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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.

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	EPU
Data analysis	RELION v3.0, MotionCor2 v1, Gctf v1.06, COOT v0.8.9.1, REFMAC v5.7.0032, MOLPROBITY, BWA v1.1.4, Bwakit v0.7.15, ExpansionHunter v2.5.5, Strelka2 v2.9.9

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. 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

Cryo-EM maps for case 1 have been deposited in the Electron Microscopy Data Bank (EMDB) under accession numbers EMD-0527 for CTE type I tau filament and EMD-0528 for CTE type II tau filament. Refined atomic models for case 1 have been deposited in the Protein Data Bank (PDB) under accession numbers 6NWP for CTE type I tau filament and 6NWQ for CTE type II tau filament. Whole-exome and whole-genome sequencing, and C9orf72 hexanucleotide repeat expansion results, have been deposited in the National Institute on Aging Alzheimer's Disease Data Storage Site (NIAGADS) under accession number NG00077.

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	Temporal cortex samples from 3 cases of CTE, chosen based on availability of tissue (maximum available sample size).
Data exclusions	No data were excluded from the analyses.
Replication	All attempts at replication were successful. At least three independent biological repeats per experiment where representative data is shown.
Randomization	Not relevant to study. Samples were allocated into one experimental group (temporal cortex samples from cases of CTE) based on neuropathological examination.
Blinding	Not relevant to study. Only one experimental group (temporal cortex samples from cases of CTE).

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
☒	☐ Animals and other organisms
☐	☒ Human research participants
☒	☐ Clinical data

Methods

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

Antibodies

Antibodies used	Primary antibodies used are presented in the Methods section with validation referenced. They are: BR133 (Diluted 1:4,000 for immunoblotting), BR134 (Diluted 1:4,000 for immunoblotting), BR136 (Diluted 1:50 for immunogold negative-stain EM and 1:1,000 for immunoblotting), Anti-4R (Cosmo Bio CAC-TIP-4RT-P01; diluted 1:50 for immunogold negative-stain EM, 1:2,000 for immunoblotting and 1:400 for immunohistochemistry), BR135 (Diluted 1:50 for immunogold negative-stain EM and 1:4,000 for immunoblotting), TauC4 (Diluted 1:50 for immunogold negative-stain EM and 1:2,000 for immunoblotting), RD3 (Merck 05-803; diluted 1:3,000 for immunohistochemistry), AT8 (Thermo Fisher Scientific MN1020; diluted 1:1,000 for immunoblotting and 1:300 for immunohistochemistry), AT100 (Thermo Fisher Scientific MN1060; diluted 1:400 for immunohistochemistry), anti-phospho-TDP-43 (Cosmo Bio CAC-TIP-PTD-M01; diluted 1:1,000 for immunohistochemistry), SYN (Diluted 1:300 for immunohistochemistry) anti-poly-GA (Cosmo Bio CAC-TIP-C9-P01; diluted 1:300 for immunohistochemistry).
Validation	BR133 validated against human tau N-terminus in (Goedert et al. 1989 Neuron 3,519-526); BR134 validated against human tau C-terminus in (Goedert et al. 1989 Neuron 3,519-526); BR136 validated against human tau residues 254-257 in (Falcon et al. 2018 Nature 561,137-140) ; Anti-4R validated against human tau residues 275-291 in (Falcon et al. 2018 Nature 561,137-140) and in manufacturer's datasheet (Cosmo Bio); BR135 validated against human tau residues 323-355 in (Falcon et al. 2018 Nature 561,137-140) and in (Goedert et al. 1989 Neuron 3,519-526); Tau C4 validated against human tau residues 354-369 in (Falcon et al. 2018 Nature 561,137-140) and in (Taniguchi-Watanabe et al. 2016 Acta Neuropathol. 131, 267-280); RD3 validated against human 3R tau in manufacturer's datasheet (Millipore); AT8 validated against human tau pS202 and pT205 in manufacturer's datasheet (Thermo); AT100 validated against human tau pT212, pS214 and pT217 in manufacturer's datasheet (Thermo); anti-phospho-TDP-43 validated against TDP-43 pS409 and pS410 in manufacturer's datasheet (Cosmo Bio); SYN validated against α-

synuclein residues 119-137 in (Yamaguchi et al. 2005 Acta Neuropathol. 110, 298-305); and anti-poly-GA validated in manufacturer's datasheet (Cosmo Bio).

Human research participants

Policy information about studies involving human research participants

Population characteristics	See Methods section. Age at death: 67, 67 and 78; Gender: All male; APOE genotypes: ε2/ε3, ε3/ε4 and ε3/ε3; Diagnoses: All CTE.
Recruitment	Selected based on neuropathological examination.
Ethics oversight	The studies carried out at Indiana University and the University of Kansas were approved through each university's Institutional Review Board (IRB). Informed consent was obtained from the patients' next of kin.

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