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Background—Estimates of the heritability of plasma fibrinogen concentration, an established predictor of cardiovascular disease, range from 34% to 50%. Genetic variants so far identified by genome-wide association studies explain only a small proportion (<2%) of its variation.

Methods and Results—We conducted a meta-analysis of 28 genome-wide association studies including >90 000 subjects of European ancestry, the first genome-wide association meta-analysis of fibrinogen levels in 7 studies in blacks totaling 8289 samples, and a genome-wide association study in Hispanics totaling 1366 samples. Evaluation for association of single-nucleotide polymorphisms with clinical outcomes included a total of 40 695 cases and 85 582 controls for coronary artery disease, 4752 cases and 24 030 controls for stroke, and 3208 cases and 46 167 controls for venous thromboembolism. Overall, we identified 24 genome-wide significant ($P<5\times10^{-8}$) independent signals in 23 loci, including 15 novel associations, together accounting for 3.7% of plasma fibrinogen variation. Gene-set enrichment analysis highlighted key roles in fibrinogen regulation for the 3 structural fibrinogen genes and pathways related to inflammation, adipocytokines, and thyrotrophin-releasing hormone signaling. Whereas lead single-nucleotide polymorphisms in a few loci were significantly associated with coronary artery disease, the combined effect of all 24 fibrinogen-associated lead single-nucleotide polymorphisms was not significant for coronary artery disease, stroke, or venous thromboembolism.

Conclusions—We identify 23 robustly associated fibrinogen loci, 15 of which are new. Clinical outcome analysis of these loci does not support a causal relationship between circulating levels of fibrinogen and coronary artery disease, stroke, or venous thromboembolism. **(*Circulation*. 2013;128:1310-1324.)**

Key Words: cardiovascular diseases ■ fibrinogen ■ gene expression ■ genome-wide association study

Fibrinogen plays a major role in wound healing and thrombosis. Circulating levels of fibrinogen are upregulated in inflammatory conditions, consequently serving as an important marker of inflammation. Fibrinogen is a well-established predictor of cardiovascular disease outcomes such as myocardial infarction,[1,2] stroke,[3] and venous thromboembolism (VTE).[4,5]

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Clinical Perspective on p 1324

It is estimated that 34% (extended pedigrees study) to 44% (twins study) of the interindividual variation in fibrinogen levels is heritable,[6,7] indicating a substantial influence of genetics. Two recent meta-analyses of genome-wide association (GWA) studies, conducted in cohorts of European ancestry, identified several genetic variants affecting fibrinogen levels.[8,9] These variants account only for a small proportion (<2%) of plasma fibrinogen variation, suggesting that additional genetic variants with more modest effects may remain to be detected.

There is now increasing evidence that a substantial proportion of consequential genetic variation for many phenotypes is tagged by common single-nucleotide polymorphisms (SNPs),[10] although most of these SNPs cannot pass the restrictive genome-wide significance level of $P<5\times10^{-8}$ in a typical association study. To overcome this limitation, increased sample sizes are needed. We conducted a large meta-analysis of 28 GWA studies including >90 000 individuals of European ancestry, a 4-fold increase in sample size compared with previous meta-analyses.[8,9] We included data from an additional 8423 samples from the first GWA studies of blacks and 1447 Hispanic individuals to also explore whether ethnic differences exist in the genetic regulation of plasma fibrinogen concentration. To further elucidate possible biological mechanisms underlying fibrinogen regulation, we examined genome-wide significant loci in relation to expression levels of nearby genes and in gene pathway analyses. Finally, we examined whether fibrinogen-related genes affect risk of coronary artery disease (CAD), stroke, and VTE.[11–16]

Methods

Cohorts and Plasma Fibrinogen Measurements

Twenty-eight studies contributed to the discovery GWA study meta-analysis of European-ancestry individuals. Characteristics of all participating studies are provided in the Methods section and Table I in the online-only Data Supplement. In 7 cohorts with 33 745 individuals, plasma fibrinogen concentration was measured by an immunonephelometric method.[17] For the other 21 European-ancestry cohorts (57 578 individuals), plasma fibrinogen levels were determined by a functional method (based on the Clauss method).[18] Seven black cohorts with GWA data, including a total of 8423 individuals (5937 with Clauss and 2486 with immunonephelometric measures), and 1 cohort of 1447 Hispanics with immunonephelometric fibrinogen measures were also analyzed (Methods section and Table II in the online-only Data Supplement). Exclusion criteria applied in individual cohorts are provided in the Methods section in the online-only Data Supplement.

All studies were approved by the relevant research ethics committees.

Genotyping, Quality Control of Genotype Data, and Imputation

Commercial arrays were used for genome-wide genotyping in all cohorts, and quality-control filtering of SNP genotype data was generally performed in individual cohorts by call rate, minor allele frequency, and deviation from Hardy-Weinberg equilibrium (Methods section and Tables III and IV in the online-only Data Supplement). Approximately 2.5 million autosomal SNPs were imputed cohorts with the HapMap II white (CEU; Center d'Etude du Polymorphisme Humain) sample as reference panel for the European-ancestry cohorts, a combined CEU+YRI reference panel for the black cohorts, and a combined CEU+YRI+CHB+JPT reference panel for the Hispanic sample (CEU, European Ancestry from Centre d'Etude du Polymorphisme Humain; YRI, Yoruba in Ibadan, Nigeria; CHB, Han Chinese in Beijing, China; JPT, Japanese in Tokyo, Japan). MACH or IMPUTE software[19–21] was used in the imputation (Tables III and IV in the online-only Data Supplement).

Meta-Analysis of GWA Studies

Values of plasma fibrinogen concentration were natural logarithm–transformed before analysis. Association analyses were conducted in each cohort of measured and imputed autosomal SNP allele dosage with fibrinogen values with a linear regression model assuming additive genetic effects adjusted for age and sex. Additional adjustments for principal components or multidimensional scaling, country, or center were made when necessary by individual cohorts to account for population stratification (see Methods in the online-only Data Supplement). Relatedness was accounted for in family studies by applying linear mixed-effect models. Genotype-phenotype association results from the 28 cohorts were then meta-analyzed by use of an inverse-variance model with fixed effects in METAL (http://www.sph.umich.edu/csg/abecasis/Metal/index.html).[22]

To identify additional independent association signals in the genome-wide significant loci, conditional GWA analysis was performed as described in the Methods in the online-only Data Supplement. Overall, we selected for further analysis only SNPs from genome-wide significantly associated loci, including the lead SNP for each locus in the initial meta-analysis, along with 1 additional lead SNP representing a new clear signal identified in the conditional analysis.

To identify genes that regulate fibrinogen levels in other ethnic groups, we conducted a separate GWA meta-analysis using 7 separate GWA scans in blacks totaling 8289 samples and a single GWA analysis in a cohort of Hispanics totaling 1366 samples.

The threshold of genome-wide significance was set at $P=5.0\times10^{-8}$ for the primary analyses of GWA with plasma fibrinogen levels and their heterogeneity measures, as well as for the conditional meta-analysis. We used Bonferroni correction for the exploration of the 24 lead-SNPs in the black and Hispanic samples and for the lookups in clinical outcomes ($P<0.002$).

Genetic Risk Score

A genetic risk score was computed using data from 88 251 European-ancestry individuals to model the increase in fibrinogen levels according to the number of fibrinogen-raising alleles for each lead SNP. Methods are further described in Methods in the online-only Data Supplement.

Multivariable-Adjusted Model

We reanalyzed the association with plasma fibrinogen concentration of the lead SNPs using a linear model with further adjustment for body mass index and smoking, in addition to sex and age and the extra covariates used in each cohort in the discovery analyses. Association results from all cohorts were then meta-analyzed with the inverse-variance–weighted fixed-effects meta-analysis implemented in METAL.

Pathway Analyses

MAGENTA and GRAIL[23,24] were used to assess putative relationships between the lead SNPs and to infer genes and pathways underlying SNP associations with plasma fibrinogen levels. MAGENTA version 2 analysis was performed as described,[24] including gene sets from Gene Ontology, KEGG, PANTHER, and Ingenuity downloaded in June 2011 (http://www.broadinstitute.org/mpg/magenta/). Gene-set statistics were determined for an empirically derived 95th percentile threshold of gene-wide adjusted P values. Only gene sets meeting a false discovery rate <0.05 were considered for further inspection. Candidate SNPs were identified in the MAGENTA analysis as SNPs with nominal locus-wide corrected P values (corrected $P<0.05$) mapping to genes in gene sets that met the false discovery rate of <0.05. GRAIL analysis was performed as described (http://www.broadinstitute.org/mpg/grail/) using the pair-wise similarity metric compiled from the literature in December 2006 to limit bias, as recommended.[25]

Association With Gene Expression in Human Liver

The lead SNPs and their perfect proxies ($r^2=1$) were further analyzed with respect to association with expression levels of nearby genes (located within ±200 kb of the SNP).

Global gene expression data from human liver were obtained from the Advanced Study of Aortic Pathology (ASAP).[26] Details of the ASAP biobank and the methods for gene expression analysis and genotyping are provided in the Methods section in the online-only Data Supplement. Further queries were made against significant results from 4 other liver eQTL analyses with methods that were published previously.[27–30]

Associations With Clinical Outcomes

We examined associations of the 24 lead SNPs with prevalent CAD, stroke, and VTE. Genotype-CAD association results for the selected SNPs were obtained from the Coronary Artery Disease Genome-wide Replication and Meta-analysis (CARDIoGRAM) and Europe South Asia Coronary Artery Disease Genetics (C4D) consortia, including a total of 40 695 CAD cases and 85 582 controls. Lead SNP associations with stroke were explored in data generated from 4 large cohorts composing the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium, including 1544 incident strokes (1164 ischemic strokes) developed over an average follow-up of 11 years, and 18 058 controls and in data generated from 4 cohorts making up the Welcome Trust Case Control Consortium (WTCCC), including 3548 cases with ischemic stroke and 5972 controls. The SNP genotype–VTE association results were generated in 3208 VTE cases and 46 167 controls from the French Marseille Thrombosis Association Study (MARTHA) and the CHARGE studies. Definitions of the disease phenotypes adopted in each individual study are detailed elsewhere.[11–15,31] Each of the 24 fibrinogen-associated SNPs was tested for association with each of the clinical outcomes by logistic regression with adjustment for age and sex. The log odds ratios and their standard errors for each SNP were standardized for direction and magnitude to correspond to the change in allele dosage that accounted

for a 3.1% relative increase in circulating fibrinogen level (fibrinogen effect associated with the FGB variant rs1800789). These harmonized effect estimates were then pooled by fixed-effects (inverse-variance–weighted) meta-analysis (stroke and VTE) or by random-effects meta-analysis (for CAD owing to significant heterogeneity in both the direction and magnitude of the harmonized log odds ratios).

Results

Meta-Analysis in European-Ancestry Samples

Meta-analysis was performed for 2 515 567 SNPs on individual GWA study results generated in 28 European-ancestry cohorts including a total of 91 323 individuals. A total of 985 SNPs, located in 23 chromosomal loci, passed the genome-wide significance threshold of $P=5.0\times10^{-8}$ (Figure 1). Among the 23 loci (designated according to nearest gene), 8 (*IL6R, NLRP3, IL1RN, CPS1, PCCB, FGB, IRF1*, and *CD300LF*) represent replications of previously identified fibrinogen-associated loci, and 15 are novel associations (*JMJD1C, LEPR, PSMG1, CHD9, SPPL2A, PLEC1, FARP2, MS4A6A, TOMM7/IL6, ACTN1, HGFAC, IL1R1, DIP2B,* and *SHANK3/CPT1B*). More information about these genes is provided in Table V in the online-only Data Supplement. Further information about the lead SNPs and their association with fibrinogen levels is given in Table 1.

To search for further independent association signals within the 23 loci, we repeated the individual GWA analyses, conditioning on the 23 lead SNPs. This analysis revealed 2 genome-wide significant SNPs located in the *FGA* gene (rs2070016; $P=3.9\times10^{-8}$) and on chromosome 5 (rs11242111; $P=1.60\times10^{-21}$; Figure I in the online-only Data Supplement). Accordingly, rs11242111 was added to the list of independent lead SNPs selected for further analyses (Table 1). rs2070016, in *FGA*, showed evidence of correlation with the lead SNP rs1800789 in *FGB* ($r^2=0.364$ according to 1000 Genomes Map Pilot 1); hence, we did not select this SNP for further analyses. After adjustment for the number of tests, none of the 24 lead SNPs showed significant heterogeneity across European-ancestry cohorts. Regional association plots for the 24 loci are shown in Figure II in the online-only Data Supplement.

Further adjustment for body mass index and smoking, which together explained 5.3% of the variation in plasma fibrinogen level among 81 511 individuals from the European-ancestry meta-analysis, resulted in stronger associations for most of the lead SNPs but no new discoveries (Table 1).

Meta-Analysis and Validation of European-Ancestry Loci in the Black and Hispanic Samples

The Manhattan and QQ plots ($\lambda=1.012$) reporting the results for the black samples are shown in Figure III in the online-only Data Supplement. Only the *FGA/FGB/FGG* locus on chromosome 4 reached genome-wide significance in the black cohort meta-analysis, with the most strongly associated SNP being rs4463047 ($P=4.63\times10^{-10}$) at 12 790 bp from rs1800789 ($P=4.02\times10^{-7}$). No single SNP attained genome-wide significance in the Hispanic samples (Figure III in the online-only Data Supplement).

We tested the association of the 24 European-ancestry lead SNPs in the black cohort meta-analysis (Table VI in the online-only Data Supplement). After correction for 24 statistical tests (P value threshold <0.002), only the 2 lead SNPs, rs1800798 (*FGB*) and rs6734238 (*ILRN*), passed the significant threshold. However, 5 other lead SNPs, located in the *IRF1*, *IL6R, CHD9, JMJD1C*, and *MS4A6A* loci, were associated at $P<0.05$, with consistent directions of effect in both populations (Table VII in the online-only Data Supplement). Furthermore, at 20 of the 24 lead SNPs, the direction of the β estimate was the same in the European and black samples ($P=0.00077$, sign test).

In the Hispanic samples, 3 European-ancestry lead SNPs, in *FGB* (rs1800798), *IL6R* (rs6734238), and *CHD9* (rs7204230), passed the significance threshold (24 SNPs; $P<0.002$) for association, and 3 additional lead SNPs were associated at a nominally significant threshold of $P<0.05$, with consistent directions of effect in both populations (Table VI in the online-only Data Supplement). In addition, the direction of the β estimate at 20 of the 24 lead SNPs was the same in the European and Hispanic samples ($P=0.00077$, sign test).

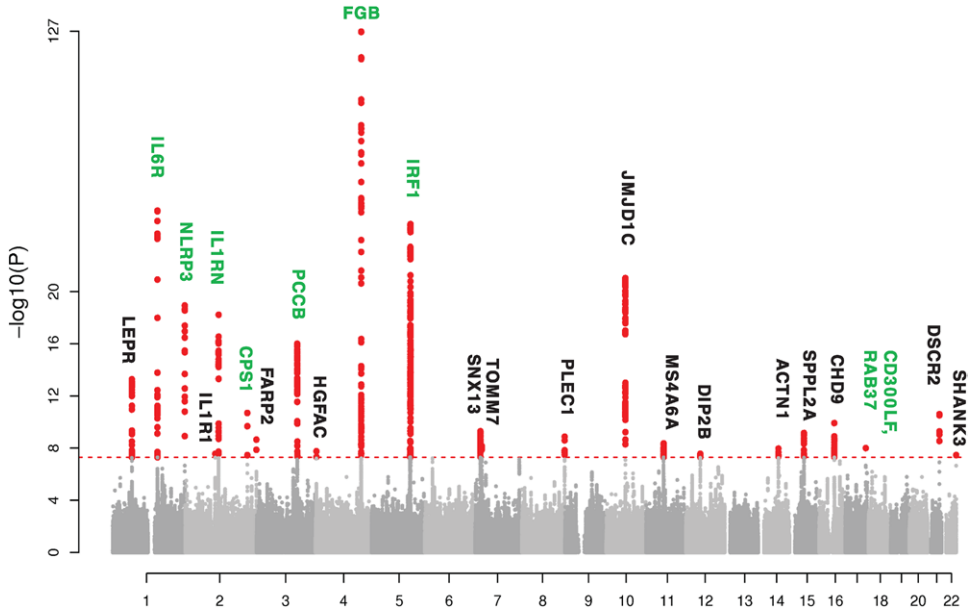

Figure 1. Manhattan plot of the association *P* values for plasma fibrinogen concentration in the meta-analysis performed on European-ancestry samples. Analyzed single-nucleotide polymorphisms are plotted on the *x* axis ordered by chromosomal position. The *y* axis plots the logarithm of the *P* values. Gene loci labeled in green were previously known; gene loci labeled in black are novel discoveries in this meta-analysis. The dotted line indicates the threshold for genome-wide significance ($P=5\times10^{-8}$).

Table 1. Details of the 24 Lead SNPs and Association β and *P* Values for the Original Meta-Analysis Performed With the European-Ancestry Cohorts (Adjusted for Age and Sex) Together With the Corresponding Values Obtained in the Same Cohorts With Further Adjustments for BMI and Smoking

								Original Meta-Analysis					Further Adjustment for BMI and Smoking			
SNP	Band	Position	Closest Gene	In Gene	Distance, bp	A1	A2	Frequency	β	SE	*P*	*P* Heterogeneity	n	β	SE	*P*
rs1938492	1p31.3	65890417	*LEPR*		14653	A	C	0.62	0.008	0.001	5.28×10^{-14}	0.438	89330	0.008	0.001	1.12×10^{-15}
rs4129267	1q21.3	152692888	*IL6R*	Intron		T	C	0.39	−0.011	0.001	5.97×10^{-27}	0.724	91419	−0.011	0.001	4.57×10^{-30}
rs10157379	1q44	245672222	*NLRP3*	Intron		T	C	0.62	0.010	0.001	1.15×10^{-19}	0.416	86730	0.010	0.001	3.12×10^{-22}
rs12712127	2q11.2	102093093	*IL1R1*/IL1R2*		43740	A	G	0.41	0.006	0.001	2.72×10^{-08}	0.097	91406	0.006	0.001	3.66×10^{-10}
rs6734238	2q13	113557501	*IL1F10*/IL1RN*		7603	A	G	0.58	−0.009	0.001	5.77×10^{-19}	0.487	91426	−0.010	0.001	6.66×10^{-22}
rs715	2q34	211251300	*CPS1*	Exon		T	C	0.68	0.009	0.001	1.98×10^{-11}	0.153	74715	0.011	0.001	3.95×10^{-19}
rs1476698	2q37.3	241945122	*FARP2*	Intron		A	G	0.65	0.007	0.001	2.24×10^{-09}	0.420	91419	0.007	0.001	1.44×10^{-10}
rs1154988	3q22.3	137407881	*MSL2*/PCCB*		10503	A	T	0.78	−0.010	0.001	9.64×10^{-17}	0.154	91416	−0.012	0.001	2.98×10^{-24}
rs16844401	4p16.2	3419450	*HGFAC*/ LRPAP1*	Exon		A	G	0.08	0.015	0.003	1.74×10^{-08}	0.077	74680	0.014	0.002	7.07×10^{-09}
rs1800789	4q32.1	155702193	*FGB*		1388	A	G	0.21	0.031	0.001	1.68×10^{-127}	0.001	91301	0.031	0.001	1.94×10^{-140}
rs11242111	5q31.1	131783957	*C5orf56*/IRF1*	Intron		A	G	0.05	0.023	0.002	1.60×10^{-21}	0.353	91423	0.024	0.002	1.14×10^{-23}
rs2106854	5q31.1	131797073	*C5orf56/IRF1*	Intron		T	C	0.21	−0.019	0.001	1.72×10^{-48}	0.082	91406	−0.019	0.001	1.93×10^{-54}
rs10226084	7p21.1	17964137	*SN×13*/ PRPS1L1*		17481	T	C	0.52	−0.007	0.001	5.05×10^{-10}	0.441	91403	−0.007	0.001	6.68×10^{-11}
rs2286503	7p15.3	22823131	*TOMM7*	Intron		T	C	0.36	−0.006	0.001	6.88×10^{-09}	0.845	91413	−0.005	0.001	2.26×10^{-07}
rs7464572	8q24.3	145093155	*PLEC1*	Intron		C	G	0.60	−0.007	0.001	1.33×10^{-09}	0.123	82730	−0.006	0.001	7.41×10^{-09}
rs7896783	10q21.3	64832159	*JMJD1C*	Intron		A	G	0.48	−0.010	0.001	8.90×10^{-22}	0.754	91412	−0.009	0.001	4.43×10^{-20}
rs1019670	11q12.1	59697175	*MS4A6A*	Exon		A	T	0.36	−0.007	0.001	4.37×10^{-09}	0.696	9018	−0.006	0.001	8.09×10^{-08}
rs7968440	12q13.13	49421008	*DIP2B*	Intron		A	G	0.64	0.006	0.001	2.74×10^{-08}	0.360	91405	0.006	0.001	1.37×10^{-09}
rs434943	14q24.1	68383812	*ACTN1*		26780	A	G	0.31	0.007	0.001	1.08×10^{-08}	0.014	86189	0.008	0.001	1.73×10^{-10}
rs12915708	15q21.2	48835894	*SPPL2A*	Intron		C	G	0.30	−0.007	0.001	6.87×10^{-10}	0.625	91434	−0.007	0.001	3.45×10^{-11}
rs7204230	16q12.2	51749832	*CHD9*	Intron		T	C	0.70	0.008	0.001	1.18×10^{-10}	0.493	82835	0.008	0.001	6.40×10^{-12}
rs10512597	17q25.1	70211428	*CD300LF*	Intron		T	C	0.18	−0.008	0.001	9.92×10^{-09}	0.108	86737	−0.009	0.001	4.23×10^{-11}
rs4817986	21q22.2	39387382	*PSMG1*		81871	T	G	0.28	−0.008	0.001	2.46×10^{-11}	0.539	85293	−0.009	0.001	3.39×10^{-14}
rs6010044	22q13.33	49448804	*SHANK3*/ARSA*		11131	A	C	0.80	−0.008	0.001	3.41×10^{-08}	0.582	89138	−0.008	0.001	7.07×10^{-09}

β Values and frequencies refer to A1. A1 indicates allele 1; A2, allele 2; BMI, body mass index; and SNP, single-nucleotide polymorphism.
*The closest gene.

Genetic Risk Score and Proportion of Variance Explained

Figure 2 presents the average fibrinogen values across categories of the genetic risk score. The mean percentage of residual variance (after adjustment for age and sex) explained by 24 lead SNPs was 3.7% in all European-ancestry cohorts (range, 1.4%–7.6% in individual cohorts). The heritability of plasma fibrinogen concentration estimated from the family cohorts within this study (Netherlands Twin Registry, CROATIA-Vis, CROATIA-Korcula, ORCADES, FHS, and SardiNIA) ranged from 15% to 51% (mean±SD, 31±15%; see Results in the online-only Data Supplement). The proportion of variance in fibrinogen levels explained by common SNPs (minor allele frequency >0.01) was calculated in 1 of our participant cohorts (WGHS, n=21,336) using the method proposed by Yang et al.[10] Results showed that 16% (SE=0.017) of the variance in fibrinogen levels was explained by common SNPs.

Finally, the genetic risk score was strongly associated with levels of fibrinogen in the combined black cohorts (P=1.5×10^{-8}) and the Hispanic cohort (P=3.8×10^{-15}).

Pathway and Expression QTL Analyses

We performed additional in silico pathway analyses using GRAIL and MAGENTA (Table VIII in the online-only Data Supplement). The GRAIL results identified 6 SNPs (rs6734238, rs12712127, rs8192284, rs10157379, rs1938492, and rs6831256) that were located within or near genes (*IL1RN, IL1R1, IL6R, NLRP3, LEPR,* and *LRPAP1*) with significantly related function among all of the genes in the vicinity of the 24 lead SNPs, suggesting that these genes should be prioritized as the most plausible functional candidate genes within the associated loci. Gene-set enrichment analysis using MAGENTA (based on the whole genome-wide genetic data set) identified several gene sets and pathways that were enriched in the analysis (Table IX in the online-only Data Supplement). Apart from the 3 structural genes, the most represented pathways were related to inflammation (acute-phase response, interleukin signaling), adipocytokine signaling, and thyrotrophin-releasing hormone signaling. According to these results, several genes (*LEPR, IL6R, IL1R, IL1F10/IL1F5/IL1F8/IL1RN, FGA/FGB, ACTN1,* and *CPT1B*) were prioritized as plausible candidate genes within our 23 genomic regions. A comprehensive SNP list, which includes both the 24 lead SNPs and the SNPs selected by either GRAIL or MAGENTA on the whole genome-wide genetic data set, is given in Table IX in the online-only Data Supplement.

We then interrogated the 24 lead SNPs and their perfect proxies with respect to their associations with expression levels of nearby genes (located within ±200 kb of the lead SNP) in 5 human liver databases. Expression levels of *LEPR*, *PCCB*, *MSL2L1*, *NGFRAP1*, *FGB*, and *TOMM7* were significantly associated with allelic differences in 1 of the 24 lead SNPs (results are shown in Table VIII in the online-only Data Supplement). Finally, to assess the functional role of SNPs in fibrinogen genes, we also studied the eQTL associations of all SNPs within 100 kb of the fibrinogen gene cluster. The highest association with expression of fibrinogen transcripts within the fibrinogen cluster was found for SNP rs4220 (P=1.38×10^{-20}), causing a missense mutation in the FGB gene. All positive associations with fibrinogen transcripts are shown in Table X in the online-only Data Supplement.

Associations With Clinical Outcomes

After correction for multiple testing (P<0.002 threshold), rs4129267 located in the *IL6R* locus, rs6734238 in the *IL1F10/IL1RN* locus, and rs1154988 in the *PCCB* locus were found to be significantly associated with CAD; however, the directions of the effects on CAD and fibrinogen levels were consistent only for rs4129267 in the *IL6R* locus. The pooled association for the 24 lead SNPs with CAD was not significant (odds ratio, 1.00; 95% confidence interval, 0.97–1.03). None of the fibrinogen-associated lead SNPs were significantly associated with stroke or VTE after correction for multiple testing. The pooled results

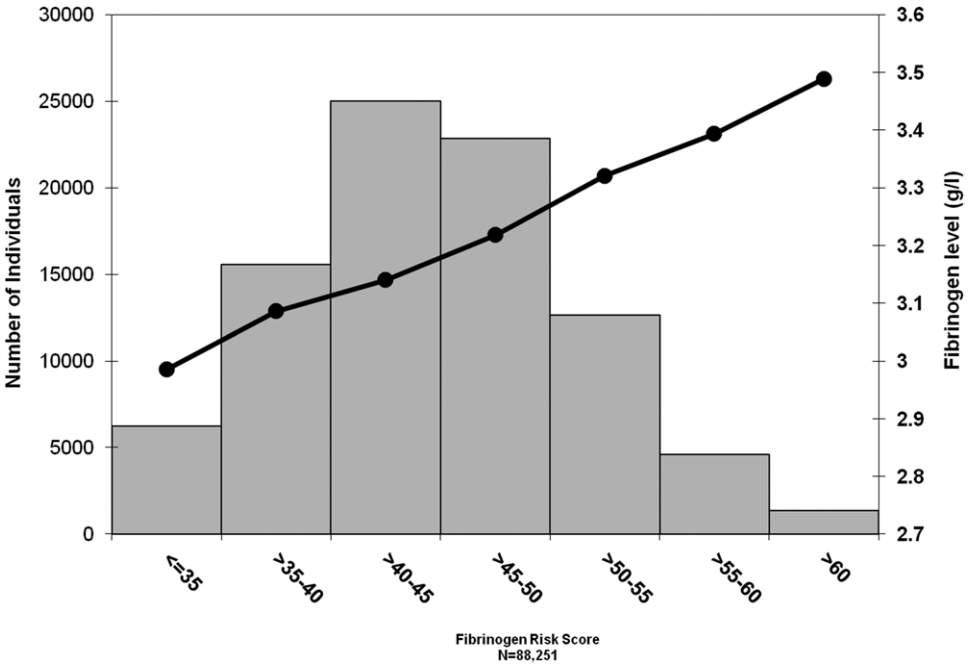

Figure 2. Mean values for plasma fibrinogen concentration in grams per liter (right *y* axis) plotted by categories of fibrinogen-associated single-nucleotide polymorphism score (*x* axis), represented by the black dots. Number of individuals in each category is represented by the gray bars (left *y* axis).

were suggestive for stroke (odds ratio, 1.03; 95% confidence interval, 1.00–1.07) but not for VTE (odds ratio, 0.96; 95% confidence interval, 0.92–1.01; Table 2). Additional results from the WTCCC stroke consortium, generated according to clinical subphenotypes, are shown in Table XI in the online-only Data Supplement. No significant associations with stroke subphenotypes were found after correction for multiple hypothesis testing.

Discussion

The present study represents the largest effort to identify novel gene loci regulating plasma fibrinogen levels. Overall, we identified 24 independent genome-wide significant SNPs in 23 loci, including 15 loci with newly discovered fibrinogen associations. Using our genetic findings, we found no evidence for a causal role of fibrinogen in CAD, stroke, and VTE.

The proportion of variance in plasma fibrinogen level accounted for by all 24 fibrinogen-associated lead SNPs increased to 3.7% (a detailed description of the novel nearby candidate genes is presented in Table V in the online-only Data Supplement). These results support the notion that regulation of plasma fibrinogen levels is driven by multiple genes, each having a modest effect on the phenotype. It is likely that even more loci with smaller effects remain to be discovered.

Relevance of the Fibrinogen-Related Loci in Non–European-Ancestry Individuals

We performed the first meta-analysis of GWA studies on black samples, and we provide evidence for a significant association of a weighted SNP score based on the 24 lead SNPs from the European-ancestry meta-analysis with levels of fibrinogen in both blacks (P=1.5×10^{-8}) and Hispanics (P=3.8×10^{-15}). Thus, despite differences in allele frequencies or differences in the relative impact of covariates associated with fibrinogen among populations, loci identified in European-ancestry samples collectively contribute to the regulation of plasma fibrinogen in black and Hispanic populations. Twenty of 24 lead SNPs showed the same direction of effect when the European sample was compared with either the black or the Hispanic sample. The substantially smaller size of the black and Hispanic cohorts compared with the total sample with European ancestry restricted available power and may have limited the significance of the candidate SNP associations in these populations (see Power Calculations in the Methods section of the online-only Data Supplement).

Pathways Involved in Regulation of Plasma Fibrinogen Level

It is interesting to note that several of the genome-wide significant loci identified in the present study harbor inflammatory genes, a remarkable set of which relate to the interleukin-1 pathway, indicating the importance of this pathway in the regulation of fibrinogen. Most of these inflammatory genes have previously been reported in relation to other inflammation-related phenotypes and diseases. For example, *IL6R, NLRP3, IL1RN/ILF10,* and *IRF1* were recently identified in a GWA study meta-analysis of C-reactive protein conducted on European samples.[32] Both fibrinogen and C-reactive protein are acute-phase proteins with levels that are largely influenced by inflammatory triggers. It is thus not surprising that they are both partly regulated by a common group of genes that are implicated in the immune response. These results are also consistent with our in silico gene-set enrichment analyses, which showed that inflammation-related pathways, including acute-phase response and interleukin signaling, were most enriched for fibrinogen-associated genes. In this regard, interesting new plausible candidate genes could be discerned within the newly identified loci, including *IL6*, located in the *TOMM7-IL6* locus on chromosome 7, and *IL1R1*, located in the cytokine receptor gene cluster on chromosome 2.

Our gene-set enrichment analysis also highlighted genes regulating fat metabolism as important in the control of plasma fibrinogen concentration, as indicated by the strong representation of adipocytokine signaling genes. This is consistent with our observation that smoking and body mass index contributed ≈5.3% of the plasma fibrinogen variation and with data from the Fibrinogen Studies Collaboration, reporting that 7% of the variation in plasma fibrinogen concentration was accounted for by smoking, body mass index, and high-density lipoprotein cholesterol.[33]

Relations to Cardiovascular Disease

Although plasma fibrinogen concentration has been identified as a predictor of incident CAD events,[1,34] it has been argued that increased plasma fibrinogen levels in population subgroups at increased CAD risk could be attributable to other mechanisms, including existing atherosclerosis, which might induce a proinflammatory state with a subsequent increase in acute-phase reactants such as fibrinogen or C-reactive protein. Given the associations of fibrinogen levels with other established CAD risk factors (eg, smoking and body mass index), it remains uncertain whether these other factors may confound the association of fibrinogen with disease risk. Prior studies that assessed the causality of the association between plasma fibrinogen concentration and risk of CAD by mendelian randomization using 2 common SNPs located in the promoter region of the FGB gene found no significant association of this locus with CAD, concluding that the relationship was noncausal.[35,36] One limitation of these studies is that this single locus might have biologically unusual effects on measured fibrinogen levels.[35,36] Our analysis of 23 other fibrinogen-associated SNPs offers a broader perspective and thus a more robust and generalizable evaluation of the causal relationship between fibrinogen and cardiovascular events. A further strength of our study is that we present estimates of the effects on risk of clinical outcomes individually for each SNP and globally for all SNPs combined.

Our results do not support a causal relationship between plasma fibrinogen level and CAD. In fact, consistent with the negative results from previous mendelian randomization, the lead SNP located in the *FGB* gene showed no association with CAD. Whereas SNPs rs4129267, rs6734238, and rs1154988, located in the *IL6R, IL1F10/IL1RN,* and *PCCB* loci, respectively, were significantly associated with CAD in CARDIoGRAM and C4D, the direction of effect was consistent only for the SNP located in the *IL6R* locus (ie, the allele that lowered the plasma fibrinogen concentration also lowered CAD risk). Furthermore, the global effect of all 24 fibrinogen-associated SNPs was not associated with CAD risk (odds ratio, 1.00; 95% confidence interval, 0.97–1.03).

Table 2. Association Results for the 24 Lead SNPs With Coronary Artery Disease, Stroke, and Venous Thromboembolism

						CAD*			Stroke†			VTE‡		
SNP	Band	A1	A2	Freq1	Closest Gene	OR	SE	*P*	OR	SE	*P*	OR	SE	*P*
rs1938492	1p31.3	A	C	0.597	*LEPR*	0.98	0.011	0.038	0.98	0.025	0.405	1.00	0.032	0.892
rs4129267	1q21.3	T	C	0.378	*IL6R*	0.96	0.011	1.73×10^{-05}	0.97	0.024	0.212	1.01	0.032	0.838
rs10157379	1q44	T	C	0.603	*NLRP3*	1.00	0.011	0.883	1.02	0.025	0.329	1.04	0.032	0.204
rs12712127	2q11.2	A	G	0.451	*IL1R1/ IL1R2*	1.00	0.011	0.985	0.98	0.025	0.423	1.00	0.032	0.909
rs6734238	2q13	A	G	0.589	*IL1F10/ IL1RN*	1.04	0.011	9.44×10^{-05}	1.00	0.025	0.974	1.01	0.032	0.702
rs715	2q34	T	C	0.685	*CPS1*	1.03	0.013	0.011	1.01	0.029	0.822	0.91	0.054	0.081
rs1476698	2q37.3	A	G	0.615	*FARP2*	1.00	0.011	0.873	1.02	0.026	0.388	1.06	0.033	0.089
rs1154988	3q22.3	A	T	0.778	*MSL2/ PCCB*	1.04	0.013	0.002	0.95	0.029	0.100	0.95	0.037	0.186
rs16844401	4p16.2	A	G	0.089	*HGFAC/ LRPAP1*	1.03	0.024	0.263	1.01	0.052	0.848	0.92	0.082	0.285
rs1800789	4q32.1	A	G	0.2	*FGB*	1.00	0.014	0.939	0.99	0.031	0.828	0.89	0.04	0.004
rs11242111	5q31.1	A	G	0.101	*C5orf56/ IRF1*	0.95	0.024	0.02	1.09	0.057	0.145	0.97	0.079	0.72
rs2106854	5q31.1	T	C	0.267	*C5orf56/ IRF1*	0.98	0.012	0.068	0.99	0.030	0.671	1.05	0.039	0.191
rs2286503	7p15.3	T	C	0.397	*TOMM7*	0.97	0.011	0.005	0.97	0.025	0.173	0.99	0.033	0.641
rs10226084	7p21.1	T	C	0.543	*SN×13/ PRPS1L1*	1.01	0.011	0.497	1.02	0.024	0.379	0.98	0.032	0.614
rs7464572	8q24.3	C	G	0.624	*PLEC1*	1.02	0.011	0.03	0.98	0.028	0.526	0.99	0.041	0.724
rs7896783	10q21.3	A	G	0.508	*JMJD1C*	1.02	0.01	0.14	0.98	0.024	0.449	0.98	0.032	0.512
rs1019670	11q12.1	A	T	0.381	*MS4A6A*	1.01	0.012	0.311	0.96	0.028	0.173	1.02	0.036	0.597
rs7968440	12q13.13	A	G	0.69	*DIP2B*	1.00	0.012	0.825	1.00	0.025	0.989	1.01	0.033	0.819
rs434943	14q24.1	A	G	0.305	*ACTN1*	1.01	0.013	0.314	1.03	0.027	0.256	0.97	0.035	0.366
rs12915708	15q21.2	C	G	0.3	*SPPL2A*	0.98	0.012	0.063	1.00	0.027	0.889	1.00	0.034	0.915
rs7204230	16q12.2	T	C	0.682	*CHD9*	0.99	0.012	0.419	1.01	0.029	0.721	0.96	0.044	0.401
rs10512597	17q25.1	T	C	0.202	*CD300LF*	1.02	0.014	0.218	1.00	0.032	0.909	0.99	0.041	0.781
rs4817986	21q22.2	T	G	0.268	*PSMG1*	1.02	0.013	0.182	1.00	0.027	0.928	1.03	0.035	0.486
rs6010044	22q13.33	A	C	0.777	*SHANK3/ ARSA*	0.97	0.014	0.012	0.97	0.030	0.364	0.96	0.042	0.368

A1 indicates allele 1; A2, allele 2; CAD, coronary artery disease; Freq1, frequency of A1; OR, odds ratio; SNP, single-nucleotide polymorphism; and VTE, venous thromboembolism.

*Joint meta-analysis of results from the Coronary Artery Disease Genome-wide Replication and Meta-analysis (CARDIoGRAM) and Europe South Asia Coronary Artery Disease Genetics (C4D) consortia.

†Joint meta-analysis of results from the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium and the Wellcome Trust Case-Control Consortium (WTCCC).

‡Meta-analysis result from the French Marseille Thrombosis Association (MARTHA) Consortium and the CHARGE Consortium Studies on Venous Thrombosis.

Overall, our results suggest that systemic inflammation both causes raised fibrinogen level and (by a different mechanism) is associated with increased risk of CAD. The lack of overlap between the top CAD-associated SNPs from the literature and the fibrinogen-associated SNPs identified in our study further argues against a reverse causality hypothesis in which inflammation caused by the atherosclerosis process would raise the fibrinogen level.

Although not as consistent as for CAD or myocardial infarction, some studies have also suggested that an elevated fibrinogen concentration is a risk factor for stroke.[3,37–39] In the present study, none of the fibrinogen-associated SNPs were significantly associated with stroke. Our findings suggest that similar to what we observed for CAD, a raised fibrinogen concentration is not causally related to stroke, although a positive trend was observed that warrants further investigation. Similarly, our results show that none of the fibrinogen-associated SNPs were significantly associated with VTE after correction for multiple testing, although rs1800789G in the fibrinogen gene cluster, which is associated with higher fibrinogen level in our discovery study, showed a clear trend (P=0.004). However, given the small sample size of the VTE cases examined, the power for detection of VTE association in our data is substantially lower than for stroke and CAD (see Methods in the online-only Data Supplement).

Conclusions

The present meta-analysis of fibrinogen GWA studies, based on a 4-fold greater sample size than previous meta-analyses (≈91 500 individuals), identified 24 independent signals in 23 loci (of which 15 are new) and increased the proportion of variance of plasma fibrinogen level accounted for by all lead SNPs in genome-wide significant loci from <2% to 3.7%. For some of these loci, our pathway and eQTL analyses provided supporting evidence on the most plausible candidate genes. Finally, our study does not support causal involvement of fibrinogen in cardiovascular disease, particularly in clinically apparent CAD. Functional studies are needed to confirm and to characterize candidate genes suggested by the in silico analyses presented here.

Future studies aimed at explaining the substantial missing heritability of plasma fibrinogen concentration should focus on exploring gene-gene and gene-environment interactions and on applying resequencing technologies to elucidate the role of rare variants.

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CLINICAL PERSPECTIVE

Plasma fibrinogen concentration is a predictor of cardiovascular disease independently of other traditional risk factors, and variation in fibrinogen concentration has a substantial heritable component. We conducted a meta-analysis of 28 genome-wide association studies, including >90 000 subjects of European ancestry and substantial numbers of blacks and Hispanics. We identified 24 genome-wide significant ($P<5\times10^{-8}$) independent single-nucleotide polymorphisms in 23 genetic loci, including 15 novel associations, together accounting for 3.7% of plasma fibrinogen variation. Gene-set enrichment analysis highlighted potential key roles in fibrinogen regulation for the known structural fibrinogen genes, as well as inflammation and other candidate pathways. However, in an evaluation for associations of the top fibrinogen single-nucleotide polymorphisms with coronary artery disease, stroke, and venous thromboembolism in very large case-control genome-wide studies, there was no evidence for association with any of these clinical outcomes of either the single single-nucleotide polymorphism most closely related to fibrinogen level (in the fibrinogen gene) or the combined effect of all 24 fibrinogen-associated single-nucleotide polymorphisms (across 23 distinct loci). Our findings in a very large total study population provide comprehensive data for new and known genetic variants underlying fibrinogen concentration in human populations, including multiple ethnic groups. Our findings highlight potential pathways for future study of the role of fibrinogen in the pathophysiology of atherosclerosis and cardiovascular disease. Clinical outcome analysis does not support a strong causal relationship between circulating levels of fibrinogen and coronary artery disease, stroke, or venous thromboembolism.

SUPPLEMENTAL MATERIAL

A multi-ethnic meta-analysis of genome-wide association studies in over 100,000 subjects identifies 23 fibrinogen-associated loci but no strong evidence of a causal association between circulating fibrinogen and cardiovascular disease

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Supplementary Methods:
Cohorts of European descent (see Supplementary Table S1):

The Precocious Coronary Artery Disease Study (PROCARDIS) consists of coronary artery disease (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).

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 [1].

The Women's Genome Health Study (WGHS) is a prospective cohort of initially healthy, female North American health care professionals at least 45 years old at baseline representing participants in the Women's Health Study (WHS) who provided a blood sample at baseline and consent for blood-based analyses. The WHS was a 2x2 trial beginning in 1992-1994 of vitamin E and low dose aspirin in prevention of cancer and cardiovascular disease with about 10 years of follow-up. Since the end of the trial, follow-up has continued in observational mode. Additional information related to health and lifestyle were collected by questionnaire throughout the WHS trial and continuing observational follow-up. Detailed information about the study can be found in [2].

The SardiNIA study has been previously described [3]. Briefly, it is a large population-based study which consists of 6,148 individuals, males and females, ages 14-102 y, that were recruited from a cluster of four towns in the Lanusei Valley of Sardinia. Samples have been characterized for several quantitative traits and medical conditions, including fibrinogen.

The Rotterdam Study is a prospective, population-based cohort study of determinants of several chronic diseases in older adults [4]. In brief, the study comprised 7,983 inhabitants of Ommoord, a district of Rotterdam in the Netherlands, who were 55 years or over. Subjects are of European ancestry based on their self-report. The baseline examination took place between 1990 and 1993.

The Study of Health in Pomerania (SHIP) is a longitudinal cohort study in West Pomerania, the north-east area of Germany and has been described previously [5, 6]. From the entire study population of 212,157 inhabitants living in the area, a sample was selected from the population registration offices, where all German inhabitants are registered. Only individuals with German citizenship and main residency in the study area were included. A two-stage cluster sampling method was adopted from the WHO MONICA Project Augsburg, Germany. In a first step, the three cities of the region (with 17,076 to 65,977

inhabitants) and the 12 towns (with 1,516 to 3,044 inhabitants) were selected. Further 17 out of 97 smaller towns (with less than 1,500 inhabitants) were drawn at random. In a second step, from each of the selected communities, subjects were drawn at random, proportional to the population size of each community and stratified by age and gender. Finally, 7,008 subjects aged 20 to 79 years were sampled, with 292 persons of each gender in each of the twelve five-year age strata. In order to minimize drop-outs by migration or death, subjects were selected in two waves. The net sample (without migrated or deceased persons) comprised 6,267 eligible subjects. The SHIP population finally comprised 4,308 participants at baseline (corresponding to a final response of 68.8%).

The Coronary Artery Risk Development in Young Adults (CARDIA) Study is a prospective multicenter study with 5115 adults Caucasian and African American participants of the age group 18-30 years, 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 previously published [7]. Seven examinations have been completed since initiation of the study in 1985–1986, respectively in the years 0, 2, 5, 7, 10, 15 and 20. Written informed consent was obtained from participants at each examination and all study protocols were approved by the institutional review boards of the participating institutions.

PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) was a prospective multicenter randomized placebo-controlled trial to assess whether treatment with pravastatin diminishes the risk of major vascular events in elderly. Between December 1997 and May 1999, we screened and enrolled subjects in Scotland (Glasgow), Ireland (Cork), and the Netherlands (Leiden). Men and women aged 70-82 years were recruited if they had pre-existing vascular disease or increased risk of such disease because of smoking, hypertension, or diabetes. A total number of 5804 subjects were randomly assigned to pravastatin or placebo. A large number of prospective tests were performed including Biobank tests and cognitive function measurements. A detailed description of the study has been published elsewhere[8, 9].

The **Cardiovascular Health Study (CHS)** is a population-based cohort study of risk factors for CHD and stroke in adults ≥65 years conducted across 4 field centers [10]. 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.

The Lothian Birth Cohort (LBC) studies, **LBC1936 & LBC1921,** were ascertained as follows.
The LBC1936 consists of 1,091 relatively healthy individuals assessed on cognitive and medical traits at 70 years of age. They were born in 1936, most took part in the Scottish Mental Survey of 1947, and almost all lived independently in the Lothian region of Scotland (Edinburgh City and surrounding area). A full description of participant recruitment and testing can be found elsewhere.[11, 12] The LBC1921 cohort consists of 550 relatively healthy individuals, 316 females and 234 males, assessed on cognitive and medical traits at 79 years of age. They were born in 1921, most took part in the Scottish Mental Survey of 1932, and almost all lived independently in the Lothian region in Scotland. A full description of participant recruitment and testing can be found elsewhere. [11, 13] Ethics permission for the study was

obtained from the Multi-Centre Research Ethics Committee for Scotland (MREC/01/0/56) and from Lothian Research Ethics Committee (LBC1936: LREC/2003/2/29 and LBC1921: LREC/1998/4/183). The research was carried out in compliance with the Helsinki Declaration. All subjects gave written, informed consent.

The MARseille THrombosis Association (MARTHA) project has been previously described [14]. Briefly, MARTHA consist in 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.

The **CROATIA-Split study**, Croatia, is a population-based, cross-sectional study in the Dalmatian City of Split that includes 1000 examinees aged 18-95. Blood samples were collected in 2009 and 2010 along with many clinical and biochemical measures and lifestyle and health questionnaires. A detailed description of the study has been published elswhere[15].

The **CROATIA-Korcula study**, Croatia, is a family-based, cross-sectional study in the isolated island of Korcula that included 965 examinees aged 18-95. Blood samples were collected in 2007 along with many clinical and biochemical measures and lifestyle and health questionnaires. A detailed description of the study has been published elswhere[16].

The **CROATIA-Vis study**, Croatia, is a family-based, cross-sectional study in the isolated island of Vis that included 1,056 examinees aged 18-93. Blood samples were collected in 2003 and 2004 along with many clinical and biochemical measures and lifestyle and health questionnaires. A detailed description of the study has been published elswhere[16].

The **Orkney Complex Disease Study (ORCADES)** was performed in the Scottish archipelago of Orkney and collected data between 2005 and 2011 (mean age 53). Data for 889 participants aged 18 to 100 years from a subgroup of ten islands, were used for this analysis. A detailed description of the study has been published elswhere[17].

The British 1958 birth cohort (B58C) is a national population sample followed periodically from birth. At age 44-45 years, 9377 cohort members were examined by a research nurse in the home as described previously[18] and non-fasting blood samples were collected with permission for DNA extraction and creation of immortalised cell cultures (http://www.b58cgene.sgul.ac.uk/collection.php). DNA samples from unrelated subjects of white ethnicity, with nationwide geographic coverage, were genotyped either by the Wellcome Trust Case Control Consortium (WTCCC)[19], the Type 1 Diabetes Genetics Consortium[20] or the GABRIEL consortium[21].

The MONICA/KORA Augsburg Study consisted of a series of independent population-based epidemiological surveys of participants living in the region of Augsburg, Southern Germany[22]. All survey participants are residents of German nationality identified through the registration office. The presented data were derived from the third and fourth population-based Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA)/ Cooperative Health Research in the Region of Augsburg (KORA) surveys S3 and S4. These cross-sectional surveys covering the city of Augsburg (Germany) and two adjacent counties were conducted in 1994/95 (S3) and 1999/2001 (S4) with 4,856 (S3) and 4,261 (S4) individuals aged 25 to 74 years. S3 was part of the WHO MONICA study. In a follow-up examination of S3 conducted in 2004/05 (MONICA/KORA F3) and of S4 conducted in 2006/08 (MONICA/KORA F4), a number of 3,006 (F3) and 3,080 (F4) subjects participated. All participants underwent standardized examinations including blood withdrawals for plasma and DNA. For the MONICA/KORA genome-wide association study, a number of 1,644 and 1,814 subjects were selected from F3 and F4 samples[23]. After excluding subjects with no albumin measurements available, the final populations for the MONICA/KORA data comprised 1,523 (S3/F3) and 1,788 (S4/F4) subjects.

The Aging in the Chianti Area (InCHIANTI) study is a population-based epidemiological study aimed at evaluating the factors that influence mobility in the older population living in the Chianti region in Tuscany, Italy. The details of the study have been previously reported[24]. Briefly, 1616 residents were selected from the population registry of Greve in Chianti (a rural area: 11,709 residents with 19.3% of the population greater than 65 years of age), and Bagno a Ripoli (Antella village near Florence; 4,704 inhabitants, with 20.3% greater than 65 years of age). The participation rate was 90% (n=1453).

The **TwinsUK** cohort was derived from the UK adult twin registry based at King's College London (www.twinsUK.ac.uk). These unselected twins have been recruited from the general population through national media campaigns in the United Kingdom and shown to be comparable to age-matched population singletons in terms of disease-related and lifestyle characteristics [25]. Informed consent was obtained from all participants and the study was approved by the St. Thomas' Hospital Ethics Committee.

The Helsinki Birth Cohort Study (HBCS) is composed of 8 760 individuals born between the years 1934-44 in one of the two main maternity hospitals in Helsinki, Finland. Between 2001 and 2003, a randomly selected sample of 928 males and 1 075 females participated in a clinical follow-up study with a focus on cardiovascular, metabolic and reproductive health, cognitive function and depressive symptoms. Detailed information on the selection of the HBCS participants and on the study design can be found elsewhere [26, 27]. Research plan of of the HBCS was approved by the Institutional Review Board of the National Public Health Insitute and all participants have signed an informed consent.

The Netherlands Twin Registry (NTR): Between January 2004 and July 2008, 9.530 participants from 3,477 families registered in the NTR were visited at home between 7:00 and 10:00 am for collection of blood samples. Fertile women were bled on day 2–4 of the menstrual cycle, or in their pill-free week. Body composition was measured and information about physical health and lifestyle (e.g. smoking and drinking behavior, physical exercise, medication use) was obtained. For more detailed information about the methodology of the NTR Biobank study, see [28]. Valid GWA data were available for 2490 individuals.

The Atherosclerosis Risk in Communities (ARIC): The Atherosclerosis Risk in Communities (ARIC) Study recruited 15,792 adults aged 45 to 64 years in 1987 through 1989 by probability sampling from Forsyth County, North Carolina; Jackson, Mississippi; suburbs of Minneapolis, Minnesota; and Washington County, Maryland [29]. The Jackson sample comprised African Americans only; the other three samples represent the ethnic mix of their communities. Extensive information was collected at baseline on cardiovascular risk factors. The ARIC study was approved by the institutional review board of each field center institutes and participants gave informed consent including consent for genetic testing. In this study we included only European American and African American participants.

Multi-Ethnic Study of Atherosclerosis (**MESA):** The MESA is a cohort study designed to investigate the characteristics of subclinical cardiovascular disease and the risk factors that predict progression to clinically overt cardiovascular disease or progression of the subclinical disease. MESA comprises a diverse, population-based sample of 6,814 asymptomatic men and women aged 45-84. Thirty-eight percent of the recruited participants are Caucasian, 28 percent African-American, 22 percent Hispanic, and 12 percent Asian, predominantly of Chinese descent [30]. Participants were recruited from six field centers across the United States: Wake Forest University, Columbia University, Johns Hopkins University, University of Minnesota, Northwestern University and University of California - Los Angeles.

Cohorts of African American and Hispanic descent (see Supplementary Table S2)

The Atherosclerosis Risk in Communities (ARIC): See information in the *Cohorts of European descent* section.

The Genetic Study of Atherosclerosis Risk (GeneSTAR) is an ongoing prospective study begun in 1983 to determine environmental, phenotypic, and genetic causes of premature cardiovascular disease [31]. Participants came from European and African American families identified from probands with a premature coronary disease event prior to 60 years of age who were identified at the time of hospitalization in any of 10 Baltimore area hospitals. Their apparently healthy 30-59 year old siblings without known CAD were recruited and underwent phenotypic measurement and characterization between 1983 and 2006; offspring of the siblings and probands, as well as the co-parent of these offspring, were recruited and assessed between 2003 and 2006.

The Women's Health Initiative (WHI) is one of the largest (n=161,808) studies of women's health ever undertaken in the U.S [1]. There are two major components of WHI: (1) a Clinical Trial (CT) that enrolled and randomized 68,132 women ages 50 – 79 into at least one of three placebo-control clinical trials (hormone therapy, dietary modification, and calcium/vitamin D); and (2) an Observational Study (OS) that enrolled 93,676 women of the same age range into a parallel prospective cohort study[32]. A diverse population including 26,045 (17%) women from minority groups were recruited from 1993-1998 at 40 clinical centers across the U.S. Of the CT and OS minority participants enrolled in WHI, 12,157 (including 8,515 self identified African American and 3,642 self identified Hispanic subjects) who had consented to genetic research were eligible for the WHI SHARe GWAS project. DNA was

extracted by the Specimen Processing Laboratory at the Fred Hutchinson Cancer research Center (FHCRC) using specimens that were collected at the time of enrollment. Only African American participants with fibrinogen measured at baseline were included in this analysis.

Cleveland Family Study (CFS): The CFS is a family-based longitudinal study designed to study the risk factors for sleep apnea.[33] Participants include first-degree or selected second-degree relatives of a proband with either laboratory diagnosed obstructive sleep apnea or neighborhood control of an affected proband. In total, 2,534 individuals (46% African American) from 352 families were studied on up to 4 occasions over a period of 16 years (1990-2006). The initial aim of the study was to quantify the familial aggregation of sleep apnea. Over time, the aims were expanded to characterize the natural history of sleep apnea, sleep apnea outcomes, and to identify the genetic basis for sleep apnea.

Phenotyping methods (see Supplementary Tables S1 and S2)

PROCARDIS: Plasma fibrinogen concentrations for the Procardis_clauss sub-sample were measured in fasting citrate plasma samples by the Clauss method using the IL Test Fibrinogen C kit and IL Test Calibration Plasma, on the ACL-9000 coagulometer (all from Instrumentation Laboratory Spa, Milan, Italy). The inter- assay CV was 7% (n=106). For the Procardis_immunonephelometric, fibrinogen was measured in EDTA plasma samples using Dade Behring reagents on the Dade-Behring Nephelometer II analyzer (Dade-Behring, Marburg, Germany). The inter-assay CV was 5.5%.

FHS: Fibrinogen levels were measured using the Clauss method[34] in the offspring and the third-generation subjects, and a modified method of Ratnoff and Menzie in the original cohort subjects [35].

WGHS: Fibrinogen was measured by a mass-based immunoturbidimetric assay (DiaSorin) with reproducibility of 5.20% and 3.99% at concentrations of 0.99 and 2.74 g/L respectively.

SardiNIA: The study measured fibrinogen levels using the Clauss method[34].

RS: Fibrinogen levels were derived from the clotting curve of the prothrombin time assay using Thromborel S as a reagent on an automated coagulation laboratory 300 (ACL 300, Instrumentation Laboratory, Zaventem, Belgium).

SHIP: A non-fasting blood sample was drawn from the antecubital vein in the supine position and immediately analyzed or stored at -80°C. Plasma fibrinogen concentrations were assayed according to Clauss[34] using an Electra 1600 analyzer (Instrumentation Laboratory, Barcelona, Spain). Coagulation time is measured and transferred into the result in g/L by applying a reference curve calculated in the laboratory. The assay proves linearity between 0.7 – 7 g/L. The analytical sensitivity of the assay was 0.7 g/L. Internal quality control measures were performed daily using two levels of manufacturers' control materials. External quality control measures were performed on a regular basis by participating in analysis programs. The inter-assay coefficients of variation were 4.61 % at low levels (mean value = 0.95 g/L) and 1.82% at high levels (mean value = 3.22 g/L) of control material.

CARDIA: Total fibrinogen concentration at the Y7 examination was determined at the University of Vermont using immunonephelometry (BNII Nephelometer 100 Analyzer; Dade Behring, Deerfield, IL, USA). The amount of immuno-reactive fibrinogen present in the sample was quantitatively determined by light scatter intensity. The immunoassay was calibrated using reference plasma, and the results reported in mg dL^{-1}. The intra-assay and inter-assay coefficient of variation (CVs) for the immunoassay were 2.7% and 2.6%, respectively.

PROSPER: Fibrinogen levels were measured by the Clauss method[34] using aMDA180 coagulometer (Trinity Biotech; calibrant 9th British standard National Institute for Biological Standards and Control).

CHS: 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[36]. For fibrinogen determination, an additional citrate-containing tube was processed at 4° C. The study measured fibrinogen levels using the Clauss methods.

LBC: Fibrinogen levels were measured using HemosIL™ based on the Clauss method. No exclusions were applied. Outliers were removed (>3.3SD). Plasma fibrinogen was in g/L, natural log transformed.

MARTHA: Blood samples were collected by antecubital venipuncture into Vacutainer® tubes 0.105 M trisodium citrate (ratio 9:1, Becton Dickinson) for the coagulation test and the thrombin generation assay. 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. Fibrinogen levels were measured using the Clauss[34] method on STAR automatic coagulomater.

CROATIA-ORCADES: All 4 studies used the Clauss method for measuring plasma fibrinogen.

B58BC: Details of the blood collection, fibrinogen measurement and covariate adjustment have been described elsewhere [37]. In brief, fibrinogen was measured by the Clauss method[34] using an MDA 180 coagulometer (Biomerieux, Basingstoke, UK).

KORA: Fibrinogen was determined by an immunonephelometric method (Dade Behring Marburg GmbH, Marburg, Germany) on a Behring Nephelometer II analyzer.

InCHIANTI: Overnight fasted blood samples were used for genomic DNA extraction, and measurement of fibrinogen. Plasma fibrinogen concentrations were measured by the Clauss method[34] using STA fibrinogen assay (Diagnostic Stago, Roche Diagnostics, France). The intra- and inter-assay CV was 4.1%.

Twins UK: Fasting blood samples was taken from samples into 0.13 trisodium citrate containers (Becton Dickinson, Oxford, United Kingdom) at room temperature, centrifuged at 2560*g* for 20 minutes to obtain platelet-poor plasma within 1 hour of collection and stored at –40°C until analysis. Fibrinogen levels were determined using the Clauss method [38].

HBCS: Fibrinogen levels were measured using the Clauss method [39] with an electrical impedance end point . Plasma fibrinogen was measured in g/L and was natural log transformed to attain normality.

NTR: Fibrinogen was measured in a 4.5 ml CTAD tube that was stored during transport in melting ice and upon arrival at the laboratory, centrifuged for 20 minutes at 2000x g at 4° C, after which citrated plasma was harvested, aliquoted (0.5 ml), snapfrozen in dry ice, and stored at –30° C. Fibrinogen levels were determined on a STA Compact Analyzer Diagnostica Stago, France), using STA Fibrinogen (Diagnostica Stago, France).

ARIC: Fibrinogen was measured at baseline in the entire ARIC cohort after an 8-hour fasting period.Circulating plasma fibrinogen was measured by the Clauss clotting rate method[39]. Participants whose fibrinogen measurement was off 6SD from the mean were also excluded.

MESA: Fasting blood samples were collected, processed and stored using standardized procedures[36]. Fibrinogen antigen was measured using the BNII nephelometer (N Antiserum to Human Fibrinogen; Dade Behring Inc., Deerfield, IL). The assay was performed at the Laboratory for Clinical Biochemistry Research (University of Vermont, Burlington, VT). Intra- and inter-assay analytical coefficients of variation were 2.7% and 2.6%, respectively.

GeneSTAR: Blood was obtained from venipuncture and collected into vacutainer tubes containing 3.2% sodium citrate. Plasma fibrinogen was measured using a modified Clauss method on an automated optical clot detection device (Dade-Behring, Newark, DE). Excess thrombin was added to citrated plasma, and the time needed for clot formation was recorded. This clotting time was then compared with that of a standardized fibrinogen preparation.

WHI: Blood samples were collected from all participants at baseline and stored at −70° Celsius. Fibrinogen was measured using a turbidometric fibrinogen clot rate assay (MLA ELECTRA 1400C; Medical Laboratory Automation Inc., Mt. Vernon, NY).

CFS: Fibrinogen levels were assayed at the University of Vermont Laboratory for Clinical Biochemistry Research using fasting blood samples collected at an examination performed between 2001-2006 (STa-R automated coagulation analyzer, Diagnostica Stago; Parsippany, NJ), which used the clotting method developed by Clauss[39].

Genotyping methods (see Supplementary Table S3 and S4)

PROCARDIS: PROCARDIS was genotyped using Illumina Human 1M and 610K quad arrays on a total of 6000 patients with CAD and 7,500 control subjects. Genotype quality control excluded SNPs with a call rate <95%, MAF <0.01, HWE p<10e-6. After quality filtering, SNPs were imputed to HapMap22, build 36, using MACHv1.0.16. After imputation, a total of 2,543,888 remained available for analyses.

FHS: Genotyping was carried out as a part of the SNP Health Association Resource project using the Affymetrix 500K mapping array (250K Nsp and 250K Sty arrays) and the Affymetrix 50K supplemental

gene focused array on 9274 individuals. Genotyping resulted in 503 551 SNPs with successful call rate > 95% and HWE P >1E-6 on 8481 individuals with call rate > 97%. Imputation of ~2.5 million autosomal SNPs in HapMap with reference to release 22 CEU sample was conducted using the algorithm implemented in MACH. The final population for fibrinogen analysis included 7022 individuals (original cohort, n=383; offspring, n=2806; third generation, n=3833).

WGHS: Genotyping in the WGHS sample was performed using the HumanHap300 Duo ''+'' chips or the combination of the HumanHuman300 Duo and iSelect chips (Illumina, San Diego, CA) with the Infinium II protocol. In either case, the custom SNP content was the same; these custom SNPs were chosen without regard to minor allele frequency (MAF) to saturate candidate genes for cardiovascular disease as well as to increase coverage of SNPs with known or suspected biological function, e.g. disease association, non-synonymous changes, substitutions at splice sites, etc. For quality control, all samples were required to have successful genotyping using the BeadStudio v. 3.3 software (Illumina, San Diego, CA) for at least 98% of the SNPs. A subset of 23,294 individuals were identified with self-reported European ancestry that could be verified on the basis of multidimensional scaling analysis of identity by state using1443 ancestry informative markers in PLINK v. 1.06. In the final dataset of these individuals, SNPs were retained with MAF >1%, successful genotyping in 90% of the subjects, and deviations from Hardy-Weinberg equilibrium not exceeding P=10-6 in significance. Among the final 23,294 individuals of verified European ancestry, genotypes for a total of 2,608,509 SNPs were imputed from the experimental genotypes and LD relationships implicit in the HapMap r. 22 CEU samples.

SardiNIA: Genotyping started on 2004, and different subset of samples have been genotyped with different SNP arrays. Specifically, 1,412 were genotyped with the 500K Affymetrix Mapping Array set; 3,329 with the 10K Mapping Array set, with 436 individuals genotyped with both arrays; 1,097 individuals with the 6.0 Affymetrix chip, of which 1,004 and 66 of those were typed with the 10K and 500K chips respectively. Quality controls filters for the 500K and 10K array have been previously described (Scuteri et al Plos Genetics 2007; Sanna et al Nat Gen 2008). For the Affymetrix 6.0 chip, we removed SNPs with call rate <95%, MAF <1% and HWEpvalue<10-6 (Naitza et al Plos Genet 2011, submitted). We also discarded SNPs that showed an excess of mendelian errors and SNPs in common with the 500K showing an excess of discordant genotypes (>3 over 66 samples).
After performing quality control checks and merging genotypes from the three gene chip platform, we used 731,209 QCed autosomal markers to estimates genotypes for all polymorphic SNPs in the CEU HapMap population (release 22, The International HapMap Consortium, 2007) in the individuals genotyped with the 500K Array and the 6.0 Affymetrix chip separately, using the MaCH software (Li et al 2009, http://www.sph.umich.edu/csg/abecasis/mach/). Taking advantage of the relatedness among individuals in the SardiNIA sample, we carried out a second round of computational analysis to impute genotypes at all SNPs in the individuals who were genotyped only with the Affymetrix Mapping 10K Array, being mostly offspring and siblings of the individuals genotyped at high density. At this second round of imputation, we focused on the SNPs for which the imputation procedure predicted r2>0.30 between true and imputed genotypes and for which the inferred genotype did not generate an excess of Mendelian Errors. The within-family imputation procedure is implemented in Merlin software (Abecasis et al., 2002; Chen W-M & Abecasis G-R, 2007). Overall, a total of 2,325,920 autosomal SNPs were selected for GWAS.

Due to computational constraints, we divided large pedigrees into sub-units with "bit-complexity" of 21 or less (typically, 25-30 individuals) before analysis.
The CROATIA-Vis study genotyping used the Illumina HAP300v1 SNP chip. Genotype quality control excluded SNPs with a call rate <95%, MAF <0.01, HWE p<10e-6 . Analysis was performed using GenABEL with first 3 principal components accounting for population stratification and "mmscore " option to account for relationships. SNPs were imputed to HapMap22, build 36, using MACHv1.16. and GenABEL derived residuals were analysed using ProbABEL.

RS: Genotyping was conducted using the Illumina 550K array. SNPs were excluded for minor allele frequency ≤1%, Hardy-Weinberg equilibrium (HWE) p<10-5, or SNP call rate ≤90% resulting in data on 530,683 SNPs. Imputation was done with reference to HapMap release 22 CEU using the maximum likelihood method implemented in MACH.

The **SHIP** samples were genotyped using the Affymetrix Human SNP Array 6.0. Hybridisation of genomic DNA was done in accordance with the manufacturer's standard recommendations. The genetic data analysis workflow was created using the Software InforSense. Genetic data were stored using the database Caché (InterSystems). Genotypes were determined using the Birdseed2 clustering algorithm. For quality control purposes, several control samples where added. On the chip level, only subjects with a genotyping rate on QC probesets (QC callrate) of at least 86% were included. All remaining arrays had a sample callrate > 92%. The overall genotyping efficiency of the GWA was 98.55 %. Imputation of genotypes in SHIP was performed with the software IMPUTE v0.5.0 based on HapMap II.

CARDIA (European): Study samples from were genotyped using the Affymetrix Genome-Wide Human SNP Array 6.0 (Santa Clara, California); only participants of European descent were included in the GWAS analyses. Samples with high missing rate, cryptic IBS, and population stratification outliers were excluded from the analysis. Genotyping was completed for 1720 individuals with a sample call rate ≥ 98%. A total of 578,568 SNPs passed quality control (MAF ≥ 2%, call rate ≥ 95%, HWE ≥ 10-4) and were used for imputation. For this study, complete genotype and phenotype information were available for 1435 individuals.

PROSPER/PHASE: A whole genome wide screening has been performed in the sequential PHASE project with the use of the Illumina 660K beadchip. Of 5763 subjects DNA was available for genotyping. After QC (call rate <95%) 557,192 SNPs and 5244 subjects were left for analysis were left for analysis. The SNPs were imputed to 2.5 million SNPs based on the HAPMAP built 36 with MACH imputation software.

CHS: In 2007-2008, genotyping was performed on CHS European-ancestry participants at the General Clinical Research Center's Phenotyping/Genotyping Laboratory at Cedars-Sinai using the Illumina 370CNV BeadChip system on 3980 CHS participants who were free of CVD at baseline, consented to genetic testing, and had DNA available for genotyping. In 2010, the African-ancestry were genotyped at the same lab using the Illumina HumanOmni1-Quad_v1 BeadChip system. Genotypes were called using the Illumina GenomeStudio software.

LBC: A detailed description of the genotyping method is available elsewhere [40]. In brief, genotyping was performed on Illumina Human 610-Quadv1 chip on blood-extracted DNA. Standard quality control measures were applied including the following thresholds: call rate ≥ 0.98, minor allele frequency ≥ 0.01, and Hardy-Weinberg Equilibrium test with P ≥ 0.001. ~2.5M common SNPs included in HapMap, using the HapMap phase II CEU data as the reference sample were imputed. NCBI build 36 (UCSC hg18) was used and genotype data were imputed using MACH software. Prior to imputation SNPs were removed that diverged from HWE with a significance $p < 1x10^{-3}$ and SNPs with a minor allele frequency < 0.01. The respective SNP call and sample call rates were 0.98 and 0.95. 2,543,887 SNPs were imputed.

MARTHA: The MARTHA08 study sample was typed with the Illumina Human610-Quad Beadchip while the MARTHA10 sample was typed with the Illumina Human660W-Quad Beadchip. SNPs showing significant ($P < 10^{-5}$) deviation from Hardy-Weinberg equilibrium, with minor allele frequency (MAF) less than 1% or genotyping call rate <99%, in each study were filtered out.
After the filtering, 494,721 and 501,773 autosomal SNPs were left for association analysis and further used for imputing ~2.5 million autosomal SNPs according to the CEU HapMap release 21 reference dataset. The imputation was performed using MACH v1.0.16.
Individuals with genotyping success rates less than 95% were excluded from the analyses, as well as individuals demonstrating close relatedness as detected by pairwise clustering of identity by state distances (IBS) and multi-dimensional scaling (MDS) implemented in PLINK software[41]. Non-European ancestry was also investigated using the Eigenstrat program (Price AL, Patterson NJ, Plenge RM, Weinblatt ME, Shadick NA, Reich D. Principal components analysis corrects for stratification in genome-wide association studies.Nat Genet 2006, 38:904-909) leading to the final selection of 972 and 570 patients left for analysis in MARTHA08 and MARTH10, respectively.

The **CROATIA-Split** study genotyping used the Illumina HAP370CNV SNP chip. Genotype quality control excluded SNPs with a call rate <98%, MAF <0.01, HWE p<10e-6 . Analysis was performed using GenABEL with first 3 principal components accounting for population stratification and "mmscore " option to account for relationships. SNPs were imputed to HapMap22, build 36, using MACHv1.16. and GenABEL derived residuals were analysed using ProbABEL

The **CROATIA-Korcula** study genotyping used the Illumina HAP370CNV SNP chip. Genotype quality control excluded SNPs with a call rate <98%, MAF <0.01, HWE p<10e-6 . Analysis was performed using GenABEL with first 3 principal components accounting for population stratification and "mmscore " option to account for relationships. SNPs were imputed to HapMap22, build 36, using MACHv1.16. and GenABEL derived residuals were analysed using ProbABEL

The **ORCADES** study study genotyping used the Illumina HAP300v2 SNP chip. Genotype quality control excluded SNPs with a call rate <98%, MAF <0.01, HWE p<10e-6 . Analysis was performed using GenABEL with first 3 principal components accounting for population stratification and "mmscore " option to account for relationships. SNPs were imputed to HapMap22, build 36, using MACHv1.16. and GenABEL derived residuals were analysed using ProbABEL

MONICA/KORA: Genotyping for F3 was performed using Affymetrix 500K Array Set consisting of two chips (Sty I and Nsp I). The F4 samples were genotyped with the Affymetrix Human SNP Array 6.0.

Hybridisation of genomic DNA was done in accordance with the manufacturer's standard recommendations. Genotypes were determined using BRLMM clustering algorithm (Affymetrix 500K Array Set) or Birdseed2 clustering algorithm (Affymetrix Array 6.0). For quality control purposes, we applied a positive control and a negative control DNA every 48 samples (F3) or 96 samples (F4). On chip level only subjects with overall genotyping efficiencies of at least 93% were included. In addition the called gender had to agree with the gender in the MONICA/KORA study database. Imputation of genotypes was performed using maximum likelihood method with the software MACH v1.0.9 (F3) and MACH v1.0.15 (F4).

INCHIANTI: Illumina Infinium HumanHap 550K SNP arrays were used for genotyping [42]. Genotyping was completed for 1210 subjects with a sample call rate $\geq$97%, heterozygosity rates $\geq$ 0.3 and correct sex specification. 495,343 autosomal SNPs that passed quality control (MAF$\geq$1%, completeness $\geq$99%, HWE $\geq 10^{-4}$) were used for imputation. The HapMap CEU sample *(*build 36) was used a reference to impute approximately 2.5 million SNPs using MACHv.1.16. Association analysis was conducted using MERLIN software.

Twins UK: Genotyping of the TwinsUK dataset was done with a combination of Illumina arrays (HumanHap300, HumanHap610Q, 1M-Duo and 1.2MDuo 1M). Intensity data for each of the three arrays were pooled separately (with 1M-Duo and 1.2MDuo 1M pooled together) and genotypes were assigned using the Illuminus calling algorithm [43]. We applied similar quality control criteria to each dataset and merged them [44]. Imputation was performed using the IMPUTE v2 using two reference panels, P0 (HapMap2, rel 22, combined CEU+YRI+ASN panels) and P1 (610k+, including the combined HumanHap610k and 1M reduced to 610k SNP content).

HBCS: DNA was extracted from blood samples and genotyping was performed with the modified Illumina 610k chip by the Wellcome Trust Sanger Institute, Cambridge, UK according to standard protocols. Genomic coverage was extended by imputation using the HapMap phase II CEU data as the reference sample and MACH software.

NTR: Three platforms were used to genotype the data : AFFY/Perlegen 660K, Illumina 370K and Illumina 660K. Per platform the quality control inclusion thresholds for SNPs were MAF > 1%, HWE > 0.00001, call rate > 95% and 0.30 < Heterozygosity < 0.35. Samples were excluded from the data if their expected sex and IBD status did not match, or if the genotype missing rate was above 10%. For each platform all SNPs were aligned to the positive strand of the Hapmap 2 Build 36 release 24 CEU reference set. The alignment was checked using individuals and family members tested on multiple platforms. SNPs were excluded per platform if allele frequencies differed more than 15% with the reference set and/or the other platforms. The data of the three chips were then imputed with the IMPUTE program on Hapmap 2 build 36rel24 (J. Marchini). From the imputed sets, SNPs were removed if the MAF had a difference larger than 0.15 between subsets (same reference alleles). The remaining SNPs were merged into one single set. Afterwards, bad imputed SNPs were removed based on HWE < 0.00001, proper info < 0.40 and MAF < 1%.

ARIC (European): Genotyping was performed using the Affymetrix Genome-Wide Human SNP Array 6.0 (Affymetrix, Santa Clara, CA, USA) at the Broad Institute of Harvard and MIT. Exclusions at

individual level included disallowing DNA use, unintentional duplicates with higher missing genotype rates, suspected mixed/contaminated samples, scans from one problem plate, samples with a mismatch between called and phenotypic sex, samples with genotype mismatch with 39 previously genotyped SNPs, suspected first-degree relative of an included individual, and genetic outliers based on average IBS statistics and principal components analysis using EIGENSTRAT [45]. SNPs were excluded due to no chromosome location, being monomorphic, call rate <95%, or HWE-p < 10^{-6} for SNPs with MAF>0.05. In addition, imputation to approximately 2.5 million autosomal SNPs identified in HapMap Phase II CEU samples was performed using MACH v1.0.16 [46]. SNPs that met the following criteria were included in the imputation: MAF ≥ 1%, call rate ≥ 95%, and HWE-p ≥ 10^{-5}.

MESA: Caucasian, Hispanic, and Chinese American participants were genotyped on the Affymetrix Genome-Wide Human SNP Array 6.0 (Affymetrix, Santa Clara, CA, USA) at the Affymetrix Research Services Lab. 6880 samples passed initial genotyping QC. African American samples were genotyped at the Broad Institute of Harvard and MIT as part of the CARe project. Affymetrix performed wet lab hybridization assay, and plate-based genotype calling using Birdseed v2. Sample QC was based on call rates and contrast QC (cQC) statistics. Broad performed similar QC for CARe sample. Additional sample and SNP QC were carried out at University of Virginia, including sample call rate, sample cQC, and sample heterozygosity by race at the sample level; Outlier plates checking by call rate, median cQC or heterozygosity at plate level. Four samples were removed due to low call rate (<95%). Cryptic sample duplicates or unresolved cryptic duplicates were dropped. Unresolved gender mismatches were also dropped. At the SNP level, we excluded monomorphic SNPs across all samples; SNPs with missing Rate was > 5% or observed heterozygosity > 53% were also excluded. Additional genotypes were imputed separately in each ethnic group using the program IMPUTE2. HapMap CEU was used as the reference population for CAU sample, while a combined CEU+YRI reference panel was used for the African-American cohorts, and a combined CEU+YRI+CHB+JPT reference panel was used for the Hispanic sample.

Candidate Gene Association Resource (CARe) AA Cohorts- ARIC, CARDIA, CFS, and MESA: African American samples in ARIC, CARDIA, CFS, and MESA were genotyped as part of the CARe at the Broad Institute of Harvard and MIT using the Affymetrix Genome-Wide Human SNP Array 6.0 (Affy6.0). Two methods of DNA quality control metrics were assessed on the samples prior to the genome scan. First, quantity of double stranded DNA was assessed using PicoGreen® (Molecular Probes, Oregon, USA). Next, to confirm sample identity, a set of 24 markers including a gender confirmation assay were genotyped using the Sequenom platform to serve as a genetic fingerprint. Each of these 24 SNPs are also on the Affy6.0 array and served as a cross-platform sample verification. Genotypes were called using Birdseed v1.33.[47, 48] Quality controls steps were performed using the software PLINK,[41] EIGENSTRAT,[45] and PREST-Plus.[49] Imputation was performed using MACH 1.0.16 (http://www.sph.umich.edu/csg/abecasis/MaCH/) with a combined CEU+YRI as the reference panel. Comparison of genotypes for SNPs that were imputed in the GWAS and also genotyped on the CARe candidate gene SNP array estimated an allelic concordance rate of ~95.6% between genotyping and imputation for those SNPs. This rate is comparable to rates calculated for individuals of African descent

imputed with the HapMap 2 YRI individuals.[50] Imputation results were filtered at an RSQ_HAT threshold of 0.3 and a minor allele frequency threshold of 0.01.

GeneSTAR: The Illumina 1Mv1_c platform was used for genotyping, and MACH v1.0.16 was used to impute to 2.5 million SNPs in HapMap II.

WHI: Genotyping was done at Affymetrix Inc on the Affymetrix 6.0 array, using 2 ug DNA at a concentration of 100 ng/ul. 2% additional samples were genotyped as blind duplicates. We first removed samples that had call rate below 95%, that were duplicates of subjects other than monozygotic twins, or that had a Y-chromosome. SNPs that were located on the Y chromosome or were Affymetrix QC probes (not intended for analysis) were excluded (n=3280). We also flagged SNPs that had call rates, calculated separately for African Americans and Hispanics, below 95% and concordance rates below 98%, leaving us 871,309 unflagged SNPs. We computed IBD coefficients between all pairs of subjects using a random subset of 100,000 SNPs from autosomal chromosomes. A more thorough confirmatory analysis using a pairwise kinship coefficient estimator was performed separately for African Americans and Hispanics that validated these relationships and identified half-siblings. We were left with 8,412 unique African-American subjects, with an average call rate of 99.8% over the unflagged SNPs. We analyzed 188 pairs of blind duplicate samples. The overall concordance rate was 99.8% (range 94.5-100% over all samples, 98.3%-100% over samples with call rate >98%, 98.1-100%% over unflagged SNPs).
Imputation in African-Americans was performed using MaCH 1.0.16. Individuals with pedigree relatedness or cryptic relatedness (pi_hat > 0.05) were filtered prior to imputation. SNPs with MAF ≥1%, call rate ≥97% and HWE P ≥10-6 were used for imputation. A combined CEU+YRI reference panel from HapMap phase 2 (release 22, build 36) was used. A randomly selected subset of individuals from each cohort sample was used to generate recombination and error rate estimates. These rates were then used to estimate genotype dosages in all sampled individuals across the entire reference panel for over 2 million SNPs. Imputation results were filtered using a minimum imputation quality score, indicated by the RSQ_HAT estimate in MaCH of >0.5 and a MAF threshold of >1%. On a small test sample (2% of the markers on three chromosomes), the average R-squared was 0.88, with an allelic discordance rate of 2.3%.

Statistical analyses in European samples

Twenty-eight cohorts contributed to the GWA study meta-analysis of European-ancestry individuals including a total of 57,813 individuals:
the Atherosclerosis Risk in Communities Study (ARIC, n=9,256), the British 1958 Birth Cohort (B58BC, n=6,085), CARDIA (n=1,435), the Cardiovascular Health Study (CHS, n=3,227), the Framingham Heart Study (FHS, n=7,022), the Helsinki Birth Cohort Study (HBCS, n=1,401), InChianti, n=1,196), KOCULA, n=801), LBC1921 (n=486), LBC1936 (n= 989), the Marseille Thrombosis Association (MARTHA08, n=613 and MARTHA10, n=374), MESA, n=2,404), the MONICA/KORA study (n=1,523+1788), NTR n=2,490, ORCADES (n=883), the Precocious Coronary Artery Disease Study (PROCARDIS) cases (n=3,489+1168) and controls (n=2,224), PROSPER (n=5,104), RSI (n=2,433), SardiNIA (n=4,691), SHIP (n=3,841), SPLIT (n=492), TwinsUK (n=2,058), VIS (n=882), and Woman's Genome Health Study (WGHS, n=23,080).

Fibrinogen levels were natural log-transformed in all cohorts except for Twins UK. Association of SNPs with fibrinogen levels was tested using a linear regression analysis assuming an additive genetic model in which allele dosage (0 to 2 copies of the minor allele) of genotyped or imputed SNPs, using MACH2QTL (LBC, MARTHA), ProbABEL 0.1-3[51] (WGHS, B58C, KORA, PROSPER, CROATIA-Vis, CROATIA-Korcula, CROATIA-Split, ORCADES, RS, CARDIA, HBCS, ARIC), Stata (PROCARDIS, B58C), SAS (KORA), MERLIN (InCHIANTI, SardiNIA), QUICKTEST v0.95 (http://toby.freeshell.org/software/quicktest.shtml) (SHIP), SNPtest v.1.2 (NTR) and PLINK[41] (MARTHA, HBCS) softwares, incorporating dosage information and including age and sex as covariates in the model. TwinsUK used a score test and variance components methods implemented in MERLIN to account for zygosity and family structure. The B58C adjusted for sex, laboratory batch, time of day, month of examination, and postal delay. ARIC also adjusted for center. Population stratification was accounted for by further adjustment for principal components, multidimentional scaling or country when necessary (MARTHA, PROCARDIS, PROSPER, CROATIA-Vis, CROATIA-Korcula, CROATIA-Split and ORCADES). Family structure was accounted for in FHS, PROCARDIS, CROATIA-Vis, CROATIA-Korcula, CROATIA-Split, and ORCADES. In FHS, a linear mixed effects model was used with a fixed additive effect for the SNP genotype, fixed covariate effects, random family-specific additive residual polygenic effects to account for within family correlations, and a random environment effect [52].
Individuals using anticoagulant therapy were excluded in B58C, PROCARDIS,MARTHA08 and MARTHA10).

Samples with high missing rate and cryptic IBS were excluded from the analysis. Participants who used warfarin or whose fibrinogen measurement was off 6SD from the mean were excluded in ARIC. Subjects were excluded when values of fibrinogen exceeded 6 pg/ml or when they were using anti-inflammatory medication or medication influencing the HPA-axis at the time of sampling in NTR.

Genomic control correction was applied to the individual cohorts. Lambda values for the individual GWAS were: PROCARDIS_Cases 1.008; PROCARDIS_Cases.imm 1.016; PROCARDIS_Controls 1.011; FHS 1.018; WGHS 1.066; SardiNIA 0.977; RS 0.998; SHIP 1.034; CARDIA 1.001; PROSPER_PHASE 1.021; CHS 1.027; LBC1921 1.002; LBC1936 1.008; MARTHA08 0.977; MARTHA10 0.977; VIS 1.006; KORCULA 1.001; SPLIT 1.005; ORCADES 1.006; B58C 1.034; MONICA_KORA_F3 1.018; MONICA_KORA_F4 1.013; InCHIANTI 1.018; TwinsUK 0.977; NTR 1.023; HBCS 1; ARIC 1.034; MESA 1.001.The overall measure of genomic inflation from the meta-analysis was λ=1.147. Additional meta-analyses were also performed in cohorts grouped by method used for plasma fibrinogen determination (immunonephelometric or activity method), and heterogeneity P values were calculated using METAL.
GWA analyses were repeated in each of the European-ancestry samples using the same model as in discovery, with additional conditioning on the SNP with the lowest *P*-value (the "lead SNP") within each genome-wide significant locus from the discovery meta-analysis. Conditional meta-analyses was performed in 21 European-ancestry cohorts, including more than 76,600 individuals, and individual cohort results were subsequently meta-analyzed as described above.

Statistical analyses in non-European samples:

For the validation in other ethnicities, allelic dosage at each SNP was used as the independent variable, adjusted for age and sex. Analyses were performed using the snpMatrix (WHI) or GWAF (GeneSTAR)

analysis packages in R. Samples with high missing rate, cryptic IBS, and population stratification outliers were excluded from the analysis. GeneSTAR accounted for familial correlations and excluded samples identified with gender discrepancy, Mendelian inconsistency rate > 5%, or as EIGENSTRAT outliers. To adjust for population stratification, 10 principal components were also incorporated as covariates in the regression models (WHI). For the four CARe AA Cohorts (ARIC, CARDIA, CFS, and MESA), measurement for fibrinogen was regressed on age, gender, and cohort-specific covariates in a linear regression model and residuals were output for use in the genetic analysis. For all CARe cohorts but CFS, the genetic analysis was performed in PLINK[41] using a linear regression model under the assumption of an additive genetic effect. Dosage information of directly measured and imputed genotypes was analyzed in the regression implemented in PLINK with the adjustment for the first ten principal components.
For CFS, the family structure was modeled in the genetic association tests by linear mixed effects (LME) models implemented in R.[53] Similar to the analysis of the cohorts of unrelated individuals, an additive genetic model was used with the adjustment for the first ten principal components, and dosage information was analyzed for genotyped and imputed SNPs in the regression model implemented in R routines.

Exclusions: Samples were excluded if they had missing gender information, genotyping success rate <95% , extreme heterozygosity rates, cryptic relationships, high number of Mendel errors in families, a high number of discordant genotypes at SNPs common to both the Affy6.0 platform and the ITMAT-BROAD-CARe (IBC) array,[54] or were contaminated samples, duplicates, outliers in the nearest neighbour and "clustering based on missingness" analyses in PLINK, and samples unlikely to be from African-Americans based on principal component analysis results. In addition, users of anti-coagulation treatment, those with extreme raw fibrinogen values (off 6SD from the mean), and genetic outliers were also excluded.

For all meta-analysis performed in this study, summary *β* and standard error (SE) estimates as well as *P* values, which were corrected for the GWA inflation coefficient computed for each cohort, were calculated for all SNPs. SNPs with low imputation quality (<0.3), low MAF (<0.01), or present in less than one third of the studies were excluded from the meta-analysis. All QC checks and meta-analyses were conducted in parallel at two sites by independent researchers. The results were later compared and differences were checked for correctness.

Expression data analyses:
Total RNA from human ASAP liver specimens was isolated using RNAlater (Ambion, Austin, Tex), Trizol (BRL-Life Technologies) and Rneasy Mini kit (Qiagen), including treatment with RNase-free DNase set (Qiagen) according to the manufacturer's instructions. RNA quality was determined with an Agilent 2100 bioanalyzer (Agilent Technologies Inc., Palo Alto, CA, USA), and quantity was measured by a NanoDrop (Thermo Scientific). Global gene expression in ASAP data was obtained for these samples using Affymetrix ST 1.0 Exon arrays and genotyping in was performed on Illumina Human 610W-Quad Beadarrays, with subsequent imputation based on the 1000 Genomes CEU reference panel. Associations between SNP genotype and gene expression level were examined using additive linear models. P values for all genotype-gene expression level combinations were included in an FDR calculation, which was conducted by using the Benjamini-Hochberg method[55], as implemented in the

multtest R-package R-2.13.0 (http://www.bioconductor.org/packages/release/bioc/html/multtest.html). Further details about the methods used in ASAP are described elsewhere[56].

Heritability estimation methods:

For **FHS**, heritability was estimated using a variance components model implemented in SOLAR[57] software adjusted for covariates age and sex (Sequential Oligogenic Linkage Analysis Routines).

The **SardiNIA** cohort is a family-based cohort including 6,148 individuals organized into 1,246 multiple complex pedigrees up to five generations each. Heritability was estimated using a variance components model to take into account different types of familial relatedness in estimating the correlation among individuals, and simultaneously adjust for non-genetic effects of covariates, such as age, age2 and gender as previously described [3].

For **Croatia-Vis Croatia-Korcula and Orcades**, effects of covariates and variance components were estimated by maximum likelihood in a general linear mixed model.

Heritability was estimated using the polygenic function of GenABEL with sex and age as fixed effects and an additive polygenic effect and a residual effect as random effects. The pair-wise kinship coefficients were estimated from the genomic data using the gkin function of GenABEL.

For the **NTR**, heritability analyses were performed by comparing the resemblance in fibrinogen of monozygotic (MZ) and dizygotic (DZ) twins as well as between non-twin siblings and parents and offspring. A total of 7707 family members were used in the analysis.

Zygosity of the same-sex twins was determined by DNA typing for 29% of the pairs. For the other twin pairs, zygosity was based on eight items on physical similarity and the frequency of confusion of the twins by parents, other family members and strangers. Agreement between zygosity based on these items and zygosity based on DNA is 97%.

Extending the classical twin design with additional family members such as non-twin siblings and parents [58, 59] makes it possible to simultaneously estimate the contribution of shared environmental as well as additive and dominant genetic factors to the variance in fibrinogen. Potential assortative mating is taken into account by co-modeling the spouse correlation. Structural equation modeling in Mx [60] was employed to obtain a saturated model that estimated the correlations between fibrinogen in twins, siblings and their parents. In total, 10 correlations were estimated: 1 correlation between the parents, 4 parent-offspring correlations (father-son, father-daughter, mother-son and mother-daughter) and 5 twin and sibling correlations (MZM, MZF, DZM = male sibling/male sibling = male sibling/male twin, DZF = female sibling/female sibling = female sibling/female twin, and DOS = opposite-sex sibling/opposite-sex sibling = opposite-sex sibling/opposite-sex twin) after establishing that the twin/twin and twin/sib correlations could be equated. Next the variance in fibrinogen in individuals in the parental and offspring generations was decomposed into genetic and environmental variances, while modeling the effects of phenotypic assortative mating between parents. We used the factor model described by Neale and colleagues.[61] The variance decomposition was assumed to be stable across generations.

In the model that best fitted the observed variance-covariance matrices, additive genetic and shared environmental factors entirely accounted for the familial resemblance. Heritability of fibrinogen was 31%, the shared environment accounted for 10% of the variance in fibrinogen. More than half of the

variance in fibrinogen (59%) was due to environmental factors unique to each individual which also include measurement error.

The proportion of variance in plasma fibrinogen concentration accounted for by the lead SNPs and the corresponding proportion of variance explained by the effect of smoking and BMI were computed using data from 88,251 European-ancestry by regressing the natural log-transformed fibrinogen residuals, after adjustment for age and sex (and cohort specific covariates), against the lead SNPs (or the effect of smoking and BMI). The mean, median and standard deviation of r^2 values obtained in individual cohorts were reported.

Given the known positive associations of BMI and smoking with the plasma fibrinogen concentration, we also calculated the proportion of variance explained by these two covariates in our sample.

GRS methods

The GRS was computed for each individual by weighting the dosage number of fibrinogen-raising alleles by the global beta value of the allele (obtained from the European-ancestry meta-analysis). The added weighted dosage number of all lead SNPs (genotype score per individual) was then rescaled from 0 to 100 for each individual. All cohorts reported fibrinogen mean and standard deviation values for a set of pre-defined genotype score intervals. In addition, we used the genotype scores from the European-ancestry discovery analysis to examine associations with plasma fibrinogen concentration in the African-American and Hispanic cohorts, using methods described elsewhere.[62]

Power calculations

We used a freely available power calculator (http://pngu.mgh.harvard.edu/~purcell/gpc/)[63] in order to assess the statistical power for the replications in African-American and Hispanic samples, as well as the lookups in stroke and VTE.

For the calculations of the replication sample size, we assumed an average variance explained by the 24 lead-SNPs of 0.16% (3.7%/24 SNPs). According to this, the replication sample size in African-American was estimated to have 72% power to detect a SNP explaining 0.16% of the variance in fibrinogen level, whereas the Hispanic sample was estimated to have 58% power to detect a SNP explaining this same proportion of the variance in fibrinogen level.

Assuming a prevalence of CAD of 0.073, we had 74% power to detect the effect of any SNP with MAF > 0.1 associated with an Odds Ratio of 1.05 (highest OR from our results, rs11242111) at the significance level of 0.002. The minimum OR required for 80% power in these conditions would be 1.052. In contrast, assuming a prevalence of stroke of 0.005, we had 4% power to detect the effect of any SNP using the same parameters. The minimum OR required for 80% power in these conditions would be 1.146. Finally, assuming a prevalence of VTE of 0.004, we had 4% power to detect the effect of any SNP using the same parameters. The minimum OR required for 80% power in these conditions would be 1.173.

Supplementary Results:
Heritability estimates and Proportion of Variance Explained by the SNPs.

Heritability estimation was conducted in participating family studies. Cohort-specific and overall average heritability estimates are summarized below:

CROATIA_Vis	0.15
CROATIA_Korcula	0.46
ORCADES	0.16
FHS	0.51
SardiNIA	0.25
NTR	0.31
average	**0.31**
SD	**0.15**

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Supplementary Table S1: Cohort characteristics for the participants in the meta-analysis performed in European-descent individuals.

Cohort name	Counts	Mean age, years (SD)	Male, %	BMI, kg/m^2 (SD)	Arterial disease hx, %	Current smokers, %	Venous disease hx, %	T2D, %	Measurement	Assay Type	Fibrinogen Mean (SD), g/l	Ln Fibrinogen Mean (SD)
Procardis imm controls	2224	55.2 (8.3)	76.1	26.3 (3.77)	0	20.8	NA	2.3	EDTA	imm-neph	3.53 (0.83)	1.24 (0.23)
Procardis imm cases	1168	63.6 (6.9)	68.4	28.7 (4.65)	100	56.3	NA	14.6	EDTA	imm-neph	4.48 (1.00)	1.48 (0.22)
Procardis Clauss	3489	61.9 (7.4)	75.5	28.3 (4.87)	100	50.3	NA	15.2	Citrate	Clauss	3.85 (0.86)	1.32 (0.22)
FHS	7022	46.6 (11.5)	46.1	27.0 (5.20)	10.8	18.9	NA	4.8	Citrate	Clauss	3.2 (0.7)	1.2 (0.2)
WGHS	23080	54.7 (7.1)	0	25.9 (5.00)	0	0.1	0.03	0.03	Citrate/EDTA	imm--turb	3.59 (0.78)	1.26 (0.21)
SardiNIA	4691	43.3 (17.6)	43.7	25.3 (4.68)	3.3	19.8	NA	2.2	Citrate	Clauss	3.28 (0.66)	1.19 (0.2)
RS	2068	70.8 (9.0)	36.8	26.5 (3.90)	7.9	22.2	NA	11.8	Citrate	Funtional*	2.81 (0.69)	1.03 (0.2)
SHIP	3841	48.8 (16.1)	48.5	27.2 (4.76)	NA	31.4	NA	8.2	Citrate	Clauss	2.99 (0.70)	1.07 (0.22)
CARDIA	1435	25.6 (3.3)	47	25.4 (5.09)	10.8	20.3	NA	1.1	Citrate/EDTA	imm-neph	3.18 (0.66)	1.14 (0.20)
PROSPER/PHASE	5244	75.3 (3.4)	47	26.8 (4.20)	45	27	0	10	EDTA	Clauss	3.60 (0.74)	1.26 (0.21)
CHS	3227	72.3 (5.4)	39	26.3 (4.42)	0	11.4	4.34	14	Citrate	Clauss	3.15 (0.62)	1.13 (0.19)
LBC1936	989	69.6 (0.8)	50.8	27.8 (4.42)	28.4*	12.6	NA	7.7	Citrate	Clauss	3.27 (0.63)	1.17 (0.19)
LBC1921	486	79.1 (0.6)	42.6	26.2 (4.11)	34.5 *	6.6	NA	4.9	Citrate	Clauss	3.59 (0.86)	1.25 (0.24)
MARTHA08	613	44.1 (14.2)	23.8	24.3 (4.41)	<1	25.9	100	NA	Citrate	Clauss	3.36 (0.68)	1.19 (0.2)
MARTHA10	374	47.3 (15.8)	36	25.7 (4.78)	<1	24.2	100	NA	Citrate	Clauss	3.41 (0.74)	1.21 (0.21)
CROATIA-Split	492	49.1 (14.6)	42.5	26.9 (4.18)	NA	24.8	NA	4.9	Citrate	Clauss	3.84 (1.17)	1.30 (0.30)
CROATIA-Korcula	801	56.3 (15.6)	35.3	28.0 (4.14)	NA	25.3	NA	8.4	Citrate	Clauss	4.56 (1.51)	1.47 (0.33)
CROATIA-Vis	882	56.3 (15.6)	42.7	27.4 (4.28)	NA	24	NA	5.7	Citrate	Clauss	3.57 (0.80)	1.25 (0.22)
ORCADES	882	53.6 (15.8)	45.2	27.7 (4.84)	NA	6.8	NA	3.4	Citrate	Clauss	3.48 (0.86)	1.22 (0.23)
B58C	6085	45.2 (0.4)	49.7	27.4 (4.85)	NA	23.5	NA	1.5	Citrate	Clauss	2.95 (0.60)	1.06 (0.20)
KORA F3	1523	52.1 (10.2)	49.3	27.2 (4.10)	0.7	18.1	NA	3.7	EDTA	imm-neph	2.89 (0.66)	1.03 (0.22)
KORA F4	1788	53.9 (8.9)	48.9	27.7 (4.50)	2.1	20.1	NA	3.5	EDTA	imm-neph	2.67 (0.60)	0.96 (0.22)
InCHIANTI	1196	68.4 (15.4)	44.4	27.2 (4.14)	15.5	18.8	NA	11.2	Citrate	Clauss	3.51 (0.77)	1.23 (0.22)
Twins UK	2049	49.3 (12.4)	4.7	25.6 (4.53)	1.1	NA	NA	NA	Citrate	Clauss	2.99 (0.78)	1.06 (0.24)
HBCS	1401	61.4 (2.9)	40.2	27.4 (4.50)	NA	23.9	NA	11.7	EDTA	Clauss	3.23 (1.04)	1.12 (0.34)
NTR	2490	48.0 (14.0)	37.6	25.5 (4.02)	2.4	20.3	6.3	3.8	Citrate	Clauss	2.79 (0.66)	1.00(0.25)
ARIC EA	9256	54.3 (5.7)	47.1	27.0 (4.80)	6.35	24.6	2.01	8.6	Citrate	Clauss	2.97 (0.61)	1.07 (0.20)
MESA	2527	62.7 (10.2)	47.7	27.7 (5.07)	NA	11.4	NA	6.0	Citrate	imm-neph	3.35 (0.70)	1.19 (0.21)

Imm-neph= immunonephelometric; imm-turb= immunoturbidimetric; *Functional PT-derived method (Rossi E, Mondonico P, Lombardi A, Preda L. Method for the determination of functional (clottable) fibrinogen by the new family of ACL coagulometers. Thromb Res. 1988;52:453-68).

Supplementary Table S2: Cohort characteristics for the participants in the meta-analysis performed in individuals of African-American- or Hispanic descent.

Cohort name	Counts	Mean age, years (SD)	Male, %	Ancestry	BMI, kg/m2 (SD)	Arterial disease, %	Current smokers, %	Venous disease, %	T2D, %	Measurem.	Assay Type	Fibrinogen Mean (SD), g/l	Ln Fibrinogen Mean (SD)
ARIC	2609	53.2 (5.8)	36.8	African American	29.6 (6.0)	5.8	30.1	3.1	17.9	Citrate	Clauss	3.19 (0.72)	1.14 (0.22)
MESA	1677	62.2 (10.1)	46.0	African American	30.1 (5.9)	NA	18.3	NA	17.1	Citrate	Imm-neph	3.60 (0.79)	1.25 (0.22)
MESA	1447	61.4 (10.3)	48.4	Hispanic	29.5 (5.1)	NA	13.4	NA	17.8	Citrate	Imm-neph	3.59 (0.75)	1.26 (0.20)
GeneSTAR	1144	44.5 (11.5)	38	African American	31.6 (7.6)	6.5	32	0	14	Citrate	Clauss	3.99 (1.3)	1.34 (0.31)
WHI-SHARe	1087	62.3 (7.2)	0	African American	31.5 (6.3)	6.4	11.3	2.7	16	Citrate	Clauss	3.25 (0.70)	1.18 (0.22)
CARDIA	809	24.5 (3.8)	38.2	African American	25.5 (5.7)	NA	29.2	NA	0.7	EDTA	Imm-neph	3.42(0.80)	1.20 (0.23)
CHS	784	72.8 (5.5)	37.0	African American	28.5 (5.5)	18.2	16.0	5.4	24.6	Citrate	Clauss	3.44 (0.75)	1.21 (0.21)
CFS	313	41.4 (18.5)	40.3	African American	33.3 (9.9)	NA	31	NA	24	Plasma	Clauss	3.23 (0.82)	1.13 (0.27)

Imm-neph= immunonephelometric; Measurem.= measurement; T2D=Type II Diabetes

Supplementary Table S3: Genotyping details for the participants in the meta-analysis performed in European-descent individuals.

				SNP exclusion criteria*								
	Platform	**Chip**	**SNPs gen**	**Call rate**	**MAF**	**HWE p-value**	**Variants included for imputation**	**Percent of variants included**	**Imputation software**	**Imputation software version**	**Genome build**	**Total # of SNPs**
PROCARDIS	Illlumina	1M,Human610-Quad	573,015 (1M) 582,892 (610)	<0.95	<0.01	<1 x 10^{-6}	498,717 (1M) 514,950 (610)	0.87 (1M) 0.88 (610)	MACH	1.0.16	36	2,543,888
FHS	Affymetrix	500K + 50K	490,700 (500K) 48,195 (50K)	≤0.97		<1 x 10^{-6}	343,361 (500K) 34,841 (50K)	0.70 (500k) 0.72 (50K)	MACH	1.0.15	36.2	2,543,887
WGHS	Illumina	HumanHap300 Duo "+"	339,596	<0.90	<0.01	<1 x 10^{-6}	328,963	0.97	MACH	1.0.16	36	2,608,508
SardiNIA	Affymetrix	10K+500K+1000K	9,941 (10K) 490,033 (500K) 893,634 (1000K)	<90% (10K/500K) and <95% (6.0)	<0.05 (10K and 500K) <0.01 (1000K)	<1 x 10^{-3} (10K) and p <1 x 10^{-6} (500K and 1000K)	7,134 (10K) 339,003 (500K) 727,541 (1000K) Combined: 731,209	0.72 (10K) 0.69 (500K) 0.81 (1000K)	MACH	1.0.10	36.3	2,325,980
RS	Illlumina	Illumina Infinium II HumanHap550	530,683	<0.95	≤0.01	<1.0x10^{-5}	491,875	0.93	MACH	1.0.15	36	2,586,725
SHIP	Affymetrix	1000K	869,224				869,224	1	IMPUTE	0.5.0	36	2,748,910
CARDIA	Affymetrix	1000K	909,622	<0.95	≤0.02	<1.0x10^{-4}	578,568	0.64	BEAGLE	3.2	36	2,276,435
PROSPER/PHASE	Illumina	Human660W-Quad	561,490	<0.97	no	<1 x 10^{-6}	557,192	0.99	MACH	1.0.15	36.2	2,543,887
CHS - EA	Illumina	370 CNV	306,655	≤0.97		<1.0x10^{-5}	291,322	0.95	BIMBAM	0.99	36	2,543,887
LBC1936	Illumina	Human610-Quad	542,050	<0.95	<0.01	<0.001	535,709	0.99	MACH	1.0.16	36	2,543,887
LBC1921	Illumina	Human610-Quad	542,050	<0.95	<0.01	<0.001	535,709	0.99	MACH	1.0.16	36	2,543,887
MARTHA08	Illlumina	Human610-Quad	567,589	<0.99	<0.01	<1 x 10^{-5}	494,721	0.87	MACH	1.0.16	35	2,557,252
MARTHA10	Illlumina	Human660W-Quad	556,776	<0.99	<0.01	<1 x 10^{-5}	501,773	0.90	MACH	1.0.16	35	2,557,252
CROATIA-Split	Illumina	HumanHap 370CNV-Quad	351,514	≤0.98	≤ 0.01	<1 x 10^{-6}	321,456		MACH	1.0.16	36	2,543,887
CROATIA-Korcula	Illlumina	HumanHap 370CNV-duo/Quad	346,034	<0.98	<0.01	<1 x 10^{-6}	307,625		MACH	1.0.16	36	2,543,887
CROATIA-Vis	Illumina	HumanHap 300v1	317,509	≤0.98	≤0.01	<1 x 10^{-6}	289,827		MACH	1.0.16	36	2,543,887
ORCADES	Illlumina	HumanHap 300v2	351,454	<0.98	<0.01	<1 x 10^{-6}	285,491		MACH	1.0.16	36	2,543,887
B58C	Illumina	550K or Human610-Quad	532,203	<0.95	<0.01	<0.0001	482,570	0.93	MACH	1.0.16	35	2,557,252
KORA F3	Affymetrix	500K	490,032	no	no	no	490,032	1	MACH	1.0.9	35;21	2,557,252
KORA F4	Affymetrix	1000K	906,716	< 0.93	no	no	651,596	0.72	MACH	1.0.15	36;22	2,543,887
InCHIANTI	Illlumina	550K	549,892	<0.99	≤0.01	<1 x 10^{-6}	495,343	0.90	MACH	1.0.16	36	2,543,887
TwinsUK	Illumina	HumanHap300, HumanHap610Q, 1M-Duo and 1.2MDuo 1M	NA	≤0.97, ≤0.99 (0.01<MAF<0.05)	≤0.01	<1 x 10^{-6}	874,733	NA	IMPUTE	2	36	2,657,660

HBCS	Illumina	modified 610k	509,947	none	none	none	---	---	MACH	---	36	2,544,887
NTR	Perlegen, Affymetrix, Illumina	660K (PA), 660K(I1), 370K (I2)	599,156 (PA) 657,366 (I1) 370,404 (I2)	<0.95	≤0.01	<0.00001	427,099 (PA) 528,027 (I1) 318,237 (I2)	71% (PA) 80%(I1) 85%(I2)	IMPUTE	1	36	2,538,588
ARIC EA	Affymetrix	1000K	841,820	<0.95	≤0.01	$<1.0x10^{-5}$	669,450	0.795	MACH	1.0.16	36	2,543,887
MESA	Affymetrix	1000K	854,756	<0.95	≤0.01	$<1.0x10^{-6}$	854,756	0.85	IMPUTE	2.1.0	36	2,545,579

SNPs gen= single nucleotide polymorphisms genotyped.

Supplementary Table S4: Genotyping details for the participants in the meta-analysis performed in African American and Hispanic-descent individuals.

Cohort	Genotyping Details			SNP exclusion criteria*			Imputation Details					
	Platform	Chip	SNPs gen	Call rate	MAF	HWE p-value	Variants included for imputation	Percent of variants included	Imputation software	Imputation software version	Genome build	Total # of SNPs
ARIC AA	Affymetrix	1000K	909,622	<0.95	<0.01	None†	Not available‡	Not available‡	MACH	1.0.16	36	2,796,485
MESA	Affymetrix	1000K	841,820	<0.95	<0.01	<1e-6	854,756	0.85	IMPUTE	2.1.0	36	~2.5M
GeneSTAR	Illumina	1Mv1_C	1,043,165	<0.90		<1e-8	687,132	0.659	MACH	1.0.16	36	2,507,621
WHI	Affymetrix	1000K	871,309	≤0.97			854,981	70% (500k) 72% (50K)	MACH	1.0.16	36.2	2,426,484
CARDIA	Affymetrix	1000K	909,622	<0.95	<0.01	None†	Not available‡	Not available‡	MACH	1.0.16	36	2,807,954
CHS – AA	Illumina	HumanOmni1-Quad_v1	1,140,419	≤0.97		$<1.0x10^{-5}$	963,248	0.95	BEAGLE	3,2.1	36	2,770,583
CFS AA	Affymetrix	1000K	909,622	<0.95	>0.01	None†	Not available‡	Not available‡	MACH	1.0.16	36	2,547,353

†Hwe: The Hardy-Weinberg equilibrium (HWE) test was performed for all SNPs, but SNPs were not excluded based uniquely on this criterion given the admixed nature of the African American cohorts genotyped; ‡Not provided by CARe.

Supplementary Table S5. Candidate genes at newly discovered susceptibility loci for fibrinogen levels.

The table lists genes of interest in the novel associated regions. For each associated region, the reported gene either contains the lead SNP or is in closest physical proximity with the lead SNP.

SNP	Location	Gene	Function
rs789678	10q21.3	*JMJD1C*	*Jumonji domain containing 1C e*ncodes thyroid-hormone-receptor interactor 8, a hormone-dependent transcription factor that regulates expression of a variety of specific target genes[64]. This locus has been found associated with levels of the liver enzyme alkaline phosphatase (ALP) and plasma lipid concentration [65-67]. In addition, it is also associated with mean platelet volume and epinephrine-induced platelet aggregation[68, 69]. The associated SNP is in intron 2 of the gene.
rs1938492	1p31	*LEPR*	Encodes the leptin receptor, an adipocyte-specific hormone that regulates body weight, and is involved in the regulation of fat metabolism, as well as in a novel hematopoietic pathway that is required for normal lymphopoiesis. Mutations in this gene have been associated with obesity and pituitary dysfunction. This locus has been associated with levels of the acute-phase proteins C-reactive protein (CRP) and serum amyloid A (A-SAA) [70, 71]. Recently, genetic variability at the *LEPR* locus has been shown to influence also plasma levels of fibrinogen[72]. The associated SNP maps in an intergenic region about 14 kb upstream of *LEPR*, which is the closest gene.
rs4817986	21q22.2	*PSMG1*	Encodes the proteasome assembly chaperone 1, involved in the maturation of mammalian 20S proteasomes[73]. This locus is found associated with two closely related inflammatory conditions, inflammatory bowel disease (IBD)[74], and, although not conclusively, with ankylosing spondylitis[75]. In addition, this locus is also found associated with levels of the acute-phase protein CRP[70]. The associated SNP maps about 82 kb downstream of the gene, which is the closest gene in the region.
rs7204230	16q12.2	*CHD9*	Encodes the chromatin-related mesenchymal modulator (CReMM), a member of the third subfamily of chromodomain helicase DNA-binding proteins (CHD) which play a role in chromatin remodeling[76]. It is expressed by osteoprogenitors, where it mediates the transcriptional response to hormones that coordinate osteoblast function. Furthermore, it binds to nuclear receptors such as PPARalpha, CAR, ERalpha, and RXR and with transcription cofactors CBP, PRIP, and PBP. In particular, CHD9 acts as a transcription coactivator by stimulating PPARalpha-mediated transcription, which is in turn involved in proliferation of peroxisomes in liver, induction of PPARalpha target genes including those involved in fatty acid oxidation, and the eventual development of liver tumors[77]. The associated SNP is in intron 2 of the gene.
rs10226084	7p21.1	*SNX13*	Encodes a PHOX domain- and RGS domain-containing protein that belongs to the sorting nexin (SNX) family and the regulator of G protein signaling (RGS) family[78]. The PHOX domain is a phosphoinositide binding domain, and the SNX family members are involved in intracellular trafficking. The RGS family members are regulatory molecules that act as GTPase activating proteins for G alpha subunits of heterotrimeric G proteins. Overexpression of this protein delayes lysosomal degradation of the epidermal growth factor receptor. Because of its bifunctional role, this protein may link heterotrimeric G protein signaling and vesicular trafficking. The associated SNP maps about 17 kb upstream of *SNX13*, which is the closest gene in the region.
rs12915708	15q21.2	*SPPL2A*	This gene is a member of the signal peptide peptidase-like protease (SPPL) family and encodes an endosomal membrane protein with a protease associated (PA) domain, which plays a role in innate and adaptive immunity. SPPL2A together with SPPL2B catalyses intramembrane cleavage of tumour necrosis factor alpha (TNFalpha), which in turn triggers expression of the pro-inflammatory cytokine interleukin-12 by activated human dendritic cells[79]. Furthermore, SPPL2A with ADAM10 is implicated in FasL processing and release of the FasL ICD, which has been shown to be important for retrograde FasL signaling[80]. The associated SNP is in intron 2 of the gene.
rs7464572	8q24	*PLEC1*	Plectin is a member of a family of structurally and in part functionally related proteins, termed plakins, that are capable of interlinking different elements of the cytoskeleton. Plakins play crucial roles in maintaining cell and tissue integrity and orchestrating dynamic changes in cytoarchitecture and cell shape, but also serve as scaffolding platforms for the assembly, positioning, and regulation of signaling

			complexes. It has been shown that, via effects on cytoskeletal organization, plectin deficiency might play an important role in the transformation of human liver cells[81]. In addition, RNA interference-mediated inhibition PLEC1 reduced IL-6 production by macrophages stimulated with LPS, suggesting a role for this gene in innate immunity[82]. Recently, this gene has been associated with HDL and total cholesterol levels[83]. The associated SNP is in intron 2 of the gene.
rs1476698	2q37.3	*FARP2*	Encodes a Dbl family guanine nucleotide exchange factor (GEF) specific for Rac1. GEFs from the Dbl family integrate extracellular signaling with appropriate activation of Rho GTPases in specific subcellular regions. FARP2 plays a key role in the regulation of Rac1 and integrin β3 throughout podosome rearrangement in osteoclastogenesis[84]. Furthermore, it is a risk locus for chronic lymphocytic leukemia (CLL) and monoclonal B-cell lymphocytosis (MBL), a condition predisposing to CLL [85, 86]. It is also a candidate gene for the high-density lipoprotein (HDL) cholesterol locus on mouse chromosome 1 and is associated with HDL cholesterol in humans[87, 88]. The associated SNP is in intron 1 of the gene.
rs1019670	11q12.1	*MS4A6A*	Encodes a member of the membrane-spanning 4A (MS4A) gene family, which display unique expression patterns among hematopoietic cells and nonlymphoid tissues. The genes in the *MS4A* cluster on chromosome 11 are characterized by similar intron/exon splice boundaries and common structural features, including transmembrane domains indicating that they are likely to be part of a family of cell surface proteins. MS46A has no known specific function and has been identified as a susceptibility locus for Alzheimer's disease[89]. Furthermore, it is associated with levels of the coagulation factor VII, supporting a role in the regulation of fibrinogen[90, 91]. The associated SNP is in exon 6 of the gene and causes a non-synonymous aminoacid change (Thr/Ser) at position 185 of the protein.
rs2286503	7p15.3	*TOMM7/IL6*	Encodes a small regulatory component of the translocase of the outer mitochondrial membrane (TOM), a general import pore complex that translocates preproteins into mitochondria. TOMM7 is a risk locus for type 2 diabetes in Mexican-Americans, although there is little literature suggesting roles for TOMM7 in diabetes[92]. In HapMap Europeans, LD extends from this region to include the susceptibility gene for type 2 diabetes *IL-6*. Interestingly, the pro-inflammatory cytokine IL-6 upregulates expression of tissue factor, a central player in the initiation of coagulation, supporting a role also in fibrinogen levels[93]. Furthermore, IL-6 is associated with CRP levels. Although the associated SNP maps in intron 3 of *TOMM7*, the best candidate in the region appears the *IL-6* gene, located about 85 kb upstream.
rs434943	14q22-q24	*ACTN1*	Encodes alpha (α) actinin, a ubiquitous cytoskeletal protein that belongs to the superfamily of filamentous actin (F-actin) crosslinking proteins, with multiple roles in different cell types. Four isoforms of α-actinin have been identified namely, the "muscles" α-actinin-2 and α-actinin-3 and the "non-muscles" α-actinin-1 and α-actinin-4, which are generally believed to represent key structural components of large-scale F-actin cohesion in cells required for cell shape and motility. The role of non-muscles α-actinin in the liver is unknown, however α-actinin is expressed on the membrane and cytosol of cells of the liver and it seems that it interacts with hepatitis C virus and is essential for the replication of the virus, suggesting that α-actinin might play a role in the pathogenesis of liver diseases. In addition, α-actinin is as a target autoantigen in the pathogenesis of autoimmune diseases, particularly systemic lupus erythematosus and autoimmune hepatitis[94]. A role in the immune response is also supported by the co-localization of ACTN1 (A-1) with actin and SPA-1 at the immunological synapse in T cells[95]. Interestingly, tyrosine phosphorylation of non-muscle α-actinin is induced by platelet activation, which is associated with a decrease in the affinity of α-actinin for actin[96]. This could in turn affect the mechanical properties of the actin cytoskeleton and induce platelet spreading. The associated SNP maps in an intergenic region about 27 kb downstream of *ACTN1*, which is the closest gene.
rs16844401	4p16	*HGFAC*	Encodes the hepatocyte growth factor activator (HGF activator), a serine protease which converts single-chain HGF to the active two-chain form. HGF activator is first synthesized as an inactive single-chain precursor, homologous to blood coagulation factor XII, that is activated to a heterodimeric form by endoproteolytic processing by thrombin. Thrombin-activated HGF activator then converts single-chain HGF, which is homologous to the fibrinolysis factor plasminogen, to the active two chain form that functions as a growth factor for

			parenchymal liver cells and may be involved in repairing the injured liver[97]. The associated SNP maps in exon 12 of *HGFAC*.
rs12712127	2q12	*IL1R1*	Encodes a cytokine receptor for interleukin alpha (IL1A), interleukin beta (IL1B), and the interleukin 1 receptor antagonist (IL1RA). This gene along with IL1R2, IL1RL2, and IL1RL1 form a cytokine receptor gene cluster in chromosome 2q12. IL1R1, together with IL-1R2, the antagonist IL-1RA, and the accessory protein IL-1R AcP, is an important mediator of IL1 signaling and is involved in many cytokine induced immune and inflammatory responses, including coagulation and fibrinolysis, with an overall prothrombotic effect. However, previous investigation of common variations in *IL1R1* was not associated with increased risk of venous thrombosis[98]. *IL1RL1* polymorphisms are associated with serum IL1RL1-a, blood eosinophils, asthma and myocardial infarction[99, 100]. The associated SNP maps in an intergenic region of the chromosome 2q12 receptor cluster, about 44 kb downstream of *IL1R1*, which is the closest gene.
rs7968440	12q13.12	*DIP2B*	Encodes a member of the disco-interacting protein homolog 2 protein family. The protein contains a binding site for the transcriptional regulator DNA methyltransferase 1 associated protein 1 as well as AMP-binding sites, suggesting that it may participate in DNA methylation. *DIP2B* is located near a folate-sensitive fragile site, FRA12A, linked to mental retardation and individuals with the fragile site show a CGG-repeat expansion in its promoter, which affects *DIP2B* transcription[101, 102]. Common variants in *DIP2B* also influence risk of developing colorectal cancer. The associated SNP is located in intron 36 of the gene.
rs6010044	22q13.3	*SHANK3*	This gene is a member of the Shank gene family, which encodes multidomain scaffold proteins of the postsynaptic density that connect neurotransmitter receptors, ion channels, and other membrane proteins to the actin cytoskeleton and G-protein-coupled signaling pathways. Shank proteins also play a role in synapse formation and dendritic spine maturation. Mutations in this gene are a cause of autism spectrum disorder and of the neurological symptoms of 22q13.3 deletion syndrome[103, 104]. Furthermore, Shank3 is present in both EPEC- and *S. typhimurium*-induced actin rearrangements and is required for optimal EPEC pedestal formation, suggesting that this molecule is a host synaptic proteins likely to play key roles in bacteria-host interactions[105]. The associated SNP maps in an intergenic region about 11 kb downstream of *SHANK3*, which is the closest gene. Gene-set enrichment analysis using MAGENTA prioritized as most plausible candidate in this region the *CPT1B* gene (see below).
rs6010044	22q13.33	*CPT1B*	Encodes a member of the carnitine/choline acetyltransferase family, which is the rate-controlling enzyme of the long-chain fatty acid beta-oxidation pathway in muscle mitochondria. This enzyme is required for the net transport of long-chain fatty acyl-CoAs from the cytoplasm into the mitochondria. Multiple transcript variants encoding different isoforms have been found for this gene, and read-through transcripts are expressed from the upstream locus that include exons from this gene. Common nonsynonymous coding variants in *CPT1B* have been associated with ectopic skeletal muscle fat among middle-aged and older African ancestry men[106]. This gene takes part in adipocytokine signaling and is located about 90 kb downstream of the associated SNP.

Supplementary Table S6: Validation *P*-values in African-American and Hispanic cohorts for the 24 lead SNPs.

						European				African-American				Hispanic			
SNP	Band	Position	Closest gene	A 1	A 2	Freq	Beta	SE	*P*	Freq	Beta	SE	*P*	Freq	Beta	SE	*P*
rs1938492*	1p31.3	65890417	*LEPR*	A	C	0.62	0.008	0.001	$5.28X10^{-14}$	0.55	0.003	0.004	0.37	0.54	-0.009	0.007	0.19
rs4129267	1q21.3	152692888	*IL6R*	T	C	0.39	-0.011	0.001	$5.97X10^{-27}$	0.14	-0.011	0.006	0.04	0.47	-0.031	0.007	$2.10X10^{-05}$
rs10157379	1q44	245672222	*NLRP3*	T	C	0.62	0.01	0.001	$1.15X10^{-19}$	0.60	0.003	0.004	0.52	0.59	0.007	0.007	0.34
rs12712127	2q11.2	102093093	***IL1R1****/IL1R2*	A	G	0.41	0.006	0.001	$2.72X10^{-08}$	0.30	0.002	0.004	0.56	0.35	0.000	0.008	1.00
rs6734238	2q13	113557501	***IL1F10****/IL1RN*	A	G	0.58	-0.009	0.001	$5.77X10^{-19}$	0.56	-0.012	0.004	$1.94X10^{-03}$	0.66	-0.011	0.008	0.17
rs715	2q34	211251300	*CPS1*	T	C	0.68	0.009	0.001	$1.98X10^{-11}$	0.80	0.007	0.005	0.16	0.74	0.007	0.009	0.40
rs1476698	2q37.3	241945122	*FARP2*	A	G	0.65	0.007	0.001	$2.24X10^{-09}$	0.62	0.006	0.004	0.13	0.47	0.013	0.007	0.07
rs1154988	3q22.3	137407881	***MSL2****/PCCB*	A	T	0.78	-0.01	0.001	$9.64X10^{-17}$	0.70	-0.001	0.004	0.76	0.78	-0.018	0.009	0.04
rs16844401	4p16.2	3419450	***HGFAC****/LRPAP1*	A	G	0.08	0.015	0.003	$1.74X10^{-08}$	0.03	0.015	0.013	0.23	0.1	0.017	0.017	0.32
rs1800789	4q32.1	155702193	*FGB*	A	G	0.21	0.031	0.001	$1.68X10^{-127}$	0.10	0.032	0.006	$4.02X10^{-07}$	0.15	0.052	0.011	$6.89X10^{-07}$
rs11242111	5q31.1	131783957	***C5orf56****/IRF1*	A	G	0.05	0.023	0.002	$1.60X10^{-21}$	0.37	-0.003	0.004	0.44	0.09	-0.001	0.012	0.92
rs2106854	5q31.1	131797073	*C5orf56/IRF1*	T	C	0.21	-0.019	0.001	$1.72X10^{-48}$	0.24	-0.009	0.004	0.04	0.21	-0.024	0.009	$7.00X10^{-03}$
rs10226084	7p21.1	17964137	***SNX13****/PRPS1L1*	T	C	0.52	-0.007	0.001	$5.05X10^{-10}$	0.61	-0.004	0.004	0.36	0.49	-0.003	0.007	0.63
rs2286503	7p15.3	22823131	*TOMM7*	T	C	0.36	-0.006	0.001	$6.88X10^{-09}$	0.67	0.000	0.004	0.95	0.48	-0.002	0.007	0.76
rs7464572	8q24.3	145093155	*PLEC1*	C	G	0.6	-0.007	0.001	$1.33X10^{-09}$	0.88	-0.002	0.007	0.74	0.72	-0.015	0.008	0.06
rs7896783	10q21.3	64832159	*JMJD1C*	A	G	0.48	-0.01	0.001	$8.90X10^{-22}$	0.32	-0.010	0.004	0.01	0.31	-0.009	0.008	0.25
rs1019670	11q12.1	59697175	*MS4A6A*	A	T	0.36	-0.007	0.001	$4.37X10^{-09}$	0.10	-0.016	0.008	0.03	0.22	0.004	0.009	0.63
rs7968440	12q13.13	49421008	*DIP2B*	A	G	0.64	0.006	0.001	$2.74X10^{-08}$	0.82	0.000	0.005	0.99	0.78	0.011	0.009	0.22
rs434943	14q24.1	68383812	*ACTN1*	A	G	0.31	0.007	0.001	$1.08X10^{-08}$	0.15	-0.009	0.006	0.14	0.28	0.013	0.009	0.17
rs12915708	15q21.2	48835894	*SPPL2A*	C	G	0.3	-0.007	0.001	$6.87X10^{-10}$	0.10	-0.001	0.006	0.93	0.22	-0.013	0.009	0.15
rs7204230	16q12.2	51749832	*CHD9*	T	C	0.7	0.008	0.001	$1.18X10^{-10}$	0.67	0.012	0.004	$3.13X10^{-03}$	0.79	0.037	0.009	$5.38X10^{-05}$
rs10512597	17q25.1	70211428	*CD300LF*	T	C	0.18	-0.008	0.001	$9.92X10^{-09}$	0.64	-0.006	0.004	0.19	0.44	-0.007	0.008	0.35
rs4817986	21q22.2	39387382	*PSMG1*	T	G	0.28	-0.008	0.001	$2.46X10^{-11}$	0.11	-0.004	0.008	0.58	0.24	-0.025	0.010	0.01
rs6010044	22q13.33	49448804	***SHANK3****/ARSA*	A	C	0.8	-0.008	0.001	$3.41X10^{-08}$	0.88	0.009	0.006	0.13	0.26	0.011	0.009	0.22

European N=91,323 individuals; African-American N=8,423 individuals, Hispanic N=1,447 individuals.

*The perfect proxy rs10789192 was used in African American and Hispanics.
Freq=frequency; SE= standard error

Supplementary Table S7: Position and association values of the 24 lead-SNPs in the European, Afican-American and Hispanic cohorts. Columns R to X and AD to AK show the values for the best associated SNP in African-American (a) and Hispanic (b)cohorts located within 200Kb of the "lead SNP" found in the European cohorts (the "proxy" SNPs). Columns AL to AN show the number of independent SNPs located within the 200Kb region based on the CEU and Yourba HapMaps and the corresponding adjusted p-value threshold of significance after correcting for multiple testing. Columns AO to AR show the LD values between the "lead-SNPs" and the "proxy-SNPs". To set the significance threshold in this exploration effort, we applied Bonferroni correction and adjusted for independent SNPs in each region (pair-wise linkage disequilibrium (LD) measure, r^2, values below 0.5).

a)

				24 LEAD SNPs in EA					24 LEAD SNPs in AA				24 "Proxy" SNPs in AA						LD between "LEAD" and "Proxy" SNPs	
SNP	CHR	POS	GENE	A 1	A 2	Freq A1	beta	P-value	Freq A1	beta	P-value	best SNP for AA	POS	A 1	A 2	Freq	beta in AA	P-value in AA	Distance (bp)	LD based on HapMap CEU (R-sq)	LD based on HapMap YRI
rs1938492	1	65890417	PDE4B	a	c	0.62	0.008	5.28E-14				rs1536467	65760750	a	g	0.96	0.102	0.007	129,667	na	na
rs4129267	1	152692888	IL6R	t	c	0.39	-0.011	5.97E-27	0.14	-0.011	0.040	rs1194592	152591008	c	g	0.82	-0.016	0.001	101,880	0.011	0.015
rs10157379	1	245672222	NLRP3	t	c	0.62	0.010	1.15E-19	0.60	0.003	0.516	rs11801091	245474761	t	c	0.93	0.027	0.002	197,461	1.000	0.020
rs12712127	2	102093093	IL1R1	a	g	0.41	0.006	2.72E-08	0.3	0.002	0.556	rs17026606	102081970	a	g	0.02	-0.048	0.005	11,123	1.000	0.004
rs6734238	2	113557501	IL1RN	a	g	0.58	-0.009	5.77E-19	0.56	-0.012	0.002	rs4251961	113590938	t	c	0.82	-0.021	2.03E-05	33,437	0.613	0.073
rs715	2	211251300	CPS1	t	c	0.68	0.009	1.98E-11	0.8	0.007	0.162	rs7607205	211197348	t	g	0.75	0.012	0.006	53,952	0.146	0.019
rs1476698	2	241945122	FARP2	a	g	0.65	0.006	2.24E-09	0.62	0.006	0.129	rs7578199	241841521	t	c	0.82	-0.015	0.002	103,601	0.165	0.019
rs1154988	3	137407881	PCCB	a	t	0.78	-0.01	9.64E-17	0.70	-0.001	0.763	rs1145101	137551976	t	c	0.15	0.016	0.002	144,095	0.649	0.328
rs16844401	4	3419450	HGFAC	a	g	0.08	0.015	1.74E-08	0.033	0.015	0.232	rs13147370	3252607	c	g	0.42	-0.009	0.030	166,843	0.032	0.000
rs1800789	4	155702193	FGB	a	g	0.21	0.031	1.68E-127	0.10	0.032	4.02E-07	rs4463047	155714983	t	c	0.87	0.041	4.63E-10	12,790	0.001	0.014
rs2106854	5	131797073	IRF1	t	c	0.21	-0.019	1.72E-48	0.24	-0.009	0.043	rs2706395	131824702	a	t	0.69	0.023	6.98E-08	27,629	0.924	0.214
rs11242111	5	131783957	IRF1	a	g	0.05	0.023	1.60E-21	0.37	-0.003	0.443	rs2706395	131824702	a	t	0.69	0.023	6.98E-08	40,745	0.008	0.050
rs2286503	7	22823131	TOMM7	t	c	0.36	-0.006	6.88E-09	0.68	-3E-04	0.946	rs2069827	22731981	t	g	0.02	0.036	0.012	91,150	0.031	-1.000
rs10226084	7	17964137	PRPS1L1	t	c	0.52	-0.007	5.05E-10	0.61	-0.004	0.358	rs17138358	17886778	c	g	0.54	-0.011	0.003	77,359	0.400	0.267
rs7464572	8	145093155	PLEC1	c	g	0.60	-0.007	1.33E-09	0.88	-0.002	0.738	rs11136341	145115531	a	g	0.47	-0.014	0.003	22,376	0.607	0.075
rs7896783	10	64832159	JMJD1C	a	g	0.48	-0.01	8.90E-22	0.32	-0.01	0.013	rs7896518	64774506	a	g	0.67	0.011	0.007	57,653	0.841	1.000
rs1019670	11	59697175	MS4A6A	a	t	0.36	-0.007	4.37E-09	0.10	-0.016	0.033	rs2081547	59746006	t	c	0.12	-0.015	0.009	48,831	0.591	0.390
rs7968440	12	49421008	DIP2B	a	g	0.64	0.006	2.74E-08	0.82	-1E-04	0.987	rs1362965	49608261	t	c	0.93	0.025	9.25E-4	187,253	0.319	0.032
rs434943	14	68383812	ACTN1	a	g	0.31	0.007	1.08E-08	0.15	-0.009	0.138	rs3809391	68330602	t	c	0.04	0.036	0.002	53,210	0.008	0.006
rs12915708	15	48835894	SPPL2A	c	g	0.30	-0.007	6.87E-10	0.10	-6E-04	0.925	rs8033085	48856352	t	c	0.08	-0.019	0.011	20,458	0.135	0.108
rs7204230	16	51749832	CHD9	t	c	0.7	0.008	1.18E-10	0.67	0.012	0.003	rs16952044	51757783	a	g	0.68	0.014	4.04E-4	7,951	1.000	1.000
rs10512597	17	70211428	CD300LF	t	c	0.18	-0.008	9.92E-09	0.64	-0.006	0.192	rs783240	70095693	a	g	0.52	0.018	0.005	115,735	0.010	0.000
rs4817986	21	39387382	PSMG1	t	g	0.28	-0.008	2.46E-11	0.11	-0.004	0.583	rs8130107	39347449	t	c	0.51	-0.012	0.002	39,933	0.050	0.049
rs6010044	22	49448804	SHANK3	a	c	0.8	-0.008	3.41E-08	0.88	0.009	0.134	rs5770957	49417151	t	c	0.09	0.051	5.3E-4	31,653	0.021	na

b)

				24 LEAD SNPs in EA					24 LEAD SNPs in Hispanics					24 "Proxy" SNPs in Hispanics						
SNP	CHR	POS	GENE	A1	A2	Freq	beta	P-value	A1	A2	Freq	beta	P-value	best SNP for Hispanics	Chr	POS	A1	A2	Freq	beta in Hispa	P value in Hispa
rs1938492	1	65890417	PDE4B	a	c	0.623	0.0081	5.28E-14						rs4384209	1	66051713	G	A	0.61	0.022	0.007
rs4129267	1	152692888	IL6R	t	c	0.392	-0.011	5.97E-27	T	C	0.47	-0.031	2.101E-05	rs8192284	1	152693594	C	A	0.47	-0.032	1.9E-05
rs10157379	1	245672222	NLRP3	t	c	0.621	0.0099	1.15E-19	T	C	0.59	0.007	0.343	rs12070953	1	245681009	T	C	0.89	-0.043	0.005
rs12712127	2	102093093	IL1R1	a	g	0.409	0.0058	2.72E-08	G	A	0.65	0.000	0.999	rs3917325	2	102160339	T	G	0.95	-0.049	0.002
rs6734238	2	113557501	IL1RN	a	g	0.584	-0.009	5.77E-19	G	A	0.34	0.011	0.166	rs874898	2	113690667	G	C	0.77	-0.026	0.003
rs715	2	211251300	CPS1	t	c	0.682	0.0087	1.98E-11	T	C	0.74	0.007	0.400	rs1588365	2	211087499	G	A	0.64	-0.025	9.7E-04
rs1476698	2	241945122	FARP2	a	g	0.647	0.0065	2.24E-09	G	A	0.53	-0.013	0.066	rs4675973	2	241845768	T	C	0.47	-0.019	0.014
rs1154988	3	137407881	PCCB	a	t	0.777	-0.01	9.64E-17	T	A	0.22	0.018	0.039	rs1154988	3	137407881	T	A	0.22	0.018	0.039
rs16844401	4	3419450	HGFAC	a	g	0.077	0.0149	1.74E-08	G	A	0.90	-0.017	0.323	rs16844280	4	3378822	T	C	0.07	0.033	0.021
rs1800789	4	155702193	FGB	a	g	0.21	0.0306	1.68E-127	G	A	0.85	-0.052	6.89E-07	rs4508864	4	155700739	T	C	0.13	0.063	4.77E-07
rs2106854	5	131797073	IRF1	t	c	0.208	-0.019	1.72E-48	T	C	0.21	-0.024	0.007	rs2631362	5	131735192	G	A	0.28	-0.027	5.71E-04
rs11242111	5	131783957	IRF1	a	g	0.051	0.0232	1.60E-21	G	A	0.91	0.001	0.917	rs2631362	5	131735192	G	A	0.28	-0.027	5.71E-04
rs2286503	7	22823131	TOMM7	t	c	0.36	-0.006	6.88E-09	T	C	0.48	-0.002	0.757	rs1880241	7	22725994	G	A	0.67	-0.020	0.008
rs10226084	7	17964137	PRPS1L1	t	c	0.523	-0.007	5.05E-10	T	C	0.49	-0.003	0.632	rs17345660	7	18151634	G	A	0.98	-0.069	0.006
rs7464572	8	145093155	PLEC1	c	g	0.596	-0.007	1.33E-09	G	C	0.28	0.015	0.058	rs11786896	8	145090342	T	C	0.05	0.063	0.010
rs7896783	10	64832159	JMJD1C	a	g	0.484	-0.01	8.90E-22	G	A	0.69	0.009	0.247	rs11817169	10	65026315	G	A	0.17	0.035	3.15E-04
rs1019670	11	59697175	MS4A6A	a	t	0.363	-0.007	4.37E-09	T	A	0.78	-0.004	0.634	rs17154445	11	59552878	T	C	0.01	-0.095	0.003
rs7968440	12	49421008	DIP2B	a	g	0.639	0.006	2.74E-08	G	A	0.22	-0.011	0.215	rs4132432	12	49276485	G	C	0.15	0.018	0.054
rs434943	14	68383812	ACTN1	a	g	0.314	0.007	1.08E-08	G	A	0.72	-0.013	0.165	rs7141959	14	68427126	G	C	0.53	0.020	0.018
rs12915708	15	48835894	SPPL2A	c	g	0.304	-0.007	6.87E-10	G	C	0.78	0.013	0.151	rs8023464	15	48659366	C	A	0.94	0.035	0.025
rs7204230	16	51749832	CHD9	t	c	0.7	0.0078	1.18E-10	T	C	0.79	0.037	5.378E-05	rs8050349	16	51897377	T	C	0.18	-0.042	2.63E-05
rs10512597	17	70211428	CD300LF	t	c	0.177	-0.008	9.92E-09	T	C	0.44	-0.007	0.350	rs492256	17	70115771	T	A	0.53	-0.019	0.011
rs4817986	21	39387382	PSMG1	t	g	0.279	-0.008	2.46E-11	T	G	0.24	-0.025	0.011	rs8129630	21	39229095	G	A	0.02	0.077	0.003
rs6010044	22	49448804	SHANK3	a	c	0.8	-0.008	3.41E-08	C	A	0.26	-0.011	0.215	rs6010065	22	49504883	G	C	0.54	0.016	0.042

Supplementary Table S8: Results of pathway analyses using MAGENTA and GRAIL and expression quantitative trait locus (eQTL) analysis in human liver.

SNP	Band	Closest gene	P	Additional evidence	Candidate gene	Pathway
rs1938492	1p31.3	*LEPR*	$5.28X10^{-14}$	Grail/Magenta	*LEPR*	Adipocytokine signaling pathway
				eQTL_liver	*LEPR* (P=$4.37x10^{-10}$)	
rs4129267	1q21.3	*IL6R*	$5.97X10^{-27}$	Grail/Magenta	*IL6R*	Acute phase.R response signaling/JAK-STAT cascade
rs10157379	1q44	*NLRP3*	$1.15X10^{-19}$	Grail	*NLRP3*	
rs12712127	2q11.2	*IL1R1/IL1R2*	$2.72X10^{-08}$	Grail/Magenta	*IL1R1*	Acute phase response signaling
rs6734238	2q13	*IL1F10/IL1RN*	$5.77X10^{-19}$	Grail/Magenta	*IL1RN/IL1F10,IL1F5,IL1F8,IL1RN*	interleukin-1 receptor binding
rs715	2q34	*CPS1*	$1.98X10^{-11}$			
rs1476698	2q37.3	*FARP2*	$2.24X10^{-09}$			
rs1154988	3q22.3	*MSL2/PCCB*	$9.64X10^{-17}$	eQTL_liver	*PCCB* (P=1.44x10-6) *MSL2L1* (P=3.91x10-14) *NGFRAP1* (P=7.61x10-12)	
rs16844401	4p16.2	*HGFAC/LRPAP1*	$1.74X10^{-08}$	Grail	*LRPAP1*	
rs1800789	4q32.1	*FGB*	$1.68X10^{-127}$	Magenta	*FGA,FGB*	Acute phase response signaling
				eQTL_liver	*FGB* (P=1.2x10-8)	
rs2106854	5q31.1	*C5orf56/IRF1*	$1.72X10^{-48}$			
rs11242111	5q31.1	*C5orf56/IRF1*	$1.60X10^{-21}$			
rs2286503	7p15.3	*TOMM7*	$6.88X10^{-09}$	eQTL_liver	*TOMM7* (P=2.23x10-5)	
rs10226084	7p21.1	*SNX13/PRPS1L1*	$5.05X10^{-10}$			
rs7464572	8q24.3	*PLEC1*	$1.33X10^{-09}$			
rs7896783	10q21.3	*JMJD1C*	$8.90X10^{-22}$			
rs1019670	11q12.1	*MS4A6A*	$4.37X10^{-09}$			
rs7968440	12q13.13	*DIP2B*	$2.74X10^{-08}$			
rs434943	14q24.1	*ACTN1*	$1.08X10^{-08}$	Magenta	*ACTN1*	Systemic Lupus Erythematosus
rs12915708	15q21.2	*SPPL2A*	$6.87X10^{-10}$			
rs7204230	16q12.2	*CHD9*	$1.18X10^{-10}$			
rs10512597	17q25.1	*CD300LF*	$9.92X10^{-09}$			
rs4817986	21q22.2	*PSMG1*	$2.46X10^{-11}$			
rs6010044	22q13.33	*SHANK3/ARSA*	$3.41X10^{-08}$	Magenta	*CPT1B*	Adipocytokine signaling pathway

Supplementary Table S9: Extended list of the lead candidate SNPs, including those obtained through the genome-wide association meta-analysis (the 24 "lead-SNPs") plus those candidate SNPs obtained through pathway analyses in GRAIL and MAGENTA.

Category	SNP	Chr	A1	A2	Freq1	Effect	StdErr	P-value	GRAIL.FDR	GRAIL.GWAS	MAGENTA.GENEs.PATHWAYs
Genome-wide Significant	rs1938492	1	a	c	0.62	0.008	0.001	5.28E-14	-	0.042000252@LEPR	LEPR@KEGG-KEGG_ADIPOCYTOKINE_SIGNALING_PATHWAY
Genome-wide Significant	rs4129267	1	t	c	0.39	-0.011	0.001	5.97E-27			
Genome-wide Significant	rs10157379	1	t	c	0.62	0.010	0.001	1.15E-19	-	0.026496169@NLRP3	-
Genome-wide Significant	rs12712127	2	a	g	0.41	0.006	0.001	2.72E-08	-	0.001451751@IL1R1	IL1R1@Ingenuity-Acute.Phase.Response.Signaling
Genome-wide Significant	rs6734238	2	a	g	0.58	-0.009	0.001	5.77E-19	-	0.000351036@IL1RN	IL1F10,IL1F5,IL1F8,IL1RN@GOTERM-interleukin-1.receptor.binding,PANTHER_MOLECULAR_FUNCTION-Interleukin
Genome-wide Significant	rs715	2	t	c	0.68	0.009	0.001	1.98E-11	-	-	-
Genome-wide Significant	rs1476698	2	a	g	0.65	0.007	0.001	2.24E-09	-	-	-
Genome-wide Significant	rs1154988	3	a	t	0.78	-0.010	0.001	9.64E-17	-	-	-
Genome-wide Significant	rs16844401	4	a	g	0.08	0.015	0.003	1.74E-08			
Genome-wide Significant	rs1800789	4	a	g	0.21	0.031	0.001	1.68E-127	-	-	FGA,FGB@Ingenuity-Acute.Phase.Response.Signaling
Genome-wide Significant	rs11242111	5	a	g	0.05	0.023	0.002	1.60E-21			
Genome-wide Significant	rs2106854	5	t	c	0.21	-0.019	0.001	1.72E-48			
Genome-wide Significant	rs10226084	7	t	c	0.52	-0.007	0.001	5.05E-10	-	-	-
Genome-wide Significant	rs2286503	7	t	c	0.36	-0.006	0.001	6.88E-09			
Genome-wide Significant	rs7464572	8	c	g	0.60	-0.007	0.001	1.33E-09	-	-	-
Genome-wide Significant	rs7896783	10	a	g	0.48	-0.010	0.001	8.90E-22	-	-	-
Genome-wide Significant	rs1019670	11	a	t	0.36	-0.007	0.001	4.37E-09	-	-	-
Genome-wide Significant	rs7968440	12	a	g	0.64	0.006	0.001	2.74E-08			
Genome-wide Significant	rs434943	14	a	g	0.31	0.007	0.001	1.08E-08	-	-	ACTN1@KEGG-KEGG_SYSTEMIC_LUPUS_ERYTHEMATOSUS
Genome-wide Significant	rs12915708	15	c	g	0.30	-0.007	0.001	6.87E-10			
Genome-wide Significant	rs7204230	16	t	c	0.70	0.008	0.001	1.18E-10	-	-	-
Genome-wide Significant	rs10512597	17	t	c	0.18	-0.008	0.001	9.92E-09	-	-	-
Genome-wide Significant	rs4817986	21	t	g	0.28	-0.008	0.001	2.46E-11	-	-	-
Genome-wide Significant	rs6010044	22	a	c	0.80	-0.008	0.001	3.41E-08	-	-	CPT1B@KEGG-KEGG_ADIPOCYTOKINE_SIGNALING_PATHWAY
GRAIL-FDR	rs2272163	3	a	c	0.38	-0.005	0.001	6.10E-05	0.044313377@ROBO2	-	-
GRAIL-FDR	rs2161374	5	t	c	0.45	-0.005	0.001	2.22E-06	0.025228345@DUSP1	-	-
GRAIL-FDR	rs732839	8	a	g	0.23	0.006	0.001	1.11E-05	0.04285248@PPP1R3B	-	-
GRAIL-FDR	rs10814489	9	a	g	0.35	-0.005	0.001	7.40E-06	0.045550713@PAX5	-	-
GRAIL-FDR	rs11186629	10	a	t	0.70	0.005	0.001	3.08E-05	0.002919608@PPP1R3C	-	-
GRAIL-FDR	rs17101410	10	t	c	0.09	-0.008	0.002	8.89E-06	0.02878597@BRWD2	-	-

GRAIL-FDR	rs224628	11	t	c	0.84	-0.006	0.001	2.25E-05	0.041547845@PAX6	-	-
GRAIL-FDR/MAGENTA-FDR	rs7118744	11	a	g	0.38	0.005	0.001	1.15E-05	0.037380292@ETS1	-	ETS1@Ingenuity-GM-CSF.Signaling
GRAIL-FDR	rs1871143	12	t	g	0.22	0.006	0.001	1.23E-06	0.009746531@GYS2	-	-
GRAIL-FDR	rs1887826	13	a	g	0.53	-0.004	0.001	1.19E-04	0.032901685@ATXN8OS	-	-
GRAIL-FDR	rs3803522	15	a	g	0.80	-0.005	0.001	2.89E-05	0.030742241@MAP2K5	-	-
GRAIL-FDR	rs4334315	16	a	t	0.70	-0.006	0.002	1.37E-05	0.021271154@MAF	-	-
GRAIL-FDR	rs11079035	17	a	g	0.17	0.006	0.001	6.43E-06	0.00416818@STAT5B	-	-
GRAIL-FDR/MAGENTA-FDR	rs3817294	17	a	g	0.39	-0.006	0.001	7.73E-07	0.03318157@SOCS3	-	SOCS3@Ingenuity-IL-10.Signaling,KEGG-KEGG_ADIPOCYTOKINE_SIGNALING_PATHWAY,PANTHER_BIOLOGICAL_PROCESS-JAK-STAT_cascade
GRAIL-FDR/MAGENTA-FDR	rs11080606	18	t	c	0.70	0.006	0.001	6.40E-07	0.047692543@PTPN2	-	PTPN2@PANTHER_BIOLOGICAL_PROCESS-JAK-STAT_cascade
GRAIL-FDR	rs1460191	18	a	c	0.18	0.006	0.001	3.11E-05	0.005129877@DCC	-	-
GRAIL-FDR	rs1800961	20	t	c	0.03	-0.016	0.003	1.60E-06	0.033484871@HNF4A	-	-
GRAIL-FDR	rs5765575	22	t	g	0.66	0.005	0.001	5.15E-05	0.017445336@ATXN10	-	-
MAGENTA-FDR	rs2404715	1	t	c	0.09	-0.007	0.002	1.61E-04	-	-	PRKAA2@KEGG-KEGG_ADIPOCYTOKINE_SIGNALING_PATHWAY
MAGENTA-FDR	rs8192284	1	a	c	0.61	0.011	0.001	6.75E-27	-	0.001503629@IL6R	IL6R@Ingenuity-Acute.Phase.Response.Signaling,PANTHER_BIOLOGICAL_PROCESS-JAK-STAT_cascade
MAGENTA-FDR	rs10206961	2	t	c	0.39	0.004	0.001	0.000102	-	-	VAMP8@Panther-Thyrotropin-releasing_hormone_receptor_signaling_pathway
MAGENTA-FDR	rs12053091	2	t	c	0.74	0.006	0.001	2.15E-06	-	-	IL1A,IL1B@GOTERM-interleukin-1.receptor.binding
MAGENTA-FDR	rs11689250	2	a	g	0.67	0.006	0.001	1.48E-07	-	-	IL1F6@GOTERM-interleukin-1.receptor.binding
MAGENTA-FDR	rs11235	3	t	c	0.58	-0.004	0.001	7.26E-05	-	-	ITIH3@Ingenuity-Acute.Phase.Response.Signaling
MAGENTA-FDR	rs1872111	3	a	g	0.88	-0.008	0.002	6.94E-07	-	-	H1FOO@PANTHER_MOLECULAR_FUNCTION-Histone
MAGENTA-FDR	rs2227401	4	t	c	0.21	0.031	0.001	2.32E-127	-	-	FGG@Ingenuity-Acute.Phase.Response.Signaling
MAGENTA-FDR	rs10070876	5	t	c	0.91	0.009	0.002	5.04E-05	-	-	C9@Ingenuity-Acute.Phase.Response.Signaling
MAGENTA-FDR	rs10078535	5	a	g	0.97	-0.017	0.003	1.00E-08	-	-	ACSL6,IL3@Ingenuity-Fc.Epsilon.RI.Signaling,KEGG-KEGG_ADIPOCYTOKINE_SIGNALING_PATHWAY,KEGG-KEGG_ASTHMA,PANTHER_BIOLOGICAL_PROCESS-JAK-STAT_cascade
MAGENTA-FDR	rs3843502	5	a	g	0.03	0.017	0.003	1.05E-08	-	-	CSF2@Ingenuity-Fc.Epsilon.RI.Signaling,Ingenuity-GM-CSF.Signaling,PANTHER_BIOLOGICAL_PROCESS-JAK-STAT_cascade
MAGENTA-FDR	rs4705952	5	a	g	0.78	0.013	0.001	4.26E-24	-	-	IL5@Ingenuity-Fc.Epsilon.RI.Signaling,KEGG-KEGG_ASTHMA,PANTHER_BIOLOGICAL_PROCESS-JAK-STAT_cascade,PANTHER_MOLECULAR_FUNCTION-Interleukin
MAGENTA-FDR	rs2244012	5	a	g	0.79	0.011	0.001	1.07E-16	-	-	IL13,IL4@Ingenuity-Fc.Epsilon.RI.Signaling,KEGG-KEGG_ASTHMA,PANTHER_BIOLOGICAL_PROCESS-JAK-STAT_cascade,PANTHER_MOLECULAR_FUNCTION-Interleukin
MAGENTA-FDR	rs1408268	6	a	t	0.24	0.007	0.001	6.40E-08	-	-	HIST1H2AA@KEGG-KEGG_SYSTEMIC_LUPUS_ERYTHEMATOSUS,PANTHER_MOLECULAR_FUNCTION-Histone
MAGENTA-FDR	rs1572982	6	a	g	0.46	0.005	0.001	6.16E-06	-	-	HIST1H1A,HIST1H1C,HIST1H1E,HIST1H2AB,HIST1H2AC,HIST1H2BB,HIST1H2BC,HIST1H2BD,HIST1H2BE,HIST1H2BF,HIST1H3B,HIST1H4B,HIST

											1H4C@KEGG-KEGG_SYSTEMIC_LUPUS_ERYTHEMATOSUS,PANTHER_MOLECULAR_FUNCTION-Histone
MAGENTA-FDR	rs1321196	6	t	c	0.63	0.005	0.001	3.42E-05	-	-	PLG@Ingenuity-Acute.Phase.Response.Signaling
MAGENTA-FDR	rs1880241	7	a	g	0.51	0.006	0.001	1.08E-07	-	-	IL6@Ingenuity-Acute.Phase.Response.Signaling,Ingenuity-IL-10.Signaling,PANTHER_BIOLOGICAL_PROCESS-JAK-STAT_cascade
MAGENTA-FDR	rs6981930	8	t	c	0.45	0.005	0.001	6.09E-06	-	-	TRHR@Panther-Thyrotropin-releasing_hormone_receptor_signaling_pathway
MAGENTA-FDR	rs10857567	10	t	c	0.99	-0.033	0.009	1.97E-04	-	-	MAPK8@Ingenuity-IL-10.Signaling,KEGG-KEGG_ADIPOCYTOKINE_SIGNALING_PATHWAY
MAGENTA-FDR	rs4939312	11	t	c	0.42	-0.006	0.001	2.48E-07	-	-	MS4A2@Ingenuity-Fc.Epsilon.RI.Signaling
MAGENTA-FDR	rs3372	11	a	g	0.36	0.005	0.001	1.76E-05	-	-	RELA@KEGG-KEGG_ADIPOCYTOKINE_SIGNALING_PATHWAY
MAGENTA-FDR	rs12801144	11	a	g	0.89	-0.009	0.002	5.93E-05	-	-	IL10RA@Ingenuity-IL-10.Signaling
MAGENTA-FDR	rs11066301	12	a	g	0.56	0.005	0.001	5.80E-07	-	-	PTPN11@Ingenuity-Acute.Phase.Response.Signaling,Ingenuity-Fc.Epsilon.RI.Signaling,Ingenuity-GM-CSF.Signaling,KEGG-KEGG_ADIPOCYTOKINE_SIGNALING_PATHWAY,PANTHER_BIOLOGICAL_PROCESS-JAK-STAT_cascade
MAGENTA-FDR	rs1475938	14	a	g	0.34	-0.005	0.001	5.91E-06	-	-	SERPINA3@Ingenuity-Acute.Phase.Response.Signaling
MAGENTA-FDR	rs12438453	15	a	g	0.86	-0.007	0.002	3.32E-06	-	-	SNAP23@Panther-Thyrotropin-releasing_hormone_receptor_signaling_pathway
MAGENTA-FDR	rs11864453	16	t	c	0.40	0.006	0.001	9.98E-08	-	-	HPR@Ingenuity-Acute.Phase.Response.Signaling
MAGENTA-FDR	rs7503353	17	t	g	0.53	-0.005	0.001	1.24E-06	-	-	VAMP2@Panther-Thyrotropin-releasing_hormone_receptor_signaling_pathway
MAGENTA-FDR	rs1053023	17	t	c	0.81	0.006	0.001	1.73E-05	-	-	STAT3,STAT5A,STAT5B@Ingenuity-Acute.Phase.Response.Signaling,Ingenuity-GM-CSF.Signaling,Ingenuity-IL-10.Signaling,KEGG-KEGG_ADIPOCYTOKINE_SIGNALING_PATHWAY,PANTHER_BIOLOGICAL_PROCESS-JAK-STAT_cascade
MAGENTA-FDR	rs3745474	19	t	c	0.19	0.007	0.002	1.58E-06	-	-	CPT1C@KEGG-KEGG_ADIPOCYTOKINE_SIGNALING_PATHWAY

Supplementary Table S10: Predicted function of SNPs in the 250 kb window surrounding the fibrinogen genes according to Snp137 database (only SNPs included in the meta-analysis that had association p-values with fibrinogen plasma levels < 10^{-6} are included in this table). In addition, significant associations between SNPs located in the same region and Fibrinogen transcripts are also included, to show functional effect on transcript level. Both missense mutations (rs6050 and rs4220) were predicted to be bening according to PolyPhen scores. Rs7659024 has been associated with venous thromboembolism[107].

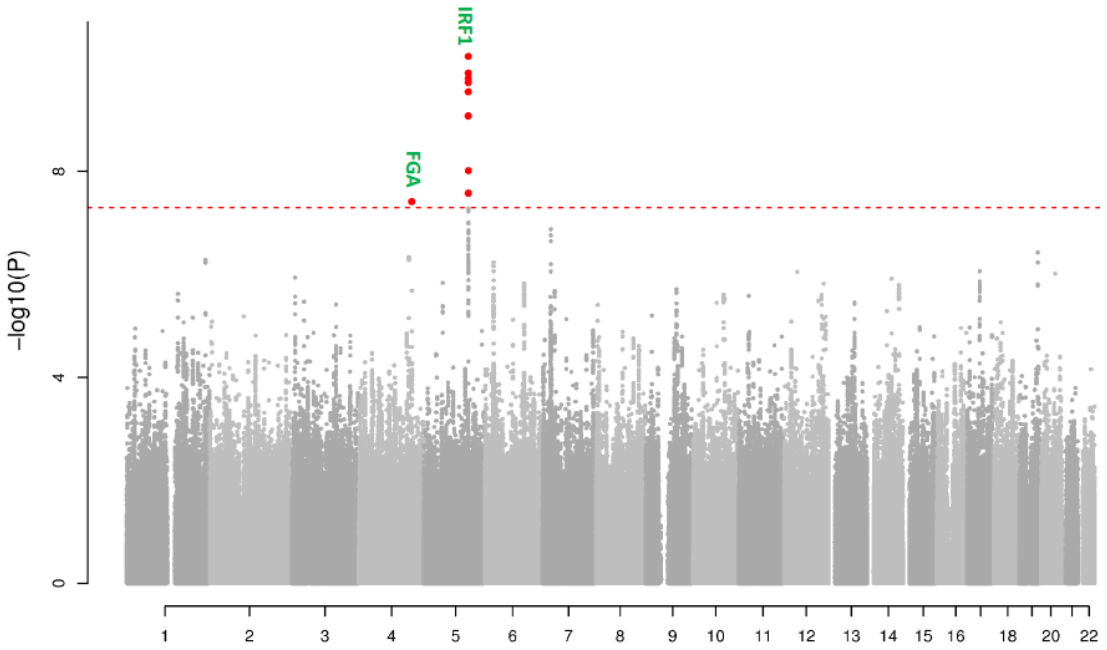
SNP	chrom	position	Function	Tissue	eSNP p-value	Transcript
rs2404478	4	155408038	unknown	Liver (ASAP)	1,90E-03	FGB
rs871540	4	155409030	unknown	Liver (ASAP)	1,90E-03	FGB
rs10019863	4	155427505	unknown	Liver (ASAP)	3,39E-03	FGG
rs4508864	4	155481289	unknown	Liver (Schadt)	1,20E-08	FGB
rs6050	4	155507590	missense			
rs7659024	4	155520930	unknown	Liver(Greenawalt)	2,17E-16	FGG
rs10517596	4	155627814	unknown	Liver(UChicago)	8,08E-03	FGA
rs17031728	4	155412581	5PRIME_UTR			
rs2227401	4	155486381	3PRIME_UTR			
rs4220	4	155491759	missense	Liver(Greenawalt)	1,38E-20	FGB

Supplementary Table S11: Results of the associations between the lead-SNPs and different stroke phenotypes. These results are based on 790 cardioembolic stroke cases, 844 large vessel disease ischaemic stroke cases and 580 small vessel disease ischaemic stroke cases.

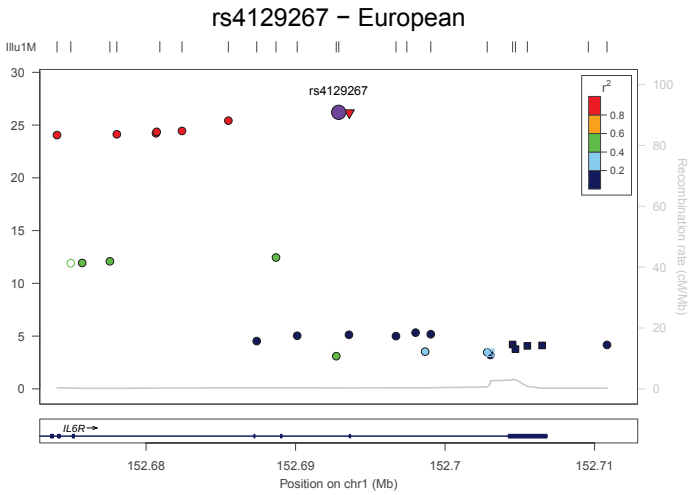
						CE			LAA			SVD		
SNP	**Chrom**	**Position**	**Allele1**	**Allele2**	**Freq1**	**OR**	**SE**	***P***	**OR**	**SE**	***P***	**OR**	**SE**	***P***
rs4817986	21	39387382	t	g	0.27	1.11	0.06	0.10	1.06	0.06	0.33	0.92	0.07	0.26
rs434943	14	68383812	a	g	0.33	1.05	0.06	0.40	0.97	0.06	0.55	1.07	0.07	0.33
rs1154988	3	137407881	a	t	0.78	0.89	0.07	0.07	0.94	0.06	0.31	0.97	0.07	0.72
rs7896783	10	64832159	a	g	0.48	0.98	0.06	0.76	1.08	0.05	0.17	0.88	0.06	0.04
rs7464572	8	145093155	c	g	0.60	1.03	0.06	0.56	0.93	0.05	0.21	1.07	0.06	0.26
rs2286503	7	22823131	t	c	0.36	0.93	0.06	0.20	0.93	0.06	0.20	1.00	0.06	0.96
rs16844401	4	3419450	a	g	0.07	0.94	0.12	0.62	0.98	0.11	0.82	0.87	0.13	0.28
rs7968440	12	49421008	a	g	0.66	1.14	0.06	0.03	0.91	0.06	0.11	1.03	0.07	0.66
rs1938492	1	65890417	a	c	0.62	0.96	0.06	0.53	1.05	0.06	0.37	0.94	0.06	0.30
rs715	2	211251300	t	c	0.66	1.06	0.06	0.36	1.00	0.06	0.95	1.01	0.07	0.93
rs6010044	22	49448804	a	c	0.75	0.91	0.07	0.14	1.03	0.07	0.70	0.98	0.08	0.80
rs11242111	5	131783957	a	g	0.05	1.19	0.13	0.17	1.20	0.12	0.15	0.70	0.18	0.04
rs12915708	15	48835894	c	g	0.30	1.13	0.06	0.04	0.97	0.06	0.60	0.98	0.07	0.80
rs12712127	2	102093093	a	g	0.41	1.00	0.06	0.97	1.07	0.05	0.21	1.03	0.06	0.66
rs6734238	2	113557501	a	g	0.60	1.07	0.06	0.24	1.00	0.05	0.98	1.00	0.06	0.99
rs10512597	17	70211428	t	c	0.18	0.90	0.07	0.17	0.97	0.07	0.68	0.98	0.08	0.79
rs1800789	4	155702193	a	g	0.21	1.07	0.07	0.34	1.04	0.07	0.56	0.97	0.08	0.74
rs1019670	11	59697175	a	t	0.35	1.02	0.06	0.70	0.92	0.06	0.18	0.95	0.07	0.44
rs2106854	5	131797073	t	c	0.20	0.98	0.07	0.73	0.98	0.07	0.80	0.92	0.08	0.30
rs10157379	1	245672222	t	c	0.63	1.00	0.06	0.95	1.06	0.06	0.29	1.03	0.06	0.66
rs7204230	16	51749832	t	c	0.70	1.05	0.06	0.39	1.09	0.06	0.12	1.00	0.07	0.95
rs4129267	1	152692888	t	c	0.40	0.98	0.06	0.72	1.04	0.05	0.44	0.95	0.06	0.42
rs10226084	7	17964137	t	c	0.52	1.09	0.06	0.10	0.90	0.05	0.06	1.06	0.06	0.36
rs1476698	2	241945122	a	g	0.65	1.02	0.06	0.73	1.08	0.06	0.16	0.98	0.06	0.71

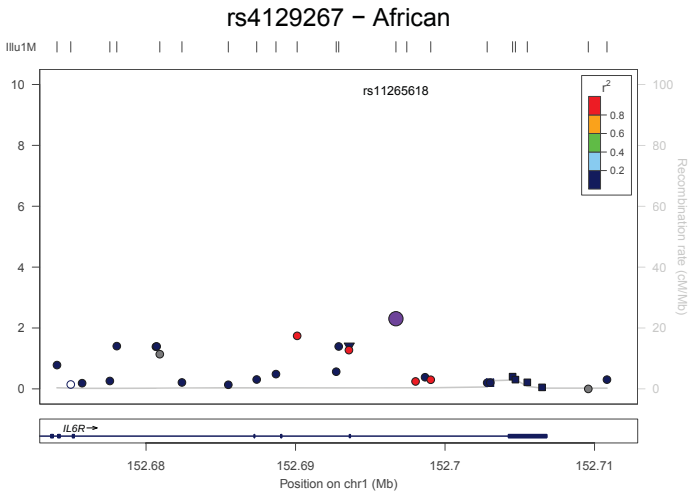
Abbreviations: Chrom= chromosome; Freq1= frequency of allele1; OR= Odds ratio; SE= Standard error; CE= cardioembolic stroke; LAA= Large vessel disease ischaemic stroke; SVD= small vessel disease ischaemic stroke.

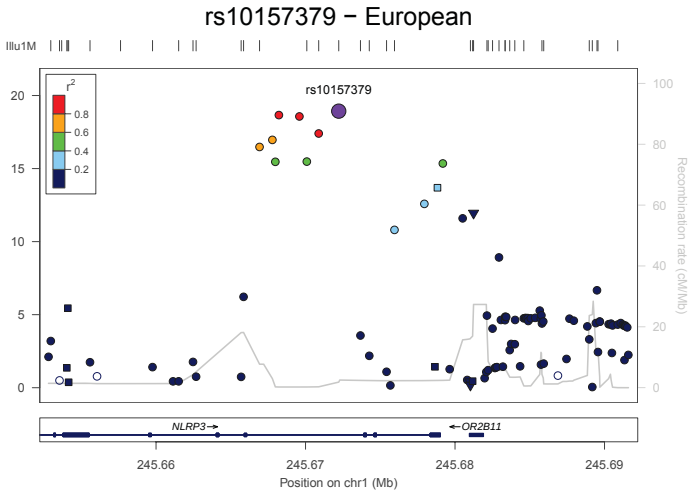
Supplementary Figure S1: analysis conditional on the 23 lead SNPs (European samples). The main signal was located in the *IRF1* locus about 25 kb upstream of *SLC22A5*, indicating that the *IRF1* locus harbors 2 independent signals located 13 kb apart (r^2 =0.010 according to 1000 Genomes Map Pilot 1) represented by rs11242111 and rs2106854. A significant signal was also found in *FGA* gene (rs2070016, P=3.9x10^{-8}) which showed evidence of correlation with the lead SNP rs1800789 in *FGB* (r^2 =0.364 according to 1000 Genomes Map Pilot 1);

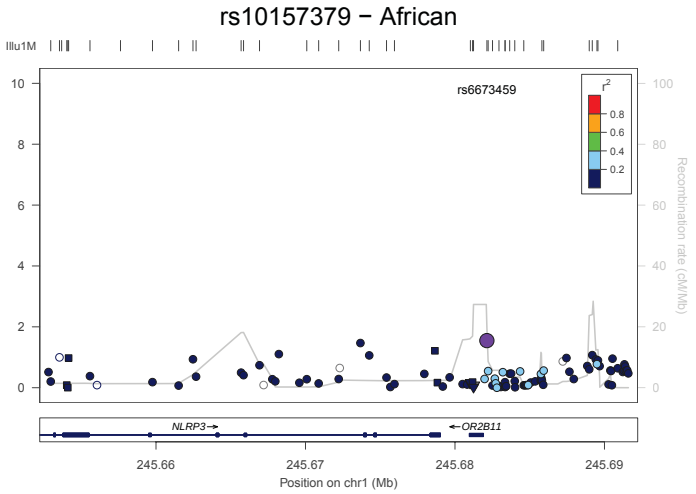


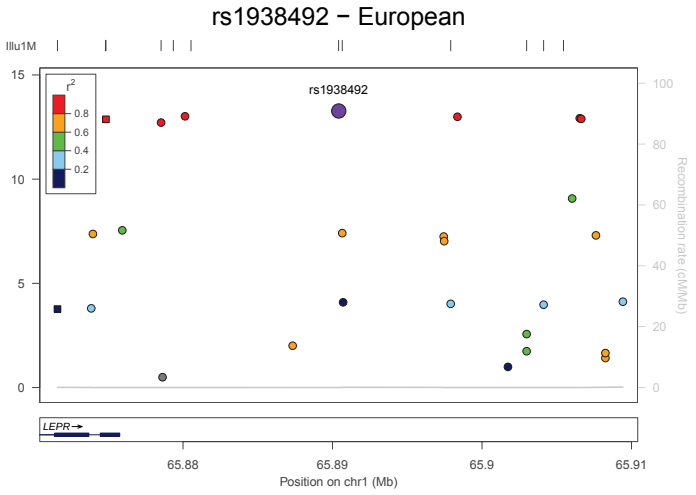
Supplementary Figure S2: Regional Plots for the 23 loci found in the discovery European meta-analysis (pdf attached).

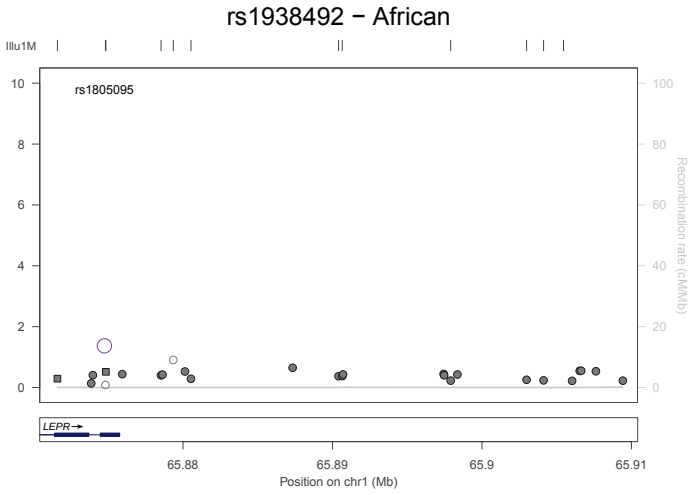












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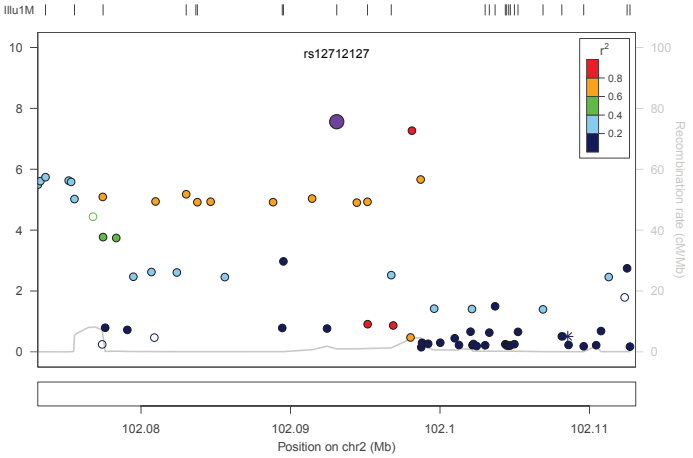

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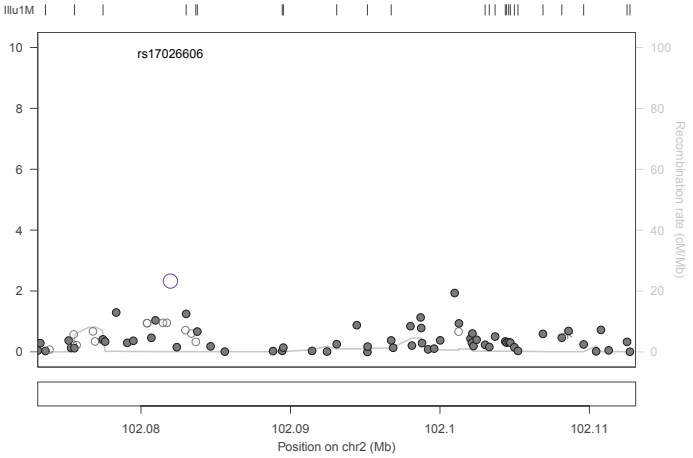

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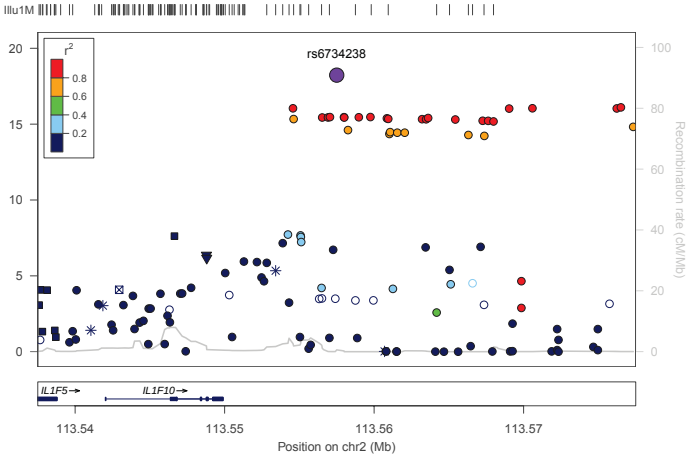

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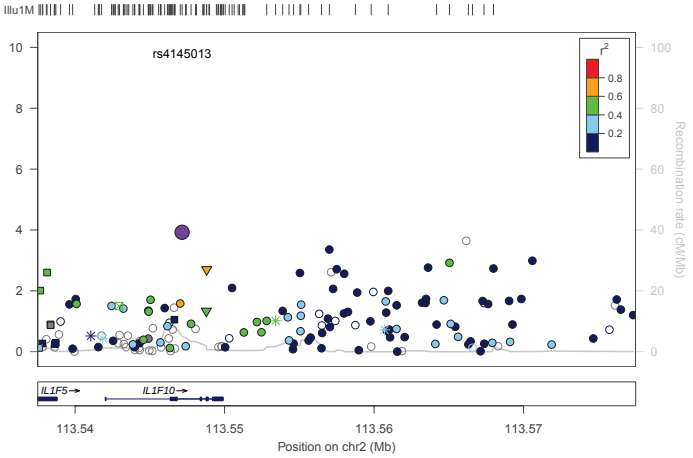

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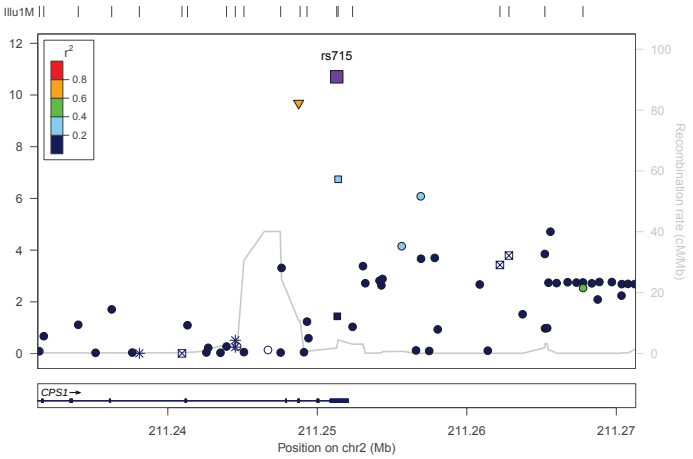

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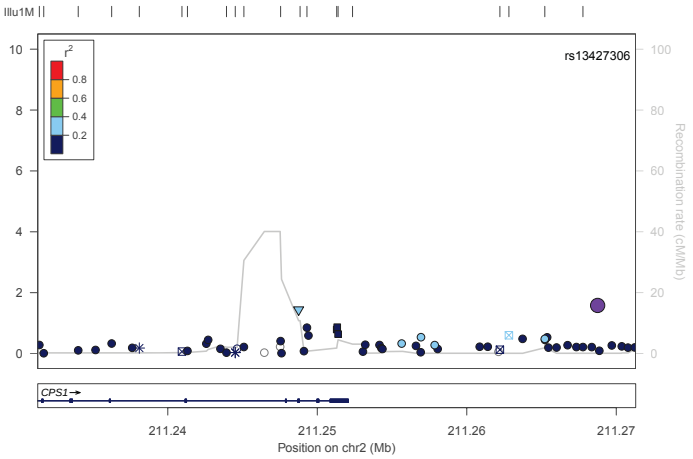

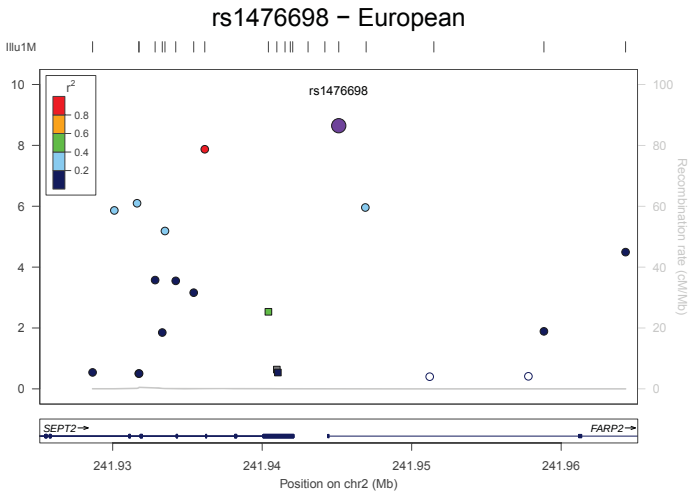

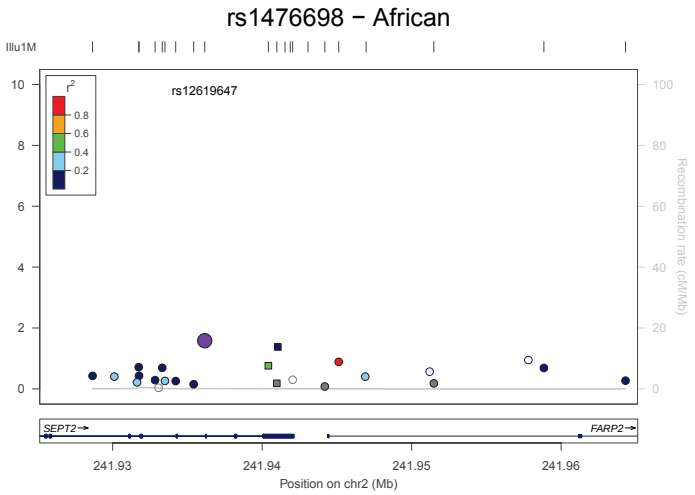

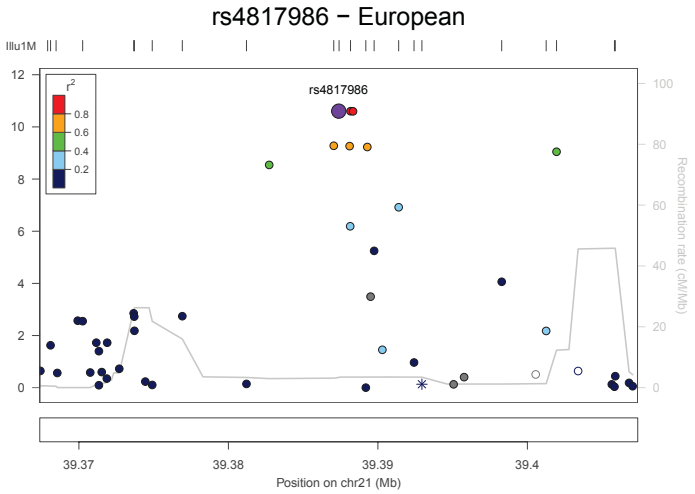

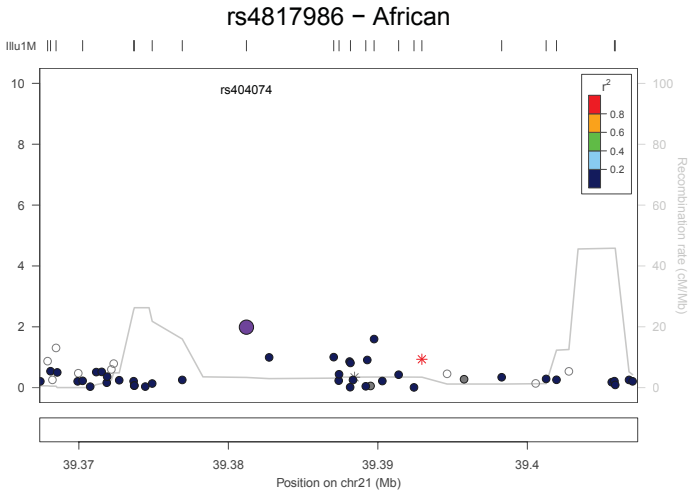

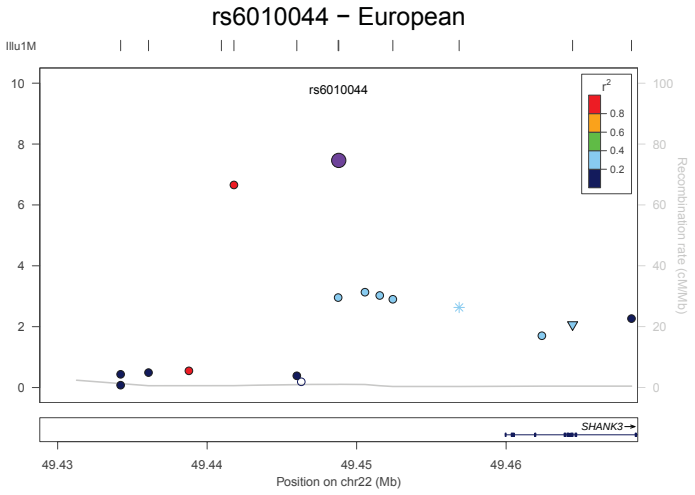

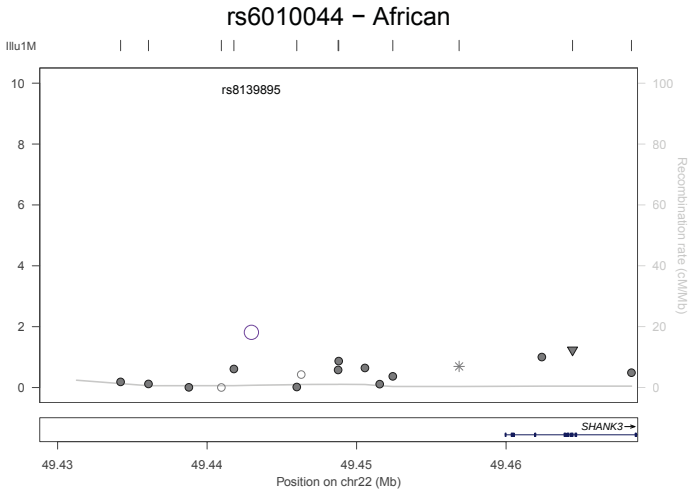

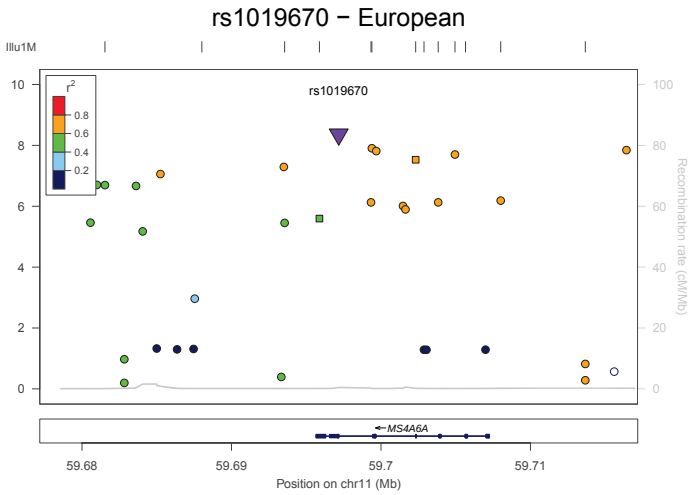

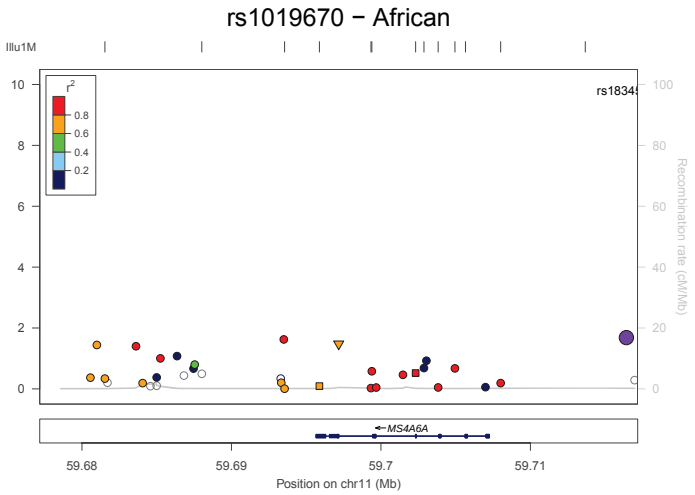

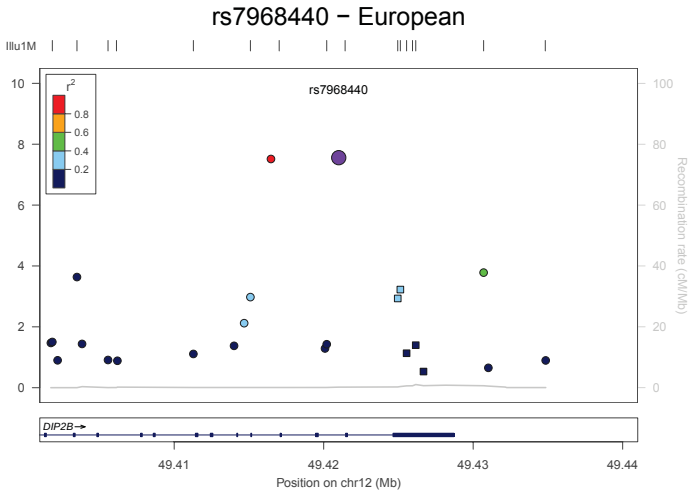

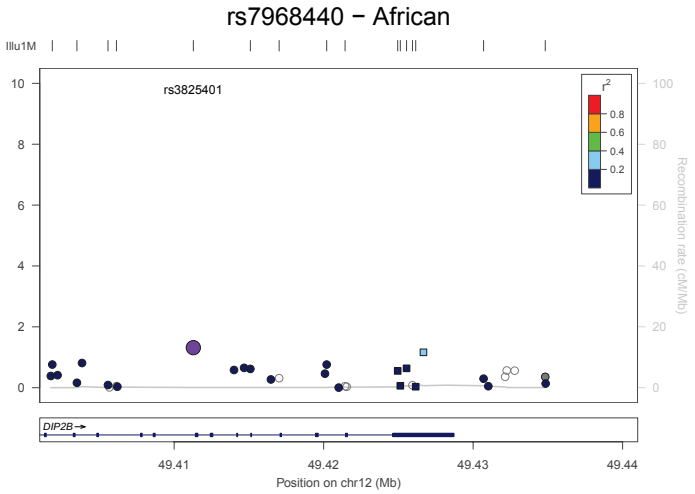

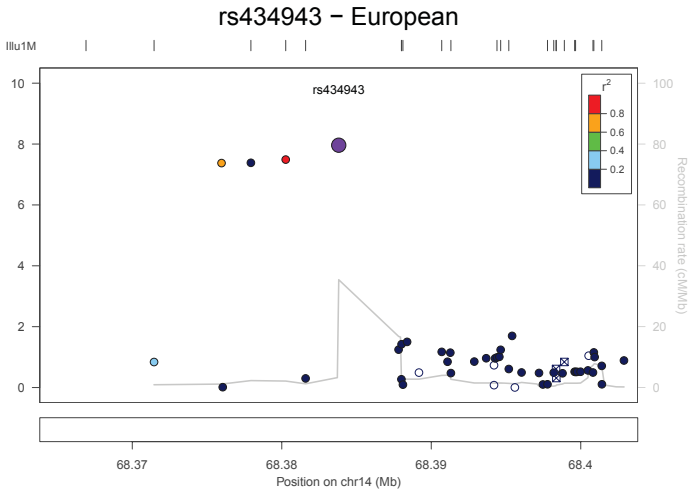

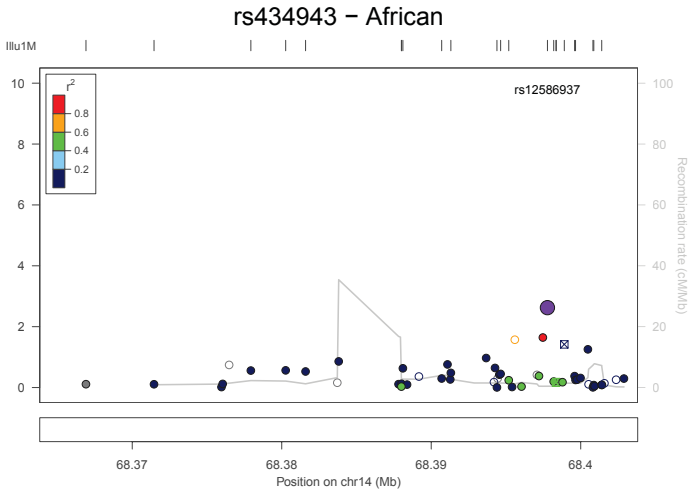

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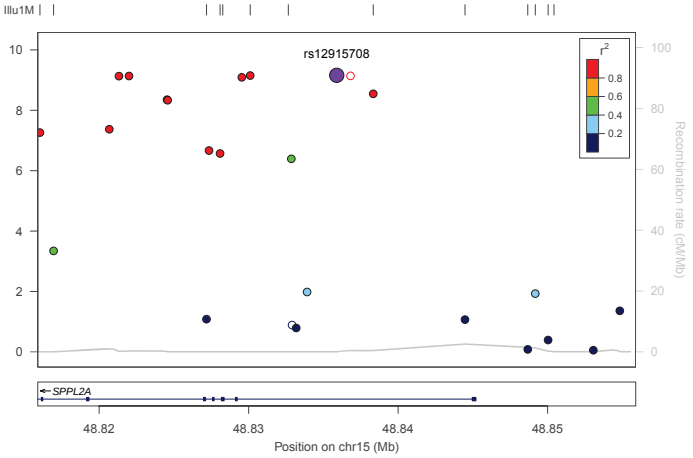

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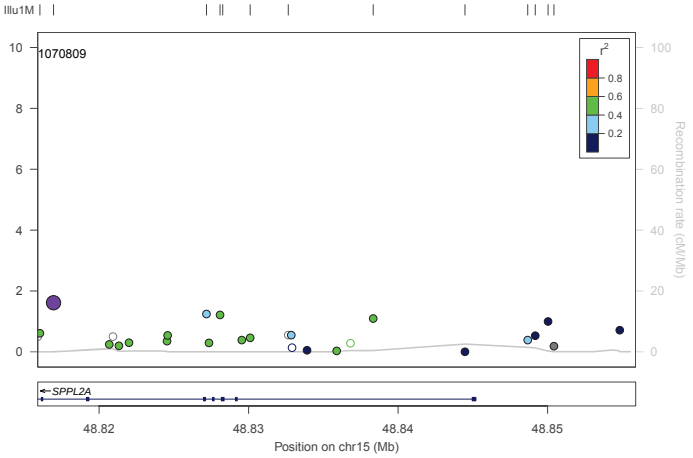

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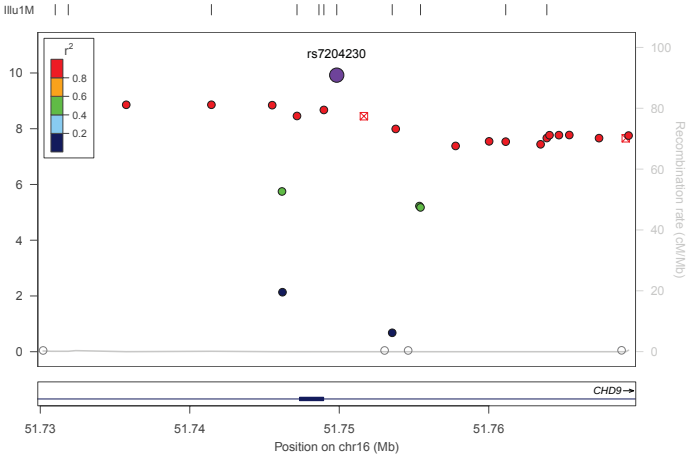

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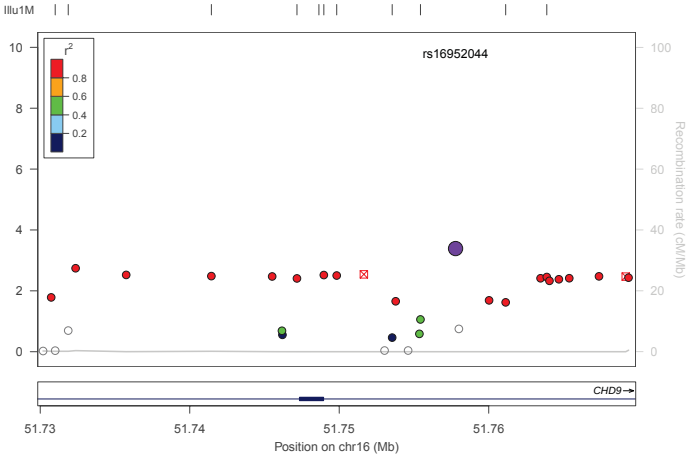

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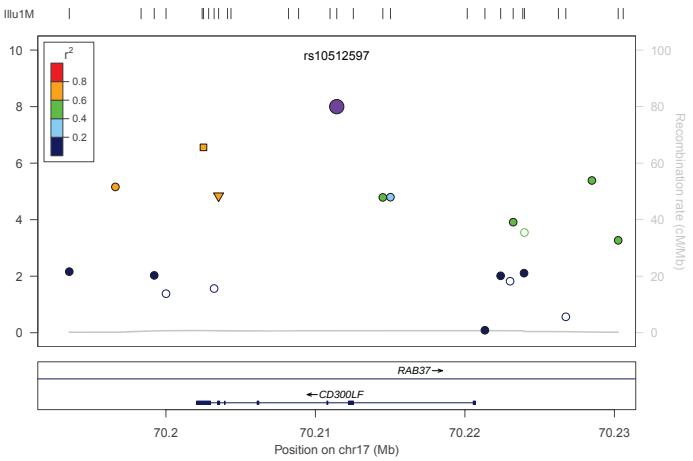

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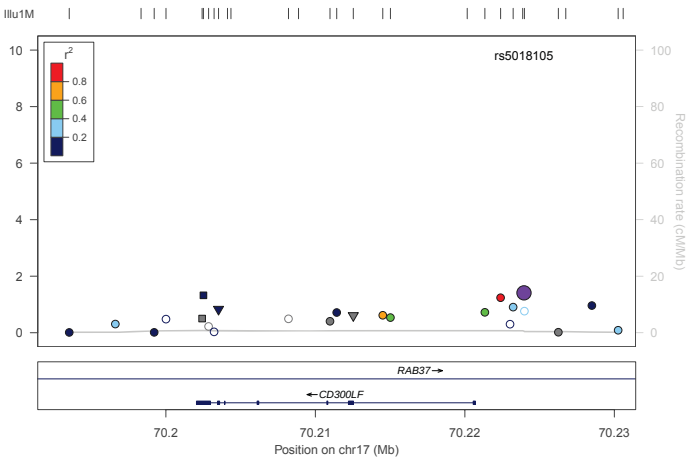

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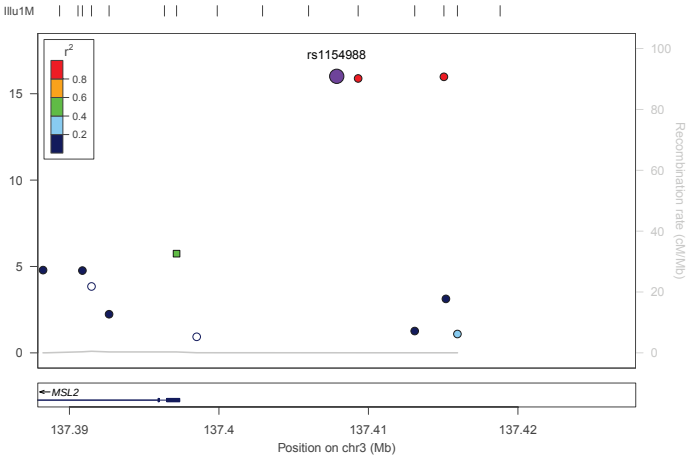

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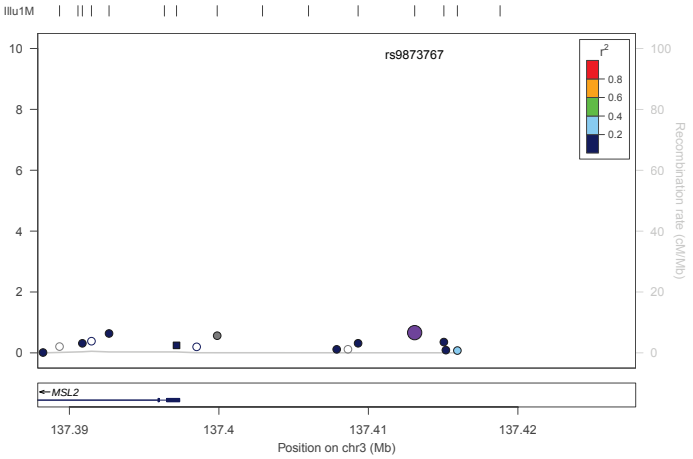

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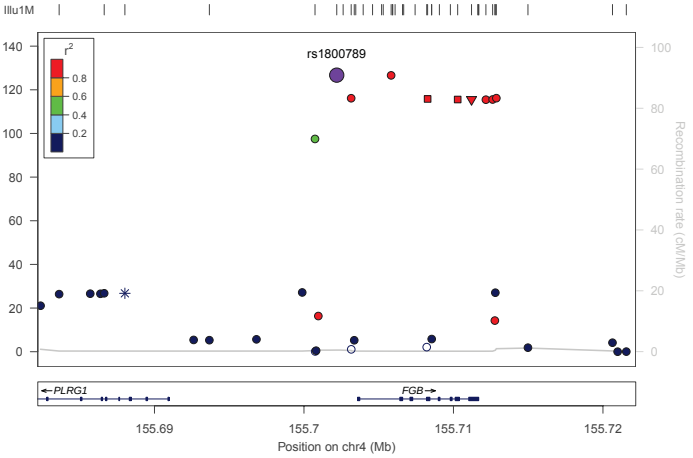

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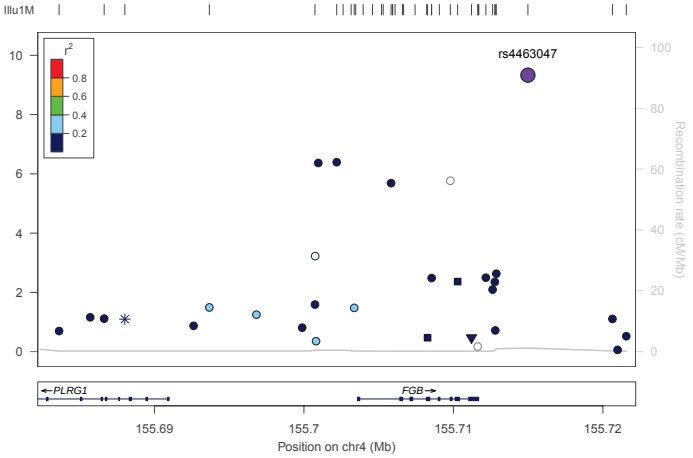

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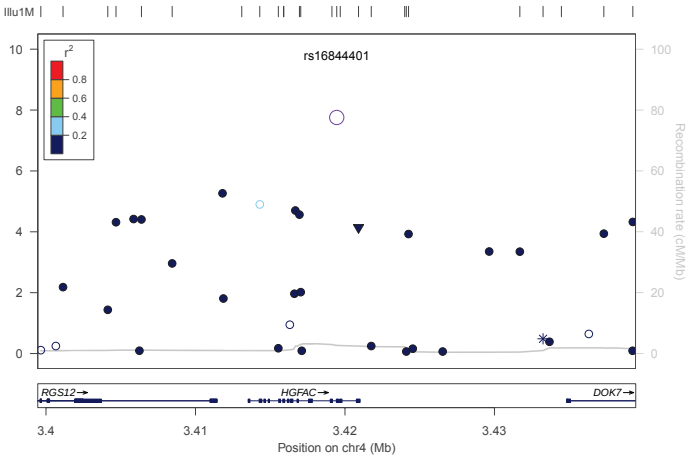

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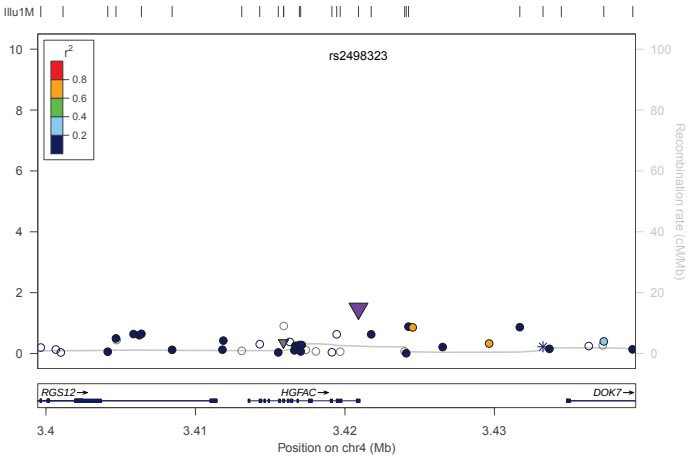
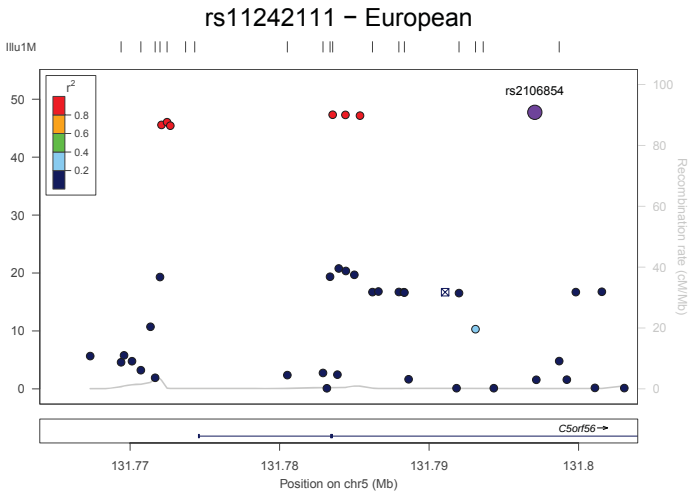
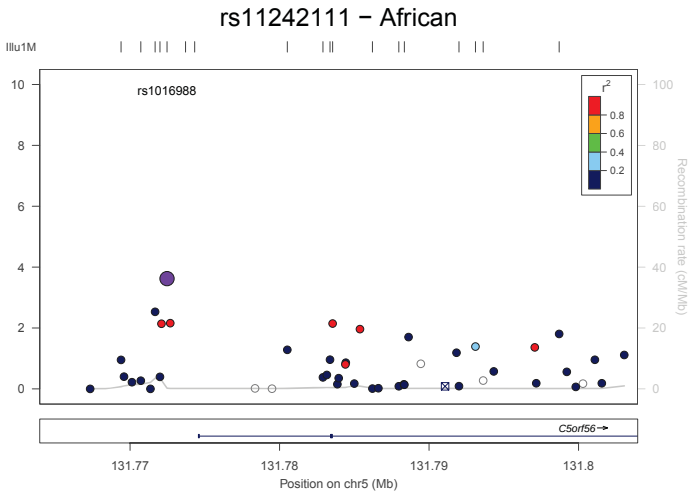
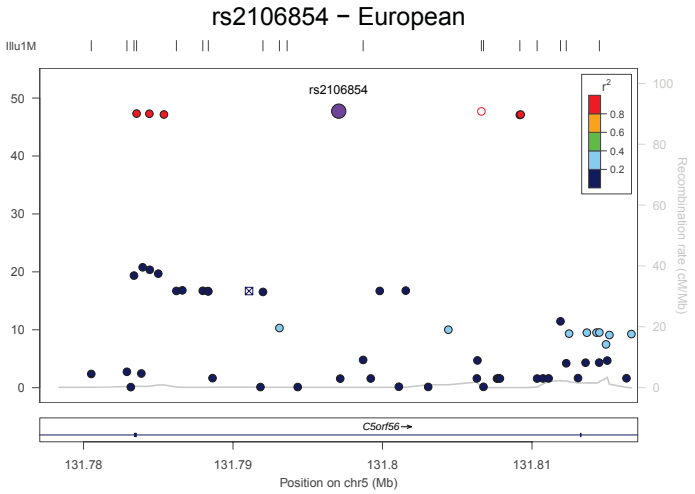
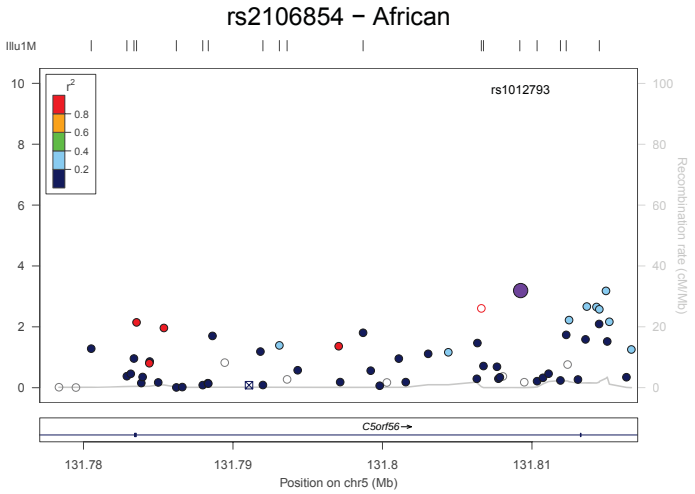
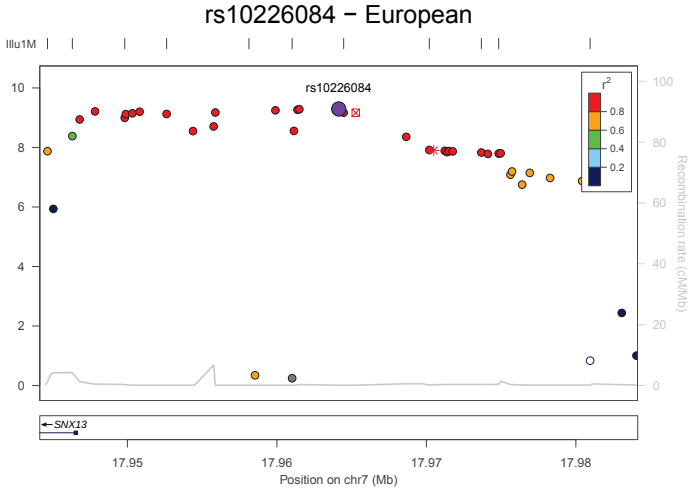


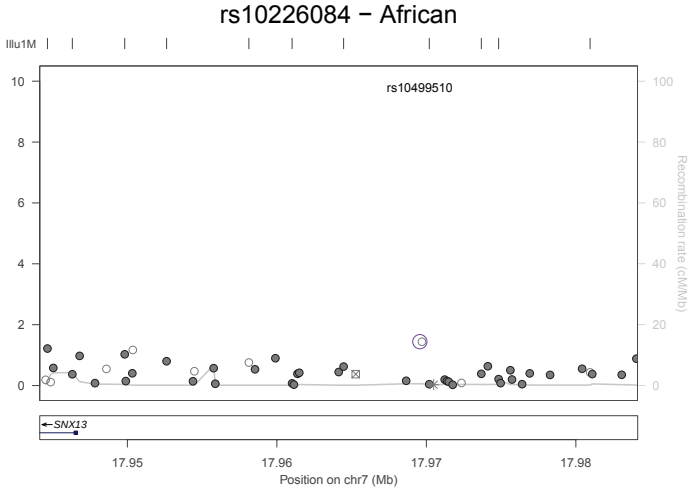


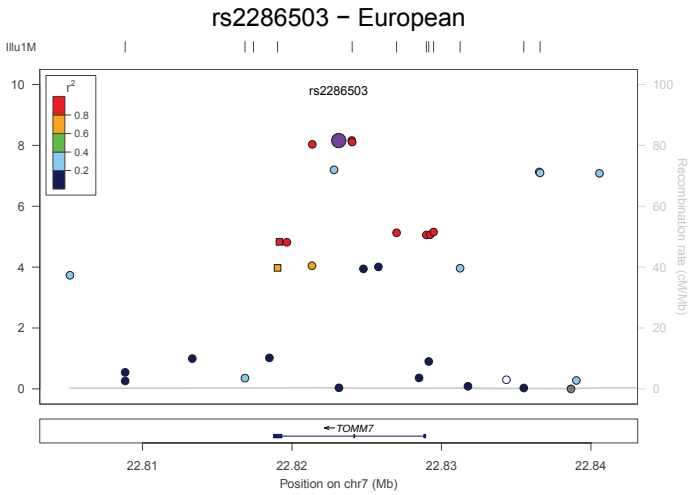


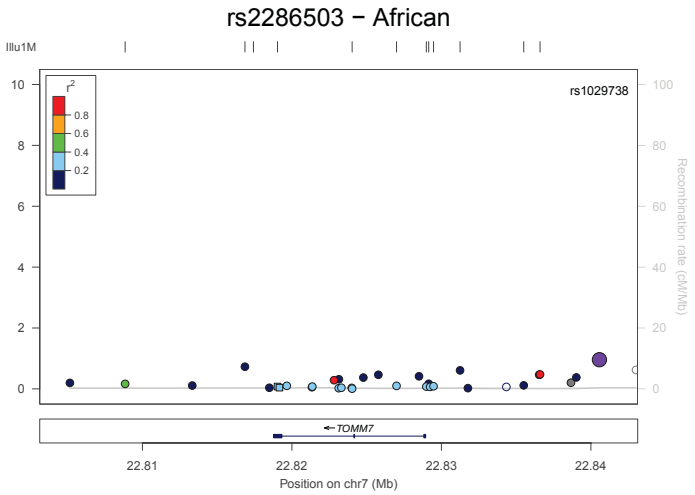


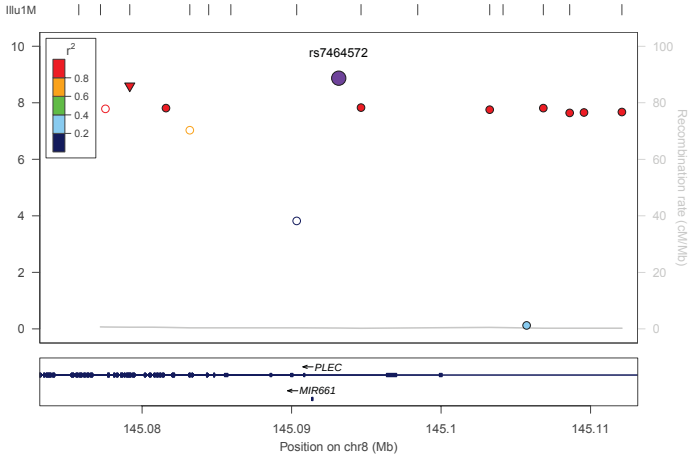


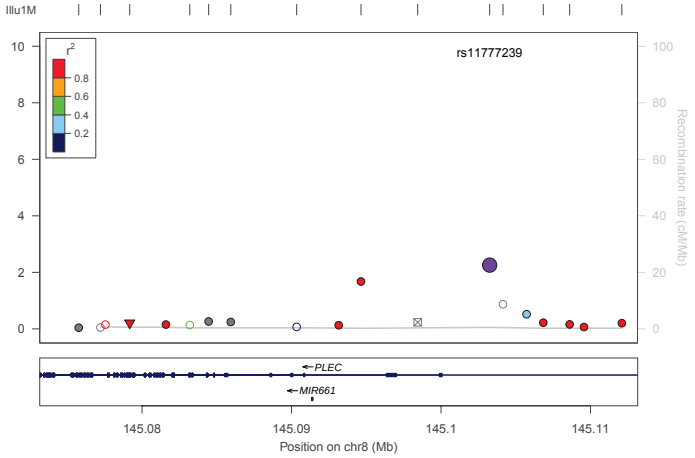




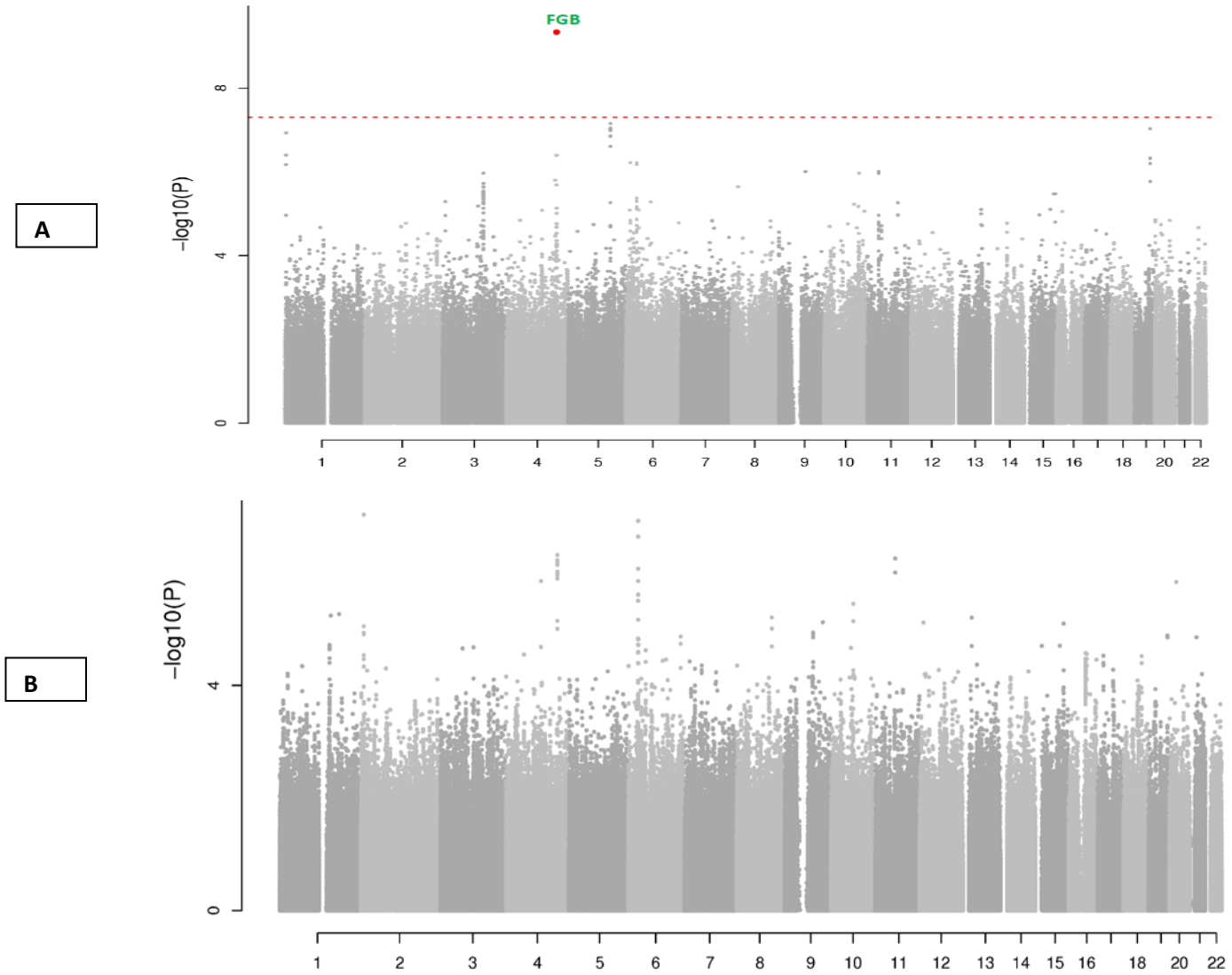




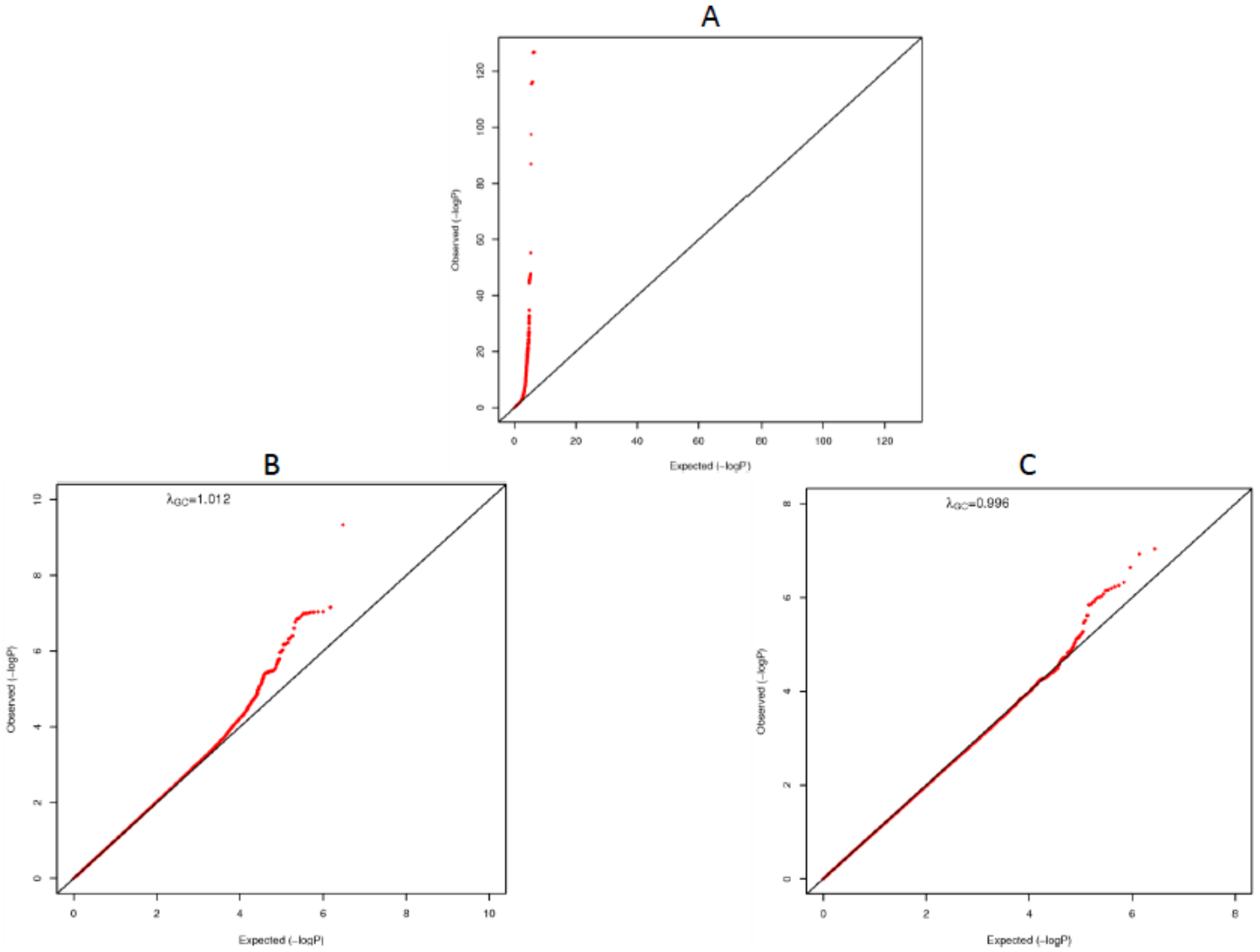




Supplementary Figure S3: Manhattan plot showing the results for the meta-analysis in (A) African American and (B) Hispanic Samples.



Supplementary Figure S4: QQ-plots for the meta-analysis in (A) European, (B) African American, and (C) Hispanic Samples.



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