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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	MinKNOW v.1.14.0 (Oxford Nanopore Technologies) RSII data were analyzed with SMRT analysis v2.3.0 (Pacific Biosciences)
Data analysis	LinkDataGen; http://bioinf.wehi.edu.au/software/linkdatagen/ Merlin: http://csg.sph.umich.edu/abecasis/merlin/ LAST:http://last.cbrc.jp tandem-genotypes: https://github.com/mcfrith/tandem-genotypes MAFFT: https://mafft.cbrc.jp Genemapper Software 5 (Release 5.0, Build ID: 3.0) Flappie v.1.1.0 (https://github.com/nanoporetech/flappie)

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

Personal sequencing data will be deposited to the Human Genetic Variation Database with accession ID: HGV0000008 (http://www.hgvd.genome.med.kyoto-u.ac.jp/repository/HGV0000008.html).

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	9 families with NIID, 39 sporadic NIID patients, 200 controls. In 1968, the first NIID case was described. Until 2011, when we reported the usefulness of skin biopsy in the diagnosis of NIID, only approximately 40 NIID cases (including our 8 cases) have been reported. At that time, NIID was an extremely rare disease. We included most consecutive NIID cases into our research until today.
Data exclusions	No data was excluded.
Replication	NIID is a rare disease. Therefore we included most relevant NIID cases into our research until now. Therefore replication is impossible.
Randomization	The main objective of this study is to discover the genetic cause of NIID. Therefore, randomization is not applicable to this study.
Blinding	Skin biopsy was examined by two independent neuropathologists with no information of patients.

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	anti-ubiquitin antibody (Z0458, Dako). anti-p62 antibody (Santa Cruz Biotechnology, catalog No. sc-28359, clone D-3, Lot D1117, dilution 1:100).
Validation	SQSTM1 (D-3) is validated by Santa Cruz Biotechnology, and recommended for detection of sequestosome 1 of human origin by Western Blotting, immunoprecipitation, immunofluorescence, and immunohistochemistry (including paraffin-embedded sections), and used in many recent researches as described in the following datasheet of Santa Cruz Biotechnology.

Human research participants

Policy information about studies involving human research participants

Population characteristics	All NIID patients were diagnosed by skin biopsy (with intranuclear inclusion). We include Japanese participants at the ages ranging from 18 to 76 years. They are NIID patients diagnosed by skin biopsy, and their family members without any neurological symptoms. Gender details is 28 males and 46 females.
Recruitment	Participants were recruited by multiple research institutes/hospitals in Japan. We included NIID patients based on the results of histopathological findings that p62 positive intranuclear inclusions were widely observed in autopsy samples or skin biopsy samples as described in previous NIID skin biopsy reports. The abnormal high intensity signal of cortico-medurally junction in DWI image of brain MRI led clinicians to consider possible NIID and plan to perform skin biopsy for patients presenting dementia. Therefore, we may not include NIID patient with very mild change in head MRI findings or without abnormal findings in head MRI, but this may not influence the result of this study.

Ethics oversight	Informed consent was obtained from all the patients and their familial members. IRBs of Yokohama City University Faculty of Medicine and Nagoya University School of Medicine approved this experimental protocols.

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