

Article | Published: 10 February 2025

Longitudinal analysis of a dominantly inherited Alzheimer disease mutation carrier protected from dementia

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Nature Medicine **31**, 1267–1275 (2025)

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Abstract

We conducted an in-depth longitudinal study on an individual carrying the *presenilin 2* p.Asn141Ile mutation, traditionally associated with dominantly inherited Alzheimer's disease (AD), who has remarkably remained asymptomatic past the expected age of clinical onset. This study combines genetic, neuroimaging and biomarker analyses to explore the underpinnings of this resilience. Unlike typical progression in dominantly inherited AD, tau pathology in this case was confined to the occipital region without evidence of spread, potentially explaining the preservation of cognitive functions. Genetic analysis revealed several variants that, although not previously associated with protection against AD, suggest new avenues for understanding disease resistance. Notably, environmental factors such as significant heat exposure and a unique proteomic profile rich in heat shock proteins might indicate adaptive mechanisms contributing to the observed phenotype. This case underscores the complexity of

Alzheimer's pathology and suggests that blocking tau deposition could be a promising target for therapeutic intervention. The study highlights the need for further research to identify and validate the mechanisms that could inhibit or localize tau pathology as a strategy to mitigate or delay the onset of Alzheimer's dementia.

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Data availability

Data and study samples (for example, CSF, plasma) supporting the findings of this study are available on request and will follow the policies of the DIAN (<https://dian.wustl.edu>), which comply with the guidelines established by the Collaboration for Alzheimer's Prevention. De-identified whole-genome sequencing data will be made available through NIAGADS as part of the DIAN data-sharing process.

Code availability

The codes used in this study, including those applied for segregation analysis, are openly accessible at the following repository:

<https://github.com/NeuroGenomicsAndInformatics/escapee>.

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Acknowledgements

We acknowledge the altruism of the participants and their families and contributions of the DIAN research and support staff at each of the participating sites for their contributions to this study. This manuscript has been reviewed by DIAN Study investigators for scientific content and consistency of data interpretation with previous DIAN Study publications. Funding information: Data collection and sharing for this project was supported by the Dominantly Inherited Alzheimer Network (grant no. U19AG032438), funded by the National Institute on Aging (NIA), the Alzheimer's Association (grant no. SG-20-690363-DIAN), the German Center for Neurodegenerative Diseases (DZNE) and the Raul Carrea Institute for Neurological Research (FLENI). Partial support by Research and Development Grants for Dementia from the Japan Agency for Medical Research and Development, AMED grant no. JP22dk0207049, and the Korea

Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), Spanish Institute of Health Carlos III (ISCIII), Canadian Institutes of Health Research (CIHR), Canadian Consortium of Neurodegeneration and Aging, Brain Canada Foundation and Fonds de Recherche du Québec—Santé.

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Contributions

J.J.L.-G. and R.J.B. initiated this work, supervised the study and drafted the manuscript. J.J.L.-G., A.J.A., E.M. and W.S. collected and analyzed the clinical and phenotypic data. N.J.-M., B.A.G., T.L.S.B. and D.H. collected and analyzed the imaging data. M.V.F., C.P., M.J., A.E.R., A.M.G. and C.C. contributed to the genetic analyses and data interpretation. S.B., K.C., M.V.F., D.W., C.W. and E.C.B.J. conducted and analyzed the proteomic studies. L.I., N.B., J.J.L.-G. and R.J.B. assisted with molecular and biomarker data collection and analysis. All authors contributed to reviewing the manuscript and refining data analysis. J.J.L.-G. had direct access to and verified the data reported in the manuscript. J.J.L.-G., M.V.F. and N.J.-M. are first authors and contributed equally. C.C., E.C.B.J. and R.J.B. are senior authors and jointly supervised this work.

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Ethics declarations

Competing interests

The authors declare no competing interests.

Peer review

Peer review information

Nature Medicine thanks Yann Le Guen and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. Primary Handling Editor: Jerome Staal, in collaboration with the *Nature Medicine* team.

Additional information

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Supplementary information

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Appendix 1: Extended Methods, Appendix 2: Extended Results and Supplementary Figs. 1–11 and Tables 1 and 2.

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Cite this article

Llibre-Guerra, J.J., Fernandez, M.V., Joseph-Mathurin, N. *et al.* Longitudinal analysis of a dominantly inherited Alzheimer disease mutation carrier protected from dementia. *Nat Med* **31**, 1267–1275 (2025). <https://doi.org/10.1038/s41591-025-03494-0>

Received

22 July 2024

Accepted

06 January 2025

Published

10 February 2025

Version of record

10 February 2025

Issue date

April 2025

DOI<https://doi.org/10.1038/s41591-025-03494-0>

Nature Medicine (*Nat Med*) | ISSN 1546-170X (online) | ISSN 1078-8956 (print)