

Reporting Summary

Nature Portfolio 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 Portfolio 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 (<i>n</i>) 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 <i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i>
☐	☒ 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. <i>F</i> , <i>t</i> , <i>r</i>) with confidence intervals, effect sizes, degrees of freedom and <i>P</i> value noted <i>Give P values as exact values whenever suitable.</i>
☒	☐ 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 <i>d</i> , Pearson's <i>r</i>), 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	Nanoparticle tracking analysis: ParticleMetrix Zetaview software, version 8.02.31.
Data analysis	Microscopy: Zeiss Zen 2.3 software. Columbus Image Analysis Server website via a VPN (Version 2.2.2). CellProfiler 4.1.3. Statistics: GraphPad Prism 7 version 7.02;

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 Portfolio [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 description of any restrictions on data availability
 - For clinical datasets or third party data, please ensure that the statement adheres to our [policy](#)

Data is available upon reasonable request from the corresponding author.

Research involving human participants, their data, or biological material

Policy information about studies with [human participants or human data](#). See also policy information about [sex, gender \(identity/presentation\), and sexual orientation](#) and [race, ethnicity and racism](#).

Reporting on sex and gender	We used iPSC (Induced pluripotent stem cell) from the National Institute of Neurological Disorders and Stroke (NINDS). The detailed information is: Control (Cell Line ID: NN0003920. Note: Male, 64) and TDP-43G298S mutant (Cell line ID: NN0004048, Note: ALS, Male, 64).
Reporting on race, ethnicity, or other socially relevant groupings	Subject NDS00209, Gender: M, Age: 64.0, Race: Caucasian, Ethnicity: Not Hispanic or Latino. Subject NDS00159, Gender: M, Age: 64.0. No info on Race or Ethnicity.
Population characteristics	Subject NDS00209, Gender: M, Age: 64.0, Race: Caucasian, Ethnicity: Not Hispanic or Latino, Disease Collections: Amyotrophic Lateral Sclerosis, Cytobands: 1p36.2, Genes: TDP43, Genetic Variants: GLY298SER. Subject NDS00159, Gender: M, Age: 64.0. No info on Race or Ethnicity, Disease Collections: Controls
Recruitment	The iPSC lines were sourced from the National Institute of Neurological Disorders and Stroke (NINDS).
Ethics oversight	According to Canadian guidelines, as consent and REB approval was obtained by the NINDS source, and the cells used are not embryo derived no local REB approval is required. We obtained approval nonetheless from the University of Ottawa REB: protocol H-02-21-6676

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

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 size was determined on the basis of anticipated variability between measures.
Data exclusions	No data were excluded
Replication	All attempts at data replication were successful. Experiments were replicated with independent samples, as indicated in the figure legends
Randomization	Sex-matched mice were randomly assigned among groups while ensuring balance in age and littermates.
Blinding	In experiments with mice, the experimenters were blinded to the sample being injected until the quantifications were complete.

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
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

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

Antibodies

Antibodies used	Anti-G3BP1 (Abcam, Ab181149), Anti-TDP-43 (C-terminal) antibody produced in rabbit (Sigma-Aldrich, T1580), TDP43 antibody [GT225] (Host Mouse, Genetex, GTX630196), Anti-HA Tag Antibody (Sigma-Aldrich, 05-904), Phospho-Tau (Thr231) Monoclonal Antibody (AT180) (Thermo Fisher Scientific, MN1040), Phospho-Tau (Ser202, Thr205) Monoclonal Antibody (AT8) (Thermo Fisher Scientific, MN1020), Tau Monoclonal Antibody (TAU-5) (Thermo Fisher Scientific, MA5-12808), anti-TSG101 antibody (Genetex, GTX70255), Anti-CD9 Antibody, clone MM2/57 (Sigma, CBL162), Anti-Flotillin-2 antibody (Cell signaling Technology, 3436S), Anti-Alix antibody (Cell signaling Technology, 2171S), anti-alpha Tubulin antibody mouse (Sigma-Aldrich, T6199), Monoclonal Anti-β-Actin antibody produced in mouse (Sigma-Aldrich, A5441), GAPDH Antibody (6C5) (SantaCruz Biotechnology, sc-32233), Anti-Rabbit IgG (Jackson ImmunoResearch Labs, 111-035-144), goat anti-mouse HRP (light chain) (Jackson ImmunoResearch Labs, 115-035-174), Anti-Rabbit IgG Alexa Fluor 488 (Thermo Fisher Scientific, A-11034), goat anti-mouse IgG Alexa546 (Thermo Fisher Scientific, A-11030), and goat anti-mouse IgG Alexa 488 (Thermo Fisher Scientific, A11029), Anti-FLAG (Sigma, F1804), Anti-HRP-488 (Jackson ImmunoResearch Labs, 123-545-021), Rat Anti-Mouse CD31(BD bioscience, 553370), Goat anti- Mouse/Rat CD31 (R&D systems, AF3628), anti-Beta-Tubulin 3 (Cedarlane, TUJ-0020), Goat anti-Chicken, Alexa Fluor™ 568 (ThermoFisher, A-11041), Goat anti-Chicken, Alexa Fluor™ 647 (ThermoFisher, A-21469). Anti-TDP43 (1HCLC) (ThermoFisher, 711051). Antibodies were used at a dilution of 1/1000 in Western blot and 1/50 for microscopy.
Validation	Antibodies were used with species recommended by the manufacturers. The anti-TDP43 antibodies (Anti-TDP-43 (C-terminal) antibody produced in rabbit (Sigma-Aldrich, T1580), TDP43 antibody [GT225] (Host Mouse, Genetex, GTX630196)) were confirmed using siRNA knockdown in the assays they were to be used in (Western blotting and/or immunofluorescent microscopy). For detection of sEVs by immunofluorescent microscopy, the specificity of antibodies was validated using mice not injected with sEVs as a negative control. Goedert, M., Jakes, R. & Vanmechelen, E. Monoclonal antibody AT8 recognises tau protein phosphorylated at both serine 202 and threonine 205. <i>Neurosci. Lett.</i> 189, 167–169 (1995). AT180 antibody: Mercken, M. et al. Monoclonal antibodies with selective specificity for Alzheimer tau are directed against phosphatase-sensitive epitopes. <i>Acta Neuropathol.</i> 84, 265–272 (1992). Tau5 antibody: The Porzig et al. study provided definitive epitope mapping for the monoclonal antibodies AT8 and TAU-5, identifying the TAU-5 binding site within amino acids 218–225 of human tau (<i>Biochemistry</i> 46, 8170–8178; 2007).

Eukaryotic cell lines

Policy information about [cell lines and Sex and Gender in Research](#)

Cell line source(s)	Hela cells (CCL-2, ATCC), 293 T cells (CRL-3216, ATCC), U-118 MG (HTB-15, ATCC), pInducer MAPT-SHSY106 cells were a gift from Dr. Rousseaux (University of Ottawa). Adult mouse neurons were isolated and cultured using a mixed-gender cohort, maintained at a 1:1 male-to-female ratio. Control (Cell Line ID: NN0003920. Note: Male, 64) and TDP-43G298S mutant (Cell line ID: NN0004048, Note: ALS, Male, 64) induced pluripotent stem cells were sourced from the National Institute of Neurological Disorders and Stroke (NINDS)
Authentication	None of the cell lines used were authenticated. All cell lines were recently purchased from ATCC.
Mycoplasma contamination	The cell lines were tested for mycoplasma by staining with DAPI and via assessment for cytoplasmic DNA by microscopy. The cell lines used in this study were negative for mycoplasma contamination.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used.

Palaeontology and Archaeology

Specimen provenance	<i>Provide provenance information for specimens and describe permits that were obtained for the work (including the name of the issuing authority, the date of issue, and any identifying information). Permits should encompass collection and, where applicable, export.</i>
Specimen deposition	<i>Indicate where the specimens have been deposited to permit free access by other researchers.</i>
Dating methods	<i>If new dates are provided, describe how they were obtained (e.g. collection, storage, sample pretreatment and measurement), where they were obtained (i.e. lab name), the calibration program and the protocol for quality assurance OR state that no new dates are provided.</i>
☐ Tick this box to confirm that the raw and calibrated dates are available in the paper or in Supplementary Information.	
Ethics oversight	<i>Identify the organization(s) that approved or provided guidance on the study protocol, OR state that no ethical approval or guidance was required and explain why not.</i>

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

Animals and other research organisms

Policy information about [studies involving animals](#); [ARRIVE guidelines](#) recommended for reporting animal research, and [Sex and Gender in Research](#)

Laboratory animals	Tau P301S mice obtained from the Jackson Laboratory (008169). Mice inducibly expressing hTDP-43-ΔNLS were generated by crossing tetO-hTDP-43-ΔNLS (Stock 014650) with NEFH-tTa (Stock 025397). Wild-type C57S mice from Jackson Laboratory.
Wild animals	The study did not involve wild animals.
Reporting on sex	Sex-matched mice were randomly assigned among groups while ensuring balance in age and littermates.
Field-collected samples	The study did not involve samples collected from the field.
Ethics oversight	Ethical approval for experimentation with mice was obtained from the Animal Care Committee of the University of Ottawa, and performed according to guidelines of the Canadian Council on Animal Care and the International Guiding Principles for Biomedical Research Involving Animals. Ethics protocols used for these studies included a breeding protocol (4353, formerly 3357), extracellular vesicle injection protocols (4356, formerly 3367), and AAV protocols (4431, formerly 3374). AAV protocol: current-4431; When experiments were performed- 3374

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

Plants

Seed stocks	<i>Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.</i>
Novel plant genotypes	<i>Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.</i>
Authentication	<i>Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosaicism, off-target gene editing) were examined.</i>