nature research

Corresponding author(s): Paul J. Tesar

Last updated by author(s): Jun 6, 2020

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	Images were acquired with Leica Application Suite X, Hamamatsu NDP 2.0, or Perkin Elmer Operetta Harmony software. Videos were acquired using an Apple iPhone. Optic nerve conduction velocity was recorded using AxoScope software(Molecular Devices). Behavioral measurements were recorded using ANY-maze software version 5.0 (open field) and Rota Rod Rotomax 5 (rotarod). Breathing was recorded on the IOX2 software (Emka).
Data analysis	Graphpad Prism was used to generate graphs and perform statistics. Adobe Photoshop, NIH ImageJ, and Perkin Elmer Harmony and Columbus software were used for calculations and cell counting. spCas9 CRISPR sgRNA design tool at crispr.mit.edu was used to design sgRNAs. CRISPR-induced indels were analyzed using the OutKnocker tool at outknocker.org, GATK RealignerTargetCreator, IndelRealigner (version 3.3-2-gec30cee), Blat (v. 36x2), CCTop, RGEN Cas-OFFinder, CRISPOR, and the Integrative Genomics Viewer. Bowtie aligner 58 was used to identify putative ASO off-target transcript sequences. Adobe Photoshop and Illustrator were used to assemble images. Blots were analyzed with the Odyssey Fc imaging system (Li-Cor). LC-MS/MS data was analyzed using BioinformaticsSolutions PeaksStudio software.

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

All data generated or analyzed during this study are included in this article and its supplementary information files. Source data for animal survival cohorts in Figs. 1b, k-l, and 3b, 4a-b are provided in Supplementary Data 1 and 6. Raw annotated western blot images for Extended Data Fig. 2b, d and Extended Data Fig. 7a, c are

provided as Supplementary Data 2 and 7. Source data for all graphs are provided as separate Excel files. Animals and iPSC lines are available from P.J.T. upon request.

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 statistical test was used to predetermine sample size. Instead, sample sizes were rationalized by considering sufficient replication (weighing the level of biological variation) as well as censoring (due to tissue harvesting at pre-determined time-points and inadvertent losses).
Data exclusions	All data points were included in analyses except for certain animals that were censored from survival analyses to use in pre-determined terminal assays. Metadata for all mice in this study including censoring of animals in the survival analyses are found in Supplementary Figs. 1 and 3.
Replication	The ASO therapeutic response was tested with two independent ASOs and all data were replicated.
Randomization	Sample allocation was not random. Instead, biological controls were employed in all experiments.
Blinding	Investigators were blinded to animal genotype at the time of ASO injection. Investigators were blinded to genotype and treatment for immunohistochemistry quantifications. For other experiments (i.e. animal behavior, electrophysiology, and respiratory analysis) blinding was not possible due to the overt jimpy phenotype.

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

Primary antibodies used for IHC: mouse anti-MBP (2µg/mL; 808401, Biolegend; RRID:AB_2564741), rabbit anti-MBP (1:1000; Abcam, ab40390; RRID:AB_1141521), rabbit anti-MyRF polyclonal antibody (1:500; kindly provided by Dr. Michael Wegner), goat anti-SOX10 (0.4µg/mL; AF2864, R&D Systems; RRID:AB_442208), rabbit anti-GFAP (1:1000; Z0334, Dako; RRID:AB_10013382), goat anti-IBA1 (0.1mg/mL; ab5076, Abcam), rabbit anti-IBA1 (1:2000; 019–19741, WAKO; RRID:AB_839504), rabbit anti-ASO (1:2500; Ionis Pharmaceuticals, Carlsbad, CA), rabbit anti-HDAC2 (1:250; Abcam, ab16032; RRID:AB_2118543), mouse anti-APC/CC1 (2.5 µg/ml; ab16794, Abcam; RRID:AB_443473), mouse anti-APC/CC1 (1:250; MABC200, Millipore; RRID:AB_11203645), rat anti-NG2 (25 µg/mL; MAB6689, R&D Systems; RRID:AB_10890940), goat anti-PDGFRα (1:500; AF1062, R&D systems; RRID:AB_2236897), and rabbit anti-OLIG2 (1:250; 13999-1-AP, ProteinTech; RRID:AB_2157541).

Primary antibodies used for western blot: mouse anti-MBP antibody (1µg/mL; 808401, Biolegend; RRID:AB_2564741) and rat anti-PLP antibody (1:1000; clone AA3, Lerner Research Institute Hybridoma Core, Cleveland, OH).

Primary antibodies used for ICC: mouse anti-MBP (1:500; 808401, Biolegend; RRID:AB_2564741), rat anti-PLP (1:5000; clone AA3, Lerner Research Institute Hybridoma Core, Cleveland, OH), goat anti-SOX10 (2µg/mL; AF2864, R&D Systems; RRID:AB_442208), rabbit anti-OLIG2 (1:1000; 13999-1-AP, ProteinTech; RRID:AB_2157541), rabbit anti-NANOG (0.4µg/mL; AB21624, Abcam; RRID:AB_446437), mouse anti-OCT3/4 (0.4µg/mL; SC-5279, Santa Cruz; RRID:AB_628051).

Validation	Primary antibodies used in this study are well accepted in the field and purchased from reputable suppliers with provided quality control metrics.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	Mouse iPSC lines were generated in-house
Authentication	Cells lines were genotyped, karotyped, and stained for canonical markers of OPCs and iPSCs.
Mycoplasma contamination	Laboratory cell lines are routinely tested for mycoplasma contamination with consistently negative results.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used in this study.

Animals and other organisms

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

Laboratory animals	Male jimpy mice (B6CBACa-Aw-J/A-Plp1jp EdaTa/J; RRID:IMSR_JAX:000287), CRISPR modified jimpy (CR-impy) mice (this paper) and wild-type controls. All mice were on a B6CBACa background.
Wild animals	No wild animals were used in this study.
Field-collected samples	No field-collected samples were used in this study.
Ethics oversight	All procedures were in accordance with the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals and were approved by the Case Western Reserve University Institutional Animal Care and Use Committee (IACUC).

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