

Reporting Summary

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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                                                                                                                                                                                                                                                                                      |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> The exact sample size ( <i>n</i> ) for each experimental group/condition, given as a discrete number and unit of measurement                                                                                                                               |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly                                                                                                                                    |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> The statistical test(s) used AND whether they are one- or two-sided<br><i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i>                                                               |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> A description of all covariates tested                                                                                                                                                                                                                     |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons                                                                                                                                        |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> 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) |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> 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<br><i>Give P values as exact values whenever suitable.</i>                     |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings                                                                                                                                                                      |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes                                                                                                                                                |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> 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 | Immunofluorescence results were visualized using LC780 and LC980 microscope. Western blots were visualized using Typhoon. qPCR were performed on the Roche LightCycler® 480 real-time PCR detection system. High-throughput sequencing was performed on the Mi-seq and Next-Seq platform (Illumina).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Data analysis   | Cell Ranger pipeline (version 2.1.1, 10x Genomics, RRID:SCR_017344);<br>Prism (version: 10.4.0, GraphPad, RRID:SCR_005375);<br>ZEN (Carl Zeiss, RRID:SCR_013672);<br>Imaris 9.5.1 (version 9.5.1, Bitplane, RRID:SCR_007370);<br>Image J (version 1.51m, NIH, RRID:SCR_003070);<br>MetaXpress (Molecular Devices, RRID: SCR_016654);<br>R and RStudio (Version 2023.09.0+463 (2023.09.0+463); RRID: SCR_001905);<br>Adobe Illustrator 2022 26.0.1 (Adobe, RRID: SCR_010279);<br>Adobe Photoshop 2024.005.20400 (Adobe, RRID:SCR_014199);<br><br>R packages:<br>Seurat (version 4.1.3, Satija et al 2015, RRID:SCR_016341);<br>Signac (version 1.10.0, Stuart et al 2021, RRID:SCR_021158);<br>UMAP (version 0.2.6.0, McInnes, Healy and Melville 2020, <a href="https://github.com/lmcinnes/umap">https://github.com/lmcinnes/umap</a> );<br>ggplot2 (version 3.5.1, Wickham H 2016; RRID:SCR_014601); |

clusterProfiler (version 4.6.2, Yu et al 2012, RRID: SCR\_016884)

The codes used for snMultiome sequencing data analysis were an adaptation of standard R packages, as described in the Methods section. The codes and processed data are available on GitHub at <https://github.com/jacrab-multiomic/Yen-et-al.-2025-Nat-Comm> and figshare at <https://figshare.com/projects/Yen-et-al.-2025-Nat-Comm/238025>. More detailed information is available upon request.

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](#)

### Data availability

Requests for further information or resources should be directed to and will be filled by the lead authors, Ya-Ping Yen and Jun-An Chen. All the sequencing data generated in this study have been deposited in the Gene Expression Omnibus repository under the GSE accession codes GSE290242, GSE290244, and GSE290245. Previously published human postmortem cortex RNA-seq and human iPSC~MNs are available under the accession codes GSE122649, GSE122650, GSE132972, and GSE173115. Transcriptome data from Answer ALS can be requested via the website: <https://www.answers.org/>. All data supporting the findings of this study are available within the paper and Supplementary Information section. Source data are provided in this paper.

## 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

This study involved data from human iPSC-derived neuron samples. The information of biological gender regarding the human samples is listed below:

1. 29d SOD1+/L144F iPSC line (Female)
2. CS4VFTiALS-n1 (male)
3. CS47iALS-TDP43 (male)
4. CS52iALS-C9n6A (male)

The influence of sex was not assessed in this study. Rather the effect of CPA treatment was compared between isogenic lines; the FB23-2 treatment to rescue ALS iPSC lines was compared with the vehicle control.

### Reporting on race, ethnicity, or other socially relevant groupings

reporting race:

1. 29d SOD1+/L144F iPSC line (unknown)
2. CS4VFTiALS-n1 (White)
3. CS47iALS-TDP43 (unknown)
4. CS52iALS-C9n6A (CAUA)

### Population characteristics

donor age at sample collection:

1. 29d SOD1+/L144F iPSC line (82)
2. CS4VFTiALS-n1 (29)
3. CS47iALS-TDP43 (64)
4. CS52iALS-C9n6A (49+)

### Recruitment

No recruitment.

### Ethics oversight

The study using patient samples/data was approved by Academia Sinica review boards.(AS-IRB-BM-18042 and AS-IRB-BM-23039)

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://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 statistical methods were performed for sample size predetermination, sample size was determined iteratively. We based on previous experiences and reported studies to determine the number of embryos, mice, and cells required for the study. Minimum cluster size in the study was 30 cells in vitro. Minimum size used for the statistic and quantification in the study was three embryos and mice in vivo. |
| Data exclusions | No data were excluded in mice data.<br>For snMultiome data, cells were retained for subsequent analysis if they displayed a number of genes between 1000 and 5300, UMI counts <30500, as well as <10% mitochondrial counts. During initial clustering, non-motor neurons were filtered based on expression of known markers, retaining only our cells of interest, as detailed in the methods in the manuscript.   |
| Replication     | All attempts at replication were successful and can be performed independently.                                                                                                                                                                                                                                                                                                                                    |
| Randomization   | No randomization was performed. We plated the cells in random positions in multi-well plates and randomly assigned them to different experiment groups. We randomly took fluorescence images under the microscope.                                                                                                                                                                                                 |
| Blinding        | Blinding was conducted solely during quantification comparisons between control and mutant mice. Moreover, blinding was inconsequential for high throughput sequencing as libraries were pooled prior to loading.                                                                                                                                                                                                  |

## 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                                           |
|-------------------------------------|-----------------------------------------------------------------|
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> Antibodies                  |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> Eukaryotic cell lines       |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Palaeontology and archaeology          |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> Animals and other organisms |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Clinical data                          |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Dual use research of concern           |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Plants                                 |

### Methods

| n/a                                 | Involved in the study                           |
|-------------------------------------|-------------------------------------------------|
| <input checked="" type="checkbox"/> | <input type="checkbox"/> ChIP-seq               |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Flow cytometry         |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> MRI-based neuroimaging |

## Antibodies

### Antibodies used

Primary antibodies:

Rabbit polyclonal anti-m6A (1:500) Synaptic Systems 202003; RRID:AB\_2279214

Mouse monoclonal anti-m6A (1:100) Proteintech 68055-1-Ig; RRID:AB\_2918796

Rabbit monoclonal anti-β3-Tubulin (D71G9) (1:100) Cell signaling #5568; RRID:AB\_10694505

Mouse monoclonal anti-NeuN (RBFOX3) (1:2000) Sigma-Aldrich MAB377; RRID:AB\_2298772

Mouse monoclonal anti-Neurofilament H, Nonphosphorylated (SMI32) (1:1000) BioLegend 801701 (clone SMI-32P); RRID:AB\_2564642

Rabbit polyclonal anti-Synapsin I (1:1000) Sigma-Aldrich ab1543; RRID:AB\_2200400

Rabbit polyclonal anti-Foxp1 (1:20000) Abcam ab16645; RRID:AB\_732428

Goat polyclonal anti-Isl1 (1:1000) Neuromics GT15051; RRID:AB\_2126323

Goat polyclonal anti-ChAT (1:100) Millipore AB144P; RRID:AB\_2079751

Rabbit polyclonal anti-Iba1 (1:100) Proteintech 22309-1-AP; RRID:AB\_2224377

Mouse monoclonal anti-neurofilament (1:250) DSHB #2H3; RRID:AB\_531793

Mouse monoclonal anti-SV2 (1:500) DSHB #SV2; RRID:AB\_2315387

α-Bungarotoxin, Alexa Fluor 555 conjugate (1:500) Invitrogen B35451; RRID:AB\_2617152

Rabbit polyclonal anti-TDP-43 (1:100) Proteintech 10782-2-AP; RRID:AB\_615042

Rabbit polyclonal anti-Mettl14 (1:1000) Sigma-Aldrich HPA038002; RRID:AB\_10672401

Rabbit polyclonal anti-Olig2 (1:20000) Millipore AB9610; RRID:AB\_570666

Guinea pig polyclonal anti-Olig2 (1:100) Thomas Jessell (Columbia University)

Rabbit polyclonal anti-Irx3 (1:16000) Thomas Jessell (Columbia University)

Mouse monoclonal anti-Nkx2.2 (1:100) DSHB 74.5A5; RRID:AB\_53179

Rabbit anti-Pax6 (1:300) Covance PRB-278P; RRID:AB\_291612

Mouse monoclonal anti-Neurogenin-2 (1:500) R&D MAB3314; RRID:AB\_2149520

Guinea pig polyclonal anti-Hb9/Mnx1 (1:1000) Hynek Wichterle (Columbia University)

Rabbit polyclonal anti-Lhx3 (1:2000) Abcam ab14555; RRID:AB\_301332

Mouse monoclonal anti-Isl1/2 (1:1000) DSHB 39.4D5; RRID:AB\_2314683  
 Rabbit polyclonal anti-Sox9 (1:2000) Millipore AB5535; RRID:AB\_2239761  
 Rabbit polyclonal anti-Histone H3 (tri-methyl K9) (1:1000) Abcam Ab8898; RRID:AB\_306848  
 Mouse monoclonal anti-phospho-Histone H2A.X (Ser139), clone JBW301 (1:1000) Sigma-Aldrich 05-636; RRID:AB\_309864  
 Rabbit polyclonal anti-phospho-Histone H2A.X (Ser139) (1:500) Cell signaling #2577; RRID:AB\_2118010  
 Rabbit polyclonal anti-Fto (1:1000) Proteintech 27226-1-AP; RRID:AB\_2880809  
 Rabbit polyclonal anti-Glial Fibrillary Acidic Protein (GFAP) (1:1000) Millipore AB5804; RRID:AB\_2109645  
 Rabbit polyclonal anti-GFP (1:100) Invitrogen A-11122; RRID:AB\_221569  
 Mouse monoclonal anti-β-Actin (1:4000) Sigma-Aldrich A2228; RRID:AB\_476697  
 Mouse monoclonal anti-GAPDH (1:3000) Millipore MAB374; RRID:AB\_2107445

#### Secondary antibodies:

Goat polyclonal anti-rabbit IgG-HRP (1:100000) Santa Cruz sc-2030; RRID:AB\_631747  
 Goat polyclonal anti-Guinea Pig IgG, Alexa Fluor™ 488 (1:100000) Invitrogen A-11073; RRID:AB\_2534117  
 Donkey polyclonal anti-Mouse IgG, Alexa Fluor™ 488 (1:100000) Invitrogen A-21202; RRID:AB\_141607  
 Donkey polyclonal anti-Rabbit IgG, Alexa Fluor™ 488 (1:100000) Invitrogen A-21206; RRID:AB\_2535792  
 Cy™3 AffiniPure™ Donkey polyclonal anti-Mouse IgG (1:100000) Jackson ImmunoResearch 715-165-150; RRID:AB\_2340813  
 Cy™3 AffiniPure™ Donkey polyclonal anti-Rabbit IgG (1:100000) Jackson ImmunoResearch 711-165-152; RRID:AB\_2307443  
 Cy™3 AffiniPure™ Donkey polyclonal anti-Goat IgG (1:100000) Jackson ImmunoResearch 705-165-147; RRID:AB\_2307351  
 Cy™5 AffiniPure™ Donkey polyclonal Anti-Rabbit IgG (1:100000) Jackson ImmunoResearch 711-175-152; RRID:AB\_2340607  
 Cy™5 AffiniPure™ Donkey polyclonal anti-Goat IgG (1:100000) Jackson ImmunoResearch 705-175-147; RRID:AB\_2340730  
 IRDye® 680RD Goat polyclonal anti-Mouse IgG Secondary Antibody (1:10000) Li-COR 925-68070; RRID:AB\_2651128  
 IRDye® 800CW Goat polyclonal anti-Rabbit IgG Secondary Antibody (1:10000) Li-COR 925-32211; RRID:AB\_2651127

#### Validation

All commercially acquired antibodies used in this study were thoroughly validated by manufacturer and published studies. Individual antibody profiles and relevant citations were provided in the links.

Rabbit polyclonal anti-m6A (<https://sysy.com/product/202003>)  
 Mouse monoclonal anti-m6A (<https://www.ptglab.com/products/m6A-Antibody-68055-1-Ig.htm>)  
 Rabbit monoclonal anti-β3-Tubulin (<https://www.cellsignal.com/products/primary-antibodies/b3-tubulin-d71g9-xp-rabbit-mab/5568>)  
 Mouse monoclonal anti-NeuN (RBFOX3) (<https://www.sigmaaldrich.com/TW/en/product/mm/mab377>)  
 Mouse monoclonal anti-Neurofilament H, Nonphosphorylated (SMI32) (<https://www.biolegend.com/fr-fr/products/purified-anti-neurofilament-h-nf-h-nonphosphorylated-antibody-11475?GroupID=BLG15643>)  
 Rabbit polyclonal anti-Synapsin ([https://www.merckmillipore.com/TW/zh/product/Synapsin-I-Antibody,MM\\_NF-AB1543](https://www.merckmillipore.com/TW/zh/product/Synapsin-I-Antibody,MM_NF-AB1543))  
 Rabbit polyclonal anti-Foxp1 (<https://www.abcam.com/products/primary-antibodies/foxp1-antibody-ab16645.html>)  
 Goat polyclonal anti-Isl1 ([https://www.antibodyregistry.org/AB\\_2126323](https://www.antibodyregistry.org/AB_2126323))  
 Goat polyclonal anti-ChAT ([https://www.merckmillipore.com/TW/zh/product/Anti-Choline-Acetyltransferase-Antibody,MM\\_NF-AB144P](https://www.merckmillipore.com/TW/zh/product/Anti-Choline-Acetyltransferase-Antibody,MM_NF-AB144P))  
 Rabbit polyclonal anti-Iba1 (<https://www.ptglab.com/products/IBA1-Antibody-10904-1-AP.htm>)  
 Mouse monoclonal anti-neurofilament (<https://dshb.biology.uiowa.edu/2H3>)  
 Mouse monoclonal anti-SV2 (<https://dshb.biology.uiowa.edu/SV2>)  
 α-Bungarotoxin, Alexa Fluor 555 conjugate (<https://www.thermofisher.com/order/catalog/product/B35451?SID=srch-hj-B35451>)  
 Rabbit polyclonal anti-TDP-43 (<https://www.ptglab.com/Products/TARDBP-Antibody-10782-2-AP.htm>)  
 Rabbit polyclonal anti-Mettl14 (<https://www.sigmaaldrich.com/TW/en/product/sigma/hpa038002>)  
 Rabbit polyclonal anti-Olig2 ([https://www.merckmillipore.com/TW/zh/product/Anti-Olig-2-Antibody,MM\\_NF-AB9610](https://www.merckmillipore.com/TW/zh/product/Anti-Olig-2-Antibody,MM_NF-AB9610))  
 Mouse monoclonal anti-Nkx2.2 (<https://dshb.biology.uiowa.edu/74-5A5>)  
 Rabbit anti-Pax6 ([https://www.antibodyregistry.org/AB\\_291612](https://www.antibodyregistry.org/AB_291612))  
 Mouse monoclonal anti-Neurogenin-2 ([https://www.rndsystems.com/products/human-rat-neurogenin-2-antibody-7g4\\_mab3314](https://www.rndsystems.com/products/human-rat-neurogenin-2-antibody-7g4_mab3314))  
 Rabbit polyclonal anti-Lhx3 ([https://www.antibodyregistry.org/AB\\_301332](https://www.antibodyregistry.org/AB_301332))  
 Mouse monoclonal anti-Isl1/2 (<https://dshb.biology.uiowa.edu/39-4D5>)  
 Rabbit polyclonal anti-Sox9 ([https://www.sigmaaldrich.com/TW/en/product/sigma/zrb5535?utm\\_source=google&utm\\_medium=cpc&utm\\_campaign=8809292847&utm\\_content=91641849027&gclid=Cj0KCQjwqdvBhCPARIsANrmZhOxXPHi\\_51wO2Ifpt9wbCbGOrCV-Qyvb6XrfgegngW2R6DFf4kGKwlaAuCEEALw\\_wcB](https://www.sigmaaldrich.com/TW/en/product/sigma/zrb5535?utm_source=google&utm_medium=cpc&utm_campaign=8809292847&utm_content=91641849027&gclid=Cj0KCQjwqdvBhCPARIsANrmZhOxXPHi_51wO2Ifpt9wbCbGOrCV-Qyvb6XrfgegngW2R6DFf4kGKwlaAuCEEALw_wcB))  
 Rabbit polyclonal anti-Histone H3 (<https://www.abcam.com/products/primary-antibodies/histone-h3-tri-methyl-k9-antibody-chip-grade-ab8898.html>)  
 Mouse monoclonal anti-phospho-Histone H2A.X (Ser139), clone JBW301 (<https://www.sigmaaldrich.com/TW/en/product/sigma/ZMS05636>)  
 Rabbit polyclonal anti-phospho-Histone H2A.X (Ser139) (<https://www.cellsignal.com/products/primary-antibodies/phospho-histone-h2a-x-ser139-antibody/2577>)  
 Rabbit polyclonal anti-Fto (<https://www.ptglab.com/Products/FTO-Antibody-27226-1-AP.htm>)  
 Rabbit polyclonal anti-Glial Fibrillary Acidic Protein (GFAP) ([https://www.merckmillipore.com/TW/zh/product/Anti-Glial-Fibrillary-Acidic-Protein-GFAP-Antibody,MM\\_NF-AB5804](https://www.merckmillipore.com/TW/zh/product/Anti-Glial-Fibrillary-Acidic-Protein-GFAP-Antibody,MM_NF-AB5804))  
 Mouse monoclonal anti-β-Actin (<https://www.sigmaaldrich.com/TW/en/substance/monoclonalantibactinantibodyproducedinmouse1234598765>)  
 Mouse monoclonal anti-GAPDH (<https://www.sigmaaldrich.com/TW/en/product/mm/mab374>)  
 Goat polyclonal anti-rabbit IgG-HRP ([https://www.antibodyregistry.org/AB\\_291612](https://www.antibodyregistry.org/AB_291612))  
 Goat polyclonal anti-Guinea Pig IgG, Alexa Fluor™ 488 (<https://www.thermofisher.com/antibody/product/Goat-anti-Guinea-Pig-IgG->

H-L-Highly-Cross-Adsorbed-Secondary-Antibody-Polyclonal/A-11073)  
 Donkey polyclonal anti-Mouse IgG, Alexa Fluor™ 488 (<https://www.thermofisher.com/antibody/product/Donkey-anti-Mouse-IgG-H-L-Highly-Cross-Adsorbed-Secondary-Antibody-Polyclonal/A-21202>)  
 Donkey polyclonal anti-Rabbit IgG, Alexa Fluor™ 488 (<https://www.thermofisher.com/antibody/product/Donkey-anti-Rabbit-IgG-H-L-Highly-Cross-Adsorbed-Secondary-Antibody-Polyclonal/A-21206>)  
 Cy™3 AffiniPure™ Donkey polyclonal anti-Mouse IgG (<https://www.jacksonimmuno.com/catalog/products/715-165-150>)  
 Cy™3 AffiniPure™ Donkey polyclonal anti-Rabbit IgG (<https://www.jacksonimmuno.com/catalog/products/711-165-152>)  
 Cy™3 AffiniPure™ Donkey polyclonal anti-Goat IgG (<https://www.jacksonimmuno.com/catalog/products/705-165-147>)  
 Cy™5 AffiniPure™ Donkey polyclonal Anti-Rabbit IgG (<https://www.jacksonimmuno.com/catalog/products/711-175-152>)  
 Cy™5 AffiniPure™ Donkey polyclonal anti-Goat IgG (<https://www.jacksonimmuno.com/catalog/products/705-175-147>)  
 IRDye® 680RD Goat polyclonal anti-Mouse IgG Secondary Antibody (<https://www.licor.com/bio/reagents/irdye-680rd-goat-anti-mouse-igg-secondary-antibody>)  
 IRDye® 800CW Goat polyclonal anti-Rabbit IgG Secondary Antibody (<https://www.licor.com/bio/reagents/irdye-800cw-goat-anti-rabbit-igg-secondary-antibody>)

information about antibody gifts:

Guinea pig polyclonal anti-Olig2 (1:100) Thomas Jessell (Columbia University)

Rabbit polyclonal anti-Irx3 (1:16000) Thomas Jessell (Columbia University)

Guinea pig polyclonal anti-Hb9/Mnx1 (1:1000) Hynek Wichterle (Columbia University)

## Eukaryotic cell lines

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

|                                                                   |                                                                                                                                                                              |
|-------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cell line source(s)                                               | 29d SOD1+/L144F iPSC line was obtain from HSCI iPS Core. CS4VFTiALS-n1, CS47iALS-TDP43, CS52iALS-C9n6A and their isogenetic control iPSC lines were obtain from Cedars-Sinai |
| Authentication                                                    | All iPSC lines were authenticated by the expression of neuron marker (immunostaining and qPCR) after motor neuron differentiation.                                           |
| Mycoplasma contamination                                          | No mycoplasma contamination was detected in all iPSC lines.                                                                                                                  |
| Commonly misidentified lines (See <a href="#">ICLAC</a> register) | No commonly misidentified lines were used                                                                                                                                    |

## Animals and other research organisms

Policy information about [studies involving animals](#); [ARRIVE guidelines](#) recommended for reporting animal research, and [Sex and Gender in Research](#)

|                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|--------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Laboratory animals | <p>Mus musculus (B6SJL-Tg(SOD1*G93A)1Gur/J (The Jackson Laboratory; RRID: IMSR_JAX:002726 )<br/>           Mus musculus Olig2-Cre (Tom Jessell, Columbia University)<br/>           Mus musculus Mettl14floxex (Chuan-He, University of Chicago)<br/>           Mus musculus B6.129S-Chattm1(cre)Lowl/MwarJ (The Jackson Laboratory, RRID: IMSR_JAX:031661)<br/>           Mus musculus B6;129-Gt(ROSA)26Sortm5(CAG-Sun1/sfGFP)Nat/J (The Jackson Laboratory RRID: IMSR_JAX:021039)<br/>           Mus musculus B6SJL-Tg(SOD1*G93A)1Gur/J (The Jackson Laboratory RRID: IMSR_JAX:002726 )<br/>           B6;129-Gt(ROSA)26Sortm5(CAG-Sun1/sfGFP)Nat/J</p> <p>Related to Fig.4b,c. (n mice at P40, P70, P100, P130, and P160 from males/females)<br/>           Ctrl: n = 3/3, 8/9, 5/10, 11/10, and 10/10<br/>           ChAT-Cre; Mettl14floxex: n = 3/3, 7/11, 7/15, 9/12, and 8/10</p> <p>Related to Fig.4d. (n mice at P40, P70, P100, P130, and P160 from males/females)<br/>           Ctrl: n = 3/6, 12/12, 12/14, 12/10, and 6/10<br/>           ChAT-Cre; Mettl14floxex: n = 3/6, 10/14, 10/17, 8/12, and 7/9 at P40, P70, P100, P130</p> <p>Related to Fig.4f. (n mice at P40, P70, P100, P130, and P160 from males/females)<br/>           Ctrl: n = 3/3, 7/9, 6/8, 8/9, and 8/9<br/>           ChAT-Cre; Mettl14floxex: n = 3/3, 6/11, 6/11, 7/12, and 7/9<br/>           Related to Fig.4h:n = 6 (3 from P180 and 3 from &gt; P210 mice).</p> <p>Related to Fig.9j. (n mice of male/female)<br/>           Ctrl: 5/1, 4/3, 3/3, 4/3,<br/>           Ctrl;scAAV9-shFto: 5/1, 5/2, 5/2, 5/2<br/>           SOD1G93A : 2/3, 5/6, 4/5, 4/3<br/>           SOD1G93A;scAAV9-shFto: 3/2, 5/3, 4/3, 4/3</p> <p>Related to Fig.9k (n mice of male/female)<br/>           Ctrl: 6/2, 4/3, 4/3, 4/3<br/>           Ctrl;scAAV9-shFto: 5/1, 5/2, 5/2, 5/2</p> |
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SOD1G93A : 3/4, 5/6, 5/6, 5/5  
 SOD1G93A;scAAV9-shFto: 5/2, 5/3, 5/3, 5/3  
 Related to Fig.9(n mice of male/female)  
 Ctrl: 6/2, 4/3, 4/3, 4/1  
 Ctrl;scAAV9-shFto: 5/1, 5/2, 5/2, 5/2  
 SOD1G93A : 4/4, 5/6, 5/6, 4/3  
 SOD1G93A;scAAV9-shFto: 5/2, 5/3, 5/3, 5/3

Wild animals

No wild animals were used in this study.  
 All animals were compare with the littermate controls.

Reporting on sex

no apply for one sex in this study

Field-collected samples

No field-collected samples were used in this study.

Ethics oversight

All mouse experiments conform to guidelines approved and overseen by Academia Sinica Institutional Animal Care and Use Committee. (IACUC no. 13-06-559)

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

## Plants

Seed stocks

n/a

Novel plant genotypes

n/a

Authentication

n/a