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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	pClamp (version 10.4, Molecular Device), ImSpector Microscope Controller (Version 144, LaVision Biotec)
Data analysis	Clampfit (version 10.4, Molecular Device), Origin (version 8.0, Origin Lab), Imaris (version 8.0, Oxford Instruments), ImageJ (version 1.53a, US NIH), R (RStudio, Version 1.1.456)

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

All relevant data and code are freely available from the authors. Figures 1-5 and Extended Data Figures 1-10 have raw data.
Parkinson's Progression Markers Initiative (PPMI) database: https://www.ppmi-info.org/access-data-specimens/, Genome Aggregation Database (gnomAD): https://gnomad.broadinstitute.org/, PD Gene database: http://www.pdgene.org/, PDB ID 6WCA: https://www.rcsb.org/structure/6WCA.

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 using statistical methods; they are chosen based on statistical analysis and standards in the field (e.g. Cang et. al. (2015) Cell 162:1101-12). See sections "Statistical analysis of clinical data" and "Other statistical information".
Data exclusions	No data were excluded from analyses.
Replication	All experiments were independently replicated at least in two indepependent preparations for electrophysiology and three times for protein chemistry experiments. See section "Other statistical information and reproducibility".
Randomization	Mice used in the behavioral studies were randomized. The electrophysiological and protein chemistry experiments were not as some of them are hard to be randomized.
Blinding	We did blind experiments for Fig. 1b, 1i (left panel), 2i(starvation experiment), 4d-f, 5a-d, Extended data Fig. 1a, Extended data Fig. 1d, Extended data Fig. 1e, Extended data Fig. 8b-d, Extended data Fig. 9a, Extended data Fig. 9c-e and Extended data Fig. 10a-e. The others were not blinded as blinding unlikely affects the results.

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

β-actin (rabbit monoclonal, Cell Signaling Technology, #4970, 1:3000),
GFP (mouse monoclonal, Thermo Fisher Scientific, #A11120 1:1000; mouse monoclonal, Santa Cruz Biotechnology, #sc-9996, 1:2000),
TMEM175 (rabbit polyclonal, Proteintech, #19925-1-AP 1:1000; rabbit polyclonal, Origene, #TA335429, 2 μg/ml),
Akt (rabbit polyclonal, Cell Signaling Technology, #9272, 1:1000),
pan-Akt (mouse monoclonal, R&D Systems, #MAB2055, 0.2 ug/ml),
HA (mouse monoclonal, Santa Cruz Biotechnology, #sc-7392, 1:1000),
phospho-Akt (Ser473) (rabbit polyclonal, Cell Signaling Technology, #9271, 1:2000),
phospho-Akt (Thr308) (rabbit monoclonal, Cell Signaling Technology, #4056, 1:1000),
phospho-GSK3β (Ser9) (rabbit monoclonal, Cell Signaling Technology, #9323, 1:1000),
GSK3β (rabbit monoclonal, Cell Signaling Technology, #9315, 1:1000),
phospho-PRAS40(T246) (rabbit monoclonal, Cell Signaling Technology, #2691, 1:1000),
PRAS40 (rabbit monoclonal, Cell Signaling Technology, #2997, 1:1000,
cathepsin D (rabbit polyclonal, Cell Signaling Technology, #2284, 1:200).
rabbit IgG (Cell Signaling Technology, #7074, 1:4000),
mouse IgG (Abcam, #ab131368, 1:1000; Cell Signaling Technology, #7076, 1:4000),
VeritBlot for IP detection reagent (HRP) (Abcam, #ab131366, 1:4000),
pSer129 α-synuclein (mouse clone mAb 81A, 1:8000 {Waxman, 2008 #3214})
galectin-3 (rat monoclonal, 1:100, Santa Cruz Biotechnology, # sc-81728).
Alexa Fluor 594-conjugated goat anti-mouse secondary antibody (Thermo Fisher Scientific, #A-11032, 2 μg/ml)

Alexa Fluor 488-conjugated rabbit anti-α-tubulin antibody (Cell Signaling Technology, #5063S, 1:200),
Alexa Fluor 488 conjugated rabbit anti-rat secondary antibody (Thermo Fisher Scientific, #A-21210, 2 µg/ml).
DAT (rat monoclonal, Santa Cruz Biotechnology, #sc-32258, 1:500)
TH (rabbit polyclonal, Millipore Sigma, #AB-152, 1:500),
Alexa Fluor-conjugated secondary antibody (goat anti-rat IgG, Alexa 647, Thermo Fisher Scientific, #A21247, 1:500),
Alexa Fluor-conjugated secondary antibody (goat anti-rabbit IgG Alexa 647 (Thermo Fisher Scientific, #A21245, 1:500),
Tyrosine hydroxylase (Millipore Sigma, #TH-16; 1:5,000),
NeuN (Millipore Sigma, #A60; 1:1,000),
biotinylated anti-mouse IgG (1:1,000; Vector Laboratories, #BA2000),

Validation

β-actin (rabbit monoclonal, Cell Signaling Technology, #4970, 1:3000), https://www.cellsignal.com/products/primary-antibodies/b-actin-13e5-rabbit-mab/4970
GFP (mouse monoclonal, Thermo Fisher Scientific, #A11120 1:1000), https://www.thermofisher.com/antibody/product/GFP-Antibody-clone-3E6-Monoclonal/A-11120, validated against non-transfected cells.
GFP (mouse monoclonal, Santa Cruz Biotechnology, #sc-9996, 1:2000), https://www.scbt.com/p/gfp-antibody-b-2, validated against non-transfected cells.
TMEM175 (rabbit polyclonal, Proteintech, #19925-1-AP 1:1000), https://www.ptglab.com/products/TMEM175-Antibody-19925-1-AP.htm, validated against knockout.
TMEM175 (rabbit polyclonal, Origene, #TA335429, 2 µg/ml), https://www.origene.com/catalog/antibodies/primary-antibodies/ta335429/transmembrane-protein-175-tmem175-rabbit-polyclonal-antibody, validated against knockout.
Akt (rabbit polyclonal, Cell Signaling Technology, #9272, 1:1000), https://www.cellsignal.com/products/primary-antibodies/akt-antibody/9272
pan-Akt (mouse monoclonal, R&D Systems, #MAB2055, 0.2 ug/ml), https://www.rndsystems.com/products/human-mouse-rat-akt-pan-specific-antibody-281046_mab2055
HA (mouse monoclonal, Santa Cruz Biotechnology, #sc-7392, 1:1000), https://www.scbt.com/p/ha-probe-antibody-f-7, validated against non-transfected cells.
phospho-Akt (Ser473) (rabbit polyclonal, Cell Signaling Technology, #9271, 1:2000), https://www.cellsignal.com/products/primary-antibodies/phospho-akt-ser473-antibody/9271, validated against starved cells.
phospho-Akt (Thr308) (rabbit monoclonal, Cell Signaling Technology, #4056, 1:1000), https://www.cellsignal.com/products/primary-antibodies/phospho-akt-thr308-244f9-rabbit-mab/4056, validated against starved cells.
phospho-GSK3β (Ser9) (rabbit monoclonal, Cell Signaling Technology, #9323, 1:1000), https://www.cellsignal.com/products/primary-antibodies/phospho-gsk-3b-ser9-5b3-rabbit-mab/9323, validated against starved cells.
GSK3β (rabbit monoclonal, Cell Signaling Technology, #9315, 1:1000), https://www.cellsignal.com/products/primary-antibodies/gsk-3b-27c10-rabbit-mab/9315
phospho-PRAS40(T246) (rabbit monoclonal, Cell Signaling Technology, #2691, 1:1000), https://www.cellsignal.com/products/primary-antibodies/pras40-d23c7-xp-rabbit-mab/2691, validated against starved cells.
PRAS40 (rabbit monoclonal, Cell Signaling Technology, #2997, 1:1000, https://www.cellsignal.com/products/primary-antibodies/phospho-pras40-thr246-c77d7-rabbit-mab/2997
cathepsin D (rabbit polyclonal, Cell Signaling Technology, #2284, 1:200), https://www.cellsignal.com/products/primary-antibodies/cathepsin-d-antibody/2284
HRP conjugated rabbit IgG (Cell Signaling Technology, #7074, 1:4000), https://www.cellsignal.com/products/secondary-antibodies/anti-rabbit-igg-hrp-linked-antibody/7074
mouse IgG (Abcam, #ab131368, 1:1000; Cell Signaling Technology, #7076, 1:4000), https://www.cellsignal.com/products/secondary-antibodies/anti-mouse-igg-hrp-linked-antibody/7076
VeritBlot for IP detection reagent (HRP) (Abcam, #ab131366, 1:4000), https://www.abcam.com/veriblot-for-ip-detection-reagent-hrp-ab131366.html
pSer129 α-synuclein (mouse clone mAb 81A, 1:8000 (Waxman et al. Specificity and regulation of casein kinase-mediated phosphorylation of alpha-synuclein, J Neuropathol Exp Neurol. 2008 May;67(5):402-16. doi: 10.1097/NEN.0b013e31816fc995)
galectin-3 (rat monoclonal, 1:100, Santa Cruz Biotechnology, #sc-81728), https://www.scbt.com/p/galectin-3-antibody-m3-38-1-2-8-hl-2
Alexa Fluor 594-conjugated goat anti-mouse secondary antibody (Thermo Fisher Scientific, #A-11032, 2 µg/ml), https://www.thermofisher.com/antibody/product/Goat-anti-Mouse-IgG-H-L-Highly-Cross-Adsorbed-Secondary-Antibody-Polyclonal/A-11032
Alexa Fluor 488-conjugated rabbit anti-α-tubulin antibody (Cell Signaling Technology, #5063S, 1:200), https://www.cellsignal.com/products/antibody-conjugates/a-tubulin-11h10-rabbit-mab-alexa-fluor-488-conjugate/5063?Ntk=Products&Ntt=5063
Alexa Fluor 488 conjugated rabbit anti-rat secondary antibody (Thermo Fisher Scientific, #A-21210, 2 µg/ml), https://www.thermofisher.com/antibody/product/Rabbit-anti-Rat-IgG-H-L-Cross-Adsorbed-Secondary-Antibody-Polyclonal/A-21210
DAT (rat monoclonal, Santa Cruz Biotechnology, #sc-32258, 1:500), https://www.scbt.com/p/dat-antibody-6-5g10
TH (rabbit polyclonal, Millipore Sigma, #AB-152, 1:500), https://www.sigmaaldrich.com/catalog/product/mm/ab152?lang=en&region=US&gclid=Cj0KCQiA-rj9BRCAARIsANB_4ADs7HEZA0dDtXIvjHo9R01UpsGTb3p-JbYAvodrrN-7bQnPVPE87BoaAjrZEALw_wcB
Alexa Fluor-conjugated secondary antibody (goat anti-rat IgG, Alexa 647, Thermo Fisher Scientific, #A21247, 1:500), https://www.thermofisher.com/antibody/product/Goat-anti-Rat-IgG-H-L-Cross-Adsorbed-Secondary-Antibody-Polyclonal/A-21247
Alexa Fluor-conjugated secondary antibody (goat anti-rabbit IgG Alexa 647 (Thermo Fisher Scientific, #A21245, 1:500), https://www.thermofisher.com/antibody/product/Goat-anti-Rabbit-IgG-H-L-Highly-Cross-Adsorbed-Secondary-Antibody-Polyclonal/A-21245
Tyrosine hydroxylase (Millipore Sigma, #TH-16; 1:5,000), https://www.bosterbio.com/anti-tyrosine-hydroxylase-antibody-monoclonal-ma1100-boster.html
NeuN (Millipore Sigma, #A60; 1:1,000), https://www.emdmillipore.com/US/en/product/Anti-NeuN-Antibody-clone-A60,MM_NF-MAB377
biotinylated anti-mouse IgG (1:1,000; Vector Laboratories, #BA2000), https://vectorlabs.com/biotinylated-horse-anti-mouse-igg-antibody.html

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	HEK293T and SH-SY5Y from ATCC and S2 cell from Gibco, described in section "Cell Culture".
Authentication	The cell lines were purchased and authenticated by the providers (ATCC and Gibco); we did not carry out additional authentificaiton.
Mycoplasma contamination	HEK293T and SH-SY5Y from ATCC, and S2 cell from Gibco were tested by the providers.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell line was used in this study.

Animals and other organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research

Laboratory animals	Wild-type and mutant mice (BL6 background) were used, as described in the section "Animals". Description of research mice used for each experiments can be found in the relevant figure legends. Neuronal cultures were made from P0 pups with genders undetermined. Brain proteins used work for immunoprecipitation and Western blot were collected from 3-5 month old mice (mixture of male and females) Behavior and Immunostaining comparing WT and heterozygous littermates used mice of ~12 months old (both males and females). Immunostaining comparing WT and homozygous KO littermates used mice of 18-22 months old (both males and females). Average temperature in the housing rooms was 72 degree F; humidity was approximately 40%. Light cycle was 12 hours light/12 hours dark.
Wild animals	No wild animal was used.
Field-collected samples	No field-collected sample was used.
Ethics oversight	Animal use was approved by the The University of Pennsylvania's IACUC, The Animal Care and Use Committee of the School of Medicine at Fudan University, The clinical studies were approved by The University of Pennsylvania (UPenn) Institutional Review Board

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

Human research participants

Policy information about studies involving human research participants

Population characteristics	UPenn: Participants included male and female patients (defined as biological sex assigned at birth), 50 years of age and older, diagnosed with Parkinson's disease based on UK Brain Bank Criteria by a movement disorders neurologist, prospectively enrolled at the University of Pennsylvania Parkinson's Disease and Movement Disorders Center (Philadelphia, PA). See section "Human clinical studies". PPMI: Participants included people with a diagnosis of PD for two years or less who are not taking PD medications. Please see https://www.ppmi-info.org/study-design/study-cohorts/ for more information.
Recruitment	UPenn: Participants were recruited by a movement disorders neurologist during a regularly schedule clinical office visit at the University of Pennsylvania Parkinson's Disease and Movement Disorders Center (Philadelphia, PA). All patients seen at the Parkinson's Disease and Movement Disorders Center with a diagnosis of Parkinson's disease were eligible to participate. Self-selection bias may be present in this cohort, although it is unlikely to have a significant impact on longitudinal cognitive or motor progression; Participants in this study were prospectively enrolled. See section "Human clinical studies". PPMI: Please see https://www.ppmi-info.org/study-design/study-cohorts/ for more information.
Ethics oversight	University of Pennsylvania (UPenn) Institutional Review Board

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