

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	Tandem mass tag (TMT) labeled proteomic data were acquired on Q Exactive HF Orbitrap MS (Thermo Fisher) instrument. Thermo Xcalibur (version 4.0) was used for data collection.
Data analysis	Identification of proteins and phosphopeptides: The computational processing of identification was performed with JUMP Software (http://www.stjuderesearch.org/site/lab/peng). Identification of differentially altered kinases: The analysis was performed using the KSEAapp R package (v0.99.0) within RStudio (v4.1.2), Calculation of protein turnover: The computational processing was performed with JUMPsilactmt (1.0.0) software (https://github.com/abhijitju06/JUMPsilactmt-Version-0.0.1) and JUMPt (1.0.0) software (https://github.com/abhijitju06/JUMPt-Version-1.0.0). Pathway enrichment analysis: Pathway enrichment analysis was conducted with PANTHER-based Gene Ontology (https://geneontology.org/). Differential expression analysis and principal component analysis: Differential expression (DE) and principal component analysis (PCA) were done with R statistical analysis software (version 4.4.0), limma (3.60.4), and MKmisc (1.9).

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](#)

RAW data files have been deposited in the PRIDE database (<https://www.proteomexchange.org>) with accession numbers PXD018590, PXD007974, PXD023395, PXD031545, PXD031732, PXD031734, PXD031735, PXD031769, and PXD053314 (Supplementary Table 2). The program of JUMPSilactmt (version 1.0.0) 542 is publicly available from GitHub (<https://github.com/abhijitju06/JUMPSilactmt-Version-0.0.1>). The program of JUMPt (version 1.0.0) is available from GitHub (<https://github.com/abhijitju06/JUMPt-Version-1.0.0>). The program details, along with example input and output files, are provided on the respective websites.

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](https://www.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	No statistical methods were used to pre-determine sample sizes but our sample sizes are sufficient to derive statistically significant conclusions.
Data exclusions	No data exclusions were performed.
Replication	We use biological replicates for animals related quantification. All sample replication information is in the Supplementary Data Tables.
Randomization	Randomization was not performed.
Blinding	The team members generating the data from the biological samples were blinded. Only the analysts had access to the molecular and phenotypic data to perform the planned analyses.

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

Methods

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

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

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	5xFAD, NLF, NLGF, 3xTg and BiG transgenic mouse lines and corresponding wild type controls were used in this study (C57BL/6J background strain). Both male and female mice were used in all experiments. Further information can be found in supplemental tables.
Wild animals	This study doesn't involve wild animals.
Reporting on sex	Both male and female were included. Similar ratio of male and female between WT groups and Tg groups was utilized. Detail information is in supplemental tables.
Field-collected samples	N/A
Ethics oversight	All animal experiments were approved by the Institutional Animal Care and Use Committee (Protocol# 542) at St. Jude Children's Research Hospital.

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

Plants

Seed stocks	n/a
Novel plant genotypes	n/a
Authentication	n/a