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☐ Initial submission ☐ Revised version ☒ Final submission

Life Sciences Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form is intended for publication with all accepted life science papers and provides structure for consistency and transparency in reporting. Every life science submission will use this form; some list items might not apply to an individual manuscript, but all fields must be completed for clarity.

For further information on the points included in this form, see Reporting Life Sciences Research. For further information on Nature Research policies, including our data availability policy, see Authors & Referees and the Editorial Policy Checklist.

Experimental design

1. Sample size

Describe how sample size was determined.

Power analysis of a pilot cohort (n = 3) showed that a sample size of three would be sufficient to show genotype effects; all groups have n ≥3.

2. Data exclusions

Describe any data exclusions.

No data were excluded.

3. Replication

Describe whether the experimental findings were reliably reproduced.

All attempts of replication were successful.

4. Randomization

Describe how samples/organisms/participants were allocated into experimental groups.

Samples were randomly allocated to groups.

5. Blinding

Describe whether the investigators were blinded to group allocation during data collection and/or analysis.

Investigators were not blinded to apoE genotypes during data collection and/or analysis. Eight hiPSC lines and four miPSC lines with different apoE genotypes were used in this study. Multiple iPSC lines were used in each experiment for differentiating into different types of neurons, and multiple investigators were doing similar experiments. Blinding could easily bring in confusions/mistakes across experiments and among investigators.

Note: all studies involving animals and/or human research participants must disclose whether blinding and randomization were used.

6. Statistical parameters

For all figures and tables that use statistical methods, confirm that the following items are present in relevant figure legends (or in the Methods section if additional space is needed).

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement (animals, litters, cultures, etc.)
☐	☒ A description of how samples were collected, noting whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ A statement indicating how many times each experiment was replicated
☐	☒ The statistical test(s) used and whether they are one- or two-sided (note: only common tests should be described solely by name; more complex techniques should be described in the Methods section)
☐	☒ A description of any assumptions or corrections, such as an adjustment for multiple comparisons
☐	☒ The test results (e.g. *P* values) given as exact values whenever possible and with confidence intervals noted
☐	☒ A clear description of statistics including central tendency (e.g. median, mean) and variation (e.g. standard deviation, interquartile range)
☐	☒ Clearly defined error bars

See the web collection on statistics for biologists for further resources and guidance.

Software

Policy information about availability of computer code

7. Software

Describe the software used to analyze the data in this study.	Prism 7, BD FACS Diva, and FlowJo 10.

For manuscripts utilizing custom algorithms or software that are central to the paper but not yet described in the published literature, software must be made available to editors and reviewers upon request. We strongly encourage code deposition in a community repository (e.g. GitHub). *Nature Methods* guidance for providing algorithms and software for publication provides further information on this topic.

Materials and reagents

Policy information about availability of materials

8. Materials availability

Indicate whether there are restrictions on availability of unique materials or if these materials are only available for distribution by a for-profit company.	All unique materials used are readily available from the authors.

9. Antibodies

Describe the antibodies used and how they were validated for use in the system under study (i.e. assay and species).	Primary antibodies used in this study are: apoE (178479, Calbiochem), actin (A5060, Sigma), Tuj1 (MAB1637, EMD Millipore; MRB-435P, Covance), GFAP (Z0334, Dako), PHF1 (gift from Peter Davies), AT8 (MN1020, Thermo Fisher Scientific), AT180 (MN1040, Thermo Fisher Scientific), AT270 (MN1050, Thermo Fisher Scientific), Tau-5 (577801, EMD Millipore), soluble APP-β (SIG-39138, Covance), 22C11 (MAB348, EMD Millipore), GAD65/67 (AB1511, EMD Millipore), GAD67 (MAB5406, EMD Millipore), Nanog (ab21624, Abcam), human nuclei (MAB1281, EMD Millipore), Sox2 (sc-17320, Santa Cruz Biotechnology), Oct-3/4(sc-5279, Santa Cruz Biotechnology), SSEA4 (ab16287, Abcam), TRA-1-81 (MAB4381, EMD Millipore), TRA-1-60 (MAB4360, EMD Millipore), nestin (MAB5326, EMD Millipore), Pax6 (Developmental Studies Hybridoma Bank), FoxG1 (sc-48788, Santa Cruz Biotechnology), MAP2 (MAB3418, AB5622, EMD Millipore), Tuj1 (MAB1637, EMD Millipore; MRB-435P, Covance), NKX2.1 (sc-13040, Santa Cruz Biotechnology), GABA (A2052, Sigma), and cleaved Caspase-3 (D3E9, Cell Signaling Technology). The secondary antibodies were IgG conjugated with Alexa Fluor 488 or Alexa Fluor 594 (Life Technologies) as well as IgG labeled with IRDye 800 or IRDye 680 (LI-COR).

10. Eukaryotic cell lines

a. State the source of each eukaryotic cell line used.	Eight human iPSC lines were generated and used in this study, including ApoE3/3-A, ApoE3/3-B, ApoE3/3-C, ApoE4/4-A, ApoE4/4-B, ApoE4/4-C, Isogenic ApoE3/3, and ApoE-/-. See Supplementary Table 1 for details.
b. Describe the method of cell line authentication used.	All human iPSC lines were characterized for normal pluripotency gene expression, apoE genotypes, karyotypes, and capability of differentiating into neural stem cells, different types of neurons, and astrocytes in culture.
c. Report whether the cell lines were tested for mycoplasma contamination.	All hiPSC lines were tested negative for mycoplasma.
d. If any of the cell lines used are listed in the database of commonly misidentified cell lines maintained by ICLAC, provide a scientific rationale for their use.	No commonly misidentified cells lines were used.

Animals and human research participants

Policy information about studies involving animals; when reporting animal research, follow the ARRIVE guidelines

11. Description of research animals

Provide details on animals and/or animal-derived materials used in the study.	Two mouse iPSC lines (apoE3/3-miPSC and apoE4/4-miPSC) were generated from MEF cells of apoE3-KI and apoE4-KI mice on a C57/BL6 genetic background. The apoE3/3-miPSC and apoE4/4-miPSC were characterized for normal pluripotency gene expression, apoE genotypes, karyotypes, and capability of differentiating into neural stem cells, different types of neurons, and astrocytes in culture. Immunodeficient mice were used for teratoma formation test of hiPSC lines.

Policy information about studies involving human research participants

12. Description of human research participants

Describe the covariate-relevant population characteristics of the human research participants.	Human skin fibroblasts were used to generated iPSC lines with different apoE genotypes. The general information of subjects from whom skin fibroblasts were collected are presented in Supplementary Table 1.

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Flow Cytometry Reporting Summary

Form fields will expand as needed. Please do not leave fields blank.

Data presentation

For all flow cytometry data, confirm that:

☐ 1. The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).

☐ 2. 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).

☐ 3. All plots are contour plots with outliers or pseudocolor plots.

☒ 4. A numerical value for number of cells or percentage (with statistics) is provided.

Methodological details

5. Describe the sample preparation.	hiPSC-derived MGE progenitor cells were stained with anti-NKX2.1 (1:250) and anti-GABA (1:1000).
6. Identify the instrument used for data collection.	BD LSRII Flow Cytometer.
7. Describe the software used to collect and analyze the flow cytometry data.	BD FACS Diva was used for data collection, and FlowJo Version 10 was used for data analysis.
8. Describe the abundance of the relevant cell populations within post-sort fractions.	Over 95% NKX2.1+ cell population and over 90% GABA+ cell population.
9. Describe the gating strategy used.	FSC/SSC gates were applied to specify NKX2.1+ and GABA+ cell populations. Cells stained with the secondary antibody alone were used as a negative control to set the positive/negative gates.

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