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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 is used for data collection. Microarray expression data for brain tissues were sourced from the Allen Human Brain Atlas. This study employed the STRING Protein-Protein Interaction (PPI) network (v11.5). The disease-risk genes were acquired from the following websites: (1) DisGeNet database (Accessed 12 Dec 2023); (2) Comparative Toxicogenomics Database; (3) DISEASES database (Accessed 12 Dec 2023); (4) GWAS-based gene sets from public available GWAS summary results. GWAS summary statistics of eight psychiatric disorders are available on the PGC web site.
Data analysis	Analyses were performed with Matlab (version 2018b) and R (version 4.1.0). Key R packages include ClusterProfiler (version 4.2.2) and aPEAR (version 1.0.0). The genetic correlation were computed by LD Score Regression (version 1.0.1). All code used for these analyses are publicly available at https://github.com/CaoLuolong/XomicsEnrich.

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

An open-source implementation of the mFusion method can be downloaded from https://github.com/CaoLuolong/XomicsEnrich. Microarray expression data for brain tissues were sourced from the Allen Human Brain Atlas (AHBA), refer to https://atlas.brain-map.org/. This study employed the STRING Protein-Protein Interaction (PPI) network at https://version-11-5.string-db.org/ (Version 11.5, August 12, 2021). The disease-risk genes were acquired from the following websites: (1) DisGeNet database (https://www.disgenet.org/home/. Accessed 12 Dec 2023); (2) Comparative Toxicogenomics Database (CTD, https://ctdbase.org/. Accessed 12 Dec 2023); (3) DISEASES database (https://diseases.jensenlab.org/Search. Accessed 12 Dec 2023); (4) GWAS-based gene sets from GWAS summary results as described in Methods section. GWAS summary statistics of eight psychiatric disorders are available on the PGC web site (https://www.med.unc.edu/pgc/results-and-downloads).

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Sex-and gender-based analysis was not performed due to lack of sufficient sample size in the AHBA dataset (n=6, 1 female).
Reporting on race, ethnicity, or other socially relevant groupings	We did not collect new data for this work. We used genetically inferred ancestry or reported in the study. The Allen Human Brain Atlas contains three Caucasians, two African Americans, and one Hispanic.
Population characteristics	The AHBA dataset brains have mean age of 42.5 (SD 13.4).
Recruitment	Recruitment of the AHBA data was as detailed on the Allen Institute website. Specifically, postmortem tissue from males and females between 18 – 68 years of age and no known history of neuropsychiatric or neurological conditions ('control' cases) were eligible for inclusion.
Ethics oversight	Ethics oversight was performed by the Allen Institute for Brain Science.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

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	The gene expression data were downloaded from the Allen Institute for Brain Science, include data from six adult brains (two contributed both hemispheres, and four contributed one hemisphere), for a total of 3,702 brain samples.
Data exclusions	No data was excluded from the analysis.
Replication	While replication was not possible as the AHBA is the only transcriptomic data of the entire human cortex with high spatial resolution. We have used previous GWAS summary data (from PGC) and multiple public databases (DisGeNet; CTD; DISEASES) to define disease risk genes.
Randomization	Randomization was not relevant to our analysis as we were identifying disease risk genes across all patients. We proposed the analysis on multiple diseases as a proxy for generalisability.
Blinding	Blinding was not relevant to our study as we did not perform randomized experiments.

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
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

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

Plants

Seed stocks	Not Applicable
Novel plant genotypes	Not Applicable
Authentication	Not Applicable