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	LABORAS 2.6 (Metris) SmartEP (Intelligent hearing systems) pClamp 10.1 (Molecular Devices) Multiclamp Commander 700B (Molecular Devices) DigitalMicrograph (Gatan) ZEN Microscopy Software (Carl Zeiss)
Data analysis	Clampfit 10 (Molecular Devices) Ethovision XT 17 (Noldus) Image Studio Lite 4.0 (Li-COR Biosciences) ImageJ (NIH) Integrated Proteomic Pipeline (Bruker) Prism 9 (GraphPad) ZEN Microscopy Software (Carl Zeiss)

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 mass spectrometry proteomics data generated in this study have been deposited in the ProteomeXchange Consortium via the MassIVE partner repository with the dataset identifier PXD052848 (Total proteomic analysis) [https://massive.ucsd.edu/ProteoSAFe/dataset.jsp?task=43ef149aed3049ae9b781085ededf7ed] and via the PRIDE partner repository with the dataset identifier PXD053554 (Phospho-tyrosine proteomic analysis) [https://www.ebi.ac.uk/pride/archive/projects/PXD053554]. Source Data are provided with this paper.
Biological materials used in this study are available from the corresponding authors upon request.

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	*Use the terms sex (biological attribute) and gender (shaped by social and cultural circumstances) carefully in order to avoid confusing both terms. Indicate if findings apply to only one sex or gender; describe whether sex and gender were considered in study design; whether sex and/or gender was determined based on self-reporting or assigned and methods used.* *Provide in the source data disaggregated sex and gender data, where this information has been collected, and if consent has been obtained for sharing of individual-level data; provide overall numbers in this Reporting Summary. Please state if this information has not been collected.* *Report sex- and gender-based analyses where performed, justify reasons for lack of sex- and gender-based analysis.*
Reporting on race, ethnicity, or other socially relevant groupings	*Please specify the socially constructed or socially relevant categorization variable(s) used in your manuscript and explain why they were used. Please note that such variables should not be used as proxies for other socially constructed/relevant variables (for example, race or ethnicity should not be used as a proxy for socioeconomic status).* *Provide clear definitions of the relevant terms used, how they were provided (by the participants/respondents, the researchers, or third parties), and the method(s) used to classify people into the different categories (e.g. self-report, census or administrative data, social media data, etc.)* *Please provide details about how you controlled for confounding variables in your analyses.*
Population characteristics	*Describe the covariate-relevant population characteristics of the human research participants (e.g. age, genotypic information, past and current diagnosis and treatment categories). If you filled out the behavioural & social sciences study design questions and have nothing to add here, write "See above."*
Recruitment	*Describe how participants were recruited. Outline any potential self-selection bias or other biases that may be present and how these are likely to impact results.*
Ethics oversight	*Identify the organization(s) that approved the study protocol.*

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 determined based on relevant published literature (Park et al., The EMBO Journal, 2020; Kim et al., eLife, 2020). Sample sizes were not pre-determined using power analysis or other statistical approaches.
Data exclusions	Outliers were excluded based on the results of the Grubbs' test (alpha = 0.05).
Replication	All experiments were replicated using multiple cohorts (more than 2) or multiple mice (more than 2).
Randomization	Mice were allocated into specific cohorts at random, except genotype per cage post-weaning was set at a 1:1 ratio for WT vs mutant. Male cohorts were caged separately from females when weaned.

Blinding	All experimenters were blind to the genotype of the mice (sex could not be occluded from the experimenter, due to obviousness of the features). All analyses were performed in a blind manner. Cohorts were grouped at random at time of weaning.

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	Guinea pig anti-PTPδ N-term (home-made, #2063, IIQHKPKNSEEPYKEIDGIATTRYSVAGLSPYSDYEFR; 1:500) Guinea pig anti-PTPδ C-term (home-made, #2061, RPAMVQTEDQYQFCYRAALEYLGSFDHYAT; 1:500) Mouse anti-beta-actin (Sigma, A5316; 1:3000) Rabbit anti-IL1RAP (Cell Signaling, #52686; 1:1000) Rabbit anti-Neuroligin-3 (SYSY, 129 113; 1:1000) Rabbit anti-p38 (Cell Signaling, #9212; 1:1000) Rabbit anti-Phospho-p38 (Cell Signaling, #9211; 1:500) Guinea pig anti-VGLUT1 (Synaptic Systems, 135-304; 1:1000) Rabbit anti-PV (Swant, PV 25; 1:1000) Goat anti-tdTomato (SICGEN, AB8181-200; 1:600)
Validation	All in-house anti-PTPδ antibodies have been previously validated and published (Park et al., The EMBO Journal, 2020). All commercial antibodies have also been validated and published, with relevant information available on the respective websites.

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	The following mouse strains were used: Ptprd-meB mutant (Biocytogen) Ptprd-meA mutant (Park et al., The EMBO Journal, 2020) Ptprd mutant (Park et al., The EMBO Journal, 2020) PTPδ-tdTomato reporter (Park et al., The EMBO Journal, 2020) Il1rap mutant (The Jackson Laboratory, #003284) Emx1-Cre (The Jackson Laboratory, #005628) Vgat-Cre (The Jackson Laboratory, #028862) C56BL/6J strain were used as background of all wildtype/mutant mouse used in the study. All animals were fed ad libitum and housed under 12 h light/dark cycle (light phase from 1 am to 1 pm) under 21 degree Celsius and 50-60% humidity. Our studies involved adult mice (> postnatal day 56).
Wild animals	The study did not involve wild animals
Reporting on sex	Behavior data from adult male and female Ptprd-meB+/– mice were disaggregated in the data presentation. Male Ptprd-meB+/– mice were used exclusively for whole-cell recording, electron microscopy, and proteomics analysis experiments because male and female mice exhibited similar behaviors.
Field-collected samples	The study did not involve samples collected from the field.
Ethics oversight	All animals used in this study were maintained and procedures performed in accord with the Requirements of Animal Research at KAIST. All experimental procedures were approved by KAIST Institutional Animal Care and Use Committee (KA2023-071).

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

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.