

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 (<i>n</i>) 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 <i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i>
☐	☒ 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. <i>F</i> , <i>t</i> , <i>r</i>) with confidence intervals, effect sizes, degrees of freedom and <i>P</i> value noted <i>Give P values as exact values whenever suitable.</i>
☒	☐ 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 <i>d</i> , Pearson's <i>r</i>), 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
Data analysis	Ingenuity Pathway Analysis (IPA, version 60467501, QIAGEN Digital Insights) was used to predict activated or inhibited biological functions. FlowJo Software157 v10.9.0 Salmon158 v1.7.0 Alevin-fry159 v0.5.0 Seurat160 v4.0.4 SCTransform161 v2 Speckle162 V1.2.0 zUMIs163 v2.9.4d Samtools164 v1.10 Fiji GraphPad Prism version 10.4.2 Matlab version 23.2.0

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 data (FASTQ files) and processed data (count matrices) were deposited in NIH GEO (RRID:SCR_005012) under accession no. GSE253230. The code used to perform the analysis described in this study is available at https://github.com/synthetic-keung-lab/scRNAseq_UBE3A_knockout_human_cerebral_organoids. All data needed to evaluate the conclusions in the paper are present in the paper and/or the Supplementary Materials. All other data are available from the corresponding author on reasonable request.

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

Reporting on race, ethnicity, or other socially relevant groupings

Population characteristics

Recruitment

Ethics oversight

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](https://www.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

Data exclusions

Replication

Randomization

Blinding

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

Antibodies

Antibodies used

Antigen Host Supplier Cat. No. RRID Dilution
 SOX2 Goat R&D Systems AF2018 AB_355110 1:20
 UBE3A Rabbit Bethyl Laboratories
 A300-351A AB_185563 1:250
 pVimentin Mouse MBL International
 D076-3S AB_592962 1:200
 MAP2 Mouse Millipore Sigma M1406 AB_477171 1:250
 MAP2 Chicken Abcam AB92434 AB_2138147 1:300
 TTR Sheep BIO-RAD AHP1837 AB_2212089 1:100
 EMX1 Rabbit Atlas Antibodies
 HPA006421 AB_1078739 1:50
 Ki-67 Rabbit Abcam AB15580 AB_443209 1:800
 Caspase-3 Rabbit R&D Systems AF835 AB_2243952 1:20
 p16INK4a Mouse Abcam AB54210 AB_881819 1:1000
 CTIP2 Rat Abcam AB18465 AB_2064130 1:100
 SATB2 Mouse Abcam AB51502 AB_882455 1:100
 GLI3 Goat AF3690 AB_2232499 1:200

Validation

Manufacturers provided validating images and references.

Eukaryotic cell lines

Policy information about [cell lines and Sex and Gender in Research](#)

Cell line source(s)	H9(WA09) female, ASdel (UCONN), ASmut (UCONN), H9UBE3Am-/p- (UCONN), H9UBE3Am-/p+ (UCONN) cell lines were used.
Authentication	STR analysis (WiCell & Thermo), RNAseq verification of deletions
Mycoplasma contamination	Mycoplasma was not detected.
Commonly misidentified lines (See ICLAC register)	<i>Name any commonly misidentified cell lines used in the study and provide a rationale for their use.</i>

Plants

Seed stocks	n/a
Novel plant genotypes	n/a
Authentication	n/a

Plots

- Confirm that:
- ☒ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).
 - ☒ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).
 - ☒ All plots are contour plots with outliers or pseudocolor plots.
 - ☒ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation	The cells used were cell lines maintained in culture.
Instrument	MACSQuant® VYB flow cytometer (Miltenyi Biotec).
Software	FlowJo Software (v10.9.0, Becton Dickinson Life Sciences)
Cell population abundance	n/a
Gating strategy	Intact cells were gated based on FSC/SSC. The gates for the cell cycle stages are shown in the figures.

☒ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.