nature portfolio

Corresponding author(s): Chengqi Yi

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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	Next-generation sequencing data was collected and demultiplexed by BGI MGI-2000 platform and Illumina Hiseq.
Data analysis	Bowtie2(2.2.9),TrimGalore(0.6.5), HOMER(4.10), Seurat(3.0), ChromHMM(1.23), ChromVAR(3.12), Louvain (iGraphl.2.6), Monocle3(0.2.3), Samtools(1.14), deepTools(3.5.1), IGV(2.15.4), bedtools(2.27.1), David(2021)

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

Raw sequencing and processed data generated in this study are available from GEO (http://www.ncbi.nlm.nih.gov/geo/) with accession number GSE197740. Other external datasets were downloaded from NCBI GEO with the following accession numbers: WGBS and TAPS of mESC56 (GSE112520), RNA-seq of mESC (2i and serum)67 (GSE23943), TAB-seq of mESC47 (GSE36173), Joint-snhmC-seq of mouse brain84 (GSE236798), Paired-Tag of mouse brain85 (GSE152020); ArrayExpress

with the following accession numbers: scRNA-seq of mESC115 (E-MTAB-2600); 10x Genomics website: scRNA-seq of PBMC (https://www.10xgenomics.com); ENCODE with the following accession numbers: DNase-seq ChIP-seq of E14 mESC (ENCSR000CMW), H3K4me1 ChIP-seq of E14 mESC (ENCSR000CGN), H3K27ac ChIP-seq of E14 mESC (ENCSR000CGQ), H3K4me1 ChIP-seq of immune cells (ENCSR777RWW (CD4+ T cell), ENCSR631BPS (CD8+ T cells), ENCSR214VUB (B cells), ENCSR963TKB (NK cells), and ENCSR400VWA (Monocytes)), H3K4me3 ChIP-seq of immune cells (ENCSR263WLD (CD4+ T cell), ENCSR231FDF (CD8+ T cells), ENCSR269OVV (B cells), ENCSR570AUC (NK cells), and ENCSR796FCS (Monocytes)), H3K27ac ChIP-seq of immune cells (ENCSR546SDM (CD4+ T cell), ENCSR835OJV (CD8+ T cells), ENCSR191ZQT (B cells), ENCSR391EQV (NK cells), and ENCSR012PII (Monocytes)), H3K27me3 ChIP-seq of immune cells (ENCSR043SBG (CD4+ T cell), ENCSR797GOJ (CD8+ T cells), ENCSR522EGW (B cells), ENCSR939JZW (NK cells), and ENCSR080XUB (Monocytes)), H3K9me3 ChIP-seq of immune cells (ENCSR453GNY (CD4+ T cell), ENCSR905SHH (CD8+ T cells), ENCSR295PSK (B cells), ENCSR021FSY (NK cells), and ENCSR236JVK (Monocytes)), H3K36me3 ChIP-seq of immune cells (ENCSR828WZG (CD4+ T cell), ENCSR694CDP (CD8+ T cells), ENCSR789RGI (B cells), ENCSR519SOC (NK cells), and ENCSR244XWL (Monocytes)), ChromHMM States of NK cells (ENCSR972ZND).

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	N/A
Reporting on race, ethnicity, or other socially relevant groupings	N/A
Population characteristics	N/A
Recruitment	N/A
Ethics oversight	N/A

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	No sample size calculation was performed. The sample size was determined based on prior published data from similar experiments (Mulqueen et.al., Nat. Biotechnol, 2018; Zhu et.al., Nat. Methods, 2021).
Data exclusions	Cells (mESC, PBMC and mouse brain cells) with less than 10,000 bins covered and bins with less than 50% of cells covered were removed.
Replication	48 technical replicates were performed for mESC, PBMC and mouse brain cells, respectively. All datasets from independent replicates showed similar results and shown in the manuscript.
Randomization	Allocation was random.
Blinding	Experiments were not blinded in our studies because experimental conditions were evident. All samples were treated identically through standard procedures.

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

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	mouse embryonic stem cells were provided by the Laboratory of Prof. Peng Du (source: v6.5 mESC); HEK293T(CRL-3216) and NIH/3T3(CRL-158) were purchased from ATCC.
Authentication	No method of cell line authentication was used.
Mycoplasma contamination	All cell lines are tested negative for mycoplasma contamination.
Commonly misidentified lines (See ICLAC register)	No such cell lines listed as commonly misidentifiedl lines were used in this study.