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Life Sciences Reporting Summary

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For final submission: please carefully check your responses for accuracy; you will not be able to make changes later.

Experimental design

1. Sample size

   Describe how sample size was determined.

   For all animal work, appropriate statistical tests were used and outlined in the materials and methods section, as well as in the figure legend. For sample size estimations we proceeded as follows. For behavioral studies, we estimated to need 12 animals per group to reach statistically meaningful conclusions (significance level of p smaller than 0.05) according to the Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research (National Academies Press, Washington (DC), 2003). This estimation is based on
   n=1+2C 〖(s/d)〗 ^2
   where C is determined by the power (1-β, here 90%) and the significance level (α, here 5%), the standard deviation (s, here 14% for behavioral tests such as the ones being used based on our own experience) and the difference we would like to detect (d, here 20%).
   For biochemical and imaging analyses, 5 animals per treatment group suffice (Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research (National Academies Press, Washington (DC), 2003). This estimation is based on the criteria of whether or not the treated animals will display AD-related pathologies. Thus, the effect size (n) is determined by the probability of committing a Type II error (β) and by p, the proportion of animals that do not show any changes. This proportion is estimated at 70% based on our own previous experience with AD-related pathologies and virus-related interventions.
   n=logβ/logp

2. Data exclusions

   Describe any data exclusions.

   Mice with bad injection sites, showing stereotypy, or exploring less than 10 seconds the objects in the novel object recognition test (NOR) were excluded. Also, mice in which no increase of PM20D1 for the AAV.PM20D1 overexpression group or in which no decrease of PM20D1 for the ASO.PM20D1 repression group was observed in hippocampus were excluded. Outliers were determined by Grubb's outlier calculation's.

3. Replication

   Describe the measures taken to verify the reproducibility of the experimental findings.

   All experiments were reproduced three or more times using the same experimental approach (unless otherwise stated). Number of replicates and sample sizes are provided for each of the experiments in figure legends.Findings and conclusions in the manuscript represent those that were consistent across independent experiments.

4. Randomization

   Describe how samples/organisms/participants were allocated into experimental groups.

   All animals were randomly assigned to the treatment groups.

5. Blinding

   Describe whether the investigators were blinded to group allocation during data collection and/or analysis.

   All in vitro and in vivo experiments were conducted by experimenters blinded to the experimental conditions.

Note: all in vivo studies must report how sample size was determined and whether blinding and randomization were used.

6. Statistical parameters

For all figures and tables that use statistical methods, confirm that the following items are present in relevant figure legends (or in the Methods section if additional space is needed).

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement (animals, litters, cultures, etc.)
☐	☒ A description of how samples were collected, noting whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ A statement indicating how many times each experiment was replicated
☐	☒ 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 any assumptions or corrections, such as an adjustment for multiple comparisons
☐	☒ Test values indicating whether an effect is present *Provide confidence intervals or give results of significance tests (e.g. P values) as exact values whenever appropriate and with effect sizes noted.*
☐	☒ A clear description of statistics including central tendency (e.g. median, mean) and variation (e.g. standard deviation, interquartile range)
☐	☒ Clearly defined error bars in all relevant figure captions (with explicit mention of central tendency and variation)

See the web collection on statistics for biologists for further resources and guidance.

Software

Policy information about availability of computer code

7. Software

Describe the software used to analyze the data in this study.	Data was analyzed using R Lumi, Genefilter, Ggplot2, Bismark, SAMtools, Bedtools, Tabix, PLIN v1.07, and Prism 6.0 (GraphPad) software. Source codes are available upon request.

For manuscripts utilizing custom algorithms or software that are central to the paper but not yet described in the published literature, software must be made available to editors and reviewers upon request. We strongly encourage code deposition in a community repository (e.g. GitHub). *Nature Methods* guidance for providing algorithms and software for publication provides further information on this topic.

Materials and reagents

Policy information about availability of materials

8. Materials availability

Indicate whether there are restrictions on availability of unique materials or if these materials are only available for distribution by a third party.	No resctrictions.

9. Antibodies

Describe the antibodies used and how they were validated for use in the system under study (i.e. assay and species).	Immunohistochemical analysis of PM20D1 expression in mice and human samples was performed with the PM20D1 antibody from Sigma-Aldrich (HPA017571; dilution 1:150). The omission of the primary antibody in some section was used as a control of the immunostaining; no signal was obtained with the only incubation of the secondary antibody.

10. Eukaryotic cell lines

a. State the source of each eukaryotic cell line used.	American Type Culture Collection (ATCC) SH-SY5Y (CRL-2266).
b. Describe the method of cell line authentication used.	Only SH-SY5Y cells with less than 40 passages were used. Number of passages, usage, and phenotypic characteristics were traced. No further authentication was performed.
c. Report whether the cell lines were tested for mycoplasma contamination.	Cell lines were tested and negative for mycoplasma contamination.
d. If any of the cell lines used are listed in the database of commonly misidentified cell lines maintained by ICLAC, provide a scientific rationale for their use.	None of the cell lines used for this study are listed in the ICLAC database.

Animals and human research participants

Policy information about studies involving animals; when reporting animal research, follow the ARRIVE guidelines

11. Description of research animals

Provide all relevant details on animals and/or animal-derived materials used in the study.

APP/PS1 mice (JAX mice reference number 005864) were maintained under standard animal housing conditions in a normal 12h light-dark cycle with ad libitum access to food and water. All experiments were conducted exclusively on males.

Policy information about studies involving human research participants

12. Description of human research participants

Describe the covariate-relevant population characteristics of the human research participants.

This study do not involve human research participants.