SUPPLEMENTAL MATERIAL

25 novel loci for carotid intima-media thickness: a genome-wide association study in >45,000 individuals and meta-analysis of >100,000 individuals

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Supplementary Methods

CVD risk factors measurements in UK Biobank

Cholesterol and triglyceride were measured using enzymatic assays; High density lipoprotein cholesterol (HDL-C) was measured using an enzyme Immuno-inhibition method while low density lipoprotein cholesterol (LDL-C) was measured using an enzymatic selective protection method[121]. Cholesterol/LDL-C levels of individuals with cholesterol lowering medication at time of inclusion were adjusted by dividing by 0.8/0.7 respectively.

Systolic and diastolic blood pressure were measured twice at a sitting position during participants' visits to assessment centers. The measurements were done first with an automated blood pressure device (Omron 705 IT electronic blood pressure monitor; OMRON Healthcare Europe B.V. Kruisweg 577 2132 NA Hoofddorp) (Field ID 4079, 4080)[122]; In case of unsuccessful automatic measurements, the blood pressures were manually measured by trained nurses (Field ID 93, 94). The average of multiple available measurements was taken as the blood pressure for each participant.

eQTL colocalization analysis with summary data based Mendelian randomization (SMR)

To prioritize genes identified in GWAS, we performed SMR analysis (version 0.710) to test for association between the expression level of each gene and cIMT by using the top-associated expression quantitative trait locus (eQTL) as an instrumental variable[123]. We conducted SMR analysis using the GTEx dataset (v7) but only on tissues relevant to cIMT, namely artery aorta, artery coronary and artery tibial[25]. Genes with p-value (P_{SMR}) passing Bonferroni-corrected thresholds, which was corrected based on the number of genes tested, were submitted to HEterogeneity In Dependent Instruments (HEIDI) test. Genes significant at SMR analysis and not rejected by HEIDI test (P_{HEIDI} >tissue specific Bonferroni-corrected thresholds).

Gene expression analysis in single-cell RNA-sequencing data in human carotid atherosclerotic plaques

The expression levels genes prioritized in GWAS along with other bioinformatic analyses were explored in a RNA-sequencing dataset of carotid artery plaque tissues from 38 patients on a single-cell level with a total of 6191 cells[102]. Analysis was done using PlaqView[124].

Gene prioritization with DEPICT

we used the bioinformatic tool DEPICT (v1.1beta, obtained from https://data.broadinstitute.org/mpg/depict/) to identify candidate causal genes whilst taking gene-gene similarities and LD structures between loci into consideration[125]. Variants at a P-value threshold of $P<1 \times 10^{-8}$ were submitted to this analysis.

Table S1. Clinical characteristics of the study population at imaging visit

Characteristics	All	Men	Women
N	45185	21827	23358
Age (years), mean (SD)	64.68 (7.72)	65.41 (7.81)	64.01 (7.56)
Sex (men)	21827 (48.3%)		
BMI (kg/m2), mean (SD)	26.52 (4.38)	26.97 (3.89)	26.09 (4.76)
LDL-C in mmol/l, median (IQR) *	3.54 (3.00,4.11)	3.54 (2.99, 4.10)	3.54 (3.01, 4.13)
HDL-C in mmol/l, median (IQR) *	1.43 (1.20,1.70)	1.26 (1.09, 1.48)	1.60 (1.37,1.86)
Cholesterol in mmol/l, median (IQR)*	5.68 (4.98, 6.42)	5.56 (4.85, 6.28)	5.79 (5.11, 6.55)
Triglyceride in mmol/l, median (IQR)*	1.40 (0.99, 2.02)	1.63 (1.15, 2.35)	1.22 (0.90, 1.72)
Blood pressure (mm Hg), mean (SD)			
Systolic	134.43 (17.96)	140.18 (16.15)	129.01 (17.88)
Diastolic	79.24 (8.54)	81.7 (8.15)	76.92 (8.24)
$cIMT_{min}$ (mm), mean (SD)	0.58 (0.11)	0.6 (0.12)	0.57 (0.1)
$cIMT_{mean}$ (mm), mean (SD)	0.69 (0.03)	0.71 (0.14)	0.67 (0.11)
$cIMT_{max}$ (mm), mean (SD)	0.8 (0.15)	0.83 (0.16)	0.77 (0.13)
Ethnicity			
White	43775 (96.9%)	21123 (96.8%)	22652 (97.0%)
Asian	612 (1.4%)	356 (1.6%)	256 (1.1%)
Black	291 (0.6%)	138 (0.6%)	153 (0.7%)
Mixed	215 (0.5%)	77 (0.4%)	138 (0.6%)
Other/Unknown	292 (0.6%)	133 (0.6%)	159 (0.7%)
Current smoker	3165 (7.0%)	1814 (8.3%)	1348 (5.8%)
Hypertension	15384 (34.0%)	8616 (39.5%)	6157 (26.4%)
Hyperlipidemia	12763 (28.2%)	8082 (37.0%)	4681 (20.0%)
Abdominal aortic aneurysm	146 (0.3%)	127 (0.6%)	19 (0.1%)
Cerebral infarction	367 (0.8%)	253 (1.2%)	114 (0.5%)
Coronary artery disease	2718 (6.0%)	2073 (9.5%)	645 (2.8%)
Peripheral artery disease	490 (1.1%)	281 (1.3%)	209 (0.9%)

* Measurements collected at the baseline visit.

Table S2. Variable definitions used in the UK Biobank

Variable	ICD-9	ICD-10	OPCS-4	Self-reported fields
Abdominal aortic aneurysm	4414,4413,44102	I714, I713	L183, L184, L185, L186, L193, L194, L195, L196, L271, L272, L275, L281, L282, L464	20002(1492, 1591, 1592), 20004(1104)
Coronary artery disease	414, 410, 412	I24, I25, Z955, I21, I22, I23, I252, Z951	K40, K41, K42, K43, K44, K45, K46, K49, K50, K75	20002(1075), 20004(1070, 1095, 1523)
Ischemic stroke	434	I63, I693, G951, H341, H342		20002(1583)
Hypertension	402, 403, 404, 405, 401	I11, I12, I13, I15, O10, I10		20002(1065, 1072)
Hyperlipidemia	272	E78		20002(1473)
Peripheral artery disease in extremities (include aneurysms)	4439	I739	L37, L381, L383, L384, L391, L392, L395, L48, L49, L50, L51, L52, L53, L541, L542, L544, L56, L57, L58, L59, L60, L62, L631, L632, L635, L638, L639, L653	20002(1087, 1067), 20004(1102, 1103, 1108)
Cholesterol lowering medication				6177(1), 6153(1),20003

Variable definitions constructed using ICD-9, ICD-10 and OPCS-4 codes as well as self-reported data fields with disease- or procedure-specific codes between brackets are shown. Abbreviations: ICD, International Classification of Diseases; OPCS, Office of Population, Censuses and Surveys: Classification of interventions and Procedure

Table S3. Replication of loci from UK Biobank data in CHARGE/UCLEB consortia meta-analysis

			$cIMT_{min}$		$cIMT_{mean}$		$cIMT_{max}$		Franceschini *et al*						
#	**SNP**	**EA**	**Beta (SE)**	***P***	**Beta (SE)**	***P***	**Beta (SE)**	***P***	**Proxy SNP**	**EA**	**I^2**	**Beta (SE)**	***P***	**N**	**consistent**
1*	rs222476	T	0.095 (0.017)	1.60E-08	0.086 (0.017)	2.70E-07	0.08 (0.017)	1.50E-06		T	0	-0.001 (0.0027)	8.16E-01	64611	n
2*	rs6744377	T	0.046 (0.008)	6.50E-09	0.039 (0.008)	3.20E-07	0.031 (0.008)	3.90E-05	rs144206469	D	17.7	0.003 (0.001)	**3.41E-03**	57141	y
3*	2:216300905_ACCCG_A	ACCCG	-0.039 (0.006)	2.20E-09	-0.036 (0.006)	3.30E-09	-0.032 (0.006)	3.40E-07	rs1250237	T	0	0.0015 (0.0007)	**3.69E-02**	64953	y
4*	rs1553085	A	0.038 (0.006)	2.60E-09	0.038 (0.006)	6.00E-10	0.034 (0.006)	4.50E-08		A	14.7	0.001 (0.0008)	7.74E-02	58694	y
5*	rs6795735	C	0.039 (0.006)	9.90E-11	0.039 (0.006)	4.20E-11	0.035 (0.006)	3.90E-09		T	24.1	-0.003 (0.0007)	**4.93E-06**	58799	y
6*	rs10305838	T	-0.051 (0.009)	2.10E-10	-0.052 (0.008)	7.90E-11	-0.046 (0.008)	5.50E-09		T	20.0	-0.004 (0.001)	**7.85E-05**	68002	y
7*	rs4235201	G	-0.04 (0.007)	4.00E-09	-0.04 (0.007)	2.40E-09	-0.039 (0.007)	1.60E-08		T	0.0	0.003 (0.0009)	**3.73E-03**	57794	y
8	rs224805	A	0.096 (0.014)	4.70E-12	0.091 (0.013)	6.30E-12	0.079 (0.013)	2.20E-09		T	1.3	0.009 (0.0016)	**8.07E-08**	68010	y
9	rs310503	G	-0.035 (0.006)	1.60E-08	-0.038 (0.006)	3.80E-10	-0.037 (0.006)	2.10E-09		T	14.4	0.003 (0.0008)	**7.27E-06**	67971	y
10*	rs72801051	A	-0.043 (0.008)	1.30E-06	-0.046 (0.008)	3.90E-08	-0.043 (0.008)	6.00E-07		A	0.0	-0.001 (0.001)	4.44E-01	67974	y
11*	rs11242713	G	-0.037 (0.006)	5.70E-09	-0.036 (0.006)	2.20E-09	-0.034 (0.006)	5.10E-08		A	0.0	0.002 (0.0007)	**6.62E-03**	67107	y
12	rs342988	C	0.046 (0.007)	3.20E-12	0.052 (0.007)	1.70E-15	0.054 (0.007)	2.10E-16		T	7.4	-0.003 (0.0008)	**1.53E-04**	64995	y
13	rs3020263	G	0.056 (0.007)	2.20E-17	0.055 (0.007)	8.10E-18	0.049 (0.007)	9.30E-14		A	4.3	-0.004 (0.0008)	**2.78E-08**	68003	y
14	rs2980478	T	-0.042 (0.006)	2.70E-12	-0.041 (0.006)	4.10E-12	-0.039 (0.006)	1.10E-10	rs2945319	T	0.0	-0.0018 (0.0009)	5.66E-02	35439	y
15	rs11250097	T	0.045 (0.006)	2.10E-14	0.045 (0.006)	1.30E-14	0.041 (0.006)	2.00E-12		T	33.3	0.004 (0.0007)	**8.36E-07**	67107	y
16*	rs4739742	T	0.035 (0.006)	3.80E-09	0.032 (0.006)	4.80E-08	0.027 (0.006)	5.00E-06		T	9.0	0.002 (0.0008)	**4.82E-03**	57795	y
17	rs10110725	T	0.036 (0.006)	3.80E-09	0.037 (0.006)	6.10E-10	0.034 (0.006)	1.30E-08		A	36.1	-0.004 (0.0007)	**2.35E-08**	67996	y
18	rs6470156	G	-0.056 (0.007)	2.80E-17	-0.056 (0.007)	2.90E-17	-0.05 (0.007)	3.80E-14		A	0.0	0.003 (0.0008)	**4.65E-04**	67952	y

			$cIMT_{min}$		$cIMT_{mean}$		$cIMT_{max}$		Franceschini *et al*						
#	**SNP**	**EA**	**Beta (SE)**	***P***	**Beta (SE)**	***P***	**Beta (SE)**	***P***	**Proxy SNP**	**EA**	**I^2**	**Beta (SE)**	***P***	**N**	**consistent**
19*	rs10817556	C	-0.037 (0.006)	2.80E-09	-0.031 (0.006)	3.00E-07	-0.026 (0.006)	3.00E-05		T	0.0	0.002 (0.0007)	**4.26E-03**	64623	y
20*	rs11371318	G	-0.028 (0.006)	5.40E-06	-0.031 (0.006)	1.30E-07	-0.033 (0.006)	1.20E-08	rs7907935	T	20.8	-0.0011 (0.0007)	1.17E-01	58645	y
21	rs914279	T	0.039 (0.006)	4.10E-10	0.038 (0.006)	2.10E-10	0.033 (0.006)	2.60E-08		A	5.1	0.003 (0.0008)	**4.44E-05**	51484	y
22	rs2019090	A	0.041 (0.007)	1.10E-09	0.046 (0.006)	3.20E-12	0.046 (0.007)	3.80E-12		A	25.3	0.002 (0.0008)	**4.55E-03**	68937	y
23*	rs11172113	T	-0.042 (0.006)	4.90E-12	-0.038 (0.006)	2.60E-10	-0.03 (0.006)	1.40E-06		T	28.5	-0.003 (0.0008)	**1.80E-04**	60726	y
24*	rs61930625	C	-0.029 (0.007)	9.80E-06	-0.036 (0.007)	7.60E-08	-0.038 (0.007)	2.80E-08		T	0.0	0.001 (0.0008)	1.60E-01	62082	y
25	rs9515203	T	-0.059 (0.007)	2.90E-18	-0.059 (0.007)	1.50E-18	-0.056 (0.007)	9.70E-17		T	32.1	-0.004 (0.0009)	**3.12E-06**	61467	y
26*	rs2455925	T	0.066 (0.01)	6.80E-11	0.061 (0.01)	2.60E-10	0.05 (0.01)	3.00E-07		A	3.3	0.005 (0.0013)	**3.54E-04**	55625	y
27*	rs4774437	A	-0.031 (0.006)	8.60E-08	-0.034 (0.006)	3.00E-09	-0.032 (0.006)	1.70E-08		A	0.0	-0.003 (0.0007)	**4.44E-05**	65570	y
28	rs1808435	T	-0.044 (0.006)	9.00E-13	-0.044 (0.006)	1.30E-13	-0.04 (0.006)	2.30E-11		A	16.9	-0.004 (0.0007)	**2.74E-07**	67997	y
29*	rs7500448	A	0.037 (0.007)	6.10E-08	0.038 (0.007)	1.60E-08	0.035 (0.007)	5.60E-07		A	42.4	0.004 (0.0009)	**1.71E-05**	62395	y
30	rs488327	T	0.05 (0.006)	5.00E-16	0.049 (0.006)	1.00E-15	0.047 (0.006)	5.40E-14		T	51.7	0.004 (0.0009)	**1.54E-06**	48337	y
31*	rs12051555	A	-0.083 (0.011)	1.10E-14	-0.083 (0.011)	5.70E-15	-0.074 (0.011)	2.80E-12		A	0.0	-0.005 (0.0014)	**7.80E-04**	57795	y
32	rs112009052	T	-0.188 (0.026)	1.30E-12	-0.183 (0.026)	3.20E-12	-0.178 (0.026)	2.90E-11		A	0.0	0.01 (0.0032)	**2.74E-03**	56919	y
33	rs1065853	G	0.119 (0.011)	4.40E-27	0.126 (0.011)	4.70E-31	0.13 (0.011)	7.60E-32	rs7412	T	46.2	-0.0119 (0.0015)	**1.01E-14**	56530	y
34*	rs6120880	C	-0.038 (0.006)	5.70E-10	-0.035 (0.006)	4.30E-09	-0.033 (0.006)	5.90E-08		C	0.0	-0.003 (0.0007)	**3.06E-04**	68071	y
35*	rs5757983	C	-0.033 (0.006)	2.00E-08	-0.035 (0.006)	1.10E-09	-0.033 (0.006)	1.60E-08		C	9.5	-0.004 (0.0007)	**5.29E-07**	62319	y

Chr: Chromosome; EA: Effective allele; I^2: Heterogeneity I^2 statistics in the meta-analysis; NEA: Non-effective allele; EAF: Effective allele frequency; #: Locus number; *: novel loci discovered in the current study. Proxy SNP rs144206469, rs1250237, rs2945319, rs7907935 and rs7412 are in high LD (R^2>0.7) with lead SNP. Marked in bold: associations in CHARGE/UCLEB consortia meta-analysis with $P < 0.05$.

Table S4. Association results of previously reported cIMT loci not replicated in the current UK Biobank sample

							$cIMT_{min}$		$cIMT_{mean}$		$cIMT_{max}$	
SNP	**Closest gene**	**Reported literature**	**Chr**	**Position**	**EA**	**EAF**	**Beta (SE)**	***P***	**Beta (SE)**	***P***	**Beta (SE)**	***P***
rs201648240	*LINC01717*	Franceschini *et al.*	1	208953176								
rs6907215	*AIG1*	Franceschini *et al.*	6	143608968	C	0.39	0.024 (0.006)	2.20E-04	0.023 (0.006)	2.80E-04	0.019 (0.006)	4.00E-03
rs13225723	*PIK3CG*	Franceschini *et al.*	7	106416467	G	0.89	-0.046 (0.011)	8.50E-06	-0.041 (0.011)	8.10E-05	-0.034 (0.011)	1.30E-03
rs11196033	*VTI1A*	Franceschini *et al.*	10	114410998	C	0.50	0.002 (0.006)	6.60E-01	0.001 (0.006)	8.70E-01	-0.002 (0.006)	8.00E-01
rs11025608	*PRMT3, SLC6A5*	Strawbridge *et al.*	11	20554790	G	0.45	-0.022 (0.006)	5.30E-04	-0.023 (0.006)	3.00E-04	-0.023 (0.006)	3.00E-04

Four of five loci was reported in a meta-analysis by Franceschini *et al.*[12], one of which was not found in current results; the additional locus not replicated was reported in Strawbridge *et al.*[13] using a subset of current sample. Chr: Chromosome; EA: Effective allele; EAF: Effective allele frequency.

Table S5. Lead variants in loci associated with $cIMT_{min}$

SNP	Chr	Position	EA	NEA	EAF	Beta	SE	*P*	Region	Closest gene
rs222476	2	42659267	T	C	0.03	0.095	0.017	1.60E-08	p21	*COX7A2L,KCNG3*
rs6744377	2	102069748	T	A	0.184	0.046	0.008	6.50E-09	q11.2	*RFX8*
2:216300905_ACCCG_A	2	216300905	ACCCG	A	0.463	-0.039	0.006	2.20E-09	q35	*FN1*
rs1553085	3	21976118	A	G	0.33	0.038	0.006	2.60E-09	p24.3	*ZNF385D*
rs6795735	3	64705365	C	T	0.582	0.039	0.006	9.90E-11	p14.1	*ADAMTS9*
rs10305838	4	148400256	T	C	0.855	-0.051	0.009	2.10E-10	q31.22	*EDNRA*
rs188848834	4	174681501	C	T	0.748	-0.04	0.007	3.30E-09	q34.1	*HAND2*
rs224805	5	81683739	A	G	0.051	0.096	0.014	4.70E-12	q14.2	*ATP6AP1L*
rs310503	5	82891552	G	T	0.661	-0.035	0.006	1.60E-08	q14.2	*VCAN*
rs11242713	6	1668142	G	A	0.53	-0.037	0.006	5.70E-09	p25.3	*GMDS*
rs342988	7	35467026	C	T	0.278	0.046	0.007	3.20E-12	p14.2	*TBX20*
rs2912062	8	6485295	C	G	0.704	0.056	0.007	1.30E-17	p23.1	*MCPH1*
rs2980478	8	8088230	T	C	0.527	-0.042	0.006	2.70E-12	p23.1	*ZNF705B*
rs10096511	8	10810451	A	G	0.472	0.046	0.006	9.30E-15	p23.1	*XKR6*
rs4739742	8	81308435	T	C	0.558	0.035	0.006	3.80E-09	q21.13	*ZBTB10*
8:123413770_GA_G	8	123413770	GA	G	0.545	0.036	0.006	2.60E-09	q24.13	*ZHX2*
rs6470156	8	124579985	G	A	0.721	-0.056	0.007	2.80E-17	q24.13	*FBXO32*
rs10817556	9	116775859	C	T	0.661	-0.037	0.006	2.80E-09	q32	*ZNF618*
rs914279	10	30170487	T	G	0.416	0.039	0.006	4.10E-10	p11.23	*JCAD*
rs2019090	11	103668962	A	T	0.294	0.041	0.007	1.10E-09	q22.3	*PDGFD*
rs11172113	12	57527283	T	C	0.59	-0.042	0.006	4.90E-12	q13.3	*STAT6,LRP1*
rs9515203	13	111049623	T	C	0.741	-0.059	0.007	2.90E-18	q34	*COL4A2*
rs2455925	15	48893649	T	C	0.906	0.066	0.01	6.80E-11	q21.1	*FBN1*
rs35633915	16	75408954	T	TA	0.411	-0.044	0.006	8.20E-13	q23.1	*CFDP1*
rs488327	16	88989005	T	C	0.662	0.05	0.006	5.00E-16	q24.3	*CBFA2T3*
rs12051555	17	12447601	A	C	0.917	-0.083	0.011	1.10E-14	p12	*MYOCD*
rs112009052	19	41099501	T	A	0.986	-0.188	0.026	1.30E-12	q13.2	*SHKBP1,LTBP4*
rs1065853	19	45413233	G	T	0.921	0.119	0.011	4.40E-27	q13.32	*TOMM40,APOE,APOC1*
rs6120880	20	33829406	C	G	0.568	-0.038	0.006	5.70E-10	q11.22	*EDEM2,MMP24*
rs5757983	22	40920236	C	G	0.468	-0.033	0.006	2.00E-08	q13.2	*MRTFA*

Chr: Chromosome; EA: Effective allele; NEA: Non-effective allele; EAF: Effective allele frequency.

Table S6. Lead variants in loci associated with $cIMT_{mean}$

SNP	Chr	Position	EA	NEA	EAF	Beta	SE	*P*	Region	Closest gene
2:216300905_ACCCG_A	2	216300905	ACCCG	A	0.463	-0.036	0.006	3.30E-09	q35	*FN1*
rs1553085	3	21976118	A	G	0.33	0.038	0.006	6.00E-10	p24.3	*ZNF385D*
rs6795735	3	64705365	C	T	0.582	0.039	0.006	4.20E-11	p14.1	*ADAMTS9*
rs10305838	4	148400256	T	C	0.855	-0.052	0.008	7.90E-11	q31.22	*EDNRA*
rs4235201	4	174677572	G	T	0.759	-0.04	0.007	2.40E-09	q34.1	*HAND2*
rs224805	5	81683739	A	G	0.051	0.091	0.013	6.30E-12	q14.2	*ATP6AP1L*
rs310503	5	82891552	G	T	0.661	-0.038	0.006	3.80E-10	q14.2	*VCAN*
rs72801051	5	142685670	A	T	0.84	-0.046	0.008	3.90E-08	q31.3	*NR3C1*
rs11242713	6	1668142	G	A	0.53	-0.036	0.006	2.20E-09	p25.3	*GMDS*
rs342988	7	35467026	C	T	0.278	0.052	0.007	1.70E-15	p14.2	*TBX20*
rs3020263	8	6487449	G	A	0.718	0.055	0.007	8.10E-18	p23.1	*MCPH1*
rs2980478	8	8088230	T	C	0.527	-0.041	0.006	4.10E-12	p23.1	*ZNF705B*
rs4314618	8	10816772	A	G	0.471	0.045	0.006	1.10E-14	p23.1	*XKR6*
rs9632837	8	81318125	C	G	0.578	0.033	0.006	3.10E-08	q21.13	*ZBTB10*
rs10110725	8	123415086	T	A	0.543	0.037	0.006	6.10E-10	q24.13	*ZHX2*
rs6470156	8	124579985	G	A	0.721	-0.056	0.007	2.90E-17	q24.13	*FBXO32*
rs914279	10	30170487	T	G	0.416	0.038	0.006	2.10E-10	p11.23	*JCAD*
rs796784254	11	103669291	T	TTATTGAA	0.295	0.046	0.006	3.00E-12	q22.3	*PDGFD*
rs11172113	12	57527283	T	C	0.59	-0.038	0.006	2.60E-10	q13.3	*STAT6,LRP1*
rs9515203	13	111049623	T	C	0.741	-0.059	0.007	1.50E-18	q34	*COL4A2*
15:48737340_CACATATATATAT_C	15	48737340	CACATATATAT	C	0.908	0.063	0.01	1.50E-10	q21.1	*FBN1*
rs4774437	15	62834113	A	G	0.543	-0.034	0.006	3.00E-09	q22.2	*TLN2*
rs1808435	16	75425819	T	C	0.411	-0.044	0.006	1.30E-13	q23.1	*CFDP1*
rs7500448	16	83045790	A	G	0.75	0.038	0.007	1.60E-08	q23.3	*CDH13*
rs488327	16	88989005	T	C	0.662	0.049	0.006	1.00E-15	q24.3	*CBFA2T3*
rs12051555	17	12447601	A	C	0.917	-0.083	0.011	5.70E-15	p12	*MYOCD*
rs112009052	19	41099501	T	A	0.986	-0.183	0.026	3.20E-12	q13.2	*SHKBP1,LTBP4*
rs1065853	19	45413233	G	T	0.921	0.126	0.011	4.70E-31	q13.32	*TOMM40,APOE, APOC1*

SNP	Chr	Position	EA	NEA	EAF	Beta	SE	*P*	Region	Closest gene
rs6120880	20	33829406	C	G	0.568	-0.035	0.006	4.30E-09	q11.22	*EDEM2,MMP24*
rs5757983	22	40920236	C	G	0.468	-0.035	0.006	1.10E-09	q13.2	*MRTFA*

Chr: Chromosome; EA: Effective allele; NEA: Non-effective allele; EAF: Effective allele frequency.

Table S7. Lead variants in loci associated with $cIMT_{max}$

SNP	Chr	Position	EA	NEA	EAF	Beta	SE	*P*	Region	Closest gene
rs7628630	3	21977337	G	A	0.329	0.034	0.006	4.20E-08	p24.3	*ZNF385D*
rs4611812	3	64699445	C	T	0.584	0.035	0.006	3.70E-09	p14.1	*ADAMTS9*
rs10305838	4	148400256	T	C	0.855	-0.046	0.008	5.50E-09	q31.22	*EDNRA*
rs4235201	4	174677572	G	T	0.759	-0.039	0.007	1.60E-08	q34.1	*HAND2*
rs224805	5	81683739	A	G	0.051	0.079	0.013	2.20E-09	q14.2	*ATP6AP1L*
rs310503	5	82891552	G	T	0.661	-0.037	0.006	2.10E-09	q14.2	*VCAN*
rs342988	7	35467026	C	T	0.278	0.054	0.007	2.10E-16	p14.2	*TBX20*
rs3020263	8	6487449	G	A	0.718	0.049	0.007	9.30E-14	p23.1	*MCPH1*
rs2980478	8	8088230	T	C	0.527	-0.039	0.006	1.10E-10	p23.1	*ZNF705B*
rs11250097	8	10811829	T	C	0.467	0.041	0.006	2.00E-12	p23.1	*XKR6*
rs10110725	8	123415086	T	A	0.543	0.034	0.006	1.30E-08	q24.13	*ZHX2*
rs6470156	8	124579985	G	A	0.721	-0.05	0.007	3.80E-14	q24.13	*FBXO32*
rs11371318	10	28230429	G	GAA	0.509	-0.033	0.006	1.20E-08	p12.1	*ARMC4*
rs2150562	10	30162423	A	G	0.311	0.037	0.006	7.40E-09	p11.23	*SVIL*
rs796784254	11	103669291	T	TTATTGAA	0.295	0.046	0.007	3.10E-12	q22.3	*PDGFD*
rs61930625	12	86167409	C	T	0.755	-0.038	0.007	2.80E-08	q21.31	*RASSF9*
rs9515203	13	111049623	T	C	0.741	-0.056	0.007	9.70E-17	q34	*COL4A2*
rs7176966	15	62817568	A	G	0.536	-0.033	0.006	1.30E-08	q22.2	*TLN2*
rs1808435	16	75425819	T	C	0.411	-0.04	0.006	2.30E-11	q23.1	*CFDP1*
rs488327	16	88989005	T	C	0.662	0.047	0.006	5.40E-14	q24.3	*CBFA2T3*
rs740854	17	12449192	A	G	0.915	-0.074	0.011	2.40E-12	p12	*MYOCD*
rs111689747	19	41333152	G	A	0.988	-0.189	0.028	2.10E-11	q13.2	*CYP2A6*
rs1065853	19	45413233	G	T	0.921	0.13	0.011	7.60E-32	q13.32	*TOMM40,APOE,APOC1*
rs369739453	20	32968411	CT	C	0.563	0.038	0.007	5.60E-09	q11.22	*ITCH*
rs5757983	22	40920236	C	G	0.468	-0.033	0.006	1.60E-08	q13.2	*MRTFA*

Chr: Chromosome; EA: Effective allele; NEA: Non-effective allele; EAF: Effective allele frequency.

Table S8. Variants identified by FINEMAP associated with $cIMT_{mean}$

#	Sentinel SNP	Chr	Position	Gene closest to sentinel SNP	Variants identified by FINEMAP	Gene closest to variants identified by FINEMAP	Coding variants (gene)
1	rs222476	2	42659267	*COX7A2L, KCNG3*	rs6736913	*EML4*	NP_061936.3: p.Lys283Gln/Glu/Ter (*EML4*)
2	rs6744377	2	102069748	*RFX8*	2:102054690_AT_A	*RFX8*	XP_011510074.1:p.Tyr65Cys/Phe/Ser (*RFX8*)
					rs6543078	*RFX8*	
3	2:216300905_ACCCG_A	2	216300905	*FN1*	2:216300905_ACCCG_A	*FN1*	
4	rs1553085	3	21976118	*ZNF385D*	rs1553085	*ZNF385D*	
5	rs6795735	3	64705365	*ADAMTS9*	rs67311847	*ADAMTS9*	
					rs71300731	*ADAMTS9*	
6	rs10305838	4	148400256	*EDNRA*	rs10305838	*EDNRA*	
7	rs4235201	4	174677572	*HAND2*	rs4235201	*HAND2*	
8	rs224805	5	81683739	*ATP6AP1L*	rs226208	*ATP6AP1L*	
					rs224805	*ATP6AP1L*	
					rs7702764	*ATP6AP1L*	
9	rs310503	5	82891552	*VCAN*	rs310503	*VCAN*	
					rs1563553	*HAPLN1*	
10	rs72801051	5	142685670	*NR3C1*	rs258811	*ARHGAP26*	
					rs72801051	*NR3C1*	NP_001018084.1:p.Asn766Lys (*NR3C1*)
11	rs11242713	6	1668142	*GMDS*	rs11242713	*GMDS*	
					rs9392347	*GMDS*	
12	rs342988	7	35467026	*TBX20*	rs342988	*TBX20*	
13	rs3020263	8	6487449	*MCPH1*	rs3020263	*MCPH1*	
14	rs2980478	8	8088230	*ZNF705B*	rs2980478	*ZNF705B*	
15	rs4314618	8	10816772	*XKR6*	rs4314618	*XKR6*	
16	rs9632837	8	81318125	*ZBTB10*	rs9632837	*ZBTB10*	
17	rs10110725	8	123415086	*ZHX2*	8:123413770_GA_G	*ZHX2*	
18	rs6470156	8	124579985	*FBXO32*	rs6470156	*FBXO32*	

#	SNP	Chr	Position	Gene closest to sentinel SNP	Variants identified by FINEMAP	Gene closest to variants identified by FINEMAP	Coding variants (gene)
19	rs10817556	9	116775859	*ZNF618*	rs10982031	*ZNF618*	NP_001304969.1:p.Tyr115Ter (*ZNF618*), NP_001304969.1:p.Cys299Ter/Trp (*ZNF618*)
20	rs11371318	10	28230429	*ARMC4*	rs11371318	*ARMC4*	NP_060546.2:p.Asn686Lys (*ARMC4*)
21	rs914279	10	30170487	*JCAD*	rs914279	*JCAD*	NP_065899.1:p.His668Gln (*JCAD*)
					rs9337951	*JCAD*	
22	rs796784254	11	103669291	*PDGFD*	rs796784254	*PDGFD*	
					rs36179007	*PDGFD*	
23	rs11172113	12	57527283	*STAT6, LRP1*	rs11172113	*LRP1*	NP_005529.1:p.Arg322Gln/Pro/Leu (*INHBC*)
					rs7484541	*R3HDM2*	
24	rs61930625	12	86167409	*RASSF9*	rs17345028	*RASSF9*	
25	rs9515203	13	111049623	*COL4A2*	rs12429386	*COL4A1*	
					rs9515203	*COL4A2*	
26	15:48737340_CACATATATATAT_C	15	48737340	*FBN1*	rs1678982	*FBN1*	
27	rs4774437	15	62834113	*TLN2*	rs12441323	*TLN2*	
28	rs1808435	16	75425819	*CFDP1*	rs4888367	*BCAR1*	
					rs35633915	*CFDP1*	
29	rs7500448	16	83045790	*CDH13*	rs7500448	*CDH13*	
					rs8059012	*CDH13*	
30	rs488327	16	88989005	*CBFA2T3*	rs488327	*CBFA2T3*	
31	rs12051555	17	12447601	*MYOCD*	rs4442861	*MAP2K4*	
					rs12051555	*MYOCD*	
					rs35712872	*MYOCD*	
					rs12150137	*MYOCD*	
32	rs112009052	19	41099501	*SHKBP1, LTBP4*	rs112009052	*LTBP4*	

#	SNP	Chr	Position	Gene closest to sentinel SNP	Variants identified by FINEMAP	Gene closest to variants identified by FINEMAP	Coding variants (gene)
33	rs1065853	19	45413233	*TOMM40, APOE, APOC1*	rs1065853	*APOE*	NP_001289617.1:p.Arg202 Cys/Gly/Ser (*APOE*)
					rs56131196	*APOC1*	
34	rs6120880	20	33829406	*EDEM2, MMP24*	rs6120880	*MMP24*	
35	rs5757983	22	40920236	*MRTFA*	rs5757983	*MRTFA*	

Chr: Chromosome; #: Locus number. Coding variants (gene): coding variants that are in high LD (r^2>0.8) with the variant identified by FINEMAP.

Table S9. cIMT loci with sex difference

Chr	SNP	EAF_{female}	EAF_{male}	INFO	$Beta_{female}$	SE_{female}	P_{female}	$Beta_{male}$	SE_{male}	P_{male}	T_{int}	$P_{sexdiff}$	Gene
							$cIMT_{min}$						
8	rs1834451	0.61	0.62	0.99	0.020	0.008	0.0096	0.069	0.010	**7.3E-13**	-3.98	**6.81E-05**	*MCPH1*
							$cIMT_{mean}$						
8	rs12543564	0.67	0.67	0.97	0.020	0.008	0.0084	0.066	0.010	**2E-11**	-3.67	**2.44E-04**	*MCPH1*
8	rs71217283	0.58	0.59	0.91	-0.016	0.008	0.061	-0.058	0.010	**2.2E-09**	3.42	**6.36E-04**	*ZNF705B*
8	rs10100333	0.39	0.39	0.98	0.009	0.008	0.22	0.053	0.009	**1.5E-08**	-3.69	**2.23E-04**	*SOX7*
8	rs745379	0.50	0.49	1.00	0.008	0.008	0.33	0.053	0.009	**7.8E-09**	-3.87	**1.09E-04**	*GATA4,C8orf49*
14	rs1187729	0.58	0.59	1.00	-0.007	0.008	0.33	0.051	0.009	**3.3E-08**	-4.93	**8.35E-07**	*SYNE3*
							$cIMT_{max}$						
5	rs7447467	0.51	0.51	0.99	-0.043	0.008	**3.5E-08**	-0.005	0.009	0.62	-3.27	**1.08E-03**	*HAPLN1*
8	rs71217283	0.58	0.59	0.91	-0.013	0.008	0.1	-0.058	0.010	**1.9E-09**	3.59	**3.35E-04**	*ZNF705B*
8	rs7005905	0.38	0.38	0.98	0.008	0.008	0.29	0.051	0.009	**4.5E-08**	-3.52	**4.30E-04**	*SOX7*
8	rs745379	0.50	0.49	1.00	0.008	0.008	0.31	0.051	0.009	**2.6E-08**	-3.64	**2.71E-04**	*GATA4,C8orf49*
17	rs80019927	0.75	0.75	0.95	-0.052	0.009	**1.7E-08**	-0.003	0.011	0.81	-3.54	**3.96E-04**	*MAP2K4*

Chr: Chromosome; EA: Effective allele; NEA: Non-effective allele; EAF: Effective allele frequency; Tint: t test statistics of the interaction analysis; $P_{sexdiff}$: *P* for sex interaction test.

Table S10. Cross-tissue TWAS associations at $P < 3.33\times10^{-6}$

		$cIMT_{min}$		$cIMT_{mean}$		$cIMT_{max}$	
Gene	**Chr**	**Test score**	***P***	**Test score**	***P***	**Test score**	***P***
ASAP2	2	13.66	**8.32E-07**	8.96	1.01E-04	5.00	6.52E-03
SH3RF3	2	6.37	1.20E-03	12.21	**2.54E-06**	11.00	9.03E-06
XRCC4	5	13.27	**1.38E-06**	14.74	**3.08E-07**	14.45	**4.12E-07**
MFHAS1	8	21.24	**3.11E-10**	20.75	**5.03E-10**	17.20	**1.73E-08**
ERI1	8	25.31	**4.44E-12**	23.25	**2.43E-11**	19.47	**8.06E-10**
PPP1R3B	8	21.37	**3.98E-10**	20.34	**1.18E-09**	16.11	**9.26E-08**
TNKS	8	17.13	**2.12E-08**	17.32	**1.74E-08**	14.99	**2.06E-07**
MSRA	8	19.04	**2.30E-09**	17.46	**1.06E-08**	14.17	**3.22E-07**
SOX7	8	156.95	**8.40E-11**	29.85	**1.13E-13**	23.04	**1.03E-10**
PINX1	8	359.34	**1.81E-11**	361.45	**1.81E-11**	311.12	**1.81E-11**
XKR6	8	223.65	**2.18E-11**	215.65	**2.18E-11**	186.46	**2.19E-11**
MTMR9	8	28.41	**7.19E-13**	28.97	**4.35E-13**	23.63	**5.72E-11**
SLC35G5	8	392.60	**1.78E-11**	384.30	**1.78E-11**	25.69	**4.26E-12**
C8orf12	8	17.10	**1.67E-08**	17.29	**1.38E-08**	15.03	**1.37E-07**
FAM167A	8	26.74	**5.60E-12**	27.95	**2.09E-12**	22.84	**1.47E-10**
BLK	8	84.07	**1.10E-11**	85.90	**1.09E-11**	29.99	**4.11E-14**
GATA4	8	18.11	**1.43E-08**	16.49	**7.45E-08**	14.31	**6.82E-07**
C8orf49	8	12.50	**1.79E-06**	13.39	**7.27E-07**	11.30	5.99E-06
NEIL2	8	16.59	**1.24E-08**	16.42	**1.49E-08**	13.11	**5.22E-07**
DEFB134	8	26.70	**1.31E-12**	28.99	**1.37E-13**	25.48	**4.33E-12**
FAM86B1	8	17.25	**8.50E-09**	18.08	**3.76E-09**	15.45	**5.28E-08**
FAM86B2	8	24.66	**1.26E-11**	29.00	**3.79E-13**	22.91	**5.50E-11**
GTF2E2	8	13.31	**1.45E-06**	12.21	4.66E-06	8.91	1.57E-04
SFRP5	10	13.16	**2.02E-06**	9.96	5.07E-05	8.84	1.60E-04
ARHGAP42	11	12.70	**1.11E-06**	15.46	**6.03E-08**	11.62	3.58E-06
TMEM133	11	10.05	1.73E-05	13.46	**4.58E-07**	10.73	8.61E-06
PDGFD	11	16.96	**2.49E-08**	24.11	**1.82E-11**	26.84	**1.09E-12**
COQ10A	12	21.33	**5.40E-10**	23.17	**8.83E-11**	18.64	**7.46E-09**
LRP1	12	30.64	**5.44E-14**	22.97	**7.32E-11**	12.39	3.12E-06
TLN2	15	13.02	**1.41E-06**	16.52	**4.02E-08**	13.41	**9.47E-07**
RFWD3	16	11.68	**2.84E-06**	10.03	1.57E-05	8.05	1.18E-04
LDHD	16	20.17	**1.92E-09**	19.30	**4.44E-09**	13.02	**1.97E-06**
BCAR1	16	28.98	**6.60E-13**	308.52	**3.04E-11**	22.41	**1.34E-10**
CFDP1	16	23.10	**2.49E-11**	421.76	**2.12E-11**	19.78	**4.99E-10**
TMEM170A	16	256.66	**1.05E-11**	274.30	**1.05E-11**	23.49	**3.37E-11**
CDH13	16	22.01	**2.04E-10**	26.97	**1.38E-12**	22.75	**9.67E-11**
MVD	16	19.01	**3.87E-09**	20.39	**9.40E-10**	15.77	**1.04E-07**
CBFA2T3	16	28.63	**1.04E-13**	27.85	**2.27E-13**	25.68	**2.06E-12**
KANK2	19	9.71	3.42E-05	12.39	**2.28E-06**	13.14	**1.08E-06**
PVRL2	19	10.76	1.43E-05	14.97	**2.04E-07**	16.36	**5.07E-08**
ZNF296	19	11.66	8.52E-06	16.71	**6.78E-08**	15.46	**2.22E-07**
DMPK	19	9.54	2.29E-05	12.25	**1.44E-06**	10.55	8.23E-06
DMWD	19	7.85	1.90E-04	11.92	**2.71E-06**	10.16	1.76E-05

		$cIMT_{min}$		$cIMT_{mean}$		$cIMT_{max}$	
Gene	**Chr**	**Test score**	***P***	**Test score**	***P***	**Test score**	***P***
ZNF341	20	11.33	7.34E-06	12.32	**2.54E-06**	11.08	9.55E-06
ITCH	20	12.46	3.82E-06	13.77	**9.56E-07**	13.47	**1.32E-06**
MMP24	20	14.07	**4.79E-07**	15.88	**7.72E-08**	13.80	**6.27E-07**
FAM83C	20	15.49	**2.21E-08**	13.73	**1.46E-07**	12.36	**6.14E-07**
GDF5OS	20	12.54	3.67E-06	12.36	4.42E-06	13.11	**2.09E-06**
GDF5	20	14.54	**3.58E-07**	13.76	**8.32E-07**	13.00	**1.87E-06**
RBM12	20	171.47	**6.53E-11**	184.61	**2.97E-11**	23.61	**3.19E-11**
NFS1	20	19.12	**2.37E-09**	20.02	**9.11E-10**	19.12	**2.36E-09**
ST13	22	12.90	**1.57E-06**	15.68	**7.83E-08**	13.22	**1.12E-06**
EP300	22	11.67	4.22E-06	14.83	**1.33E-07**	11.95	3.11E-06

The test statistics of 44 tissues was combined using the Generalized Berk-Jones test to derive the test score. Chr: Chromosome.

Table S11. Result of single-tissue TWAS in arterial tissues for $cIMT_{mean}$

Gene	Chromosome	$P_{artery\ aorta}$	$P_{artery\ coronary}$	$P_{artery\ tibial}$
MRAS	3	1.7E-05	1.0E-05	**1.8E-06**
FER	5	**2.3E-06**	1.3E-05	4.1E-05
ERI1	8	**2.7E-08**	**3.4E-08**	**1.2E-10**
FAM167A	8	**2.0E-06**	NA	NA
FAM86B1	8	1.9E-05	**1.6E-07**	1.5E-02
FAM86B2	8	2.0E-04	**3.7E-08**	**3.2E-06**
MSRA	8	**4.1E-06**	**1.1E-08**	**6.0E-07**
NEIL2	8	1.4E-05	4.3E-04	**8.4E-08**
PINX1	8	1.9E-01	NA	**3.5E-12**
PPP1R3B	8	NA	NA	**9.0E-07**
SLC35G5	8	**1.7E-11**	**5.0E-08**	**1.1E-09**
SOX7	8	2.1E-05	1.5E-03	**1.4E-09**
SVIL	10	**1.2E-06**	9.8E-02	6.8E-05
ARHGAP42	11	**1.4E-07**	**3.7E-07**	**1.0E-07**
TMEM133	11	**7.8E-08**	**8.1E-08**	**6.4E-08**
LRP1	12	**7.1E-09**	**1.1E-08**	**1.6E-10**
TLN2	15	**3.5E-08**	2.5E-05	**1.6E-06**
BCAR1	16	**1.2E-12**	1.0E-05	**3.1E-12**
CBFA2T3	16	**1.1E-08**	1.8E-05	6.7E-01
CDH13	16	**8.1E-12**	**1.7E-07**	**2.3E-12**
CFDP1	16	4.1E-01	**6.1E-12**	**3.4E-06**
NDRG4	16	**2.4E-06**	NA	**2.4E-06**
ZNF469	16	8.5E-01	6.7E-01	**3.1E-06**
APOE	19	6.3E-01	**1.9E-07**	1.7E-04
DMPK	19	**1.1E-06**	**9.7E-07**	**9.4E-07**
DMWD	19	**3.1E-06**	**2.4E-06**	**1.9E-06**
RBM12	20	1.6E-01	**1.4E-09**	6.1E-03
ARVCF	22	**1.3E-06**	7.6E-06	1.4E-05
EP300	22	NA	**5.6E-07**	8.7E-06
ST13	22	NA	**1.6E-08**	2.3E-01

Marked in bold: significant associations passing respective Bonferroni corrected thresholds.

Table S12. Genes associated with cIMT via SMR analysis of the cIMTmean GWAS summary statistics and the eQTL summary statistics from GTEx.

Probe ID	Chr	Gene	Top SNP	A1	A2	Freq	P_{GWAS}	P_{eQTL}	P_{SMR}	P_{HEIDI}
Artery Aorta										
ENSG00000253893.2	8	*FAM85B*	rs2945886	G	C	0.44094	1.50E-08	1.17E-14	6.82E-06	6.18E-02
ENSG00000197321.10	10	*SVIL*	rs10826719	A	G	0.58167	9.40E-10	2.56E-12	4.32E-06	4.41E-01
ENSG00000165895.13	11	*ARHGAP42*	rs604723	C	T	0.71758	1.10E-07	7.32E-21	3.22E-06	1.56E-01
ENSG00000170647.2	11	*TMEM133*	rs604723	C	T	0.71758	1.10E-07	4.25E-16	7.51E-06	2.08E-02
ENSG00000171914.10	15	*TLN2*	rs956006	T	C	0.33367	1.10E-08	8.39E-19	2.49E-06	4.61E-01
ENSG00000050820.12	16	*BCAR1*	rs4887824	C	T	0.58773	3.70E-13	3.00E-15	9.89E-08	6.98E-01
ENSG00000140945.11	16	*CDH13*	rs7500448	G	A	0.25238	1.60E-08	1.10E-14	5.77E-06	7.66E-01
Artery Coronary										
ENSG00000255310.2	8	*AF131215.2*	rs6996846	G	C	0.53497	6.40E-11	1.09E-09	1.10E-05	1.74E-01
ENSG00000170647.2	11	*TMEM133*	rs633185	C	G	0.71003	9.10E-08	1.58E-11	2.38E-05	9.10E-01
Artery Tibial										
ENSG00000253893.2	8	*FAM85B*	rs2955581	C	G	0.45954	1.00E-10	2.00E-20	1.37E-07	1.67E-01
ENSG00000255310.2	8	*AF131215.2*	rs2061830	G	C	0.48864	9.70E-12	8.48E-11	3.16E-06	6.16E-01
ENSG00000079459.8	8	*FDFT1*	rs1736057	A	G	0.57633	4.30E-09	1.44E-37	1.76E-07	1.97E-01
ENSG00000197321.10	10	*SVIL*	rs1571759	C	T	0.58211	7.40E-10	1.43E-19	3.80E-07	3.21E-01
ENSG00000165895.13	11	*ARHGAP42*	rs604723	C	T	0.71758	1.10E-07	1.82E-30	1.17E-06	6.21E-01
ENSG00000170647.2	11	*TMEM133*	rs604723	C	T	0.71758	1.10E-07	2.06E-34	8.91E-07	7.35E-01
ENSG00000123384.9	12	*LRP1*	rs11172113	C	T	0.40633	2.60E-10	1.92E-17	3.43E-07	1.91E-01
ENSG00000050820.12	16	*BCAR1*	rs3784935	G	T	0.59185	1.10E-11	2.06E-23	2.14E-08	1.80E-01

Chr: probe chromosome, A1: effect allele of the top SNP, A2: other allele; Freq: frequency of the A1 of the top SNP, P_{GWAS}: p-value from GWAS, P_{eQTL} : p-value from eQTL study, P_{SMR} :p-value from SMR analysis and P_{HEIDI} : p-value from HEIDI test. A total of 4705, 1975 and 6305 genes were tested in artery aorta, artery coronary and artery tibial tissues respectively. The corresponding significance levels (P_{SMR}) after correcting for multiple testing for SMR analyses were 1.06×10^{-5}, 2.53×10^{-5} and 7.93×10^{-6} respectively. The significance level for rejecting HEIDI test (P_{HEIDI})were 0.05/8=0.00625, 0.05/3=0.0167 and 0.05/9=0.00556 respectively; One gene RP11-252K23.2 on chromosome 16 was filtered out in all three tissues based on HEIDI test.

Table S13. Associations in MAGMA gene-based analysis.

Gene identifier	Gene symbol	Chr	$cIMT_{min}$	$cIMT_{mean}$	$cIMT_{max}$
ENSG00000152518	*ZFP36L2*	2	1.06E-05	**1.91E-06**	4.85E-06
ENSG00000196460	*RFX8*	2	**1.74E-08**	**1.89E-08**	**1.19E-06**
ENSG00000151617	*EDNRA*	4	**2.88E-07**	**5.12E-08**	**1.44E-06**
ENSG00000152348	*ATG10*	5	**8.18E-07**	**2.31E-06**	3.74E-05
ENSG00000186468	*RPS23*	5	**2.26E-07**	**5.56E-07**	9.96E-06
ENSG00000205464	*ATP6AP1L*	5	**2.10E-11**	**2.35E-11**	**4.27E-09**
ENSG00000113580	*NR3C1*	5	3.37E-05	**2.38E-06**	1.84E-05
ENSG00000164463	*CREBRF*	5	**1.89E-06**	**7.82E-08**	**2.78E-07**
ENSG00000113734	*BNIP1*	5	**1.65E-06**	**8.21E-08**	**5.56E-07**
ENSG00000112699	*GMDS*	6	2.74E-06	**1.08E-07**	**6.97E-07**
ENSG00000182611	*HIST1H2AJ*	6	1.07E-05	**2.38E-06**	5.22E-05
ENSG00000184357	*HIST1H1B*	6	7.18E-06	**1.42E-06**	7.15E-05
ENSG00000147316	*MCPH1*	8	**4.56E-10**	**1.33E-07**	**4.03E-08**
ENSG00000147324	*MFHAS1*	8	**1.28E-14**	**5.72E-14**	**4.26E-12**
ENSG00000104626	*ERI1*	8	**1.71E-10**	**3.71E-10**	**1.01E-08**
ENSG00000173281	*PPP1R3B*	8	**7.00E-08**	**4.78E-07**	3.44E-05
ENSG00000173273	*TNKS*	8	**8.89E-07**	**2.38E-06**	2.08E-05
ENSG00000175806	*MSRA*	8	**1.25E-11**	**1.05E-11**	**2.79E-10**
ENSG00000183638	*RP1L1*	8	**8.68E-11**	**3.93E-11**	**1.25E-09**
ENSG00000171056	*SOX7*	8	**7.60E-09**	**1.89E-08**	**4.54E-07**
ENSG00000258724	*SOX7*	8	**5.30E-08**	**1.16E-07**	**1.90E-06**
ENSG00000254093	*PINX1*	8	**3.42E-08**	**8.71E-08**	**1.57E-06**
ENSG00000171044	*XKR6*	8	**3.09E-16**	**6.39E-16**	**2.30E-13**
ENSG00000215346	*AF131215.5*	8	**1.28E-10**	**3.24E-10**	**8.28E-09**
ENSG00000104643	*MTMR9*	8	**6.46E-10**	**2.22E-10**	**3.11E-09**
ENSG00000177710	*SLC35G5*	8	**4.60E-07**	**3.01E-07**	**2.51E-06**
ENSG00000184608	*C8orf12*	8	**5.24E-11**	**4.55E-11**	**5.00E-10**
ENSG00000154319	*FAM167A*	8	**3.78E-09**	**4.24E-09**	**5.48E-08**
ENSG00000136573	*BLK*	8	**8.20E-12**	**6.43E-12**	**8.71E-11**
ENSG00000136574	*GATA4*	8	**2.89E-11**	**8.39E-11**	**2.49E-09**
ENSG00000255046	*RP11-297N6.4*	8	**1.62E-06**	**1.94E-06**	3.44E-05
ENSG00000205882	*DEFB134*	8	**3.79E-07**	**9.71E-07**	1.82E-05
ENSG00000255098	*RP11-481A20.11*	8	**2.55E-06**	**2.57E-06**	1.13E-05
ENSG00000157657	*ZNF618*	9	**1.06E-06**	4.74E-05	1.37E-03
ENSG00000169126	*ARMC4*	10	7.85E-05	**1.44E-06**	**1.45E-07**
ENSG00000135517	*MIP*	12	**5.15E-07**	**6.54E-07**	6.46E-06
ENSG00000176422	*SPRYD4*	12	3.43E-06	**2.06E-06**	1.91E-05
ENSG00000135423	*GLS2*	12	**2.30E-06**	**9.08E-07**	**2.41E-06**
ENSG00000198774	*RASSF9*	12	6.06E-06	**1.26E-07**	**1.36E-07**
ENSG00000134871	*COL4A2*	13	**1.74E-07**	**4.11E-07**	2.88E-06
ENSG00000171914	*TLN2*	15	3.74E-05	**1.73E-06**	4.42E-06
ENSG00000166949	*SMAD3*	15	**2.32E-06**	9.25E-06	3.88E-04
ENSG00000129038	*LOXL1*	15	**1.06E-06**	**1.66E-06**	**1.65E-06**
ENSG00000125107	*CNOT1*	16	4.74E-06	**5.14E-07**	**1.75E-06**
ENSG00000153774	*CFDP1*	16	**3.58E-12**	**2.37E-12**	**1.45E-10**
ENSG00000261717	*RP11-77K12.1*	16	**2.65E-11**	**7.80E-12**	**6.22E-10**
ENSG00000166822	*TMEM170A*	16	**4.40E-10**	**1.05E-10**	**5.80E-09**
ENSG00000183196	*CHST6*	16	1.02E-05	**1.38E-06**	7.63E-06
ENSG00000103335	*PIEZO1*	16	**3.66E-07**	**1.69E-06**	8.11E-06
ENSG00000129993	*CBFA2T3*	16	**3.53E-12**	**1.44E-11**	**2.37E-10**
ENSG00000205018	*RP11-830F9.6*	16	**1.46E-13**	**5.17E-13**	**4.44E-12**

Gene identifier	Gene symbol	Chr	$cIMT_{min}$	$cIMT_{mean}$	$cIMT_{max}$
ENSG00000130203	*APOE*	19	**3.33E-16**	**7.55E-11**	**2.22E-16**
ENSG00000130208	*APOC1*	19	**4.96E-07**	**1.40E-07**	**6.87E-08**
ENSG00000078804	*TP53INP2*	20	**1.10E-06**	**1.74E-06**	9.36E-06
ENSG00000088298	*EDEM2*	20	**3.37E-07**	**1.50E-06**	1.16E-05
ENSG00000124126	*PREX1*	20	1.78E-05	**4.13E-07**	**1.85E-06**

Chr: Chromosome. Marked in bold: significant association with $P<2.63\times10^{-6}$.

Table S14. Top ten genes prioritized by DEPICT to be associated with cIMT

Locus	Nr of genes in locus	Chromosome and position	Ensembl Gene ID	Gene symbol	Nominal P value	Gene closest to lead SNP	Gene bio-type	Top cis eQTL SNP (Westra et al. Nature Genetics 2014)	False discovery rate < 5%
				$cIMT_{min}$					
rs12549144;rs13262031;rs7831557	29	chr8:9106927-11726957	ENSG00000136574	*GATA4*	5.10E-06	FALSE	protein coding+ processed transcript+ retained intron	-	Yes
rs342988	1	chr7:35242042-35293758	ENSG00000164532	*TBX20*	7.09E-03	TRUE	protein coding+ retained intron	rs1833130;rs17676885	No
rs914279	1	chr10:30301729-30404423	ENSG00000165757	*JCAD*	7.19E-03	TRUE	protein coding+ processed transcript	-	No
rs12549144;rs13262031;rs7831557	29	chr8:9106927-11726957	ENSG00000171056	*SOX7*	8.02E-03	FALSE	protein coding	rs10092781;rs7001281	No
rs12549144;rs13262031;rs7831557	29	chr8:9106927-11726957	ENSG00000255394	*C8orf49*	2.98E-02	FALSE	protein coding	-	No
rs9515203	1	chr13:110958159-111165374	ENSG00000134871	*COL4A2*	9.68E-02	TRUE	protein coding+ processed transcript	-	No
rs12549144;rs13262031;rs7831557	29	chr8:9106927-11726957	ENSG00000184608	*C8orf12*	1.06E-01	FALSE	processed transcript+ protein coding	-	No
rs12549144;rs13262031;rs7831557	29	chr8:9106927-11726957	ENSG00000173273	*TNKS*	1.07E-01	TRUE	protein coding+ processed transcript+ retained intron+nonsense mediated decay	rs17737611	No
rs2019090	1	chr11:103777914-104035107	ENSG00000170962	*PDGFD*	1.10E-01	TRUE	protein coding	rs481552;rs11226008	No
rs12549144;rs13262031;rs7831557	29	chr8:9106927-11726957	ENSG00000253887	-	1.20E-01	FALSE	lincRNA	-	No
				$cIMT_{mean}$					
rs342988	1	chr7:35242042-35293758	ENSG00000164532	*TBX20*	1.10E-02	TRUE	protein coding+ retained intron	rs1833130;rs17676885	No
rs914279	1	chr10:30301729-30404423	ENSG00000165757	*JCAD*	4.92E-02	TRUE	protein coding+ processed transcript	-	No
rs9329221	17	chr8:9911778-11296167	ENSG00000171056	*SOX7*	5.16E-02	FALSE	protein coding	rs10092781;rs7001281	No
rs224960	1	chr5:81575281-81682796	ENSG00000205464	*ATP6AP1L*	6.75E-02	TRUE	protein coding+ processed transcript+ retained intron	-	No
rs4774437	1	chr15:62682725-63136830	ENSG00000171914	*TLN2*	1.25E-01	TRUE	processed transcript+ protein coding+ retained intron	-	No
rs6795735	1	chr3:64670585-64997143	ENSG00000241684	*ADAMTS9-AS2*	1.37E-01	TRUE	processed transcript+ retained intron	-	No
rs7500448	1	chr16:82660663-83829174	ENSG00000140945	*CDH13*	1.54E-01	TRUE	protein coding	rs16962255;rs6565105	No
rs9329221	17	chr8:9911778-11296167	ENSG00000255310	-	1.79E-01	FALSE	protein coding	-	No
rs9329221	17	chr8:9911778-11296167	ENSG00000184608	*C8orf12*	2.25E-01	FALSE	processed transcript+protein coding	-	No
rs9515203	1	chr13:110958159-111165374	ENSG00000134871	*COL4A2*	2.52E-01	TRUE	protein coding+processed transcript	-	No

Locus	Nr of genes in locus	Chromosome and position	Ensembl Gene ID	Gene symbol	Nominal P value	Gene closest to lead SNP	Gene bio-type	Top cis eQTL SNP (Westra et al. Nature Genetics 2014)	False discovery rate < 5%
				$cIMT_{max}$					
rs342988	1	chr7:35242042-35293758	ENSG00000164532	*TBX20*	3.65E-03	TRUE	protein coding+retained intron	rs1833130;rs17676885	No
rs740854	1	chr17:12569207-12672266	ENSG00000141052	*MYOCD*	2.20E-02	TRUE	protein coding+processed transcript	-	No
rs7831557	17	chr8:9911778-11296167	ENSG00000171056	*SOX7*	6.62E-02	FALSE	protein coding	rs10092781;rs7001281	No
rs224960	1	chr5:81575281-81682796	ENSG00000205464	*ATP6AP1L*	6.73E-02	TRUE	protein coding+processed transcript+retained intron	-	No
rs7176966	1	chr15:62682725-63136830	ENSG00000171914	*TLN2*	8.28E-02	TRUE	processed transcript+protein coding+retained intron	-	No
rs4611812	1	chr3:64670585-64997143	ENSG00000241684	*ADAMTS9-AS2*	9.69E-02	TRUE	processed transcript+retained intron	-	No
rs2150562	1	chr10:29746267-30025710	ENSG00000197321	*SVIL*	1.07E-01	TRUE	protein coding+processed transcript	-	No
rs4235201	1	chr4:174818403-174850676	ENSG00000250708	-	1.12E-01	TRUE	lincRNA	-	No
rs7831557	17	chr8:9911778-11296167	ENSG00000255310	-	1.18E-01	FALSE	protein coding	-	No
rs9515203	1	chr13:110958159-111165374	ENSG00000134871	*COL4A2*	3.19E-01	TRUE	protein coding+processed transcript	-	No

Table S15. Gene prioritization results for GWAS loci identified in the UK Biobank

			SNP-level analysis			Gene-level analysis			
Gene	Chr	Region	Closest to the lead variant	Closest to fine-mapped variant	Coding variant in high LD to fine-mapped variant*	Cross-tissue TWAS†	Arterial TWAS	SMR analysis	DEPICT
EML4	2	p21		y	y				
COX7A2L	2	p21	main						
KCNG3	2	p21	main						
ZFP36L2	2	p21							
RFX8	2	q11.2	main	y	y				
FN1	2	q35	main	y					
ZNF385D	3	p24.3	main	y					
ADAMTS9	3	p14.1	main	y					
EDNRA	4	q31.22	main	y					
HAND2	4	q34.1	main	y					
RPS23	5	q14.2							
ATP6AP1L	5	q14.2	main	y					
XRCC4	5	q14.2				y			
VCAN	5	q14.2	main	y					
HAPLN1	5	q14.2	sex interaction (female)	y					
ARHGAP26	5	q31.3		y					
NR3C1	5	q31.3	main	y	y				
GMDS	6	p25.3	main	y					
TBX20	7	p14.2	main	y					
HERPUD2	7	p14.2	male						
MCPH1	8	p23.1	main	y					
FAM85B	8	p23.1						y	
ZNF705B	8	p23.1	main	y					
MFHAS1	8	p23.1				y			
ERI1	8	p23.1				y	y		
PPP1R3B	8	p23.1				y	y		
TNKS	8	p23.1				y			
MSRA	8	p23.1				y	y		
RP1L1	8	p23.1							
SOX7	8	p23.1	sex interaction (male)			y	y		
PINX1	8	p23.1				y	y		

XKR6	8	p23.1	main	y			y					
AF131215.5	8	p23.1								y		
MTMR9	8	p23.1					y					
SLC35G5	8	p23.1					y	y				
C8orf12	8	p23.1					y					
FAM167A	8	p23.1					y	y				
BLK	8	p23.1					y					
GATA4	8	p23.1	sex interaction (male)				y					y
C8orf49	8	p23.1	sex interaction (male)				y					
NEIL2	8	p23.1					y	y				
FDFT1	8	p23.1								y		
DEFB134	8	p23.1					y					
FAM86B1	8	p23.1					y	y				
FAM86B2	8	p23.1					y	y				
ZBTB10	8	q21.13	main	y								
ZHX2	8	q24.13	main	y								
FBXO32	8	q24.13	main	y								
ZNF618	9	q32	main	y		y						
ARMC4	10	p12.1	main	y		y						
SVIL	10	p11.23	main					y		y		
JCAD	10	p11.23	main	y		y						
PDGFD	11	q22.3	main	y			y					
GLS2	12	q13.3										
STAT6	12	q13.3	main									
LRP1	12	q13.3	main	y			y	y				
R3HDM2	12	q13.3		y								
INHBC	12	q13.3				y						
RASSF9	12	q21.31	main	y								
COL4A1	13	q34		y								
COL4A2	13	q34	main	y								
SYNE3	14	q32.13	sex interaction (male)									
FBN1	15	q21.1	main	y								
TLN2	15	q22.2	main	y			y	y		y		
LOXL1	15	q24.1	meta-analysis	y								
RFWD3	16	q23.1					y					
LDHD	16	q23.1					y					
BCAR1	16	q23.1		y			y	y		y		
CFDP1	16	q23.1	main	y								
RP11-77K12.1	16	q23.1										

TMEM170A	16	q23.1					y			
CDH13	16	q23.3	main	y				y	y	
MVD	16	q24.2					y			
ZNF469	16	q24.2						y		
CBFA2T3	16	q24.3	main	y				y		
RP11-830F9.6	16	q24.3								
MAP2K4	17	p12	sex interaction (female)	y						
MYOCD	17	p12	main	y						
SHKBP1	19	q13.2	main							
LTBP4	19	q13.2	main	y						
CYP2A6	19	q13.2	main							
PVRL2	19	q13.32					y			
TOMM40	19	q13.32	main							
APOE	19	q13.32	main	y	y			y		
APOC1	19	q13.32	main	y						
ZNF296	19	q13.32					y			
DMPK	19	q13.32						y		
DMWD	19	q13.32						y		
ZNF341	20	q11.22					y			
ITCH	20	q11.22	main				y			
EDEM2	20	q11.22	main							
MMP24	20	q11.22	main	y			y			
FAM83C	20	q11.22					y			
GDF5OS	20	q11.22					y			
GDF5	20	q11.22					y			
RBM12	20	q11.22					y	y		
NFS1	20	q11.22					y			
MRTFA	22	q13.2	main							
ST13	22	q13.2					y	y		
EP300	22	q13.2					y	y		

Genes located within loci identified in the UK Biobank via the main GWAS, sex interaction analysis and meta-analysis were included; Rows with alternate colors indicate different loci. Genes closest to the lead variant included the nearest gene and any additional gene within 10 KB of the lead variant. Chr: Chromosome; *: if there existed non-synonymous variant in LD R^2>0.8 with the fine-mapped variant; †: genes consistently prioritized in all cIMT traits were noted.

Table S16 Top ten results from MAGMA gene-set analyses for three cIMT phenotypes

Gene Set	N_{genes}	Beta	Beta STD	SE	*P*	P_{bon}
$cIMT_{min}$						
Curated gene sets:reactome crosslinking of collagen fibrils	16	1.337	0.039	0.258	1.15E-07	**0.002**
Curated gene sets:nikolsky breast cancer 20q11 amplicon	31	1.426	0.057	0.284	2.66E-07	**0.004**
Curated gene sets:reactome signaling by pdgf	58	0.583	0.032	0.127	2.18E-06	**0.034**
GO cc:go collagen type iv trimer	4	2.414	0.035	0.535	3.18E-06	**0.049**
GO bp:go peptidyl lysine oxidation	5	1.984	0.032	0.457	7.26E-06	0.112
GO mf:go protein lysine 6 oxidase activity	5	1.984	0.032	0.457	7.26E-06	0.112
GO cc:go cell substrate junction	395	0.196	0.028	0.045	7.65E-06	0.118
Curated gene sets:ji carcinogenesis by kras and stk11 dn	16	1.017	0.029	0.235	7.81E-06	0.121
GO bp:go regulation of platelet derived growth factor receptor beta signaling pathway	8	1.350	0.027	0.314	8.49E-06	0.131
GO bp:go platelet derived growth factor receptor beta signaling pathway	14	1.068	0.029	0.253	1.22E-05	0.188
$cIMT_{mean}$						
Curated gene sets:nikolsky breast cancer 20q11 amplicon	31	1.424	0.057	0.284	2.68E-07	**0.004**
Curated gene sets:reactome crosslinking of collagen fibrils	16	1.279	0.037	0.258	3.65E-07	**0.006**
Curated gene sets:reactome signaling by pdgf	58	0.620	0.034	0.127	4.95E-07	**0.008**
Curated gene sets:nakamura adipogenesis late dn	35	0.697	0.030	0.160	6.70E-06	0.104
GO bp:go artery development	84	0.464	0.031	0.108	9.34E-06	0.145
GO bp:go regulation of low density lipoprotein particle receptor catabolic process	5	1.802	0.029	0.422	9.68E-06	0.150
Curated gene sets:reactome chylomicron clearance	5	1.888	0.030	0.447	1.20E-05	0.185
Curated gene sets:tsai response to radiation therapy	33	0.732	0.030	0.173	1.20E-05	0.185
GO bp:go ameboidal type cell migration	368	0.201	0.027	0.048	1.64E-05	0.253
GO bp:go low density lipoprotein particle remodeling	14	1.069	0.029	0.258	1.76E-05	0.273
$cIMT_{max}$						
Curated gene sets:nikolsky breast cancer 20q11 amplicon	31	1.362	0.055	0.280	5.64E-07	**0.009**
Curated gene sets:reactome crosslinking of collagen fibrils	16	1.216	0.035	0.254	8.85E-07	**0.014**
Curated gene sets:reactome signaling by pdgf	58	0.559	0.031	0.125	3.68E-06	0.057
GO bp:go artery development	84	0.478	0.031	0.107	3.80E-06	0.059
Curated gene sets:reactome chylomicron clearance	5	1.959	0.032	0.440	4.31E-06	0.067
GO bp:go regulation of low density lipoprotein particle receptor catabolic process	5	1.795	0.029	0.416	7.90E-06	0.122
GO bp:go low density lipoprotein particle remodeling	14	1.096	0.030	0.254	8.27E-06	0.128
GO bp:go dephosphorylation	451	0.171	0.026	0.041	1.55E-05	0.240
GO bp:go protein containing complex remodeling	30	0.717	0.028	0.174	1.99E-05	0.307
Curated gene sets:hellebrekers silenced during tumor angiogenesis	75	0.444	0.028	0.108	2.02E-05	0.312

P_{bon} : Bonferroni corrected P-value.

Table S17. cIMT variants significantly associated with CAD

cIMT lead SNP	CAD meta-analysis SNP	Chr	Position	Effect	SE	*P*	Gene
rs515135	rs515135	2	21286057	-0.0555	0.0066	**5.74E-17**	*APOB*
rs6795735	rs7428936	3	64710850	-0.019	0.0052	**2.87E-04**	*ADAMTS9*
rs59415853	rs6841581	4	148401190	0.0751	0.0074	**5.18E-24**	*EDNRA*
rs17477177	rs12705390	7	106410777	0.03	0.0062	**1.21E-06**	*PIK3CG*
rs7004066	rs6995692	8	10587008	-0.0189	0.0058	**1.18E-03**	*SOX7*
rs55917128	rs11189523	10	100011077	-0.0268	0.0056	**1.96E-06**	*LOXL4*
rs974819	rs974819	11	103660567	0.0614	0.0055	**1.12E-28**	*PDGFD*
rs11172113	rs11172113	12	57527283	-0.0227	0.0051	**1.04E-05**	*STAT6,LRP1*
rs9515203	rs9515203	13	111049623	0.0596	0.006	**3.89E-23**	*COL4A2*
rs12441130	rs12441130	15	74234902	0.0199	0.0056	**4.13E-04**	*LOXL1*
rs3851740	rs8046696	16	75442143	-0.0479	0.0058	**1.91E-16**	*BCAR/CFDP151*
rs7500448	rs7500448	16	83045790	0.0557	0.0068	**1.61E-16**	*CDH13*
rs7412	rs7412	19	45412079	-0.1368	0.011	**2.14E-35**	*APOE,APOC,TOMM40*
rs8139974	rs139064	22	40886557	0.0215	0.0057	**1.56E-04**	*MRTFA*

Chr: Chromosome; SE: standard error. Marked in bold: significant association after Bonferroni correction with $P<1.19\times10^{-3}$ (0.05/42). Associations of CAD were obtained in a meta-analysis of UK Biobank and CARDIoGRAMplusC4D. If a cIMT lead SNP was not available in the meta-analysis, a proxy SNP in high LD ($R^2>0.8$) was selected.

Supplementary figures

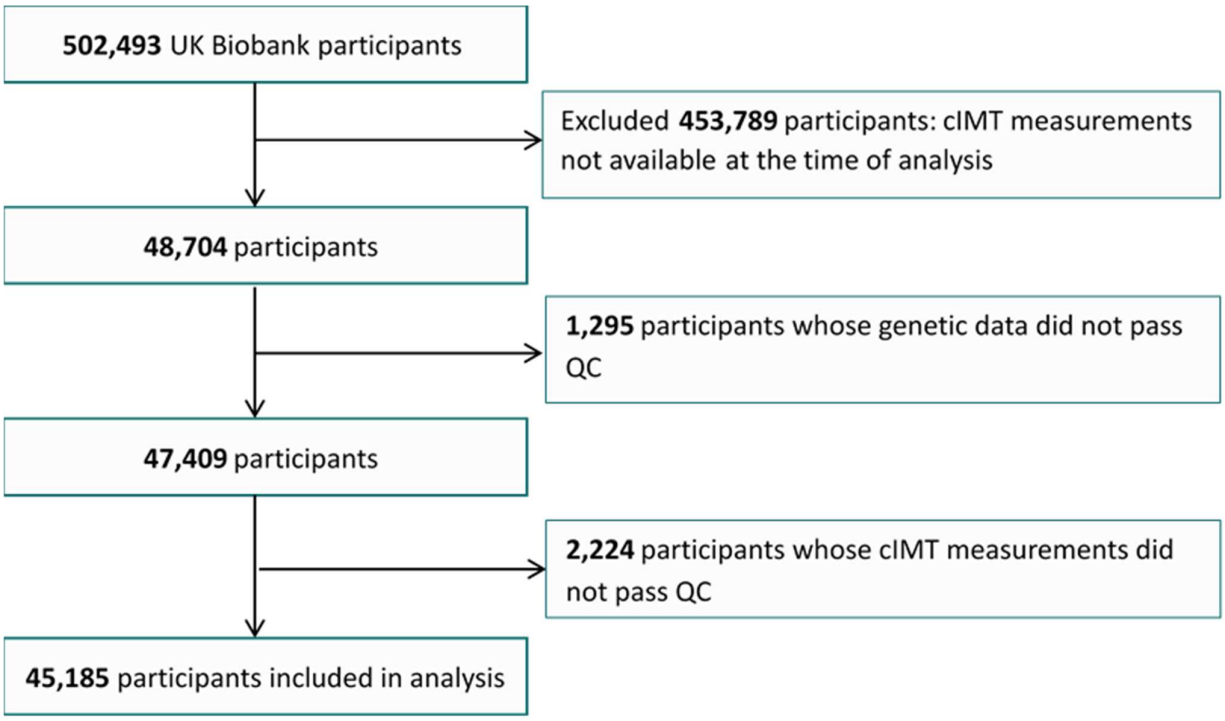


Figure S1. Study population.

GWAS on cIMT measurements were performed in 45,185 participants in the UK Biobank.

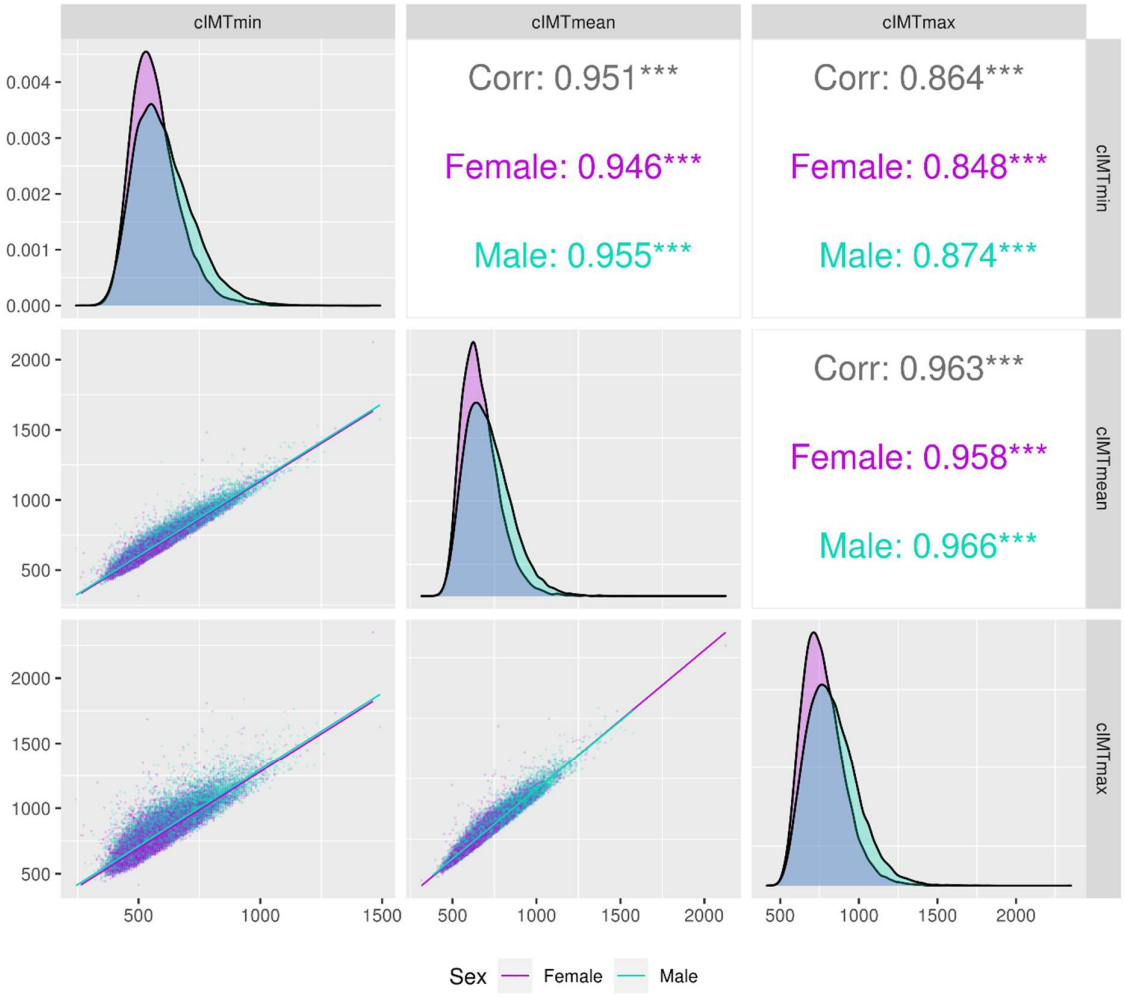


Figure S2. Distribution and correlations Between cIMT measurements. Diagonal: Distribution of $cIMT_{min}$, $cIMT_{mean}$, $cIMT_{max}$ stratified by sex; lower triangular panels: scatterplots against cIMT measurements; upper triangular panels: Spearman rank correlations between cIMT measurements in overall sample (Corr) and sex-stratified.

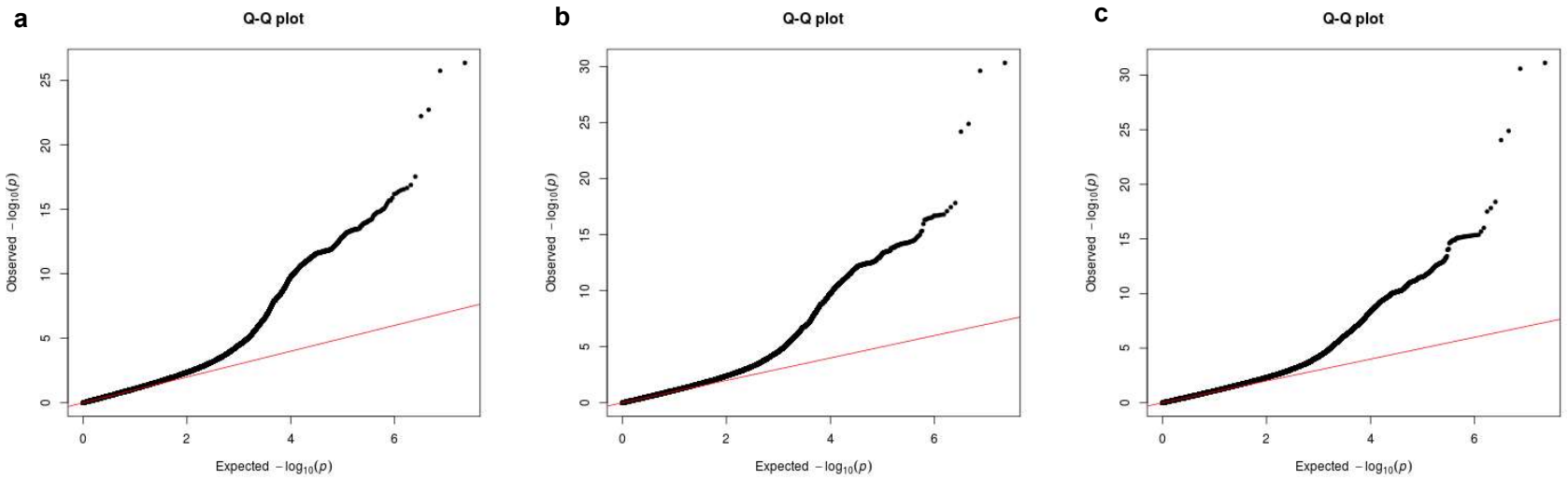
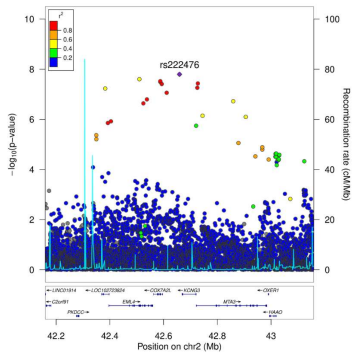


Figure S3. Q-Q plot for the three cIMT measurements

a: $cIMT_{min}$; b: $cIMT_{mean}$; c: $cIMT_{max}$. The genomic inflation factor λ are1.06,1.07 and 1.07 for $cIMT_{min}$, $cIMT_{mean}$ and $cIMT_{max}$ respectively

– rs222476



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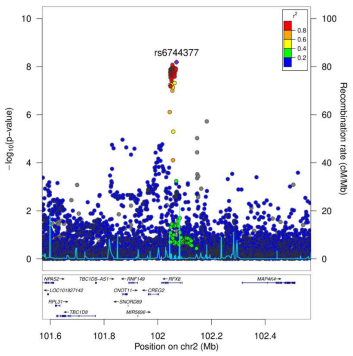

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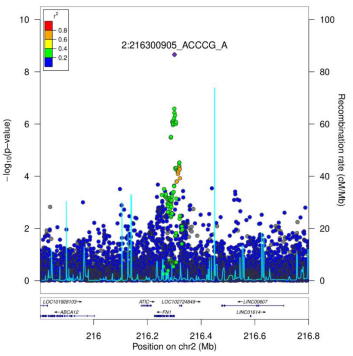

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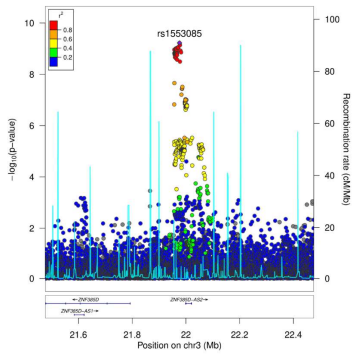

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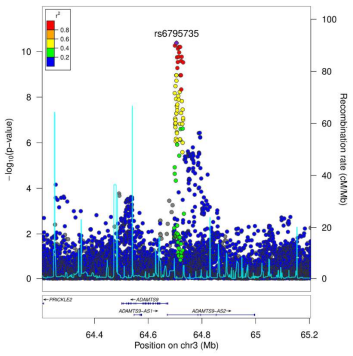

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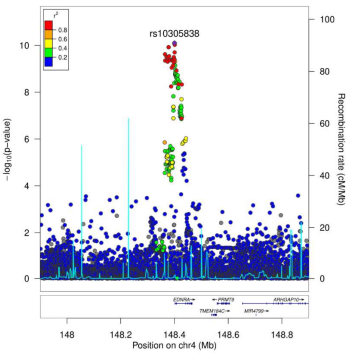

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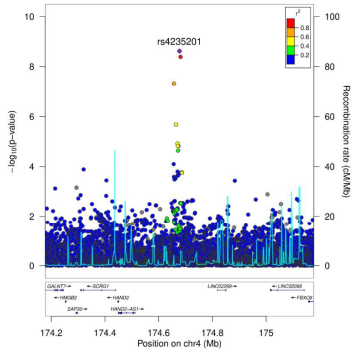

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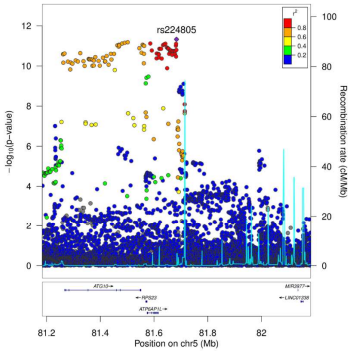

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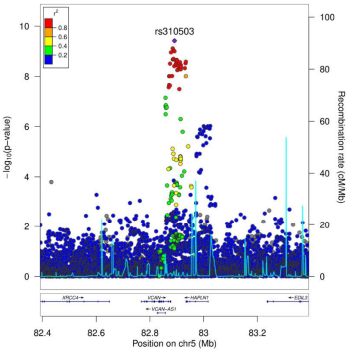

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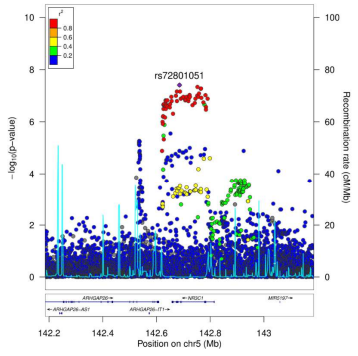

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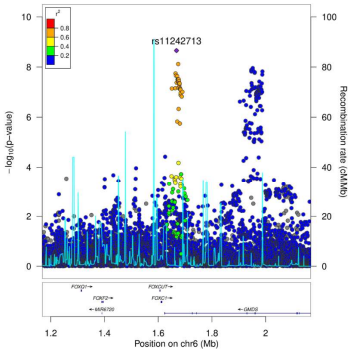

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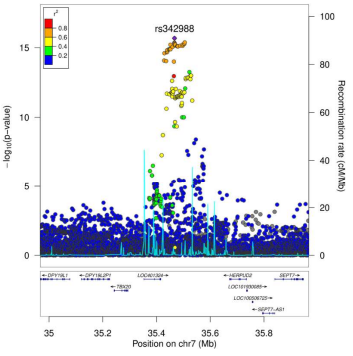

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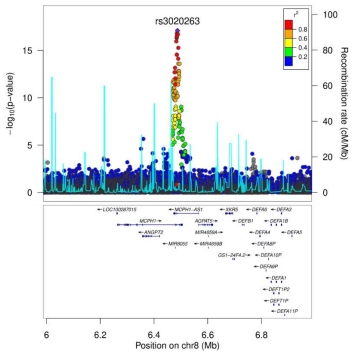

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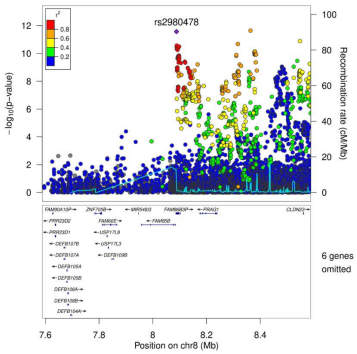

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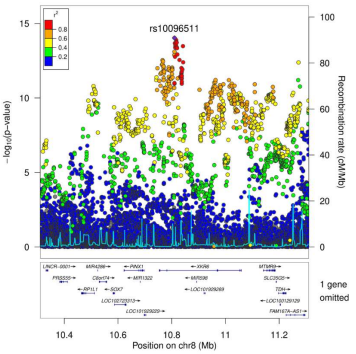

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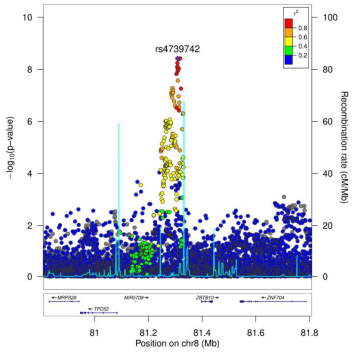

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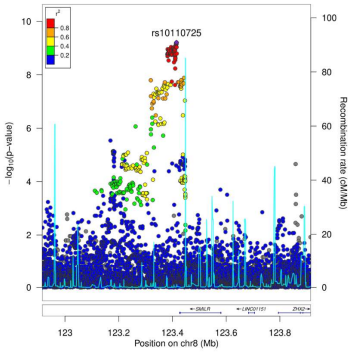

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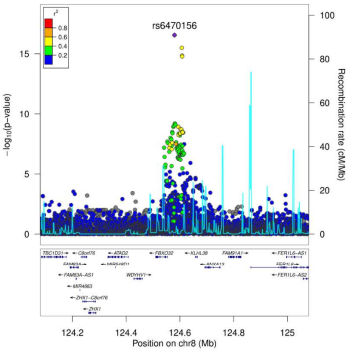

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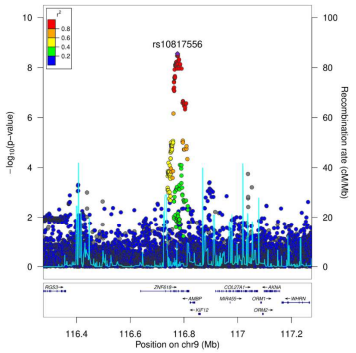

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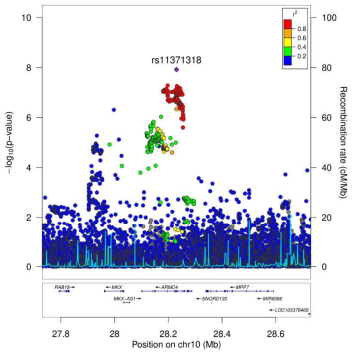

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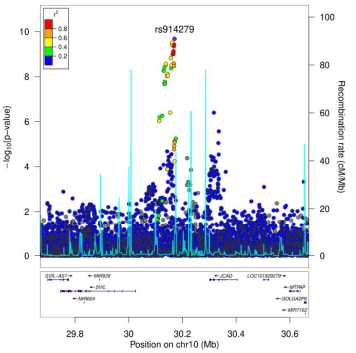

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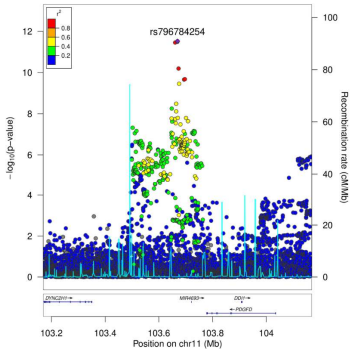

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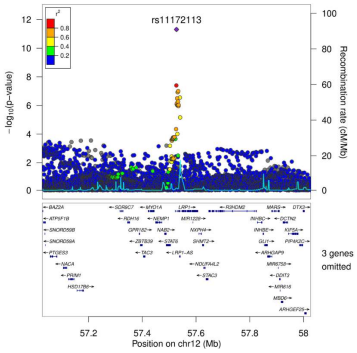

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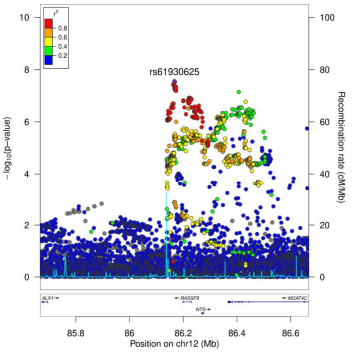

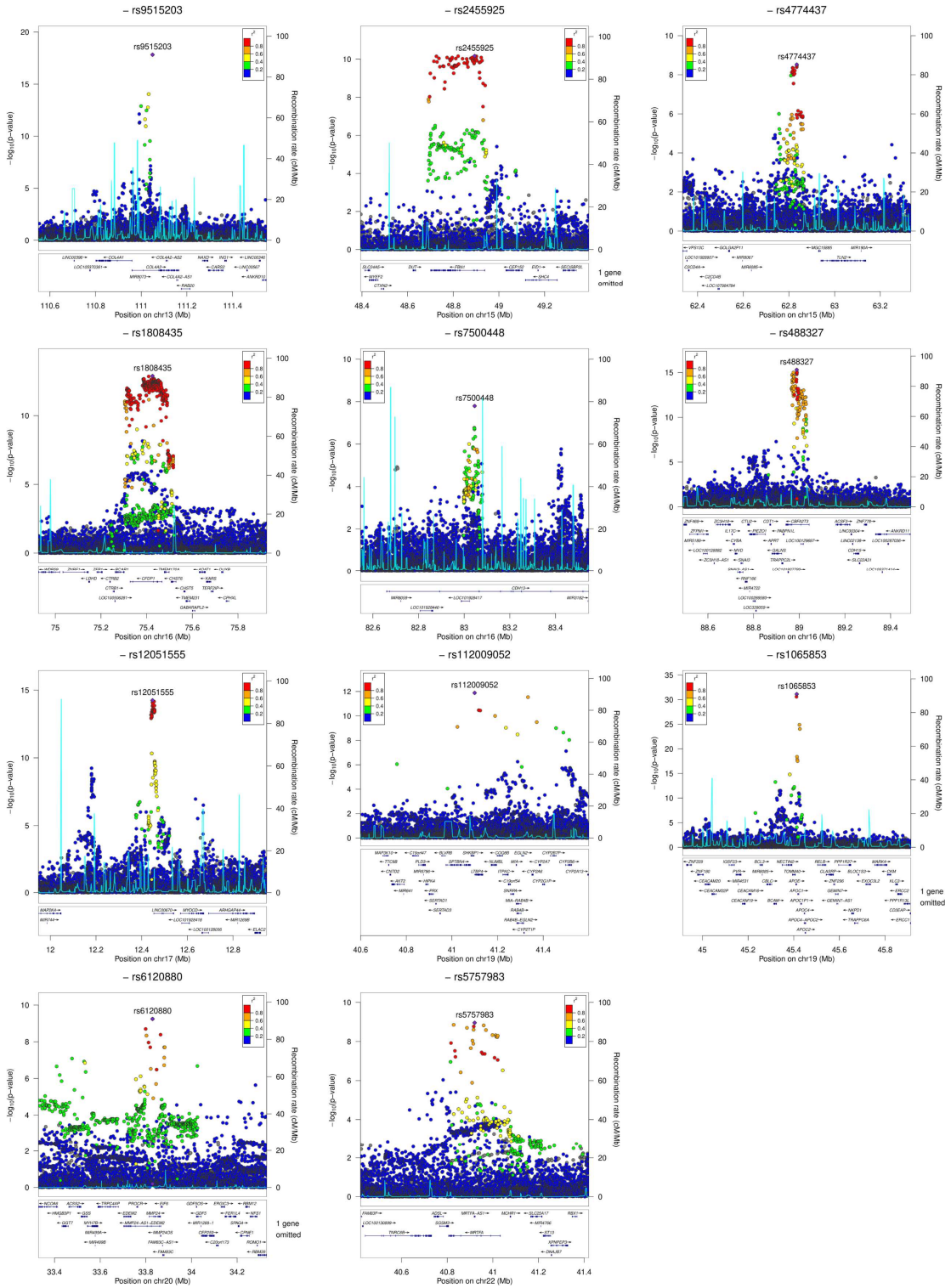

Figure S4. Locus zoom plots for 35 independent cIMT loci.

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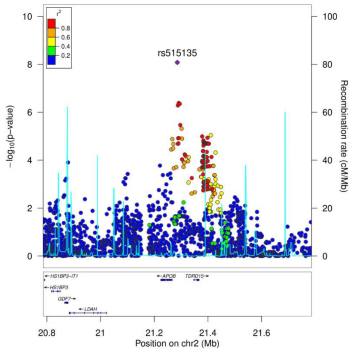

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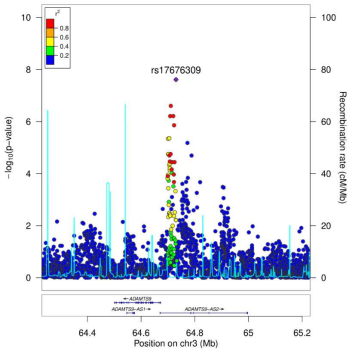

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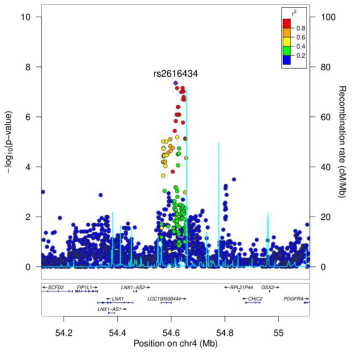

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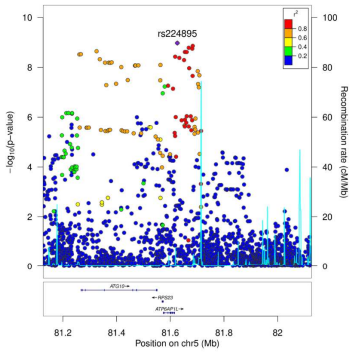

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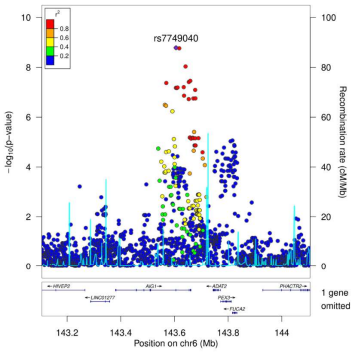

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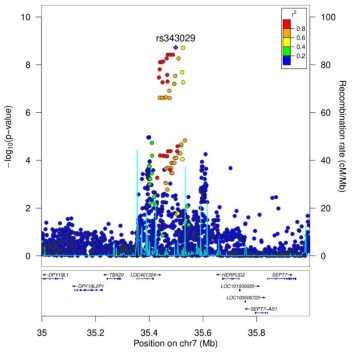

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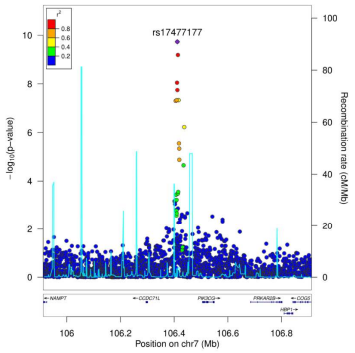

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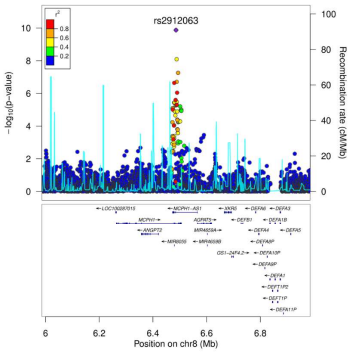

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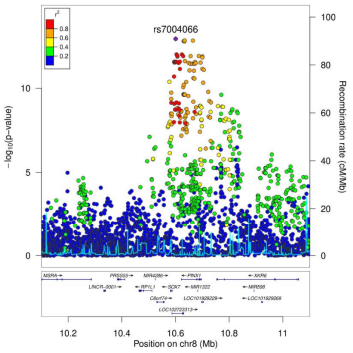

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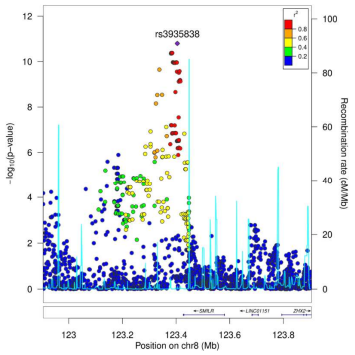

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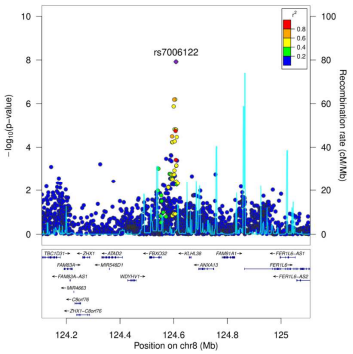
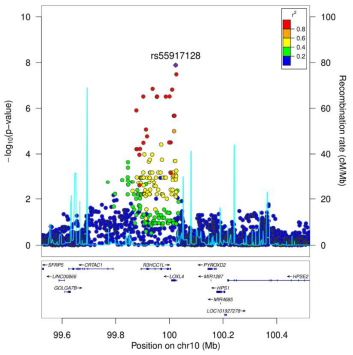


– rs55917128



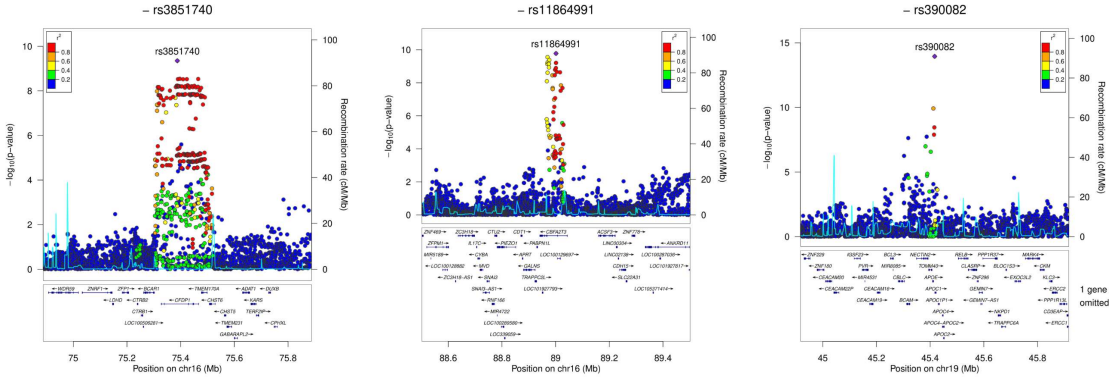


Figure S5. Locus zoom plots for cIMT$_{max}$ loci from the meta-analysis of UK Biobank and CHARGE/UCLEB consortia.

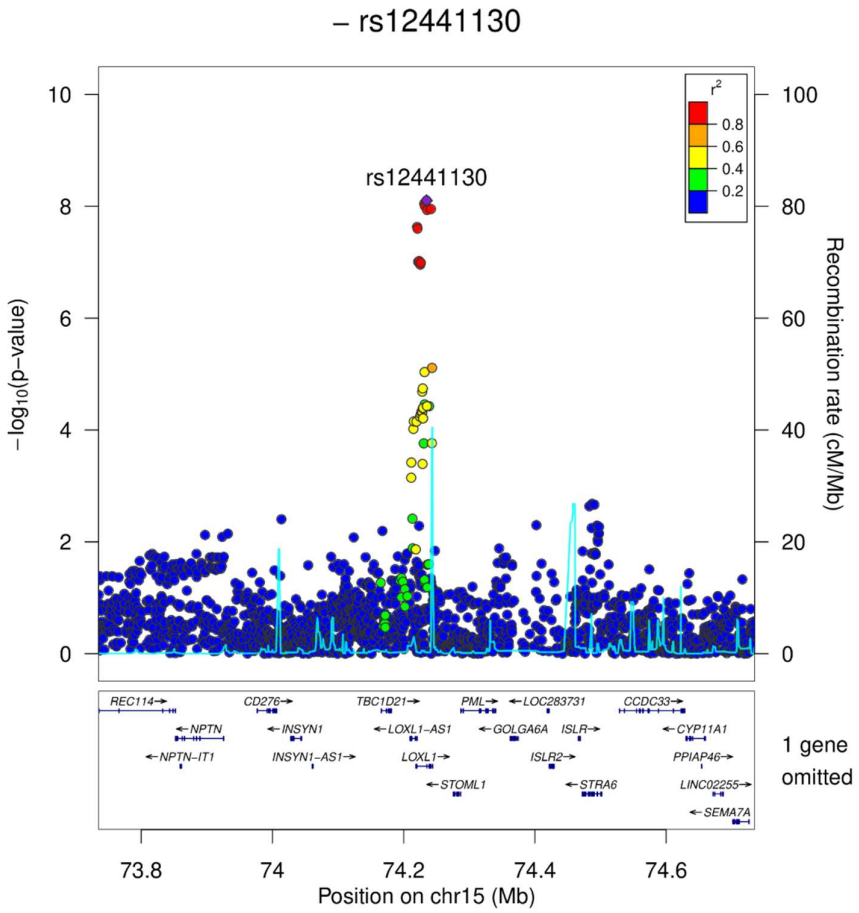
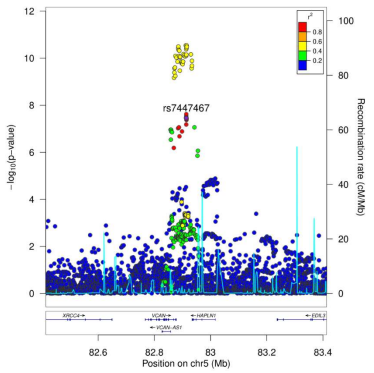
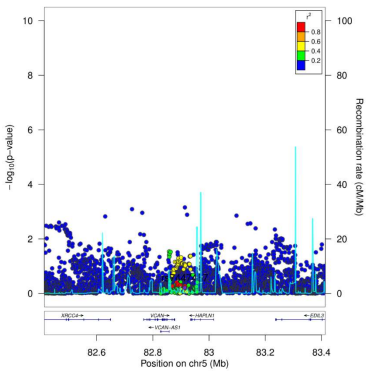


Figure S6. Locus zoom plot for *LOXL1* identified in the meta-analysis of the three cIMT measurements.

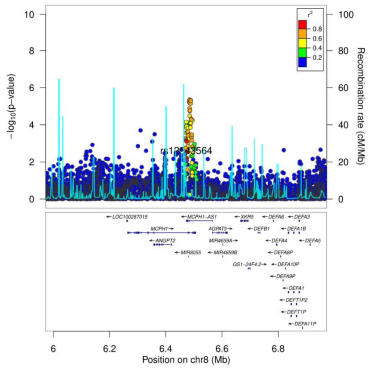
– rs7447467



– rs7447467



– rs12543564



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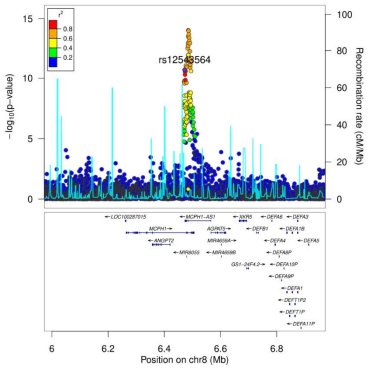
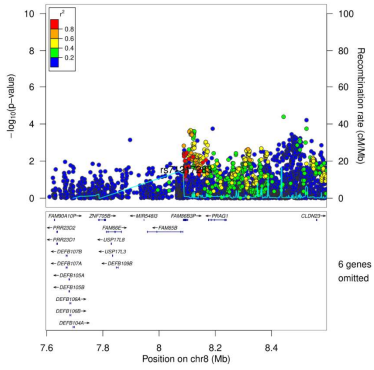


– rs71217283



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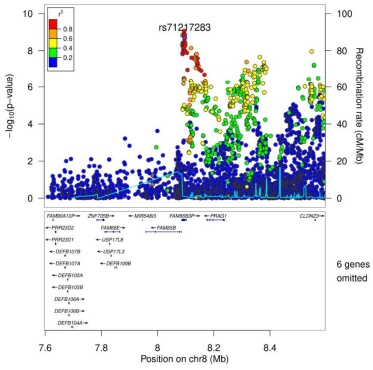
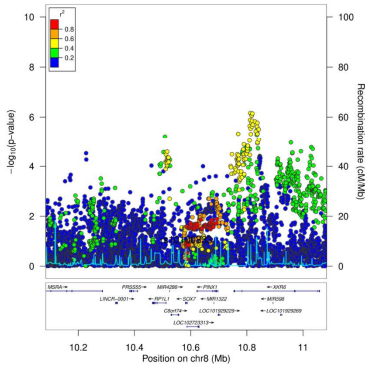


– rs10100333



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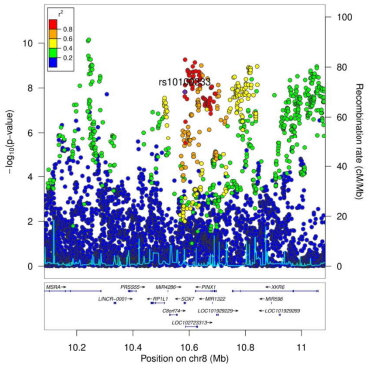


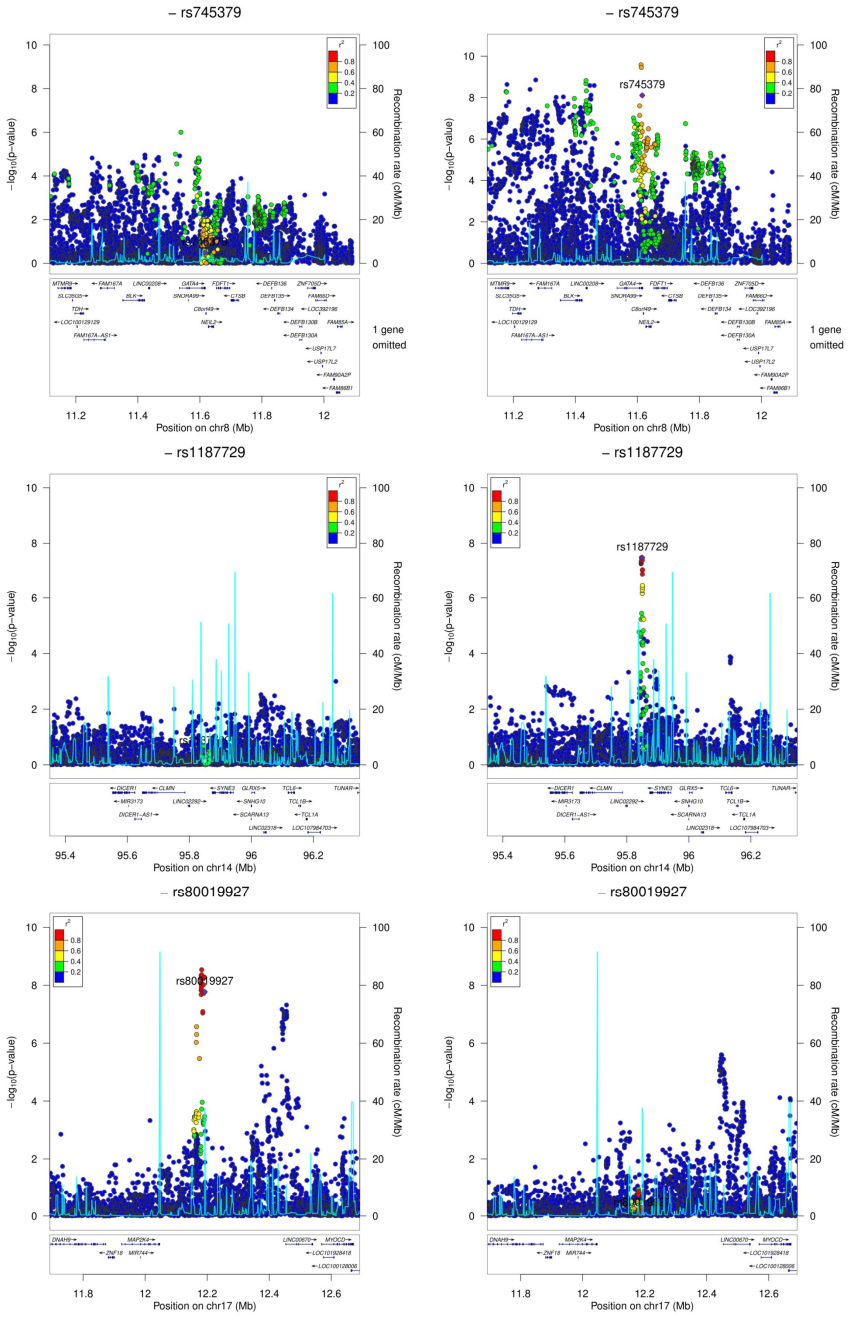


Figure S7. Locus zoom plots for sex specific loci.

The variants with the strongest interaction effect were marked as the reference variant in each plot. Each row shows one locus in females (left) and males (right) respectively.

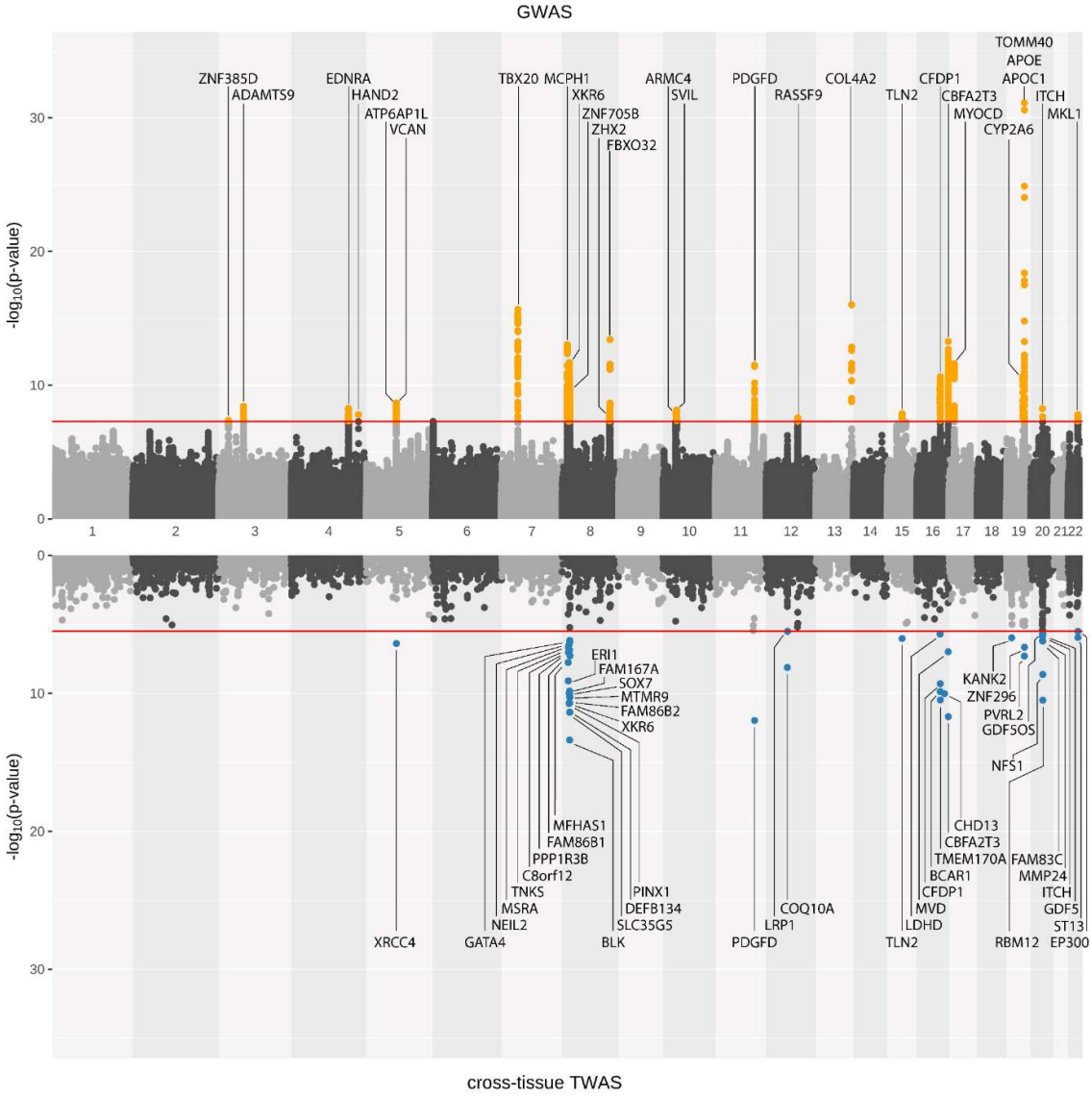


Figure S8. Miami plot of $cIMT_{max}$

The top panel shows the GWAS results while the bottom panel shows results from cross-tissue TWAS. Orange dot: variants passing genome-wide significance threshold ($P<5\times10^{-8}$) in GWAS; Blue dots: genes passing significance threshold after Bonferroni correction ($P<3.3\times10^{-6}$) in TWAS.

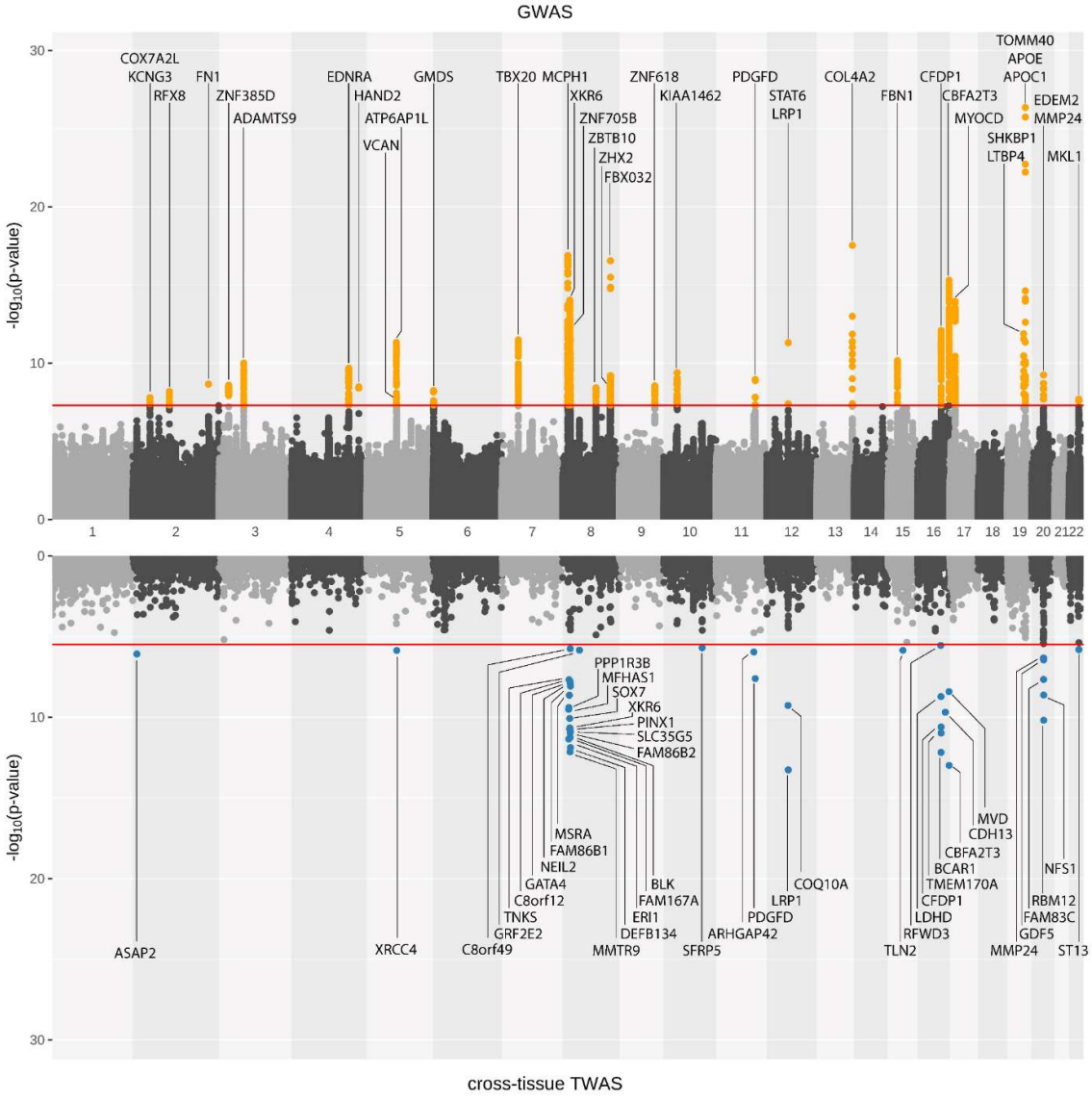
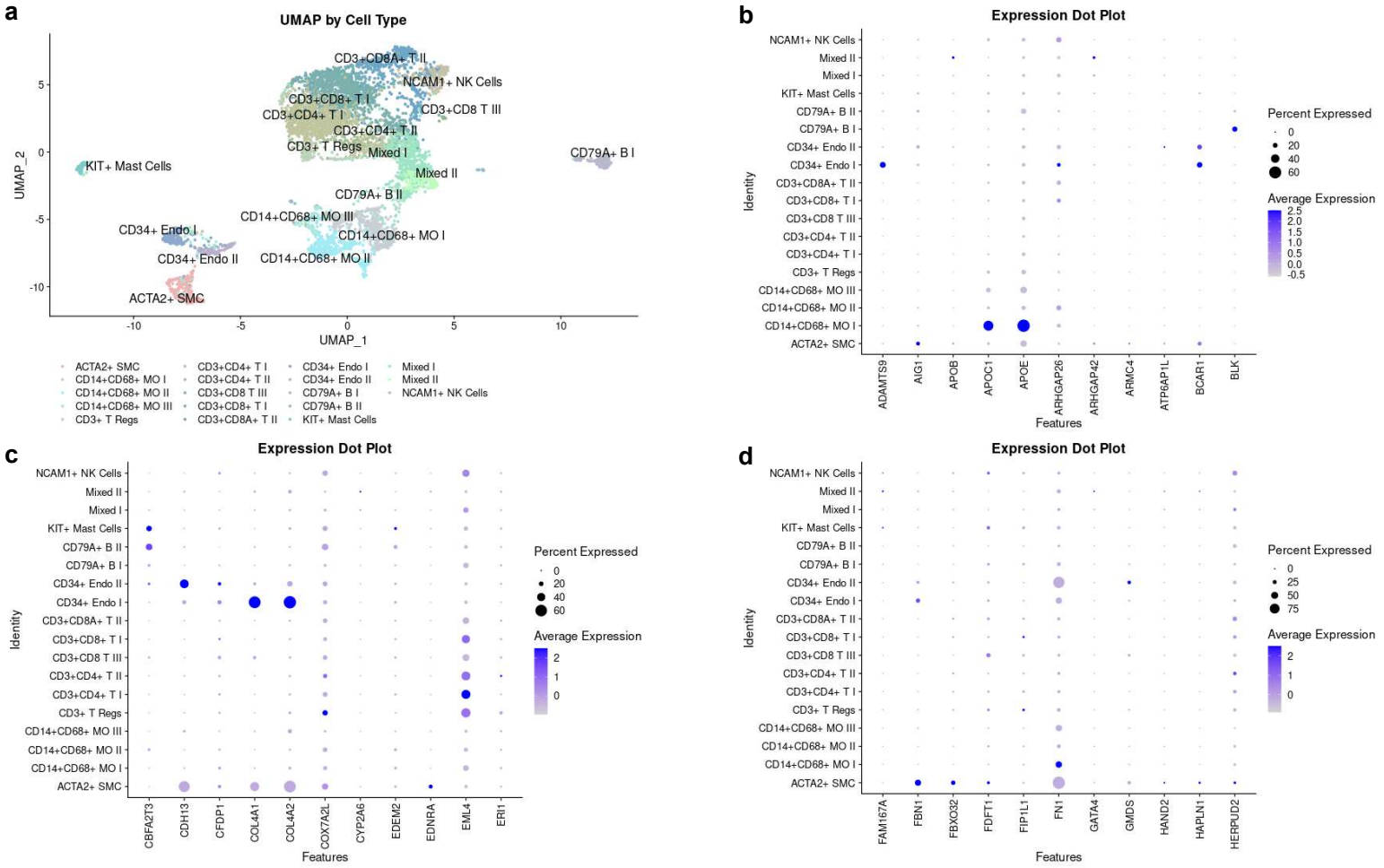


Figure S9. Miami plot of $cIMT_{min}$

The top panel shows the GWAS results while the bottom panel shows results from cross-tissue TWAS. Orange dot: variants passing genome-wide significance threshold ($P<5\times10^{-8}$) in GWAS; Blue dots: genes passing significance threshold after Bonferroni correction ($P < 3.3\times10^{-6}$) in TWAS.


a
UMAP by Cell Type
CD3+CD8A+ T II
NCAM1+ NK Cells
CD3+CD8+ T I
CD3+CD8 T III
CD3+CD4+ T I
CD3+CD4+ T II
CD3+ T Regs
Mixed I
CD79A+ B I
KIT+ Mast Cells
Mixed II
CD79A+ B II
CD14+CD68+ MO III
CD34+ Endo I
CD14+CD68+ MO I
CD34+ Endo II
CD14+CD68+ MO II
ACTA2+ SMC
UMAP_2
UMAP_1
ACTA2+ SMC
CD14+CD68+ MO I
CD14+CD68+ MO II
CD14+CD68+ MO III
CD3+ T Regs
CD3+CD4+ T I
CD3+CD4+ T II
CD3+CD8 T III
CD3+CD8+ T I
CD3+CD8A+ T II
CD34+ Endo I
CD34+ Endo II
CD79A+ B I
CD79A+ B II
KIT+ Mast Cells
Mixed I
Mixed II
NCAM1+ NK Cells
b
Expression Dot Plot
Identity
Features
Percent Expressed
Average Expression
ADAMTS9
AIG1
APOB
APOC1
APOE
ARHGAP26
ARHGAP42
ARMC4
ATP6AP1L
BCAR1
BLK
c
Expression Dot Plot
CBFA2T3
CDH13
CFDP1
COL4A1
COL4A2
COX7A2L
CYP2A6
EDEM2
EDNRA
EML4
ERI1
d
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FN1
GATA4
GMDS
HAND2
HAPLN1
HERPUD2

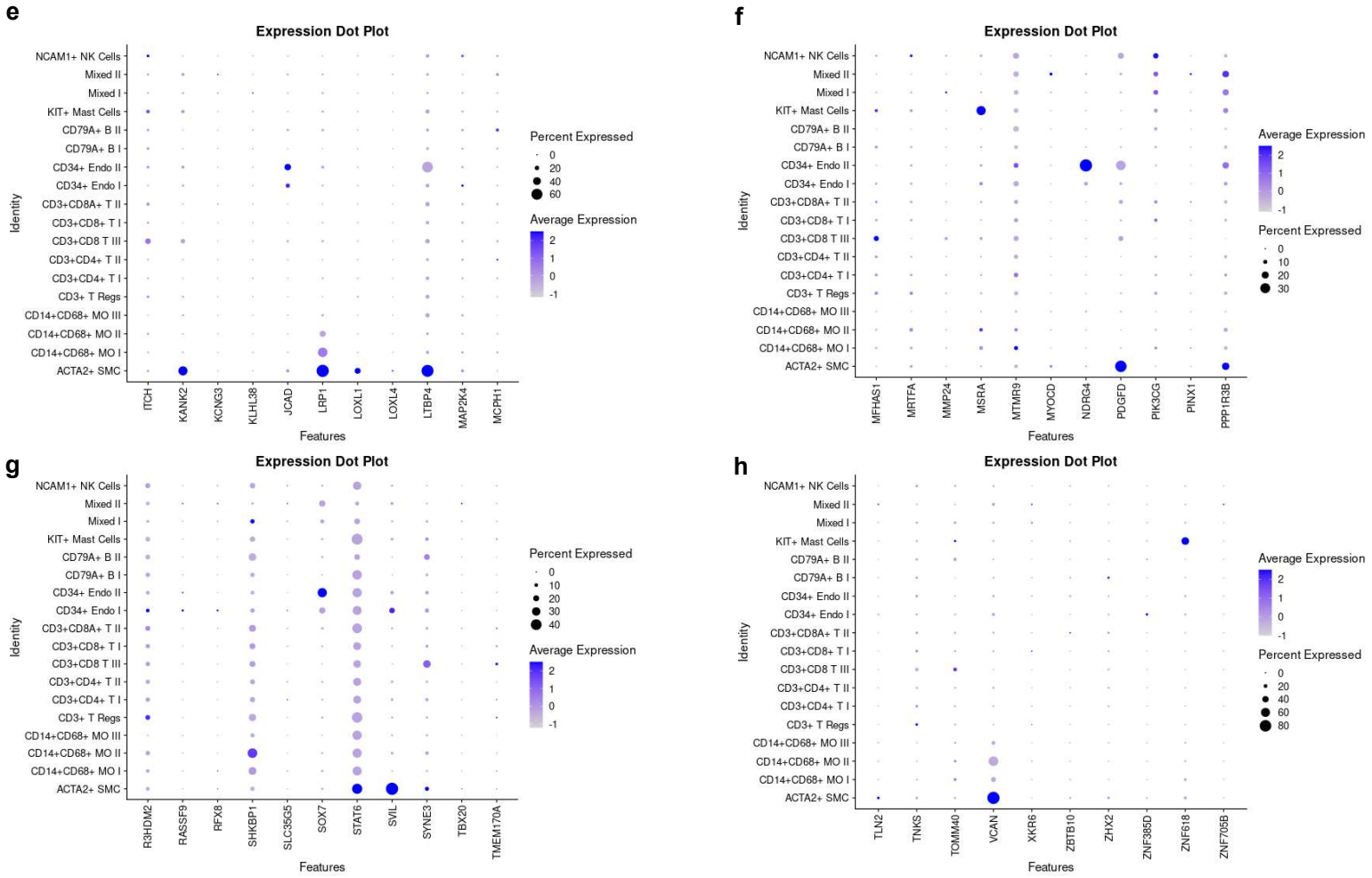

Figure S10. Expression of prioritized genes in human carotid plaque tissues.

a. UMAP clustering plots on cell populations denoted with corresponding identities (determined by marker expressions). b-h: Expression levels of genes, which are the closest genes to GWAS loci or prioritized in subsequent bioinformatic analyses, stratified by cell populations. B: B cells; Endo: endothelial; MO: macrophage; NK: natural killer; SMC: smooth muscle cell; T: T cells; T Regs: regulatory T cells.

Major Resources Table

Data & Code Availability

Description	Source / Repository	Persistent ID / URL
Summary statistics of cIMT GWAS in 45,185 UK Biobank participants	Mendeley	doi: 10.17632/47gd92pbn9.1
UK Biobank data	UK Biobank	Available for researchers upon approved request by the UK Biobank https://www.ukbiobank.ac.uk/
CARDIoGRAMplusC4D summary statistics	CARDIoGRAMplusC4D consortium	http://www.cardiogramplusc4d.org/data-downloads/
CHARGE summary statistics	dbGaP	Available for researchers upon approved request by data access committee from NIH dbGaP Study Accession: phs000930.v9.p1 Analysis Accession: pha004762.1
GERA summary statistics on blood pressure traits	GWAS catalog	Systolic blood pressure: https://www.ebi.ac.uk/gwas/studies/GCST007095 Diastolic blood pressure: https://www.ebi.ac.uk/gwas/studies/GCST007098
GLGC summary statistics	GLGC	http://csg.sph.umich.edu/willer/public/lipids2013/
GTEx summary statistics	GTEx portal	https://gtexportal.org/home/datasets
MEGASTROKE summary statistics	MEGASTROKE consortium	https://www.megastroke.org/download.html
BOLT-LMM		https://alkesgroup.broadinstitute.org/BOLT-LMM/downloads/
dbNSFP		https://sites.google.com/site/jpopgen/dbNSFP
DEPICT		https://data.broadinstitute.org/mpg/depict/
FINEMAP		http://www.christianbenner.com/
FUMA		https://fuma.ctglab.nl/
LDSC	GitHub	https://github.com/bulik/ldsc
LocusZoom		http://locuszoom.org/
MTAG	GitHub	https://github.com/JonJala/mtag
PlaqView	GitHub	https://github.com/MillerLab-CPHG/PlaqView
PLINK 1.9		https://www.cog-genomics.org/plink/
SMR		https://cnsgenomics.com/software/smr/#Overview
UTMOST	GitHub	https://github.com/Joker-Jerome/UTMOST

Supplementary Note

MEGASTROKE CONSORTIUM

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Reference

121. Fry D, Almond R, Moffat S, Gordon M, Singh P. UK Biobank Biomarker Project Companion Document to Accompany Serum Biomarker Data. Published online 2019. Accessed August 5, 2021. http://www.ukbiobank.ac.uk/uk-biobank-biomarker-panel/.

122. UK Biobank Blood Pressure. Accessed July 31, 2021. http://www.ukbiobank.ac.uk/

123. Zhu Z, Zhang F, Hu H, Bakshi A, Robinson MR, Powell JE, Montgomery GW, Goddard ME, Wray NR, Visscher PM, et al. Integration of summary data from GWAS and eQTL studies predicts complex trait gene targets. *Nat Genet*. 2016;48:481-487. doi:10.1038/ng.3538

124. Ma WF, Hodonsky CJ, Turner AW, Wong D, Song Y, Barrientos NB, Mosquera JV, Miller CL. Single-cell RNA-seq analysis of human coronary arteries using an enhanced workflow reveals SMC transitions and candidate drug targets. *bioRxiv*. Published online March 17, 2021:2020.10.27.357715. doi:10.1101/2020.10.27.357715

125. Pers TH, Karjalainen JM, Chan Y, Westra HJ, Wood AR, Yang J, Lui JC, Vedantam S, Gustafsson S, Esko T, et al. Biological interpretation of genome-wide association studies using predicted gene functions. *Nat Commun*. 2015;6:5890. doi:10.1038/ncomms6890