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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	BD Accuri C6 software was used to acquire flow cytometry data. Quantstudio Design and Analysis Software v1.4 was used to acquire qPCR data. Odyssey software was used to capture western blot images. Image stacks were collected sequentially using the Olympus Flouview software version 4.2 with 5% overlap between individual tiles.
Data analysis	Prism 8 was used to perform statistical analysis on all data presented. Image registration of individual z-stacks was performed in a semi-automated fashion using the bio-image software Imago 1.5 (Mayachitra Inc.).

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

An excel file containing source data for the following figures has been included with submission (Fig. 1B, 1C, 1D, 1E, 2A, 2B, 2D, 2E, 2F, 3B, 3C, 4D, 4E, 4F, 4G, Extended Data Fig. 1B,1C, 1D, 2A, 2B, 2C, 2E, 2G, 3A, 3B, 3C). Fully scanned western blot gels can be found in the Supplementary Information. All other data available from the corresponding author upon reasonable 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 calculations were performed to predetermine sample size, sample sizes were based on previously published work and chosen to support meaningful conclusions. The sample size (n) of each experiment is provided in the figure captions.
Data exclusions	No animals or samples were excluded from the displayed datasets. To determine statistical significance, Shapiro-Wilk tests were first used to evaluate the assumption of normality of the data. Given a p>0.05 then normality assumptions were not rejected and ANOVA tests were used. In certain cases, outliers were removed to meet the normality assumption and then an ANOVA test was performed, however data is displayed in full.
Replication	All in vitro experiments were performed in biological duplicates or triplicates over three independent experiments. In vivo analysis was performed on n=7 animals per experimental group. All replications were consistent across multiple experiments.
Randomization	No specific method of randomization was used. However, four male and three female animals were used in this study.
Blinding	Animal mosaics were quantified under blinding conditions, file names were withheld until after image analysis was completed.

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	anti-Tau13 (Biolegend, cat no. 835201; mouse 1:200), anti-Iba1 (Wako laboratory chemicals, cat no. 019-19741; rabbit 1:200), MC-1 (Peter Davies; mouse 1:200), anti-Tuj1 (Sigma cat no. T3952; rabbit 1:200), anti-HA (Sigma, cat no. H3663; mouse 1:1000), anti-GAPDH (Abcam, cat no. 181602; rabbit 1:10000), anti-LRP1 (Sigma, cat no. L2295; rabbit 1:1000), anti-actin (Sigma, cat no. A5441, mouse 1:10000), anti-ApoE (Abcam, cat no. 52607; rabbit 1:1000), anti-Sox2 (Abcam, cat no. 97959; rabbit 1:200), anti-myc (Cell signaling, cat no. 2272; rabbit 1:1000), anti-LRP1 (Abcam, cat no. 92544; rabbit 1:200).
Validation	All commercially purchased antibodies were validated for their respective application by their manufacturer. MC-1 antibody obtained from Peter Davies has been validated in the literature previously (Jicha et. al, J NeuroSci 1997).

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	Cell lines (H4, HEK293T) were obtained from the ATCC. CRISPRi H4 and CRISPRi iPSc were provided by Martin Kampmann, UCSF (Tian, R. et al. CRISPR Interference-Based Platform for Multimodal Genetic Screens in Human iPSC-Derived Neurons. Neuron, doi:10.1016/j.neuron.2019.07.014 (2019))
Authentication	None of the cell lines have been authenticated.

Mycoplasma contamination	All cell lines used tested negative for mycoplasma contamination using a PCR Mycoplasma test kit (VWR 10181-030).
Commonly misidentified lines (See ICLAC register)	None used.

Animals and other organisms

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

Laboratory animals	Experiments were performed on six-week old mice, (FVB/B6, four males/three females were used for each experimental cohort).
Wild animals	The study did not involve wild animals.
Field-collected samples	The study did not involve samples collected from the field.
Ethics oversight	All procedures were done with approval from the Institutional Animal Care and Use Committee and in compliance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals, the Animal Welfare Act, and guidelines from the University of California, Santa Barbara.

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

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	Cells were obtained from culture conditions and were lifted and analyzed without fixation.
Instrument	BD Accuri C6 for routine analysis and Sony SH800 for sorting
Software	BD Accuri C6 software for collection and Prism 8 software for data analysis.
Cell population abundance	Cells that were infected with mLRP constructs were sorted using a Sony SH800 Cell Sorter on EGFP expression. Cells were sorted using a standard two-way sort. Cells were determined to be >99% positive after sorting.
Gating strategy	Cells were gated on FSC/SSC (Mean FSC-A: ~ 8,000,000/Mean SSC-A: ~800,000). Cells were gated on FSC-H vs. Width to discriminate doublets. Dead cells were removed from analysis using propidium iodide as a stain, and positive cells were determined by gating on a negative (no tau added) population. See Extended Data Fig. 1a.

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