

## 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

For ALLFTD, clinical, neuropsychological, and biomarker data are recorded in a customized iMedidata RAVE database. MRI images and metadata are uploaded and entered into a restricted access archive at the Laboratory of NeuroImaging (LONI). For GENFI, data entry is carried out via a customised XNAT database, specifically designed to accept all data collected as part of the GENFI study including MRI, clinical and neuropsychological data.

#### Data analysis

Data analyses were performed using the R (1.4.2) JAGS package with custom code available through Zenodo (10.5281/zenodo.6687486), Stata (17.0), nonparametric nonuniform intensity normalization (N3) algorithm, and SPM12.

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 datasets analyzed for the current study reflect collaborative efforts of two research consortia: ALLFTD and GENFI. Each consortium provides clinical data access based on established policies for data use: processes for request are available for review at [allftd.org/data](http://allftd.org/data) for ALLFTD data and by emailing [genfi@ucl.ac.uk](mailto:genfi@ucl.ac.uk) for

## 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](https://www.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	The sample for this study drew from all available participants with this condition from the two major United States and European consortia. The sample size for this study is over 1000 participants, which gives us broad representation across the disease spectrum. Between group comparisons included a minimum of 138 participants, which provides sufficient power to detect clinically relevant effect sizes for between-group comparisons.
Data exclusions	The parent studies from which these data were drawn have exclusion criteria that are described in the manuscript. All available data were included in the study.
Replication	To verify the reproducibility of our findings, we fit models in two consortia separately. These separate models, including raw data points, are presented in the manuscript and illustrated the high degree of replicability in progression across cohorts.
Randomization	This study built models using observational data to model the natural history of familial frontotemporal dementia. Randomization was not relevant to our study design.
Blinding	This study built models using observational data. The presence or absence of a mutation was relevant to model parameters and therefore was required to build the models. Randomization was not performed and therefore no blinding occurred related to randomization.

## 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

### Methods

n/a	Involved in the study	n/a	Involved in the study
<input type="checkbox"/>	<input checked="" type="checkbox"/> Antibodies	<input checked="" type="checkbox"/>	<input type="checkbox"/> ChIP-seq
<input checked="" type="checkbox"/>	<input type="checkbox"/> Eukaryotic cell lines	<input checked="" type="checkbox"/>	<input type="checkbox"/> Flow cytometry
<input checked="" type="checkbox"/>	<input type="checkbox"/> Palaeontology and archaeology	<input type="checkbox"/>	<input checked="" type="checkbox"/> MRI-based neuroimaging
<input checked="" type="checkbox"/>	<input type="checkbox"/> Animals and other organisms		
<input type="checkbox"/>	<input checked="" type="checkbox"/> Human research participants		
<input type="checkbox"/>	<input checked="" type="checkbox"/> Clinical data		
<input checked="" type="checkbox"/>	<input type="checkbox"/> Dual use research of concern		

## Antibodies

Antibodies used

ALLFTD plasma NfL Measurement: Plasma NfL light concentrations were measured at the Mayo Clinic in Jacksonville using the Quanterix (Lexington, MA) single-molecule array technology (Simoa) @ NF-Light Advantage Kit (Cat#103186, Lot 501992) and the HD-X instrument according to the instructions provided

GENFI plasma NfL measurement: Plasma NfL concentrations were measured at baseline with single-molecule array technology (Simoa), using the commercially available Simoa Neurology 4-Plex A kit (Quanterix, Lexington, MA, Cat# 102153).

Validation

ALLFTD: Samples were tested in duplicate using kits from the same lot. In addition to the two quality control samples provided with the kit, all assays included five inter-assay controls. Prior to each assay, plasma samples were thawed, mixed thoroughly by low-speed vortexing, centrifuged at 10,000 g for five minutes, and transferred to 96-well plates that were then sealed to minimize sample evaporation. Samples were diluted four times by the instrument. If levels of NfL in a sample exceeded the upper limit of the calibration curve, the sample was retested at a higher dilution. Across all assays, the percent coefficient of variations of the mean NfL concentration for the inter-assay controls were below 10%.

GENFI: Plasma samples were thawed at room temperature (one cycle), mixed thoroughly, and centrifuged at 14,000g for 3 minutes. The supernatant was loaded onto a Quanterix HD-1 Analyzer with a 1:4 specified dilution. Measures were completed in duplicate

over a total of six batches, each with an eight-point calibration curve tested in triplicate and two controls tested in duplicate. Plasma concentrations were interpolated from the calibration curve within the same batch and corrected for the dilution. All samples were quantifiable within the dynamic range of 0.69 to 2,000 pg/mL and with an average coefficient of variation below 10%. Instrument operators were blinded to clinical and genetic information.

## Human research participants

Policy information about [studies involving human research participants](#)

Population characteristics	This study enrolled participants from families with known familial FTD mutations. Participants above the age of 18 were included. Participants were included across a range of clinical phenotypes, with most participants presenting with behavioral variant FTD or primary progressive aphasia. We consider the impacts of known covariates such as age (mean=50.2, SD=1.9), sex (56.1% female), education (mean=14.4, SD=3.2), and language of testing.
Recruitment	Participants were recruited from the major familial FTD research consortia in the United States and Europe. Participants were recruited from subjects/kindreds already identified at the collaborating centers. Referrals were also solicited from other centers interested in familial FTD, non-profit organizations that support FTD research and patient advocacy, and consortia websites. There is currently a lack of ethnic and sociocultural diversity in FTD research populations which may limit the generalizability of these results to underrepresented populations. Patients were recruited from academic research centers that are specialized in these diseases. This may not reflect true population.
Ethics oversight	The ALLFTD study was approved through the Trial Innovation Network (TIN) at Johns Hopkins University. Local ethics committees (Institutional Review Boards) at each of the sites approved the study, and all participants provided written informed consent or assent with proxy consent.

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

## Clinical data

Policy information about [clinical studies](#)

All manuscripts should comply with the ICMJE [guidelines for publication of clinical research](#) and a completed [CONSORT checklist](#) must be included with all submissions.

Clinical trial registration	NCT02365922; NCT04363684; NCT02372773
Study protocol	<a href="https://clinicaltrials.gov/ct2/show/NCT02365922">https://clinicaltrials.gov/ct2/show/NCT02365922</a> ; <a href="https://clinicaltrials.gov/ct2/show/NCT04363684">https://clinicaltrials.gov/ct2/show/NCT04363684</a> ; <a href="https://clinicaltrials.gov/ct2/show/NCT02372773">https://clinicaltrials.gov/ct2/show/NCT02372773</a>
Data collection	Participants were enrolled through Advancing Research and Treatment for Frontotemporal Lobar Degeneration (ARTFL) and Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects (LEFFTDS), which recently combined into the ARTFL/LEFFTDS Longitudinal Frontotemporal Lobar Degeneration (ALLFTD) Study. ALLFTD enrolled participants through a consortium of 18 centers across the US and Canada between 2015 and 2020. Participants were also enrolled through the Genetic Frontotemporal Initiative (GENFI), which involves 25 research centers across Europe and Canada. GENFI participants from the 5th Data Freeze (2015-2019) were included
Outcomes	Data was acquired from ongoing observational studies. Outcomes were clinical measures and biomarkers that were readily available across the GENFI and ALLFTD consortia and are related to the symptoms of FTD. The Clinical Dementia Rating Scale (CDR <sup>®</sup> ) plus Behavioral and Language Domains from the National Alzheimer's Coordinating Center (NACC) FTLD module, neuropsychological tests from the Uniform Data Set and the Revised Self Monitoring Scale were scored according to standardized procedures. Volumetric brain MRI was analyzed using predefined regions of interests and voxelwise analyses. Plasma neurofilament light chain levels were assessed using Quanterix Simoa technology as described below.

## Magnetic resonance imaging

### Experimental design

Design type	Region of interest comparison and voxelwise display of effect sizes
Design specifications	Gray matter volume in each of several preselected ROIs was entered into the model as a percentage of total intracranial volume. In addition, we conducted sensitivity analyses in which gray matter volume at each voxel was converted to a W-scores based on a reference group, covarying for head size and scanner. The mean W-score for each region of interest was extracted and modeled in the disease progression model. Voxelwise W-scores were also presented as a sensitivity analysis.
Behavioral performance measures	No behavioral data was gathered during this volumetric sequence.

### Acquisition

Imaging type(s)	Structural
Field strength	1.5 and 3 Tesla.
Sequence & imaging parameters	T1-weighted images from ALLFTD were acquired as Magnetization Prepared Rapid Gradient Echo (MP-RAGE) images

Sequence & imaging parameters	using the following parameters: 240x256x256 matrix; about 170 slices; voxel size = 1.05x1.05x1.25 mm <sup>3</sup> ; flip angle, TE and TR varied by vendor. T1-weighted images from GENFI were acquired using the following parameters: 256x256x208 matrix; 208 slices; voxel size = 1.1 mm isotropic, flip angle = 8 degrees, TE and TR varied by vendor.
Area of acquisition	Whole brain scans.
Diffusion MRI	<input type="checkbox"/> Used <input checked="" type="checkbox"/> Not used

## Preprocessing

Preprocessing software	T1-weighted images underwent bias field correction using N3 algorithm. The segmentation was performed using SPM12 (Wellcome Trust Center for Neuroimaging, London, UK, <a href="http://www.fil.ion.ucl.ac.uk/spm">http://www.fil.ion.ucl.ac.uk/spm</a> ) unified segmentation.
Normalization	A customized group template was generated from the segmented gray and white matter tissues and cerebrospinal fluid by non-linear registration template generation using the Large Deformation Diffeomorphic Metric Mapping framework. <sup>12</sup> Subjects' native space gray and white matter were geometrically normalized to the group template, modulated, and then smoothed in the group template. The applied smoothing used a Gaussian kernel with 8~mm full width half maximum. Every step of the transformation was carefully inspected from the native space to the group template.
Normalization template	ICBM
Noise and artifact removal	The applied smoothing used a Gaussian kernel with 8~mm full width half maximum.
Volume censoring	Volume censoring was not performed.

## Statistical modeling & inference

Model type and settings	Modeling was not performed on the raw images; regions of interest were extracted and included in the disease progression models along with other clinical variables and plasma NfL levels, and thus were treated like other clinical measures. Voxelwise images were used for display purposes and were not used to conduct statistical tests.
Effect(s) tested	Statistical tests were not performed on the raw images; regions of interest were extracted and included in the disease progression models along with other clinical variables and plasma NfL levels.
Specify type of analysis:	<input type="checkbox"/> Whole brain <input type="checkbox"/> ROI-based <input checked="" type="checkbox"/> Both
Anatomical location(s)	Regions of interest were extracted using the Desikan atlas. Parcellation was conducted based on historical precedence in this disease.
Statistic type for inference (See <a href="#">Eklund et al. 2016</a> )	Statistical inference was not performed at the voxel or cluster level.
Correction	For between-group ROI comparisons, multiple comparisons were controlled for using the Tukey method.

## Models & analysis

n/a	Involvement in the study
<input checked="" type="checkbox"/>	<input type="checkbox"/> Functional and/or effective connectivity
<input checked="" type="checkbox"/>	<input type="checkbox"/> Graph analysis
<input checked="" type="checkbox"/>	<input type="checkbox"/> Multivariate modeling or predictive analysis