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Corresponding author(s): Eichler Evan E

Reporting Summary

Nature Research 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 Research policies, see Authors & Referees and the Editorial Policy Checklist.

Statistical parameters

When statistical analyses are reported, confirm that the following items are present in the relevant location (e.g. 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
☐	☒	An indication of 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 statistics 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
☐	☒	Clearly defined error bars *State explicitly what error bars represent (e.g. SD, SE, CI)*

Our web collection on statistics for biologists may be useful.

Software and code

Policy information about availability of computer code

Data collection	All samples were obtained through the denovodb v. 1.5 web server (denovo-db.gs.washington.edu/)
Data analysis	We utilized two published algorithms (CH, and denovolyzer R package version 0.2.0) for detecting enrichment of de novo variation. Both have been previously described in cited manuscripts. All additional statistics were calculated using standard functions in the R statistical environment (v3.2.4).

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/reviewers upon request. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research 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 list of figures that have associated raw data
- A description of any restrictions on data availability

All variant data in this study is available to download from denovo-db v.1.5 (see URLs). Human MTG single-nucleus RNA-seq data and clusters can be downloaded from the Allen Institute for Brain Science web site: http://celltypes.brain-map.org/download.

Field-specific reporting

Please select 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/authors/policies/ReportingSummary-flat.pdf

Life sciences study design

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

Sample size	The sample size represents all published samples with de novo variation in neurodevelopmental disorders that were available through denovo-db at the time of the study (v1.5). Sample size was chosen to be as large as possible to maximize power.
Data exclusions	We selected samples with diagnoses of autism or intellectual disability or developmental delay and associated unaffected individuals. Samples from epilepsy-only studies were not included as they did not match our target phenotypes of autism or intellectual disability or developmental delay
Replication	This study is based on a meta-analysis of genetic data and no experimental (biological) assays were used.
Randomization	This study represents a meta-analysis of published de novo variation in neurodevelopmental cases. All cases were assigned to either a bulk group of ASD or ID/DD based on the primary dataset's description.
Blinding	As this meta-analysis primarily represents a single group enrichment, test blinding was neither possible nor performed.

Reporting for specific materials, systems and methods

Materials & experimental systems

n/a	Involved in the study
☒	☐ Unique biological materials
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology
☒	☐ Animals and other organisms
☐	☒ Human research participants

Methods

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

Human research participants

Policy information about studies involving human research participants

Population characteristics	All studies present in this meta-analysis are described in their source manuscripts. Briefly, samples represent childhood genetic profiling of individuals with broad neurodevelopmental diagnoses of ASD (n=5,624), ID, or DD (ID/DD n= 5,303). Additional

	phenotypes and covariates were not consistently availible and thus not examined.
Recruitment	As this study is a meta-analysis no patient recruitment was performed.