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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.

Statistical parameters

When statistical analyses are reported, confirm that the following items are present in the relevant location (e.g. 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
☐	☒	An indication of 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 statistics 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
☐	☒	Clearly defined error bars *State explicitly what error bars represent (e.g. SD, SE, CI)*

Our web collection on statistics for biologists may be useful.

Software and code

Policy information about availability of computer code

Data collection	DNA gel and Western blot: BioRad Molecular Imager ChemiDoc XRS+ and Image Lab Software 4.0. Southern blot: Fujifilm FLA-5100 phosphorimager. Microscopy: Zeiss AX10 Imager. M2 microscope and ZEN2 software. PacBio CCS sequencing: PacBio Sequel sequencing platform. Sequencing data was processed from pre-CCS (circular consensus sequence) bam format to fastq using the publicly available circular consensus program in SMRTLink. Software analysis pipelines used BLAST 2.6.0, STAR 2.5.3a, and Picard 2.1.1 as described in the methods section. QPCR: BioRad CFX384 RealTime System and BioRad CFX Manager 3.1. Illumina sequencing: Illumina NextSeq 500. Sequences were aligned to the human reference genome (GRCh38) using STAR (version 2.5.3a). Duplicate reads were marked and removed using Picard (version 2.1.1).
Data analysis	ImageJ 1.50i and Graphpad Prism 7 were used for quantitative analysis of ISH. Appropriate software pipelines were used to classify and characterize sequencing data, these included SMRTLink 5.1.0.26412 and SMRTTools 5.1.0.26366 from Pacific Biosciences for analysis of SMRT sequencing results and STAR 2.5.3a and Picard 2.1.1 for Illumina sequencing. Reads were informatically analyzed using IGV 787, the UCSC Genome Browser (GRCh38/hg38), and the custom pipeline created as described in the methods section. Code will be uploaded to GitHub upon acceptance of the manuscript.

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 upon request. 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

Fastq files of the Illumina short read sequences (Fig. 2q, Extended Data Fig. 2i) and PacBio long read sequences (Fig. 3) used in the analysis will be made available on the NCBI Sequence Read Archive upon acceptance of the manuscript. Sanger sequences are provided in Supplementary Information.

Field-specific reporting

Please select 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/authors/policies/ReportingSummary-flat.pdf

Life sciences study design

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

Sample size	Sample sizes indicated in figures and text were determined based on the availability of post-mortem human brain samples, the experience of the authors, and comparison with similar published studies in order to ensure appropriate statistical power.
Data exclusions	No data was excluded from analysis.
Replication	All attempts at replication were successful. Replications of ISH and cell viability assays were all provided in Figures and Extended Data Figures. A summary of reproducibility for each experiment is shown in Extended Data Table 1.
Randomization	Samples were allocated randomly.
Blinding	All ISH counts were blinded for quantification and assessment. Automatic, unbiased quantification of foci number and size was performed via imageJ.

Reporting for specific materials, systems and methods

Materials & experimental systems

n/a	Involved in the study
☐	☒ Unique biological materials
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology
☐	☒ Animals and other organisms
☒	☐ Human research participants

Methods

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

Unique biological materials

Policy information about availability of materials

Obtaining unique materials	Fresh frozen human brain tissues were obtained from the University of California San Diego (UCSD) Alzheimer's Disease Research Center (ADRC) and the University of California Irvine (UCI) Institute for Mind Impairments and Neurological Disorders (MIND). Material limitations are present for post-mortem human brain analysis, where the reasons for restrictions included limited sample quantity with requests to individual brain banks granted on a case by case basis. Brain sample and donor data are provided in Extended Data Table 2.

Antibodies

Antibodies used	All antibodies used are listed (clone number, dilution, supplier, catalog number) FANS (cell sorting): Rabbit monoclonal anti-NeuN antibody (27-4, 1:800, Millipore, MABN140) Alexa Fluor 488 donkey anti-rabbit IgG antibody (N/A, 1:500, Invitrogen, Ref# A21206) Western blot: Rat anti-HA antibody (3F10, 1:500, Roche,11867423001) Mouse anti-a-tubulin antibody (DM1A, 1:500, Sigma, T9026) HRP-conjugated goat anti-rat antibody (N/A, 1:10000, Cell Signaling, 7077S) HRP-conjugated goat anti-mouse antibody (N/A, 1:10000, Pierce, 1858413)
Validation	These antibodies are all published and validated by immunofluorescence staining (anti-NeuN, anti-a-tubulin, anti-rabbit), immunohistochemistry (anti-NeuN and anti-a-tubulin), immunoprecipitation (anti-HA) and Western blot (anti-NeuN, anti-HA, anti-a-tubulin, anti-rat and anti-mouse). Additional validation and peer-reviewed papers are available on the manufacturer's websites.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	NIH-3T3, CHO-K1, SH-SY5Y, IMR-90 and HEK-293 cells were all purchased from ATCC.
Authentication	Validated by ATCC.
Mycoplasma contamination	Cells from ATCC and all reagents used are verified Mycoplasma free.
Commonly misidentified lines (See ICLAC register)	HEK cells were used to show protein expression of our targets in mammalian cells no APP gencDNA as a negative control. For the indicated purpose, there is no concern regarding this cell line in the manuscript.

Animals and other organisms

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

Laboratory animals	J20 (strain: B6.Cg-Zbtb20Tg(PDGFB-APPSwInd)20Lms/2Mmjax, genetic background: C57BL/6) mice were purchased from The Jackson Laboratory. J20 transgenic mice and wild type controls used for experiments were obtained from crosses of mice hemizygous for the transgene with wild type mice from the colony. Sex and age (day) of mice used for experiments are listed : F177, M566, M661, M661, M728, F748, F829, and M861. All animals were cared under Sanford Burnham Prebys Medical Discovery Institute IACUC guidelines.
Wild animals	This study did not involve wild animals
Field-collected samples	This study did not involve wild animals