nature portfolio

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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 (*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	All cryo-EM data were automatically collected on the Titan Krios G3 using EPU 2.3.
Data analysis	MotionCor2, Gctf 1.18, UCSF Chimera X 1.8, Phenix 1.20.1, Coot 0.9.6, CryoSPARCv4.3.1, Prism 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 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

The density maps and structure coordinates have been deposited to the EMDB and the PDB under accession numbers EMD-61943 and 9K0C (TauT-Apo); EMD-61970 and 9K1B (TauT-Tau); EMD-61948 and 9K0N (TauT-β-Ala); EMD-61949 and 9K0O (TauT-GAA); EMD-61974 and 9K1F (TauT-GABA); EMD-61975 and 9K1H (TauT-P4S); EMD-61976 and 9K1I (TauT-I4AA); EMD-61983 and 9KIX (TauT-GES); EMD-61981 and 9K1V (TauT-5AVA); EMD-61987 and 9K21 (TauT-Htau); EMD-61985 and 9K1Z (TauT-nipecotic acid).

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	N/A
Reporting on race, ethnicity, or other socially relevant groupings	N/A
Population characteristics	N/A
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.

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 by statistical methods. For cryo-EM data, the number of micrographs was determined by the availability of microscope time and the particle density on the grids. For all the functional assay, we use a sample size of at least three independent biological experiments, commonly exploited by researchers in this filed.
Data exclusions	For cryo-EM analysis, micrographs with CTF fitting worse than 3.5-angstrom were discarded. Subsequent cryo-EM data processing only kept high-resolution and homogeneous particles to generate the final high-resolution maps.
Replication	Functional experiments were repeated at least three biological independent times, consistently yielding comparable results and reproducibility.
Randomization	Randomization was not relevant to this study, as the data were collected automatically and did not involve choosing.
Blinding	No blinding used in this study. Blinding is not relevant for cryo-EM analysis and biochemical assay as the results are not subjective.

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	The fragment antigen binding (Fab) used in the current study is a recombinant version of Fab used in https://www.nature.com/

Antibodies used	articles/nature12533/. The methodology of heterologous expression and purification of Fab is detailed in the methods section and adopted from the previous study https://www.nature.com/articles/s41467-021-22385-9.
Validation	The activity of the recombinant Fab was validated by checking its ability to bind to the target protein and measuring the shifts in chromatogram with Fab bound and unbound protein as shown in the study.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	HEK293F (FreeStyle 293F cells, Gibco, USA); HEK293T (Gibco, USA)
Authentication	We did not authenticate the cell lines.
Mycoplasma contamination	Not tested for mycoplasma contamination.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used.

Plants

Seed stocks	N/A
Novel plant genotypes	N/A
Authentication	N/A