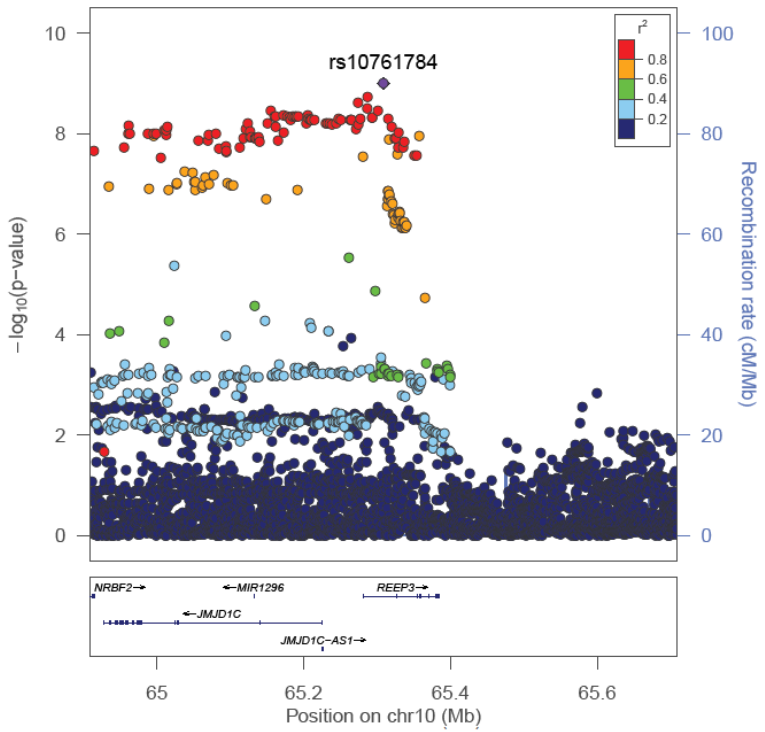

rs7935829
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
STX3
OOSP2
MS4A6A
MS4A4A
MS4A7
MS4A12
MRPL16
MS4A3
MIR6503
MS4A14
MS4A13
GIF
MS4A2
MS4A6E
MS4A5
TCN1
MS4A1
59.6
59.8
60
60.2
Position on chr11 (Mb)

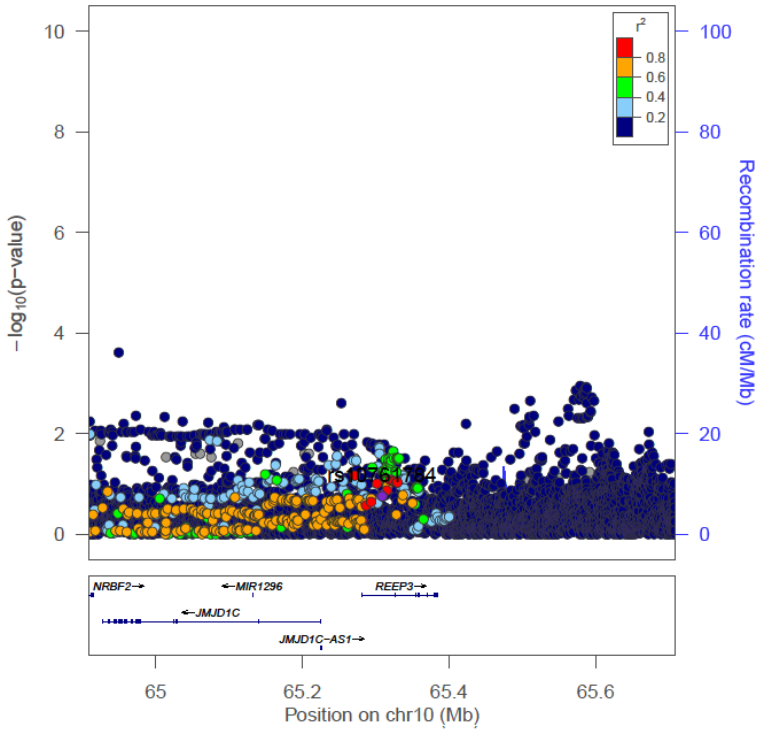

rs6532796
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
EIF4E
METAP1
LOC100507053
ADH7
MIR3684
ADH4
ADH6
ADH1B
C4orf17
ADH5
ADH1A
2 genes omitted
Position on chr4 (Mb)

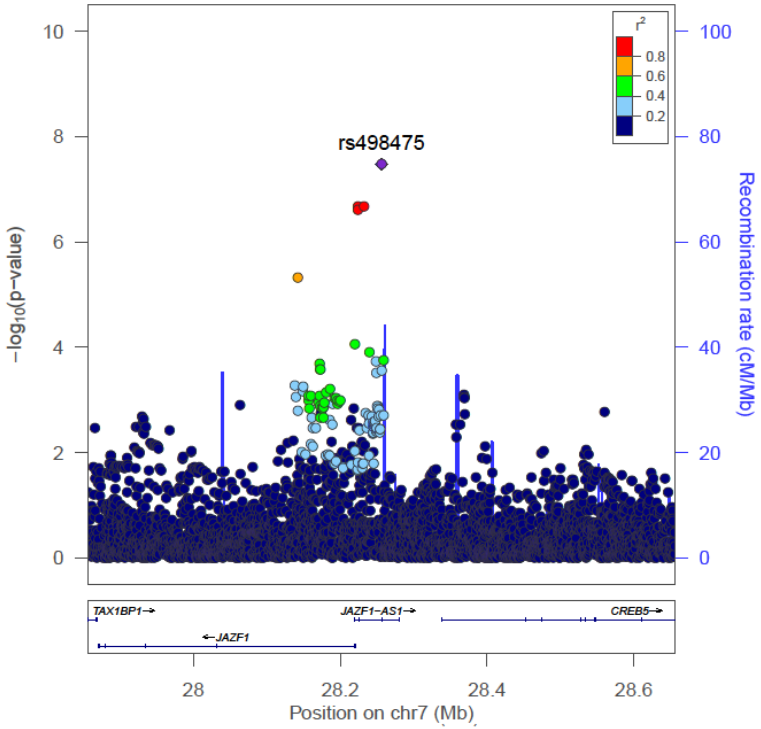

rs6532796
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
EIF4E
METAP1
LOC100507053
ADH7
MIR3684
ADH4
ADH6
ADH1B
C4orf17
ADH5
ADH1A
2 genes omitted
Position on chr4 (Mb)

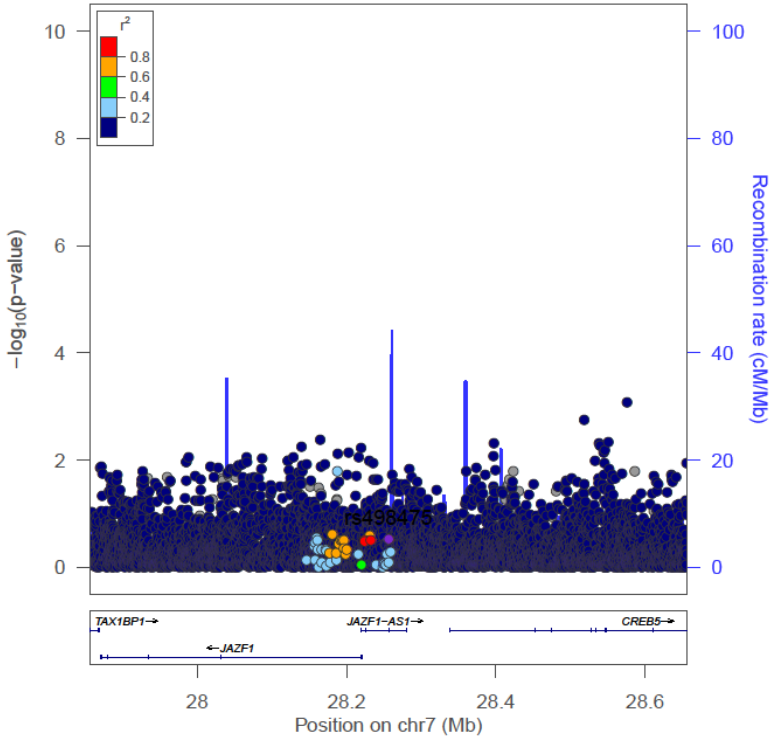

rs1149616
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
LOC100506127
LRRC32
TSKU
ACER3
CAPN5
C11orf30
GUCY2EP
B3GNT6
MYO7A
LOC101928837
OMP
Position on chr11 (Mb)


rs1149616
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
LOC100506127
LRRC32
TSKU
ACER3
CAPN5
C11orf30
GUCY2EP
B3GNT6
MYO7A
LOC101928837
OMP
Position on chr11 (Mb)

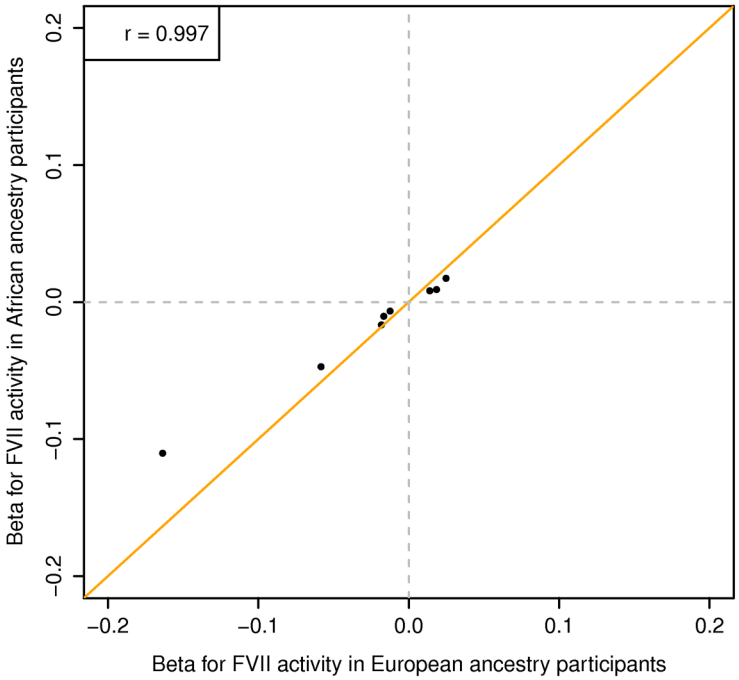

rs10761784
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
NRBF2
MIR1296
REEP3
JMJD1C
JMJD1C−AS1
65
65.2
65.4
65.6
Position on chr10 (Mb)


r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
NRBF2
MIR1296
REEP3
JMJD1C
JMJD1C−AS1
65
65.2
65.4
65.6
Position on chr10 (Mb)

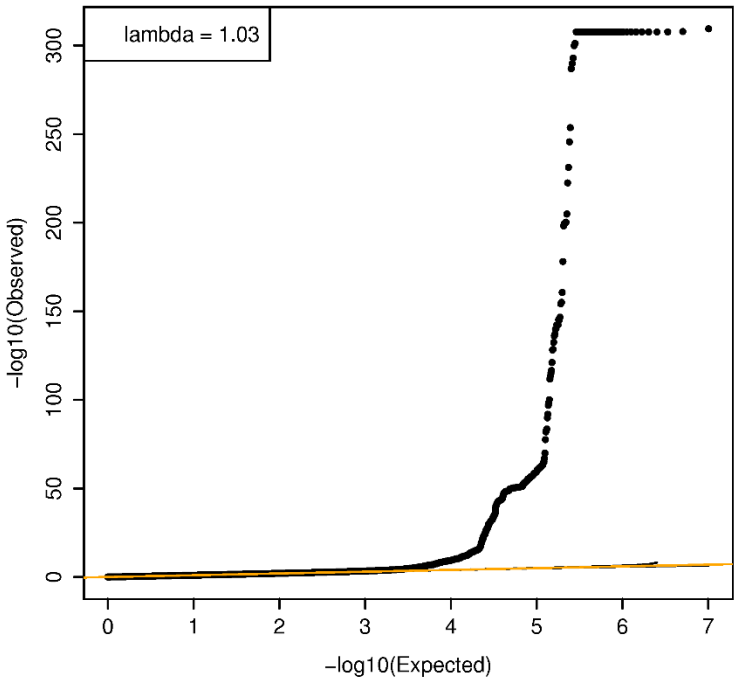

rs498475
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
TAX1BP1→
JAZF1−AS1→
CREB5→
←JAZF1
Position on chr7 (Mb)


r²
0.8
0.6
0.4
0.2
rs498475
−log10(p−value)
Recombination rate (cM/Mb)
TAX1BP1→
JAZF1−AS1→
CREB5→
←JAZF1
Position on chr7 (Mb)

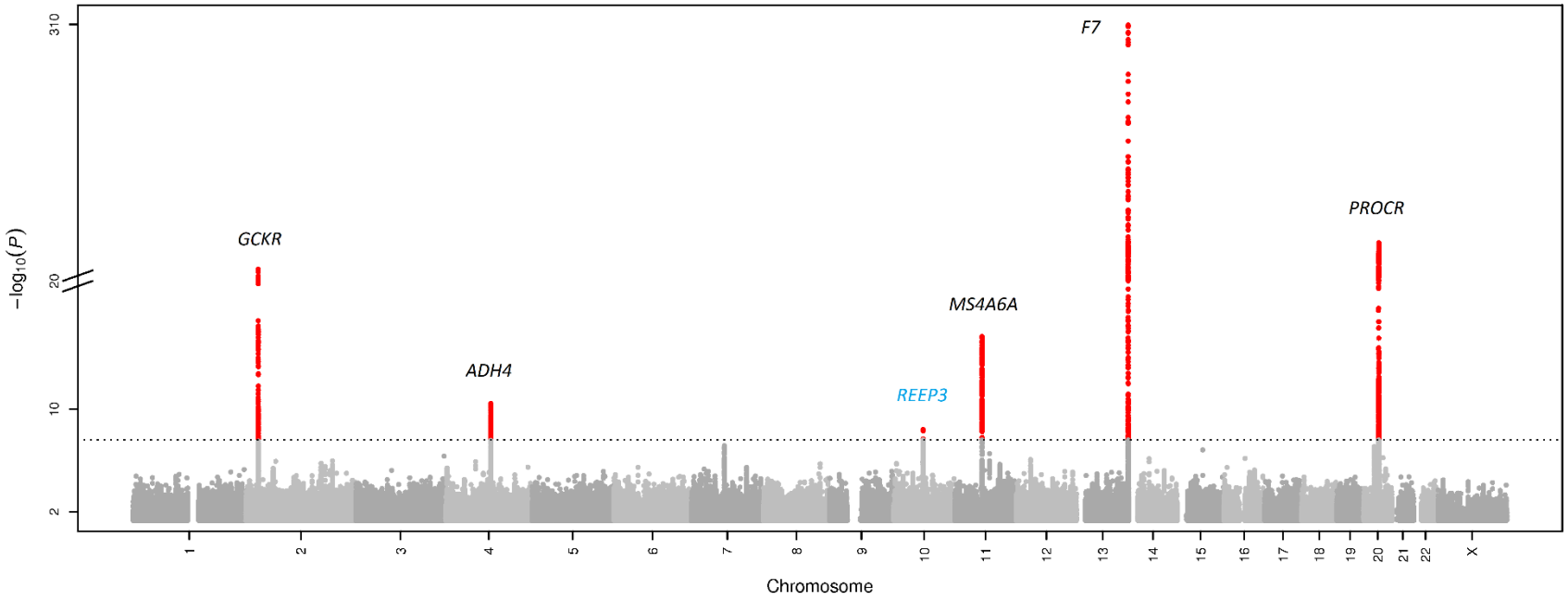
Supplementary Figure 9: Comparison of the betas for FVII activity between European-ancestry and African-ancestry participants.



Supplementary Figure 10: QQ plot of the trans-ancestry combined meta-analysis of FVII activity and antigen.

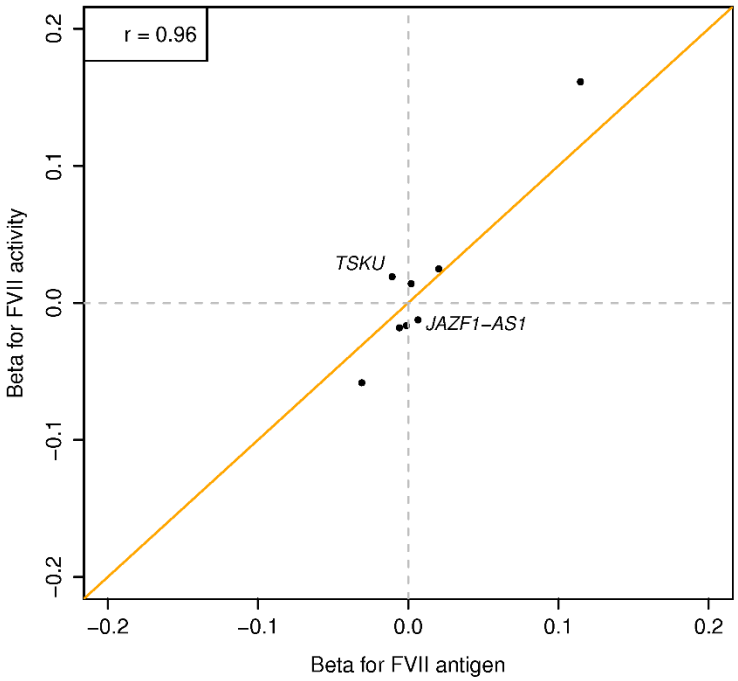


Supplementary Figure 11: Manhattan plot of the trans-ancestry combined meta-analysis of FVII activity and antigen.

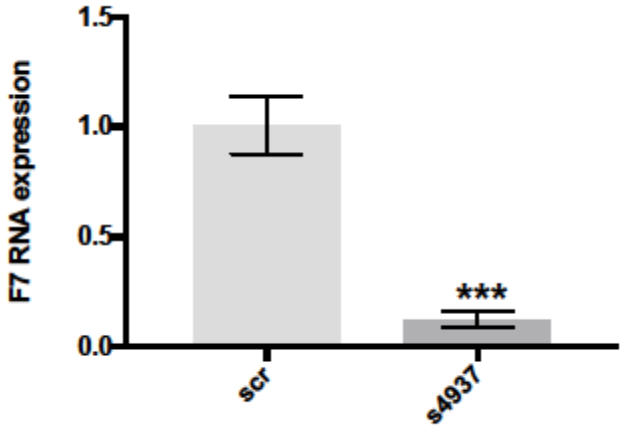


Genome-wide significant loci are annotated with the name of the closest gene. Gene names in blue indicate novel loci.

Supplementary Figure 12: Comparison of the betas for FVII activity and antigen in European-ancestry participants.



Supplementary Figure 13: Effect of silencing the *F7* gene on *F7* mRNA levels: a positive control.



INVENT consortium authors and affiliations

Philippe Amouyel,[1] Mariza de Andrade,[2] Saonli Basu,[3] Claudine Berr,[4] Jennifer A Brody,[5] Daniel I Chasman,[6] Jean-Francois Dartigues,[7] Aaron R Folsom,[8] Marine Germain,[9] Hugoline de Haan,[10] John Heit,[11] Jeanine Houwing-Duitermaat,[12] Christopher Kabrhel,[13] Peter Kraft,[14] Grégoire Legal,[15,16] Sara Lindström,[14] Ramin Monajemi,[12] Pierre-Emmanuel Morange,[17] Bruce M Psaty,[5,18] Pieter H Reitsma,[19] Paul M Ridker,[20] Lynda M Rose,[21] Frits R Rosendaal,[10] Noémie Saut,[17] Eline Slagboom,[22] , David Smadja[23] Nicholas L Smith,[18,24,25] Pierre Suchon,[17] Weihong Tang,[8] Kent D Taylor,[26] David-Alexandre Trégouët,[9] Christophe Tzourio,[27] Marieke CH de Visser,[19] Astrid van Hylckama Vlieg,[10] Lu-Chen Weng,[8] Kerri L Wiggins,[24]

1 Institut Pasteur de Lille, Université de Lille Nord de France, INSERM UMR_S 744, Lille, France; Centre Hospitalier Régional Universitaire de Lille, Lille, France.

2 Division of Biomedical Statistics and Informatics Mayo Clinic, Rochester, MN, USA.

3 University of Minnesota, Division of Biostatistics, Minneapolis, MN, USA.

4 INSERM Research Unit U1061 , University of Montpellier I , Montpellier, France.

5 Cardiovascular Health Research Unit, Departments of Medicine, Epidemiology, and Health Services, University of Washington, Seattle, WA, USA.

6 Division of Preventive Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA 02215, USA.

7 INSERM Research Center U897, University of Bordeaux, Bordeaux, France.

8 University of Minnesota, Division of Epidemiology and Community Health Minneapolis, MN, USA.

9 Institut National pour la Santé et la Recherche Médicale (INSERM), Unité Mixte de Recherche en Santé (UMR_S) 1166, F-75013, Paris, France; Sorbonne Universités, Université Pierre et Marie Curie (UPMC Univ Paris 06), UMR_S 1166, Team Genomics & Pathophysiology of Cardiovascular Diseases, F-75013, Paris, France; Institute for Cardiometabolism and Nutrition (ICAN), F-75013, Paris, France.

10 Department of Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, The Netherlands; Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands.

11 Division of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, USA.

12 Department of Medical Statistics and Bioinformatics, Leiden University Medical Center, 2300 RC Leiden, Netherlands.

[13] Department of Emergency Medicine, Massachusetts General Hospital, Channing Network Medicine, Harvard Medical School, Boston, MA 2114, USA.

[14] Program in Genetic Epidemiology and Statistical Genetics, Department of Epidemiology, Harvard School of Public Health, Boston, MA 2115, USA.

[15] Université de Brest, EA3878 and CIC1412, Brest, France.

[16] Ottawa Hospital Research Institute at the University of Ottawa, Ottawa, ON, Canada.

[17] Laboratory of Haematology, La Timone Hospital, F-13385, Marseille, France; INSERM, UMR_S 1062, Nutrition Obesity and Risk of Thrombosis,F-13385, Marseille, France; Aix-Marseille University, UMR_S 1062, Nutrition Obesity and Risk of Thrombosis, F-13385, Marseille, France.

[18] Group Health Research Institute, Group Health Cooperative, Seattle WA 98101, USA.

[19] Einthoven Laboratory for Experimental Vascular Medicine, Department of Thrombosis and Hemostasis, Leiden University Medical Center, Leiden,2300 RC, Netherlands.

[20] Division of Preventive Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA 02215, USA.

[21] Division of Preventive Medicine, Brigham and Women's Hospital, Boston, MA 02215, USA.

[22] Department of Molecular Epidemiology, Leiden University Medical Center, 2300 RC Leiden, Netherlands.

[23] Université Paris Descartes, Sorbonne Paris Cité, Paris, France; AP-HP, Hopital Européen Georges Pompidou, Service d'hématologie Biologique, Paris, France; INSERM, UMR_S 1140, Faculté de Pharmacie, Paris, France.

[24] Department of Epidemiology, University of Washington, Seattle WA 98195, USA.

[25] Seattle Epidemiologic Research and Information Center, VA Office of Research and Development, Seattle WA 98108, USA.

[26] Los Angeles Biomedical Research Institute and Department of Pediatrics, Harbor-UCLA Medical Center, Torrence CA 90502, USA.

[27] INSERM Research Center U897, University of Bordeaux, Bordeaux, France.

MEGASTROKE consortium authors and affiliations

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

168 A full list of members and affiliations appears at the end of the manuscript

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

Supplementary References

1. Winkler TW, Day FR, Croteau-Chonka DC, et al. Quality control and conduct of genome-wide association meta-analyses. *Nat Protoc*. 2014;9(5):1192-1212.
2. Willer CJ, Li Y, Abecasis GR. METAL: fast and efficient meta-analysis of genomewide association scans. *Bioinformatics*. 2010;26(17):2190-2191.
3. Cronin KR, Mangan TP, Carew JA. Upregulation of the coagulation factor VII gene during glucose deprivation is mediated by activating transcription factor 4. *PLoS One*. 2012;7(7):e40994.
4. Livak KJ, Schmittgen TD. Analysis of relative gene expression data using real-time quantitative PCR and the 2(-Delta Delta C(T)) Method. *Methods*. 2001;25(4):402-408.
5. Burgess S, Butterworth A, Thompson SG. Mendelian randomization analysis with multiple genetic variants using summarized data. *Genet Epidemiol*. 2013;37(7):658-665.
6. Fall T, Hagg S, Magi R, et al. The role of adiposity in cardiometabolic traits: a Mendelian randomization analysis. *PLoS Med*. 2013;10(6):e1001474.
7. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *Int J Epidemiol*. 2015;44(2):512-525.
8. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent Estimation in Mendelian Randomization with Some Invalid Instruments Using a Weighted Median Estimator. *Genet Epidemiol*. 2016;40(4):304-314.
9. Burgess S, Bowden J, Fall T, Ingelsson E, Thompson SG. Sensitivity Analyses for Robust Causal Inference from Mendelian Randomization Analyses with Multiple Genetic Variants. *Epidemiology*. 2017;28(1):30-42.
10. Greco MF, Minelli C, Sheehan NA, Thompson JR. Detecting pleiotropy in Mendelian randomisation studies with summary data and a continuous outcome. *Stat Med*. 2015;34(21):2926-2940.
11. Burgess S, Davies NM, Thompson SG. Bias due to participant overlap in two-sample Mendelian randomization. *Genet Epidemiol*. 2016;40(7):597-608.
12. 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(4):524-537.
13. Nikpay M, Goel A, Won HH, et al. A comprehensive 1,000 Genomes-based genome-wide association meta-analysis of coronary artery disease. *Nat Genet*. 2015;47(10):1121-1130.
14. Germain M, Chasman DI, de Haan H, et al. Meta-analysis of 65,734 individuals identifies TSPAN15 and SLC44A2 as two susceptibility loci for venous thromboembolism. *Am J Hum Genet*. 2015;96(4):532-542.
15. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. *Am J Epidemiol*. 1989;129(4):687-702.
16. Folsom AR, Wu KK, Rosamond WD, Sharrett AR, Chambless LE. Prospective study of hemostatic factors and incidence of coronary heart disease: the Atherosclerosis Risk in Communities (ARIC) Study. *Circulation*. 1997;96(4):1102-1108.
17. Chambless LE, McMahon R, Wu K, Folsom A, Finch A, Shen YL. Short-term intraindividual variability in hemostasis factors. The ARIC Study. Atherosclerosis Risk in Communities Intraindividual Variability Study. *Ann Epidemiol*. 1992;2(5):723-733.
18. Cushman M, Cornell ES, Howard PR, Bovill EG, Tracy RP. Laboratory methods and quality assurance in the Cardiovascular Health Study. *Clin Chem*. 1995;41(2):264-270.
19. Friedman GD, Cutter GR, Donahue RP, et al. CARDIA: study design, recruitment, and some characteristics of the examined subjects. *J Clin Epidemiol*. 1988;41(11):1105-1116.
20. Feinleib M, Kannel WB, Garrison RJ, McNamara PM, Castelli WP. The Framingham Offspring Study. Design and preliminary data. *Prev Med*. 1975;4(4):518-525.
21. Feng D, Tofler GH, Larson MG, et al. Factor VII gene polymorphism, factor VII levels, and prevalent cardiovascular disease: the Framingham Heart Study. *Arterioscler Thromb Vasc Biol*. 2000;20(2):593-600.

22. Blom JW, Doggen CJ, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. *JAMA*. 2005;293(6):715-722.
23. Hofman A, Brusselle GG, Darwish Murad S, et al. The Rotterdam Study: 2016 objectives and design update. *Eur J Epidemiol*. 2015;30(8):661-708.