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	No software was used for data collection.
Data analysis	NetFlow3D GitHub repository is available at https://github.com/haiyuan-yu-lab/NetFlow3D. Version 1.0.0 was used for this study. All other analyses were conducted using Python v3.9.10.

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 availability: The TCGA MC3 dataset was downloaded from https://gdc.cancer.gov/about-data/publications/mc3-2017. TCGA RNA-seq data and proteome profiling data was downloaded from https://portal.gdc.cancer.gov/. The ID mapping file was downloaded from https://ftp.uniprot.org/pub/databases/uniprot/

current_release/knowledgebase/idmapping/by_organism/HUMAN_9606_idmapping.dat.gz. SIFTS data was downloaded from https://www.ebi.ac.uk/pdbe/docs/sifts/index.html. The Human Protein Structurome generated in this study has been made available in the NetFlow3D GitHub repository [https://github.com/haiyuan-yu-lab/NetFlow3D]. The protein mass spectrometry raw data generated in this study have been deposited in MassIVE under accession code [http://massive.ucsd.edu/ProteoSAFe/dataset.jsp?task=9413e64fd9da4254924538fd8e265914]. Supplementary Data and source data have been deposited in Zenodo under DOI 10.5281/zenodo.13755995 [https://zenodo.org/doi/10.5281/zenodo.13755995]. Source data are provided with this paper.

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	Not applicable. Human research participants are not involved in this study
Reporting on race, ethnicity, or other socially relevant groupings	Not applicable. Human research participants are not involved in this study
Population characteristics	Not applicable. Human research participants are not involved in this study
Recruitment	Not applicable. Human research participants are not involved in this study
Ethics oversight	Not applicable. Human research participants are not involved in this study

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 by sample and data availability. All available samples and data were used in our analyses.
Data exclusions	No data were excluded from our results or analyses.
Replication	Each experiment was conducted with three independent biological replicates, yielding consistent results to ensure reproducibility.
Randomization	In our study, random sample allocation was not applicable as we compared the wild-type PPP2R1A protein with the PPP2R1A p.Arg258Cys mutant, with sample allocation based on biological relevance. Covariates were controlled by maintaining identical experimental conditions across groups, including consistent reagents, timing, and instrumentation, and by using multiple biological replicates to ensure the reliability and reproducibility of the results.
Blinding	Not applicable as all analyses were performed using all available samples.

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-FLAG (Sigma, F1804, M2), and Anti-MYC (Invitrogen, 13-2500, 9E10) at both 1:5000 dilutions were used for immunoblotting analysis.

Validation: All primary antibodies used in this study have been validated by the manufacturers, with detailed validation data available on their respective websites, including applications such as WB, IF, and IHC. The c-Myc monoclonal antibody was validated through relative expression analysis to confirm specific binding to the intended antigen (http://www.thermofisher.com/antibody/product.c-Myc-Antibody-clone-9E10-Monoclonal /13-2500). The Anti-FLAG monoclonal antibody has been similarly validated, and the data can be accessed through the manufacturer's website (https://www.sigmaaldrich.com/US/en/product/sigma/f1804).

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s): HEK293T cells (Catalog Number: CRL-3216) were obtained from ATCC.

Authentication: The HEK 293T cell line was authenticated using short tandem repeat (STR) profiling to confirm its genetic identity. Morphological checks were performed regularly under a microscope to verify the typical morphology of HEK 293T cells.

Mycoplasma contamination: HEK 293 T cells are tested negative for mycoplasma contamination.

Commonly misidentified lines (See ICLAC register): No commonly misidentified cell lines were used in the study.

Plants

Seed stocks: *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.*

Novel plant genotypes: *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.*

Authentication: *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, mosiacism, off-target gene editing) were examined.*