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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	LAS X (Leica) was used for imaging; V-PLEX Aβ Peptide Panel 1 (6E10) Kit (Meso Scale Discovery) was used for ELISA; illumina HiSeq was used for deep sequencing; illumina NovaSeq was used for whole-genome sequencing.
Data analysis	GraphPad Prism 6 was used for all statistical analysis and graphing; ImageJ (Version 1.51h) and MetaMorph Offline (Version 7.8.8.0) , were used for image analysis; CRISPResso was used to analyze deep sequencing data; Trimmomatic (version 0.32), BWA mem (version 0.7.12-r1039), and Genome Analysis Toolkit (GATK) Best Practices (Version 4.1.2.0) were used to analyze whole-genome sequencing data.

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 main data supporting the results in this study are available within the paper and its Supplementary Information. The raw data of whole-genome sequencing have been deposited in the NCBI Sequence Read Archive (SRA), with accession code PRJNA733582. The other raw and analyzed datasets generated during the study are available for research purposes from the corresponding authors on reasonable request as they are too large to be publicly shared.

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 methods were used to predetermine sample size. Sample sizes were determined on the basis of previous experimental experience and similar published studies.
Data exclusions	No data were excluded from the study.
Replication	Multiple mice were examined for each endpoint. All findings were reproduced in multiple mice with the same methodology.
Randomization	Transgenic mice were randomly selected for virus injection.
Blinding	The investigators were blinded to group allocation during data collection and analysis.

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	We used the following primary antibodies: anti-HA tag antibody (1:50; #3724,rabbit; #2367,mouse; Cell Signaling Technology); anti–β-amyloid, 17-24 antibody (1:1,000, clone 4G8, 800701, mouse, BioLegend); anti-Iba 1 antibody (1:500, 019-19741, rabbit, Wako); anti-GFAP antibody (1:5,000, #3670, mouse, Cell Signaling Technology); anti-PSD-95 antibody (1:500, ab2723, rabbit, Abcam); anti-synaptophysin 1 antibody (1:500, 101011, mouse, Synaptic Systems); anti-LAMP-1 antibody (1:500, 1D4B, rat, Developmental Studies Hybridoma Bank); and anti-NeuN antibody (1:100, MAB377, mouse, Millipore).
Validation	All antibodies were validated by the manufacturer or in relevant publications (Fu A., 2016, PNAS; FU A., 2014, PNAS; Tunc-Ozcan E., 2019, Nat Commu; Shikanai M., 2018 iScience; Andrejewski N., 1999, J Biol Chem).

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	HEK293T cells from American Type Culture Collection (ATCC).
Authentication	None of the cell lines were authenticated.
Mycoplasma contamination	The HEK293T cells were tested, and confirmed to be negative.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used.

Animals and other organisms

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

Laboratory animals	5XFAD transgenic mice, which harbour 5 familial AD mutations (APP K670N/M671L [Swedish], I716V [Florida], V717I [London], and PS1 M146L and L286V), and APP/PS1 transgenic mice, which harbour the APP K670N/M671L (Swedish) mutation and the PS1 exon-9 deletion, were obtained from the Jackson Laboratory (stock numbers: 008730 and 004462, respectively). For research, male transgenic mice and their wild-type littermates were used.
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 Ethics Committee of the Hong Kong University of Science and Technology.

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