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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 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	Published software: a combination of NGS analysis tools, CellRanger (version 2.1.0), STAR (version 020201), GATK (version 3.7.0), demuxlet (version 1.0), R (Harmony, MNN) and Python (Scanpy version 1.4, see details in Methods). Unpublished data analysis scripts are available at https://github.com/single-cell-genetics/singlecell_neuroseq_paper/

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 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

Managed access data from single-cell RNA sequencing are accessible in the European Genome-phenome Archive (EGA, https://www.dev.ebi.ac.uk/ega/) under the study number EGAS00001002885 (dataset: EGAD00001006157).
Open access single-cell RNA sequencing data are available in the European Nucleotide Archive (ENA) under the study ERP121676 (https://www.ebi.ac.uk/ena/browser/view/PRJEB38269).
Processed single cell count data and eQTL summary statistics are available from Zenodo: https://zenodo.org/record/4333872.

Data availability statement including URLs for both the new data generated here and other publicly available datasets used are reported in the main 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	Sample size was based on results from many previous human eQTL studies (e.g. PMID: 29022597), where above 100-200 samples provide power to map eQTL, with power increasing with sample size.
Data exclusions	Single-cell RNA-seq data were excluded based on quality control criteria, as described in the Methods
Replication	We consider the main dataset (sc-RNA-seq from differentiating neurons) to be a single dataset, albeit including data from many repeated differentiation assays. In particular, the differentiation assay was repeated across 19 experiments and the measure of differentiation efficiency was robust across replicates of the same cell line in different experimental batches. While some additional differentiation assays failed in the course of generating the dataset, these were not attempts to replicate any findings we report. For 12 lines, the measure of differentiation efficiency was also replicated in another independent scRNA-seq cerebral organoid dataset. The identification of a subpopulation of iPSC cells was replicated in an independent dataset (see Extended Figure 3).
Randomization	iPSC lines were allocated to groups/experimental batches at random.
Blinding	Investigators were blinded during collection, as the origin of each assayed cell was only determined during data analysis (by assessment of RNA-sequencing data).

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

Antibodies

Antibodies used	The following antibodies were used: FOXA2 (Santa Cruz, sc101060 - 1/100),LMX1A (Millipore, AB10533 - 1/500), TH (Santa Cruz, sc-25269 - 1/200), MAP2 (Abcam, 5392 - 1/2000), Donkey anti-chicken AF647 (Thermo Fisher Scientific, A21449), Donkey antimouse AF488 (Thermo Fisher Scientific, A11008), Donkey anti-mouse AF555 (Thermo Fisher Scientific, A31570), Donkey antirabbit AF488 (Thermo Fisher Scientific, A21206), Donkey anti-rabbit AF555 (Thermo Fisher Scientific, A27039)
Validation	All commercially available antibodies have been validated by the manufacturer with supporting publications found on manufacturer websites. Antibodies were further validated in-house using relevant positive and negative controls.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	All cell lines are iPSCs from the HipSci project (www.hipsci.org)
Authentication	All cell lines were matched to the original donor by genotype, using RNA-sequencing data.
Mycoplasma contamination	Cells were not tested for mycoplasma contamination
Commonly misidentified lines (See ICLAC register)	NA

Human research participants

Policy information about studies involving human research participants

Population characteristics	25 to 79 years old phenotypically 'healthy' donors (male and female) with no diagnosed genetic disease.
Recruitment	All samples for the HipSci resource were collected from consented research volunteers recruited from the NIHR Cambridge BioResource (http://www.cambridgebioresource.org.uk).
Ethics oversight	Samples were collected initially under ethics for iPSC derivation (REC Ref: 09/H0304/77, V2 04/01/2013), with later samples collected under a revised consent (REC Ref: 09/H0304/77, V3 15/03/2013).

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