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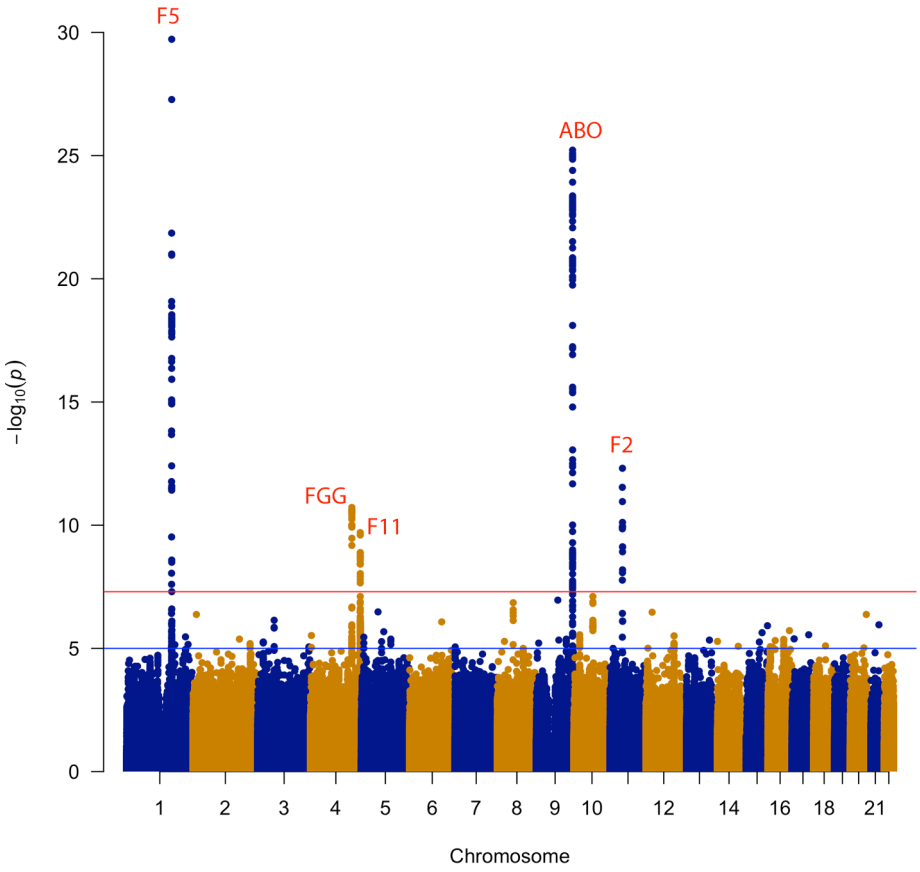
INVENT Consortium Investigators and Affiliations

Marine Germain,[1,2,3] Daniel I Chasman,[4] Hugoline de Haan,[5] Weihong Tang,[6] Sara Lindström,[7] Lu-Chen Weng,[6] Mariza de Andrade,[8] Marieke CH de Visser,[9] Kerri L Wiggins,[10] Pierre Suchon,[11,12,13] Noémie Saut,[11,12,13] David Smadja[14,15,16] Grégoire Legal,[17,18] Astrid van Hylckama Vlieg,[5] Antonio Di Narzo,[19] Ke Hao,[19] Christopher P Nelson,[20,21] Ares Rocanin-Arjo,[1,2,3] Lasse Folkersen,[22] Ramin Monajemi,[23] Lynda M Rose,[24] Jennifer A Brody,[25] Eline Slagboom,[26] Dylan Aissi,[1,2,3] France Gagnon,[27] Jean-Francois Deleuze,[28] Panos Deloukas,[29,30] Christophe Tzourio,[31] Jean-Francois Dartigues,[31] Claudine Berr,[32] Kent D Taylor,[33] Mete Civelek,[34] Per Eriksson,[35] Cardiogenics Consortium, Bruce M Psaty,[25,36] Jeanine Houwing-Duitermaat,[23] Alison H Goodall,[20,21] François Cambien,[1,2,3] Peter Kraft,[7] Philippe Amouyel,[37,38] Nilesh J Samani,[20,21] Saonli Basu,[39] Paul M Ridker,[4] Frits R Rosendaal,[5] Christopher Kabrhel,[40] Aaron R Folsom,[6] John Heit,[41] Pieter H Reitsma,[9] David-Alexandre Trégouët,[1,2,3] Nicholas L Smith,[10,36,42,*] Pierre-Emmanuel Morange[11,12,13,*]

[1.] Institut National pour la Santé et la Recherche Médicale (INSERM), Unité Mixte de Recherche en Santé (UMR_S) 1166, F-75013, Paris, France.
[2] Sorbonne Universités, Université Pierre et Marie Curie (UPMC Univ Paris 06), UMR_S 1166, Team Genomics & Pathophysiology of Cardiovascular Diseases, F-75013, Paris, France.
[3] Institute for Cardiometabolism and Nutrition (ICAN), F-75013, Paris, France.
[4] Division of Preventive Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA 02215, USA.
[5] Department of Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, The Netherlands; Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands.
[6] University of Minnesota, Division of Epidemiology and Community Health Minneapolis, MN, USA.
[7] Program in Genetic Epidemiology and Statistical Genetics, Department of Epidemiology, Harvard School of Public Health, Boston, MA 2115, USA.
[8] Division of Biomedical Statistics and Informatics Mayo Clinic, Rochester, MN, USA.
[9] Einthoven Laboratory for Experimental Vascular Medicine, Department of Thrombosis and Hemostasis, Leiden University Medical Center, Leiden,2300 RC, Netherlands.
[10] Department of Epidemiology, University of Washington, Seattle WA 98195, USA.
[11] Laboratory of Haematology, La Timone Hospital, F-13385, Marseille, France.
[12] INSERM, UMR_S 1062, Nutrition Obesity and Risk of Thrombosis,F-13385, Marseille, France.
[13] Aix-Marseille University, UMR_S 1062, Nutrition Obesity and Risk of Thrombosis, F-13385, Marseille, France.
[14] Université Paris Descartes, Sorbonne Paris Cité, Paris, France.
[15] AP-HP, Hopital Européen Georges Pompidou, Service d'hématologie Biologique, Paris, France.
[16] INSERM, UMR_S 1140, Faculté de Pharmacie, Paris, France.
[17] Université de Brest, EA3878 and CIC1412, Brest, France.
[18] Ottawa Hospital Research Institute at the University of Ottawa, Ottawa, ON, Canada.

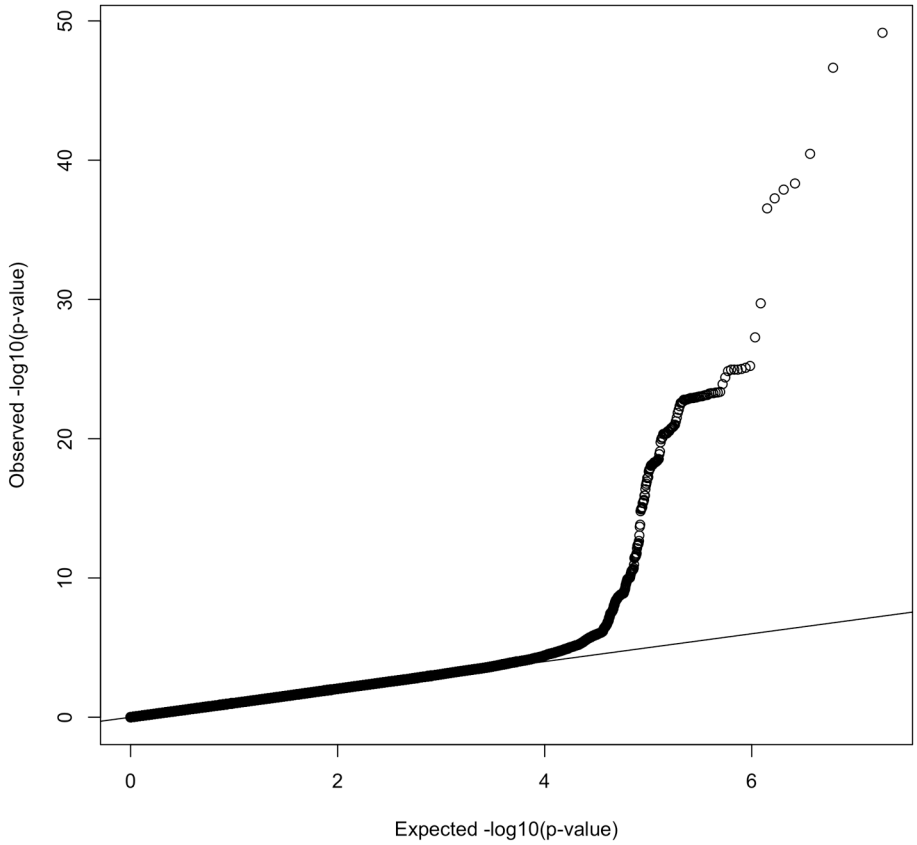
[19] Department of Genetics and Genomic Sciences, Mount Sinai School of Medicine, New York, NY, USA.
[20] Department of Cardiovascular Sciences, University of Leicester, Leicester, UK.
[21] National Institute for Health Research (NIHR) Leicester Cardiovascular Biomedical Research Unit, Leicester, UK.
[22] Department of PharmacoGenetics, Novo Nordisk Park 9.1.21, Copenhagen, Denmark.
[23] Department of Medical Statistics and Bioinformatics, Leiden University Medical Center, 2300 RC Leiden, Netherlands.
[24] Division of Preventive Medicine, Brigham and Women's Hospital, Boston, MA 02215, USA.
[25] Cardiovascular Health Research Unit, Departments of Medicine, Epidemiology, and Health Services, University of Washington, Seattle, WA, USA.
[26] Department of Molecular Epidemiology, Leiden University Medical Center, 2300 RC Leiden, Netherlands.
[27] Division of Epidemiology, Dalla Lana School of Public Health, University of Toronto, Toronto, Canada.
[28] Commissariat à l'Energie Atomique/Direction des Sciences du Vivant/Institut de Génomique, Centre National de Génotypage, 91057 Evry, France.
[29] William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK.
[30] Princess Al-Jawhara Al-Brahim Centre of Excellence in Research of Hereditary Disorders (PACER-HD), King Abdulaziz University, Jeddah 21589, Saudi Arabia.
[31] Inserm Research Center U897, University of Bordeaux, Bordeaux, France.
[32] Inserm Research Unit U1061 , University of Montpellier I , Montpellier, France.
[33] Los Angeles Biomedical Research Institute and Department of Pediatrics, Harbor-UCLA Medical Center, Torrence CA 90502, USA.
[34] Department of Medicine, University of California, Los Angeles, CA USA.
[35] Atherosclerosis Research Unit, Center for Molecular Medicine, Department of Medicine, Karolinska Institutet, Stockholm, Sweden.
[36] Group Health Research Institute, Group Health Cooperative, Seattle WA 98101, USA.
[37] Institut Pasteur de Lille, Université de Lille Nord de France, INSERM UMR_S 744, Lille, France.
[38] Centre Hospitalier Régional Universitaire de Lille, Lille, France.
[39] University of Minnesota, Division of Biostatistics, Minneapolis, MN, USA.
[40] Department of Emergency Medicine, Massachusetts General Hospital, Channing Network Medicine, Harvard Medical School, Boston, MA 2114, USA.
[41] Division of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, USA.
[42] Seattle Epidemiologic Research and Information Center, VA Office of Research and Development, Seattle WA 98108, USA.

Supplementary Figure S1. Manhattan plot for the discovery venous thromboembolism genome-wide association study



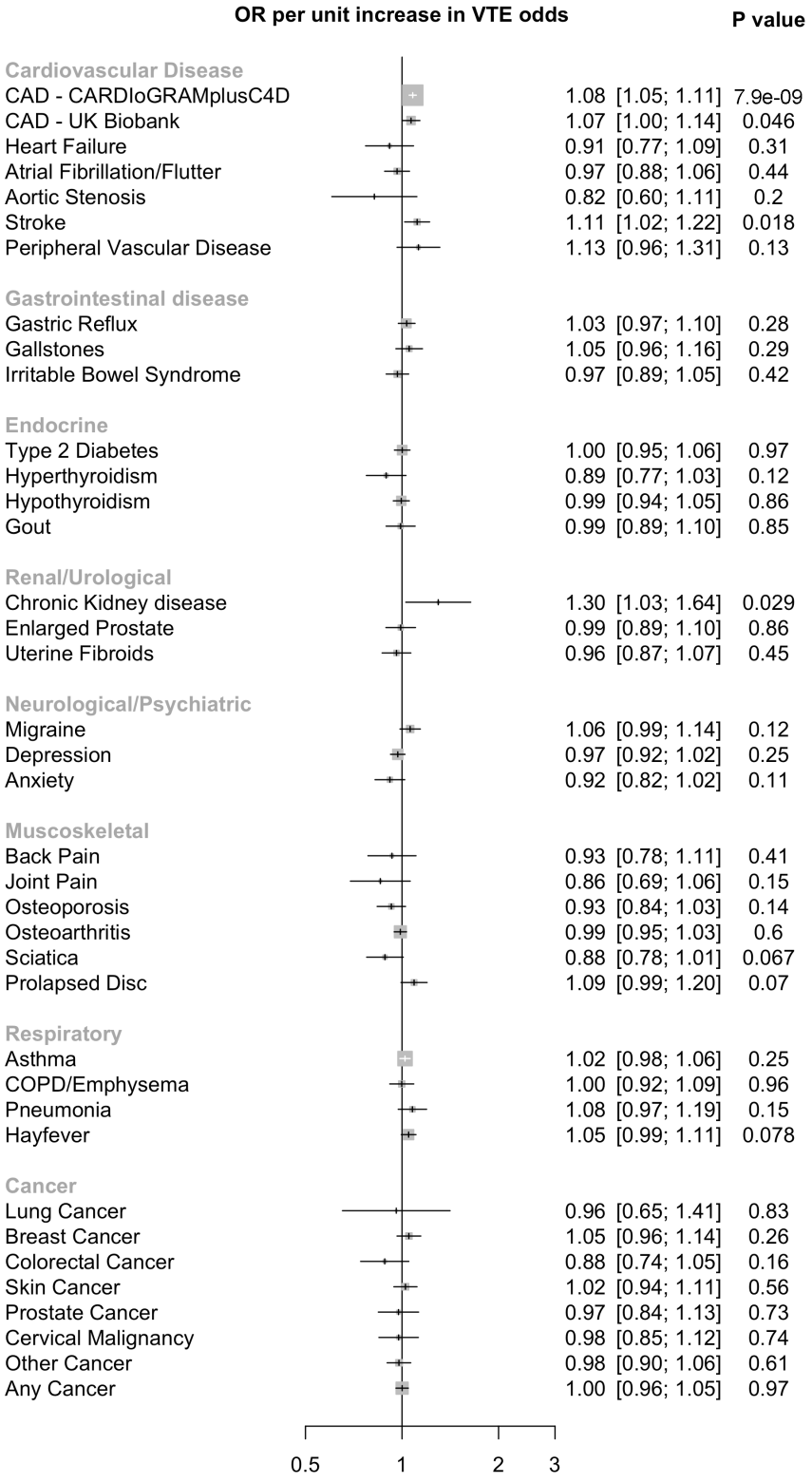
Plot of -log10(*P*) for association of genotyped variants by chromosomal position for all autosomal polymorphisms analyzed in the UK Biobank VTE GWAS. The genes associated with the top associated variants are displayed.

Supplementary Figure S2. Quantile-quantile plot for the discovery venous thromboembolism genome-wide association study



The expected association P values for the distribution of genotyped versus the observed distribution of P values for VTE association is displayed. Significant systemic inflation is not observed (λ_{GC} = 1.05).

Supplementary Figure S3. Phenome-wide association results for the ten variant VTE genetic risk score across 37 disorders



Odds ratio per unit increase in VTE odds on 37 diseases within CARDIoGRAMplusC4D data and UK Biobank. For the CARDIOGRAMplusC4D coronary artery disease summary statistics, we performed an inverse-variance weighted fixed effects meta-analysis. Estimates in UK Biobank were derived using logistic regression adjusting for age, sex, chip-array, and ten principal components of ancestry. Abbreviations: CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; OR, odds ratio

Supplementary Table S1. Ten independent (R^2 <0.01) SNPs utilized in the VTE genetic risk score PheWAS. Eight of the SNPs have been previously reported, and rs4602861 and rs3136516 were identified in the UK Biobank GWAS.

SNP	Chr	Gene	OR for VTE	EA	EAF	References
rs6025	1	*F5*	3.25	T	0.02	[1]
rs2066865	4	*FGG*	1.24	A	0.24	[1]
rs2289252	4	*F11*	1.35	T	0.41	[1,2]
rs4602861	8	*ZFPM2*	1.11	A	0.73	N/A
rs2519093	9	*ABO*	1.68	T	0.19	[3]
rs78707713	10	*TSPAN15*	1.28	C	0.88	[1]
rs1799963	11	*F2*	2.29	A	0.01	[1]
rs3136516	11	*F2*	1.1	G	0.48	N/A
rs2288904	19	*SLC44A2*	1.19	G	0.79	[1]
rs6087685	20	*PROCR*	1.15	C	0.30	[1]

Abbreviations: PheWAS, phenome-wide association study; GWAS, genome-wide association study; SNP, single nucleotide polymorphism; Chr, chromosome; OR, odds ratio; EA, effect allele; EAF, effect allele frequency;

Supplementary Table S2. BMI associated variants used in the Mendelian randomization analysis

SNP	Chr.	Gene	Alleles		GIANT β	GIANT Effect Allele Frequency	UK Biobank Effect Allele Frequency	Variance explained	UK Biobank Imputation INFO Score
			Effect	Other					
rs12566985	1	*FPGT-TNNI3K*	G	A	0.024	0.446	0.438	0.03%	0.994
rs17024393	1	*GNAT2*	C	T	0.066	0.04	0.025	0.03%	0.986
rs2820292	1	*NAV1*	C	A	0.02	0.555	0.568	0.02%	1
rs3101336	1	*NEGR1*	C	T	0.033	0.613	0.600	0.05%	1
rs543874	1	*SEC16B*	G	A	0.048	0.193	0.209	0.07%	1
rs657452	1	*AGBL4*	A	G	0.023	0.394	0.392	0.03%	0.986
rs11165643	1	*PTBP2*	T	C	0.022	0.583	0.584	0.02%	0.995
rs11583200	1	*ELAVL4*	C	T	0.018	0.396	0.398	0.02%	0.986
rs12401738	1	*FUBP1*	A	G	0.021	0.352	0.369	0.02%	0.995
rs1016287	2	*LINC01122*	T	C	0.023	0.287	0.300	0.02%	0.993
rs10182181	2	*ADCY3*	G	A	0.031	0.462	0.487	0.05%	0.994
rs11126666	2	*KCNK3*	A	G	0.021	0.283	0.255	0.02%	0.994
rs11688816	2	*EHBP1*	G	A	0.017	0.525	0.545	0.02%	0.98
rs13021737	2	*TMEM18*	G	A	0.06	0.828	0.830	0.10%	0.991
rs1528435	2	*UBE2E3*	T	C	0.018	0.631	0.621	0.02%	0.997
rs2121279	2	*LRP1B*	T	C	0.025	0.152	0.126	0.02%	0.986
rs7599312	2	*ERBB4*	G	A	0.022	0.724	0.731	0.02%	0.97
rs13078960	3	*CADM2*	G	T	0.03	0.196	0.201	0.03%	0.991
rs1516725	3	*ETV5*	C	T	0.045	0.872	0.863	0.05%	0.992
rs16851483	3	*RASA2*	T	G	0.048	0.066	0.066	0.03%	0.999
rs3849570	3	*GBE1*	A	C	0.019	0.359	0.347	0.02%	0.995
rs6804842	3	*RARB*	G	A	0.019	0.575	0.575	0.02%	0.987
rs2365389	3	*FHIT*	C	T	0.020	0.582	0.581	0.02%	0.992
rs10938397	4	*GNPDA2*	G	A	0.04	0.434	0.434	0.08%	1
rs11727676	4	*HHIP*	T	C	0.036	0.91	0.903	0.02%	1

rs2112347	5	*POC5*	T	G	0.026	0.629	0.640	0.03%	1
rs13191362	6	*PARK2*	A	G	0.028	0.879	0.874	0.02%	0.989
rs2207139	6	*TFAP2B*	G	A	0.045	0.177	0.169	0.06%	0.999
rs205262	6	*C6orf106*	G	A	0.022	0.273	0.273	0.02%	0.997
rs9400239	6	*FOXO3*	C	T	0.019	0.688	0.696	0.02%	0.991
rs1167827	7	*HIP1*	G	A	0.02	0.553	0.565	0.02%	1
rs2245368	7	*PMS2L11*	C	T	0.032	0.180	0.173	0.03%	1.000
rs17405819	8	*HNF4G*	T	C	0.022	0.7	0.702	0.02%	0.998
rs2033732	8	*RALYL*	C	T	0.019	0.747	0.744	0.01%	1
rs10733682	9	*LMX1B*	A	G	0.017	0.478	0.472	0.02%	0.953
rs10968576	9	*LINGO2*	G	A	0.025	0.32	0.324	0.03%	1
rs1928295	9	*TLR4*	T	C	0.019	0.548	0.571	0.02%	1
rs4740619	9	*C9orf93*	T	C	0.018	0.542	0.553	0.02%	0.997
rs6477694	9	*EPB41L4B*	C	T	0.017	0.365	0.354	0.01%	0.989
rs11191560	10	*NT5C2*	C	T	0.031	0.089	0.076	0.02%	1
rs17094222	10	*HIF1AN*	C	T	0.025	0.211	0.212	0.02%	0.968
rs7899106	10	*GRID1*	G	A	0.04	0.052	0.050	0.02%	0.983
rs12286929	11	*CADM1*	G	A	0.022	0.523	0.525	0.02%	0.99
rs2176598	11	*HSD17B12*	T	C	0.02	0.251	0.245	0.02%	1
rs3817334	11	*MTCH2*	T	C	0.026	0.407	0.408	0.03%	1
rs4256980	11	*TRIM66*	G	C	0.021	0.646	0.656	0.02%	0.992
rs11057405	12	*CLIP1*	G	A	0.031	0.901	0.894	0.02%	1
rs7138803	12	*BCDIN3D*	A	G	0.032	0.384	0.369	0.05%	1
rs12429545	13	*OLFM4*	A	G	0.033	0.133	0.130	0.03%	0.974
rs9581854	13	*MTIF3*	T	C	0.030	0.203	0.180	0.03%	0.986
rs10132280	14	*STXBP6*	C	A	0.023	0.682	0.701	0.02%	0.974
rs12885454	14	*PRKD1*	C	A	0.021	0.642	0.641	0.02%	0.995
rs7141420	14	*NRXN3*	T	C	0.024	0.527	0.516	0.03%	0.98
rs11847697	14	*PRKD1*	T	C	0.049	0.042	0.049	0.02%	1.000
rs16951275	15	*MAP2K5*	T	C	0.031	0.784	0.775	0.03%	0.998

rs3736485	15	*DMXL2*	A	G	0.018	0.454	0.462	0.02%	0.986
rs12446632	16	*GPRC5B*	G	A	0.04	0.865	0.858	0.04%	1
rs2650492	16	*SBK1*	A	G	0.021	0.303	0.298	0.02%	0.98
rs758747	16	*NLRC3*	T	C	0.023	0.265	0.287	0.02%	0.968
rs1000940	17	*RABEP1*	G	A	0.019	0.32	0.301	0.02%	0.996
rs12940622	17	*RPTOR*	G	A	0.018	0.575	0.559	0.02%	0.998
rs1808579	18	*C18orf8*	C	T	0.017	0.534	0.517	0.01%	0.998
rs6567160	18	*MC4R*	C	T	0.056	0.236	0.235	0.11%	0.996
rs7243357	18	*GRP*	T	G	0.022	0.812	0.825	0.01%	0.989
rs17724992	19	*PGPEP1*	A	G	0.019	0.746	0.733	0.01%	0.982
rs2287019	19	*QPCTL*	C	T	0.036	0.804	0.818	0.04%	0.977
rs29941	19	*KCTD15*	G	A	0.018	0.669	0.672	0.02%	1
rs3810291	19	*ZC3H4*	A	G	0.028	0.666	0.662	0.04%	1.000

Abbreviations: SNP, single nucleotide polymorphism; Chr, chromosome;

Supplementary Table S3. Odds ratios and P values for the ten autosomal, genome-wide associated VTE SNPs previously reported in the literature and in UK Biobank.

SNP	Chr	Gene	Published OR	Published P Value	UK Biobank OR	UK Biobank P Value	References
rs4524	1	*F5*	1.20	2.65×10^{-11}	1.14	3.6×10^{-6}	[1]
rs6025	1	*F5*	3.25	1.10×10^{-96}	3.49	7.10×10^{-50}	[1]
rs2066865	4	*FGG*	1.24	1.03×10^{-16}	1.21	3.10×10^{-11}	[1]
rs2036914	4	*F11*	1.35	1.88×10^{-20}	1.16	1.20×10^{-8}	[1, 2]
rs2289252	4	*F11*	1.35	2.56×10^{-23}	1.17	1.90×10^{-9}	[1, 2]
rs2519093	9	*ABO*	1.68	8.08×10^{-16}	1.41	6.00×10^{-26}	[3]
rs78707713	10	*TSPAN15*	1.28	5.74×10^{-11}	1.22	1.5×10^{-7}	[1]
rs1799963	11	*F2*	2.29	1.73×10^{-9}	2.63	4.90×10^{-13}	[1]
rs2288904	19	*SLC44A2*	1.19	1.07×10^{-9}	1.11	4.2×10^{-4}	[1]
rs6087685	20	*PROCR*	1.15	1.65×10^{-8}	1.08	0.005	[1]

Odds ratio $R^2 = 0.97$

Abbreviations: SNP, single nucleotide polymorphism; Chr, chromosome; OR, Odds Ratio

Supplementary Table S4. Top eleven novel variants identified in UK Biobank discovery analysis brought forward for replication**.** The mixed modeling P value for VTE discovery and logistic regression P value for replication are shown.

SNP	Description	Gene	EA	Chr	EAF	INFO	UKB OR	UKB P Value*	INVENT OR	INVENT P Value†	Combined P Value	Heterogeneity P Value
rs1500426	intergenic	*(VENTXP)*	T	3	0.41	0.996	1.12	5.60×10^{-6}	0.99	0.944	NA‡	6.88×10^{-4}
rs13074062	intronic	*PTPRG*	C	3	0.46	1	1.13	1.50×10^{-6}	1.04	0.062	1.80×10^{-5}	0.023
rs76950881	intronic	*SEMA5A*	A	5	0.14	0.979	1.18	3.50×10^{-6}	0.97	0.294	NA‡	3.48×10^{-5}
rs247518	intronic	*STARD4-AS1*	G	5	0.80	0.964	1.16	4.20×10^{-6}	1.03	0.236	3.10×10^{-4}	.0084
rs6468473	intergenic	*(LOC100500773)*	A	8	0.37	0.998	1.12	1.00×10^{-5}	0.99	0.696	NA‡	4.10×10^{-4}
rs4602861	intronic	*ZFPM2*	A	8	0.73	0.979	1.08	0.0045	1.13	5.04×10^{-7}	4.88×10^{-10}	0.26
rs3136516§	intronic	*F2*	G	11	0.48	0.994	1.10	0.00033	1.10	5.65×10^{-6}	7.60×10^{-9}	0.85
rs1107756	intronic	*APPL2*	G	12	0.40	0.995	1.13	3.10×10^{-6}	1.00	0.845	4.70×10^{-3}	.0011
rs117316396	intergenic	*(KIAA1024)*	G	15	0.94	0.947	1.28	2.30×10^{-6}	1.04	0.445	8.70×10^{-4}	.0060
rs117477387	intergenic	*(TMEM114)*	C	16	0.05	0.979	1.30	8.50×10^{-6}	1.05	0.394	0.0011	.0064
rs79814466	intronic	*NDRG4*	G	16	0.96	0.961	1.34	4.30×10^{-6}	1.07	0.327	5.90×10^{-4}	.021

* - P value based on linear mixed modeling analysis
† - P value based on logistic regression analysis

‡ - P Values were not calculated for SNPs with effects in opposing directions in discovery/replication
§ - Results after conditioning on rs1799963

Genes for SNPs that are outside the transcript boundary of the protein-coding gene are shown in parentheses [eg, (*TMEM114*)].

Chr = Chromosome, EA = Effect Allele, EAF = Effect Allele Frequency, OR = Odds Ratio, UKB = UK Biobank

Supplementary Table S5. 14 genome-wide associated VTE SNPs included in h_{GWAS}^2 calculation

SNP	Gene	EAF	OR	V_g
rs4602861	ZFPM2	0.766	1.11	0.0004
rs3136516	*F2*	0.48	1.1	0.0005
rs114209171	*F8*	0.78	1.15	0.0008
rs6087685	*PROCR*	0.3	1.15	0.001
rs2288904	*SLC44A2*	0.79	1.19	0.0012
rs78707713	*TSPAN15*	0.88	1.28	0.0015
rs4524	*F5*	0.74	1.2	0.0015
rs1799963	*F2*	0.01	2.29	0.0018
rs2066865	*FGG*	0.24	1.24	0.002
rs2289252	*F11*	0.41	1.35	0.0052
rs2036914	*F11*	0.52	1.35	0.0053
[O,A2 vs. A1,B]	*ABO*	0.3	1.5	0.0083
rs6025	*F5*	0.03	3.25	0.0111
rs2519093	*ABO*	0.24	1.68	0.0118
			$h_{GWAS}^2 = 0.0524$	

EAF = Effect Allele Frequency, OR = Odds Ratio, V_g = individual SNP variance in liability

Supplementary Table S6. Definitions of diseases included in the phenome-wide association study

Outcome-Data Source	Definition	Total Case Number
Coronary Artery Disease-CARDIoGRAMplusC4D	Confirmed MI, > 50% stenosis in at least one coronary vessel at angiography with validation from hospital records, validated history of percutaneous transluminal coronary angioplasty or coronary artery bypass graft surgery, or validated angina, defined as symptoms + confirmation from at least non-invasive provocation test e.g. scintigraphy or exercise treadmill test at case ascertainment	60,801 cases and 123,504 controls
Coronary Artery Disease-UK Biobank	History of myocardial infarction, coronary artery bypass grafting, or coronary artery angioplasty during verbal interview, hospitalization for ICD-10 code for acute myocardial infarction (I21.0, I21.1, I21.2, I21.4, I21.9, hospitalization for OPCS-4 coded procedure: coronary artery bypass grafting (K40.1-40.4, K41.1-41.4, K45), or hospitalization for OPCS-4 coded procedure: coronary angioplasty with or without stenting (K49.1-49.2, K49.8-49.9, K50.2, K75.1-75.4, K75.8-75.9)	4,461
Heart failure-UK Biobank	History of heart failure during verbal interview or hospitalization for ICD code I50/UK Biobank	599
Atrial Fibrillation/Flutter-UK Biobank	History of atrial fibrillation or flutter during verbal interview or hospitalization for ICD code I48/UK Biobank	2,208
Aortic stenosis-UK Biobank	History of aortic stenosis during verbal interview or hospitalization for ICD code I350/UK Biobank	193
Stroke-UK Biobank	History of stroke, ischemic stroke, or subarachnoid hemorrhage during verbal interview or hospitalization for ICD codes I60-I64/UK Biobank	2,066

Peripheral vascular Disease-UK Biobank	History of peripheral vascular disease or intermittent claudication during verbal interview or hospitalization for ICD code I73.1, I73.8, I173.9, I74.3, I74.4, I74.5/UK Biobank	692
Gastric reflux-UK Biobank	History of gastric reflux during verbal interview/UK Biobank	4,881
Gallstones-UK Biobank	History of gallstones during verbal interview/UK Biobank	1,831
Irritable bowel syndrome-UK Biobank	History of irritable bowel syndrome during verbal interview/UK Biobank	2,679
Type 2 Diabetes-UK Biobank	History of diabetes unspecified or type 2 diabetes during verbal interview or current use of insulin medication/UK Biobank	5,741
Hyperthyroidism-UK Biobank	History of hyperthyroidism during verbal interview/UK Biobank	868
Hypothyroidism-UK Biobank	History of hypothyroidism during verbal interview/UK Biobank	5,433
Gout-UK Biobank	History of gout during verbal interview/UK Biobank	1,612
Chronic Kidney Disease-UK Biobank	History of chronic kidney disease on verbal interview/UK Biobank	275
Enlarged prostate-UK Biobank	History of enlarged prostate during verbal interview/UK Biobank	1,573
Uterine fibroids-UK Biobank	History of uterine fibroids during verbal interview/UK Biobank	1,634
Migraine-UK Biobank	History of migraine during verbal interview/UK Biobank	3,161
Depression-UK Biobank	History of depression during verbal interview/UK Biobank	6,667
Anxiety-UK Biobank	History of anxiety/panic attacks during verbal interview/UK Biobank	1,545
Back Pain-UK Biobank	History of back pain during verbal interview/UK Biobank	584
Joint Pain-UK Biobank	History of joint pain during verbal interview/UK Biobank	377
Osteoporosis-UK Biobank	History of osteoporosis during verbal interview/UK Biobank	1,740
Osteoarthritis-UK Biobank	History of osteoarthritis during verbal interview/UK Biobank	9,693
Sciatica-UK Biobank	History of sciatica during verbal interview/UK Biobank	1,035

Prolapsed Disc-UK Biobank	History of prolapsed disc/slipped disc during verbal interview/UK Biobank	1,856
Asthma-UK Biobank	History of asthma during verbal interview/UK Biobank	13,941
COPD/Emphysema-UK Biobank	History of chronic obstructive pulmonary disease, emphysema/chronic bronchitis or emphysema during verbal interview/UK Biobank	2,363
Pneumonia-UK Biobank	History of pneumonia during verbal interview/UK Biobank	1,581
Hayfever-UK Biobank	History of hayfever during verbal interview/UK Biobank	6,263
Lung Cancer-UK Biobank	History of lung cancer, small cell lung cancer or non-small cell lung cancer during verbal interview/UK Biobank	115
Breast Cancer-UK Biobank	History of breast cancer during verbal interview/UK Biobank	2,383
Colorectal Cancer-UK Biobank	History of large bowel cancer/colorectal cancer, colon cancer/sigmoid cancer or rectal cancer during verbal interview/UK Biobank	616
Skin Cancer-UK Biobank	History of skin cancer, malignant melanoma, non-melanoma skin cancer, basal cell carcinoma or squamous cell carcinoma during verbal interview/UK Biobank	2,482
Prostate Cancer-UK Biobank	History of prostate cancer during verbal interview/UK Biobank	840
Cervical Malignancy-UK Biobank	History of cervical cancer or CIN cells at the cervix during verbal interview/UK Biobank	872
Other Cancer-UK Biobank	History of any other cancer than lung cancer, breast cancer, colorectal cancer, skin cancer, prostate cancer or cervical malignancy during verbal interview/UK Biobank	2,409
Any Cancer-UK Biobank	History of any cancer during verbal interview/UK Biobank	9,530

Abbreviations: CIN, cervical intraepithelial neoplasia; COPD, chronic obstructive pulmonary disease; ICD, International Classification of Diseases; OPCS, Office of Population and Censuses and Surveys;

Supplemental References

1. Germain M, Chasman DI, de Haan H, Tang W, Lindstrom S, Weng LC, et al. Meta-analysis of 65,734 individuals identifies TSPAN15 and SLC44A2 as two susceptibility loci for venous thromboembolism. *Am J Hum Genet*. 2015;96:532-42.
2. Morange PE, Suchon P, Tregouet DA. Genetics of Venous Thrombosis: update in 2015. *Thromb Haemost*. 2015;114:910-9.
3. Heit JA, Cunningham JM, Petterson TM, Armasu SM, Rider DN, M DEA. Genetic variation within the anticoagulant, procoagulant, fibrinolytic and innate immunity pathways as risk factors for venous thromboembolism. *J Thromb Haemost*. 2011;9:1133-42.