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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	Fluorescent images were obtained using a confocal microscope (Zeiss LSM900) or Microscope Slide Scanner (Axio Scan Z1). RNA-seq data was generated using illumina sequencing. Preprocessing and integration were performed using Seurat (v.4.3.0. and v.5) pipelines.
Data analysis	Image analysis was done using Fiji (version 1.51f). Gene expression differential analyses were conducted using the R package DESeq2 v3.18. Enrichment analyses of Gene Ontology terms were analyzed using the Cytoscape plug-in ClueGO and EnrichR based on related terms and statistical significance. R version 4.2.2 was used for statistical analysis and plotting. The filtered gene-cell barcode matrices which were generated with CellRanger 3.0.2 (10x Genomics) based on the human GRCh38 reference genome were used for further analysis with the R package Seurat v4.3.0. and Seurat v5.0.1.

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 gene expression data generated in this manuscript have been uploaded to the NCBI Sequence Read Archive (SRA) under BioProject ID PRJNA1180266 - SRA - NCBI) . The metadata for Adams et al. (accession number GSE193688 GEO Accession viewer) and Piras et al. (accession number GSE199724 GEO Accession viewer, GSE199715 GEO Accession viewer, and GSE199258 GEO Accession viewer), Martirosyan et al. (accession number GSE243639 GEO Accession viewer), Wang et al. (accession number GSE184950 GEO Accession viewer) were downloaded from Gene Expression Omnibus (GEO).

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	Detailed information of sex is presented in Supplementary Table 10.
Reporting on race, ethnicity, or other socially relevant groupings	No data on race, ethnicity, or other socially relevant groupings was used or shared. Therefore, those variables were not included in this study and are not represented.
Population characteristics	Detailed information on all clinically relevant population characteristics are presented in Supplementary Table 10.
Recruitment	Human postmortem brain tissue was obtained from Seoul National University Hospital, Seoul, Republic of Korea (SNUH Brain Bank) after approval of the Institutional Review Board of SNUH.
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 chosen based on (i) previously published work from our group and the field demonstrating effect sizes for the used assays, (ii) availability of biological material (for human postmortem samples) and (iii) standard practice for the mouse model and in vitro assays. Exact sample numbers for each experiment are given in the figure legends and Supplementary Table 10 in the revised manuscript.
Data exclusions	In single-cell analysis, cells with markedly low nuclei number in relation to the remaining dataset were removed before integration.
Replication	For all experiments, n refers to independent biological replicates (i.e., individual animals, independent cell preparations, or separate tissue samples). The unit of study for each experiment has been defined in the figure legends. Control and experimental groups are explicitly described, and the total number of biological replicates is indicated as an exact value.
Randomization	Randomization was not relevant to this study. We have used all the samples available to us that fulfilled the diagnostic requirements
Blinding	In the case of analysis of publicly accessible datasets, blinding was not carried out.

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
[ ]	[x] Antibodies
[ ]	[x] Eukaryotic cell lines
[x]	[ ] Palaeontology and archaeology
[ ]	[x] Animals and other organisms
[x]	[ ] Clinical data
[x]	[ ] Dual use research of concern
[x]	[ ] Plants

Methods

n/a	Involved in the study
[x]	[ ] ChIP-seq
[x]	[ ] Flow cytometry
[x]	[ ] MRI-based neuroimaging

Antibodies

Antibodies used

The following antibodies were used for immunofluorescence staining: anti-α-synuclein (#610787, 1:100; BD biosciences, San Diego, CA, USA), anti-phospho-α-synuclein (ab59264, 1:1,000; Abcam, Waltham, MA, USA), anti-MBP (IGX3421, ab209328, 1:500; Abcam), anti-TPPP (EPR3316, ab92305, 1:200; Abcam), and anti-ubiquitin (ab7780, 1:50; Abcam), anti-TPPP (ab92305, 1:250; Abcam), anti-phospho-α-synuclein (#825702, 1:1,000; Biolegend, San Diego, CA, USA), anti-Olig2 (AB9610, 1:500; EMD Millipore, Billerica, MA, USA), anti-GFAP (ab7260, 1:500; Abcam), anti-Iba-1 (ab5076, 1:500; Abcam), anti-Cd68 (MCA1957, 1:100; Bio-Rad), anti-GSTP1 (LS-B2376-50, 1:500; LifeSpan Biosciences, Seattle, WA), anti-CNPase (PA1-4712, 1:500; Thermo Fisher Scientific), anti-PLP (ab254363, 1:1000; Abcam,), anti-MBP (ab7349, 1:500; Abcam), and anti-IBA1 (019-19741, 1:500; FUJIFILM Wako, Osaka, Japan)
The following antibodies were used for western blotting : anti-α-synuclein (#610787, 1:1,500; BD biosciences), anti-phospho-α-synuclein (ab51253, 1:1,000; Abcam), and anti-β-actin (AC-15, 1:10,000; Sigma-Aldrich).

Validation

The antibodies used in this study were validated by the manufacturer in WB, ICC/IF in human and mouse samples.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)

Stempro hNSCs (Thermo Fisher, Waltham, MA, USA) were cultured in the OPC medium (CTS KnockOut DMEM/F12 with B-27™ supplement minus vit. A (12587-010, 1:50; Thermo Fisher), N2 supplement (17502-048, 1:100; Thermo Fisher), human FGFβ (100-188, final 20 ng/ml; PeproTech, Rocky Hill, NJ, USA), PDGF-AA (CYT-341, 20 ng/mL, ProSpec, Rehovet, Israel), GlutaMAX Supplement (1:100), and penicillin-streptomycin (1:100)).

Authentication

The cell line was not authenticated in the laboratory

Mycoplasma contamination

The cell line tested negative for mycoplama

Commonly misidentified lines
(See ICLAC register)

N/A

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

Male αSyn A53T Tg mice (line G2-3) which express human αSyn A53T under the PrP promoter were purchased from Jackson Laboratory (stock #006823; Bar Harbor, ME, USA).

Wild animals

C57BL/6 mice

Reporting on sex

This study involved male mice.

Field-collected samples

This study did not involve field-collected samples.

Ethics oversight

Mice maintenance and experiments were conducted by CHAON Ltd. in compliance with the NIH guideline for Institutional Animal Care and Use Committee (IACUC) (CE20026, CE20192, CE20196, and CE21019). Primary culture were prepared in accordance with the regulations of the Seoul National University Institutional Animal Care and Use Committee (SNU-230511-2).

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