nature portfolio

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Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒ A description of all covariates tested
☐	☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☐	☒ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	No software was used for data collection
Data analysis	CellRanger (v3.1.0) for single nuclei read mapping, SampleQC (v0.4.5) for quality control of single nuclei, Plink (v1.9) to process genotyping data, fastQTL (v2.0) for eQTL analysis, QTLtools (v1.3.1) for independent eQTL analysis and epigenomic enrichment analysis, CaveMan (v1.01) for fine-mapping eQTL, MAGMA (v1.08) for genetic enrichment of gene sets, SNP2TFBS to check whether SNPs are predicted to disrupt TF motifs, METAL (2011-03-25) for GWAS meta-analysis, R (4.0.1) for statistical analysis, scDblFinder (v1.4.0) to identify doublets, Conos (v1.4.6) for sample integration. Harmony (v.0.1.0) for sample integration, DropletUtils (v1.14.1) for maximum ambientRNA estimation, qvalue (v2.26.0) for pi1 estimation and eQTL multiple testing correction, glmmTMB (v1.1.2.3) for the negative binomial mixed modelling, LDlinkR (v1.1.2) for LD information, Coloc (v5.1.0) for GWAS-eQTL colocalization. The analysis code described in this study is available here: https://jbryois.github.io/snRNA_eqtl/

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

A shinyApp to browse the result of this study is available at: https://malhotralab.shinyapps.io/brain_cell_type_eqtl/

The full eQTL summary statistics are available on zenodo at: https://doi.org/10.5281/zenodo.5543734

Single nuclei RNA-seq sequencing data and genotype data for the Roche datasets have been deposited at the European Genome-phenome Archive (EGA), which is hosted by the EBI and the CRG, under accession number EGAS00001006345.

Genotypes for the ROSMAP datasets are available at:
https://www.synapse.org/#!Synapse:syn10901595

Single nuclei RNA-seq sequencing data for the ROSMAP datasets are available at:
https://www.synapse.org/#!Synapse:syn18485175
https://www.synapse.org/Portal.html#!Synapse:syn3157322
https://adknowledgeportal.synapse.org/Explore/Studies?Study=syn21670836
https://www.synapse.org/#!Synapse:syn16780177

GRCh38 reference human genome: http://ftp.ensembl.org/pub/release-96/fasta/homo_sapiens/dna/
Ensembl Homo_sapiens GRCh38.96 reference annotation: http://ftp.ensembl.org/pub/release-96/gtf/homo_sapiens/
Ensembl Homo_sapiens GRCh38.91 reference annotation: http://ftp.ensembl.org/pub/release-91/gtf/homo_sapiens/

GWAS summary statistics are available here:
Alzheimer's disease: http://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST90012001-GCST90013000/GCST90012877/GCST90012877_buildGRCh37.tsv.gz
Parkinson's disease: https://drive.google.com/drive/folders/10bGj6HfAXgl-JslpI9ZJIL_JIgZyktxn
Multiple sclerosis: https://imsgc.net/?page_id=31
Schizophrenia: https://www.med.unc.edu/pgc/download-results

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	We performed single nuclei RNA-seq on all brain samples available to us. The sample size of this study (N=192) is the largest (to our knowledge) for an eQTL study using single nuclei RNA-seq data.
Data exclusions	Single nuclei RNA-seq samples with less than 500 total UMI were excluded. For related individuals (estimated from genotyping data), only one individual from the pair was kept. Samples originating from non-european individuals (estimated from the genotyping data) were excluded. Individuals with less than 10 single nuclei for a specific cell type were removed. All criteria for sample exclusion were pre-determined.
Replication	We replicated our eQTLs in a large eQTL study from the brain at the tissue level (Metabrain). 77-100% of the SNP-gene pairs replicated at a 5% false discovery rate (91-100% of those with the same direction of effect).
Randomization	All samples were processed in a randomized fashion
Blinding	There are no group allocations in this study.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☒	☐ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging