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Reporting Summary

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Statistical parameters

When statistical analyses are reported, confirm that the following items are present in the relevant location (e.g. 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
☐	☒	An indication of 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 statistics 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
☐	☒	Clearly defined error bars *State explicitly what error bars represent (e.g. SD, SE, CI)*

Our web collection on statistics for biologists may be useful.

Software and code

Policy information about availability of computer code

Data collection	Data entry is implemented in two separate web-based systems. MRI and PET image data and meta-data are uploaded and entered into the Central Neuroimaging Data Archive (CNDA) as are the computerized psychometric data. All other data are entered through the ADCS web-based data entry system and then transferred over secure, encrypted network protocols to the CNDA.
Data analysis	FreeSurfer 5.3; R Version 3.4.2; RStudio Version 1.1.453; Jmp Version 13.0; Jmp Version 14.0; STAN Version 2.17.4

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 upon request. 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

DIAN data availability is mentioned after the method

Field-specific reporting

Please select 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/authors/policies/ReportingSummary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	The DIAN study is an ongoing study. We took all available data from the latest data freeze (data freeze 11). CSF data from are data freeze 9
Data exclusions	Exclusion of data are detailed in the legend of supplementary Table 1
Replication	all measurements were done in duplicates as outlined in the method
Randomization	all samples had a random code and the experimentator was blinded towards the code.
Blinding	all samples had a random code and the experimentator was blinded towards the code.

Reporting for specific materials, systems and methods

Materials & experimental systems

n/a	Involved in the study
☒	☐ Unique biological materials
☐	☒ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology
☒	☐ Animals and other organisms
☐	☒ Human research participants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☐	☒ MRI-based neuroimaging

Antibodies

Antibodies used	We usee the capture monoclonal antibody (mAB) 47:3 and the biotinylated detector antibody mAB 2:1 (Uman Diagnostics, Umeå, Sweden).
Validation	The samples were measured in duplicate on a Simoa HD-1 platform (Quanterix) using a 2-step neat assay. Serum samples were measured at 1:4 and CSF at 1:10 dilution (tris base saline (TBS), 0.1% Tween 20, 1% nonfat milk powder, Heteroblock (300 ug/ml, Omega Biologicals, Bozeman, MT, USA)). Batch prepared calibrators (bovine lyophilized NfL) ranging from 0 to 10,000 pg/ml were stored at −80°C (Uman Diagnostics). All samples were measured blinded. For serum, the mean intra-assay coefficient of variation (CV) of duplicate determinations for concentration was 4.2%. In CSF, the mean intra-assay CV was 3.7%. Inter-assay variability was evaluated with 3 native serum samples and 3 native CSF samples. Inter-assay CVs for serum were 7.7% (mean concentration 13.3 pg/ml), 2.9% (30.9 pg/ml), and 3.7% (269.9 pg/ml). In CSF, inter-assay CVs were 2.4% (445.4 pg/ml), 12.2% (1486.3 pg/ml), and 13.3% (14049.0 pg/ml).

Human research participants

Policy information about studies involving human research participants

Population characteristics	all this information is given in Supplementary Table 1 and Table 2 of the manuscript in full detail.
Recruitment	all members of families (>18 years of age) with an autosomal mutations were invited to participate.

Magnetic resonance imaging

Experimental design

Design type	Structural
Design specifications	none
Behavioral performance measures	none

Acquisition

Imaging type(s)	Structural
Field strength	3T
Sequence & imaging parameters	Accelerated 3D sagittal T1-weighted MPRAGE, 1.1x1.1x1.2mm, TR=2300 msec, TE2.95, FA=9%, FOV=whole brain
Area of acquisition	whole brain

Diffusion MRI ☐ Used ☒ Not used

Preprocessing

Preprocessing software	Processed through FreeSurfer image analysis (5.3-HCP-patch)
Normalization	PET-underwent linear registration
Normalization template	MRI- data were taken from subject specific space; PET- data were aligned to MR
Noise and artifact removal	Reviewed by ADNI team for quality control, including inspection of processing pipeline workflows, visual inspection of the data for erroneous sessions, and the correct application of edits to volumes when errors persist.
Volume censoring	none

Statistical modeling & inference

Model type and settings	Only structural MRI used in analyses with ROI-based approach. Additional details on statistical methods, including all model parameters can be found in Methods and Supplements Methods sections.
Effect(s) tested	No tasks or stimulus conditions were used in our analyses

Specify type of analysis: ☐ Whole brain ☒ ROI-based ☐ Both

Anatomical location(s): automated labeling algorithms (FreeSurfer)

Statistic type for inference (See Eklund et al. 2016)	neither voxel-wise or cluster-wise used
Correction	Monte Carlo

Models & analysis

n/a	Involved in the study
☒	☐ Functional and/or effective connectivity
☒	☐ Graph analysis
☒	☐ Multivariate modeling or predictive analysis