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Supplemental information

Cross-ancestry analysis of brain QTLs enhances interpretation of schizophrenia genome-wide association studies

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Supplementary Methods

Plasmid construction

We obtained the 55 bp SNP-centered DNA sequence from UCSC Genome Browser (GRCh38/hg38), then added the sticky end of restriction enzymes KpnI and NheI at both ends of the 55bp sequence to synthesis primers. Primer annealing to obtained double-strand sequence and then inserted into pGL3-Promoter Vector (Promega) using FastDigest enzymes (ThermoFisher) and T4 DNA Ligase (Invitrogen). We valid the vector sequence using sanger sequence.

Dual Luciferase Reporter Assay

We utilized H9 embryonic stem cells (ESCs) and B6 induced pluripotent stem cells (iPSCs), both generously provided by Prof. Desheng Liang from Central South University. All cell lines were regularly karyotyped and screened for mycoplasma contamination. These pluripotent stem cells were subsequently differentiated into neural progenitor cells (NPCs) following established protocols. Reporter assays were conducted with six technical replicates for each sample, and the experiments were independently repeated three times. For transfection, we used SH-SY5Y and HS-683 cell line to perform the experiments. Transfecting cells at 50-60% confluency, cells were co-transfected with 500ng reconstruction vector and 10ng pRL-TK using Lipofectamine 3000 Transfection Reagent (ThermoFisher) in 24 well plates. The cells were incubated under standard conditions of 37℃, 95% air, and 5% CO2. After 48h transfection, using Dual Luciferase Reporter Assay Kit (Promega) to measure the

firefly luciferase activity and renilla luciferase activity, the luminescence was detected using Tube Luminometer (Berthold Sirius).

Supplementary Figures

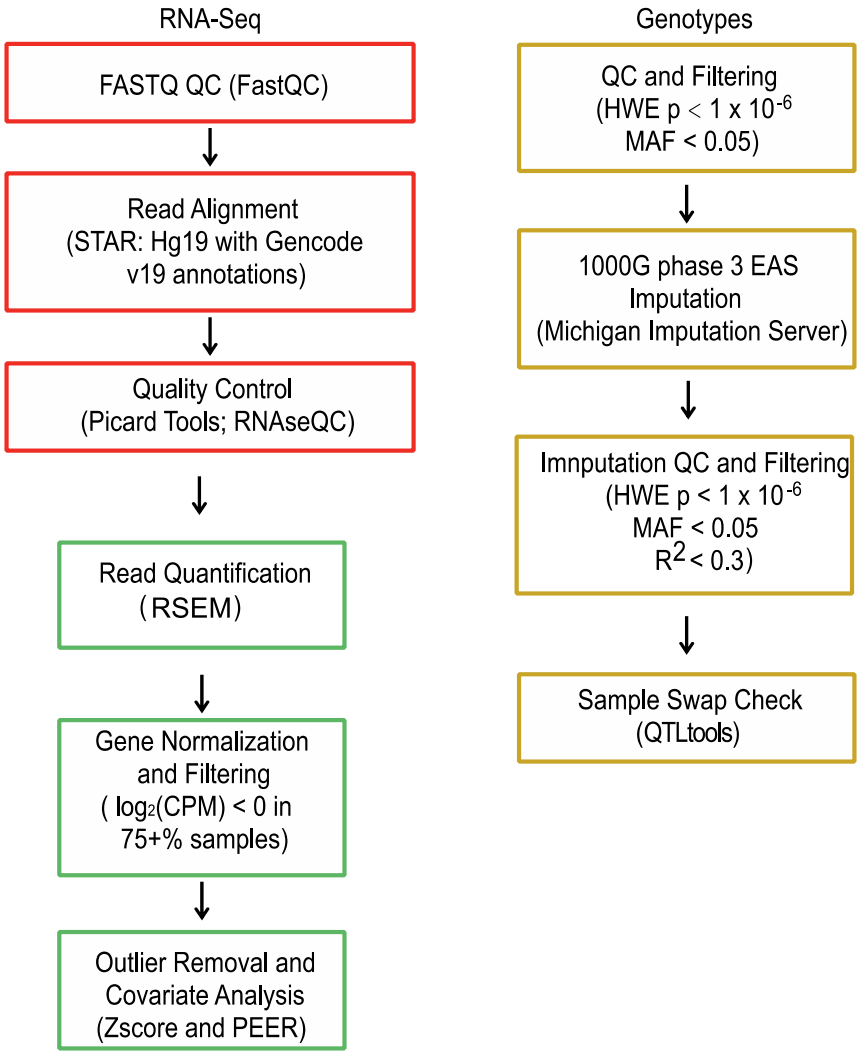

Figure S1: Overview of methods and QC pipeline for EAS samples.

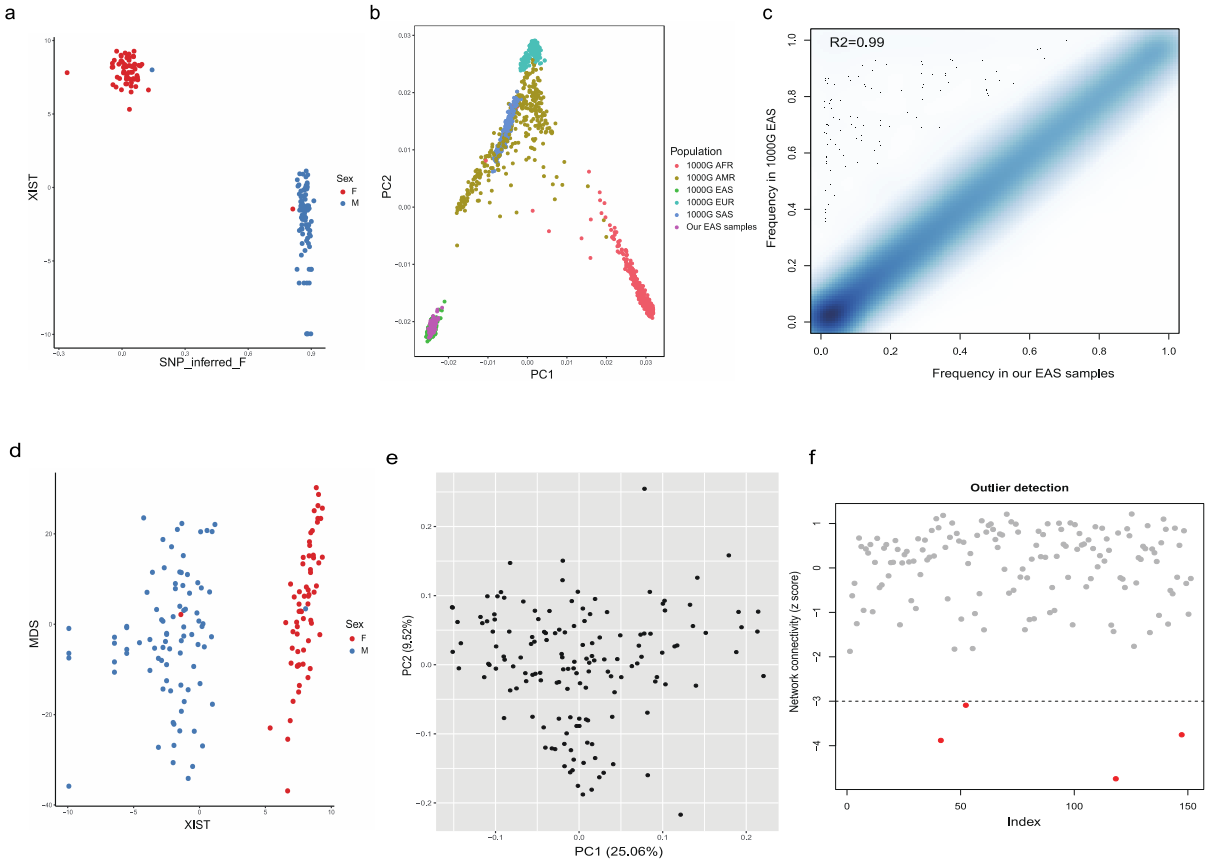

Figure S2: Preprocessing of RNA-sequencing and whole-genome sequencing (WGS) data of EAS samples. a, Sex-mismatch checked by WGS data. b, Population PCA plot with 1000G genotype data. c, Imputation accuracy. d, Sex-mismatch checked by Xist expression. e, PCA plot for EAS samples. f, Distribution of Z-score.

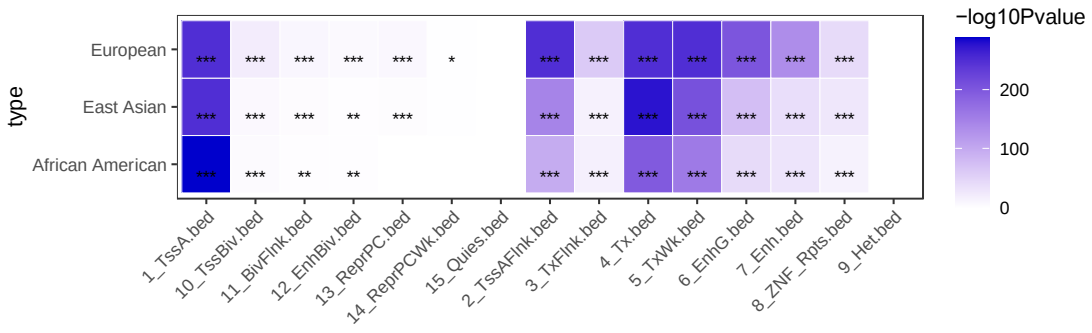

Figure S3: Enrichment of eSNPs in 15 core regulatory models. *: P-value < 0.05; **: P-value < 0.01; ***: P-value < 0.001

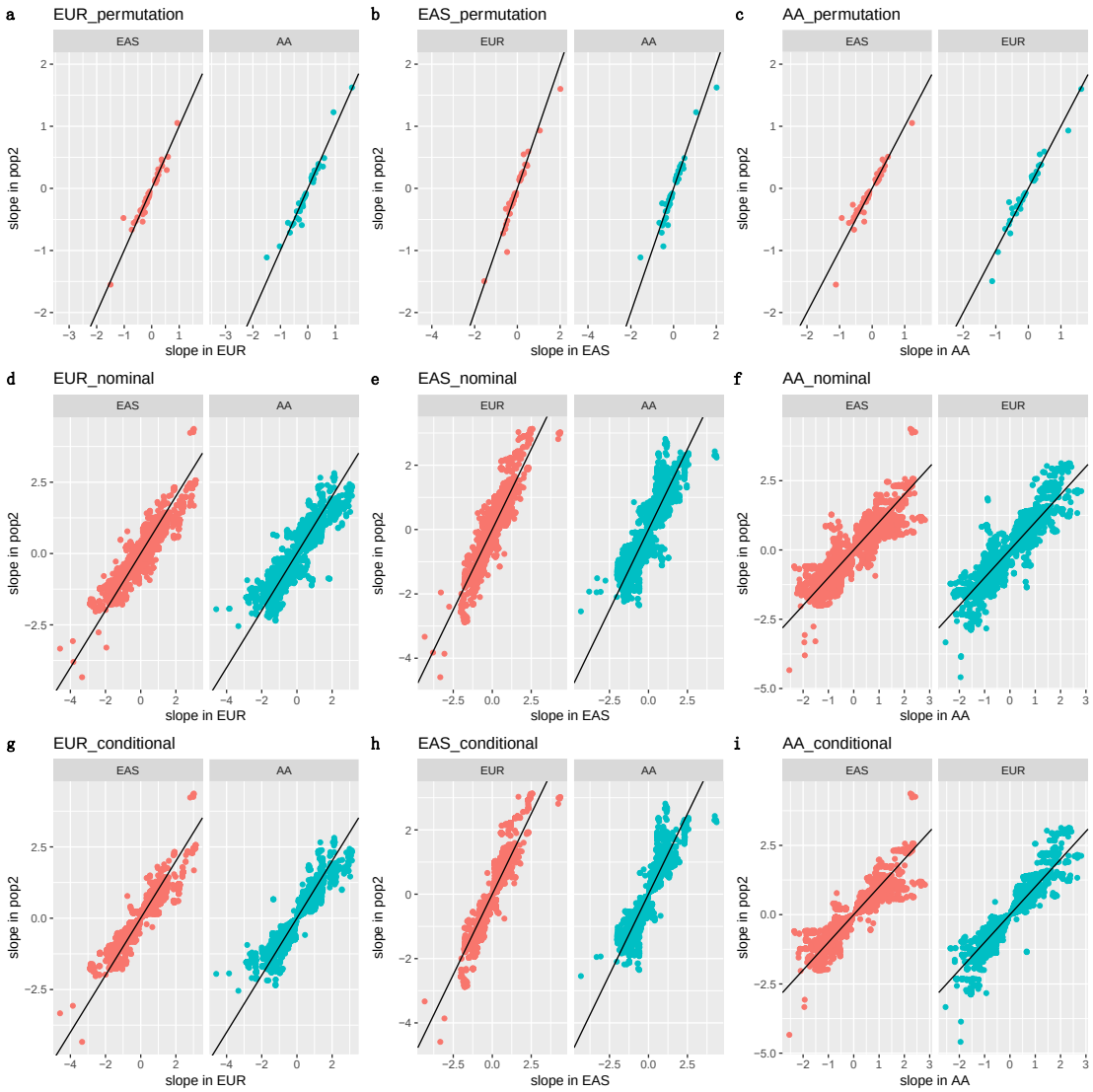

Figure S4: Effect size correlation of population-shared eQTLs between EUR and non-EUR population. (a-c) permutation pass; (d-f) nominal pass; (g-i) conditional pass. None of these loci showed heterogeneity across populations ($P > 0.05$).

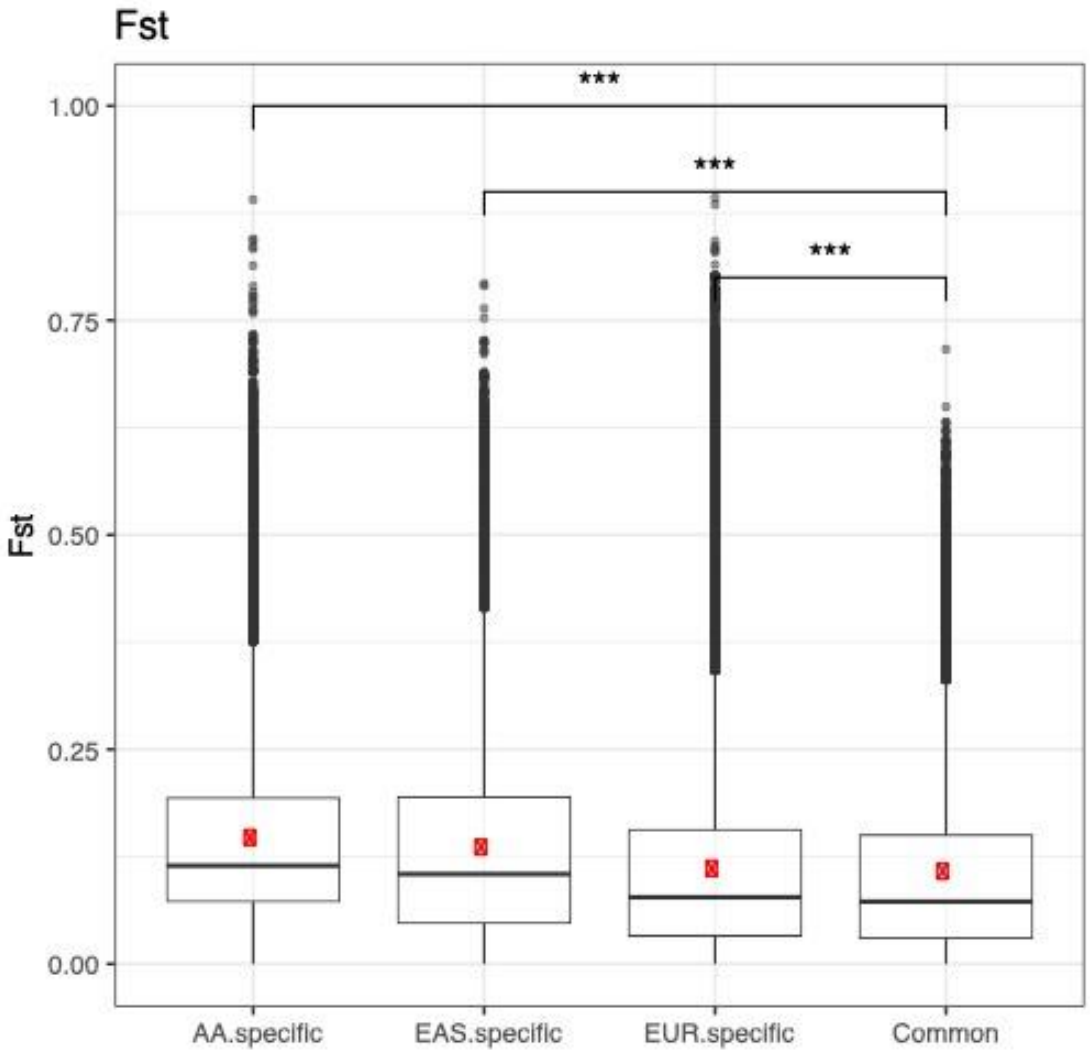

Figure S5: Comparison of FST between population-shared and population-specific eSNPs.

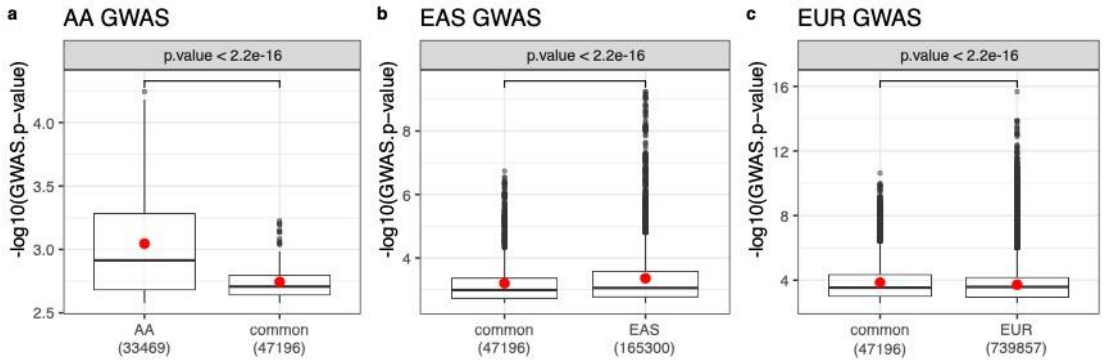

Figure S6: Comparison of GWAS p-value between population-shared and population-specific eSNPs. (a) AA-specific eSNPs and population-shared eSNPs in AA GWAS. (b) EAS-specific eSNPs and population-shared eSNPs in EAS GWAS. (c) EUR-specific eSNPs and population-shared eSNPs in EUR GWAS.

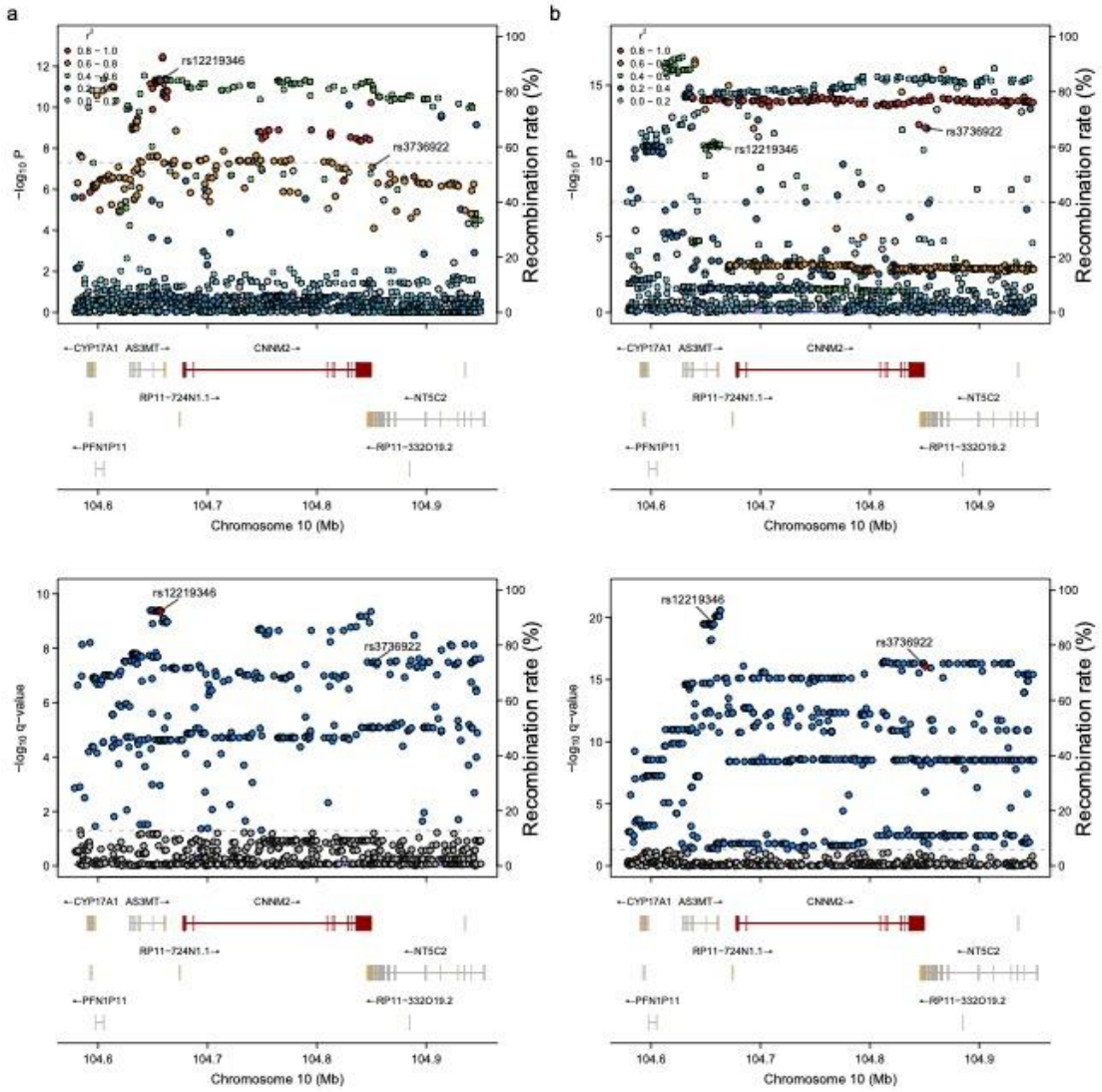

Figure S7: LocusZoom plots demonstrating the genetic colocalization evidence between SCZ GWAS signals (upper) and brain eQTLs (lower) at the *CNNM2* locus for (a) the EAS population and (b) the EUR population, respectively.

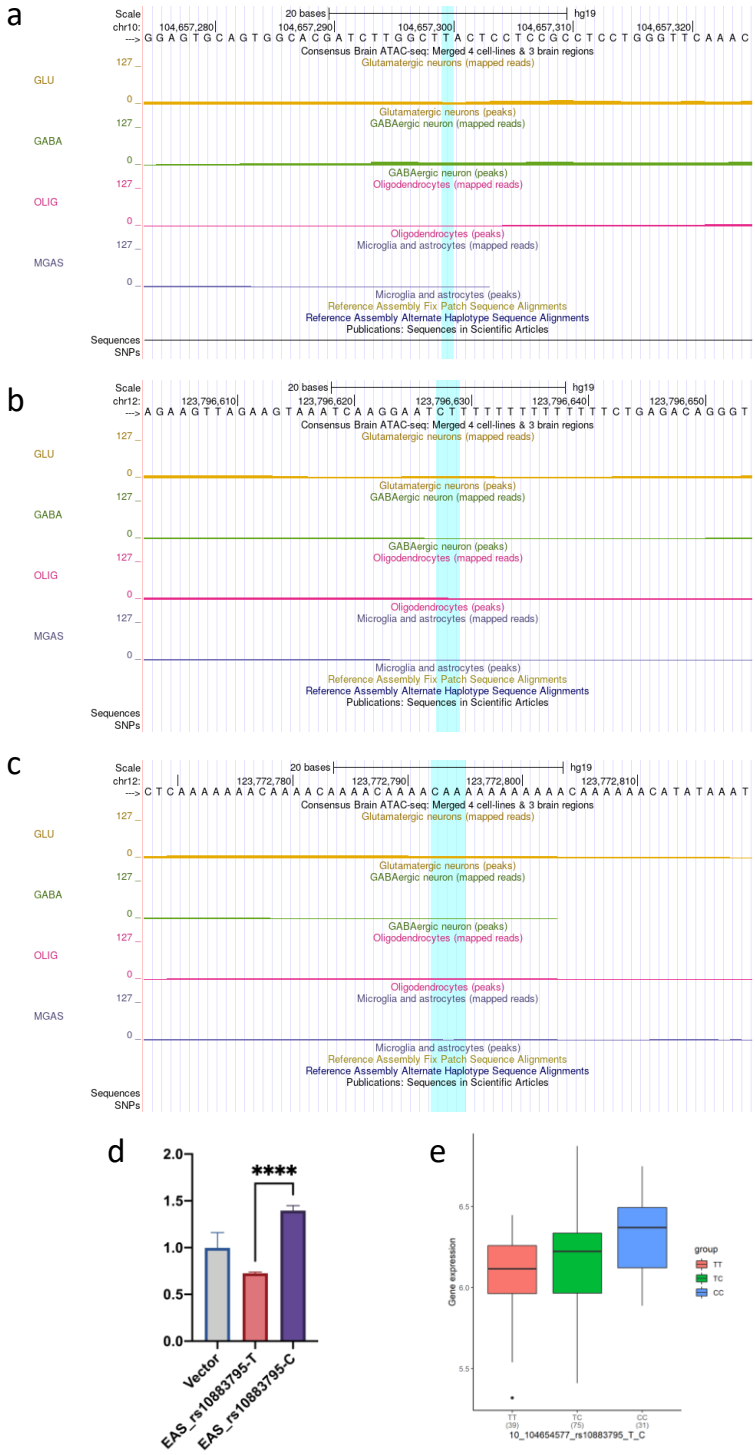

Figure S8: Regulatory effect across glutamate neuron, GABA neuron, oligodendrocytes, and microglia for new regulatory SNPs within population-shared risk genes for (a) CNNM2, (b)C12orf65, (c) MPHOSPH9. The SNPs were highlighted in the blue stripe. (d) Dual luciferase reporter assay for EAS eSNP at risk gene CNNM2. **** means p-value < 2.2e-16. (e) eQTL result for the eSNP and expression risk gene CNNM2 in EAS cohort (P-value = 8.57e-11).

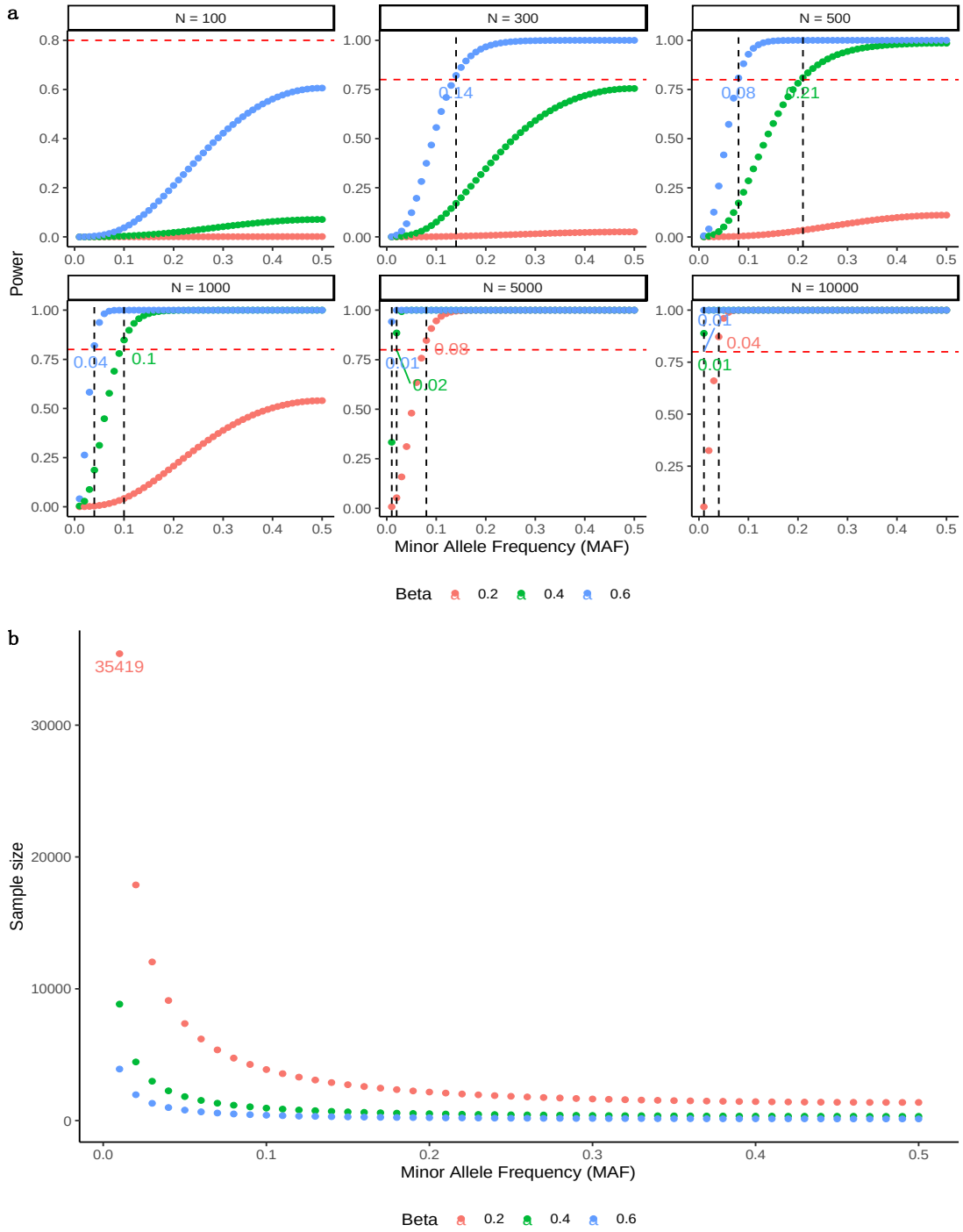

Figure S9: The sample size required for well-powered brain eQTL detection in diverse populations. (a) The percentage of brain eQTLs detected power under different sample sizes and effect sizes is shown as a function of log-scaled sample size. (b) The required sample size achieving 80% power based on the effect size estimated form non-EUR specific eQTLs.