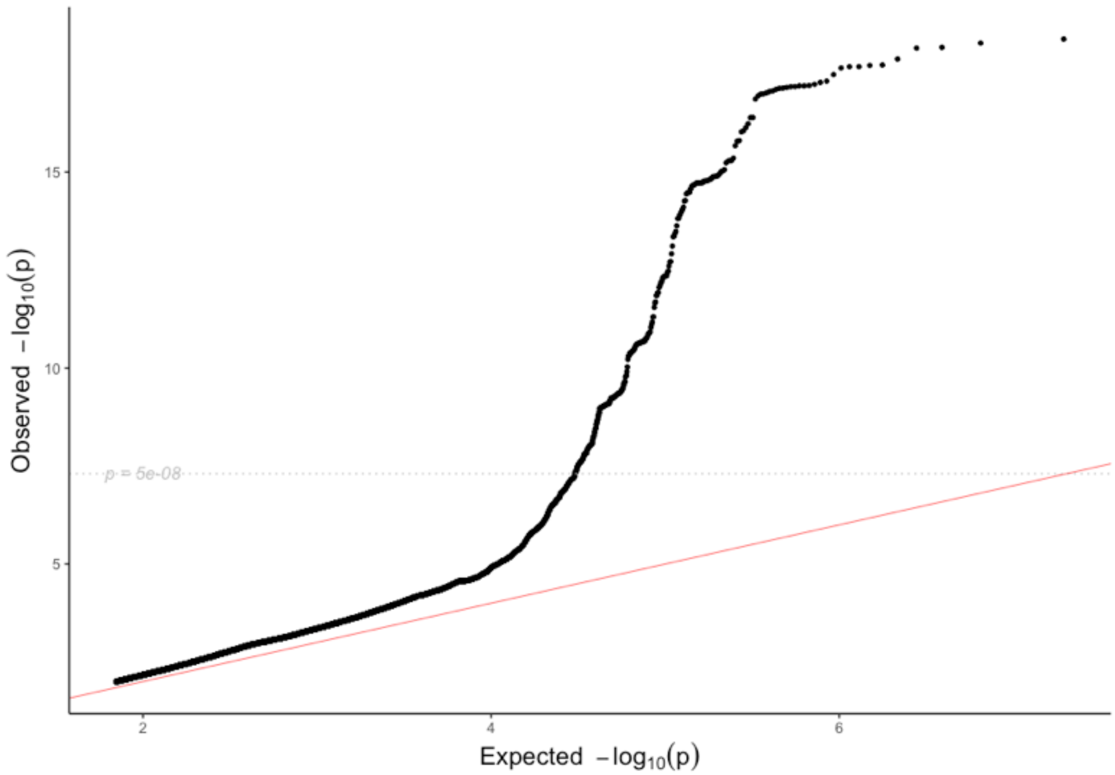
Genome-wide association study of MRI markers of cerebral small vessel disease in 42310 participants

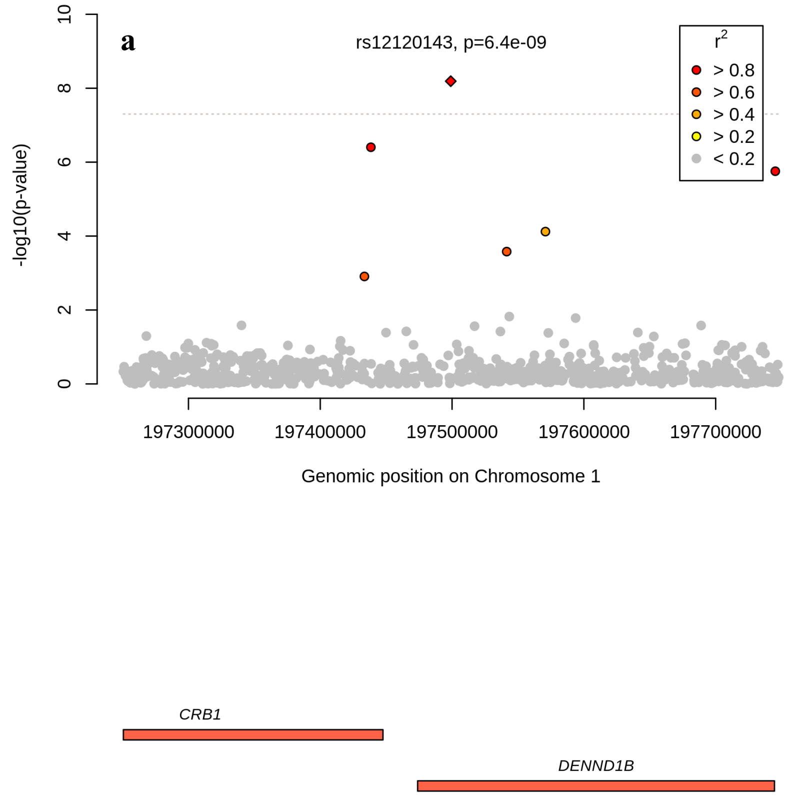
Persyn et al.

Supplementary Figures

Supplementary Tables



Supplementary Figure 1. QQ plot for WMH GWAS in UK Biobank.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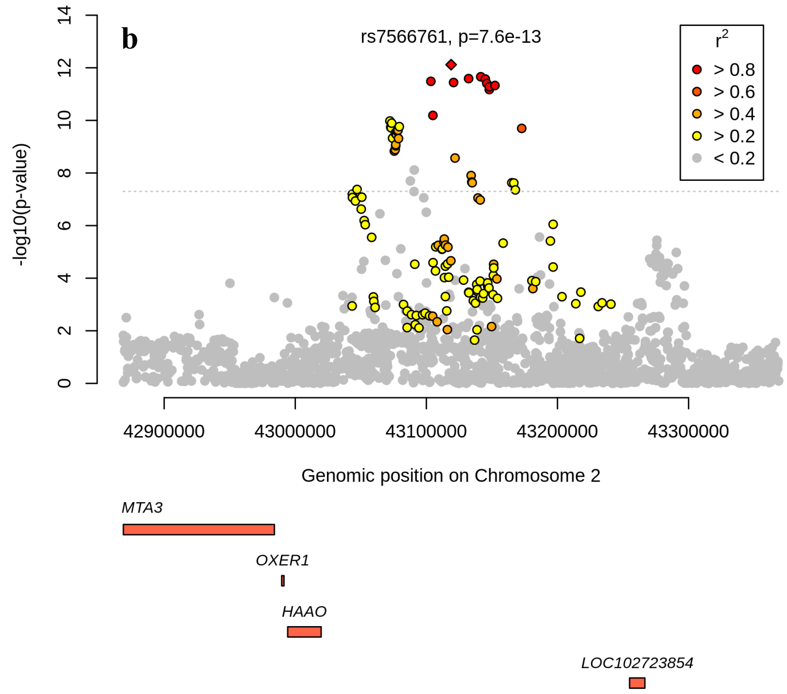
DENND1B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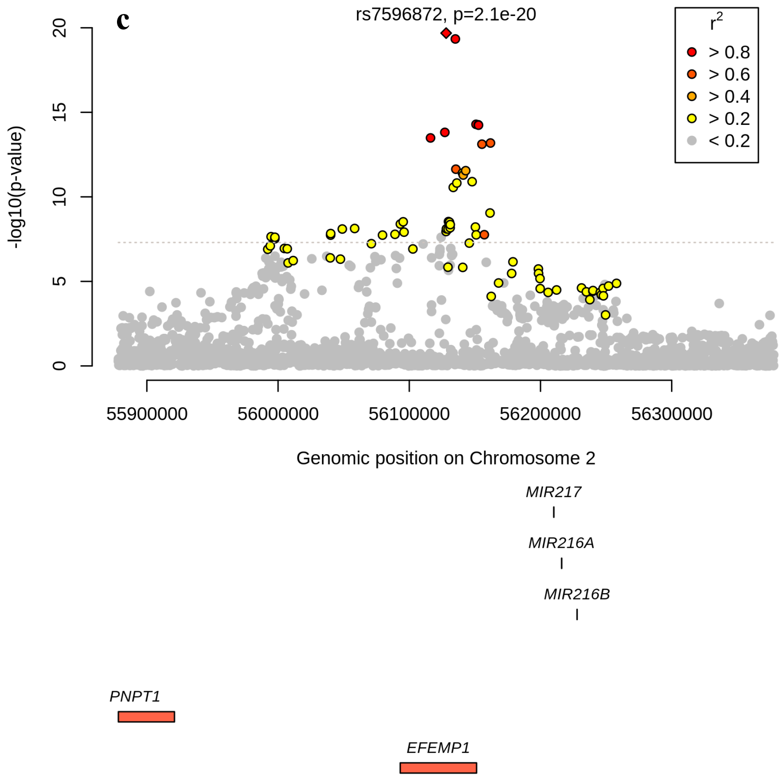
OXER1
HAAO
LOC102723854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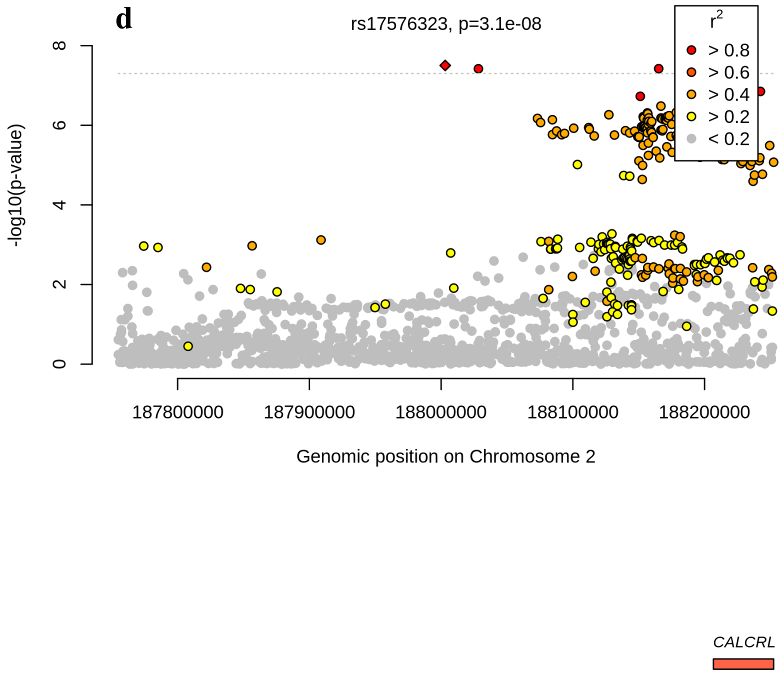
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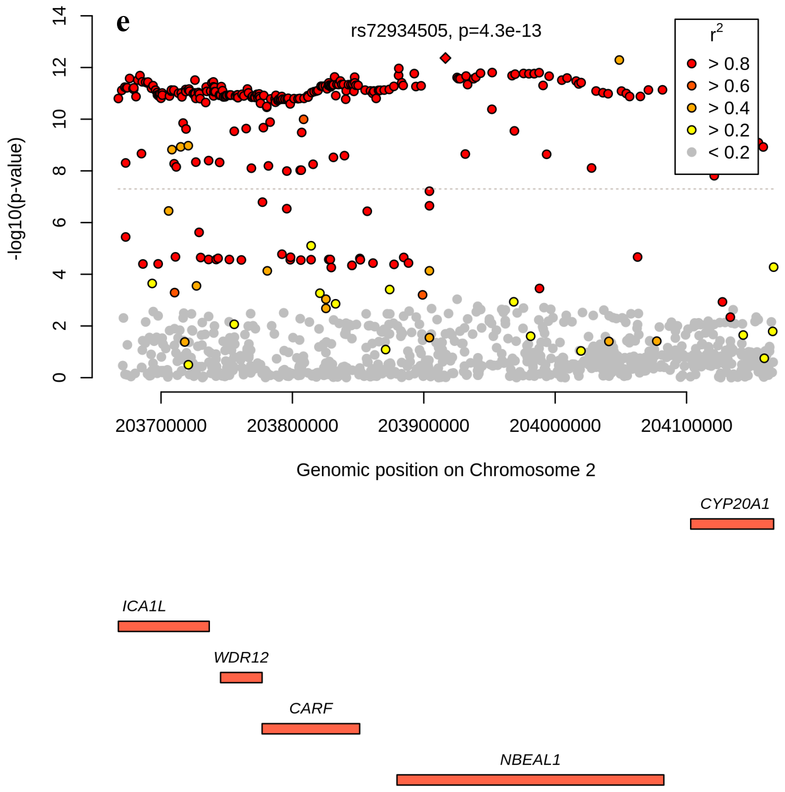
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CARF
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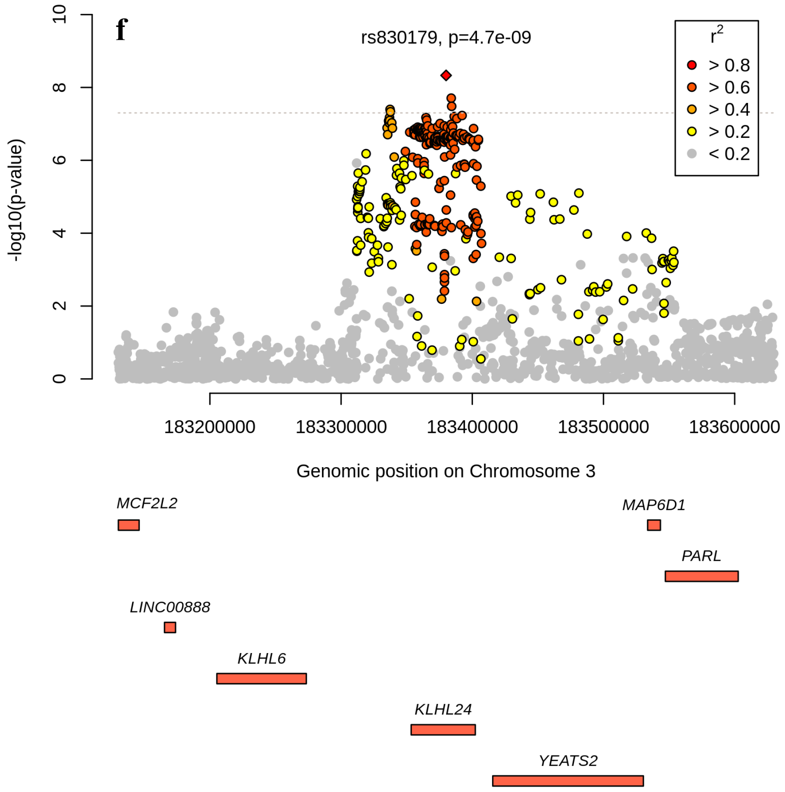
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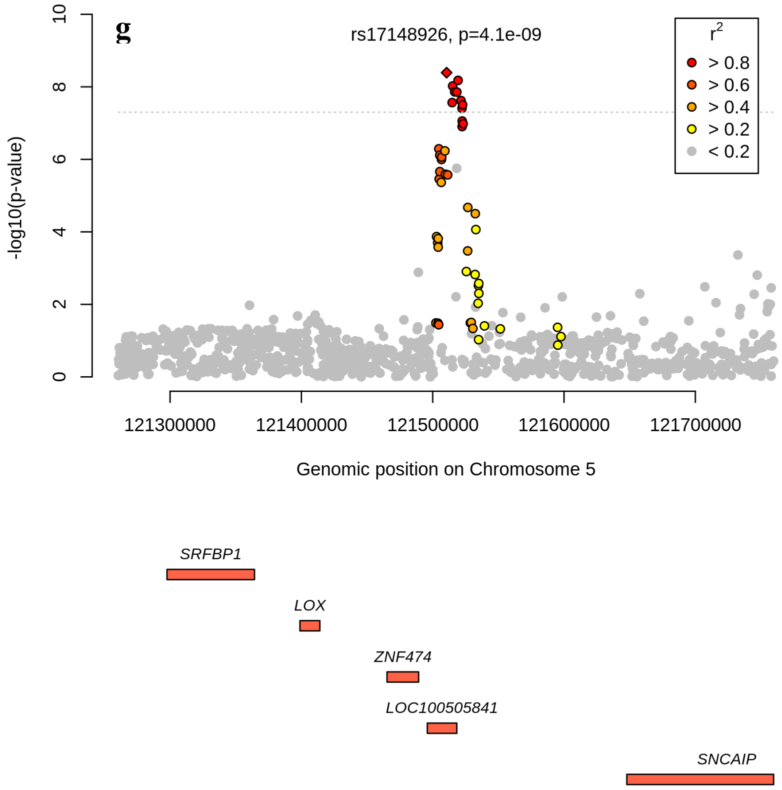
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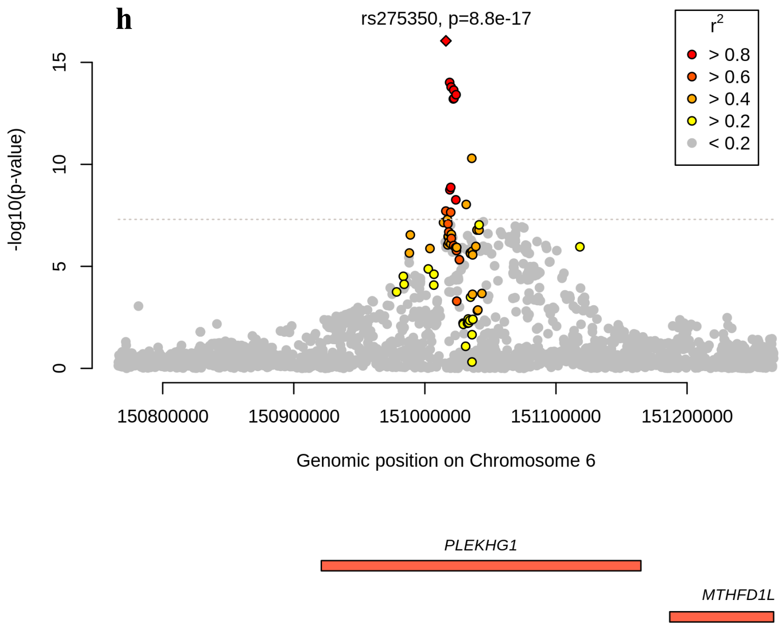
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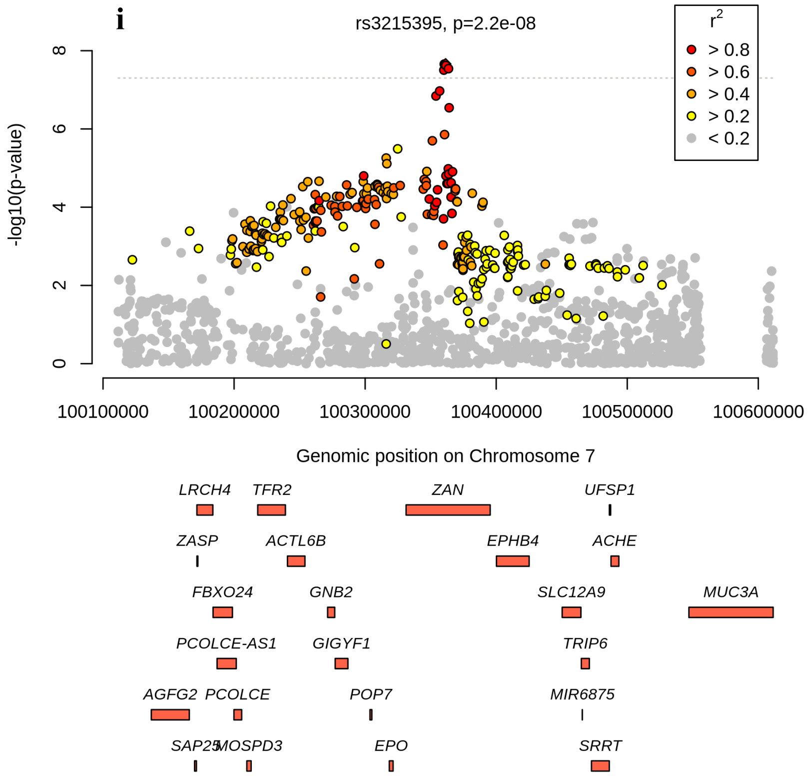
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ZAN
UFSP1
ZASP
ACTL6B
EPHB4
ACHE
FBXO24
GNB2
SLC12A9
MUC3A
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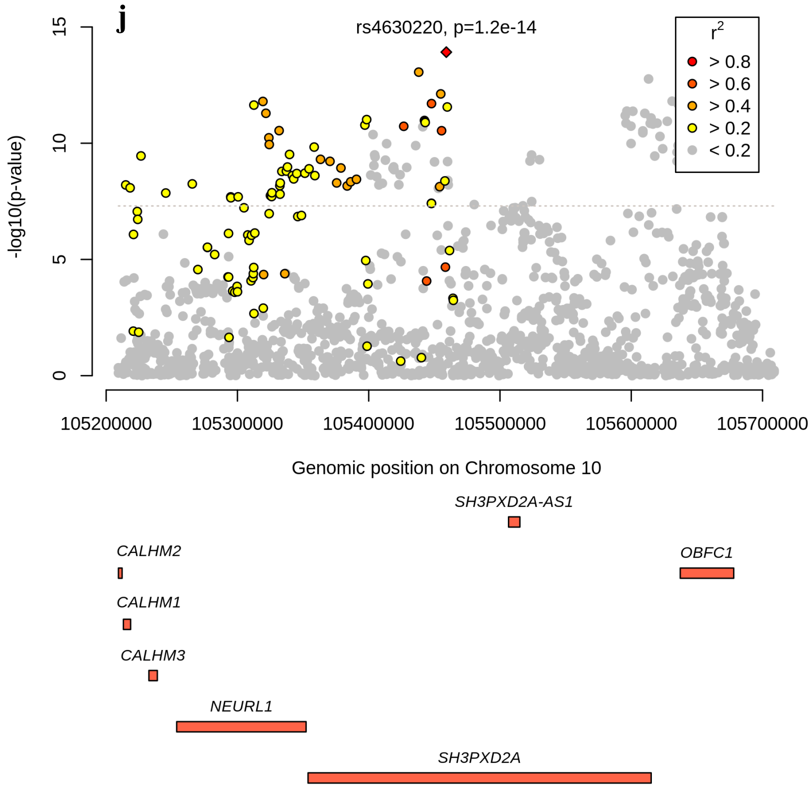
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CALHM1
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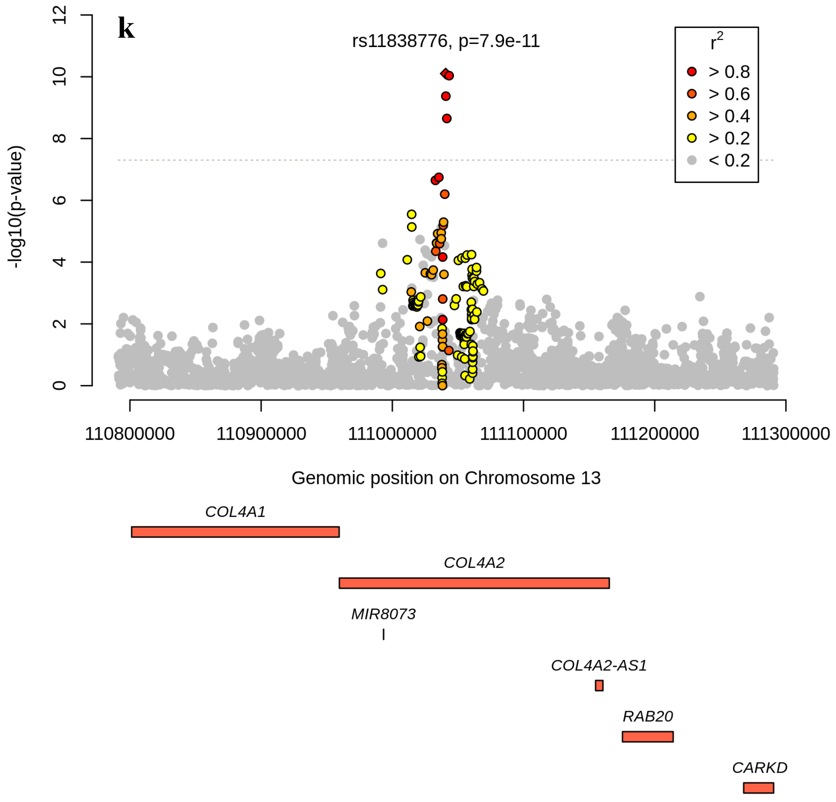
NEURL1
SH3PXD2A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MIR8073
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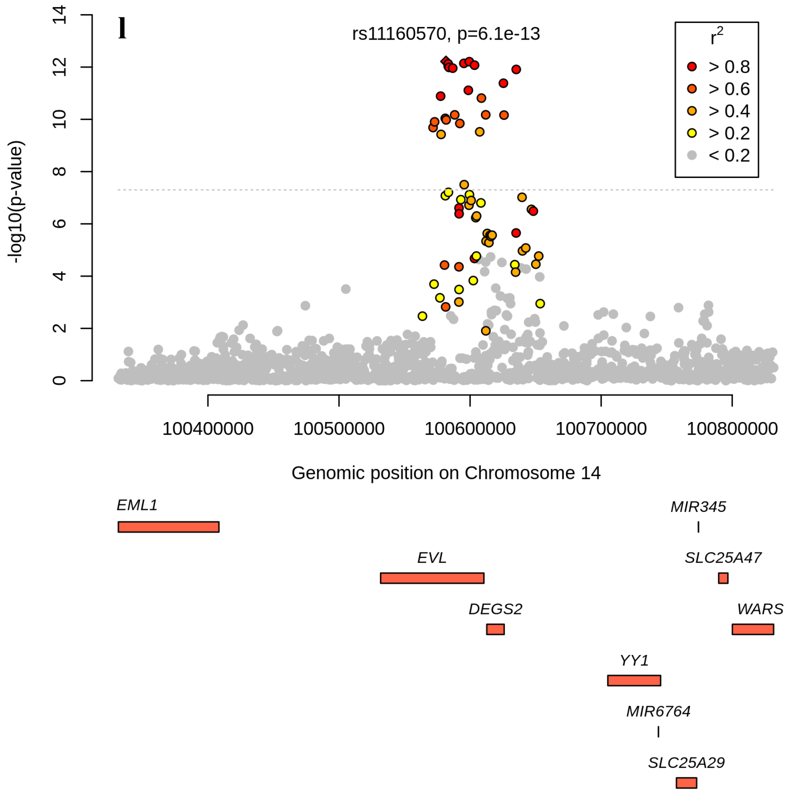
RAB20
CARKD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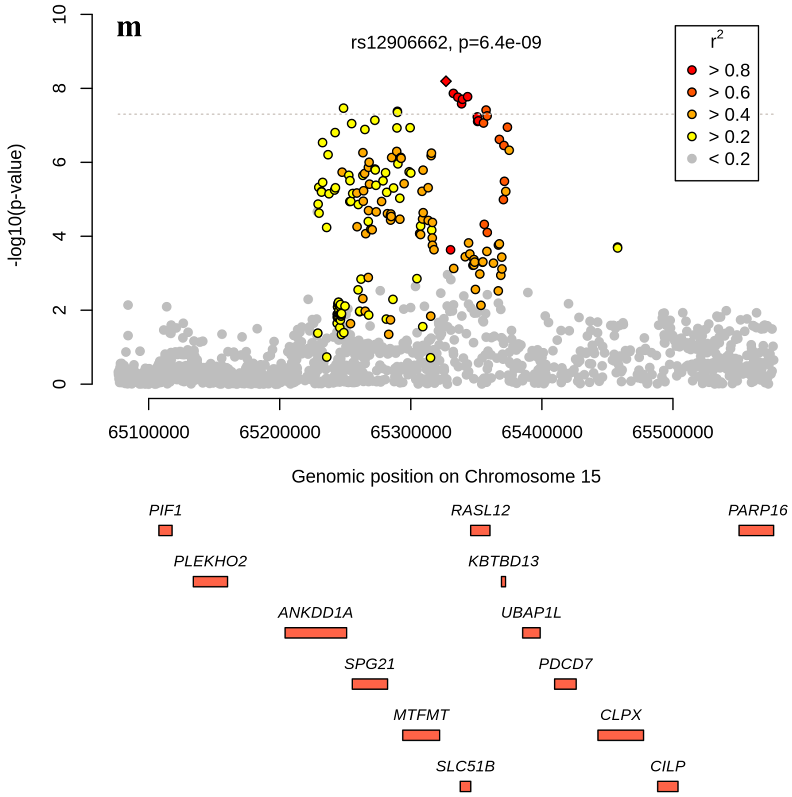
EVL
DEGS2
WARS
YY1
MIR6764
SLC25A29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RASL12
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ANKDD1A
UBAP1L
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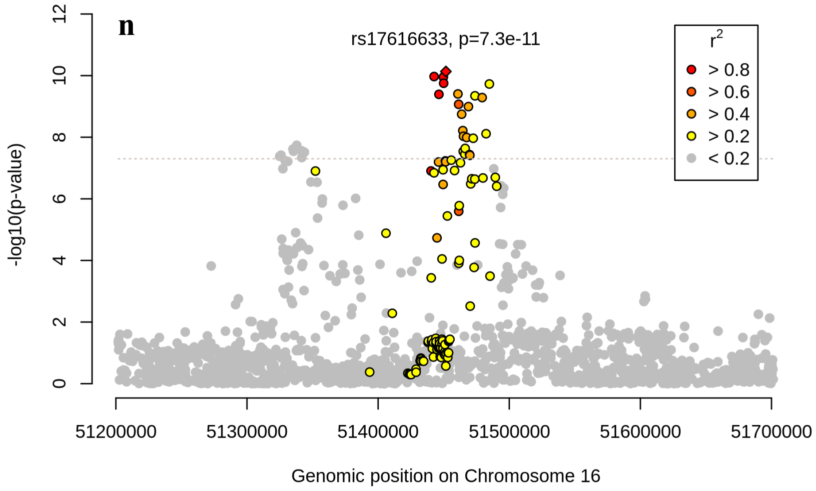
CLPX
SLC51B
CILP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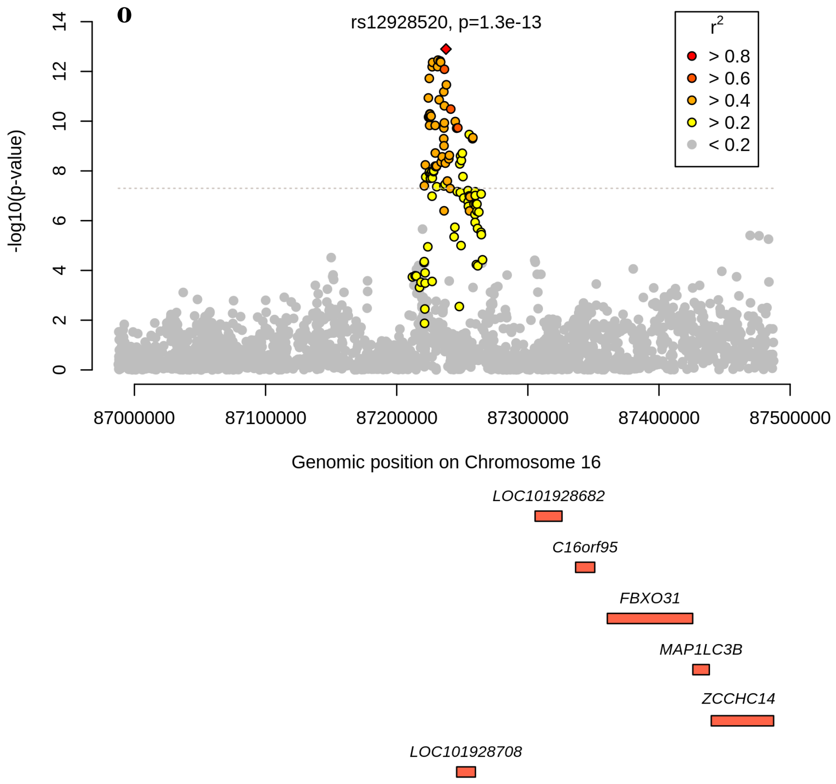
Genomic position on Chromosome 16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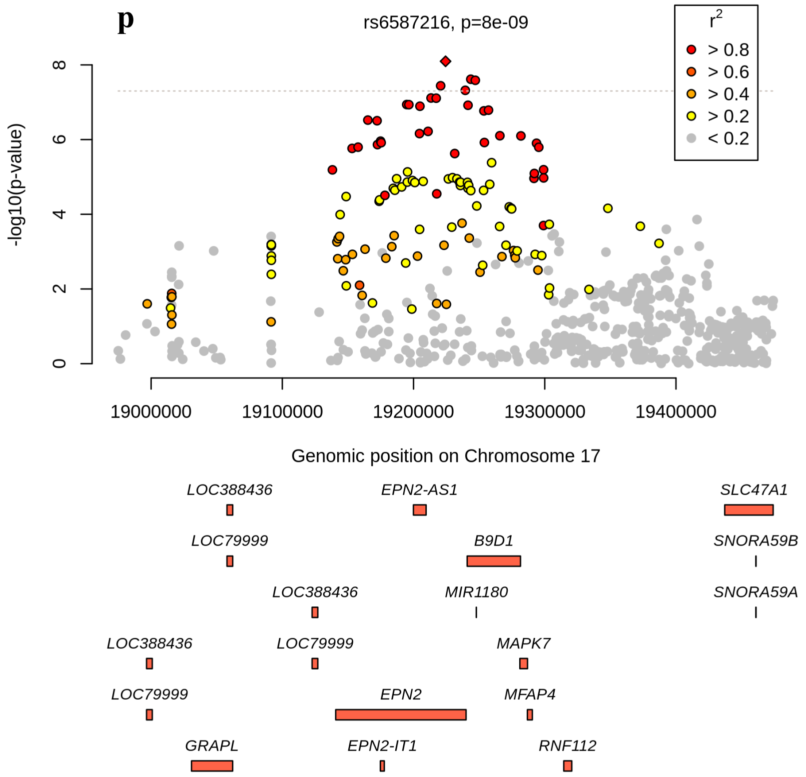
MAP1LC3B
ZCCHC14
LOC101928708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EPN2-AS1
SLC47A1
LOC79999
B9D1
SNORA59B
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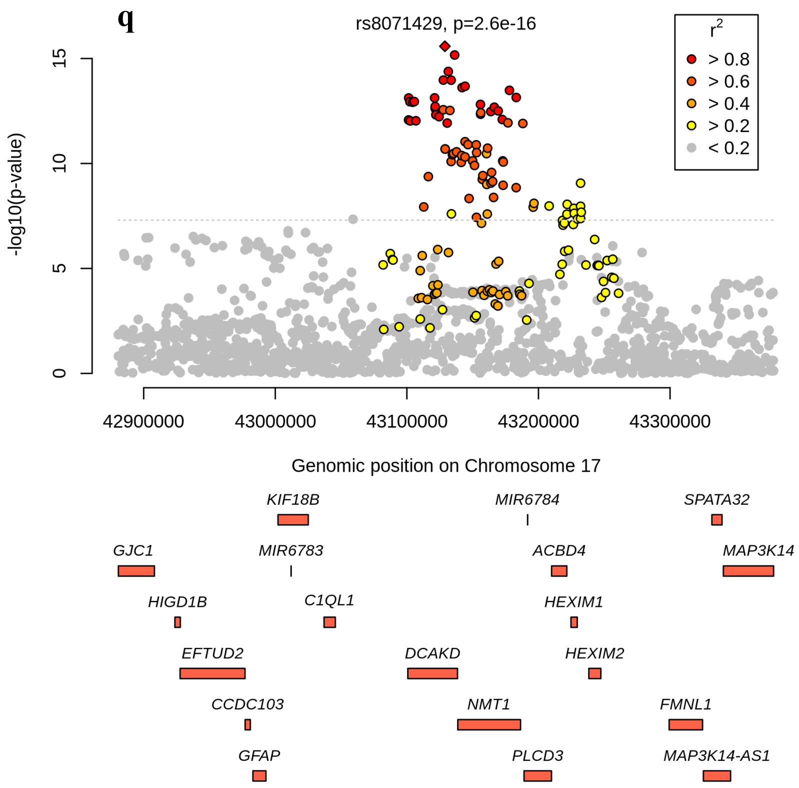
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10
15
42900000
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Genomic position on Chromosome 17
KIF18B
MIR6784
SPATA32
GJC1
MIR6783
ACBD4
MAP3K14
HIGD1B
C1QL1
HEXIM1
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DCAKD
HEXIM2
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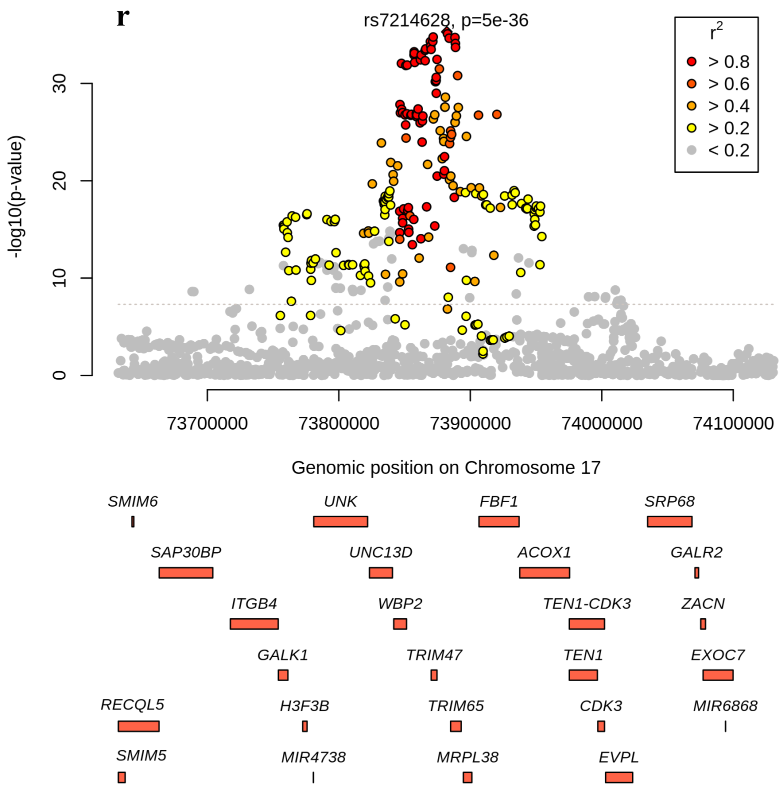
FMNL1
GFAP
PLCD3
MAP3K14-AS1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> 0.4
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Genomic position on Chromosome 17
SMIM6
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UNC13D
ACOX1
GALR2
ITGB4
WBP2
TEN1-CDK3
ZACN
GALK1
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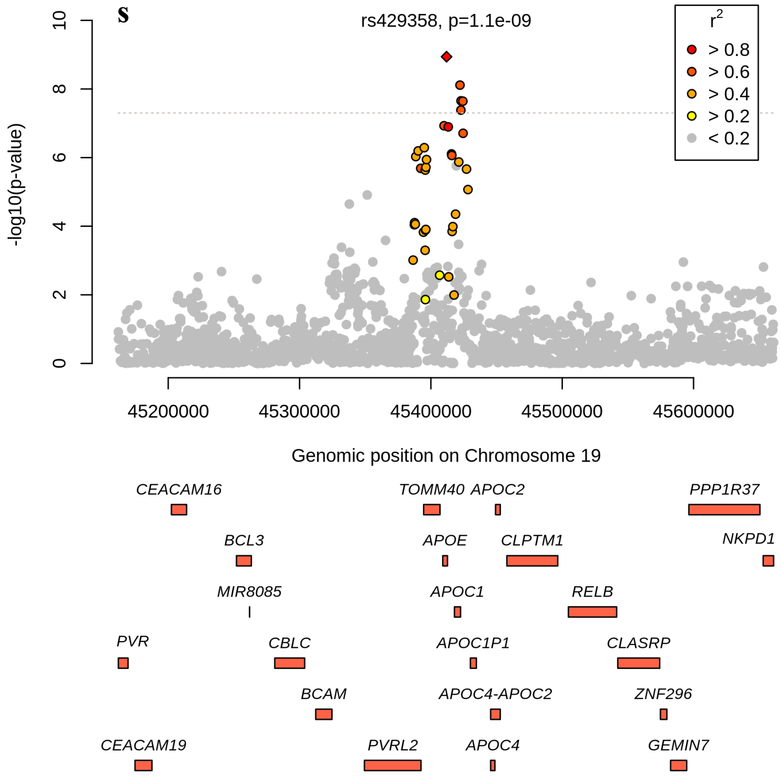
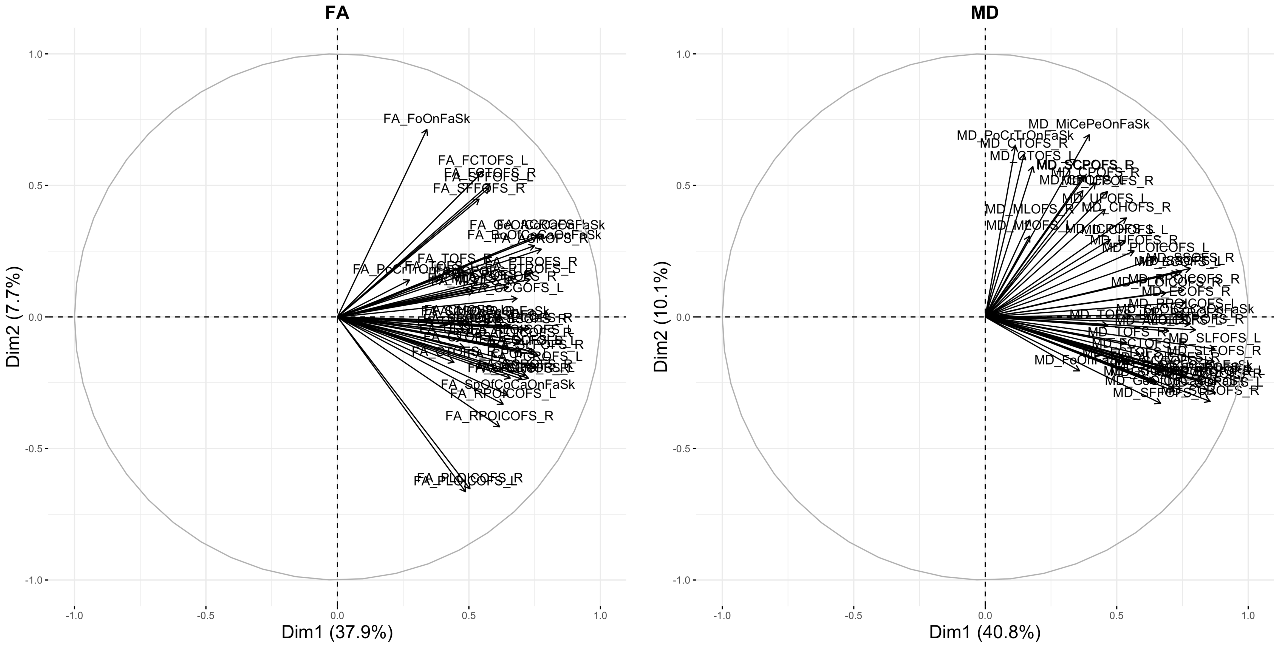
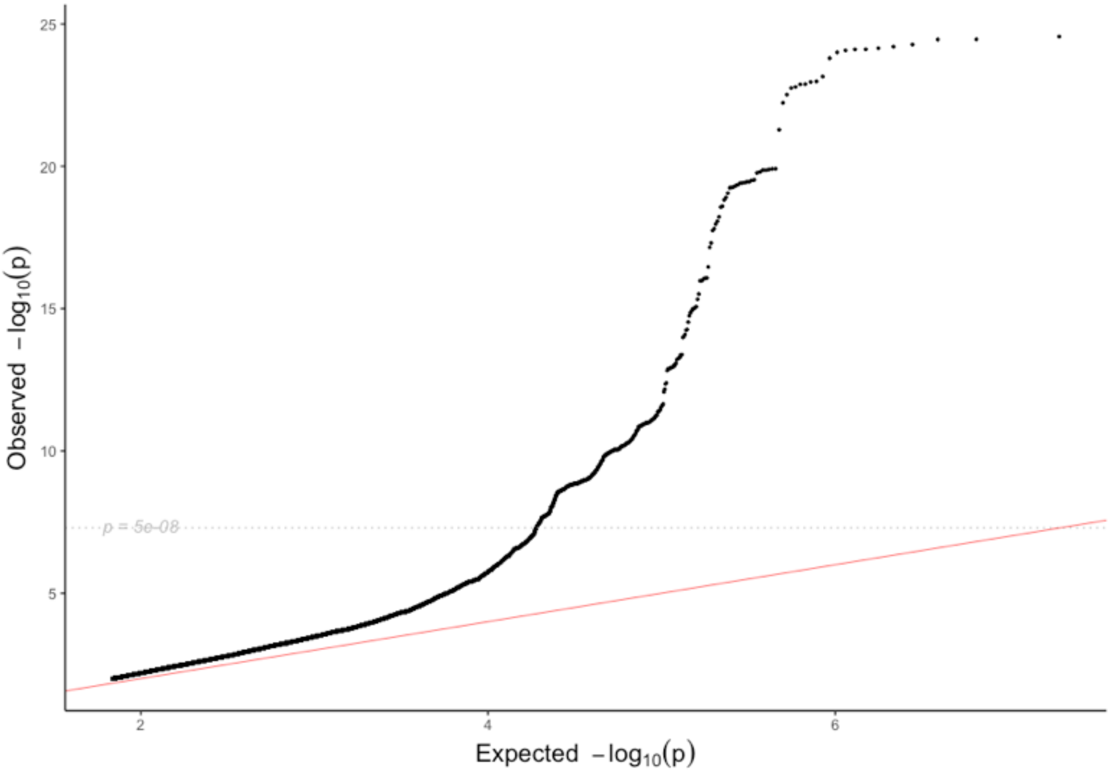


Supplementary Figure 2. Regional plots of WMH significant association results. The different panels correspond to the following top SNPs: **a.** rs12120143, **b.** rs7566761, **c.** rs7596872, **d.** rs17576323, **e.** rs72934505, **f.** rs830179, **g.** rs17148926, **h.** rs275350, **i.** rs3215395, **j.** rs4630220, **k.** rs11838776, **l.** rs11160570, **m.** rs12906662, **n.** rs17616633, **o.** rs12928520, **p.** rs6587216, **q.** rs8071429, **r.** rs7214628 and **s.** rs429358.

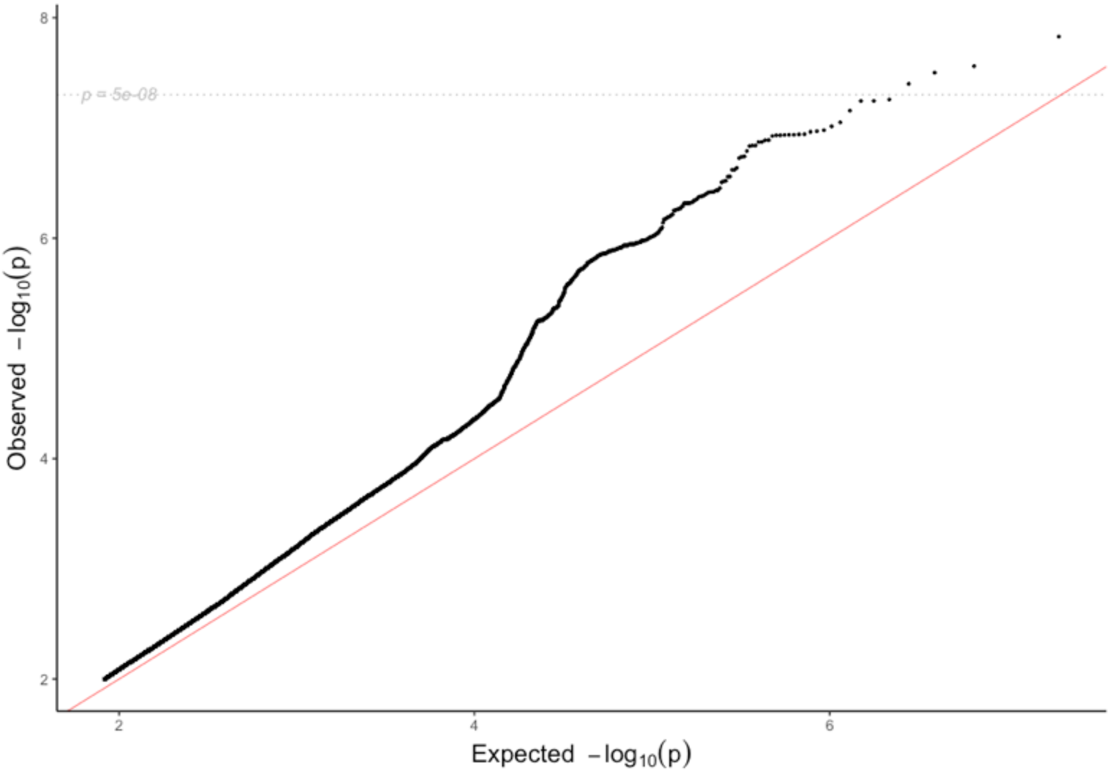
Supplementary Figure 3. Comparison between European and trans-ethnic results for WMH reported top SNPs. Beta coefficients were estimated from meta-analysis Z-scores and sample sizes, and allele frequencies in UK Biobank. Error bars, mean ± 1.96 s.e..



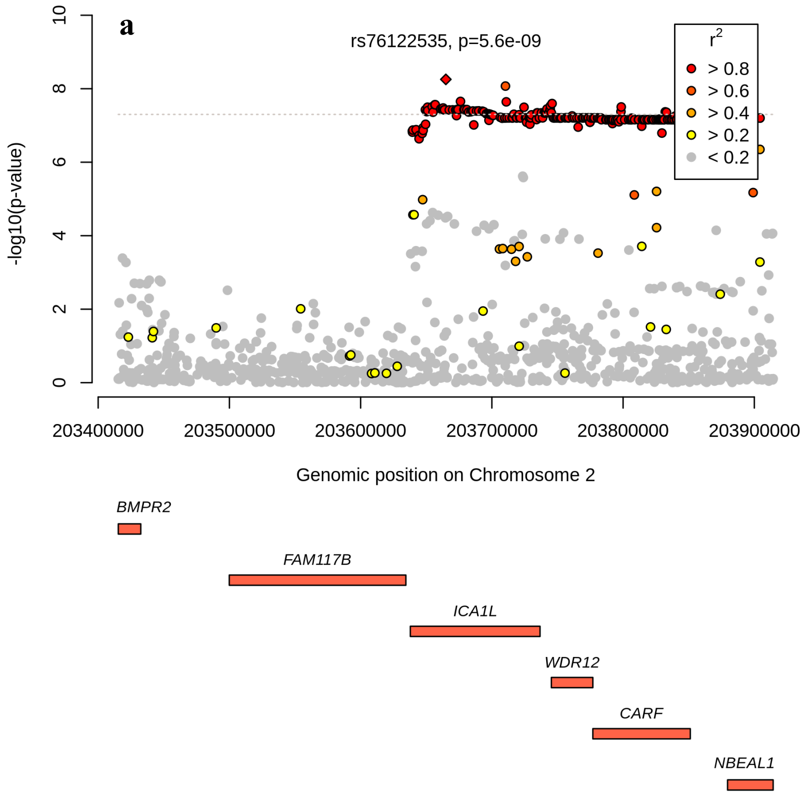
Supplementary Figure 4. PCA correlation plots.



Supplementary Figure 5. QQ plot for FA GWAS in UK Biobank.



Supplementary Figure 6. QQ plot for MD GWAS in UK Biobank.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> 0.6
> 0.4
> 0.2
< 0.2
203400000
203500000
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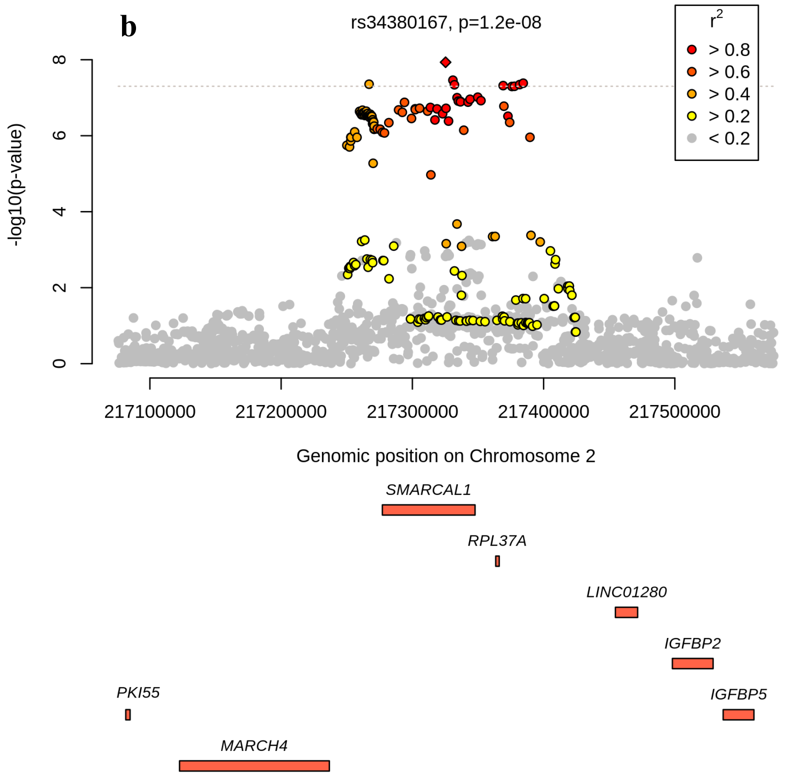
Genomic position on Chromosome 2
BMPR2
FAM117B
ICA1L
WDR12
CARF
NBEAL1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6
8
r^2
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> 0.6
> 0.4
> 0.2
< 0.2
217100000
217200000
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Genomic position on Chromosome 2
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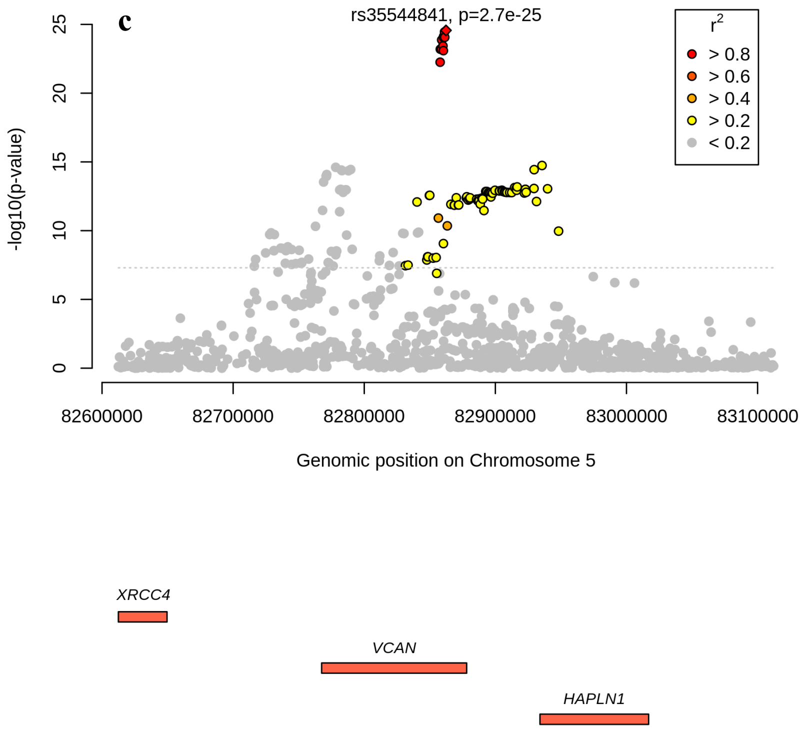
PKI55
IGFBP5
MARCH4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> 0.4
> 0.2
< 0.2
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Genomic position on Chromosome 5
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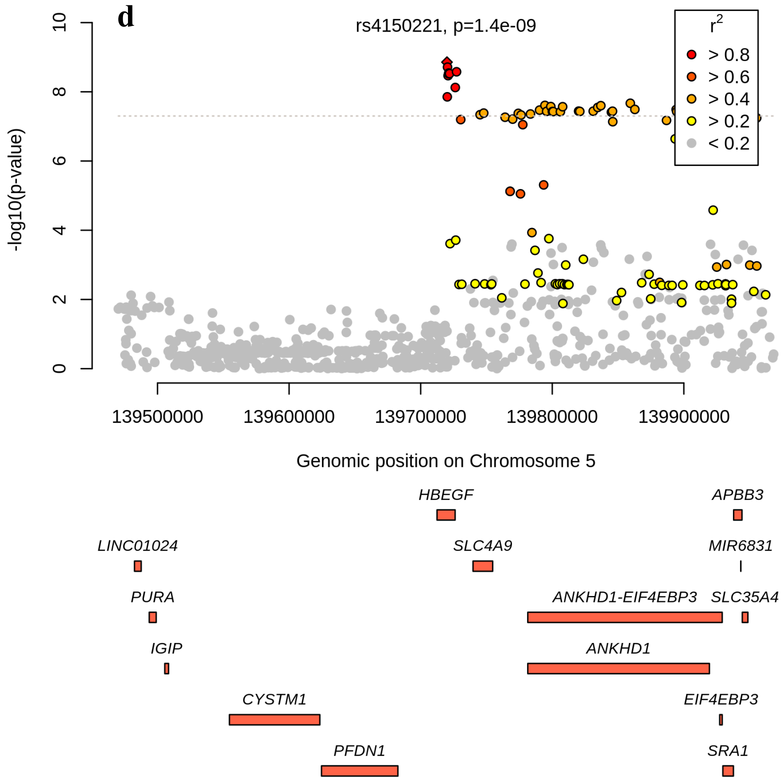
VCAN
HAPLN1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> 0.4
> 0.2
< 0.2
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139600000
139700000
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139900000
Genomic position on Chromosome 5
HBEGF
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SLC4A9
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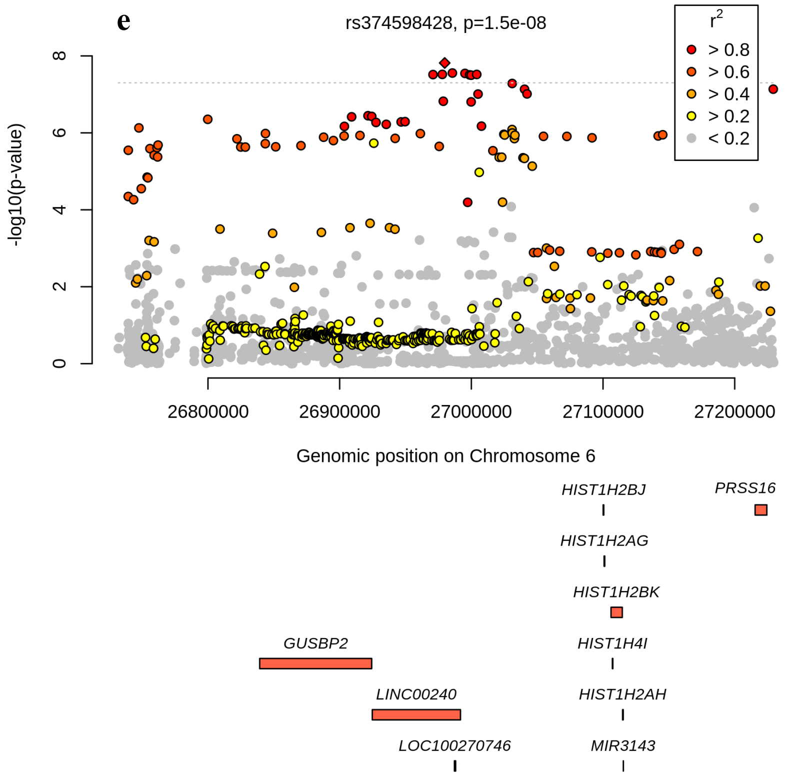
IGIP
ANKHD1
CYSTM1
EIF4EBP3
PFDN1
SRA1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● > 0.6
● > 0.4
● > 0.2
● < 0.2
-log10(p-value)
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2
4
6
8
26800000
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27200000
Genomic position on Chromosome 6
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LINC00240
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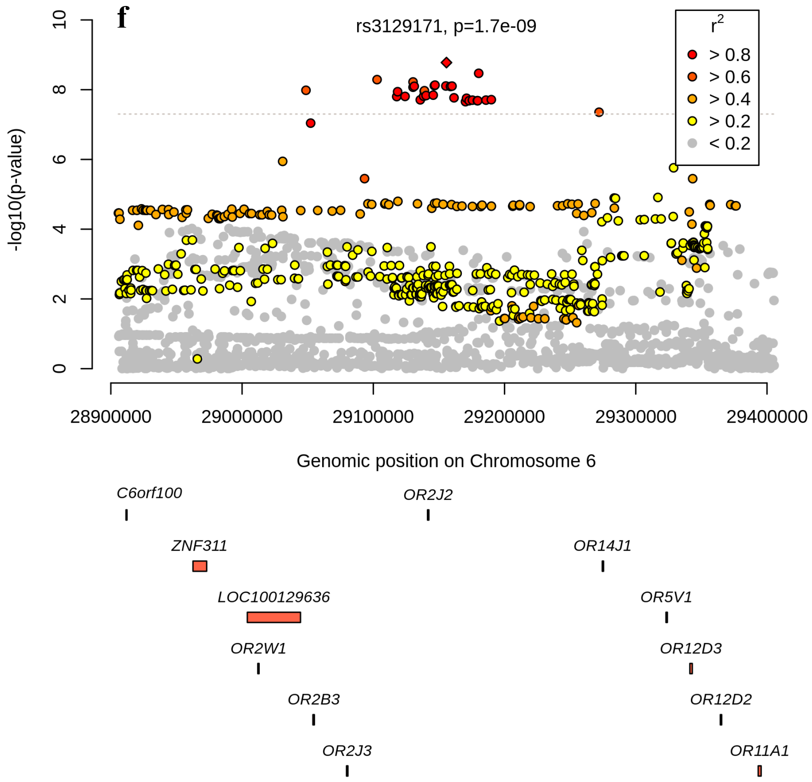
MIR3143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● < 0.2
-log10(p-value)
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6
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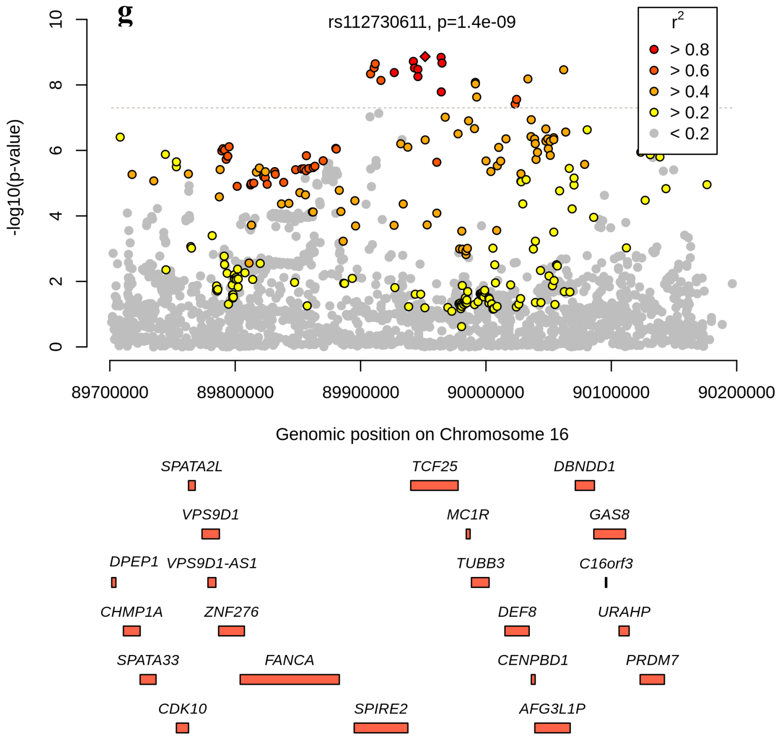
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8
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Genomic position on Chromosome 16
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DBNDD1
VPS9D1
MC1R
GAS8
DPEP1
VPS9D1-AS1
TUBB3
C16orf3
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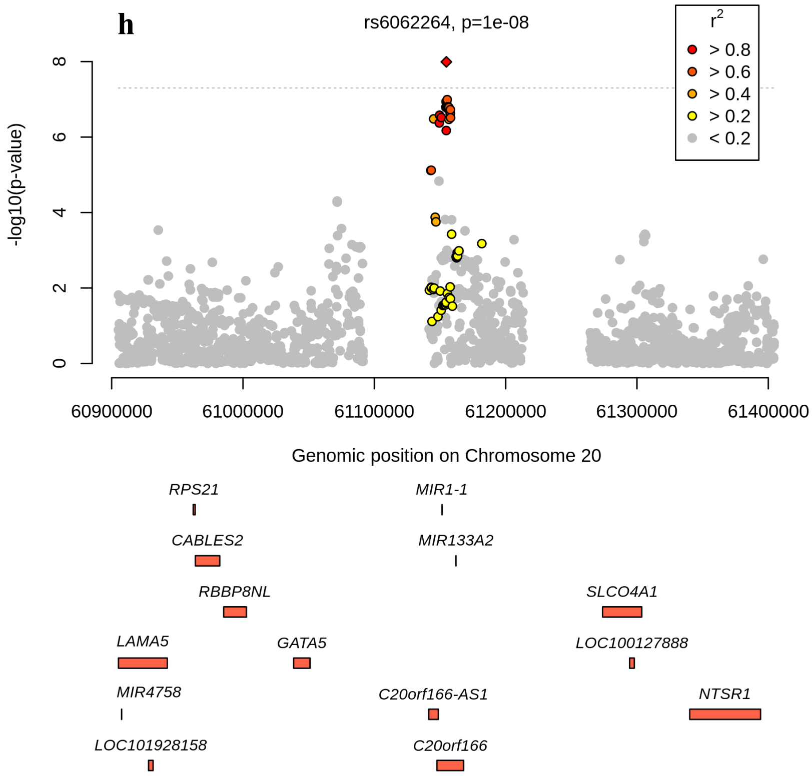
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8
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Genomic position on Chromosome 20
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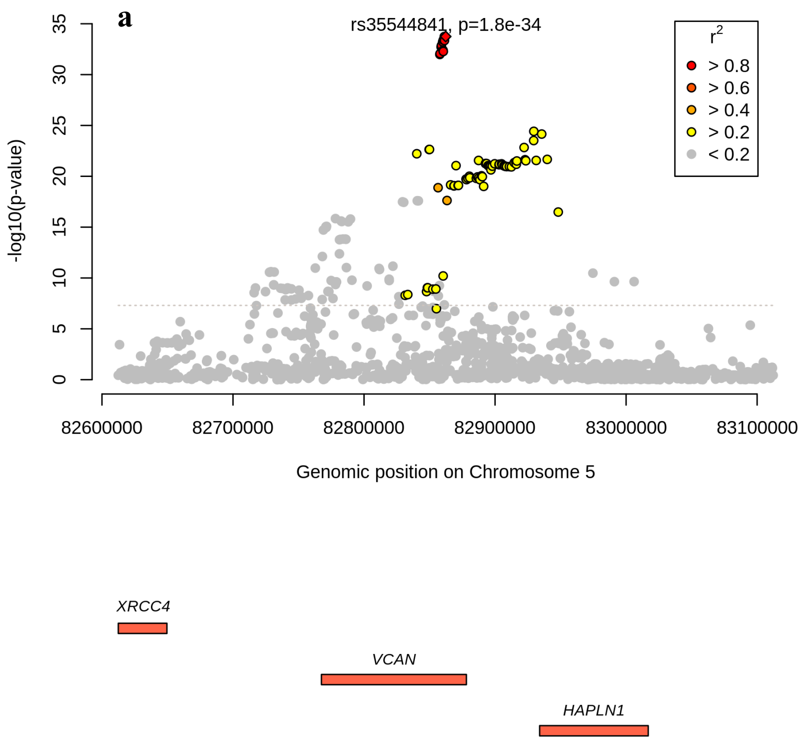
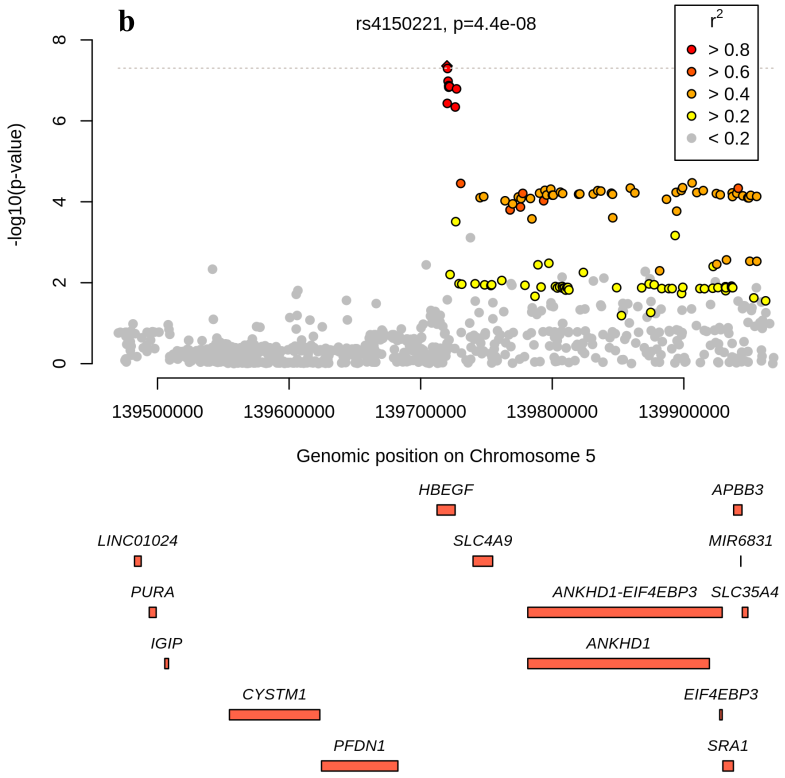
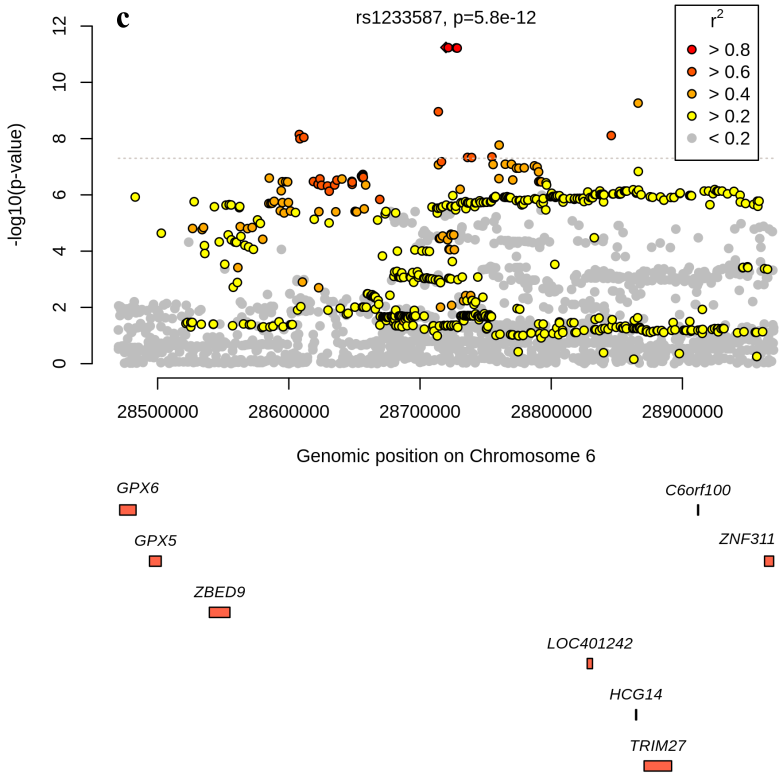
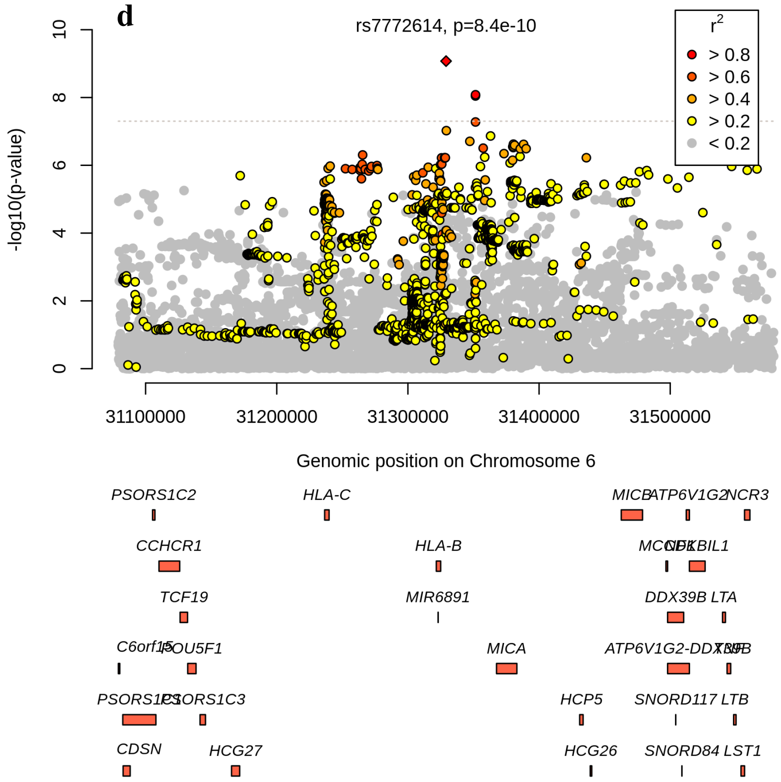
C20orf166-AS1
NTSR1
LOC101928158
C20orf166

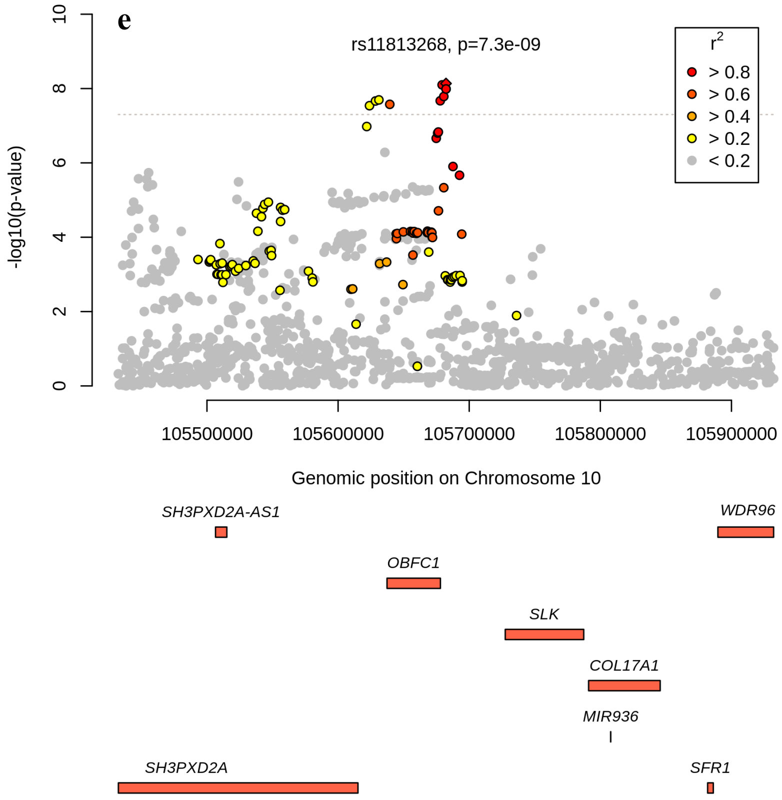
Supplementary Figure 7. Regional plots of FA significant association results. The different panels correspond to the following top SNPs: **a.** rs76122535, **b.** rs34380167, **c.** rs35544841, **d.** rs4150221, **e.** rs374598428, **f.** rs3129171, **g.** rs112730611 and **h.** rs6062264.

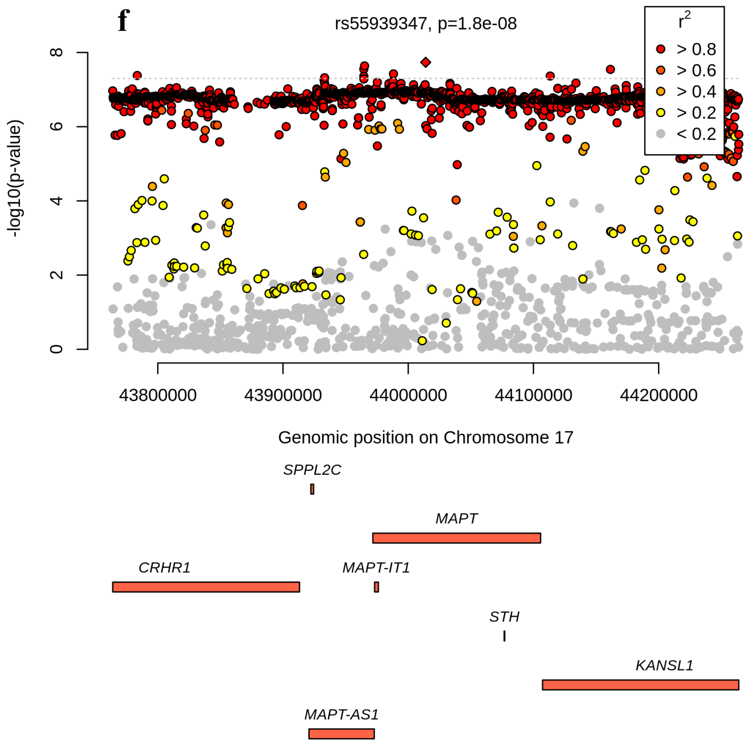

a
rs35544841, p=1.8e-34
r²
> 0.8
> 0.6
> 0.4
> 0.2
< 0.2
-log10(p-value)
0
5
10
15
20
25
30
35
82600000
82700000
82800000
82900000
83000000
83100000
Genomic position on Chromosome 5
XRCC4
VCAN
HAPLN1


b
rs4150221, p=4.4e-08
r²
> 0.8
> 0.6
> 0.4
> 0.2
< 0.2
-log10(p-value)
0
2
4
6
8
139500000
139600000
139700000
139800000
139900000
Genomic position on Chromosome 5
HBEGF
APBB3
LINC01024
SLC4A9
MIR6831
PURA
ANKHD1-EIF4EBP3
SLC35A4
IGIP
ANKHD1
CYSTM1
EIF4EBP3
PFDN1
SRA1

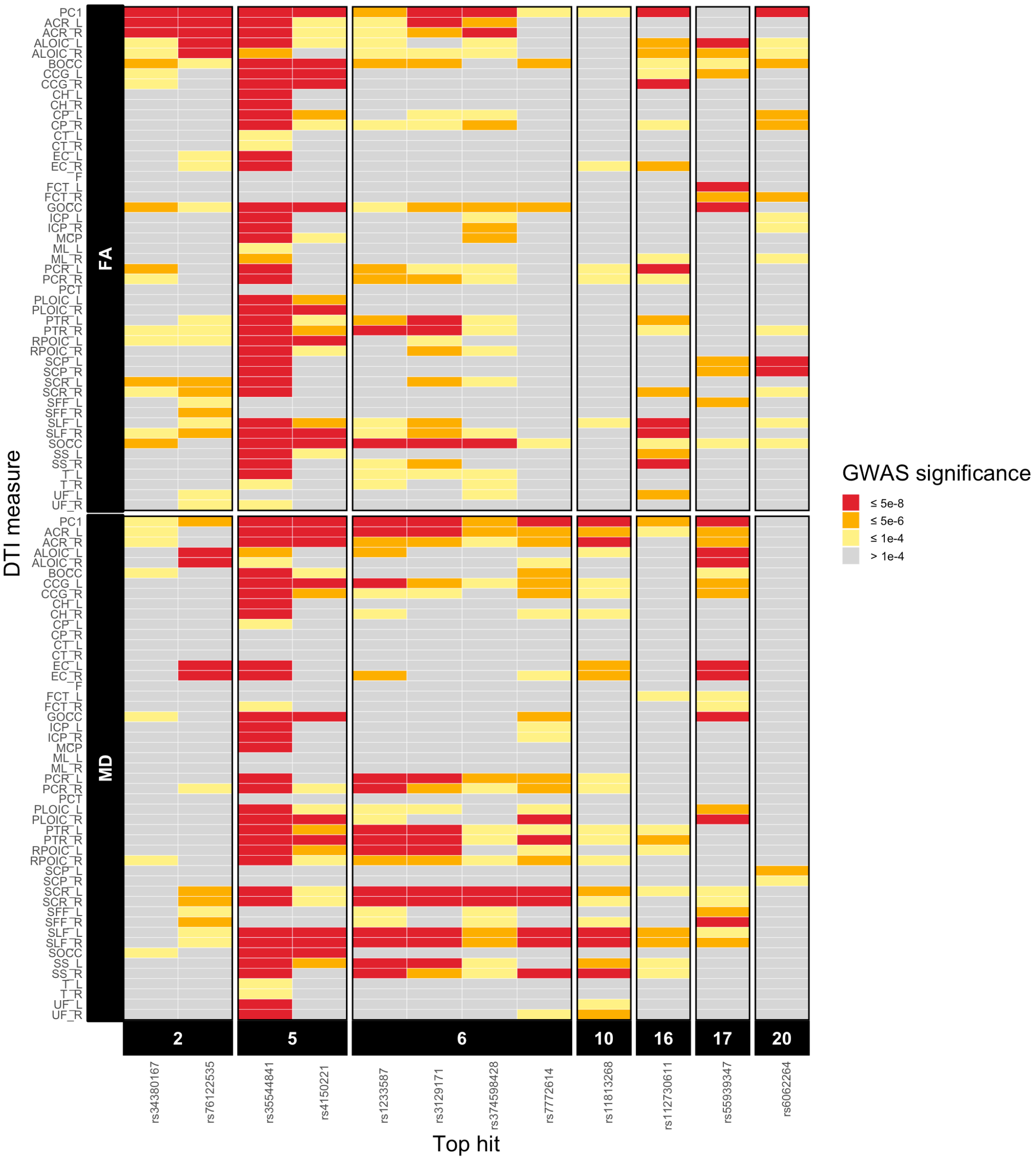

c
rs1233587, p=5.8e-12
-log10(p-value)
0
2
4
6
8
10
12
r^2
> 0.8
> 0.6
> 0.4
> 0.2
< 0.2
28500000
28600000
28700000
28800000
28900000
Genomic position on Chromosome 6
GPX6
C6orf100
GPX5
ZNF311
ZBED9
LOC401242
HCG14
TRIM27


d
rs7772614, p=8.4e-10
-log10(p-value)
0
2
4
6
8
10
r^2
> 0.8
> 0.6
> 0.4
> 0.2
< 0.2
31100000
31200000
31300000
31400000
31500000
Genomic position on Chromosome 6
PSORS1C2
HLA-C
MICB
ATP6V1G2
NCR3
CCHCR1
HLA-B
MCCD1
NFKBIL1
TCF19
MIR6891
DDX39B
LTA
C6orf15
POU5F1
MICA
ATP6V1G2-DDX39B
TNF
PSORS1C1
PSORS1C3
HCP5
SNORD117
LTB
CDSN
HCG27
HCG26
SNORD84
LST1


e
rs11813268, p=7.3e-09
r2
> 0.8
> 0.6
> 0.4
> 0.2
< 0.2
-log10(p-value)
0
2
4
6
8
10
105500000
105600000
105700000
105800000
105900000
Genomic position on Chromosome 10
SH3PXD2A-AS1
WDR96
OBFC1
SLK
COL17A1
MIR936
SH3PXD2A
SFR1

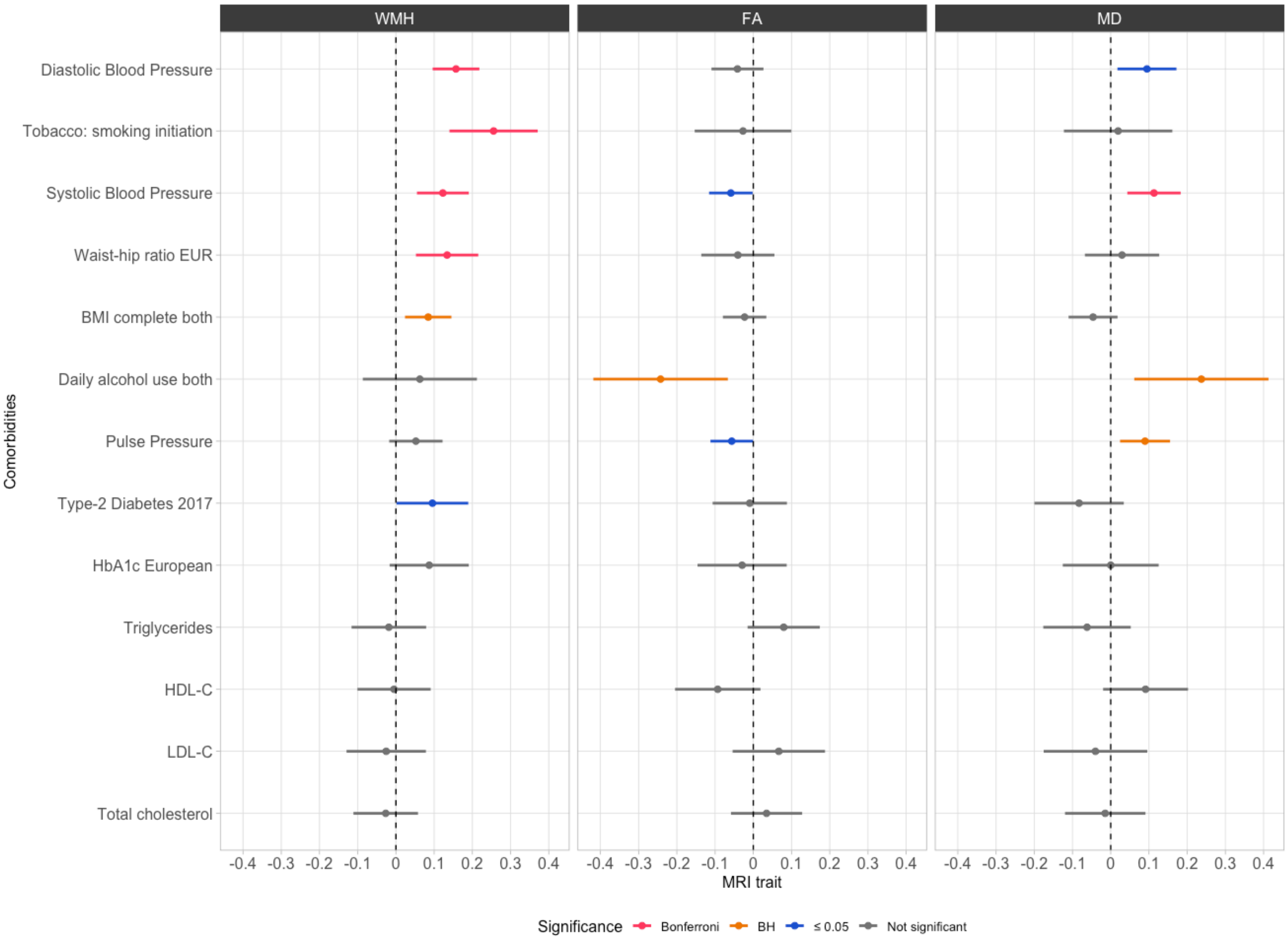

f
rs55939347, p=1.8e-08
r2
> 0.8
> 0.6
> 0.4
> 0.2
< 0.2
-log10(p-value)
0
2
4
6
8
43800000
43900000
44000000
44100000
44200000
Genomic position on Chromosome 17
SPPL2C
MAPT
CRHR1
MAPT-IT1
STH
KANSL1
MAPT-AS1

Supplementary Figure 8. Regional plots of MD significant association results. The different panels correspond to the following top SNPs: **a.** rs35544841, **b.** rs4150221, **c.** rs1233587, **d.** rs7772614, **e.** rs11813268 and **f.** rs55939347.

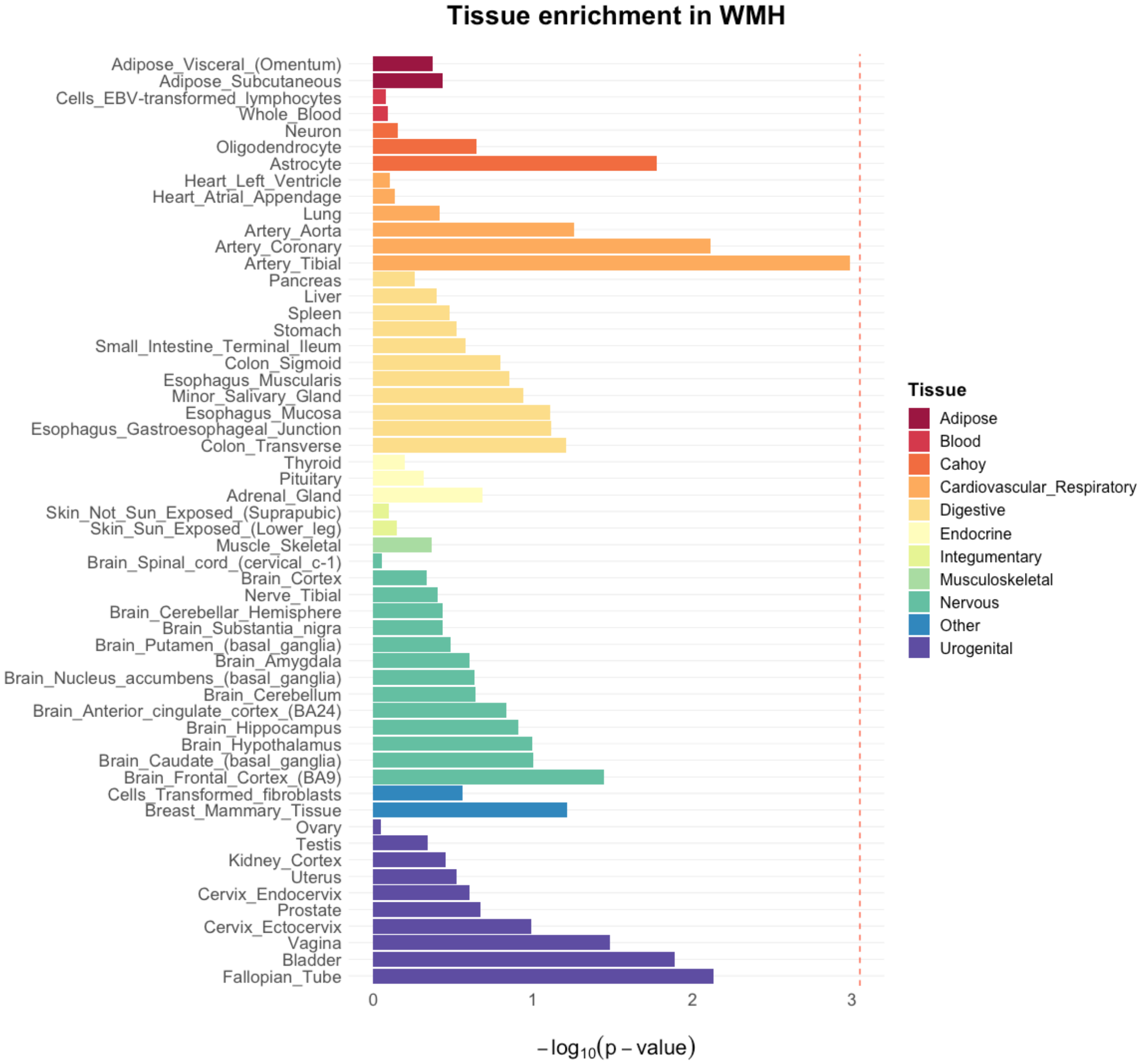


Supplementary Figure 9. Association results in the different brain regions.

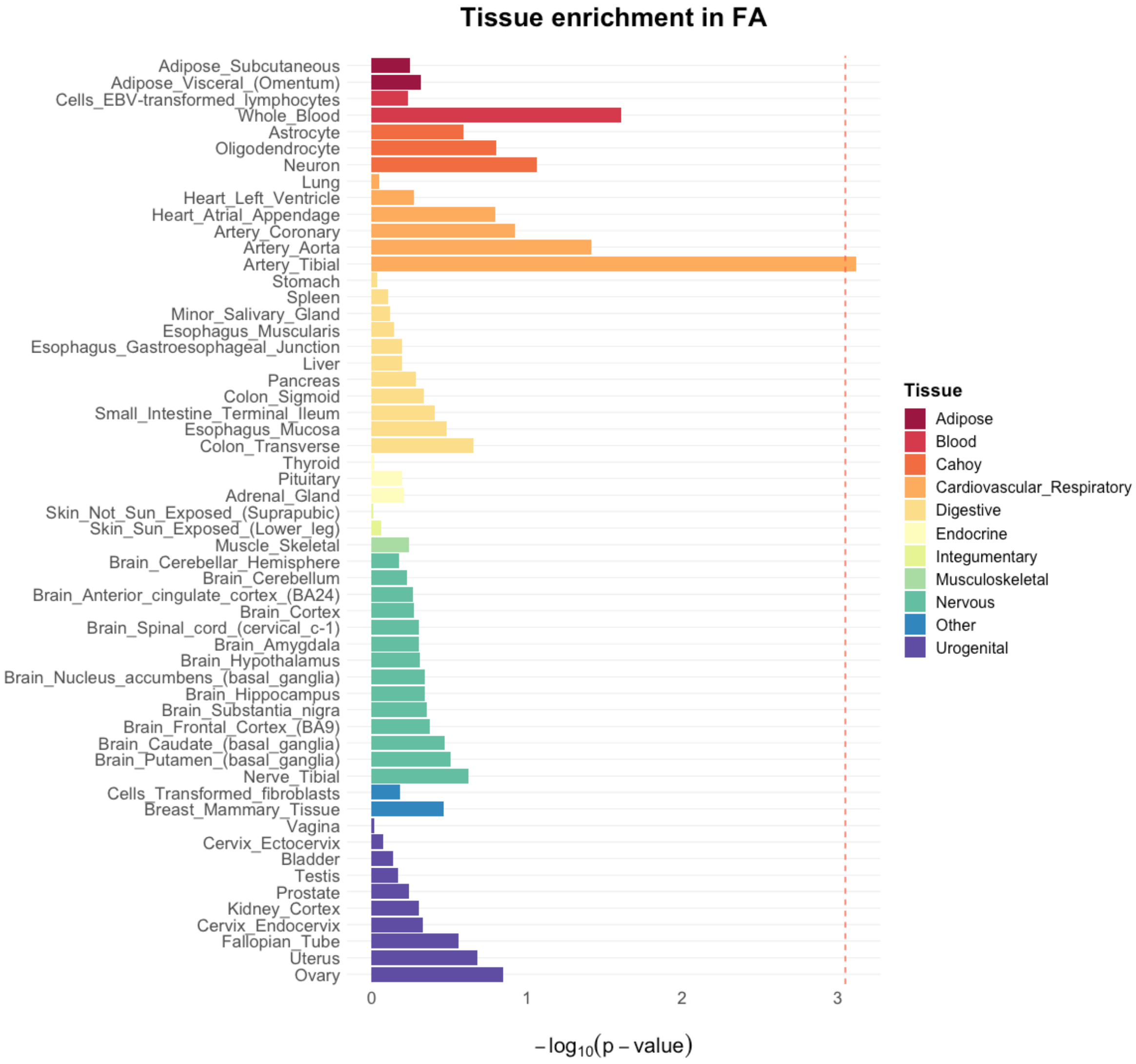
Abbreviations: PC1: first principal component, as the global measure of white matter DTI signal; L: left; R: right; ACR: anterior corona radiata; ALOIC: anterior limb of internal capsule; BOCC: body of corpus callosum; CCG: cingulum cingulate gyrus; CH: cingulum hippocampus; CP: cerebral peduncle; CT: corticospinal tract; EC: external capsule; F: fornix; FCT: fornix cres/stria terminalis; GOCC: genu of corpus callosum; ICP: inferior cerebellar peduncle; MCP: middle cerebellar peduncle; ML: medial lemniscus; PCR posterior corona radiata; PCT: pontine crossing tract; PLOIC: posterior limb of internal capsule; PTR: posterior thalamic radiation; RPOIC: retrolenticular part of internal capsule; SCP: superior cerebellar peduncle; SCR: superior corona radiata; SFF: superior fronto-occipital fasciculus; SLF: superior longitudinal fasciculus; SOCC: splenium of corpus callosum; SS sagittal stratum; T: tapetum; UF: uncinate fasciculus



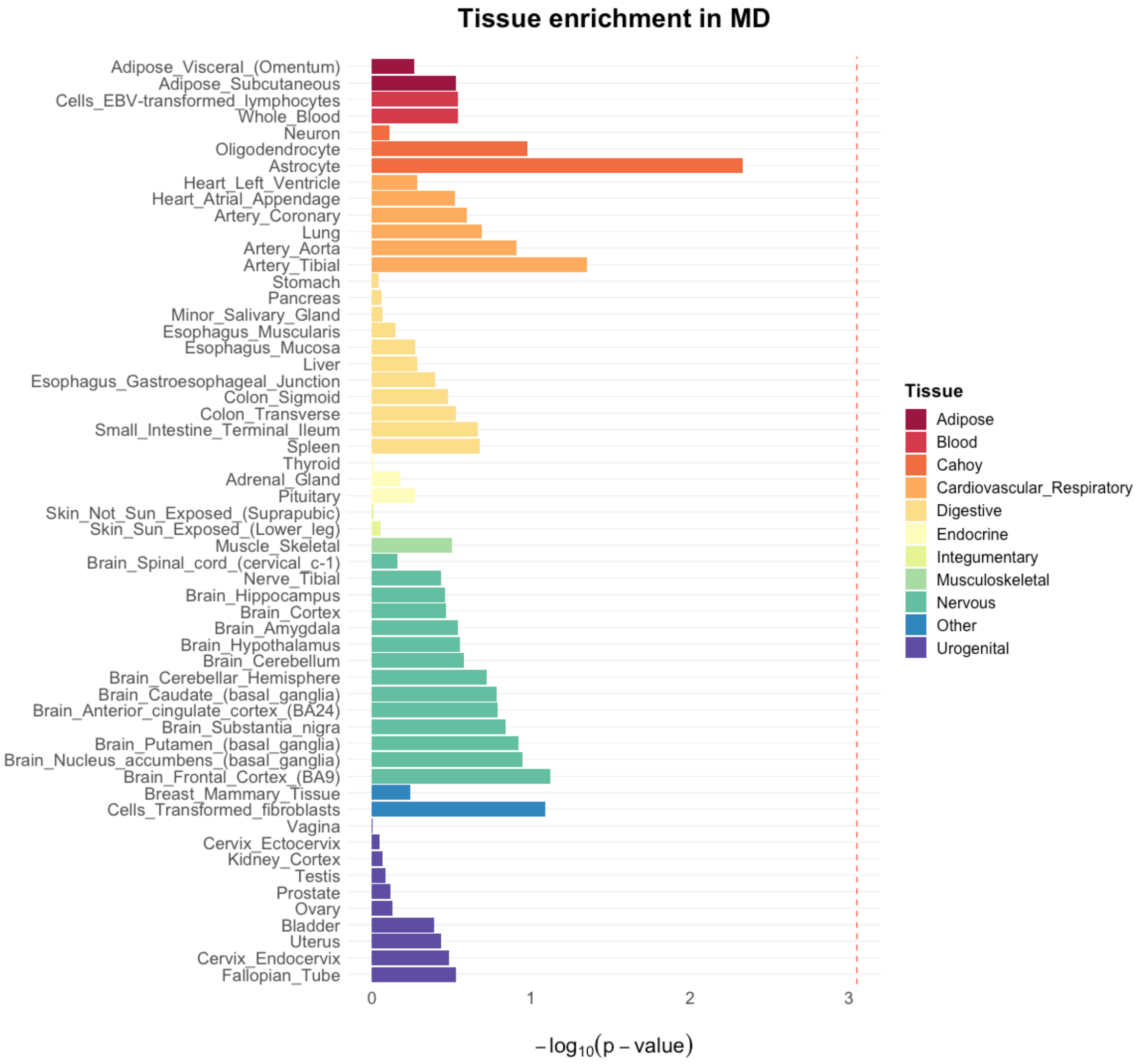
Supplementary Figure 10. Genetic correlation results with CSVD comorbidities. Bonferroni and Benjamini and Hochberg multiple testing corrections were applied considering only p-values for genetic correlation with these cardiovascular risk factors. Error bars, mean ± 1.96 s.e..



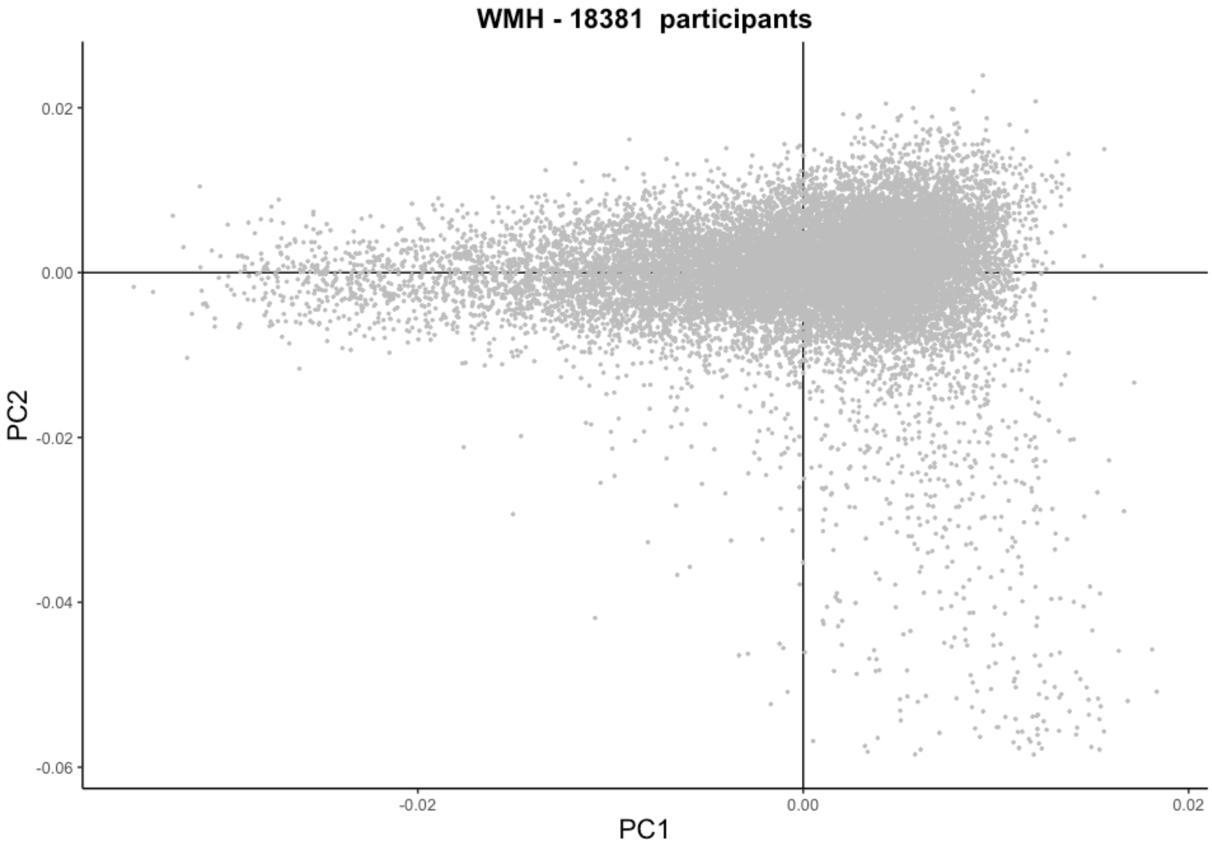
Supplementary Figure 11. Tissue enrichment in WMH GWAS meta-analysis summary statistics.



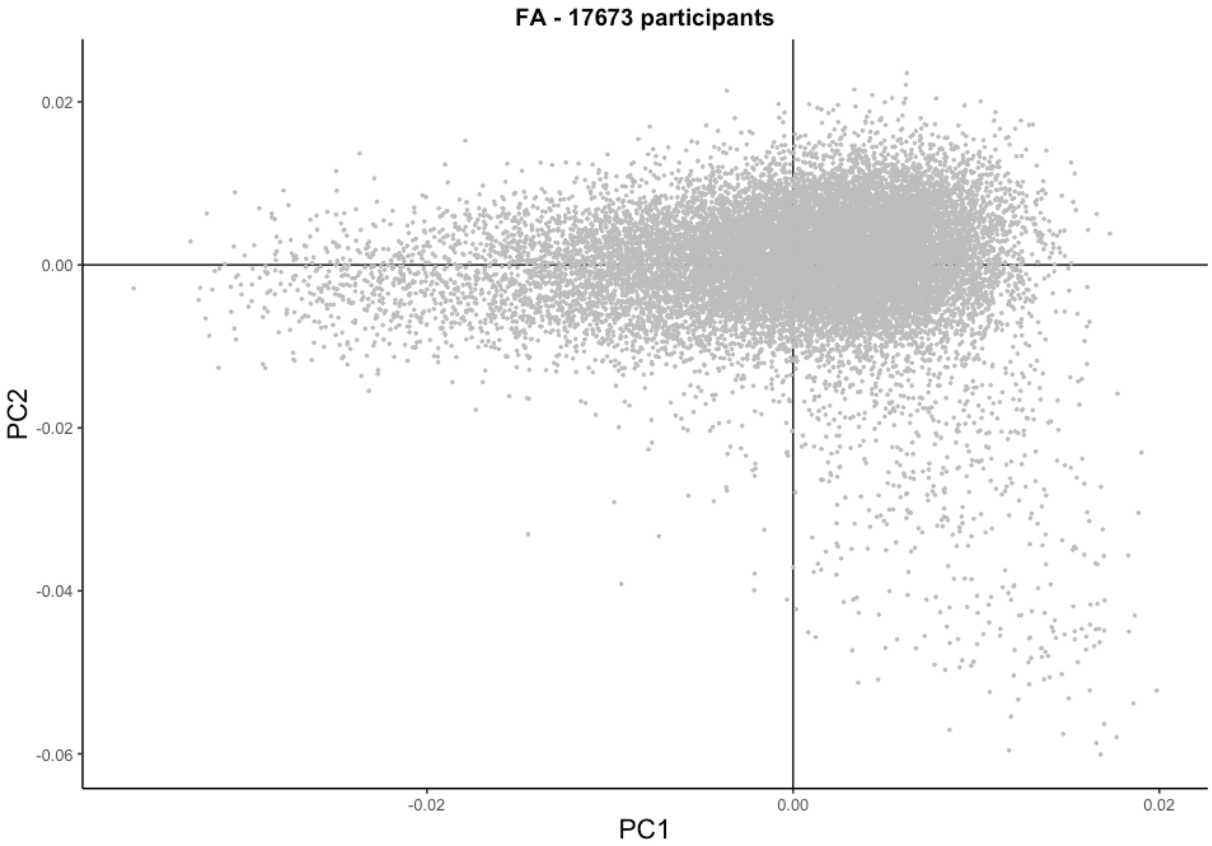
Supplementary Figure 12. Tissue enrichment in FA GWAS summary statistics.



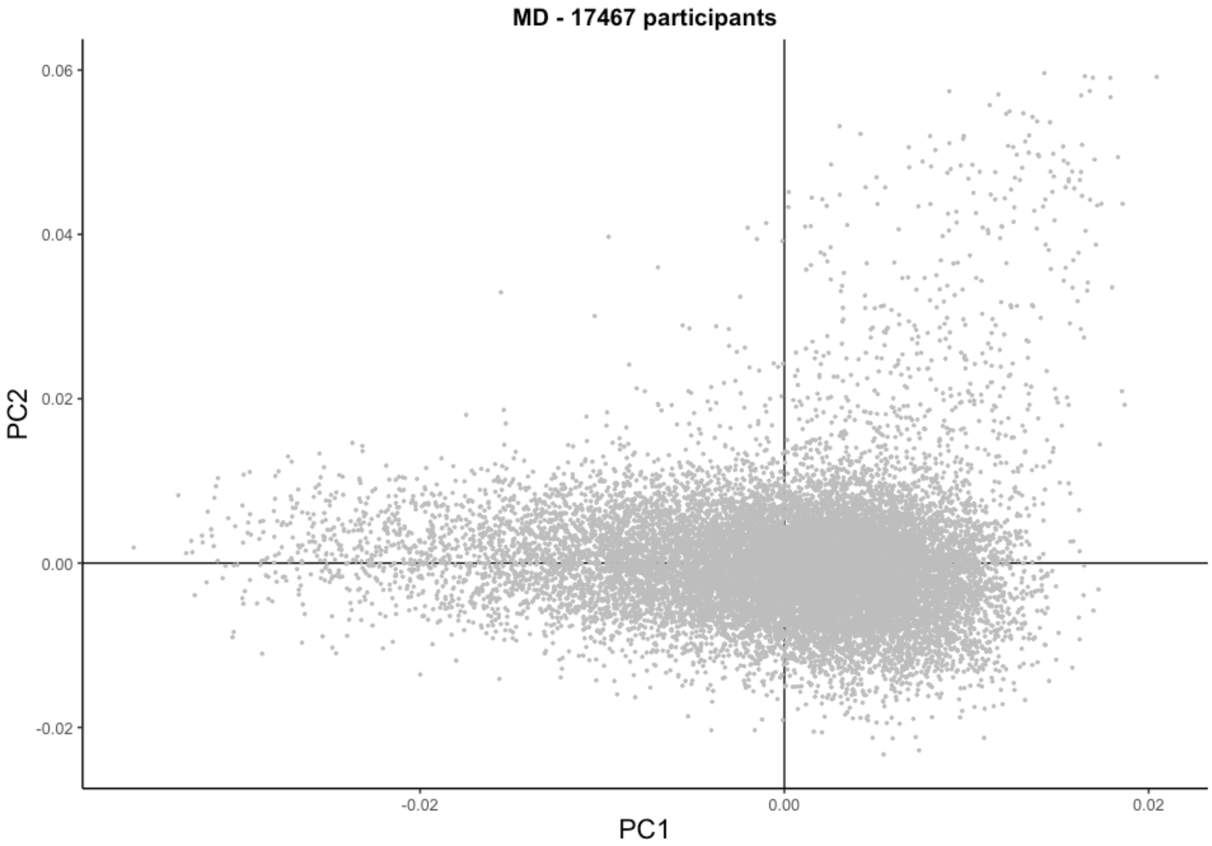
Supplementary Figure 13. Tissue enrichment in MD GWAS summary statistics.



Supplementary Figure 14. Graph of individuals for PCA on WMH dataset.



Supplementary Figure 15. Graph of individuals for PCA on FA dataset.



Supplementary Figure 16. Graph of individuals for PCA on MD dataset.

Supplementary Table 1. PCA eigenvalues and explained percentages of variance for FA and MD measure derivation

PC	Eigen value	Percentage of variance	Cumulative percentage of variance	Eigen value	Percentage of variance	Cumulative percentage of variance
1	18.17	37.86	37.86	19.57	40.76	40.76
2	3.7	7.71	45.58	4.86	10.13	50.9
3	2.62	5.46	51.04	3.58	7.47	58.36
4	1.86	3.87	54.91	2.4	5.01	63.37
5	1.72	3.59	58.5	2.13	4.43	67.8

Supplementary Table 2. GO enrichment analysis.

TRAIT	SET	NGENES	BETA	BETA_STD	SE	P	Name	Category	pBH
WMH	GO:0098910	3	2.31	0.0294	0.553	1.51E-05	regulation of atrial cardiac muscle cell action potential	biological process	0.04085
WMH	GO:0048050	3	2.39	0.0305	0.584	2.08E-05	post-embryonic eye morphogenesis	biological process	0.04085
WMH	GO:0005925	397	0.181	0.0263	0.0416	6.47E-06	focal adhesion	cell component	0.031746
WMH	GO:0031752	3	1.87	0.0239	0.405	1.95E-06	D5 dopamine receptor binding	molecular function	0.019137
WMH	GO:0016176	7	1.17	0.0228	0.285	2.05E-05	superoxide-generating NADPH oxidase activator activity	molecular function	0.04085
WMH	GO:0004713	81	0.363	0.024	0.0903	3.01E-05	protein tyrosine kinase activity	molecular function	0.049283
MD	GO:0098912	3	2.67	0.034	0.564	1.09E-06	membrane depolarization during atrial cardiac muscle cell action potential	biological process	0.003555
MD	GO:0086045	5	1.71	0.0281	0.415	1.99E-05	membrane depolarization during AV node cell action potential	biological process	0.048783
MD	GO:0086056	3	2.68	0.0341	0.543	4.09E-07	voltage-gated calcium channel activity involved in AV node cell action potential	molecular function	0.003555
MD	GO:0005540	24	0.77	0.0278	0.162	1.01E-06	hyaluronic acid binding	molecular function	0.003555

TRAIT: imaging trait; SET: gene set as the GO term ID; NGENES: the number of genes in the data that are in the set; BETA: the regression coefficient of the variable; BETA_STD: the semi-standardized regression coefficient; SE: the standard error of the regression coefficient; P: p-value for gene-set enrichment; Name: the GO term name; Category: the GO category; pBH: p-value after Benjamini-Hochberg FDR multiple testing correction.

Supplementary Table 3. Contribution of cardiovascular risk factors to WMH measure in UK Biobank population.

Risk factors	Field derivation	Sample size	Adjusted R2	P-value
Average systolic blood pressure, automated reading	mean(f4080_2_0,f4080_2_1)	15444	0.0108	1.34×10-38
Average diastolic blood pressure, automated reading	mean(f4079_2_0,f4079_2_1)	15444	0.0096	2.49×10-34
Waist/hip ratio	f48_2_0/f49_2_0	17979	0.0067	2.34×10-28
Average weekly alcohol intake	f1588_2_0 + f1578_2_0 + f1608_2_0 + f5364_2_0 + f1598_2_0	13226	0.0058	1.15×10-18
Body mass index	f21001_2_0	17926	0.0047	1.93×10-20
Diabetes diagnosed by doctor	f2443_2_0	18225	0.0039	2.48×10-17
Ever smoked	f20160_2_0	18197	0.0013	8.33×10-07

Supplementary Table 4. Mouse brain cell-type enrichment analysis.

GENE_SET_DEF	SET	NGENES	BETA	BETA_STD	SE	P
TOP100	aaSMC	91	0.136	0.00953	0.0852	0.054989
TOP100	AC	84	-0.0768	-0.00517	0.0897	0.80392
TOP100	aEC	115	0.0169	0.00133	0.0808	0.41737
TOP100	aSMC	95	0.15	0.0108	0.088	0.04386
TOP100	capilEC	102	-0.0576	-0.00427	0.0784	0.76877
TOP100	EC1	109	0.0904	0.00693	0.0827	0.13715
TOP100	EC2	110	-0.12	-0.00922	0.0793	0.93471
TOP100	EC3	95	0.0404	0.00289	0.0836	0.3142
TOP100	FB1	113	-0.16	-0.0125	0.0832	0.97263
TOP100	FB2	106	0.109	0.00825	0.0869	0.10442
TOP100	MG	117	-0.0472	-0.00374	0.0786	0.7258
TOP100	OL	97	0.0376	0.00272	0.0816	0.32244
TOP100	PC	102	-0.0551	-0.00408	0.08	0.75441
TOP100	vEC	89	0.0563	0.0039	0.0823	0.24676
TOP100	vSMC	89	-0.125	-0.00866	0.0896	0.91862
TOP500	aaSMC	535	0.0319	0.00535	0.037	0.19425
TOP500	AC	460	0.0322	0.00503	0.0396	0.20749
TOP500	aEC	545	0.0299	0.00506	0.0357	0.20154
TOP500	aSMC	528	0.0519	0.00864	0.0377	0.08441
TOP500	capilEC	519	0.0564	0.00931	0.0363	0.060042
TOP500	EC1	515	0.026	0.00427	0.0368	0.23995
TOP500	EC2	541	-0.0915	-0.0154	0.0355	0.99502
TOP500	EC3	526	0.0244	0.00406	0.0365	0.25171
TOP500	FB1	485	-0.00884	-0.00141	0.038	0.59196
TOP500	FB2	500	0.0759	0.0123	0.0391	0.026026
TOP500	MG	544	-0.0273	-0.00462	0.0365	0.77292
TOP500	OL	480	0.0522	0.0083	0.0378	0.083886
TOP500	PC	494	0.0124	0.002	0.0381	0.37261
TOP500	vEC	507	0.0129	0.00211	0.0368	0.36306
TOP500	vSMC	500	0.033	0.00535	0.0383	0.19469

Abbreviations: SMC: smooth muscle cell; EC: endothelial cell; PC: pericytes; vSMC: venous SMC; aaSMC: arteriolar SMC; aSMC: arterial SMC; MG: microglia; FB1: fibroblast-like type I; FB2: fibroblast-like type II; OL: oligodendrocytes; EC1: EC type 1; EC2: EC type 2; EC3: EC type 3; vEC: venous EC; capilEC: capillary EC; aEC: arterial EC; AC: astrocyte; GENE_SET_DEF: gene-set definition, i.e. top 100 or top 500 differentially expressed genes between the cell type vs other cell types; SET: cell-type gene set; NGENES: the number of genes in the data that are in the set; BETA: the regression coefficient of the variable; BETA_STD: the semi-standardized regression coefficient; SE: the standard error of the regression coefficient; P: p-value for gene-set enrichment

Supplementary Table 5. Removed field codes description.

	Non-cancer illness code, self-reported	ICD9	ICD10
	(20002)	(41203, 41205)	(41202, 41204)
Stroke	1081, 1086, 1491, 1583	430, 431, 434, 436	I60, I61, I63, I64
Multiple sclerosis	1261	340	G35
Parkinson	1262	332	G20
Dementia	1263	290	F00-F03
Neurodegenrative	1397	341	G30-G32, G36, G37

Supplementary Table 6. Sample quality control description.

	WMH	**FA**	**MD**
Individuals with phenotype data	20,200	19,395	19,395
With a disease code	-409	-398	-398
Remaining	19,791	18,997	18,997
Outliers	0	-71	-282
Remaining	19,791	18,926	18,715
No QC information	-508	-471	-260
Remaining	19,283	18,455	18,455
(1) Kinship >= 0.0884	-156	-145	-144
(2) Gender mismatch	-15	-14	-13
(3) Outliers (het. missing.)	-37	-36	-36
(3) Missing rate > 0.05	-14	-14	-14
(4) No European ancestry	-481	-455	-449
Intersect from (1) to (4)	-688	-649	-641
Remaining	18,595	17,806	17,605
Outliers with smartpca	-213	-143	-138
Individuals for GWAS analysis	18,381	17,663	17,467

Supplementary Table 7. UK Biobank field codes to derive covariates.

Covariate	Field code	Description
Sex	31	Sex
Age at MRI	34	Year of birth
	52	Month of birth
	53	Date of attending assessment centre
UKB centre	54	UK Biobank assessment centre
Genotype Batch	Note: From sample QC file	
Mean rfMRI	25741	Mean rfMRI head motion, averaged across space and time points
Mean rfMRI	25742	Mean tfMRI head motion, averaged across space and time points
PC1 – PC10	Note: Derived from PCA on genotype data	

Supplementary Table 8. Covariate description.

Covariate		**WMH**	**FA**	**MD**
		N = 18,381	**N = 17,673**	**N = 17,467**
Sex	Female	9,688	9,362	9,278
		(52.7%)	(53.0%)	(53,1%)
	Male	8,693	8,311	8,189
		(47.3%)	(47.0%)	(46.9%)
Age at MRI	Mean (Sd)	63.3 (7.4)	63.2 (7.4)	63.1 (7.4)
UKB centre	Cheadle	15,431	14,802	14,622
		(84.0%)	(83.8%)	(83.7%)
	Newcastle	2,950	2,871	2,845
		(16.0%)	(16.2%)	(16.3%)
Genotype Batch	UKBB	16,582	15,943	15,759
		(90.2%)	(90.2%)	(90.2%)
	UKBL	1,799	1,730	1,708
		(9.8%)	(9.8%)	(9.8%)
Mean rfMRI	Number of missing values	799	58	57
Mean tfMRI	Number of missing values	1847	1109	1095
PC1-PC10				

Supplementary Table 9. Description of covariates in relation to WMH, FA and MD phenotypes

Covariate			WMH	FA	MD
			N = 18,381	N = 17,673	N = 17,467
Sex	Female	Mean (Sd)	7.80 (1.15)	-0.14 (4.2)	-0.38 (4.33)
	Male	Mean (Sd)	8.13 (1.18)	0.16 (4.33)	0.43 (4.48)
Age at MRI	r2		0.6	-0.35	0.4
UKB centre	Cheadle	Mean (Sd)	7.91 (1.18)	0.09 (4.24)	0.19 (4.39)
	Newcastle	Mean (Sd)	8.21 (1.12)	-0.47 (4.35)	-0.96 (4.45)
Genotype Batch	UKBB	Mean (Sd)	7.95 (1.18)	0.01 (4.26)	-0.01 (4.42)
	UKBL	Mean (Sd)	7.98 (1.20)	-0.11 (4.30)	0.06 (4.50)
Mean rfMRI	r2		0.23	-0.15	0.11
Mean rfMRI	r2		0.27	-0.18	0.14
PC1	r2		-0.019	-0.008	0.037
PC2	r2		0.006	-0.01	-0.035
PC3	r2		0.03	0.01	0.006
PC4	r2		0	0.001	-0.008
PC5	r2		0.007	-0.004	0.011
PC6	r2		-0.006	0.008	-0.008
PC7	r2		0.003	-0.004	0
PC8	r2		0.007	0.005	0.005
PC9	r2		0.005	0.007	-0.012
PC10	r2		0.007	-0.008	0.004