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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 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 (*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	Illumina HiSeq 4000, Orbitrap Fusion Lumos Mass Spectrometer
Data analysis	RNA-Seq analysis: htseqcount package, DESeq2 package, GSEA java package (gsea2-2.2.1.jar) ChIP-Seq analysis: FastQC, Bowtie version 1.2.2, Trimmomatic v0.33, SAMtools version 1.9, MACS version 1.4.2. Mass pectrometry: Proteome Discoverer version 2.2 Leica LAS 3.7.1 was used for analyzing the dendritic morphological features. GraphPad Prism 8.0 was utilized for statistical analysis and generating graphs. Image J 1.53a was used for image quantitation.

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 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 RNA-seq data have been deposited in Gene Expression Omnibus (GEO) under accession numbers GSE163523, GSE163524 and GSE163525, and the ChIP-seq data in Sequence Read Archive (SRA) under accession numbers PRJNA633993 and PRJNA633994. The mass spectrometry data have been deposited in MassIVE under accession numbers MSV000088190.

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	Predetermined sample sizes were not determined. Sample sizes were determined based on prior observations and publications in addition to feasibility of experiments (PMID: 21113150, PMID: 21307849, PMID: 27929004). A minimum of three animals were used per experiment, and we also included up to 9 animals in behavior tests. The precise number of animals and cells is reported in the figure legends and methods section.
Data exclusions	No data was excluded.
Replication	All attempts at replication were successful. At least three independent biological repeats per experiment where representative data is shown. A number of biological replicates is as described in the figure legends.
Randomization	We ensured that the animals were age- and genotype-matched for in vivo experiments as well as for primary cell isolations. Otherwise, mice were randomly allocated to the experimental groups. Samples were analyzed in an arbitrary order.
Blinding	The investigators were generally not blinded to allocation during experiments and outcome assessment.

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
☒	☐ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

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

Antibodies

Antibodies used	The Primary antibodies used are presented in the Methods section with validation referenced. Anti-BDNF (ab108319, Abcam, 1:1,000), anti-Aβ (Clone 6E10, SIG-39320, Covance, 1:1,000), anti-TERT (ab32020, Abcam, 1:500), anti-H3K9me3 (ab8898, Abcam, 1:30), anti-KDM1A (ab17721, Abcam, 1:300), anti-GFAP (Z-0334, Dako, 1:4,000), anti-IBA-1 (019-19741, Wako, 1:1,000), anti-APOE (NB110-60531, Novus, 1:2,000), anti-SIRT1 (ab32441, Abcam, 1:1,000), anti-LRP1 (ab92544, Abcam, 1:3,000), anti-HSP90 (4877, Cell Signaling Tech, 1:1,000), anti-HSP70 (4872, Cell Signaling Tech, 1:1,000), anti-FOXO3A (ab12162, Abcam, 1:1,000), anti-CREBBP (7389, Cell Signaling Tech, 1:1,000), anti-non-phospho (active) β-Catenin (8814, Cell Signaling Tech, 1:500), anti-β-Catenin (total) (8480, Cell Signaling Tech, 1:500), anti-POLR2A (MA1-46093, Thermo Scientific, 1:1,000), anti-TCF7 (2206, Cell Signaling Tech, 1:30), anti-Flag (Clone M2, F1804, Sigma, 1:3,000), anti-Tubulin (T5168, Sigma, 1:10,000), anti-mouse IgG, HRP-linked secondary antibody (7076, Cell Signaling Tech, 1:10,000) and anti-rabbit IgG, HRP-linked secondary antibody (7074, Cell Signaling Tech, 1:10,000)
Validation	All antibodies are from commercially available sources and have been validated from the manufacturers with supporting data and publications found on the manufacturers' website. See below for summary: anti-BDNF (ab108319, Abcam, 1:1,000) Species reactivity: Mouse, Rat, Human Applications: Flow Cyt, WB, IHC-P, IHC-Fr, ICC/IF anti-Aβ (Clone 6E10, SIG-39320, Covance, 1:1,000) Species reactivity: human, mouse, rat

Applications: WB, ELISA, IHC, EM, ICC

anti-TERT (ab32020, Abcam, 1:500)
Species reactivity: Human
Applications: WB, IP

anti-H3K9me3 (ab8898, Abcam, 1:30)
Species reactivity: Mouse, Rat, Chicken, Human
Applications: IHC, ICC/IF, ChIP, WB, ChIP/Chip, Flow Cyt, ChIP-seq

anti-KDM1A (ab17721, Abcam, 1:300)
Species reactivity: Mouse, Human, Pig
Applications: ChIP, IHC, IP, ICC/IF, WB

anti-GFAP (Z-0334, Dako, 1:4,000)
Species reactivity: Human, Mouse, Rat, Cat, Dog, Sheep
Applications: IHC, IF, ICC, WB

anti-IBA-1 (019-19741, Wako, 1:1,000)
Species reactivity: human, mouse, rat
Applications: IHC

anti-APOE (NB110-60531, Novus, 1:2,000)
Species reactivity: Human, Mouse
Applications: WB, IHC, ELISA, Flow Cyt, IP

anti-SIRT1 (ab32441, Abcam, 1:1,000)
Species reactivity: Human
Applications: ICC/IF, IHC, WB, IP, Flow Cyt

anti-LRP1 (ab92544, Abcam, 1:3,000)
Species reactivity: Human, Mouse, Rat, Pig
Applications: IHC, WB, IP, Flow Cyt, ICC/IF

anti-HSP90 (4877, Cell Signaling Tech, 1:1,000)
Species reactivity: Human, Mouse, Rat
Applications: WB, IHC, ICC/IF

anti-HSP70 (4872, Cell Signaling Tech, 1:1,000)
Species reactivity: Human, Mouse, Rat
Applications: WB, IHC

anti-FOXO3A (ab12162, Abcam, 1:1,000)
Species reactivity: Human, Mouse, Pig
Applications: IHC, IP, WB, ICC/IF, ChIP

anti-CREBBP (7389, Cell Signaling Tech, 1:1,000)
Species reactivity: Human, Mouse, Rat
Applications: WB, IP, ICC/IF, ChIP, ChIP-seq

anti-non-phospho (active) β-Catenin (8814, Cell Signaling Tech, 1:500)
Species reactivity: Human, Mouse, Rat
Applications: WB, IP, IHC, ICC/IF, ChIP, ChIP-seq

anti-β-Catenin (total) (8480, Cell Signaling Tech, 1:500)
Species reactivity: Human, Mouse, Rat
Applications: WB, IP, IHC, ICC/IF, ChIP, ChIP-seq

anti-POLR2A (MA1-46093, Thermo Scientific, 1:1,000)
Species reactivity: Human, Mouse, Yeast
Applications: WB, ICC/IF, IHC, IP, ChIP, ELISA

anti-TCF7 (2206, Cell Signaling Tech, 1:30)
Species reactivity: Human, Mouse, Rat
Applications: WB, IP

anti-Flag (Clone M2, F1804, Sigma, 1:3,000)
Reactivity: Epitope tag / Fusion protein
Applications: WB, IP, ICC/IF, ChIP

anti-Tubulin (T5168, Sigma, 1:10,000),
Species reactivity: Human, Mouse, Rat, Chicken
Applications: WB, IF

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	Neural progenitor cells (NPCs) derived from induced pluripotent stem cells (iPSCs) from familial Alzheimer's disease patients harboring genomic duplication of APP gene (APP Dp) or from non-demented control individual (NDC) were obtained from Dr. Li-Huei Tsai. And, primary mouse cortical and hippocampal neuronal cultures were prepared from E18.5 ~ E19.5 embryos from 3xTg-AD, its wildtype control (B6;129S background), 5xFAD and its wildtype littermate control using methods and procedures as previously described and presented in the Methods section. HEK293 cells were purchased from ATCC.
Authentication	NPCs from APP Dp and NDC individuals have been validated using PCR assays with specific primers to determine APP copy number as shown in previously published literatures (PMID: 22278060, PMID: 27622770). And, primary mouse neurons were prepared from E18.5 ~ E19.5 embryos of 3xTg-AD, 5xFAD, and their non-transgenic control mice, and each embryo was validated by genotyping before performing experiments. HEK293 cells were purchased from ATCC.
Mycoplasma contamination	All the cell lines used were mycoplasma-free.
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	Tert deficient LSL-mTert mice generated by inserting a transcriptional stopper cassette flanked by loxP sites (LSL) in the endogenous Tert locus to prevent the expression of Tert gene were previously described (PMID: 32958778). Homozygous 3xTg-AD, its non-transgenic control B6129SF2/J, hemizygous 5xFAD, and Camk2a-CreERT2 mice were purchased from The Jackson Laboratory. To generate Cre-inducible Tert knock-in allele, we used a previously established knock-in strategy. Linearized CAG-LSL-mTert-IRES-EGFP-pA construct was targeted into C57BL/6-derived JM8F6 embryonic stem (ES) cells by electroporation, and the Rosa26 locus was modified by targeted insertion of ubiquitously expressed CAG promoter, followed by a lox-STOP-lox cassette-controlled mTert gene (CAG-LSL-mTert). Positive ES clones were identified by Long Range PCR and PCR products were sent to sequencing to confirm the correct recombination and karyotyping. The chimeric mice from each clone produced germline transmission. To generate our TERT-AD model, the resulting mice were mated to 3xTg-AD or 5xFAD mice, then subsequently bred with Camk2a-CreERT2 strain. All animals were housed in pathogen-free, ambient temperatures 21-23 °C, humidity 45-55%, a 12-h dark/light cycle conditions and cared for in accordance with the International Association for Assessment and Accreditation of Laboratory Animal Care policies and certification. Mice were used at multiple age points (as described in the manuscript) and both male and female mice were used in this study.
Wild animals	This study did not involve wild animals.
Field-collected samples	This study did not involve samples collected from the field.
Ethics oversight	All procedures for performing mouse behavioral test were approved by the University of Texas MD Anderson Cancer Center Institutional Animal Care and Use Committee

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

ChIP-seq

Data deposition

☒ Confirm that both raw and final processed data have been deposited in a public database such as GEO.

☒ Confirm that you have deposited or provided access to graph files (e.g. BED files) for the called peaks.

Data access links *May remain private before publication.*	The raw sequenced data generated in this study were deposited in the NCBI Sequence Read Archive under accession numbers PRJNA633993 and PRJNA633994.
Files in database submission	m-nonTg-Input m-5FAD-Input m-nonTg-H3K9me3 m-5FAD-H3K9me3 h-NDC-Input h-AD-Input h-NDC-H3K9me3 h-AD-H3K9me3 h-AD-Input-biological replicate 1 h-AD-Input-biological replicate 2 h-AD-Input-biological replicate 3 h-AD-TERT-biological replicate 1 h-AD-TERT-biological replicate 2

h-AD-TERT-biological replicate 3
h-AD-TERT-biological replicate 4
h-AD-TERT-biological replicate 5
h-AD-TCF7-biological replicate 1
h-AD-TCF7-biological replicate 2
h-AD-bCat-biological replicate 1
h-AD-bCat-biological replicate 2

Genome browser session
(e.g. UCSC)

The raw sequenced data generated in this study were deposited in the NCBI Sequence Read Archive under accession numbers PRJNA633993 and PRJNA633994.

Methodology

Replicates

There are a ChIP-seq experiment of H3K9me3 from mouse nontransgenic and 5FAD neurons, and human control and APPDP neurons, two replicates of ChIP-seq experiments of TCF7-binding and b-Catenin-binding, and five replicates of ChIP-seq experiments of TERT-binding. Three plates of neurons were collected for each ChIP-seq measurement.

Sequencing depth

We performed the Illumina single-end 50bp sequencing. The sequence depth of each sample was described as following:

m-nonTg-Input Uniquely mapped reads: 17972871
m-5FAD-Input Uniquely mapped reads: 26306276
m-nonTg-H3K9me3 Uniquely mapped reads: 21152919
m-5FAD-H3K9me3 Uniquely mapped reads: 10120036

h-NDC-Input Uniquely mapped reads: 26095329
h-AD-Input Uniquely mapped reads:23780658
h-NDC-H3K9me3 Uniquely mapped reads: 23768853
h-AD-H3K9me3 Uniquely mapped reads: 26739238

h-AD-Input-biological replicate 1 Uniquely mapped reads: 46952416
h-AD-Input-biological replicate 2 Uniquely mapped reads: 38916926
h-AD-Input-biological replicate 3 Uniquely mapped reads: 49389162
h-AD-TERT-biological replicate 1 Uniquely mapped reads: 30866128
h-AD-TERT-biological replicate 2 Uniquely mapped reads: 39276700
h-AD-TERT-biological replicate 3 Uniquely mapped reads: 29264597
h-AD-TERT-biological replicate 4 Uniquely mapped reads: 32117144
h-AD-TERT-biological replicate 5 Uniquely mapped reads: 37286895
h-AD-TCF7-biological replicate 1 Uniquely mapped reads: 24042939
h-AD-TCF7-biological replicate 2 Uniquely mapped reads: 28786646
h-AD-bCat-biological replicate 1 Uniquely mapped reads: 27940667
h-AD-bCat-biological replicate 2 Uniquely mapped reads: 25734665

Antibodies

anti-H3K9me3 (ab8898, Abcam), anti-TERT (ab32020, Abcam), anti-TCF7 (2206, Cell Signaling Tech), and anti-non-phospho (active) β-Catenin (8814, Cell Signaling Tech)

Peak calling parameters

Model-based analysis of ChIP-seq (MACS) (version 1.4.2) was used to identify antibody enrichment over “input” background with the parameter: -g hs -p 1e-5 or -g mm -p 1e-5

Data quality

Sample name Peaks (<5% FDR, >5 fold change)
m-nonTg-H3K9me3 28
m-5FAD-H3K9me3 754
h-NDC-H3K9me3 744
h-AD-H3K9me3 454
h-TERT-1,2,3,4,5(merged) 903
h-TCF7-1,2(merged) 9764
h-bCat-1,2(merged) 7882

Software

Fastqc (version 0.11.8) was used to QC fastq data.
Trimmomatic (version 0.33) was used to trim adapter sequence.
Bowtie aligner (version 1.2.2) was used to align reads to genome.
SAMtools (version 1.9) was used to filter the SAM and BAM file to get uniquely mapped reads.
MACS (version 1.4.2) was used to identify antibody-IP enrichment over input background.
MACS2 was used to identify the differential binding of each protein in different conditions.
DeepTools (version 2.7.15) to generate bigwig files by scaling the bam files to reads per kilobase per million (RPKM).