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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 Authors & Referees 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	Leica application suite V4 software, Image Studio 2.0 (Li-Cor).
Data analysis	Excel, GraphPad Prism 6, MEGA7, ImageJ, IGV browser, SnpEff, SAMtools, Bowtie 2.

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/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

The following statement is included in the manuscript: "All data generated or analyzed during this study are included in this published article (and its supplementary information files)."

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

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Sample size for each experiment was noted in the Figure Legends. No statistical method was used to predetermine the sample size. The numbers of samples were determined by following standard practice in the field.
Data exclusions	No exclusions. All the samples used in the statistical analyses were described in the Figure legends.
Replication	The experiments were repeated in two or more independent trials. The results were consistent with the conclusions.
Randomization	Samples or animals were randomly allocated into experimental groups based on their genotypes or different treatments as described in Figure Legends.
Blinding	Data collection and analysis were not performed blind to the conditions of the experiments. In the experiments involving animals, individual animals were coded and behavioral data were collected in an unbiased manner. The molecular and cellular experiments were performed following standard practice ensuring equal treatments of all samples.

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
☐	☒ Animals and other organisms
☒	☐ Human research participants
☒	☐ Clinical data

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used	The antibodies used include the following: anti-SOD1-100 (Enzo, P00441, 1:3,000), anti-L3MBTL1 (Abcam, 1:500, and Genetex GTX103793, 1:100), anti-SETD8 (Cell Signaling Technology, C18B7, 1:1,000, and Genetex GTX119440, 1:1,000), anti-p53 7F5 (Cell Signaling Technology, #9282, 1:1,000), anti-C. elegans-SOD-1 (JH766, 1:5,000)58, anti-histone H4 (Active Motif, #61300, 1:1,000), anti-H4K20me1 (Active Motif, #39728, 1:1,000), anti-NeuN (Millipore, MAB377, 1:20), anti-YFP (Takara, #632381, 1:3,000), anti-beta-actin (Santa Cruz, sc- 47778B, 1:3,000), and anti-GAPDH (Thermo Fisher, TAB1001, 1:3,000). Secondary antibodies include goat anti-rabbit IgG IRDye, 1：40,000 (680 LT, 926–68021 or 800 CW, 926–32211, LI-COR); donkey anti-mouse IgG, 1：40,000 (680 LT, 926–68022; or 800 CW, 926–32212, LI-COR); donkey anti-mouse IgG, 1:1,000 (Alexa Fluor 488, A-21202, ThermoFisher); and goat anti-rat IgG, 1:1,000 (Alexa Fluor 555, A-21434, ThermoFisher).
Validation	The information of the validated antibodies is available at the following websites: C elegans SOD1: https://www.ncbi.nlm.nih.gov/pubmed/16234242 http://www.enzolifesciences.com/ADI-SOD-100/cu-zn-sod-polyclonal-antibody/ https://www.abcam.com/l3mbtl1-antibody-ab51880.html https://www.genetex.com/Product/Detail/L3MBTL1-antibody/GTX103793 https://www.cellsignal.com/products/primary-antibodies/set8-c18b7-rabbit-mab/2996?_=1549281172919&Ntt=C18B7&tahead=true https://www.genetex.com/Product/Detail/SETD8-antibody/GTX119440 https://www.cellsignal.com/products/primary-antibodies/p53-antibody/9282 https://www.activemotif.com/catalog/details/61299/histone-h4-antibody-pab-3 https://www.activemotif.com/catalog/details/39727/histone-h4-monomethyl-lys20-antibody-mab-clone-5e10-d8 http://www.emdmillipore.com/US/en/product/Anti-NeuN-Antibody-clone-A60,MM_NF-MAB377?ReferrerURL=https%3A%2F%2Fwww.google.com%2F https://www.takarabio.com/products/antibodies-and-elisa/fluorescent-protein-antibodies/green-fluorescent-protein-antibodies?catalog=632569 https://www.scbt.com/scbt/product/beta-actin-antibody-c4?productCanUrl=beta-actin-antibody-c4&_requestid=1024537 https://www.thermofisher.com/antibody/product/GAPDH-Antibody-Polyclonal/TAB1001 https://www.licor.com/bio/products/reagents/secondary_antibodies/irdye_680lt.html https://www.licor.com/bio/products/reagents/secondary_antibodies/irdye_800cw.html https://www.thermofisher.com/antibody/product/Donkey-anti-Mouse-IgG-H-L-Highly-Cross-Adsorbed-Secondary-Antibody-

Polyclonal/A-21202
https://www.thermofisher.com/antibody/product/Goat-anti-Rat-IgG-H-L-Cross-Adsorbed-Secondary-Antibody-Polyclonal/A-21434

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	MEFs, HEK293 cells were from ATCC. Mouse embryonic stem cell line RW4 (from Dr. Shelly E. Sakiyama-Elbert, Washington University School of Medicine, St. Louis, MO). Rat primary neurons were derived from animals in this study.
Authentication	RW4 was authenticated by their ability to differentiate into motor-neurons, and resistance to puromycin. MEFs were confirmed by their distinctive morphology and growth properties.
Mycoplasma contamination	Not tested
Commonly misidentified lines (See ICLAC register)	None

Animals and other organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research

Laboratory animals	The animals used in this study include the SOD1G93A line [B6.Cg-Tg(SOD1*G93A)1Gur/J; Jackson Laboratory, stock 004435] (5 weeks to 6 months old), the SOD1G85R-YFP (10-15 months old) and SOD1WT-YFP lines (9-15 months old) (Ref. #26), and C57BL/6J mice (Jackson Laboratory, stock (5 weeks to 10 months old). Both males and females were used as specified in the study. The ages of the animals depends on specific experiments as described and the age of disease onset as previously reported.
Wild animals	The study did not involve wild animals.
Field-collected samples	The study did not involve samples collected from the field.
Ethics oversight	The animal protocol was approved by the Animal Care and Use Committee of the Johns Hopkins Medical Institutions.

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