Appendix: Contribution of rare and common variants to plasma lipids levels and carotid stiffness and geometry - The Paris Prospective Study 3.

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I. Supplementary methods

I.1. Genotyping

DNA samples were quality checked on agarose gel and quantified by QUANT-IT Picogreen dsDNA reagent (Invitrogen). Using the picogreen concentration measurement a dilution to 50 ng/µl was prepared and verified. Concentration adjustment and aliquoting of samples was automatized on a robot (Beckman Biomek 3000) to reduce technical variability. For genotyping the Illumina HumanExome-12v1.1 BeadChip with 242,901 markers was used with standard protocol Infinium ® HD Assay Ultra, automated according to manufacturer instructions. Briefly 200 ng DNA per sample was amplified, fragmented and hybridized to the BeadChips. The extension/staining of DNA was followed by imaging of BeadChips with the iScan system 110 V/220 V (Illumina). Genotyping was performed at the Post-genomics platform (P3S) of 'Pierre and Marie Curie' Medical School (Paris 6 University, France). Genotype calling was carried out using Illumina's GenTrain version 2.0 clustering algorithm, module genotyping version = 1.9.4 in GenomeStudio v2011.1. After calling the re-clustering option provided by GenomeStudio was applied for all variants having at least one no-call.

I.2. Gene and gene set level statistical analysis

We used the *R/SKAT* package implementation of the Sequence Kernel Association Tests (*SKAT*) to assess the combined effect of rare and common variants in predefined genes and sets of genes[1].To map gene variants present on the exome array to genes we used the *Illumina HumanExome BeadChip SNP Information* file (SNPInfo) provided in the R package SkatMeta (/www.rdocumentation.org/packages/skatMeta/functions/SNPInfo). We defined candidate gene-sets based on the most recent GWAS reports for plasma lipids, coronary artery disease and blood pressure/hypertension. *SKAT* regress the phenotype on genetic variants, it therefore allows different variants to have different directions and magnitude of effects.[2] In the analysis using the *SKAT_CommonRare* function, the 'r.corr.rare' and 'r.corr.common' parameters were set to 0, which specifies a *SKAT* test for both rare and common variants. A second run of analyses was also performed with 'r.corr.rare' set to 1 and 'r.corr.common' to 0, which specifies a collapsing test for rare variants and a SKAT test for common ones. SKAT Analyses were conducted using the default beta parameters [1,25] which upweight rare variants. To check the possible influence of this choice on the results, we also set the beta paramaters at [0.5,0.5], this analysis yielded very similar results (not reported). To combine common and rare variants effects we used the combined sum test (SKAT method='C'). All analyses with *SKAT* were adjusted on age, gender, BMI, BSA and first 10 principal components (PCs) by entering these covariates in the SKAT null model. Adjustment on PCs was done to control for a possible genetic stratification of the population. PCs were computed from the genetic relationship matrix (GRM) derived from the genotype data set using the Genome-Wide Complex Trait Analysis Tool (*GCTA*)[3]. Only autosomal SNPs (MAF > 0.01) were used to derive the GRM. Because outlying phenotypic values may impact the analysis of rare variants, the possible influence of outlying values on association results was checked a posteriori.

I.3. Power Analysis

Common variants were analysed at the variant level and rare variants were analyzed at the gene/region/set levels.

Variant level power analysis. the table below reports the power of our study for minor allele frequencies (MAF) between 0.01 and 0.1 and allele effect size (ES in SD unit) ranging from 0.1 to 0.7. The computations were done with the Genetic Power Calculator algorithm[4] implemented in R (http://www.cureffi.org/2012/12/05/power-for-gwas-and-extreme-phenotype-studies/). Total QTL variance VQ = 2 x ES^2 x MAF x (1-MAF) was used given a sample size of 3681 independent individuals, no dominance, alpha = 5 x 10^7 and assuming a LD = 1 betweeen the marker and the causal variant. We note that for a MAF of 0.01, effect size must at least equal 0.7 SD to reach a power of 0.8. For a MAF of 0.1, a similar power is attained for an effect size of 0.23 SD.

Table 1. Power as a function of minor allele frequency (MAF) and effect size (ES)

	MAF=0.01	MAF=0.025	MAF=0.05	MAF=0.075	MAF=0.10	MAF=0.25	MAF=0.50
ES=0.1	0.000	0.000	0.000	0.000	0.000	0.010	0.232
ES=0.2	0.000	0.009	0.099	0.308	0.552	0.993	1
ES=0.3	0.007	0.158	0.724	0.962	0.997	1	1
ES=0.4	0.054	0.634	0.993	1	1	1	1
ES=0.5	0.226	0.955	1	1	1	1	1
ES=0.6	0.542	0.999	1	1	1	1	1
ES=0.7	0.833	1	1	1	1	1	1

gene/region/set levels power analysis. For sets of variants, power estimation requires modeling the genetic architecture (variants number, respective frequencies and effects, LD between variants). The R/SKAT package (version 1.0.7) provides an analytic method to compute power for SKAT[2]. The approach makes use of a simulated data set of 10,000 haplotypes, encompassing 3845 variants (3266 with MAF < 0.01) over a 200k BP region, generated according to a coalescent model that mimics the LD pattern, local recombination rate and population history of Europeans. Instead of directly specifying the variant effects, the MAF threshold for rare variants, proportion of causal variants among rare variants, fraction of rare variants negatively associated with the phenotype, and the effect size are specified by the user. Within this framework, effect size may be modeled either as constant or as being inversely related to MAF. Power and sample size are estimated by averaging results over a range of parameter values and to account for the heterogeneity of genetic architecture, results are averaged across a number (N.Sim) of randomly selected sub-regions whose size (number of variants) may be set to various values that are relevant for the conducted study.

In the table below power and R^2 estimates assume a sample size of 3681 independent individuals, only rare variants (MAF < 0.01, n = 3266), additivity of allele effect, “Log” beta type, alpha = 10^6 and N.Sim = 100. Variable parameters include: Length of subregion [500-8000 BP], beta weights (bw) [1,25] and [0.5,0.5], maximum beta [1.6,2.0], percentage of causal variants [0.25,0.50]. Note that given “Log” beta type, a maximum beta of 1.6 means that for MAF = 0.0001, 0.001 and 0.01, beta = 1.6, 1.2 and 0.8 respectively. For a maximum beta of 2.0, the respective beta values are 2, 1.5 and 1 (see R/SKAT package manual for details). High proportions of causal variants are considered to account for the putative functionality of the variants on the array.

Table 2. Power of set-based analysis

parameters[$]	Power (bw = 1,25)	R^2 (bw = 1,25)	Power (bw = 0.5,0.5)	R^2 (bw = 0.5,0.5)
500_25_1.6	0.0903	0.00312	0.145	0.00446
500_25_2.0	0.167	0.00559	0.185	0.00572
500_50_1.6	0.204	0.00622	0.226	0.00638
500_50_2.0	0.370	0.0105	0.466	0.0113
1000_25_1.6	0.226	0.00745	0.213	0.00723
1000_25_2.0	0.311	0.0113	0.382	0.011
1000_50_1.6	0.477	0.0147	0.609	0.0139
1000_50_2.0	0.673	0.0235	0.842	0.0216
2000_25_1.6	0.293	0.0132	0.492	0.0149
2000_25_2.0	0.479	0.0233	0.712	0.0215
2000_50_1.6	0.705	0.0283	0.907	0.0276
2000_50_2.0	0.805	0.0411	0.979	0.0416
4000_25_1.6	0.513	0.0271	0.840	0.0285
4000_25_2.0	0.693	0.0403	0.962	0.0399
4000_50_1.6	0.930	0.0537	0.999	0.052
4000_50_2.0	0.980	0.0827	1	0.0852
8000_25_1.6	0.801	0.0528	0.986	0.055
8000_25_2.0	0.918	0.0794	1	0.0838
8000_50_1.6	1	0.103	1	0.0999
8000_50_2.0	1	0.152	1	0.148

[$] parameters: region size [500-8000 BP], percentage of causal variants [25,50], maximum beta [1.6,2]. The expected number of rare variants across regions of 500, 1000, 2000, 4000 and 8000 BP are 8.1, 16.3, 32.7, 65.3 and 130.6 respectively.

assuming these sets of parameters, the analysis shows that when the number of rare variants is limited (ex. 500 BP region, ~ 8 variants), the power is low (0.466 at best with the most favorable set of parameters). The number of genes in our data set with 2-5, 6-10, 11-25, 26-50, 51-100, >100 rare variants was 7666, 2816, 1048,99,18 and 2 respectively. For the vast majority of genes in our study the power of the gene-level analysis is therefore low. On the other hand the power of the gene-set-level analysis (see number of variants in tables 5, 6, 7 below) appears more appropriate.

II. Variant-level analysis: associations with common variants

In table 3, the best associated SNPs ($p < 10^{-4}$) are reported for each phenotype. Table columns are SNP, gene locus (if located at less than 1000 bp from the SNP position, |NONE| otherwise), phenotype, chromosome, physical position, reference allele (the coded effect allele), the other allele, frequency of the reference allele, SNP effect, standard error and p-value.

In figures 1 to 3, Manhattan and QQ-plots are shown for all phenotypes.

Table 3. Variant-level analysis: Best associated SNPs (p<0.0001 and MAF > 0.01)

SNP	gene	pheno	Chr	bp	A1	A2	Freq	b	se	p
exm1479366	/APOE/	LDLc	19	45412079	A	G	0.0762	-0.139	0.0104	$2.7x10^{-40}$
exm-rs445925	/NONE/	LDLc	19	45415640	A	G	0.102	-0.097	0.00914	$4.4x10^{-26}$
exm62588	/PCSK9/	LDLc	1	55505647	A	C	0.0177	-0.121	0.0211	$1.2x10^{-08}$
exm1417699	/SNAPC2/	LDLc	19	7987428	A	G	0.0622	0.06	0.0118	$4.5x10^{-07}$
exm279108	/COL6A3/	LDLc	2	238280504	A	G	0.0698	0.051	0.0105	$1.0x10^{-06}$
exm-rs2075650	/TOMM40/	LDLc	19	45395619	G	A	0.107	0.043	0.00894	$1.7x10^{-06}$
exm-rs4420638	/APOC1/	LDLc	19	45422946	G	A	0.146	0.036	0.00778	$4.2x10^{-06}$
exm2271608	/NONE/	LDLc	11	50630255	C	A	0.478	-0.024	0.0055	$9.4x10^{-06}$
exm2264426	/NONE/	LDLc	11	50495067	C	A	0.408	-0.024	0.00558	$2.2x10^{-05}$
exm-rs769449	/APOE/	LDLc	19	45410002	A	G	0.0845	0.042	0.00994	$2.4x10^{-05}$
exm-rs579459	/NONE/	LDLc	9	136154168	G	A	0.237	0.026	0.00644	$4.2x10^{-05}$
exm-rs651007	/NONE/	LDLc	9	136153875	A	G	0.237	0.026	0.00644	$4.2x10^{-05}$
exm-rs6511720	/LDLR/	LDLc	19	11202306	A	C	0.137	-0.032	0.00801	$5.1x10^{-05}$
exm949490	/ENDOD1/	LDLc	11	94862288	A	G	0.0831	-0.039	0.00998	$7.7x10^{-05}$
exm181733	/GCKR/	TRIG	2	27730940	A	G	0.458	0.064	0.00931	$4.9x10^{-12}$
exm-rs780093	/GCKR/	TRIG	2	27742603	A	G	0.449	0.064	0.00936	$7.4x10^{-12}$
exm-rs964184	/ZNF259/	TRIG	11	116648917	C	G	0.137	0.091	0.0136	$2.1x10^{-11}$
exm-rs780094	/GCKR/	TRIG	2	27741237	A	G	0.451	0.062	0.00933	$2.9x10^{-11}$
exm-rs12678919	/NONE/	TRIG	8	19844222	G	A	0.11	-0.099	0.0149	$3.0x10^{-11}$
exm-rs10503669	/NONE/	TRIG	8	19847690	A	C	0.108	-0.098	0.0151	$6.6x10^{-11}$
exm686341	/LPL/	TRIG	8	19819724	G	C	0.113	-0.093	0.0148	$2.9x10^{-10}$
exm-rs17482753	/NONE/	TRIG	8	19832646	A	C	0.112	-0.092	0.0149	$5.2x10^{-10}$
exm-rs2266788	/APOA5/	TRIG	11	116660686	G	A	0.0694	0.113	0.0183	$6.6x10^{-10}$
exm-rs10096633	/NONE/	TRIG	8	19830921	A	G	0.148	-0.081	0.0133	$1.2x10^{-09}$
exm-rs9326246	/NONE/	TRIG	11	116611733	G	C	0.0709	0.109	0.0181	$1.7x10^{-09}$
exm-rs10790162	/BUD13/	TRIG	11	116639104	A	G	0.0702	0.108	0.0182	$3.4x10^{-09}$
exm-rs7016880	/NONE/	TRIG	8	19876746	C	G	0.115	-0.085	0.0147	$5.9x10^{-09}$
exm-rs2075290	/ZNF259/	TRIG	11	116653296	G	A	0.0728	0.103	0.0178	$8.8x10^{-09}$
exm-rs301	/LPL/	TRIG	8	19816934	G	A	0.238	-0.062	0.0109	$1.4x10^{-08}$
exm-rs2954029	/RP11-136O12.2/	TRIG	8	126490972	T	A	0.456	-0.05	0.00927	$5.2x10^{-08}$
exm-rs2197089	/NONE/	TRIG	8	19826373	G	A	0.449	0.049	0.00941	$1.7x10^{-07}$
exm181843	/C2orf16/	TRIG	2	27801759	G	A	0.301	0.052	0.0101	$2.3x10^{-07}$
exm686306	/LPL/	TRIG	8	19813529	G	A	0.0155	0.196	0.038	$2.7x10^{-07}$
exm-rs13022873	/ZNF512/	TRIG	2	27815510	C	A	0.302	0.051	0.0101	$4.1x10^{-07}$
exm-rs2083637	/NONE/	TRIG	8	19865175	G	A	0.275	-0.052	0.0104	$5.2x10^{-07}$
exm-rs7350481	/NONE/	TRIG	11	116586283	A	G	0.0701	0.091	0.0182	$5.2x10^{-07}$
exm-rs1441756	/NONE/	TRIG	8	19868386	C	A	0.273	-0.052	0.0105	$6.0x10^{-07}$
exm-rs4938303	/NONE/	TRIG	11	116584987	G	A	0.268	0.053	0.0106	$6.2x10^{-07}$
exm182139	/ZNF512/CCDC121/	TRIG	2	27851918	A	G	0.296	0.05	0.0102	$7.0x10^{-07}$
exm-rs13702	/LPL/	TRIG	8	19824492	G	A	0.308	-0.05	0.0101	$7.7x10^{-07}$
exm-rs15285	/LPL/	TRIG	8	19824667	A	G	0.306	-0.05	0.0101	$8.3x10^{-07}$

SNP	gene	pheno	Chr	bp	A1	A2	Freq	b	se	p
exm-rs326	/LPL/	TRIG	8	19819439	G	A	0.317	-0.048	0.01	$1.7x10^{-06}$
exm-rs673548	/APOB/	TRIG	2	21237544	A	G	0.221	-0.053	0.0112	$2.2x10^{-06}$
exm175699	/APOB/	TRIG	2	21231524	A	G	0.22	-0.053	0.0112	$2.6x10^{-06}$
exm175467	/APOB/	TRIG	2	21225281	G	A	0.221	-0.052	0.0112	$2.8x10^{-06}$
exm-rs264	/LPL/	TRIG	8	19813180	A	G	0.149	-0.061	0.0131	$3.9x10^{-06}$
exm2265307	/IFT172/	TRIG	2	27711893	G	A	0.42	-0.044	0.00952	$4.4x10^{-06}$
exm625685	/MLXIPL/	TRIG	7	73020337	C	G	0.105	-0.068	0.015	$5.8x10^{-06}$
exm296112	/NEK10/	TRIG	3	27338698	G	A	0.0151	-0.17	0.0383	$8.5x10^{-06}$
exm-rs2043085	/ALDH1A2/	TRIG	15	58680954	A	G	0.395	0.041	0.00951	$1.7x10^{-05}$
exm-rs17145738	/NONE/	TRIG	7	72982874	A	G	0.102	-0.065	0.0152	$1.9x10^{-05}$
exm-rs13233571	/BCL7B/	TRIG	7	72971231	A	G	0.102	-0.065	0.0152	$2.0x10^{-05}$
exm-rs2954026	/RP11-136O12.2/	TRIG	8	126484526	A	C	0.328	0.042	0.00993	$2.2x10^{-05}$
exm2258831	/NRG1/NRG1-IT1/	TRIG	8	31921721	A	G	0.422	-0.04	0.00949	$2.3x10^{-05}$
exm625652	/MLXIPL/	TRIG	7	73012042	A	G	0.105	-0.063	0.015	$2.6x10^{-05}$
exm-rs1532085	/ALDH1A2/	TRIG	15	58683366	A	G	0.39	0.04	0.00952	$3.3x10^{-05}$
exm-rs10047462	/AP006216.12/SIK3/	TRIG	11	116722041	C	A	0.102	0.065	0.0157	$3.4x10^{-05}$
exm1280666	/MYBBP1A/	TRIG	17	4457116	G	A	0.0204	0.134	0.0324	$3.5x10^{-05}$
exm-rs2954033	/RP11-136O12.2/	TRIG	8	126493746	A	G	0.327	0.041	0.00995	$3.7x10^{-05}$
exm-rs10401969	/SUGP1/	TRIG	19	19407718	G	A	0.0681	-0.077	0.0187	$4.0x10^{-05}$
exm2254231	/ITCH/	TRIG	20	32955423	G	A	0.479	-0.038	0.00938	$4.1x10^{-05}$
exm958032	/PAFAH1B2/	TRIG	11	117042377	G	A	0.112	0.062	0.0151	$4.2x10^{-05}$
exm-rs2516489	/PPIAP9/	TRIG	6	31488038	A	G	0.192	0.048	0.0118	$4.3x10^{-05}$
exm1447311	/HAPLN4/TM6SF2/	TRIG	19	19379549	A	G	0.0649	-0.078	0.0191	$4.3x10^{-05}$
exm-rs2240466	/BAZ1B/	TRIG	7	72856269	A	G	0.101	-0.062	0.0153	$4.6x10^{-05}$
exm-rs6544366	/NONE/	TRIG	2	21204025	A	C	0.239	-0.044	0.0108	$4.7x10^{-05}$
exm530862	/MCCD1/RPL15P4/	TRIG	6	31496915	A	G	0.191	0.048	0.0118	$5.2x10^{-05}$
exm-rs2523512	/DDX39B/	TRIG	6	31506801	A	G	0.192	0.048	0.0118	$5.2x10^{-05}$
exm-rs6754295	/NONE/	TRIG	2	21206183	C	A	0.239	-0.043	0.0108	$6.7x10^{-05}$
exm957713	/APOA5/	TRIG	11	116662407	G	C	0.0599	0.079	0.0198	$6.7x10^{-05}$
exm1284102	/NLRP1/	TRIG	17	5437285	A	G	0.0614	0.075	0.019	$7.5x10^{-05}$
exm-rs11902417	/NONE/	TRIG	2	21198900	A	G	0.237	-0.043	0.0108	$7.7x10^{-05}$
exm-rs7112513	/PAFAH1B2/	TRIG	11	117037361	A	G	0.113	0.059	0.015	$8.1x10^{-05}$
exm-rs2075292	/SIK3/	TRIG	11	116732512	C	A	0.113	0.059	0.015	$9.1x10^{-05}$
exm1284063	/NLRP1/	TRIG	17	5424906	G	C	0.0617	0.074	0.019	$9.3x10^{-05}$
exm-rs247616	/NONE/	HDLc	16	56989590	A	G	0.31	0.057	0.00567	$1.6x10^{-23}$
exm-rs173539	/NONE/	HDLc	16	56988044	A	G	0.318	0.056	0.00563	$5.9x10^{-23}$
exm-rs3764261	/NONE/	HDLc	16	56993324	A	C	0.313	0.055	0.00565	$2.8x10^{-22}$
exm-rs1532624	/CETP/	HDLc	16	57005479	A	C	0.42	0.05	0.00534	$3.7x10^{-21}$
exm-rs1800775	/CETP/	HDLc	16	56995236	A	C	0.481	0.049	0.00526	$1.6x10^{-20}$
exm-rs7499892	/CETP/	HDLc	16	57006590	A	G	0.184	-0.049	0.00676	$4.8x10^{-13}$
exm-rs9989419	/NONE/	HDLc	16	56985139	A	G	0.391	-0.036	0.00537	$2.6x10^{-11}$
exm-rs9939224	/CETP/	HDLc	16	57002732	A	C	0.214	-0.043	0.00644	$3.7x10^{-11}$
exm-rs12678919	/NONE/	HDLc	8	19844222	G	A	0.11	0.053	0.00837	$2.9x10^{-10}$
exm-rs17482753	/NONE/	HDLc	8	19832646	A	C	0.112	0.051	0.00834	$9.2x10^{-10}$
exm-rs10503669	/NONE/	HDLc	8	19847690	A	C	0.108	0.052	0.00845	$9.7x10^{-10}$
exm686341	/LPL/	HDLc	8	19819724	G	C	0.113	0.051	0.00827	$9.7x10^{-10}$
exm-rs7016880	/NONE/	HDLc	8	19876746	C	G	0.115	0.046	0.00823	$2.1x10^{-08}$
exm-rs10096633	/NONE/	HDLc	8	19830921	A	G	0.148	0.041	0.00744	$3.2x10^{-08}$
exm-rs301	/LPL/	HDLc	8	19816934	G	A	0.238	0.033	0.00611	$5.2x10^{-08}$
exm-rs1883025	/ABCA1/	HDLc	9	107664301	A	G	0.271	-0.03	0.00587	$2.5x10^{-07}$
exm1417699	/SNAPC2/	HDLc	19	7987428	A	G	0.0622	-0.057	0.0112	$3.4x10^{-07}$
exm-rs1441756	/NONE/	HDLc	8	19868386	C	A	0.273	0.03	0.00586	$4.2x10^{-07}$

SNP	gene	pheno	Chr	bp	A1	A2	Freq	b	se	p
exm-rs2083637	/NONE/	HDLc	8	19865175	G	A	0.275	0.029	0.00586	$5.3x10^{-07}$
exm-rs261334	/LIPC/	HDLc	15	58726744	G	C	0.213	0.031	0.00624	$6.3x10^{-07}$
exm686306	/LPL/	HDLc	8	19813529	G	A	0.0155	-0.105	0.0214	$8.1x10^{-07}$
exm-rs1800588	/ALDH1A2/LIPC/	HDLc	15	58723675	A	G	0.222	0.03	0.00619	$9.6x10^{-07}$
exm-rs264	/LPL/	HDLc	8	19813180	A	G	0.149	0.036	0.00736	$1.0x10^{-06}$
exm279108	/COL6A3/	HDLc	2	238280504	A	G	0.0698	-0.049	0.00997	$1.0x10^{-06}$
exm1242998	/CETP/	HDLc	16	57016092	G	A	0.326	0.027	0.00562	$1.1x10^{-06}$
exm-rs15285	/LPL/	HDLc	8	19824667	A	G	0.306	0.026	0.00567	$4.4x10^{-06}$
exm-rs13702	/LPL/	HDLc	8	19824492	G	A	0.308	0.026	0.00567	$6.5x10^{-06}$
exm-rs673548	/APOB/	HDLc	2	21237544	A	G	0.221	0.027	0.00625	$1.2x10^{-05}$
exm175467	/APOB/	HDLc	2	21225281	G	A	0.221	0.027	0.00626	$1.8x10^{-05}$
exm1242986	/CETP/	HDLc	16	57015091	C	G	0.0437	-0.054	0.0126	$2.0x10^{-05}$
exm175699	/APOB/	HDLc	2	21231524	A	G	0.22	0.027	0.00627	$2.1x10^{-05}$
exm1242852	/HERPUD1/	HDLc	16	56969148	A	G	0.149	-0.031	0.00734	$2.7x10^{-05}$
exm-rs326	/LPL/	HDLc	8	19819439	G	A	0.317	0.023	0.00563	$3.3x10^{-05}$
exm886065	/RRP8/	HDLc	11	6623433	A	G	0.0153	-0.087	0.0211	$3.6x10^{-05}$
exm2269795	/GPRIN3/	HDLc	4	90168572	A	G	0.465	-0.021	0.00521	$3.9x10^{-05}$
exm2263982	/NONE/	HDLc	3	34692880	A	C	0.259	-0.024	0.00594	$4.6x10^{-05}$
exm-rs2197089	/NONE/	HDLc	8	19826373	G	A	0.449	-0.021	0.00527	$6.6x10^{-05}$
exm2269094	/NONE/	Cstif	2	81583557	A	G	0.422	-0.019	0.00448	$1.9x10^{-05}$
exm-rs10784496	/RPSAP52/	Cstif	12	66160971	G	A	0.442	-0.018	0.00444	$6.2x10^{-05}$
exm-rs2903692	/CLEC16A/	Dext	16	11238783	A	G	0.39	-0.009	0.00198	$4.4x10^{-06}$
exm-rs12708716	/CLEC16A/	Dext	16	11179873	G	A	0.396	-0.009	0.00199	$1.0x10^{-05}$
exm-rs12924729	/CLEC16A/	Dext	16	11187783	A	G	0.358	-0.008	0.00201	$2.7x10^{-05}$
exm-rs10958476	/PLAG1/	Dext	8	57095808	G	A	0.201	-0.01	0.00243	$5.1x10^{-05}$
exm2269136	/NCKAP5/	Dext	2	133964894	A	G	0.473	-0.008	0.00192	$6.0x10^{-05}$
exm-rs2903692	/CLEC16A/	Dint	16	11238783	A	G	0.39	-0.011	0.00227	$4.2x10^{-07}$
exm-rs12708716	/CLEC16A/	Dint	16	11179873	G	A	0.396	-0.011	0.00227	$2.2x10^{-06}$
exm-rs12924729	/CLEC16A/	Dint	16	11187783	A	G	0.358	-0.011	0.0023	$3.4x10^{-06}$
exm-rs10958476	/PLAG1/	Dint	8	57095808	G	A	0.201	-0.012	0.00278	$1.2x10^{-05}$
exm2269136	/NCKAP5/	Dint	2	133964894	A	G	0.473	-0.009	0.00219	$2.9x10^{-05}$
exm1390708	/SERPINB12/	Dint	18	61233907	A	G	0.025	-0.029	0.00716	$6.5x10^{-05}$
exm-rs11661542	/NONE/	Dint	18	20223695	C	A	0.494	-0.009	0.00225	$6.7x10^{-05}$
exm-rs4823006	/ZNRF3/	Dint	22	29451671	G	A	0.457	-0.009	0.00221	$9.0x10^{-05}$
exm781145	/WDR38/	IMT	9	127618752	A	G	0.016	-0.064	0.0152	$2.6x10^{-05}$
exm1103361	/TBPL2/	IMT	14	55903716	A	C	0.0921	0.027	0.00656	$3.2x10^{-05}$
exm142369	/CDK18/	IMT	1	205492679	A	G	0.0481	-0.037	0.00895	$4.4x10^{-05}$
exm-rs588517	/NONE/	IMT	10	83153246	A	G	0.112	0.025	0.00602	$4.6x10^{-05}$
exm1330348	/SPATA32/MAP3K14/	IMT	17	43333125	A	G	0.429	0.015	0.00389	$9.2x10^{-05}$
exm2270260	/NONE/	MBP	5	157551411	A	C	0.392	0.012	0.00272	$1.3x10^{-05}$
exm-rs9373523	/STXBP5/	MBP	6	147701133	A	C	0.413	0.011	0.00268	$6.7x10^{-05}$
exm2265215	/AC144449.1/	MBP	2	150572567	A	G	0.454	-0.01	0.00269	$9.7x10^{-05}$
exm1614609	/ARFGAP3/	PPC	22	43206950	A	C	0.432	-0.022	0.00523	$1.9x10^{-05}$
exm729132	/PLEC/	PPC	8	144992269	A	G	0.0131	-0.091	0.0227	$5.5x10^{-05}$
exm1351175	/TTYH2/	PPC	17	72249229	A	C	0.245	-0.023	0.00599	$9.6x10^{-05}$
exm619964	/HUS1/PKD1L1/	CWS	7	47921682	T	A	0.33	0.024	0.00564	$1.9x10^{-05}$
exm648086	/MLL5/	CWS	7	104747899	A	C	0.0382	-0.056	0.0138	$4.9x10^{-05}$
exm1103361	/TBPL2/	WCSA	14	55903716	A	C	0.0921	0.033	0.00799	$2.9x10^{-05}$
exm-rs588517	/NONE/	WCSA	10	83153246	A	G	0.112	0.029	0.00732	$8.2x10^{-05}$
exm142369	/CDK18/	WCSA	1	205492679	A	G	0.0481	-0.042	0.0109	$9.9x10^{-05}$

Figure 1. Manhattan and QQplots of lipid variables

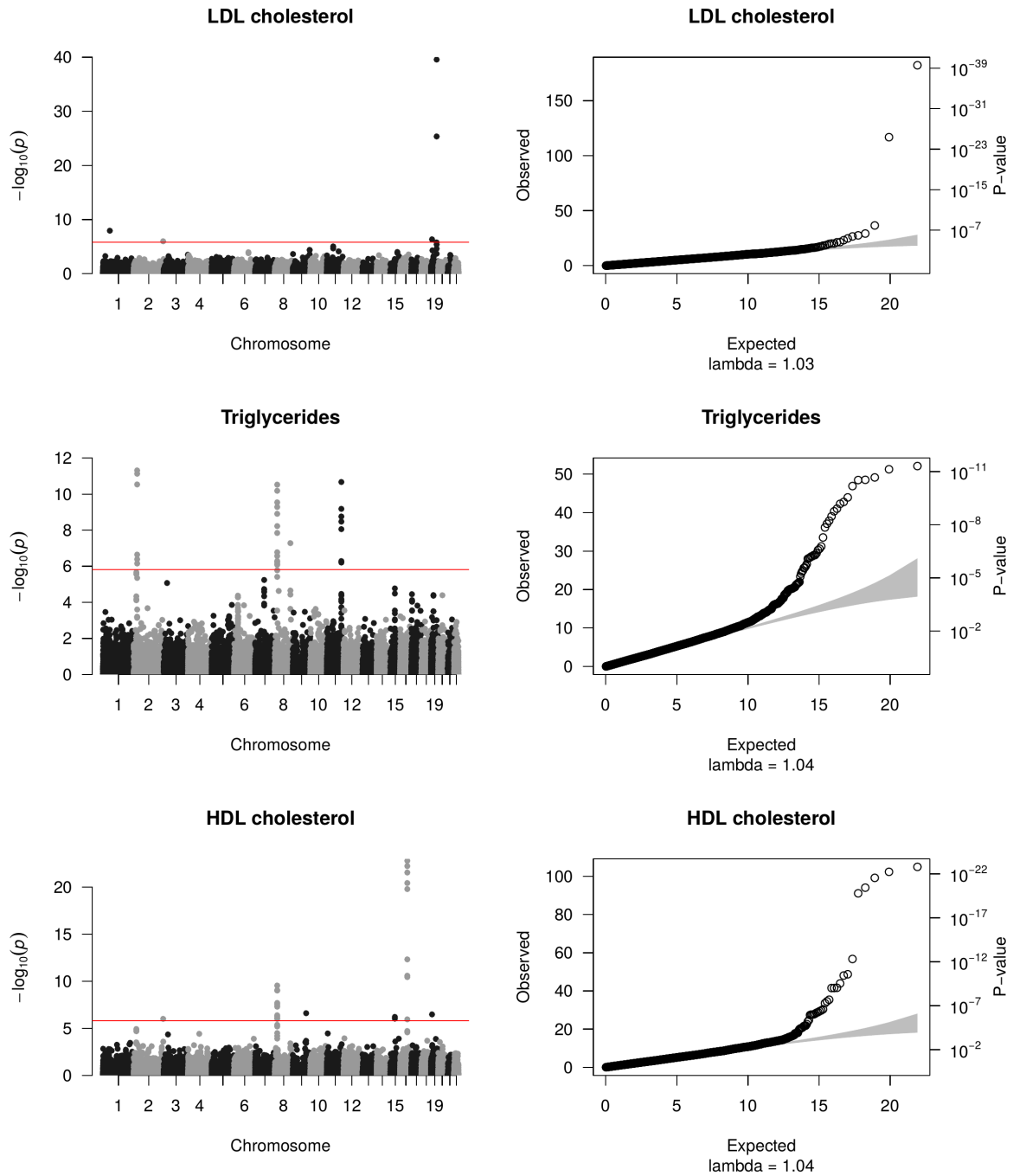


Figure 2. Manhattan and QQplots of vascular variables (1)

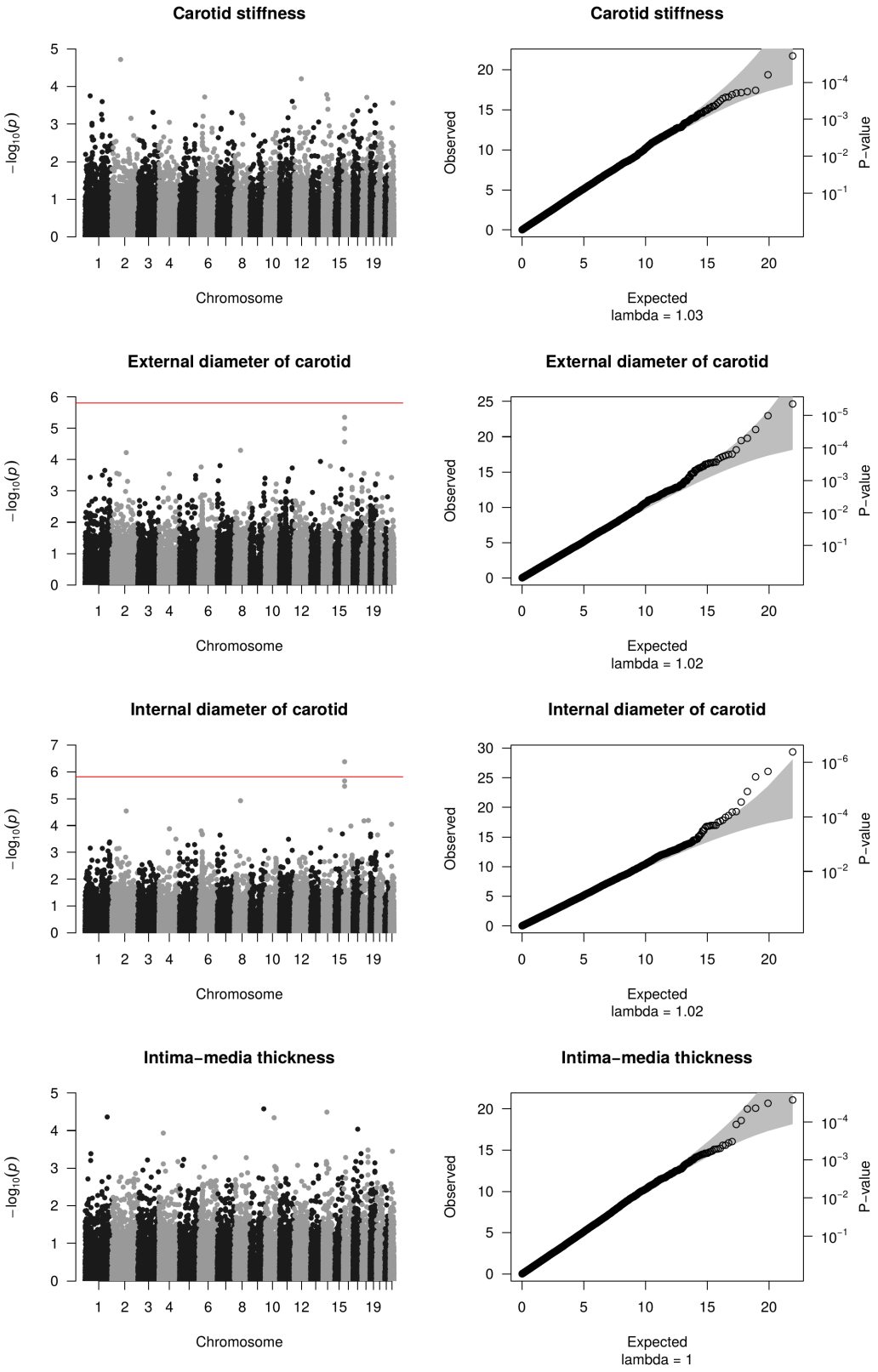
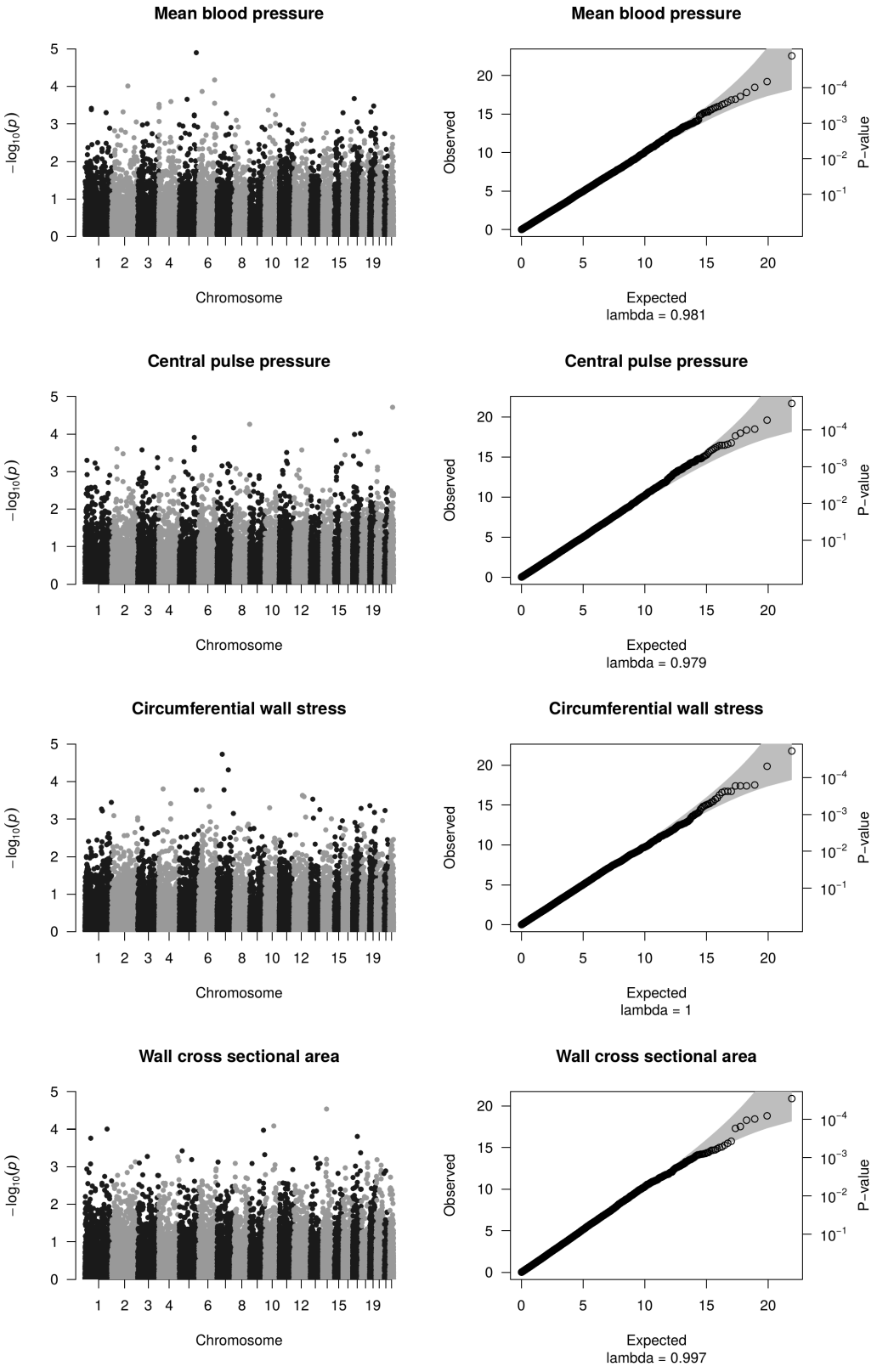


Figure 3. Manhattan and QQplots of vascular variables (2)



III. Gene-level analysis: SKAT analysis of associations of common and rare variants (MAF < 0.01) with phenotypes

For each gene, all variants located within its sequence +/- 10KB were selected and analysed using the SKAT algorithm. In table 4, the best associated genes ($p < 10^{-4}$) are reported for each phenotype. N(c/r) is the number of common and rare variants respectively. P-values for all, common and rare variants are shown. P(rare1) is the P-value obtained using the SKAT algorithm for rare variants (R/SKAT r.corr.rare=1) while P(rare2) is the P-value obtained using the collapsing test (R/SKAT r.corr.rare=1).

In figures 4 to 6, QQ-plots are shown for rare (MAF<0.01) and common variants for all phenotypes.

Table 4. Gene-level analysis: Best associated SNPs ($p < 10^{-4}$)

Gene	Phenotype	N(c/r)	P(all)	P(common)	P(rare1)	P(rare2)
APOE	LDLc	2/1	4.13e-34	2.61e-43	0.914	0.914
TOMM40	LDLc	2/0	2.27e-07	2.27e-07	-	-
SNAPC2	LDLc	2/2	4.35e-06	1.76e-06	0.0954	0.135
ITIH6	LDLc	3/8	8.89e-06	0.00931	4.83e-05	0.0433
SMC5	LDLc	2/3	1.45e-05	0.101	1.15e-05	0.000693
C1orf186	LDLc	0/2	2.21e-05	-	2.21e-05	0.00301
CACHD1	LDLc	0/9	8.02e-05	-	8.02e-05	0.124
ADAMTS7	LDLc	3/6	8.66e-05	8.75e-05	0.0684	0.0196
C1orf53	LDLc	0/2	8.77e-05	-	8.77e-05	0.105
OSTalpha	LDLc	1/2	0.000125	0.699	1.28e-05	0.0348
LDLR	LDLc	4/3	0.000152	1.19e-05	0.631	0.330
PCSK9	LDLc	5/1	0.00023	2.98e-06	0.494	0.494
LGALS8	LDLc	5/3	0.000312	0.205	6.87e-05	0.00743
F2RL3	LDLc	2/2	0.000868	0.688	0.000117	4.55e-05
TRPC6	LDLc	1/3	0.00111	0.628	6.33e-05	0.00190
C4orf29	LDLc	3/5	0.00251	0.384	0.000409	1.51e-05
TRERF1	LDLc	6/7	0.00379	0.361	0.00230	1.59e-05
LPL	TRIG	8/5	1.29e-12	2.41e-11	0.0906	0.210
APOA5	TRIG	3/5	3.64e-11	2.49e-12	0.0673	0.452
GCKR	TRIG	3/7	3.49e-10	6.07e-08	0.0362	0.161
ZNF259	TRIG	6/4	1.3e-06	4.84e-07	0.586	0.511
BUD13	TRIG	5/7	3.72e-06	9.20e-07	0.239	0.117
APOB	TRIG	12/42	2.89e-05	7.21e-06	0.586	0.537
TM6SF2	TRIG	1/8	3.95e-05	5.35e-05	0.151	0.0447
PRPS1L1	TRIG	2/4	5.4e-05	0.253	1.52e-05	7.57e-05
BAZ1B	TRIG	3/4	6.41e-05	3.39e-05	0.225	0.0555
MLXIPL	TRIG	2/7	7.26e-05	1.31e-05	0.978	0.794
ZNF512	TRIG	1/2	9.89e-05	8.84e-05	0.126	0.0817
PAFAH1B2	TRIG	3/2	0.000129	4.31e-05	0.219	0.0878
SIK3	TRIG	3/3	0.000152	9.98e-05	0.222	0.0781
MNF1	TRIG	2/2	0.000318	0.115	9.20e-05	0.00780
EFCAB9	TRIG	0/2	0.000395	-	0.000395	5.72e-05
APOC3	TRIG	0/2	0.00044	-	0.000440	5.45e-05
PRMT2	TRIG	1/2	0.000852	0.474	0.000131	4.86e-05
MYBBP1A	TRIG	7/26	0.0023	9.86e-05	0.785	0.645
CETP	HDLc	6/5	9.86e-26	1.83e-25	0.155	0.757
LPL	HDLc	8/5	3.25e-10	5.80e-10	0.625	0.695
SNAPC2	HDLc	2/2	1.17e-06	1.05e-06	0.0387	0.0243

Gene	Phenotype	N(c/r)	P(all)	P(common)	P(rare1)	P(rare2)
HERPUD1	HDLc	1/1	2.53e-05	4.53e-06	0.693	0.693
RRP8	HDLc	1/6	2.6e-05	2.94e-05	0.140	0.0119
LIPC	HDLc	6/2	3.08e-05	1.14e-06	0.636	0.378
ABCA1	HDLc	7/18	4.62e-05	3.35e-05	0.201	0.0662
AVPR2	HDLc	0/4	8.44e-05	-	8.44e-05	0.754
FAM48A	HDLc	1/1	9.02e-05	0.00789	0.000670	0.000670
SERPINA11	HDLc	1/2	0.000171	0.189	7.30e-05	0.000130
GPRIN3	HDLc	4/13	0.000308	3.79e-05	0.668	0.768
APOB	HDLc	12/42	0.000362	7.70e-05	0.666	0.580
OR2T35	HDLc	0/2	0.000423	-	0.000423	3.25e-05
MMP12	HDLc	2/3	0.000433	0.509	7.72e-05	0.0898
C3orf62	HDLc	1/4	0.00047	0.228	6.92e-05	0.000800
ARHGDIG	HDLc	0/2	0.000478	-	0.000478	4.00e-05
OR51G1	HDLc	5/8	0.000696	0.833	3.54e-05	0.00227
HPS3	HDLc	1/5	0.000741	0.793	9.67e-06	1.07e-06
APOE	HDLc	2/1	0.000916	5.95e-05	0.880	0.880
SLC25A48	HDLc	0/3	0.00114	-	0.00114	3.49e-05
FAM13A	Cstif	6/10	1.9e-05	0.0205	3.99e-05	0.0320
MEI1	Cstif	1/6	3.05e-05	0.000167	0.0145	0.149
IWS1	Cstif	0/2	7.51e-05	-	7.51e-05	0.000217
SEC23B	Cstif	3/3	0.000508	0.912	6.67e-05	0.00582
L3MBTL3	Cstif	4/2	0.000524	0.724	4.08e-05	0.0938
C17orf70	Cstif	2/11	0.0129	0.112	0.0124	3.96e-05
P2RX1	Dext	0/3	2.28e-06	-	2.28e-06	2.66e-05
HNRNPM	Dext	0/2	1.59e-05	-	1.59e-05	0.00136
KRTAP19-3	Dext	0/2	5.75e-05	-	5.75e-05	1.90e-05
CACNB3	Dext	0/2	0.000119	-	0.000119	1.44e-05
KCTD10	Dext	1/1	0.000163	0.942	2.95e-05	2.95e-05
FAM116A	Dext	0/3	0.000167	-	0.000167	6.58e-05
CLEC16A	Dext	5/5	0.000466	6.94e-05	0.868	0.949
DNAAF3	Dext	3/6	0.00115	0.479	9.34e-05	0.0329
ANKAR	Dext	5/12	0.00273	0.438	0.000849	3.77e-06
CLEC16A	Dint	5/5	2.34e-05	4.32e-06	0.377	0.991
HNRNPM	Dint	0/2	2.35e-05	-	2.35e-05	0.00225
APOBEC3G	Dint	1/1	6.32e-05	0.0273	0.000141	0.000141
OSBPL3	Dint	1/7	7.7e-05	0.000483	0.0100	0.0743
FAM116A	Dint	0/3	8.35e-05	-	8.35e-05	0.000152
LILRB4	Dint	1/10	8.59e-05	0.00435	0.00100	6.98e-05
P2RX1	Dint	0/3	9.86e-05	-	9.86e-05	0.000292
CACNB3	Dint	0/2	0.000124	-	0.000124	1.45e-05
GINS1	Dint	1/1	0.000128	0.531	2.75e-05	2.75e-05
KRTAP19-3	Dint	0/2	0.000139	-	0.000139	4.99e-05
SERPINB12	Dint	1/4	0.000264	6.65e-05	0.720	0.262
MAPK1	Dint	0/2	0.000779	-	0.000779	9.45e-05
ANKAR	Dint	5/12	0.00907	0.728	0.00150	3.08e-06
ESPL1	Dint	4/13	0.00917	0.184	0.00442	1.47e-05
CADM1	IMT	3/2	6.77e-06	0.827	1.46e-06	0.000787
PTK6	IMT	0/2	8.08e-06	-	8.08e-06	0.000694
TBPL2	IMT	1/1	9.65e-06	3.34e-05	0.0152	0.0152
LDHA	IMT	1/2	2.89e-05	0.802	2.41e-06	7.84e-06
PPP1R42	IMT	0/2	3.09e-05	-	3.09e-05	8.60e-06
MAGEB2	IMT	1/3	6.25e-05	0.317	8.95e-06	0.000496

Gene	Phenotype	N(c/r)	P(all)	P(common)	P(rare1)	P(rare2)
TEX34	IMT	1/2	0.000102	3.70e-05	0.582	0.898
KIF12	IMT	1/3	0.000123	0.0791	1.90e-05	0.0129
CDK18	IMT	2/2	0.000287	2.77e-05	0.649	0.758
WDR38	IMT	2/3	0.000324	5.15e-05	0.582	0.424
FN1	IMT	2/15	0.000538	0.381	1.75e-05	0.0423
OLFML2A	IMT	1/8	0.00127	0.522	3.08e-05	0.225
WDR33	MBP	2/4	0.000145	0.925	9.46e-06	0.000574
PDCL3	MBP	0/2	0.000164	-	0.000164	7.89e-05
CATSPERB	MBP	1/9	0.00247	0.570	9.52e-05	0.728
ANGPT1	PPC	2/1	2.94e-05	0.00523	0.000341	0.000341
TMEM173	PPC	4/5	8.69e-05	0.000260	0.0239	0.582
ARFGAP3	PPC	4/6	0.000157	2.12e-05	0.367	0.258
TRIM10	PPC	10/3	0.000441	0.340	7.85e-05	0.00176
PAPPA2	CWS	3/8	0.000406	0.735	3.15e-05	0.152
MYH6	CWS	2/12	0.00536	0.572	0.000751	1.68e-06
PPP1R42	WCSA	0/2	2.86e-06	-	2.86e-06	3.06e-06
PTK6	WCSA	0/2	3.37e-06	-	3.37e-06	0.000247
P2RX1	WCSA	0/3	2.68e-05	-	2.68e-05	0.000410
OGFOD2	WCSA	0/6	3.19e-05	-	3.19e-05	0.0514
TBPL2	WCSA	1/1	6.19e-05	3.78e-05	0.121	0.121
FBXO10	WCSA	0/4	0.000106	-	0.000106	3.17e-05
WDR38	WCSA	2/3	0.000111	3.64e-05	0.251	0.137
FN1	WCSA	2/15	0.000162	0.139	1.28e-05	0.0934
TEX34	WCSA	1/2	0.000186	6.67e-05	0.587	0.773
LDHA	WCSA	1/2	0.000199	0.602	2.37e-05	1.94e-05
CADM1	WCSA	3/2	0.000233	0.691	5.93e-05	0.00233
KIF12	WCSA	1/3	0.000711	0.237	6.64e-05	0.0354
OLFML2A	WCSA	1/8	0.000965	0.487	2.07e-05	0.244
S100A3	WCSA	1/2	0.00144	0.424	0.000411	8.06e-05

Figure 4. Gene level QQplots of lipid variables

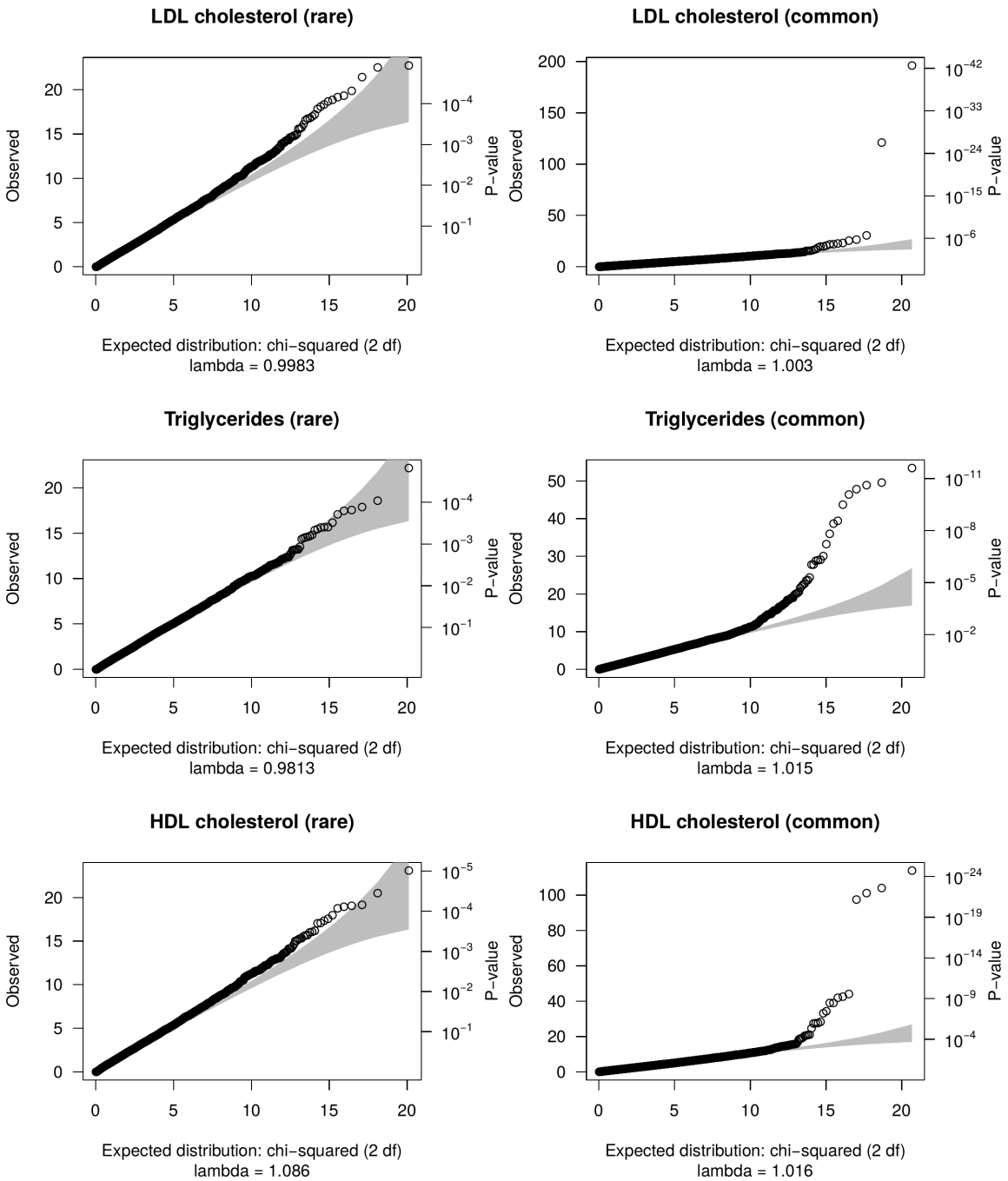


Figure 5. Gene level QQplots of vascular variables (1)

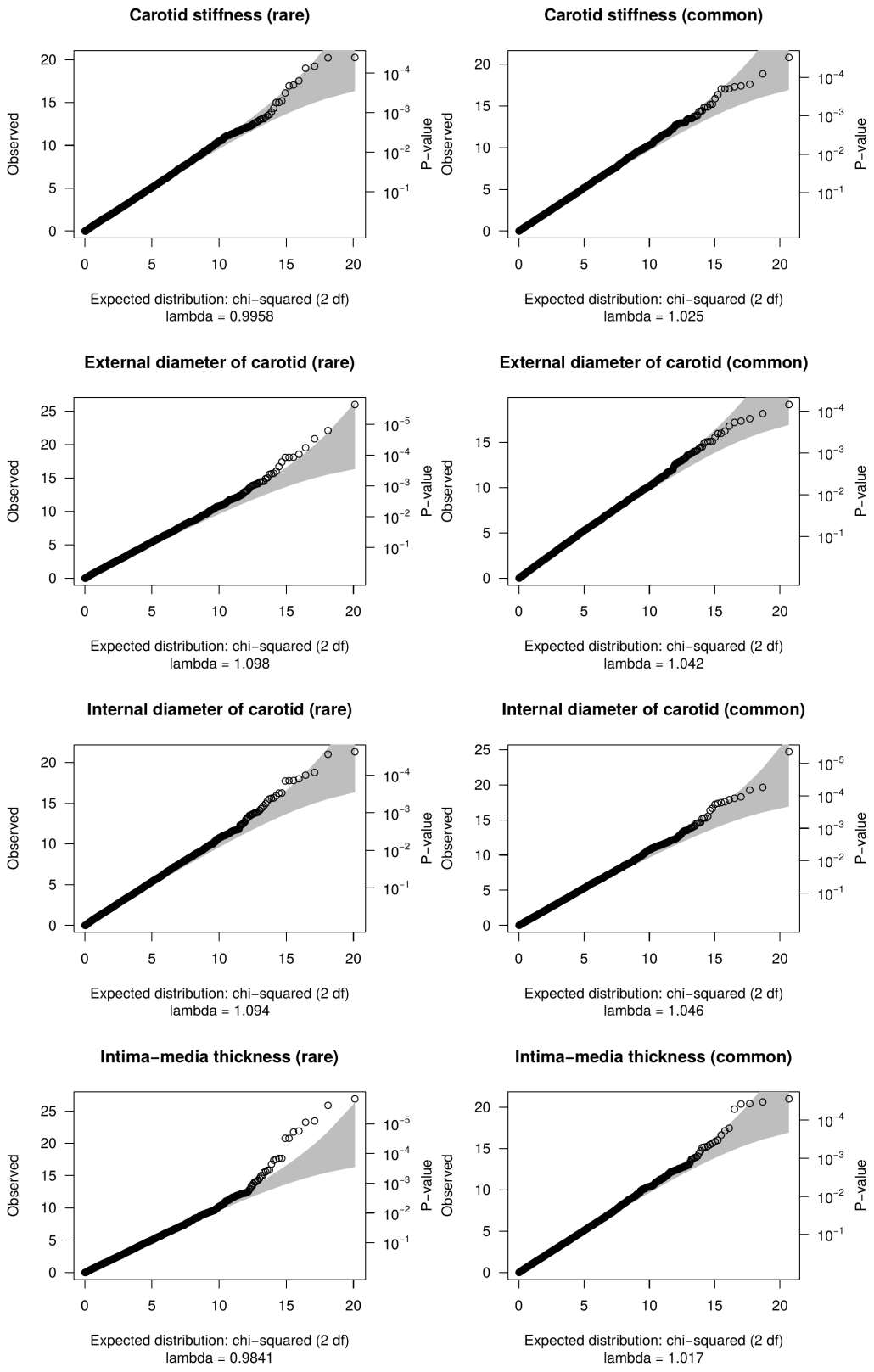
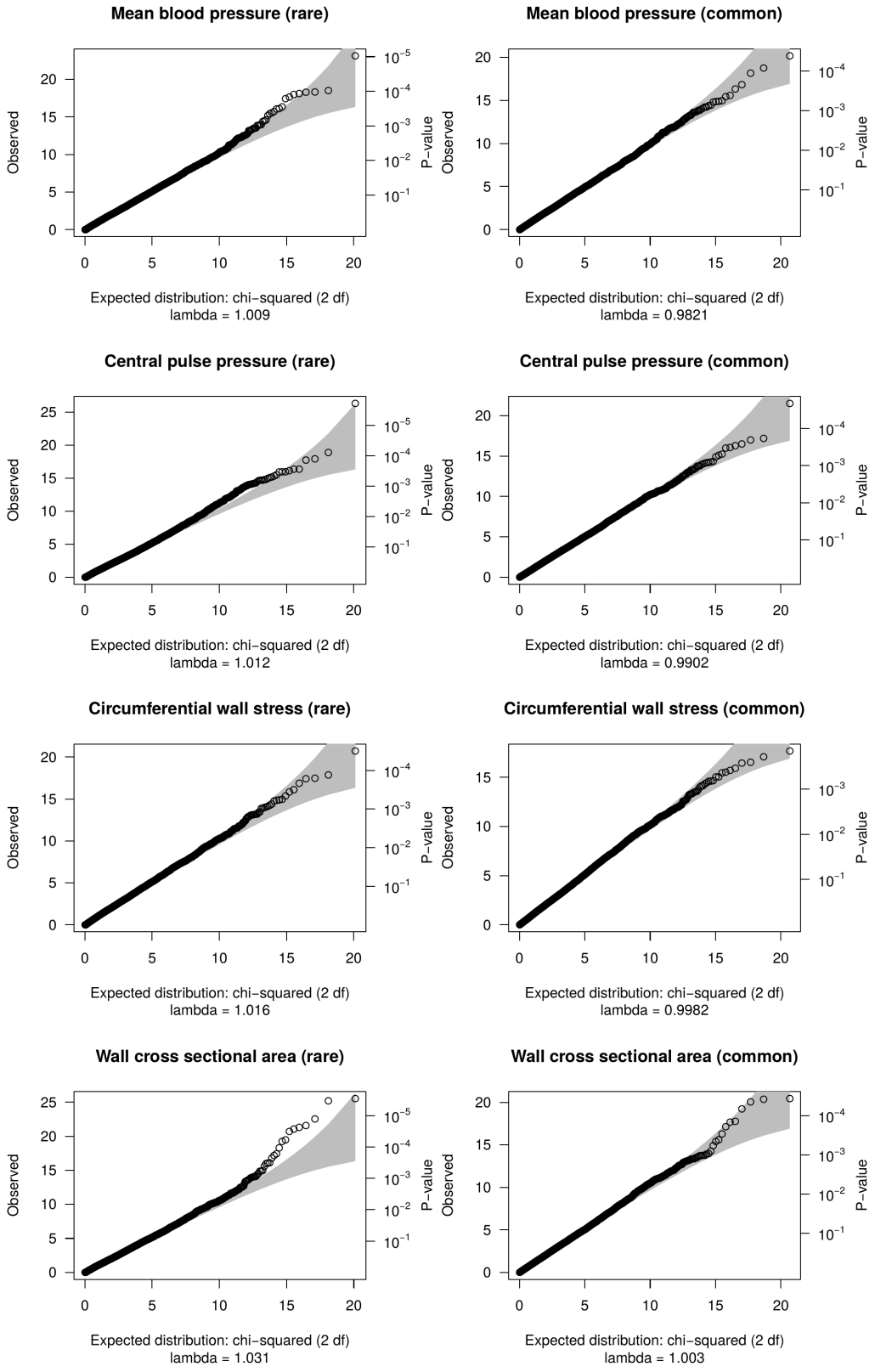


Figure 6. Gene level QQplots of vascular variables (2)



IV. Genes set-level analysis: SKAT analysis of associations of rare and common variants in gene sets

Three gene sets were constituted based on results of GWAS of blood pressure[5], coronary artery disease[6] and plasma lipids.[7]

In the tables below, we provide the results of 2 analyses, one conducted on the whole set of rare and common variants, the other limited to variants with a high severity score (CADD20). Combined-Annotation-Dependent Depletion (CADD) is a new *in silico* methodology that has the ability to score functional and pathogenic variants in coding and non coding regions of the genome. We scored the variants on the CADD web site (http://cadd.gs.washington.edu/score) using version 1.2 of the framework and selected variants with a PHRED-scaled CADD score >20.[8]

table 5. Gene Set Analysis of Plasma lipids

Genes in the set and number of variants (total number / number with CADD PHRED score > 20)

genes n= 88/67; all variants n= 902/273; rare variants (MAF<0.01) n= 563/218

ABCA1 (20/7), ABCA8 (2/1), ABCG5 (6/2), ABCG8 (4/3), ABO (35/0), AMPD3 (3/0), ANGPTL3 (10/4), ANGPTL4 (8/2), APOA1 (7/4), APOB (9/5), APOE (6/3), ARL15 (4/2), BRAP (12/4), C6orf106 (5/0), CAPN3 (5/1), CETP (14/0), CILP2 (2/0), CITED2 (1/0), CMIP (10/1), COBLL1 (5/3), CTF1 (10/3), CYP26A1 (10/6), CYP7A1 (6/3), DNAH11 (5/0), ERGIC3 (1/1), EVI5 (7/0), FADS1 (24/15), FADS2 (2/0), FADS3 (7/0), FRK (8/1), FRMD5 (9/2), GALNT2 (1/0), GCKR (17/4), GPAM (3/0), HFE (19/2), HMGCR (6/0), HNF1A (14/3), HNF4A (3/1), HPR (2/0), IRF2BP2 (5/1), IRS1 (11/3), JMJD1C (21/8), KLF14 (11/5), KLHL8 (8/3), LACTB (8/1), LCAT (10/6), LDLR (8/0), LDLRAP1 (7/4), LILRA3 (5/1), LIPC (11/5), LIPG (19/8), LPA (26/11), LPL (22/5), LRP1 (28/16), LRP4 (18/11), MAFB (3/0), MAP3K1 (10/4), MC4R (1/1), MLXIPL (10/2), MVK (11/1), MYLIP (9/5), NAT2 (11/4), NPC1L1 (15/5), NYNRIN (20/6), OSBPL7 (3/0), PABPC4 (16/9), PCSK9 (7/0), PDE3A (5/1), PGS1 (11/5), PLA2G6 (10/6), PLTP (7/1), PPP1R3B (2/0), RAB3GAP1 (35/0), RAF1 (2/1), SBNO1 (9/9), SCARB1 (5/3), SLC39A8 (54/6), SORT1 (16/6), SPTY2D1 (79/19), ST3GAL4 (4/1), STARD3 (13/1), TIMD4 (11/3), TOP1 (13/2), TRIB1 (6/4), TRPS1 (5/2), TTC39B (6/0), TYW1B (8/0), UBASH3B (4/1), UBE2L3 (5/4), ZNF648 (10/2), ZNF664 (3/2)

Phenotype	P(all)	P(common)	P(rare)	CADD20 P(all)	CADD20 P(common)	CADD20 P(rare)
LDLc	$2.8x10^{-12}$	$1.7x10^{-17}$	0.90	$1.6x10^{-14}$	$8.9x10^{-20}$	0.59
TRIG	$6.0x10^{-22}$	$9.3x10^{-23}$	0.012	$1.5x10^{-07}$	$1.8x10^{-09}$	0.21
HDLc	$3.7x10^{-38}$	$4.9x10^{-40}$	0.030	$2.7x10^{-05}$	$2.4x10^{-06}$	0.21
Cstif	0.47	0.42	0.52	0.50	0.68	0.30
Dext	0.060	0.34	0.030	0.28	0.59	0.15
Dint	0.056	0.23	0.052	0.42	0.80	0.15
IMT	0.75	0.79	0.55	0.45	0.43	0.46
MBP	0.86	0.84	0.70	0.72	0.64	0.62
PPC	0.39	0.66	0.20	0.25	0.17	0.48
CWS	0.66	0.86	0.32	0.75	0.79	0.53
WCSA	0.39	0.69	0.19	0.29	0.31	0.34

table 6. Gene Set Analysis of Blood pressure

Genes in the set and number of variants (total number / number with CADD PHRED score > 20)

genes n= 83/71; all variants n= 563/219; rare variants (MAF<0.01) n= 375/187

ABP1 (6/0), ADM (14/9), ADRB1 (11/7), AGT (16/0), ALDH2 (2/0), ATP2B1 (6/2), CACNB2 (8/2), CASZ1 (9/3), CLCN6 (5/1), CSK (2/2), CTNNB1 (20/8), CTSD (4/0), CYP17A1 (15/3), CYP1A1 (14/6), CYP1A2 (11/8), DDAH2 (12/8), EDN3 (3/1), ENPEP (13/6), ENPP2 (20/6), FBN1 (13/10), FES (1/1), FGF5 (9/1), FIGN (2/2), FURIN (14/9), GATA4 (5/1), GNAS (19/4), GOSR2 (3/2), GUCY1A3 (2/1), GUCY1B3 (8/6), H19 (6/3), HFE (19/2), HLA-DQB1 (2/2), HOXC10 (5/3), HOXC11 (7/5), HOXC12 (8/5), HOXC13 (5/3), HOXC4 (5/2), HOXC5 (6/5), HOXC6 (22/10), HOXC8 (6/2), HOXC9 (4/0), HOXC-AS1 (7/5), HOXC-AS2 (3/1), HOXC-AS3 (2/1), HOXC-AS5 (5/3), HSPA1A (12/1), HSPA1B (9/0), HSPA1L (10/1), JAG1 (5/2), KCNH2 (6/5), MAP4 (10/9), MECOM (9/2), MPI (2/0), MTHFR (6/1), MTMR9 (6/5), NFAT5 (7/5), NGFR (3/0), NOS3 (4/3), NOV (7/5), NPPA (3/0), NPPB (4/1), NUCB2 (1/0), PDE1A (11/6), PDGFRA (12/5), PGR (8/0), PINX1 (8/0), PITX2 (1/1), PLCE1 (22/10), PLEKHA7 (4/3), PRKAG2 (5/1), PTPN11 (2/1), RELA (5/2), SH2B3 (8/2), SLC16A1 (20/3), SLC39A8 (5/3), SLC4A7 (6/2), SMARCC1 (7/1), SOX6 (12/5), TBX3 (2/1), TBX5 (8/4), TRPC6 (5/2), ULK3 (4/2), ULK4 (10/5), UMOD (2/1), VCL (11/4), ZNF652 (4/0), ZNF831 (8/1)

Phenotype	P(all)	P(common)	P(rare)	CADD20 P(all)	CADD20 P(common)	CADD20 P(rare)
LDLc	0.27	0.48	0.19	0.95	0.88	0.86
TRIG	0.073	0.045	0.35	0.85	0.93	0.52
HDLc	0.42	0.15	0.79	0.40	0.46	0.37
Cstif	0.28	0.59	0.14	0.083	0.082	0.26
Dext	0.19	0.26	0.25	0.30	0.41	0.26
Dint	0.38	0.55	0.27	0.66	0.46	0.72
IMT	0.29	0.50	0.20	0.44	0.63	0.28
MBP	0.032	0.067	0.11	0.14	0.39	0.099
PPC	0.23	0.085	0.63	0.051	0.13	0.10
CWS	0.80	0.93	0.42	0.92	0.96	0.61
WCSA	0.12	0.18	0.19	0.11	0.43	0.057

table 7. Gene Set Analysis of Coronary artery disease

Genes in the set and number of variants (total number / number with CADD PHRED score > 20)

genes n= 58/42; all variants n= 552/130; rare variants (MAF<0.01) n= 326/113

ABCG5 (20/6), ABCG8 (20/7), ABO (35/0), AC074093.1 (1/1), ADAMTS7 (8/1), ANKS1A (8/6), APOA1 (14/0), APOA5 (13/4), APOB (7/1), CDKN2B (5/1), CDKN2B-AS1 (14/0), CNNM2 (4/1), COL4A1 (6/4), COL4A2 (10/4), CXCL12 (5/2), CYP17A1 (3/0), EDNRA (18/3), FES (8/2), FLT1 (9/3), FURIN (14/9), GGCX (7/5), GUCY1A3 (7/0), HDAC9 (11/6), HHIPL1 (5/2), IL6R (18/4), KCNE2 (1/0), KCNK5 (10/0), KIAA1462 (3/0), LDLR (8/0), LIPA (3/1), LPA (11/6), LPAL2 (3/1), LPL (2/0), MIA3 (20/7), MRAS (5/2), NT5C2 (17/4), PCSK9 (7/0), PDGFD (36/4), PEMT (14/4), PHACTR1 (3/0), PLG (2/0), PPAP2B (6/2), RAI1 (7/3), RASD1 (7/2), SH2B3 (5/0), SLC22A3 (22/5), SLC22A4 (4/1), SLC22A5 (12/6), SMG6 (54/6), SORT1 (19/4), TCF21 (2/1), TRIB1 (9/2), UBE2Z (5/0), VAMP5 (35/0), VAMP8 (6/4), WDR12 (8/3), ZC3HC1 (2/0), ZEB2 (5/3), ZNF259 (15/6)

Phenotype	P(all)	P(common)	P(rare)	CADD20 P(all)	CADD20 P(common)	CADD20 P(rare)
LDLc	0.00022	$3.1x10^{-05}$	0.42	0.036	0.61	0.0039
TRIG	$8.2x10^{-05}$	$1.3x10^{-05}$	0.38	0.0041	0.0094	0.075
HDLc	0.20	0.23	0.28	0.28	0.10	0.69
Cstif	0.61	0.13	0.97	0.63	0.50	0.63
Dext	0.016	0.0069	0.33	0.18	0.50	0.094
Dint	0.083	0.019	0.61	0.56	0.69	0.37
IMT	0.17	0.25	0.22	0.19	0.54	0.089
MBP	0.58	0.13	0.95	0.24	0.17	0.46
PPC	0.74	0.11	1.0	0.52	0.17	0.89
CWS	0.77	0.43	0.88	0.89	0.84	0.76
WCSA	0.023	0.037	0.12	0.090	0.43	0.041

references

1.Ionita-Laza, I., Lee, S., Makarov, V., Buxbaum, J. D. & Lin, X. Sequence kernel association tests for the combined effect of rare and common variants. *American Journal of Human Genetics* **92,** 841–853 (2013).

2.Wu, M. C. *et al.* Rare-Variant Association Testing for Sequencing Data with the Sequence Kernel Association Test. *American Journal of Human Genetics* **89,** 82–93 (2011).

3.Yang, J., Lee, S. H., Goddard, M. E. & Visscher, P. M. Genome wide complex trait analysis (GCTA): methods, data analyses, and interpretations. *Methods in molecular biology (Clifton, N.J.)* **1019,** 215–236 (2013).

4.Purcell, S., Cherny, S. S. & Sham, P. C. Genetic Power Calculator: design of linkage and association genetic mapping studies of complex traits. *Bioinformatics (Oxford, England)* **19,** 149–150 (2003).

5.Tragante, V. *et al.* Gene-centric meta-analysis in 87,736 individuals of European ancestry identifies multiple blood-pressure-related loci. *American Journal of Human Genetics* **94,** 349–360 (2014).

6.CARDIoGRAMplusC4D Consortium *et al.* Large-scale association analysis identifies new risk loci for coronary artery disease. *Nature genetics* **45,** 25–33 (2013).

7.Global Lipids Genetics Consortium *et al.* Discovery and refinement of loci associated with lipid levels. *Nature genetics* **45,** 1274–1283 (2013).

8.Kircher, M. *et al.* A general framework for estimating the relative pathogenicity of human genetic variants. *Nature Genetics* **46,** 310–315 (2014).