SUPPLEMENTARY MATERIAL

METHODS

Hierarchical clustering of quantitative traits

Clusters of highly correlated quantitative traits within 66 quantitative traits from the FINRISK study (collection years 1992-2012, sample sizes ranging from 4,792 to 26,717) were identified using hierarchical clustering. The pairwise Pearson correlation coefficients were calculated amongst inverse-rank normalized age and sex adjusted residuals of the 66 traits using complete samples for the two traits. The correlation structure of the traits is shown in Supplementary Figure 2. Hierarchical clustering was performed using the Ward agglomeration method and one minus the absolute correlation coefficient as the dissimilarity metric. P-values for the clusters were obtained via multiscale bootstrap resampling[1] . Clusters with over three traits and p-values passing the significance level 0.01 were considered.

Chip genotype data processing and QC

Samples were genotyped with Illumina (Illumina Inc., San Diego, CA, USA) and Affymetrix arrays (Thermo Fisher Scientific, Santa Clara, CA, USA). Genotype calls were made with GenCall and zCall algorithms for Illumina and AxiomGT1 algorithm for Affymetrix data. Chip genotyping data produced with previous chip platforms and reference genome builds were lifted over to build version 38 (GRCh38/hg38) following the protocol described her: dx.doi.org/10.17504/protocols.io.nqtddwn. In sample-wise quality control, individuals with ambiguous gender, high genotype missingness (>5%), excess heterozygosity (±4SD) and non-Finnish ancestry were removed. In variant-wise quality control variants with high missingness (>2%), low HWE p-value ($<1\times10^{-6}$) and minor allele count, MAC<3 were removed.

Haplotype phasing and genotype imputation

Chip-genotyped samples were pre-phased with Eagle 2.3.5 (https://data.broadinstitute.org/alkesgroup/Eagle/) with the default parameters, except the number of conditioning haplotypes was set to 20,000. Genotype imputation was carried out by using the population-specific SISu v3 imputation reference panel with Beagle 4.1 (version08Jun17.d8b, https://faculty.washington.edu/browning/beagle/b4_1.html) as described here: dx.doi.org/10.17504/protocols.io.nmndc5e. Post-imputation variant-wise quality-control involved checking expected conformity of the imputation INFO-values distribution and MAF differences between the target dataset and the imputation reference panel.

Post-imputation QC

Genotype imputation was followed by post-imputation sample QC, wherein 340 duplicate samples (kinship > 0.45) and 102 additional samples were excluded based on singleton count > 20, number of heterozygous calls falling out of hard called bounds (lower-bound 20,700, upper-bound 22,450), and over 4 standard deviation difference from the mean in number of insertion alternate alleles, number of deletion alternate alleles, insertion/deletion allele ratio, transition/transversion ratio and number of SNP alternate alleles. Sample QC was performed using 74,506 variants passing strict variant QC (autosomal single nucleotide polymorphisms with imputation INFO score > 0.99, $0.05 \leq AF \leq 0.95$, HWE p-value > 0.001, call rate > 0.99, linkage disequilibrium (LD)-pruned with r^2 threshold 0.1 and 1 MB window-size), where possible (number of heterozygous calls, number of SNP alternate alleles, transition/transversion ratio). When the strict variant set could not be used (singletons, insertions, deletions, insertion/deletion ratio), variants were restricted to those with imputation INFO score $\geq$ 0.7. Lastly, genetic variants with imputation INFO score < 0.8, minor allele frequency < 0.002 or HWE p-value < 1×10^{-6} were removed.

Principal component analysis

Principal component (PC) analysis for 26,717 FINIRISK individuals was performed using 73,072 independent high-quality variants (autosomal single nucleotide polymorphisms with imputation info score > 0.99, $0.05 \leq AF \leq 0.95$, HWE p-value > 0.001, call rate > 0.99, excluding high-LD regions, LD-pruned with r^2 threshold 0.1 and 1 MB window-size). For PC analysis 2,119 related (kinship > 0.1) were excluded. First 10 PCs were calculated for 24,598 unrelated individuals, and SNP weights were extracted. Using those weights, first 10 PCs were projected for the 2,119 individuals excluded due to relatedness.

FinnGen ethical statements

For the Finnish Institute of Health and Welfare (THL) driven FinnGen preparatory project (here called FinnGen), all patients and control subjects had provided informed consent for biobank research, based on the Finnish Biobank Act. Alternatively, older cohorts were based on study specific consents and later transferred to the THL Biobank after approval by Valvira, the National Supervisory Authority for Welfare and Health. Recruitment protocols followed the biobank protocols approved by Valvira. The Biobank Access Decisions for FinnGen samples and data utilized in FinnGen Data Freeze 4 include: Auria Biobank AB17-5154, THL Biobank BB2017_55, BB2017_111, BB2018_19, BB_2018_34, Finnish Red Cross Blood Service Biobank 7.12.2017, Helsinki Biobank HUS/359/2017 and Northern Finland Biobank Borealis BB_2017_1013. The Ethical Review Board of the Hospital District of Helsinki and Uusimaa approved the FinnGen study protocol Nr HUS/990/2017. The FinnGen preparatory project is approved by THL, approval numbers THL/2031/6.02.00/2017, amendments THL/341/6.02.00/2018, THL/2222/6.02.00/2018, THL/1101/5.05.00/2017, VRK43431/2017-3, KELA 131/522/2018, and Statistics Finland TK-53-1041-17, and THL/283/6.02.00/2019. All DNA samples and data in this study were pseudonymized.

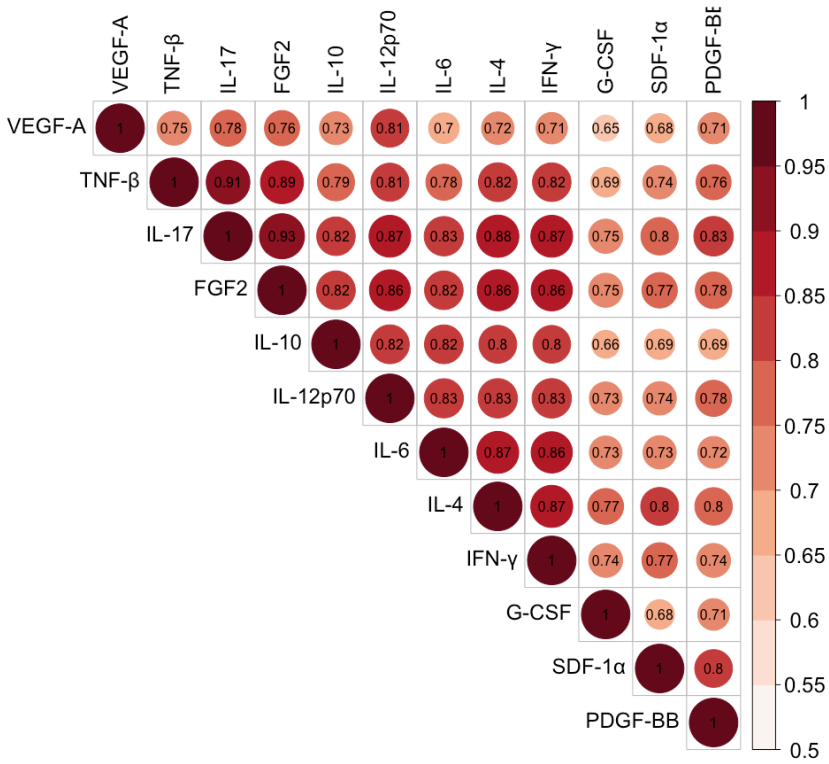
FinnGen Data availability

The FinnGen data may be accessed through Finnish Biobanks' FinnBB portal (www.finbb.fi) and THL Biobank data through THL Biobank (https://thl.fi/en/web/thl-biobank).

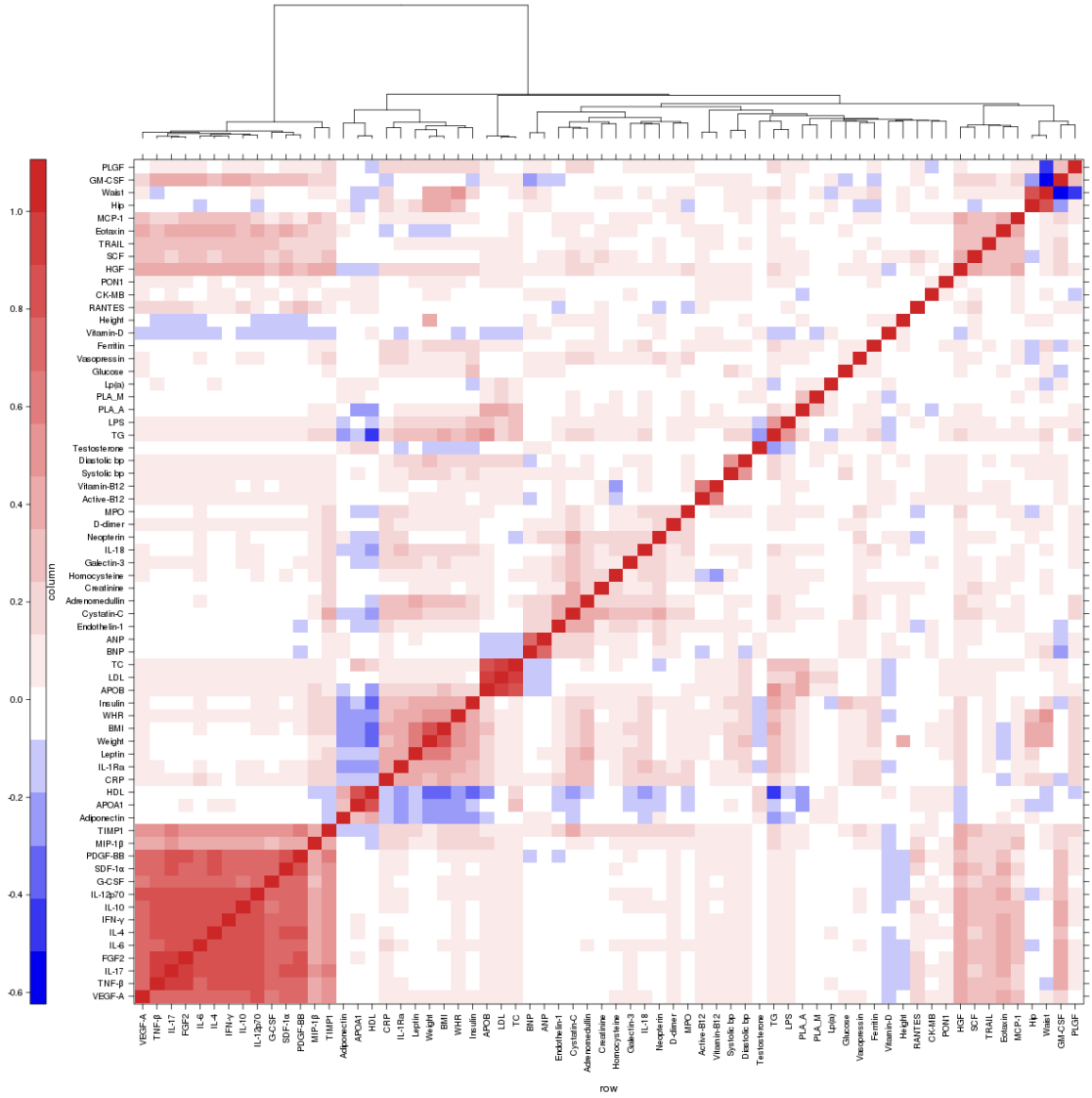
FinnGen Code availability

The full genotyping and imputation protocol for FinnGen is described at dx.doi.org/10.17504/protocols.io.nmndc5e

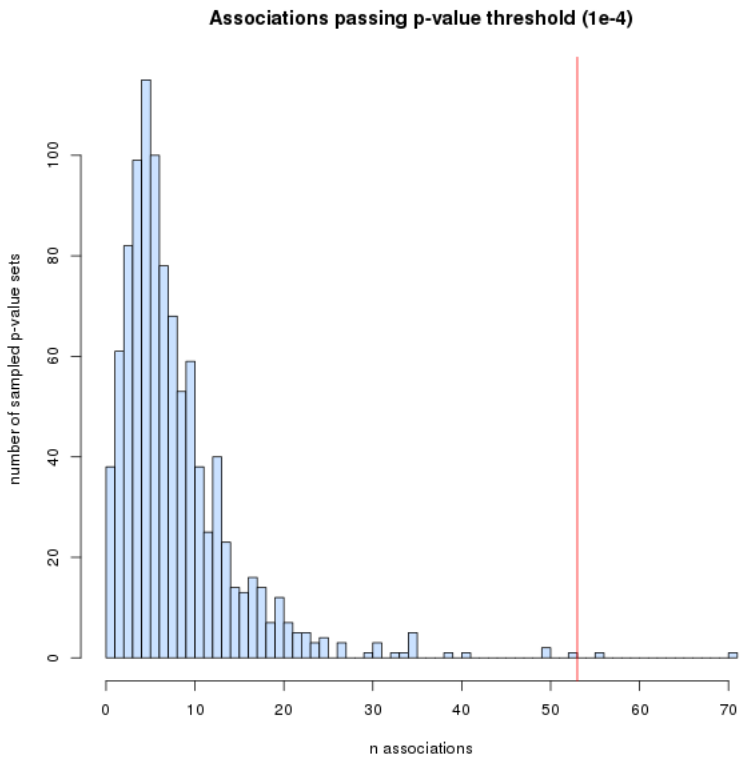
FIGURES



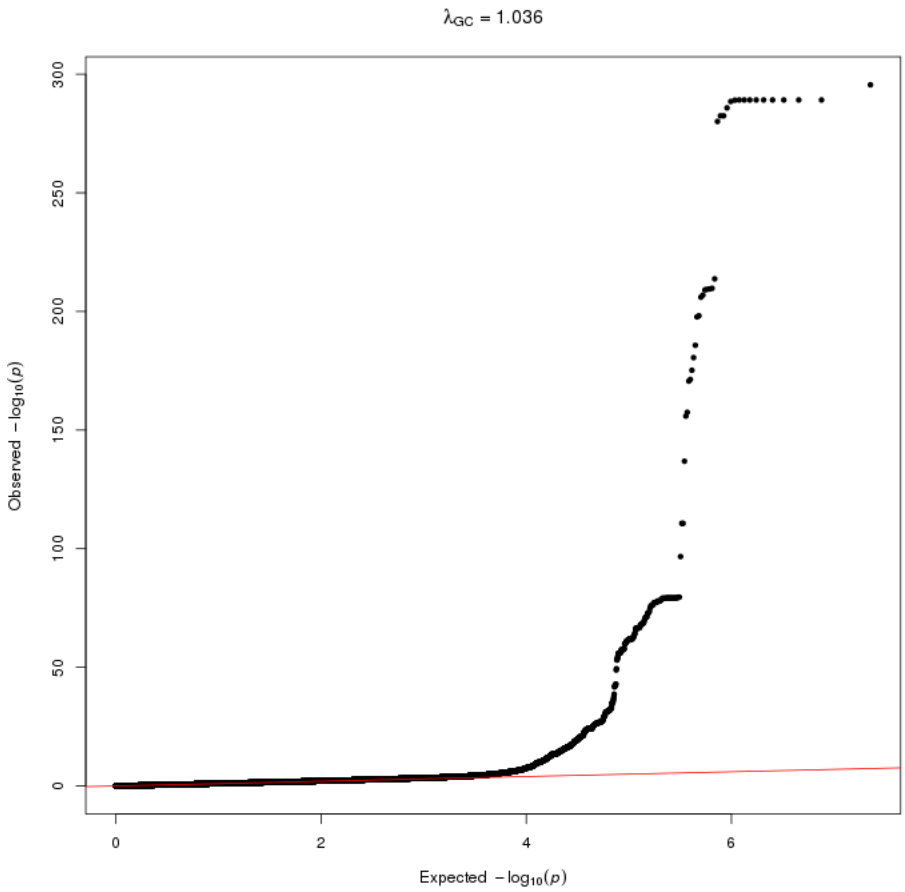
Supplementary Figure 1. Correlation structure of the 12 inflammatory biomarkers. The color and size of the circle represents the correlation of the inverse-rank normalized age and sex adjusted biomarkers. The Pearson correlations between the biomarkers ranged from 0.64 to 0.93, with a mean of 0.80.



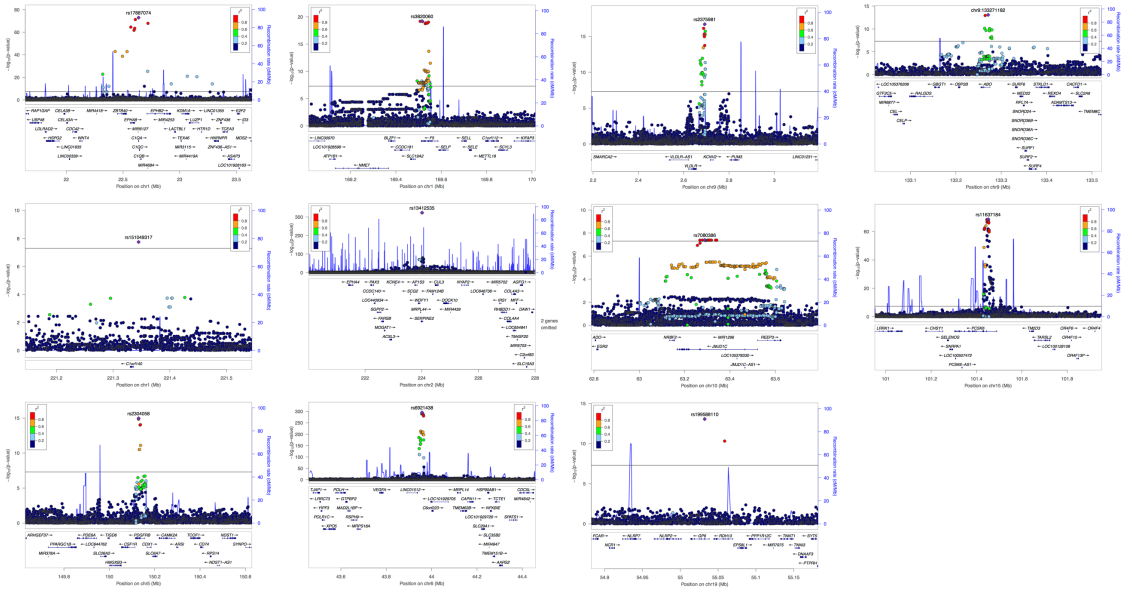
Supplementary Figure 2. Correlation structure of the 66 quantitative traits.



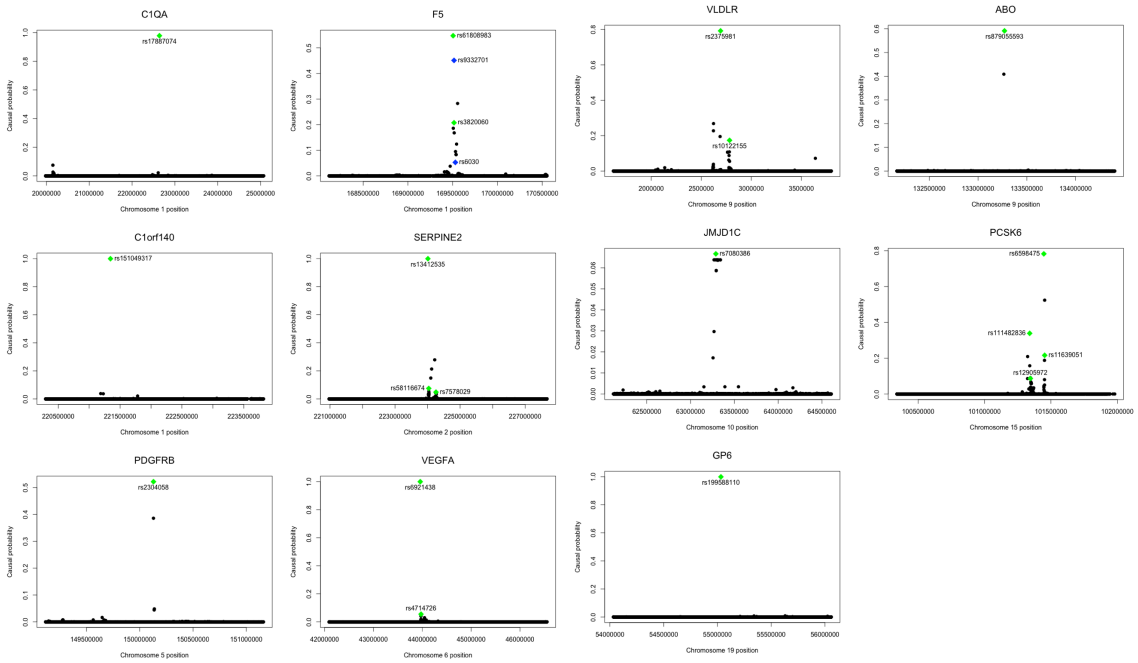
Supplementary Figure 3. Empirical testing of chosen p-value threshold. One thousand sets of 19 allele frequency-matched variants were sampled from 8.2 million non-coding variants. Allele frequencies were matched to the 19 putative casual variants selected to represent the 19 credible sets (Table 2). The number of associations passing the p-value threshold 1×10^{-4} for each of these 1,000 sets of variants is plotted above. The median of this "null distribution" was 7 and 95% of the thousand sets had 20 associations or less passing the p-value threshold. The red line represents the number of significant associations observed for the 19 putative causal variants (n = 53). Only 0.3% of the thousand sampled sets had as many significant associations, indicating that the chosen p-value threshold is stringent.



Supplementary Figure 4. Quantile-quantile plot for multivariate GWAS results.



Supplementary Figure 5. Locuszoom plots for each of the 11 genome-wide significant loci in the multivariate GWAS.



Supplementary Figure 6. **FINEMAP results of the 11 loci.** The SNP-wise causal probability is plotted on the y-axis and the chromosomal position on the x-axis. The initial representative variants are represented as green diamonds with accompanying rsids, and missense variants in high LD with them are represented as blue diamonds.

TABLES

Trait	Description
Systolic bp	Systolic blood pressure
Diastolic bp	Diastolic blood pressure
HDL	High density lipoprotein
TG	Triglycerides
TC	Total cholesterol
LDL	Low density lipoprotein
Lp(a)	Lipoprotein (a)
APOA1	Apolipoprotein A-I
APOB	Apolipoprotein B
Galectin-3	Galectin-3
LPS	Lipopolysaccharide
CRP	C-reactive protein
HGF	Hepatocyte growth factor
SCF	Stem cell factor
SDF-1α	Stromal cell derived factor 1 alpha (CXCL12)
TNF-β	Tumor necrosis factor beta
TRAIL	TNF related apoptosis inducing ligand
IL-4	Interleukin-4
IL-6	Interleukin-6
IL-10	Interleukin-10
IL-12p70	Interleukin-12p70
IL-17	Interleukin-17
Eotaxin	Eotaxin (CCLL11)
FGF2	Basic fibroblast growth factor
G-CSF	Granulocyte colony stimulating factor
GM-CSF	Granulocyte monocyte colony stimulating factor
IFN-γ	Interferon gamma
MCP-1	Monocyte chemoattractant protein 1 (CCL2)
PDGF-BB	Platelet derived growth factor BB
MIP-1β	Macrophage inflammatory protein 1 beta (CCL4)
RANTES	Regulated on Activation, Normal T cell Expressed and Secreted (CCL5)
VEGF-A	Vascular endothelial cell growth factor A
Active-B12	Active vitamin B12
Adiponectin	Adiponectin
BNP	Brain natriuretic peptide
CK-MB	Creatine kinase isoenzyme MB
Creatinine	Creatinine
Vasopressin	C-terminal pro-vasopressin
Endothelin-1	C-terminal pro-endothelin 1
Cystatin-C	Cystatin C
D-dimer	D-dimer
Ferritin	Ferritin
Homocysteine	Homocysteine
IL-18	Interleukin-18
IL-1Ra	Interleukin-1 receptor antagonist
Leptin	Leptin
MPO	Myeloperoxidase
Adrenomedullin	Mid-regional pro-adrenomedullin
ANP	Mid-regional pro-atrial natriuretic peptide
Neopterin	Neopterin
PLA_M	Phospholipase A2 mass
PLA_A	Phospholipase A2 activity
PLGF	Placental growth factor
PON1	Paraoxonase 1
TIMP1	Tissue inhibitor metalloproteinase 1
Glucose	Glucose corrected for fasting
Insulin	Insulin corrected for fasting
Testosterone	Testosterone
Vitamin-B12	Vitamin B12 (Cobalamin)
Vitamin-D	Vitamin D
BMI	Body Mass Index
Waist	Waist circumference
Hip	Hip circumference
WHR	Waist hip ratio
Weight	Weight
Height	Height

Supplementary Table 1: List of the 66 quantitative traits.

Variant[a]	Locus	AF[b] (FIN enrichment)	Most severe consequence	LD with lead variant (r^2)	Multivariate p-value	Minimum univariate p-value (biomarker)	Driver traits	Novel biomarker association[c]	FinnGen disease associations[d]	FinnGen association statistics		Novel disease association[e]
										OR	p-value	
rs45498698	*C1QA*	1.61% (1.70)	missense variant	0,87	2,97E-65	6.39E-23 (TNF-β)	TNF-β	NO	–	–	–	–
rs144329757	*C1QA*	1.56% (1.64)	missense variant	0,88	1,97E-62	2.54E-20 (TNF-β)	TNF-β	NO	–	–	–	–
rs17887074	*C1QA*	1.48% (4.64)	missense variant	1	1,21E-73	1.70E-23 (TNF-β)	TNF-β	NO	–	–	–	–
rs6027	*F5*	8,26 %	missense variant	0,21	6,06E-09	8.83E-5 (IL-4)	IL-4	YES	Venous thromboembolism DVT of lower extremities DVT of lower extremities and pulmonary embolism	1.17 1.27 1.18	1.8E-6 7.8E-8 1.5E-6	NO
									Diseases of veins, lymphatic vessels and lymph nodes, not elsewhere classified	1,11	2.4E-5	NO
rs6030	*F5*	29,71 %	missense variant	0,997	1,78E-19	1.39E-3 (VEGF-A)	IL-4, !L-12	YES	–	–	–	–
rs6032*	*F5*	21,97 %	missense variant	0,63	4,60E-09	3.14E-4 (VEGF-A)	IL-4	YES	Venous thromboembolism Phlebitis and thrombophlebitis DVT of lower extremities and pulmonary embolism	0.86 0.87 0.86	1.3E-11 6.9E-5 2.8E-11	NO
									Hypo-osmolality and hyponatraemia	1,18	9.5E-5	YES
rs12694627	*SERPINE2*	74,75 %	splice region variant	0,083	4,55E-13	5.31E-4 (IL-10)	PDGF-BB, SDF-1α	NO	–	–	–	–
rs3738952	*SERPINE2*	9,78 %	missense variant	0,013	1,21E-08	6.27E-3 (IL-10)	PDGF-BB	NO	–	–	–	–
rs115402675	*VEGFA*	6.49% (2.12)	missense variant	0,022	1,95E-12	1.65E-4 (VEGF-A)	VEGF-A	NO	–	–	–	–
rs57288791	*VEGFA*	8.83% (1.60)	frameshift variant	0,023	5,02E-11	6.49E-6 (VEGF-A)	VEGF-A	NO	–	–	–	–
rs199588110	*GP6*	0.33% (3.69)	missense variant	1	8,54E-14	1.25E-17 (IL-17)	all 12 biomarkers	NO	Benign neoplasm of meninges	6,4	4.9E-5	YES

Supplementary Table 2: Results of the 13 functional variants reaching genome-wide significance in the multivariate GWAS.

* represents two other missense variants (rs4525 and rs4524) in high LD ($r^2 > 0.98$) with the same disease associations, excluding the association with hypo-osmolality and hyponatraemia that was only observed for rs6032.

[a] Bolded variants are lead variants.

[b] AF = allele frequency, FIN enrichment = AF in Finns compared to AF in Non-Finnish Europeans excluding Estonians in the gnomAD genomes database; reported if it was at least 1.5-fold.

[c] Previous associations with the 12 biomarkers were searched for in the NHGRI-EBI GWAS Catalog within a region encompassing ±500 kB around the variant. An association was regarded novel if no associations with any of the 12 biomarkers had been reported in this region.

[d] Only associations that remain significant after conditioning are reported here. Closely related disease diagnoses are represented in a shared cell and their replication is assessed jointly. DVT = deep vein thrombosis.

[e] Novelty of disease associations was assessed at gene-level.

LD = linkage disequilibrium

1 credible set		2 credible sets				3 credible sets					4 credible sets						
Cred1	Prob1	Cred1	Prob1	Cred2	Prob2	Cred1	Prob1	Cred2	Prob2	Cred3	Prob3	Cred1	Prob1	Cred2	Prob2	Cred3	Prob3	Cred4	Prob4
C1QA		*FS*				*SERPINE2*						*PCSK6*							
chr1:22637683:G:A	0,975	chr1:169515314:T:G	0,175	chr1:169505159:C:T	0,533	chr2:224010157:G:A	0,998104	chr2:224035992:CA:C	0,067	chr2:224257750:T:A	0,046	chr15:101452793:C:A	0,321	chr15:101446425:G:T	0,704	chr15:101345122:G:A	0,127	chr15:101339772:G:A	0,537
Clorf140		chr1:169543742:G:A	0,164	chr1:169515529:A:G	0,461			chr2:224038180:A:G	0,050	chr2:224260063:A:G	0,045	chr15:101451543:G:C	0,296	chr15:101451568:T:C	0,082	chr15:101345382:A:G	0,122	chr15:101340399:T:A	0,325
chr1:22134491:4:A:G	1,000	chr1:169507088:G:A	0,148					chr2:224041598:C:T	0,040	chr2:224261196:C:T	0,043	chr15:101452832:A:G	0,252	chr15:101446466:C:T	0,065	chr15:101348606:T:C	0,109	chr15:101335494:G:T	0,058
ABO		chr1:169517529:T:G	0,141321					chr2:224034475:A:G	0,037	chr2:224263607:A:G	0,041	chr15:101451951:A:G	0,100	chr15:101446770:G:A	0,058	chr15:101352810:G:A	0,094	chr15:101333461:T:C	0,058
chr9:133271182:T:C	0,578	chr1:169531818:T:C	0,117					chr2:224036383:A:G	0,036	chr2:224261500:A:T	0,041			chr15:101447186:T:C	0,032	chr15:101351713:GT:G	0,094		
chr9:133264504:G:GAAACTGCC	0,422	chr1:169538606:G:T	0,103					chr2:224036374:A:G	0,036	chr2:224263458:T:G	0,040			chr15:101451106:A:G	0,020	chr15:101351332:T:A	0,093		
PDGFRB		chr1:169537003:A:G	0,103489					chr2:224028228:A:G	0,036	chr2:224258053:G:C	0,040					chr15:101351296:A:G	0,093		
chr5:150128981:C:G	0,546	*VEGFA*						chr2:224036011:C:A	0,033	chr2:224259370:T:C	0,040					chr15:101350243:C:A	0,093		
chr5:150128912:C:T	0,405	chr6:43957870:G:A	1,000	chr6:43974045:A:G	0,055			chr2:224035127:T:C	0,032	chr2:224252531:C:T	0,040					chr15:101350358:T:A	0,093		
IMD1C				chr6:43974829:T:C	0,053			chr2:224033438:C:T	0,032	chr2:224251564:C:G	0,040					chr15:101346648:A:G	0,0689712		
chr10:63288546:C:A	0,064			chr6:43973361:A:T	0,053			chr2:224035435:A:T	0,032	chr2:224251491:A:G	0,040								
chr10:63306426:G:T	0,062			chr6:43973945:T:C	0,053			chr2:224035116:T:TG	0,032	chr2:224255099:A:G	0,039								
chr10:63304084:T:A	0,062			chr6:43972634:A:AG	0,053			chr2:224035358:T:C	0,032	chr2:224268165:G:A	0,036								
chr10:63302248:G:C	0,0621003			chr6:43974508:A:G	0,053			chr2:224035405:CAG:C	0,032	chr2:224263185:C:T	0,034								
chr10:63318234:C:G	0,062			chr6:43974249:C:T	0,053			chr2:224033029:C:T	0,032	chr2:224268510:G:C	0,032								
chr10:63304076:ACTTTGCC:A	0,062			chr6:43974275:A:T	0,053			chr2:224035198:G:A	0,032	chr2:224229124:C:T	0,018								
chr10:63341447:G:C	0,062			chr6:43973612:A:G	0,053			chr2:224035419:T:G	0,032	chr2:224230121:C:T	0,012								
chr10:63336490:C:T	0,062			chr6:43972532:A:G	0,053			chr2:224031620:C:T	0,032	chr2:224229721:C:CA	0,012								
chr10:63303060:C:T	0,062			chr6:43972465:A:G	0,053			chr2:224031625:C:A	0,032	chr2:224229749:G:A	0,012								
chr10:63267383:G:T	0,062			chr6:43972186:G:T	0,053			chr2:224035656:A:T	0,030	chr2:224236034:A:G	0,011								
chr10:63290899:A:G	0,062			chr6:43972253:A:G	0,053			chr2:224035622:G:T	0,030	chr2:224228932:C:T	0,011								
chr10:63278270:G:C	0,062			chr6:43973908:C:T	0,053			chr2:224026230:G:A	0,030	chr2:224229526:A:T	0,011								
chr10:63311455:C:A	0,062			chr6:43974487:T:C	0,052			chr2:224038091:A:T	0,029	chr2:224230255:G:A	0,011								
chr10:63292782:C:T	0,058			chr6:43972413:C:T	0,050			chr2:224036103:C:T	0,029	chr2:224229279:G:A	0,011								
chr10:63292445:T:C	0,058			chr6:43974652:T:C	0,042			chr2:224032508:C:T	0,026	chr2:224250193:GAAACCCCATCACTACTAA:G	0,010								
chr10:63267850:A:T	0,042			chr6:43971194:A:G	0,041			chr2:224035885:T:C	0,026	chr2:224239981:C:T	0,010								
GP6				chr6:43971636:A:G	0,018			chr2:224029381:TA:T	0,026	chr2:224237902:G:C	0,010								
chr19:55032292:G:A	1,000	*VLDLR*						chr2:224033710:A:G	0,025	chr2:224242921:A:G	0,010								
		chr9:2692583:C:G	0,748	chr9:2782458:A:G	0,162			chr2:224031721:A:G	0,025	chr2:224234466:G:T	0,010								
		chr9:2687795:A:T	0,234	chr9:2780496:C:CT	0,109					chr2:224243642:G:A	0,010								
				chr9:2763894:C:A	0,109					chr2:224239836:G:C	0,010								
				chr9:2762362:T:A	0,109					chr2:224239156:G:T	0,010								
				chr9:2762263:C:A	0,109					chr2:224241641:T:C	0,010								
				chr9:2777384:T:A	0,092					chr2:224247045:C:T	0,010								
				chr9:2774758:A:G	0,067					chr2:224240716:A:G	0,010								
				chr9:2782774:T:C	0,061					chr2:224241834:C:T	0,010								
				chr9:2776401:C:G	0,023					chr2:224234172:C:G	0,010								
				chr9:2787594:C:G	0,020					chr2:224205442:C:T	0,009								
				chr9:2777062:G:T	0,017					chr2:224226428:C:T	0,008								
				chr9:2787856:A:C	0,017					chr2:224227446:A:G	0,008								
				chr9:2791828:T:C	0,011					chr2:224220047:G:A	0,008								
				chr9:2791753:A:T	0,010					chr2:224216258:T:G	0,008								
				chr9:2792552:A:C	0,009					chr2:224216965:C:T	0,008								
				chr9:2793342:A:T	0,006					chr2:224209822:A:G	0,008								
				chr9:2797082:G:A	0,006					chr2:224202443:G:C	0,008								
				chr9:2796867:G:A	0,006					chr2:224181156:C:T	0,008								
				chr9:2794338:T:C	0,005					chr2:224175988:AT:A	0,008								
				chr9:2795985:G:C	0,004					chr2:224198340:C:T	0,006								
				chr9:2796135:CCA:C	0,004					chr2:224272987:A:G	0,006								
										chr2:224229118:T:C	0,005								
										chr2:224270805:GTTAAC:G	0,005								
										chr2:224275991:AG:A	0,004								
										chr2:224275258:A:G	0,004								
										chr2:224280597:C:T	0,004								

Supplementary Table 3: Variants within the 19 fine-mapped credible sets. Missense variants are highlighted with blue font.

N	*C1QA*	*F5*	*C1orf140*	*SERPINE2*	*PDGFRB*	*JMJD1C*	*VEGFA*	*VLDLR*	*ABO*	*PCSK6*	*GP6*
1	0.451	0	**0.541**	0	**0.591**	**0.796**	0	0.00148	**0.652**	0	**0.688**
2	**0.473**	0.251	0.42	0.00164	0.399	0.206	**0.575**	0.237	0.348	0.00253	0.303
3	0.0766	**0.602**	0.0388	0.324	0.01	0	0.424	**0.586**	0	0.21	0
4	0	0.147	0	**0.671**	0	0	0.00137	0.173	0	**0.441**	0
5	0	0	0	0.00311	0	0	0	0.00293	0	0.322	0
6	0	0	0	0	0	0	0	0	0	0.024	0
7-10	0	0	0	0	0	0	0	0	0	0	0

Supplementary Table 4: Posterior probabilities estimated by multivariate FINEMAP for the number of causal signals within each locus

Locus	# Conditioning rounds	# Credible sets from FINEMAP	# FINEMAP variants in conditional analysis (%)	Conditioned variants
C1QA	1	1	1 (100)	chr1:22637683:G:A
F5	2	2	2 (100)	chr1:169515314:T:G, chr1:169505159:C:T:C
C1orf140	1	1	1 (100)	chr1:221344914:A:G
SERPINE2	3	3	1 (33,3)	chr2:224010157:G:A, chr2:224041598:C:T, chr2:224261196:C:T
PDGFRB	1	1	1 (100)	chr5:150128981:C:G
VEGFA	2	2	2 (100)	chr6:43957870:G:A, chr6:43974045:A:G:A
VLDLR	1	2	1 (50)	chr9:2692583:C:G
ABO	1	1	1 (100)	chr9:133271182:T:C
JMJD1C	1	1	1 (100)	chr10:63288546:C:A:C
PCSK6	2	4	1 (25)	chr15:101451543:G:C:G, chr15:101446425:G:T:G
GP6	1	1	1 (100)	chr19:55032292:G:A:G
Total	**16**	**19**	**13 (68,4)**	

Supplementary Table 5: Comparison of FINEMAP and conditional analysis results.

Variant[a]	Locus	AF[b] (FIN enrichment)	FinnGen disease associations[c]	FinnGen association statistics			Replication in UKBB[d]	UKBB association statistics			Novel disease association[e]
				OR	p-value	№ cases		OR	p-value	№ cases	
rs6027*	*F5*	8.26%	Venous thromboembolism DVT of lower extremities DVT of lower extremities and pulmonary embolism	1.17 1.27 1.18	1.8E-6 7.8E-8 1.5E-6	6,913 3,592 6,019	Phlebitis and thrombophlebitis	1.06	0.27	3,900	NO
			Diseases of veins, lymphatic vessels and lymph nodes, not elsewhere classified	1.11	2.4E-5	19,930	No replication phenotype	—	—	—	NO
rs6032**	*F5*	21.97%	Venous thromboembolism Phlebitis and thrombophlebitis DVT of lower extremities and pulmonary embolism	0.86 0.87 0.86	1.3E-11 6.9E-5 2.8E-11	6,913 2,506 6,019	Phlebitis and thrombophlebitis	0.82	3.4E-14	3,900	NO
			Hypo-osmolality and hyponatraemia	1.18	9.5E-5	1,648	Hypo-osmolality and hyponatraemia	1.01	0.78	1,826	YES
rs13412535	*SERPINE2*	19.8%	Hypertrophic scar	1.34	7.5E-5	591	Keloid scar Aquired keratoderma	0.90 1.52	0.35 0.02	216 87	YES
rs550057	*ABO*	31.0%	Anemias Other and unspecified anaemias Other anaemias Diseases of the blood and blood-forming organs	1.12 1.10 1.11 1.06	4.7E-5 4.9E-5 2.6E-5 2.9E-5	9,145 4,279 4,337 14,375	Other anemias Red boold cell count	0.99 NA	0.71 1.26E-212	12,256 445,000	NO
			Visual field defects Diseases of the eye and adnexa	1.24 1.04	4.4E-5 9.4E-6	885 58,498	Visual field defects	1.00	0.97	334	YES
			Diseases of the ear and mastoid process	1.04	4.8E-5	31,579	No replication phenotype	—	—	—	YES
rs199588110*	*GP6*	0.33% (3.69)	Benign neoplasm of meninges	6.40	4.9E-5	934	Benign neoplasm of brain, cranial nerves, meninges	0.09	0.31	774	YES

Supplementary Table 6: Replication of FinnGen disease associations in the UKBB.

* missense variant

**represents two other missense variants (rs4525 and rs4524) in high LD ($r^2 > 0.98$) with the same disease associations, excluding the association with hypo-osmolality and hyponatraemia that was only observed for rs6032.

[a] Bolded variants are putative causal variants identified by fine-mapping.

[b] AF = allele frequency, FIN enrichment = AF in Finns compared to AF in Non-Finnish Europeans excluding Estonians in the gnomAD genomes database; reported if it was at least 1.5-fold.

[c] Only associations that remain significant after conditioning are reported here. Closely related disease diagnoses are represented in a shared cell and their replication is assessed jointly. DVT = deep vein thrombosis.

[d] Replication in the UKBB was analyzed using the summary statistics of SAIGE analysis on ~400,000 samples run by the Lee lab, University of Michigan, https://www.leelabsg.org/resources and the study by Kichaev[2] .

[e] Novelty of disease associations was assessed at gene-level.

Variant	Locus	QTL type	Gene (tissue)	p-value	Study	high-LD QTL lead variant (r^2)
rs17887074	*C1QA*					
		—	—	—	—	—
rs3820060	*F5*					
		eQTL	F5 (whole blood)	9,2E-118	GTEX7	
		eQTL	NME7 (whole blood)	1,8E-10	GTEX7	
		high-LD pQTL	CAMK1	2,0E-110	Suhre	rs4525 (0.70)
		high-LD pQTL	SEC13	2,3E-12	Suhre	rs1800594 (0.96)
		high-LD pQTL	NPTX2	3,4E-14	Suhre	rs9287090 (0.70)
		high-LD pQTL	SIG11	9,3E-97	Suhre	rs9287090 (0.70)
		high-LD pQTL	TFPI	3,2E-24	Suhre	rs10800453 (0.70)
rs9332701	*F5*					
		pQTL	F5	1,0E-23	Suhre	
		high-LD eQTL	NME7 (blood)	1,4E-27	GTEX7	rs61808983 (0.97)
		high-LD pQTL	EHBP1	7,1E-18	Sun	rs61808983 (0.97)
rs151049317	*C1orf140*					
		—	—	—	—	
rs13412535	*SERPINE2*					
		pQTL	PDGF-BB	4,6E-13	Sun	
		high-LD pQTL	SERPINE2	1,1E-46	Sun	rs68066031 (0.99)
		high-LD pQTL	SERPINE2	5,9E-246	Emilsson	rs68066031 (0.99)
rs58116674	*SERPINE2*					
		—	—	—	—	
rs7578029	*SERPINE2*					
		—	—	—	—	
rs2304058	*PDGFRB*					
		pQTL	PDGFRB	2.3E-458	Sun	
		high-LD pQTL	PDGFRB	1,0E-300	Emilsson	rs4705415 (0.70)
		high-LD pQTL	PDGFRB	5,0E-161	Suhre	rs2240781 (0.95)
		high-LD pQTL	PDGFRB	1,0E-33	Sasayama	rs740750 (0.99)
rs6921438	*C6orf223 / VEGFA*					
		pQTL	VEGFA	7,8E-71	Sun	
		pQTL	VEGFA isoform 121	1,7E-234	Sun	
rs4714726	*C6orf223 / VEGFA*					
		—	—	—	—	—
rs2375981	*VLDLR / KCNV2*					
		—	—	—	—	—
rs10122155	*VLDLR / KCNV2*					
		—	—	—	—	—
rs550057	*ABO*					
		pQTL	ALPI	2,8E-19	Sun	
		pQTL	CHST15	1,0E-30	Sun	
		pQTL	FAM177A1	9,3E-19	Sun	
		pQTL	JAG1	8,3E-14	Sun	
rs7080386	*JMJD1C*					
		pQTL	HB-EGF	1,6E-13	Sun	
		high-LD eQTL	NRBF2 (thyroid)	2,5E-07	GTEX7	rs4595427 (0.81)
		high-LD eQTL	NRBF2 (whole blood)	4,6E-06	GTEX7	rs10995477 (0.80)
		high-LD eQTL	NRBF2 (brain frontal cortex BA9)	2,2E-09	GTEX7	rs10761729 (0.79)
rs111482836	*PCSK6*					
		—	—	—	—	—
rs12905972	*PCSK6*					
		—	—	—	—	—
rs6598475	*PCSK6*					
		—	—	—	—	—
rs11639051	*PCSK6*					
		—	—	—	—	—
rs199588110	*GP6*					
		—	—	—	—	—

Supplementary Table 7: Expression and protein quantitative trait loci of the 19 putative causal variants.

Variant (rsid)	Locus	Putative causal/Functional	Disease	N (cases/controls)	OR (P-value)		LD with FG lead
					Original	Conditinal	
chr1:169514323:T:C (rs6027)	*F5*	Functional	Diseases of veins, lymphatic vessels and lymph nodes, not elsewhere classified (FINNGEN)	19930/97214	1,11 (2,42E-05)	1,12 (2,19E-06)	0,002
			Diseases of veins, lymphatic vessels and lymph nodes, not elsewhere classified	22948/153951	1,09 (3,64E-05)	1,10 (3,86E-06)	0,002
			DVT of lower extremities and pulmonary embolism	6019/170880	1,18 (1,47E-06)	1,22 (1,22E-08)	0,002
			DVT of lower extremities	3592/153951	1,27 (7,80E-08)	1,32 (5,65E-10)	0,002
			Venous thromboembolism	6913/169986	1,17 (1,81E-06)	1,21 (8,41E-09)	0,002
chr1:169542317:T:C (rs6032)	*F5*	Functional	Hypo-osmolality and hyponatraemia	1648/160461	1,18 (9,49E-05)	0,94 (7,86E-01)	0,965
			Pulmonary heart disease	3016/173883	0,85 (8,03E-07)	0,87 (7,13E-06)	0,008
			DVT of lower extremities and pulmonary embolism	6019/170880	0,86 (2,78E-11)	0,87 (6,00E-09)	0,008
			Phlebitis and thrombophlebitis (not including DVT)	2506/153951	0,87 (6,92E-05)	0,90 (2,29E-03)	0,008
			DVT of lower extremities	3592/153951	0,86 (2,32E-07)	0,90 (3,35E-04)	0,008
			Pulmonary embolism	3016/173597	0,85 (8,43E-07)	0,87 (6,92E-06)	0,008
			Pulmonary heart disease, diseases of pulmonary circulation	3302/173597	0,87 (7,89E-06)	0,89 (7,23E-05)	0,008
			Venous thromboembolism	6913/169986	0,86 (1,25E-11)	0,88 (4,16E-09)	0,008
			Other ILD-related CVD-co-morbidities	3260/114642	0,87 (1,67E-05)	0,88 (3,35E-05)	0,008
chr1:169542496:T:C (rs4525)	*F5*	Functional	Pulmonary heart disease	3016/173883	0,86 (1,10E-06)	0,87 (9,68E-06)	0,008
			DVT of lower extremities and pulmonary embolism	6019/170880	0,86 (2,50E-11)	0,87 (5,47E-09)	0,008
			Phlebitis and thrombophlebitis (not including DVT)	2506/153951	0,87 (4,92E-05)	0,90 (1,76E-03)	0,008
			DVT of lower extremities	3592/153951	0,86 (2,03E-07)	0,90 (3,01E-04)	0,008
			Pulmonary embolism	3016/173597	0,86 (1,16E-06)	0,87 (9,40E-06)	0,008
			Pulmonary heart disease, diseases of pulmonary circulation	3302/173597	0,87 (1,08E-05)	0,89 (9,62E-05)	0,008
			Venous thromboembolism	6913/169986	0,86 (1,01E-11)	0,88 (3,43E-09)	0,008
			Other ILD-related CVD-co-morbidities	3260/114642	0,88 (2,78E-05)	0,88 (6,87E-05)	0,008
chr1:169542517:T:C (rs4524)	*F5*	Functional	Pulmonary heart disease	3016/173883	0,85 (7,91E-07)	0,87 (6,76E-06)	0,008
			DVT of lower extremities and pulmonary embolism	6019/170880	0,86 (1,95E-11)	0,87 (3,94E-09)	0,008
			Phlebitis and thrombophlebitis (not including DVT)	2506/153951	0,87 (5,79E-05)	0,90 (1,90E-03)	0,008
			DVT of lower extremities	3592/153951	0,86 (1,84E-07)	0,90 (2,81E-04)	0,008
			Pulmonary embolism	3016/173597	0,85 (8,34E-07)	0,86 (6,57E-06)	0,008
			Pulmonary heart disease, diseases of pulmonary circulation	3302/173597	0,87 (8,83E-06)	0,89 (7,77E-05)	0,008
			Venous thromboembolism	6913/169986	0,86 (8,00E-12)	0,88 (2,57E-09)	0,008
			Other ILD-related CVD-co-morbidities	3260/114642	0,87 (1,91E-05)	0,88 (3,58E-05)	0,008
chr2:224010157:G:A (rs13412535)	*SERPINE2*	Putative causal	Hypertrophic scar	591/168348	1,34 (7,51E-05)	-	0,987
chr2:224257750:T:A (rs7578029)	*SERPINE2*	Putative causal	Infections of the skin and subcutaneous tissue	7680/169219	1,12 (9,75E-05)	0,72 (2,79E-02)	0,967
chr2:224497761:C:T (rs3738952)	*SERPINE2*	Putative causal	Malignant neoplasm of male genital organs	4945/63465	0,86 (8,81E-05)	0,93 (2,55E-01)	0,580
			Disorders of lens	21994/154905	0,92 (5,70E-05)	0,97 (4,16E-01)	0,571
chr5:150128981:C:G (rs2304058)	*PDGFRB*	Putative causal	Use of disulfiram, acamprosate or naltrexone	1266/175633	1,18 (7,32E-05)	1,05 (7,76E-01)	0,943
chr9:133271182:C:T (rs550057)	*ABO*	Putative causal	Intestinal infectious diseases	16735/160164	0,95 (8,45E-05)	1,00 (8,35E-01)	0,567
			Psoriatic arthropathies related co-morbidities	37185/91355	0,95 (9,15E-05)	1,00 (8,27E-01)	0,555
			Cholelithiasis, broad definition with cholecystitis	15683/158425	0,94 (4,42E-06)	0,98 (3,71E-01)	0,465
			Anaemias	9145/50989	0,89 (4,69E-08)	-	1,000
			Other and unspecified anaemias	4279/172180	0,91 (4,90E-05)	-	1,000
			Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	14375/162524	0,95 (2,86E-05)	1,21 (4,33E-01)	0,995
			Other anaemias	4337/172180	0,90 (2,61E-05)	-	1,000
			Diabetes medication	25576/151276	0,95 (8,31E-05)	0,99 (4,88E-01)	0,513
			Other (not insulin) diabetes medications	21909/151323	0,95 (6,58E-05)	0,98 (2,32E-01)	0,513
			Other diabetes, wide definition	24662/144670	0,95 (9,45E-05)	0,99 (4,72E-01)	0,513
			Endocrine, nutritional and metabolic diseases	61193/115706	0,96 (5,56E-05)	0,99 (2,81E-01)	0,486
			Pure hypercholesterolaemia	6840/160461	0,91 (2,19E-06)	0,98 (4,68E-01)	0,555
			Disorders of lipoprotein metabolism and other lipidaemias	11042/160461	0,92 (1,28E-06)	1,01 (7,41E-01)	0,555
			Metabolic disorders	16438/160461	0,95 (2,36E-05)	1,00 (9,57E-01)	0,557
			Cardiovascular diseases (excluding rheumatic etc)	79685/97214	0,95 (5,57E-07)	0,99 (3,32E-01)	0,465
			Diseases of veins, lymphatic vessels and lymph nodes, not elsewhere classified (FINNGEN)	19930/97214	0,88 (2,29E-18)	0,96 (4,96E-02)	0,566
			Other heart diseases	43936/97214	0,95 (5,10E-07)	0,98 (1,76E-01)	0,483
			Pulmonary heart disease	3016/173883	0,87 (8,18E-07)	1,01 (7,36E-01)	0,513
			Diseases of the eye and adnexa	58498/118401	0,96 (9,42E-06)	-	1,000
			Visual field defects	885/171027	0,81 (4,42E-05)	-	1,000
			Cardiovascular diseases	86957/89942	0,96 (1,24E-06)	0,98 (1,49E-01)	0,465
			Diseases of veins, lymphatic vessels and lymph nodes, not elsewhere classified	22948/153951	0,90 (3,27E-17)	0,97 (1,15E-01)	0,566
			DVT of lower extremities and pulmonary embolism	6019/170880	0,82 (2,93E-20)	1,00 (9,19E-01)	0,553
			Other heart diseases	46991/129908	0,97 (8,84E-05)	0,99 (6,08E-01)	0,555
			Phlebitis and thrombophlebitis (not including DVT)	2506/153951	0,80 (6,27E-12)	1,03 (5,24E-01)	0,567
			DVT of lower extremities	3592/153951	0,77 (2,06E-21)	0,99 (7,51E-01)	0,553
			Pulmonary embolism	3016/173597	0,87 (8,65E-07)	1,01 (7,28E-01)	0,513
			Pulmonary heart disease, diseases of pulmonary circulation	3302/173597	0,88 (4,84E-06)	1,03 (5,08E-01)	0,514
			Other embolism and thrombosis	1416/153951	0,84 (2,26E-05)	1,03 (5,96E-01)	0,553
			Varicose veins	13928/153951	0,92 (1,30E-07)	0,96 (8,50E-02)	0,570
			Other disorders of veins	4588/153951	0,89 (1,63E-06)	0,97 (4,31E-01)	0,567
			Venous thromboembolism	6913/169986	0,83 (3,57E-22)	1,03 (3,41E-01)	0,567
			Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	13899/163000	0,94 (1,20E-05)	1,15 (5,60E-01)	0,995
			ILD-related co-morbidities	85919/90980	0,97 (4,85E-05)	0,99 (1,99E-01)	0,513
			ILD Co-morbidites, CVD and metabolic diseases	62257/90980	0,96 (9,70E-06)	0,98 (2,17E-01)	0,555
			Diseases of the circulatory system	79046/97853	0,95 (2,06E-07)	0,98 (1,94E-01)	0,465
			Chronic diseases of tonsils and adenoids	19389/136923	0,94 (1,05E-05)	0,99 (5,25E-01)	0,553
			Cholelithiasis	15012/158425	0,93 (1,48E-06)	0,98 (4,22E-01)	0,566
			Disorders of gallbladder, biliary tract and pancreas	18474/158425	0,94 (5,21E-06)	0,98 (3,20E-01)	0,465
			Endometriosis	6502/57407	0,92 (1,00E-04)	0,93 (1,62E-03)	0,027
			Co-morbidities of interest (NEURO)	125910/50989	0,96 (2,18E-05)	0,97 (1,73E-03)	0,084
			Other ILD-related CVD-co-morbidities	3260/114642	0,86 (9,60E-08)	1,01 (7,39E-01)	0,514
			Statin medication	53518/123381	0,90 (4,19E-24)	1,00 (8,35E-01)	0,557
			Diseases of the eye and adnexa	53954/122945	0,97 (6,51E-05)	1,00 (8,27E-01)	0,995
			Diseases of the ear and mastoid process	31835/145064	0,96 (4,78E-05)	0,98 (3,71E-01)	0,995
chr10:63288546:C:A (rs7080386)	*JMJD1C*	Putative causal	Cholelithiasis, broad definition with cholecystitis	15683/158425	1,05 (7,02E-05)	1,01 (6,71E-01)	0,648
			Cholelithiasis	15012/158425	1,06 (4,07E-05)	1,01 (6,75E-01)	0,648
chr15:101339772:G:A (rs111482836)	*PCSK6*	Putative causal	Anomalies of pupillary function	169/175459	1,65 (6,99E-05)	1,21 (2,26E-01)	0,407
chr19:55032292:G:A (rs199588110)	*GP6*	Putative causal	Benign neoplasm of meninges	934/175965	6,40 (4,94E-05)	-	1,000
			Benign neoplasm of meninges, all cancers excluded	934/147003	5,80 (7,73E-05)	-	1,000

Supplementary Table 8: Disease associations of the 19 putative causal variants and 13 functional variants in FinnGen.

REFERENCES

1. Suzuki R, Shimodaira H. Pvclust: An R package for assessing the uncertainty in hierarchical clustering. *Bioinformatics*. 2006;22(12):1540-1542.

2. Kichaev G, Bhatia G, Loh P, et al. Leveraging polygenic functional enrichment to improve GWAS power. *The American Journal of Human Genetics*. 2019;104(1):65-75.