Individualized atrophy scores predict dementia onset in familial frontotemporal lobar degeneration

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Thirty percent to 40% of FTLD is considered familial progression to disability and death once symptoms manifest relatively early age of onset and, in many cases, rapid amount of time.

That symptoms are likely to develop within a predictable neurodegenerative disease to identify markers that predict initiation of studies of individuals at high risk of difficulty to predict. These considerations have spurred the been initiated. In the general population, this is very when symptoms would have started had the treatment not delayed onset of symptoms requires accurate knowledge of symptoms. Demonstrating that a treatment has progression in asymptomatic familial frontotemporal lobar degeneration mutation carriers. 

Individualized quantification of baseline brain atrophy is a promising predictor of progression in asymptomatic familial frontotemporal lobar degeneration mutation carriers. © 2019 The Authors. Published by Elsevier Inc. on behalf of the Alzheimer’s Association. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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1. Introduction

Neurodegenerative diseases such as Alzheimer’s disease (AD) and frontotemporal lobar degeneration (FTLD) dementia are devastating conditions caused by the accumulation of toxic proteins in the brain. Drugs designed to reduce the levels of these proteins and modify the course of disease are being aggressively developed. Advances in biomarker research have demonstrated that the causative proteins in neurodegenerative disease begin to accumulate years before the onset of symptoms, which suggests that very early treatment in this prodromal stage might prevent or delay the development of symptoms. Demonstrating that a treatment has delayed onset of symptoms requires accurate knowledge of when symptoms would have started had the treatment not been initiated. In the general population, this is very difficult to predict. These considerations have spurred the initiation of studies of individuals at high risk of neurodegenerative disease to identify markers that predict that symptoms are likely to develop within a predictable amount of time.

FTLD is a neurodegenerative disorder characterized by relatively early age of onset and, in many cases, rapid progression to disability and death once symptoms manifest. Thirty percent to 40% of FTLD is considered familial (f-FTLD), and several causative mutations have been identified, the three most common being mutations in the MAPT, GRN, and C9orf72 genes. Although all mutations are highly penetrant, such that the likelihood of symptoms is close to 100%, the age of onset can vary dramatically, even within a family (e.g., onset in the 30s vs. the 70s in the same family). Unlike other familial disorders such as familial AD and Huntington’s disease, there are no accurate predictors of when symptoms will develop in an individual at risk for FTLD. Two projects, Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects (LEFFTDS) and Advancing Research and Treatment in Frontotemporal Lobar Degeneration (ARTFL), were recently initiated to identify better markers of disease in f-FTLD.

Several studies of f-FTLD have suggested that brain volume is reduced in mutation carriers, even when still asymptomatic, making brain volume attractive as a potential biomarker. Early tracking of imaging abnormalities in f-FTLD is difficult, however, because of the broad spectrum of presenting symptoms, which range from motor neuron disease and parkinsonism to socioemotional, language, and speech disorders that can initially occur alone or in various combinations; some syndromes even mimic AD. Each of these syndromes is associated with a specific pattern of brain atrophy, and thus the earliest imaging changes vary across individuals. Because...
there are currently no known indicators that predict which neural systems will be affected first, previous work in f-FTLD has focused on tracking whole brain changes or regional changes that might be specific to the type of mutation [19], but this type of approach does not permit optimal tracking because the measures are not tailored for each individual.

The analysis presented here examines individualized patterns of brain atrophy as a biomarker in ARTFL/LEFFTDS participants. We reasoned that symptoms in each individual might predictably begin when brain atrophy reaches a specific level of severity. In some individuals, this may represent severe atrophy in a limited number of brain regions, whereas in others, this may be caused by milder but more extensive changes. This would suggest that quantifying the specific pattern of brain atrophy in each individual, accounting for both severity and extent but ignoring portions of the brain that are less affected and presumably healthy, could produce a valuable marker for predicting symptom onset. The analysis presented here examines the utility of using individualized maps of brain atrophy, which account for variability in age, to predict symptom onset.

2. Materials and methods

2.1. Participants

The study included 268 members of families affected by f-FTLD, most of whom were enrolled in the ARTFL and/or LEFFTDS studies, which are conducted through a consortium of 18 centers across the United States and Canada (https://www.rarediseasenetwork.org/cms/artfl/). These studies enroll individuals based on a family history suggestive of f-FTLD, usually identified through interview of a symptomatic proband. Once a family member with a mutation is identified, other members of the family are contacted and invited to participate. Enrollees do not need to know their mutation status. For LEFFTDS, at least one individual in the family must have a mutation in the MAPT, GRN, or C9orf72 genes. For ARTFL, families with any f-FTLD mutation or without a known mutation can enroll, but only patients with MAPT, GRN, or C9orf72 mutations were included in the analysis reported here. The ARTFL and LEFFTDS protocols include annual follow-up with clinical reassessment. Additional participants with f-FTLD were included who had been enrolled in a longstanding study of FTLD at the University of California, San Francisco, and who had undergone a similar brain imaging protocol (AG032306-05).

Reference images for creation of atrophy maps in each of the f-FTLD family members were obtained from 383 control participants chosen to cover the age range of the mutation carriers, including 28 who enrolled a previous study of neuroimaging in FTLD at the University of California, San Francisco (AG032306), 143 nonmutation carriers from the Dominantly Inherited Alzheimer’s Network (NCT00869817) [20], 31 who participated in the Parkinson’s Progression Markers Initiative (NCT01141023) [21], and 181 from the Alzheimer’s Disease Neuroimaging Initiative (NCT02854033).
Exponentiated Lie algebra [26]; subsequently, the images were normalized and modulated in the study-specific template space using nonlinear and rigid-body registration. For longitudinal analysis, an intraparticipant template was created using nonlinear diffeomorphic and rigid-body registration implemented with Statistical Parameter Mapping [27]. The intraparticipant template was segmented and a group template was generated from the within-participant averaged gray matter, white matter, and CSF tissue maps by nonlinear and rigid-body registration. Images were finally warped into the Montreal Neurological Institute standard space, and smoothed using a 4 mm isotropic Gaussian kernel. Total intracranial volume was estimated for each participant in Montreal Neurological Institute space.

Atrophy was quantified in each family member by creating a W-score representing volume loss at each gray matter voxel. The W-score represents the gray matter content at that voxel as the number of standard deviations away from the expected mean for the reference group after fitting a multiple linear regression accounting for age, total intracranial volume, and scanner platform [28,29] (where the standard deviation is defined as the standard deviation of the residuals for the fitted model). W-scores were integrated within 179 regions of interest (ROIs) as defined by a standard brain atlas [30] to create a measure of atrophy burden for each region of the brain. The process of W-score creation is illustrated in Fig. 1. Fig. 2 shows W-score maps for six symptomatic mutation carriers.

2.5. Calculation of atrophy-based dementia risk score

We used family members carrying mutations who were clinically normal (CDR plus NACC FTLD = 0) versus those diagnosed with dementia (CDR plus NACC FTLD = 1) as a categorical outcome for developing a dementia risk score based on each person’s pattern and degree of atrophy. To retain as large a sample size as possible, participants with the MAPT, GRN, and C9orf72 mutations were all included in the analysis as one group. To be considered normal, an individual had to have been rated as CDR plus NACC FTLD = 0 for two years in a row (but images used to create a risk score were always those obtained at the first time point). Family members without mutations, carriers with CDR plus NACC FTLD = 0.5, or any carrier with more than two time points were left out of the model for use as a predictive data set in the survival analysis described below. We also left out any carrier observed to convert from CDR plus NACC FTLD 0 or 0.5 to a higher level over time. The classification model was based on a L2-regularized logistic regression algorithm [31] and implemented in a machine learning Python package [32] using the Fast Incremental Gradient Method [33]. The targeted probability distribution is

\[
P(t|w_i) = \frac{1}{1 + \exp(-2(t - 1) \times w_i^T\alpha)}
\]

where the w-burden \(w_i\) for the participant \(i\), is a vector whose dimensions represent the integral of the local w-score \(w_{ij}\) for each ROI \(j\). The label \(t \in \{0, 1\}\) indicates a patient’s mental status as healthy or impaired. The parameters vector \(\alpha\) is fitted by optimizing the empirical log-logistic loss using an \(L_2\)-regularization term [31]:

\[
\hat{\alpha} = \arg \min_{\alpha} \sum_{i=1}^{n} P(t_i|w_i) + \frac{\lambda}{2} ||\alpha||^2
\]

The predicted values from the fitted logistic regression range from 0 to 1 and represent the probability of being...
assigned to the CDR® plus NACC FTLD ≥ 1 group. Before classification, the W-scores $w_{ij}$ in each ROI $j$ were standardized across participants’ predictors such that $\sum w_{ij} = 0$ for $i = 1, \ldots, n$ and $j = 1, \ldots, p$ where $n$ is the number of participants and $p$ is the number of ROIs. To estimate model performance, a 5-fold cross-validation scheme was used [34] across a grid of values for the parameter $\lambda$, which specifies the regularization strength in equation 2. The optimal $\lambda = 10$ value was selected based on the highest mean R-squared over the 5-folds. The optimized weight distribution of the vector $\alpha$ is presented in Fig. 3.

2.6. Analysis

To assess prediction accuracy, the dementia prediction scores were binarized such that regression score values above 0.5 were set to 1 (predicting dementia/CDR® plus NACC FTLD = 1) and those equal to, or below 0.5 were set to 0 (predicting asymptomatic/CDR® plus NACC FTLD = 0). The predicted label was compared with the actual diagnosis, with accuracy being calculated as the proportion of participants correctly classified. 101 nonmutation-carrying family members of f-FTLD patients with the three mutations of interest were used as a
validation group. In addition, the risk scores were plotted in 36 f-FTLD mutation carriers with a CDR\(^{+}\) plus NACC FTLD = 0.5 and a single visit. Please note that this latter group was not used to create the logistic regression, nor were they included in the accuracy score, but rather plotted for illustrative purposes.

For those participants not included in the model used to derive the dementia risk score (i.e., stable CDR\(^{+}\) plus NACC FTLD = 0.5 for at least 2 time points, stable CDR\(^{+}\) plus NACC FTLD = 0 with more than 2 time points, and those who converted from CDR\(^{+}\) plus NACC FTLD = 0 or 0.5 to CDR\(^{+}\) plus NACC FTLD \(\geq 1\)) individual dementia risk scores from their MRIs were calculated for all available time points. These mutation carriers with longitudinal data were examined to assess the potential utility of the dementia risk score for predicting development of symptoms (e.g., converting from CDR\(^{+}\) plus NACC FTLD = 0 or CDR\(^{+}\) plus NACC FTLD = 0.5 to CDR\(^{+}\) plus NACC FTLD \(\geq 1\)). This was accomplished using Cox regression models where atrophy score was treated as a time-varying/dependent predictor and CDR\(^{+}\) plus NACC FTLD score as the outcome [35].

3. Results

3.1. Participant demographics

The total study group included 268 family members, including 101 nonmutation carriers, 127 mutation carriers were included in the logistic model and accuracy analysis (54 C9orf72, 37 GRN, and 36 MAPT), and 40 in the survival analysis (14 C9orf72, 12 GRN, and 14 MAPT). Table 1 summarizes the age, sex, and symptom severity breakdown for each analysis, including the imaging reference group. Table 2 describes the clinical diagnoses in these groups.

3.2. Atrophy-based dementia risk score fitting

The atrophy-based dementia risk score was developed using the 56 mutation carriers with CDR\(^{+}\) plus NACC FTLD \(\geq 1\) and with 35 mutation carriers with a CDR\(^{+}\) plus NACC FTLD = 0 for two years in a row. Fig. 3 shows the weight for each brain region in the final score. Fig. 4 plots the final scores in these individuals after 5-fold cross validation. The model achieved good separation of prediction scores for CDR\(^{+}\) plus NACC FTLD = 0 versus CDR\(^{+}\) plus NACC FTLD \(\geq 1\), achieving an accuracy of 90.0% (SE: 0.06) based on a cutoff score of 0.5. For comparison, scores for the 101 nonmutation carriers and those with CDR\(^{+}\) plus NACC FTLD = 0.5 are plotted in Fig. 4. As expected, nearly all noncarriers have low prediction scores. CDR\(^{+}\) plus NACC FTLD = 0.5 cases ranged from very low to very high scores.

Participants with CDR\(^{+}\) plus NACC FTLD = 0.5 are plotted in Fig. 4 for illustrative purposes but were not included in the logistic regression model. This study used
CDR® plus NACC FTLD = 1 as the criterion for the logistic regression, rather than clinical diagnosis. In most cases this corresponds, but as shown in the table, some patients with CDR® plus NACC FTLD = 1 received a clinical diagnosis of MCI rather than dementia.

### Table 2

| Baseline diagnosis | Logistic regression/accuracy | Survival analysis |
|--------------------|------------------------------|-------------------|
|                    | CDR® plus NACC FTLD = 0.5    | Stable CDR® plus NACC FTLD = 0.5 Converters |
| bvFTD              | 2                            | 32                |
| svPPA              | 1                            |                   |
| nfvPPA             | 1                            |                   |
| Logopenic variant PPA | 1                        |                   |
| FTD/ALS            | 1                            | 6                 |
| ALS                | 1                            |                   |
| CBS                | 1                            | 1                 |
| MCI—Behavior       | 6                            | 1                 |
| MCI—Other          | 11                           | 3                 |
| AD                 | 1                            | 4                 |
| AD frontal         | 1                            |                   |
| Primary psychiatric | 2                           | 4                 |
| Clinically normal  | 11                           | 2                 |
| DBL                | 1                            |                   |
| Parkinson’s disease| 1                            |                   |

Note. MCI other = MCI frontal/exec; MCI mixed/unspecified; MCI—cognitive.

Abbreviations: bvFTD, Behavioral variant frontotemporal dementia; CDR, Clinical Dementia Rating Scale; svPPA, semantic variant primary progressive aphasia; nfvPPA, nonfluent variant PPA; ALS, amyotrophic lateral sclerosis; CBS, corticobasal syndrome; MCI, mild cognitive impairment; AD, Alzheimer’s disease; DLB, dementia with Lewy bodies.

3.3. Dementia risk score testing

To test whether the model could predict likelihood of conversion, we examined longitudinal data in mutation carriers with stable CDR® plus NACC FTLD = 0 over at least 3 time points, CDR® plus NACC FTLD = 0.5 over at least 2 time points, or conversion from CDR® plus NACC FTLD = 0 to CDR® plus NACC FTLD = 0.5, CDR® plus NACC FTLD = 0 to CDR® plus NACC FTLD ≥1, or CDR® plus NACC FTLD = 0.5 to CDR® plus NACC FTLD ≥1. The numbers of cases in each category and follow-up statistics are summarized in [Supplementary Table 1](#). We fitted a number of Cox regression models to examine conversions between different CDR® plus NACC FTLD levels: model A, 0 to 0.5; model B, from 0.5 to 1 or more (i.e., 0.5+); and model C, from a 0 or 0.5 to 1 or more (1+). The hazard ratios (HR) for a 0.1 unit increase in dementia risk prediction score in those models that included participants enrolled at a CDR® plus NACC FTLD = 0.5 or (0 or 0.5), were 1.28 and 1.51, indicating a shorter time to conversion with increased dementia risk score. Results are displayed in Table 3. Both the model examining conversion from 0.5 to 1+(HR = 1.28, 𝑃 = .041), and the model examining conversion from 0 or 0.5 to 1+(HR = 1.51, 𝑃 = .001) were statistically significant, but the model examining conversion from 0 to 0.5+ was not statistically significant (HR = 0.98, 𝑃 = .932). Fig. 5 shows Kaplan-Meier curves for model C (0 or 0.5 to ≥1) after dichotomizing using a baseline cutoff dementia risk score of 0.5. Those with scores above 0.5 all converted to dementia within 2 years, whereas >80% of those with scores below 0.5 still have not converted after 5 years.
4. Discussion

The goal of this analysis was to determine whether an atrophy-based risk score could be developed to predict the onset of dementia in asymptomatic or questionably symptomatic individuals who are at high risk due to autosomal dominant mutations. Our results indicate that quantification of each person’s unique pattern of atrophy can separate those with dementia from those with no symptoms with 90% accuracy. Furthermore, in an independent subset of the data composed of longitudinal observations, we were able to show that this atrophy-based risk score increased the risk in a statistically significant manner for progression to dementia from the asymptomatic (CDR/C210 plus NACC FTLD 0 to 0.5) or questionably symptomatic state (CDR/C210 plus NACC FTLD 0.5 to 1). These results suggest that quantification of individualized atrophy patterns is a promising technique that may be useful for developing new treatments for neurodegenerative disease and for guiding the use of these treatments once they are approved.

This approach for creation of atrophy maps addresses formidable challenges in developing treatments for neurodegenerative disease. Because the age when symptoms develop varies widely across individuals with FTLD and within individual families, drug trials seeking to delay the onset of symptoms must identify biological markers that reliably indicate symptoms will develop within a short time, allowing enrichment of the trial cohort with these participants, or stratification within the study. A similar approach to constructing individualized risk estimates was developed for AD and can significantly predict risk of future decline [36] and conversion from MCI to AD [37]. This approach, however, trained a classifier to produce an atrophy score that reflected similarity with an AD pattern of atrophy. Our approach, which was agnostic to region of atrophy and accounted for age, is necessary in this cohort given the variable age of onset and diversity of brain networks affected in f-FTLD. Another study took a similar approach to distinguish f-FTLD presymptomatic carriers from noncarriers based on their resemblance to bvFTD, again using a trained classifier [38]; this method did not significantly classify presymptomatic carriers from controls. Another study in f-FTLD suggested that volume loss in specific brain regions precedes onset of symptoms [16]. Indeed, our approach can potentially identify brain changes that herald the onset of symptoms regardless of where they occur in the brain, and our validation analysis supports the value of such changes. Similarly, each person’s W-map can potentially be used to define a region of interest for tracking the effect of a drug in slowing atrophy. Once treatments are approved, this type of risk score can be used to avoid potential adverse effects of approved drugs if treatment is delayed until the time when symptoms are more likely to develop. Furthermore, these considerations are not limited to FTLD. For instance, a substantial minority of patients with AD present with symptoms of visuospatial, frontal, or language symptoms [39], and measurements targeted at the hippocampal or entorhinal cortex regions typically affected in AD may miss early brain changes indicative of oncoming symptoms. This idea could be examined in amyloid positive individuals at high risk of developing AD due to genetic risk.

Although this method appears promising, future refinements can be envisioned that will likely improve its utility. Technical factors will need to be addressed, such as the impact of specific scanner and field strength on the estimate. Although this was a multisite study, many of the participants were studied at the University of California, San Francisco, and all participants were scanned at 3T. Replication of these findings in independent data sets will be important. In addition, the regression model was created using patients who had already developed dementia an average of 3 years before the

### Table 3

Results of survival analyses

| Model | Number of conversions | Hazard ratio | 95% CI    | P value |
|-------|-----------------------|--------------|-----------|---------|
| A. CDR® plus NACC FTLD 0 to 0.5+ | 18 | 7 | 0.98 | 0.64 - 1.5 | .932 |
| B. CDR® plus NACC FTLD 0.5 to 1+ | 25 | 10 | 1.28 | 1.01 - 1.62 | .041 |
| C. CDR® plus NACC FTLD (0 or 0.5) to 1+ | 40 | 10 | 1.51 | 1.17 - 1.94 | .001 |

Abbreviations: CDR, Clinical Dementia Rating Scale; FTLD, frontotemporal lobar degeneration; NACC, National Alzheimer’s Coordinating Center.

![Fig. 5. Kaplan-Meier curve representing survival from CDR® plus NACC FTLD = (0 or 0.5) to 1+. Note: Hash marks indicate censored observations. Abbreviations: FTLD, Frontotemporal lobar degeneration; CDR, Clinical Dementia Rating Scale; NACC, National Alzheimer’s Coordinating Center.](image-url)
onset of the study. Creation of a model based on patients who were observed to convert to dementia within the last year would likely improve its sensitivity. Such patients will likely be available through projects such as ARTFL and LEFFTDS in the future. Our atrophy-based risk score was derived using 91 mutation carriers in our training group; future iterations will strive to use a larger sample. Furthermore, this model was created by pooling all three types of FTLD mutations as one group to maximize the sample size. The inherent trade-off is that we may have reduced our power to detect mutation-specific atrophy that could have improved model accuracy. With larger numbers of patients, mutation-specific models can be created. For instance, the weighting of each region in our model depicted in Fig. 3 shows that right-sided regions were heavily weighted, and only a limited number of left hemisphere regions were useful in prediction of dementia. In a group with only GRN mutation carriers, there would be a higher likelihood of asymmetric involvement and left-sided involvement, so that the left hemisphere might carry more weight for prediction. Please see the study by Olney et al. (this special issue) for a characterization of brain atrophy patterns by mutation type. In addition, it is likely that additional variables indicative of inflammation or neuronal injury, or other types of imaging or clinical data, when added to this score, could significantly improve prediction in survival analyses. Despite these limitations, these results are an important step toward predicting disease onset in neurodegenerative conditions.

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Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jalz.2019.04.007.

RESEARCH IN CONTEXT

1. Systematic review: A literature review (PubMed) revealed that although brain volume is reduced in asymptomatic familial frontotemporal lobar degeneration (f-FTLD) mutation carriers, there is no model for using baseline brain volume to predict symptom onset. Previous approaches for calculating atrophy-based risk scores in other dementias have trained classifiers using expected patterns of atrophy. Given the heterogeneity of atrophy in f-FTLD, we developed atrophy-based risk scores that quantify each patients’ atrophy regardless of the pattern.

2 Interpretation: Individualized atrophy scores separated f-FTLD mutation carriers with dementia from asymptomatic carriers with high accuracy. Moreover, atrophy-based risk scores predicted conversion from asymptomatic or mildly/questionably symptomatic stages to dementia. This biomarker could improve clinical care and enhance the power of clinical trials.

3. Future directions: This finding should be replicated in other f-FTLD cohorts. Individualized atrophy-based risk scores need to be evaluated as biomarkers of progression in the earliest stages of a variety of neurodegenerative diseases.

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