Consortia

the JPSC-AD study group

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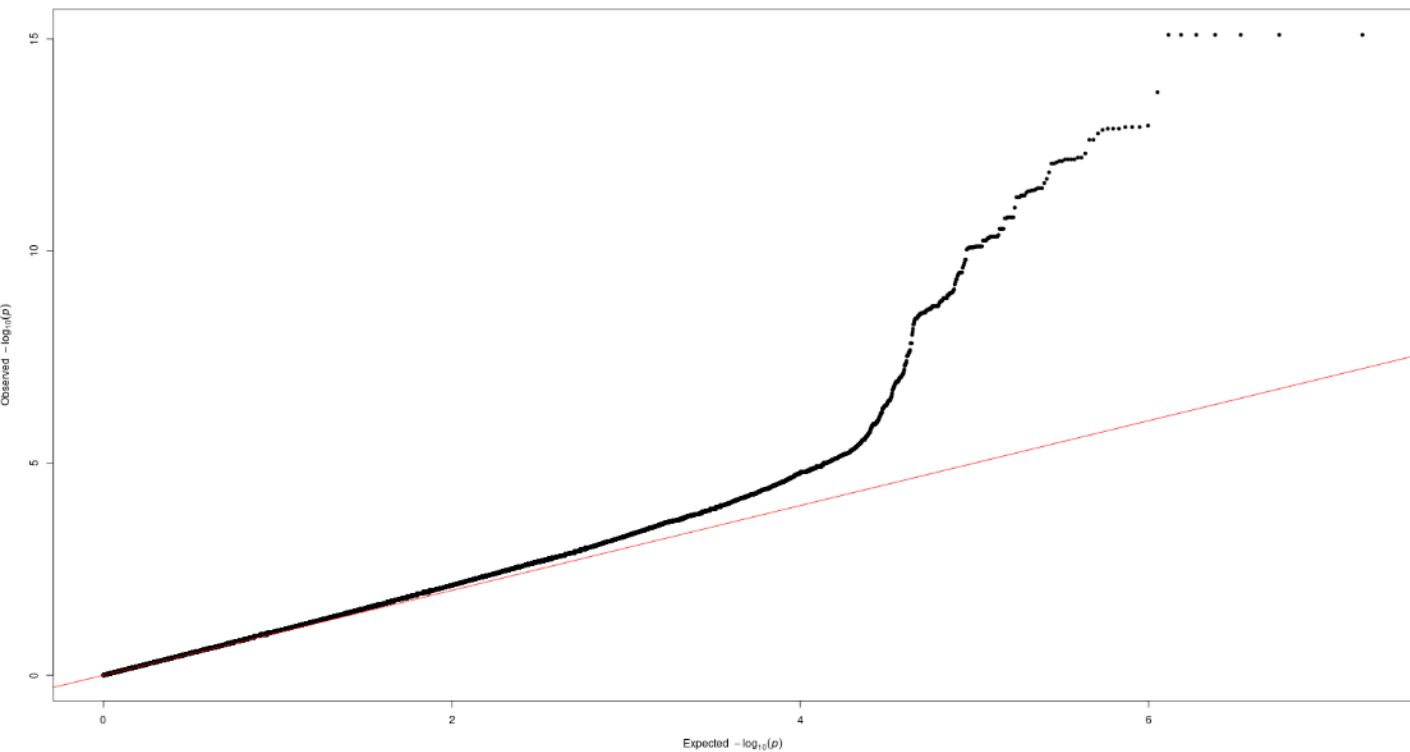
Supplementary Figure 1. Quantile-Quantile plot.
Quantile-Quantile plot of JPSC-AD GWAS p-values.
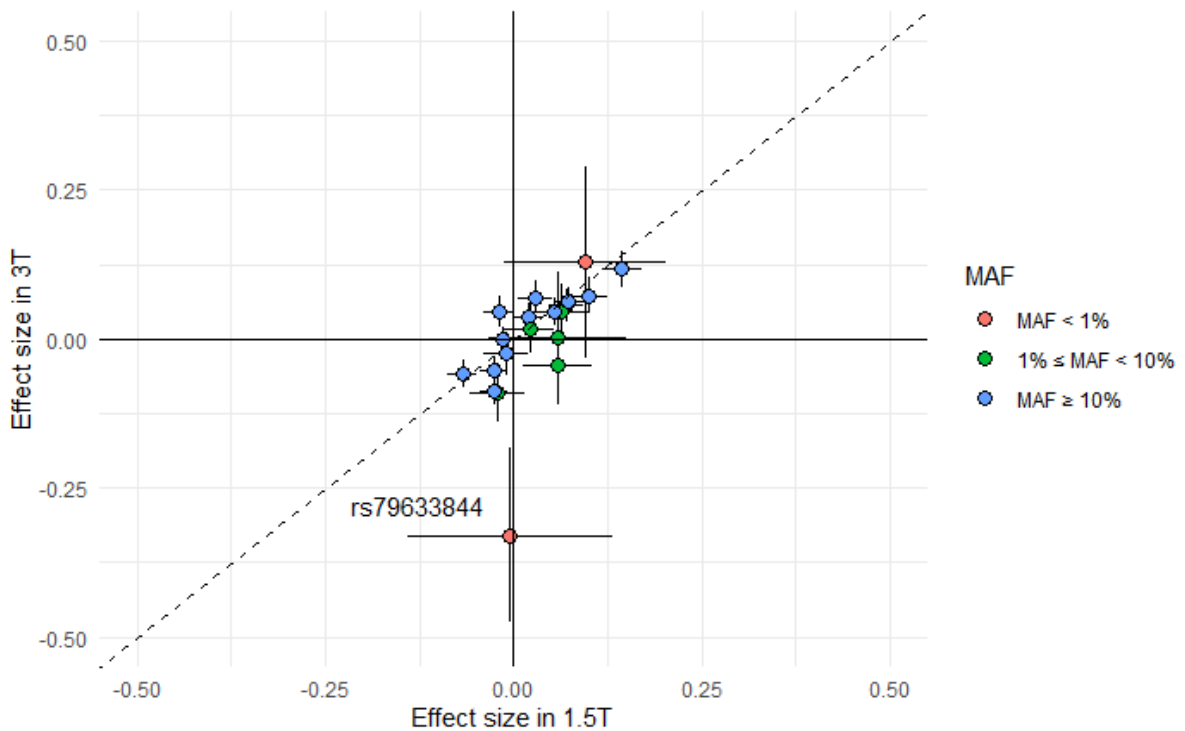
Supplementary Figure 2. Comparison of effect sizes of variants on WML between 1.5T and 3T.

The horizontal axis indicates effect sizes of variants on WML in individuals evaluated by 1.5T (N=6,229), and the vertical axis indicates effect sizes of variants in individuals evaluated by 3.0T (N=3,250). Error bars indicate standard error of the mean.
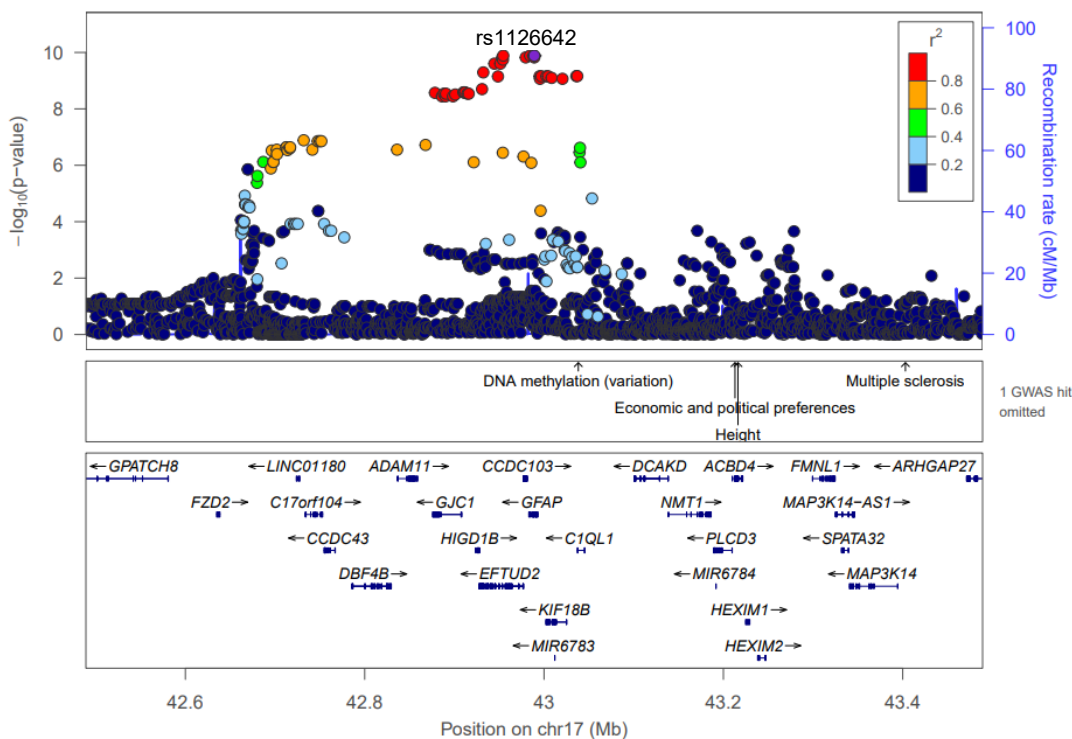
a JPSC-AD
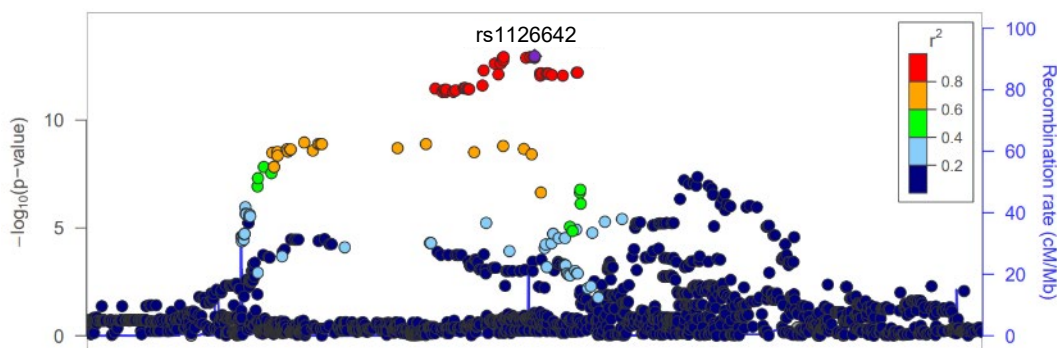
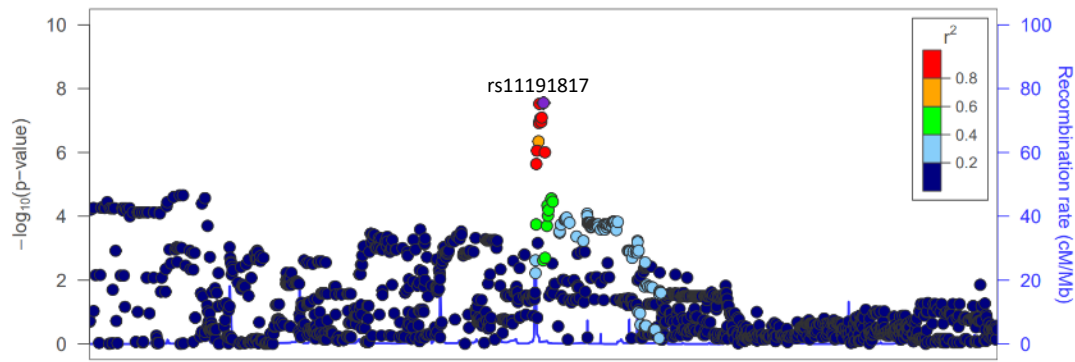**b** Conditioned by rs1126642
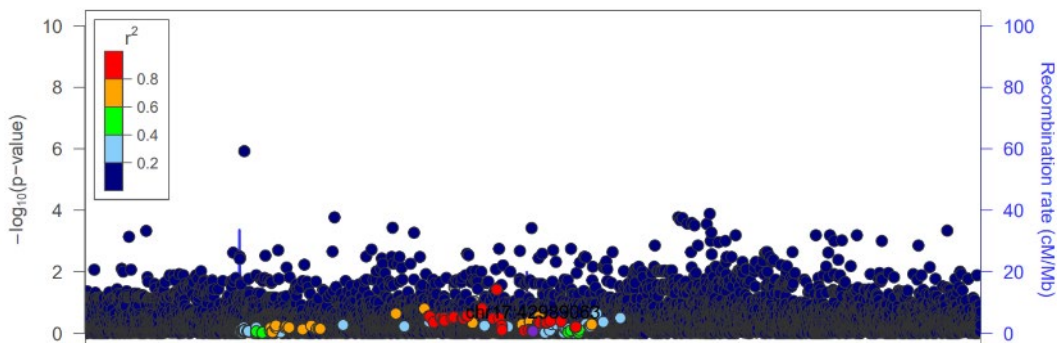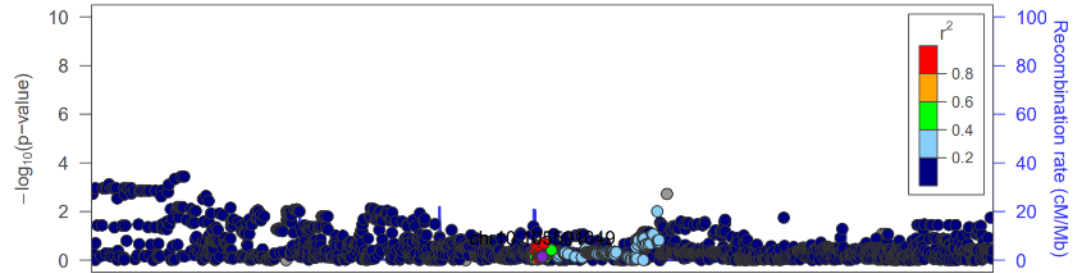
c Conditioned by rs4525538

Supplementary Figure 3. Regional association plots for the region around *GFAP*.
Panel **a** shows a plot of the JPSC-AD results. The results of condition analysis adjusted by **b** rs1126642, the lead variant of JPSC-AD, and **c** rs4525538, the lead variant of UK Biobank, are shown.
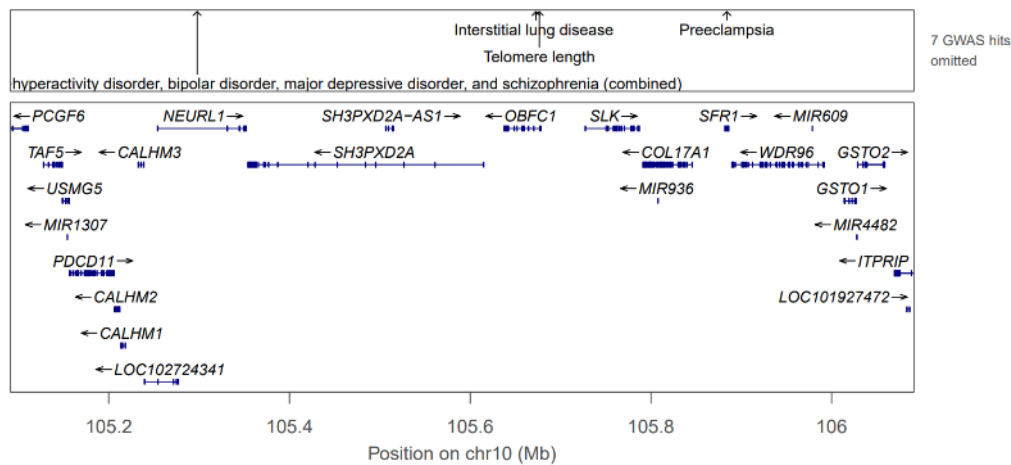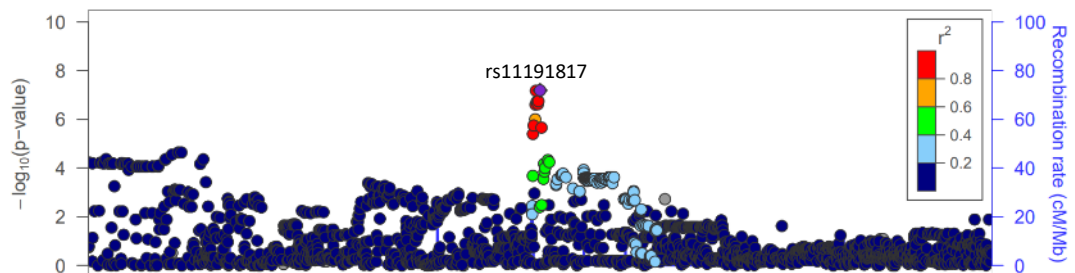
Supplementary Figure 4. Regional association plots for the region around *SH3PXD2A*.
Panel **a** shows a plot of the JPSC-AD results. The results of condition analysis adjusted by **b** rs1191817, the lead variant of JPSC-AD, and **c** rs4630220, the lead variant of UK Biobank, are shown.
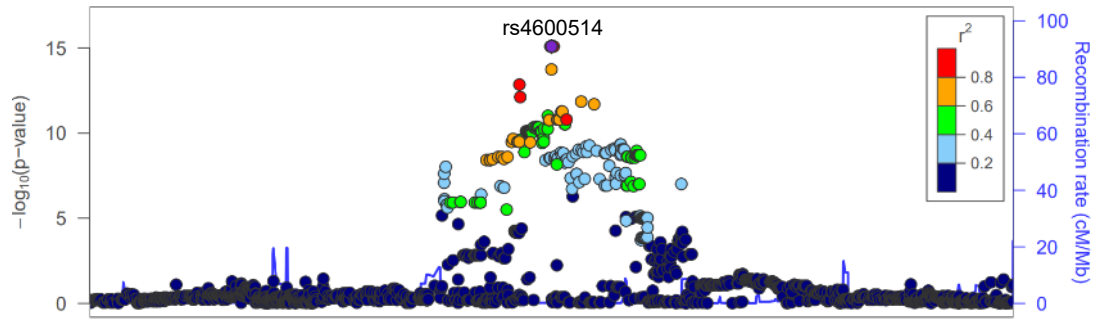
Supplementary Figure 5. Regional association plots for the region around *TRIM47*.

Panel **a** shows a plot of the JPSC-AD results. The results of condition analysis adjusted by **b** rs4600514, the lead variant of JPSC-AD, and **c** rs3744020, the lead variant of UK Biobank, are shown.
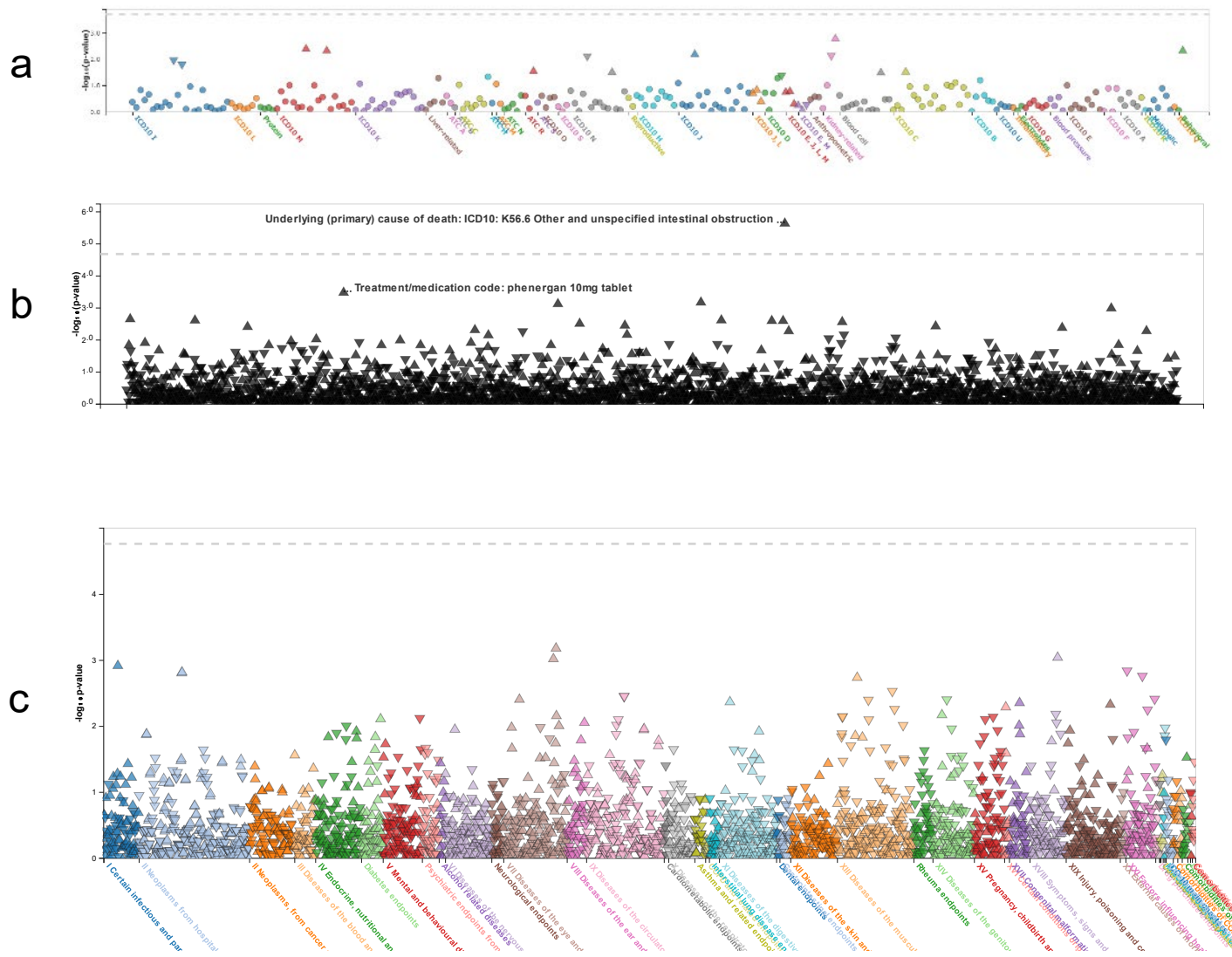
Supplementary Figure 6. PheWAS plot for rs1126642 in three large biobanks.

a Biobank Japan, **b** UK Biobank, and **c** FinnGen. The solid horizontal lines indicate PheWAS significance levels and the dotted horizontal lines indicate suggestive levels.
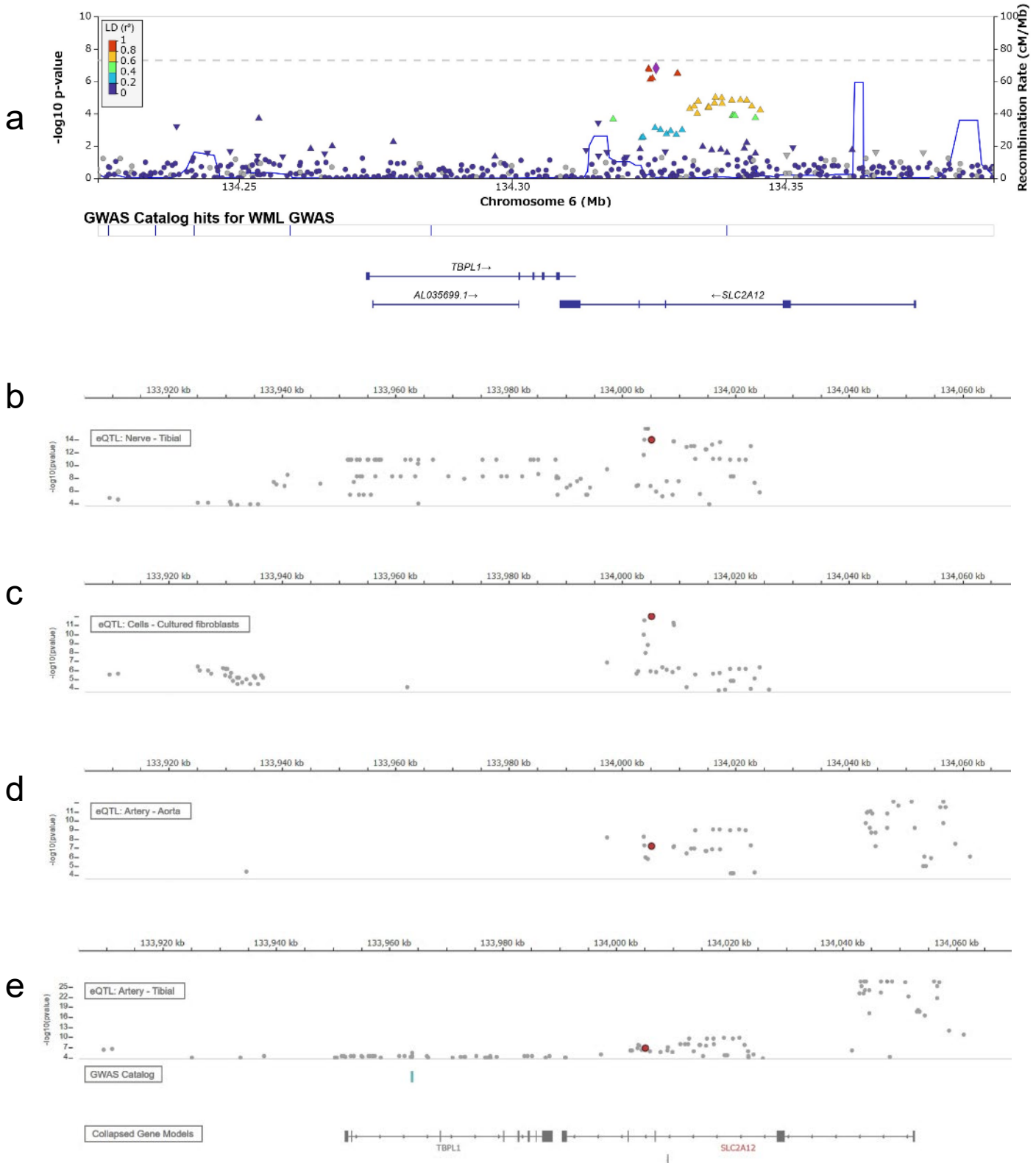
Supplementary Figure 7. **Regional association plot and eQTL plot around *SLC2A12*.**
a Regional association plot around *SLC2A12* of UK Biobank. The purple diamond indicates rs12202497, the lead variant of UK Biobank. The eQTL results for *SLC2A12* in the GTEx project are shown for **b** Nerve–Tibial, **c** Cells–Cultured fibroblasts, **d** Artery–Aorta and **e** Artery–Tibial. The red dots indicate rs1002559.
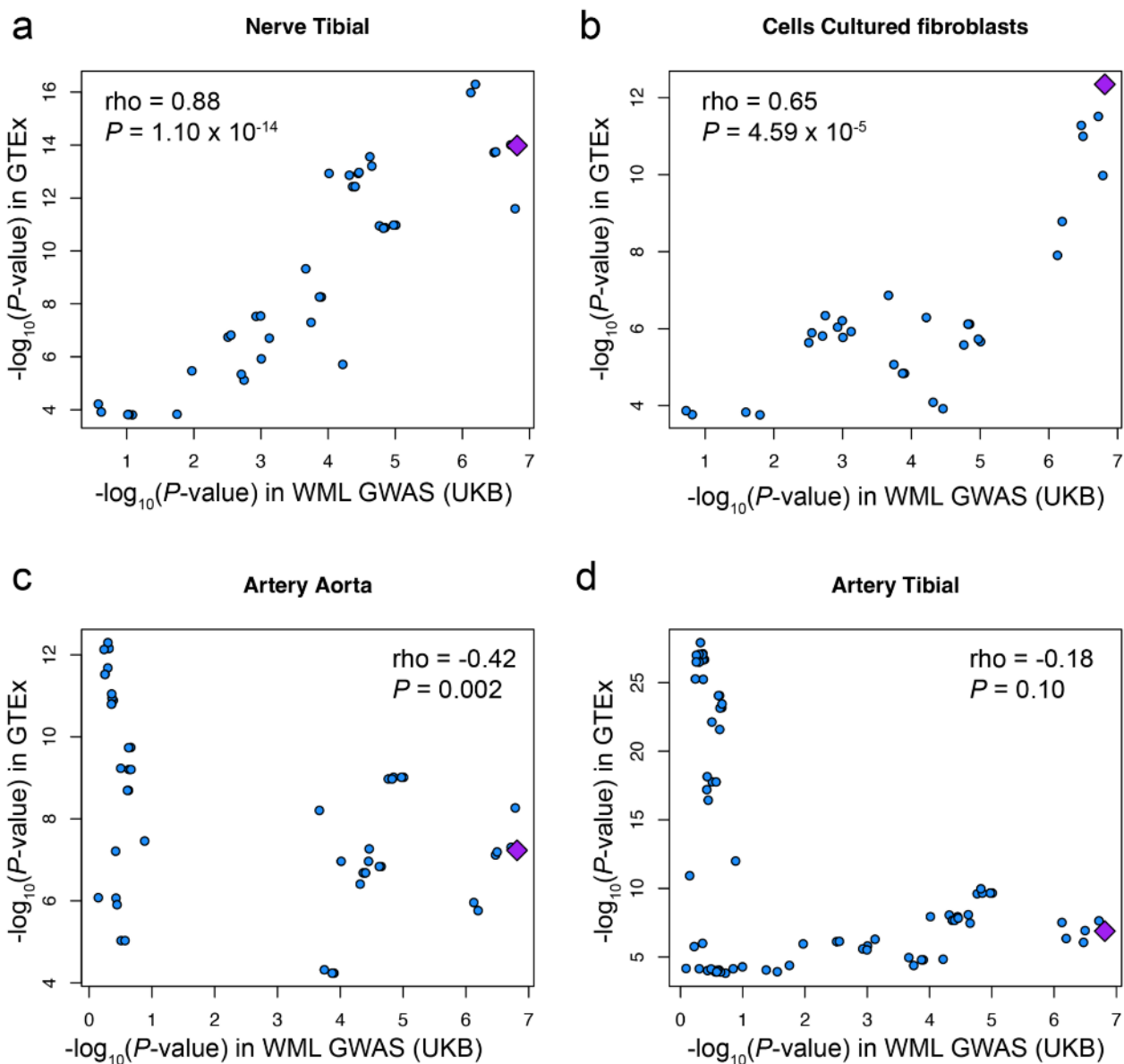
Supplementary Figure 8. Colocalization analysis.
We tried to evaluate colocalization of associated variants in the GWAS of white matter lesions (X-axis) and eQTL of *SLC2A12* (Y-axis) in three tissues and one cell-type in GTEx (v8) including **a** Nerve–Tibial, **b** Cells–Cultured fibroblasts, **c** Artery–Aorta and **d** Artery–Tibial. The purple diamonds indicate rs1002559. We selected the variants which were included in both datasets.

Supplementary Table 1. Baseline characteristics of the JPSC-AD participants, 2017.

	JPSC-AD	UK Biobank
Sample size	9,479	33,224
Female (%)	57.6	52.4
Age (years)	72.9 (6.6)	64.2
Systolic blood pressure (mmHg)	139.8 (18.6)	n/a
Diastolic blood pressure (mmHg)	78.4 (11.5)	n/a
Antihypertensive drug (%)	49.4	n/a
Hypertension (%)	73	n/a
Body mass index (kg/m^2)	23.4 (3.3)	n/a
Diabetes mellitus (%)	16	n/a
Serum total cholesterol (mg/dL)	207.5 (36.5)	n/a
Lipid lowering drug (%)	28.8	n/a
Current drinking (%)	43.3	n/a
Current smoking (%)	8.3	n/a
Regular excercise (%)	42	n/a
History of stroke (%)	5	n/a
Dementia (%)	4.2	n/a

Values are shown as means (SD) or frequencies.

Supplementary Table 2. Comparison of effect sizes of variants on WML between 1.5T and 3T.

SNP	rs ID	1.5T			3T			P for heterogeneity	q value
		Beta	SE	MAF	Beta	SE	MAF		
6:134326285:T:C	rs1002559	0.03	0.023	0.224	0.07	0.028	0.220	0.262	0.871
2:43104975:C:T	rs62137163	0.095	0.108	0.007	0.129	0.161	0.005	0.857	0.902
2:56150864:C:T	rs3762515	0.059	0.045	0.044	-0.043	0.056	0.043	0.156	0.782
2:188221793:T:C	rs36146505	-0.022	0.037	0.070	-0.09	0.049	0.058	0.264	0.871
2:203683990:A:G	rs79633844	-0.005	0.136	0.005	-0.329	0.147	0.006	0.106	0.704
3:183373567:A:G	rs10470355	-0.026	0.019	0.381	-0.086	0.024	0.382	0.049	0.564
5:82862328:G:GA	rs35544841	-0.019	0.021	0.272	0.045	0.026	0.265	0.056	0.564
6:151020020:A:T	rs12202497	0.02	0.019	0.348	0.037	0.024	0.338	0.595	0.871
8:8729761:G:C	rs907183	0.07	0.023	0.215	0.057	0.028	0.222	0.712	0.871
8:11860251:T:G	rs10103228	0.064	0.036	0.072	0.047	0.045	0.068	0.758	0.871
10:105599770:T:G	rs11191822	-0.068	0.02	0.342	-0.058	0.024	0.365	0.762	0.871
10:127675607:A:C	rs3812683	0.055	0.019	0.397	0.047	0.023	0.420	0.784	0.871
13:111040681:G:A	rs11838776	0.021	0.034	0.082	0.017	0.041	0.085	0.939	0.939
16:51442679:C:T	rs1948948	-0.01	0.03	0.111	-0.024	0.036	0.116	0.758	0.871
16:87237568:C:T	rs12928520	0.099	0.026	0.156	0.073	0.031	0.153	0.519	0.871
17:19194812:G:A	rs1969161	0.059	0.091	0.010	0.002	0.111	0.011	0.69	0.871
17:43141966:A:G	rs4525538	0.073	0.019	0.388	0.063	0.023	0.386	0.762	0.871
17:73871773:G:A	rs3744020	0.144	0.026	0.157	0.117	0.031	0.158	0.498	0.871
X:13808841:A:G	rs6527976	-0.026	0.019	0.237	-0.052	0.022	0.252	0.36	0.871
X:152601840:C:T	rs5970447	-0.015	0.017	0.316	-0.001	0.02	0.336	0.584	0.871

Supplementary Table 3. Result from summary statistics of the CHARGE Consortium.

Chr:Pos	Lead variant	Nearest gene	Meta *P*	CHARGE *P*
Variants listed in Table 1.				
17:42989063	rs1126642	*GFAP*	7.95E-09	1.72E-04
17:73874071	rs4600514	*TRIM47*	2.43E-56	1.19E-15
Variants listed in Table 2.				
2:43104975	rs62137163	*HAAO*	2.10E-09	2.25E-04
2:56150864	rs3762515	*EFEMP1*	9.05E-26	6.33E-04
2:188221793	rs36146505	*CALCRL*	3.67E-08	7.11E-05
2:203683990	rs79633844	*ICA1L*	2.18E-09	4.12E-07
6:151020020	rs12202497	*PLEKHG1*	6.48E-18	2.01E-05
10:105599770	rs11191822	*SH3PXD2A*	3.17E-13	1.04E-04
13:111040681	rs11838776	*COL4A2*	1.74E-10	2.34E-06
16:87237568	rs12928520	*C16orf95*	1.02E-21	1.62E-06
17:73871773	rs3744020	*TRIM47*	3.23E-57	6.48E-18

Supplementary Table 4. Linkage disequilibrium between the lead variants of the JPSC-AD and UK Biobank.

Chromosome	Region	Lead variant			LD (r^2)	
		JPSC-AD	UK Biobank	Distance	JPN	EUR
		rsID	rsID	(BP)		(1KGP)
17	*GFAP*	rs1126642	rs4525538	152903	0.074	0.003
10	*SX3PDX2A*	rs11191817	rs4630220	131933	0.011	0
6	*PLEKHG1*	rs34773629	rs12202497	195710	0.006	0.03

Abbreviations: LD, linkage disequilibrium; JPN, Japanese; EUR (1KGP), European population of the 1000 Genomes Project; BP, base pairs.

Supplementary Table 5. In silico prediction results of nonsynonymous variants in LD with the lead variants of JPSC-AD and meta-GWAS.

Lead variant	Gene	rsID	Chr:BP:Ref:Alt	r^2 JPSC	r^2 EUR	Annotation	SIFT	REVEL	CADD	Polyphen
JPSC-AD GWAS										
rs1126642	*GFAP*	rs1126642	17:42989063:C:T	1	1	GFAP:p.D295N	Deleterious	0.507	29.3	Possibly / probably damaging
rs4600514	*TRIM47*	rs4600514	17:73874071:G:A	1	1	TRIM47:p.R187W	Deleterious	0.172	29.9	Probably damaging
Meta-GWAS										
rs36146505	*CALCRL*	rs7586970	2:188343497:T:C	0.955	0.752	TFPI:p.N221S	Tolerated	0.12	19.9	Benign
rs1969161	*EPN2*	rs7221577	17:19246867:T:C	0.959	n/a	B9D1:p.Y256C	Deleterious low confidence	n/a	1.83	Possibly damaging

Abbreviations: LD, linkage disequilibrium; GWAS, genome-wide association study; Chr, chromosome; Pos, position; Ref, reference allele; Alt, alternative allele; SIFT, Sorting Intolerant From Tolerant; REVEL, Rare Exome Variant Ensemble Learner; CADD, Combined Annotation Dependent Depletion.

Supplementary Table 6. Genetic correlation between WML and traits reported as significant in the previous report.

Traits	JPSC-AD and Biobank Japan			UK Biobank		
	r_g	SE	*P*	r_g	SE	*P*
Ischemic stroke	0.511	0.121	2.48E-05	0.319	0.053	1.78E-09
Systolic blood pressure	0.020	0.091	0.83	0.123	0.035	4.00E-04
Diastolic blood pressure	-0.104	0.088	0.24	0.157	0.031	4.62E-07
Body mass index*	-0.017	0.055	0.76	0.191	0.055	5.00E-04
Smoking (ever vs never)	0.101	0.080	0.21	0.256	0.059	1.46E-05

* Extreme BMI for UK Biobank.

Supplementary Table 7. Comparison of genotyping, quality controls methods and phenotype calculation between JPSC-AD and UK Biobank.

	JPSC-AD	UK biobank
Sample size	9,479	33,224
Geotyping array	Illumina Japanese Screening Array.	The UK Biobank Axiom Array or the UK BiLEVE Axiom Array.
Imputation reference panel	Reference panel specified for Japanese population (Akiyama et al. *Nat Commun* 2019).	Haplotype Reference Consortium (HRC) and a merged UK10K + 1000 Genomes reference panel.
QC for genotype data	<Sample QCs> Exclusion criteria: 1. Call rate < 98%. 2. Gender discrepancy. <Variant QCs> 1. P for HWE > 1.0×10^{-6}. 2. Call rate >99%. 3. Minor allele count <5. 4. Allele frequency difference >6% with reference panel.	<Sample QCs> 1. PCA-based approach. 2. Comprehensive assessment using the metrics of missing rate and heterozygosity adjusted for population structure. 3. Gender discrepancy. <Variant QCs> 1. Marker-based QC tests to check for consistency across experimental batches. 2. Including variants with missing genotypes < 0.97%.
Post-imputation QCs	<Exclusion criteria> 1. MAF < 0.5%. 2. Rsq ≤ 0.7.	<Exclusion criteria> 3. MAF < 0.1%. 4. Imputation information score < 0.3. 5. *P*-value for HWE < 10^{-7}.
Covariates	Sex, age, squared age, estimated total intracranial volume, and facility dummy variables.	Quantile-normalization before association testing. age, sex, imaging confounds, top 40 PCs.