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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	No Software was used
Data analysis	GraphPad Prism 7. and 8; Microsoft Office 360 - Excel; ImageJ; FIJI, Chemoffice 16; R package V3.34.0; Image Studio Lite; Caseviewer, Adobe Illustrator, Adobe Photoshop, GIMP 2.10

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

Source data for Figs. 1–5 and Extended Data Figs. 1-5 and table S1 – S5 are available with the paper. All other data are available from the corresponding authors 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	Sample sizes were not predetermined. Group sizes for biochemical, cellular, mouse samples and human samples were chosen based on numbers used in previous publications to generate statistical significant results.
Data exclusions	Human brain samples: one sample was excluded because MAP2 mRNA levels were extremely low. Mouse brain tissue: one WT sample was excluded because nicastrin protein levels (determined by Western blot) were greater than 2 standard deviations below the mean value. The criteria of 2 standard deviations were pre-established.
Replication	All data was reliable reproduced and the exact number of repeats and sample sizes are provided in each figure legend and methods
Randomization	The nature and sample sizes are not suitable for randomization
Blinding	All human and mouse sample analysis was performed blinded: one investigator designed and prepared samples and a second blinded investigator performed experiment and data 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 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

PS1-NTF, PS1-CTF, nicastrin, Aph-1aL, Pen-2, human IFITM3, mouse IFITM3, APP (22C11, MAB348), β-actin (C4), β-tubulin III (T8578), tubulin (ab56676). SPP, human IFITM3 monoclonal antibody 9D11, G2-10, 10G3, SM320, cleaved Notch1 (Val1744), V-PLEX Aβ Peptide Panel 1 (4G8) Kit, V-PLEX Aβ Peptide Panel 1 (4G8) Kit, N-cadherin (D4R1H), Rab7 (B-3), EEA1 (Ab2900), NA9340V, NXA931V, IRDye 800CW goat anti-rabbit IgG (H+L), anti-mouse IgG (H+L) secondary antibodies

Validation

PS1-NTF (a kind gift from Dr. Min-Tain Lai, Merck Research Laboratories);
J Biol Chem 278, 22475-22481 (2003).

PS1-CTF (MAB5232, Millipore);
https://www.emdmillipore.com/US/en/product/Anti-Presenilin-1-Antibody-loop-a.a.-263-378-CT-clone-PS1-loop,MM_NF-MAB5232

PS2-CTF (1987-1, Epitomics);
Cell reports 15, 2226-2238, doi:10.1016/j.celrep.2016.05.013 (2016).

nicastrin was generated in our laboratory;
J Biol Chem 284, 2967-2977 (2009)

Aph-1aL (38-3600, Invitrogen);
J Biol Chem 284, 2967-2977 (2009)

Pen-2 (ab18189, Abcam);
https://www.abcam.com/pen2-antibody-ab18189.html

human IFITM3 (anti-Fragilis, ab109429, Abcam);
https://www.abcam.com/fragilis-antibody-epr5242-ab109429.html

mouse IFITM3 (anti-Fragilis, ab15592, Abcam);
https://www.abcam.com/fragilis-antibody-ab15592.html

APP (22C11, MAB348, Millipore);
https://www.emdmillipore.com/US/en/product/Anti-APP-A4-Antibody-a.a.-66-81-of-APP-NT-clone-22C11,MM_NF-MAB348

β-actin (C4, sc-47778, Santa Cruz Biotechnology);
https://www.scbt.com/p/beta-actin-antibody-c4

β-tubulin III (T8578, Sigma-Aldrich); https://www.sigmaaldrich.com/catalog/product/sigma/t8578

tubulin (ab56676, Abcam),
https://www.abcam.com/tubulin-antibody-loading-control-ab56676.html

SPP (317, generated in our laboratory),
ACS Chem Biol 10, 1925-1931, doi:10.1021/acschembio.5b00321 (2015).

human IFITM3 monoclonal antibody (9D11, generated in our laboratory).
This antibody only detects IFITM3 in U138 cells, not in IFITM3 deficient U138 cells generated in this work, validating its specificity.

G2-10: Anti A□40-Specific
https://www.emdmillipore.com/US/en/product/Anti-Amyloid-40-Antibody-clone-G2-10,MM_NF-MABN11

10G3: Anti A□42-Specific
Brain 139, 563-577, (2016)

SM320, Notch cleavage antibody
J Biol Chem 287, 17288-17296, doi:10.1074/jbc.M111.300483 (2012)

cleaved Notch1 (Val1744)
https://www.cellsignal.com/products/primary-antibodies/cleaved-notch1-val1744-antibody/2421

V-PLEX Aβ Peptide Panel 1 (6E10) Kit:
https://www.mesoscale.com/en/products/v-plex-abeta-peptide-panel-1-6e10-kit-k15200e

V-PLEX Aβ Peptide Panel 1 (4G8) Kit:
https://www.mesoscale.com/en/products/v-plex-plus-abeta-peptide-panel-1-4g8-kit-k15199g/

N-cadherin (D4R1H, #13116, Cell Signaling Technology);
https://www.cellsignal.com/products/primary-antibodies/n-cadherin-d4r1h-xp-rabbit-mab/13116

Rab7 (B-3, sc-376362, Santa Cruz Biotechnology);
https://www.scbt.com/p/rab-7-antibody-b-3

EEA1 (Ab2900, Abcam)
https://www.abcam.com/eea1-antibody-early-endosome-marker-ab2900.html

HRP-conjugated anti-rabbit and mouse secondary antibodies (NA9340V, NXA931V, GE Healthcare)
Previously sold by GE Healthcare, now by Sigma Aldrich
NA9340V
https://www.sigmaaldrich.com/catalog/product/sigma/gena93401ml?lang=en&region=US
NXA931V
https://www.sigmaaldrich.com/catalog/product/sigma/genxa9311ml?lang=en&region=US

IRDye 800CW goat anti-rabbit IgG (H+L)
(925-32211, LI-COR)
https://www.licor.com/bio/reagents/irdye-800cw-goat-anti-rabbit-igg-secondary-antibody

anti-mouse IgG (H+L) secondary antibodies
(925-32210, LI-COR)
https://www.licor.com/bio/reagents/irdye-800cw-goat-anti-mouse-igg-secondary-antibody

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	MEF (WT and PS1/2 double KO) cells ,HEK293-APP695 cells and HEK293-NotchΔE were obtained from collaborators. U-138 MG and HeLa cells were obtained from ATCC.
Authentication	All cell lines were authenticated by STR profile report.
Mycoplasma contamination	All cell lines tested negative for mycoplasma contamination. Applied biological materials (ABM) PCR mycoplasma detection kit (#G238) was used.
Commonly misidentified lines (See ICLAC register)	Hek293, HeLa, U-138 MG

Animals and other organisms

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

Laboratory animals	1. WT mice: C57BL/6J; purchased from The Jackson Laboratory; stock# 000664 For primary neuronal culture, wild type C57BL/6J or C57BL/6NJ female mice of 1.5-2 month old with timed pregnancy were obtained from the Jackson Laboratory and Charles River Laboratories. 2. 5xFAD mice: B6.Cg-Tg(APPSwFILon,PSEN1*M146L*L286V)6799Vas/Mmjax; purchased from The Jackson Laboratories; stock# 34848-JAX 3. Aged WT mouse brain samples were obtained form the NIA. Brains of C57BL/6 female and male mice at different age groups (mature adult (4-month-old) and old (28-month-old)) were collected from NIA Aged Rodent Tissue Bank. 4. Aged 5xFAD mouse brain samples were from two coauthors. Brains of female WT and 5XFAD Tg mice at 3- (mature adult) and 12-month-old (middle aged) were kindly provided by Dr. Robert J Vassar (Northwestern University). ExtFig 4g mice: Translating ribosome affinity purification (TRAP) knock-in mice were generated by crossing mice bearing a loxP-stop-loxP-EGFPRPL10a sequence in the Eef1α1 promoter (EEF1A1–LSL.EGFPL10)14 with CCK-Cre (CCKtm1.1(cre)Zjh/J), Glutamate decarboxylase 2 (65 kDa)-Cre (B6N.Cg-Gad2tm2(cre)Zjh /J), Cortistatin-Cre (Tg(Cortcre)IM42Gsat) or parvalbumin-Cre (Pvalbtm1(cre)Arbr/J) mice. 5. IFITM3-/- embryos were obtained from the European Mutant Mouse Archive and rederived in pseudopregnant host mice.
Wild animals	This study did not involved wild animals.
Field-collected samples	This study did not involved samples collected from the field.
Ethics oversight	IACUC, Memorial Sloan Kettering Cancer Center and Rockefeller University

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

Human research participants

Policy information about studies involving human research participants

Population characteristics	All human brain samples were provided by the Alzheimer's Disease Research Center (ADRC) Neuropathology Core at University of California, San Diego, after review and approval by the ADRC Biospecimen Review Committee. All human samples were obtained from subject who consented to autopsy for the UCSD ADRC. All tissues provided were deidentified and contained a number code only.
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.