

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	Bio-Rad CFX96 for qPCR NovaSeq 6000 for NGS
Data analysis	Prism and Excel for graphing and statistics Crispresso2 for analysis of NGS data RNA-STAR for analysis of exon skipping limma-voom for RNA-seq analysis

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](#)

All data necessary to evaluate the conclusions is presented within the manuscript or in supplementary material. Deep sequencing files have been deposited in the Gene Expression Omnibus, accession number GSE 246588.

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	N/A
Reporting on race, ethnicity, or other socially relevant groupings	N/A
Population characteristics	N/A
Recruitment	N/A
Ethics oversight	N/A

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	Sample size for each experiments was indicated in the figure legends.
Data exclusions	No data was excluded
Replication	All attempts at replication were successful.
Randomization	N/A
Blinding	Given the nature of the experiments performed, blinding was not needed.

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	For ELISA, antibodies were used as part of the Ultrasensitive A β 42 Human ELISA Kit (Thermo™ Scientific KHB3544). For Western blots, Cas9 antibodies were purchased from Epigentek (A-9000), GAPDH antibodies were purchased from CST (2118), and secondary antibodies were purchased from LI-COR (926-32210, 926-68073). Both primary antibodies were used at a 1:1000 dilution and the secondary was used at a 1:10000 dilution.
Validation	This ELISA kit has been used in 56 publications: https://www.thermofisher.com/elisa/product/Amyloid-beta-42-Human-ELISA-Kit-Ultrasensitive/KHB3544 . The Cas9 antibody has been used in over 30 publications: https://www.epigentek.com/catalog/crispcas9-monoclonal-antibody-7a9-p-4886.html . The GAPDH antibody has been used in thousands of publications: https://www.cellsignal.com/products/primary-antibodies/gapdh-14c10-rabbit-mab/2118 .

Eukaryotic cell lines

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

Cell line source(s)	HEK293T (CRL-3216) and BE(2)-M17 (CRL-2267) cells were obtained from the ATCC.
Authentication	The cell lines were authenticated based on morphology and species-specific PCR amplification.
Mycoplasma contamination	The cell lines were not tested for mycoplasma contamination
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used in this study.

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	B6.129-Tg(APPsW)40Btla/Mmjax mice. Injected at 4-7 weeks of age. Mice were maintained in 12 h dark / 12 h light cycles at 22 degrees C without humidity control.
Wild animals	No wild animals were used in this study.
Reporting on sex	Since the mice were used only to assess editing rates, sex was not considered as a variable in these studies.
Field-collected samples	No field-collected samples were used.
Ethics oversight	All animal procedures were approved by the Illinois Institutional Animal Care and Use Committee at the University of Illinois and conducted in accordance with the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals.

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

Flow Cytometry

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	For FACS, nuclei isolation was performed as previously described. ⁹³ Briefly, tissues were homogenized in NF1 buffer using the KIMBLE Dounce Tissue Grinder (Sigma-Aldrich) per the manufacturer's instructions, strained through a 70 µm strainer into a 50 mL conical tube underlaid with a 1.2 M sucrose cushion, and centrifuged at 3,900G for 30 minutes at 4°C. The supernatant was discarded and the pelleted nuclei were resuspended in 10 mL of NF1 buffer. Samples were spun 2X at 1,600G for 5 minutes at 4°C and resuspended in 2 mL of FANS buffer. Cells were strained through a 35 µm strainer and incubated at 37°C for 30 minutes with 0.5 µL Vybrant™ DyeCycle™ Ruby stain (Invitrogen, V10309) per mL of FANS buffer.
Instrument	ThermoFisher Bigfoot Spectral Cell Sorter Cell Sorter
Software	FCS express vs7
Cell population abundance	10,000 events were collected
Gating strategy	Tissues from uninjected mice were used to determine background fluorescence and set up gates.

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