Development and Validation of Pedigree Classification Criteria for Frontotemporal Lobar Degeneration

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IMPORTANCE A significant portion of frontotemporal lobar degeneration (FTLD) is due to inherited gene mutations, and we are unaware of a large sequential series that includes a recently discovered inherited cause of FTLD. There is also great need to develop clinical tools and approaches that will assist clinicians in the identification and counseling of patients with FTLD and their families regarding the likelihood of an identifiable genetic cause.

OBJECTIVES To ascertain the frequency of inherited FTLD and develop validated pedigree classification criteria for FTLD that provide a standardized means to evaluate pedigree information and insight into the likelihood of mutation-positive genetic test results for C9orf72, MAPT, and GRN.

DESIGN Information about pedigrees and DNA was collected from 306 serially assessed patients with a clinical diagnosis of FTLD. This information included gene test results for C9orf72, MAPT, and GRN. Pedigree classification criteria were developed based on a literature review of FTLD genetics and pedigree tools and then refined by reviewing mutation-positive and -negative pedigrees to determine differentiating characteristics.

SETTING Academic medical center.

PARTICIPANTS Patients with FTLD.

MAIN OUTCOMES AND MEASURES Familial risk.

RESULTS The rate of C9orf72, MAPT, or GRN mutation-positive FTLD in this series was 15.4%. Categories designating the risk level for hereditary cause were termed high, medium, low, apparent sporadic, and unknown significance. Thirty-nine pedigrees (12.7%) met criteria for high, 31 (10.1%) for medium, 46 (15.0%) for low, 91 (29.7%) for apparent sporadic, and 99 (32.4%) for unknown significance. The mutation-detection rates were as follows: high, 64.1%; medium, 29%; low, 10.9%; apparent sporadic, 11%; and unknown significance, 71%. Mutation-detection rates differed significantly between the high and other categories.

CONCLUSIONS AND RELEVANCE Mutation rates are high in FTLD spectrum disorders, and the proposed criteria provide a validated standard for the classification of FTLD pedigrees. The combination of pedigree criteria and mutation-detection rates has important implications for genetic counseling and testing in clinical settings.

Frontotemporal lobar degeneration (FTLD) is the second most common type of presenile dementia. Although most FTLD is sporadic, up to 50% of FTLD may be familial, and an estimated 15% to 40% is due to single-gene mutations. Mutations in MAPT, GRN, and C9orf72 account for most hereditary FTLD cases. Genetic mutations in VCP, CHMP2B, TARDBP, FUS, and PSEN1 have been documented in rare clinical cases.

Previous studies have used a variety of definitions to describe a positive family history. Chow et al used the report of FTLD disorders in first-degree relatives (FDRs) or second-degree relatives (SDRs). An epidemiologic survey used dementia before the age of 80 years in at least one FDR. Goldman et al used 4 descriptive categories: (1) autosomal dominant, (2) family aggregation, (3) a single-affected FDR with dementia or amyotrophic lateral sclerosis (ALS), and (4) noncontributory or unknown family history. A follow-up study split Goldman category 3 (single-affected FDR) according to the FDR’s age at onset. Two positive family history classes were distinguished in another study as (1) autosomal dominant and (2) 1 or more affected individuals within 1 generation or different family branches.

We are unaware of a validated family history classification system specific to FTLD that can be used in a clinical setting. The Goldman criteria, arguably the most cited in FTLD research, was not specifically designed for clinical use and was first published before the discovery of GRN and C9orf72 mutations in FTLD. This is particularly important given that, although most GRN and C9orf72 mutations are found in familial kindreds, these mutations have been reported in patients with no family history of disease. We established criteria for inheritability specifically for FTLD using a serially assessed clinical population and validated the criteria with genetic testing in the entire cohort for the 3 most common FTLD-associated genes.

Methods

Patients

All patients with a clinical diagnosis of an FTLD spectrum disorder (behavioral variant frontotemporal dementia [FTD], primary progressive aphasia, corticobasal syndrome, progressive supranuclear palsy, ALS with comorbid behavioral variant FTD or primary progressive aphasia, and excluding patients with ALS without dementia) were serially recruited during 8 years into an institutional review board–approved genetic research study at the University of Pennsylvania. Patients met published criteria for FTLD spectrum disorders. Recruitment included collection of a DNA sample and a 3-generation pedigree. All pedigrees were collected by a certified genetic counselor with experience in the field of neurodegenerative disease. Only patients originating from the Department of Neurology at the University of Pennsylvania were included in the present analysis to provide a nonbiased representation of an FTLD clinical population because outside referrals to the research study were often made based on a strong family history. Participants of all races and ethnicities were included because no data suggest that ancestry affects FTLD frequency.

Development of Family History Criteria

The initial criteria were reviewed by geneticists, neurologists, and genetic counselors and applied to an original cohort of 194 probands with FTLD. This original cohort was tested for C9orf72, MAPT, and GRN mutations. To refine the initial criteria, mutation-positive and -negative cases were reviewed, focusing on incorrectly categorized cases. Uninformative criteria providing little insight into mutation probability were eliminated, and new criteria improving categorization of mutation status were added. The original cohort was recategorized using these revised criteria, and we tested the revised criteria in a replication cohort of 112 serially recruited pedigrees of FTLD probands.

Two certified genetic counselors (E.M.W. and D.F.) independently reviewed each pedigree in both cohorts and assigned them to a family history category. Concordance for category assignment was evaluated. Modified Goldman scores were also assigned.

Genetic Testing

Genomic DNA was extracted from blood or brain tissue in all members of the cohort using commercially available reagents following manufacturer recommendations. DNA sequencing of the entire coding region of GRN and targeted regions of MAPT (exons 1 and 9-13) was performed by Beckman Coulter Genomics, as previously described. Data were analyzed with Mutation Surveyor software (Soft Genetics). C9orf72 hexanucleotide repeat expansions (defined as >30 repeats) were tested with repeat-primed polymerase chain reaction and fragment analysis, as previously described.

Results

Family History Criteria

The criteria are divided into 4 categories that indicated the likelihood of a pathogenic mutation: high, medium, low, and apparent sporadic (Table 1). A fifth category of unknown significance was used to capture pedigrees with information that was too limited or uncertain for categorization. The criteria are based primarily on the number of affected FDRs and SDRs with an FTLD spectrum disorder or another neurodegenerative disease.

Classification of Pedigrees Using Proposed Criteria

The total cohort (original and replication) consisted of 306 pedigrees, each having a proband with a diagnosis of an FTLD spectrum disorder. Demographic and clinical features of probands are summarized in Table 2 according to family history classification. Concordance rate between the 2 raters was 90.7%. Nonconsensus occurred only in low, apparent sporadic genes.
radic, and unknown significance cases; classification in the high and medium categories was 100% concordant. Nonconsensus was typically due to dementia symptoms with no medical diagnosis in key relatives.

**Genetic Testing**

Probands were tested for C9orf72, GRN, and MAPT mutations (n = 306). Mutation-detection rates for original and replication cohorts are listed in Table 3. Details on specific GRN and MAPT mutations are provided in eTable 1 in the Supplement. The Fisher exact tests comparing mutation-detection rates in the 2 cohorts were not statistically different (P = .23).

Matched demographics and mutation-detection rates of original and replication cohorts allowed us to combine these and provide an overall detection rate in our series. Of 306 clinical FTLD probands tested, pathogenic mutations were found in 47 (15.4%), including 25 C9orf72 (8.2%), 12 GRN (3.9%), and 10 MAPT (3.3%) (Table 4). The mutation-detection rate was highest in the high category, with a rate of 64.1%. This decreased to a rate of 29.0% in the medium category, 10.9% in the low category, and 1.1% in the apparent sporadic category. The Fisher exact tests found statistically different mutation-detection rates between high and each of the other categories, including medium (P = .004), and between apparent sporadic and low (P = .02). The statistical difference did not reach significance between medium and low (P = .07) and between apparent sporadic and unknown significance (P = .07). Most mutations (n = 45) were found in probands of white race with non-Hispanic ethnicity; 1 MAPT mutation was found in a proband of African American race, and 1 MAPT mutation was found in a proband of Hispanic ethnicity.

Because clinical diagnosis in FTLD can be faulty, we reexamined our findings after having considered the results of our autopsy cohort. Of 306 probands, 90 were known to be deceased, and of these 60 had autopsy results (19.6% of the cohort; see eTable 2 in the Supplement). Of this autopsy-only cohort, 14 (23.3%) had non-FTLD disease (primarily Alzheimer disease). We repeated our analysis after removing these 14 non-FTLD cases and found absolutely no changes to our findings.

We applied the modified Goldman criteria, arguably the most comparable FTLD pedigree classification system to the new criteria proposed herein, to our cohort. We found similar mutation-detection rates as a previously published cohort57 (Table 5). Our criteria for the high category identified 25 (52.2%) of our 47 mutation cases, whereas the Goldman criteria identified only 8 (17.0%) of these cases. Using the McNemar test, the above 2 percentages are significantly different (52.2% vs 17%, McNemar χ² = 15.06, P < .001). Conversely, our criteria for the apparently sporadic category included only 1 mutation case (2.1%), whereas the Goldman 4 criteria identified 7 (14.9%). Using the McNemar test, the above 2 percentages are significantly different (2.1% vs 14.9%, McNemar’s χ² = 4.17, P = .04). These observations are consistent with the possibility that the proposed criteria may have better specificity and sensitivity for categorizing the likelihood of a known FTLD genetic cause.

Table 1. Criteria for FTLD Spectrum Disorder Pedigree Categorization

<table>
<thead>
<tr>
<th>Family History Category</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>High</td>
<td>≥1 FDR with FTLD or ALS</td>
</tr>
<tr>
<td></td>
<td>1 SDR with FTLD or ALS and ≥1 FDR or SDR with FTLD, ALS, PD, AD, or dementia NOS</td>
</tr>
<tr>
<td></td>
<td>2 FDRs with PD, AD, or dementia NOS with onset at ≤65 years</td>
</tr>
<tr>
<td>Medium</td>
<td>1 SDR with FTLD or ALS</td>
</tr>
<tr>
<td></td>
<td>1 FDR with PD, AD, or dementia NOS with onset at ≤65 years</td>
</tr>
<tr>
<td>Low</td>
<td>1 FDR with PD, AD, or dementia NOS with onset at &gt;65 years</td>
</tr>
<tr>
<td>Apparent sporadic</td>
<td>≥2 SDRs with PD, AD, or dementia NOS at any age of onset</td>
</tr>
<tr>
<td>Unknown significance</td>
<td>Lack of information regarding key relatives due to adoption, early death from an unrelated cause, diagnosis or clinical details not well documented, or no diagnosis but family reports FTLD spectrum disorder symptoms</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; ALS, amyotrophic lateral sclerosis; FDR, first-degree relative; FTLD, frontotemporal lobar degeneration; NOS, not otherwise specified; PD, Parkinson disease; SDR, second-degree relative.

Only 1 criteria point needs to be met to be classified in that category. All criteria points refer to FDRs or SDRs of the proband. FTLD spectrum disorders include FTLD, primary progressive aphasia, corticobasal syndrome, progressive supranuclear palsy, FTD with ALS, and ALS with dementia. Pathologic disorders include FTD with ubiquitin-positive but t- and α-synuclein-negative inclusions, dementia lacking distinctive histopathology, tangle predominant senile dementia, Pick disease, corticobasal degeneration, progressive supranuclear palsy, neuronal intermediate filament disease, and FTLD with motor neuron disease. We included PD with or without dementia because of reports of parkinsonism in families with C9orf72, MAPT, and/or GRN mutations and families providing a history of parkinsonism without possible verification.

**Discussion**

This study ascertained mutation rate and developed family history categorization criteria to guide clinical assessment of the likelihood of FTLD pathogenic gene mutations in a large, serially ascertained clinical cohort. Clinical genetic testing is available for FTLD-associated genes, but it is not economically feasible to test every individual with FTLD in a community-based population. Given previous reports that C9orf72 expansions have been found in nonfamilial cases, decisions about genetic testing would particularly benefit from criteria that assess familial risk.1,2,23,24 We found an overall mutation rate of 15.4% and that individuals in the high likelihood group had more than twice the mutation rate as those in the medium group and almost 6 times the mutation rate as those in the low group. We conclude that mutation rate is high in FTLD and that our criteria are reasonably effective at detecting these cases.

Previous studies3-5 have estimated that 10% to 15% of FTLD cases are hereditary with autosomal dominant inheritance, and an additional 25% to 30% of cases of FTD are considered familial. Classic autosomal dominant inheritance typically relies on observing the phenotype in multiple generations, clear transmission of the disease from affected parent to affected...
offspring with equal risk among both sexes, whereas familial reflects that there is more than 1 family member with a certain phenotype. The criteria presented in this study reflect these rates, with approximately 13% categorized as high likelihood and approximately 25% categorized as medium and low likelihood. Unlike previous criteria, the classic description of autosomal dominant inheritance is not required to meet the criteria for the high category. This is because reduced penetrance, older age at onset, and death before symptom onset can hide a classic autosomal dominant condition, as reported in FTLD. Furthermore, variable clinical phenotypes within families and misdiagnosis of relatives in previous generations challenge pedigree interpretation. We also address the broad definition of familial by providing a structured ap-

### Table 2. Demographic and Clinical Characteristics of Probands for the Original, Replication, and Combined Cohorts by Category

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Original Cohort</th>
<th>Replication Cohort</th>
<th>Combined Cohort</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>No. of males/females</td>
<td>No. of males/females</td>
<td>No. of males/females</td>
</tr>
<tr>
<td>No. at onset, median (range), y</td>
<td>19/20</td>
<td>16/15</td>
<td>30/16</td>
</tr>
<tr>
<td>Ethnicity, No.</td>
<td>29/11</td>
<td>29/11</td>
<td>29/11</td>
</tr>
<tr>
<td>FTLD clinical diagnosis, No.</td>
<td>21/30</td>
<td>16/15</td>
<td>21/30</td>
</tr>
<tr>
<td>bvFTD</td>
<td>15/20</td>
<td>15/20</td>
<td>15/20</td>
</tr>
<tr>
<td>SD</td>
<td>15/20</td>
<td>15/20</td>
<td>15/20</td>
</tr>
<tr>
<td>PNFA</td>
<td>15/20</td>
<td>15/20</td>
<td>15/20</td>
</tr>
<tr>
<td>LPA</td>
<td>15/20</td>
<td>15/20</td>
<td>15/20</td>
</tr>
<tr>
<td>CBS</td>
<td>15/20</td>
<td>15/20</td>
<td>15/20</td>
</tr>
<tr>
<td>PSP</td>
<td>15/20</td>
<td>15/20</td>
<td>15/20</td>
</tr>
<tr>
<td>FTLD with ALS</td>
<td>15/20</td>
<td>15/20</td>
<td>15/20</td>
</tr>
</tbody>
</table>

**Abbreviations:** ALS, amyotrophic lateral sclerosis; bvFTD, behavioral variant frontotemporal dementia; CBS, corticobasal syndrome; FTLD, frontotemporal lobar degeneration; LPA, logopenic progressive aphasia; PNFA, progressive nonfluent aphasia; PSP, progressive supranuclear palsy; SD, semantic dementia.

### Table 3. Summary of Pedigree Classification and Mutation-Detection Rates

<table>
<thead>
<tr>
<th>Category</th>
<th>No. With Mutation/Total No. of Pedigrees</th>
<th>Detection Rate, %</th>
<th>Total No. With Mutation/Total No. of Pedigrees</th>
<th>Detection Rate, %</th>
<th>Distribution of Mutation Positive Cases, % (n = 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>19/30</td>
<td>63.3</td>
<td>25/39</td>
<td>64.1</td>
<td>53.2</td>
</tr>
<tr>
<td>Medium</td>
<td>6/20</td>
<td>30.0</td>
<td>9/31</td>
<td>29.0</td>
<td>19.1</td>
</tr>
<tr>
<td>Low</td>
<td>3/24</td>
<td>12.5</td>
<td>5/46</td>
<td>10.9</td>
<td>10.6</td>
</tr>
<tr>
<td>Apparent sporadic</td>
<td>0/55</td>
<td>0.0</td>
<td>1/91</td>
<td>1.1</td>
<td>2.1</td>
</tr>
<tr>
<td>Unknown significance</td>
<td>3/65</td>
<td>4.6</td>
<td>7/99</td>
<td>7.1</td>
<td>14.9</td>
</tr>
<tr>
<td>Total</td>
<td>31/194</td>
<td>16.0</td>
<td>47/306</td>
<td>15.4</td>
<td></td>
</tr>
</tbody>
</table>

* Fisher exact P values comparing categories: high vs medium: P = .004; medium vs low: P = .02; low vs sporadic: P = .02; and sporadic vs unknown: P = .07.

### Table 4. Detection Rate by Gene for the Combined Cohort

<table>
<thead>
<tr>
<th>Cohort</th>
<th>C9orf72 Expansion</th>
<th>GRN Mutation</th>
<th>MAPT Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (n = 39)</td>
<td>13</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Medium (n = 31)</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Low (n = 46)</td>
<td>4</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Apparent sporadic (n = 91)</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Unknown significance (n = 99)</td>
<td>5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total cohort (n = 306)</td>
<td>25 (8.2)</td>
<td>12 (3.9)</td>
<td>10 (3.3)</td>
</tr>
<tr>
<td>High and medium (n = 70)</td>
<td>15 (21.4)</td>
<td>10 (14.3)</td>
<td>9 (12.9)</td>
</tr>
<tr>
<td>Only mutation-positive cases (n = 47)</td>
<td>25 (53.2)</td>
<td>12 (25.5)</td>
<td>10 (21.3)</td>
</tr>
</tbody>
</table>
Frontotemporal Lobar Degeneration

for risk. Families with a strong family history who test negative requires clear genetic counseling because it is important to result to a family with a strong history of FTLD spectrum disorders. Explaining a negative test result to a family with a strong history of FTLD spectrum disorders requires clear genetic counseling because it is important to understand that family history alone assigns an increased risk. Families with a strong family history who test negative for C9orf72, GRN, and MAPT may benefit from additional clinical genetic testing and involvement in genetic research. Rare FTLD genes, such as VCP, TARDBP, and CHMP2B, and genetic causes of other neurodegenerative diseases, such as PSEN1 for early-onset Alzheimer disease, should be considered. Finally, unidentified genes likely contribute to the development of FTLD.

With a mutation-detection rate of 10.9%, most families in the low category will not have a mutation. However, the risk is still significant when compared with the 1.1% of the apparent sporadic group. C9orf72 was responsible for 4 of 5 autosomal dominant mutations in the low category and the single-mutation-positive apparent sporadic case. This finding is consistent with prior reports of C9orf72 expansion in sporadic families. These findings suggest that it will be important to inform patients and families about C9orf72 even when family history does not indicate a hereditary risk and for clinicians to exercise clinical judgment regarding genetic testing in patients who meet the criteria for the low or apparent sporadic category.

The category of unknown significance poses a genetic risk assessment challenge. An unknown significance category was necessary because some patients do not know medical family history information. Because relatives may have died of unrelated causes before exhibiting symptoms, a complete 3-generation pedigree is vital for providing the most accurate categorization. In this series, 32.4% of pedigrees were classified as unknown significance. Many were classified as unknown because of limited information about SDRs and thus could not be categorized definitively as apparent sporadic. In reviewing the 7 mutation-positive unknown significance pedigrees, it was noted that 4 were classified because of family stories that suggested the possibility of relatives with FTLD-like symptoms, and 2 were from FTLD with ALS probands who knew little about their family history. Clinicians may need to provide additional case-by-case insight to help guide genetic testing decisions in pedigrees of unknown significance.

Clinical factors, such as early age at onset or a diagnosis of FTLD with ALS, may influence a clinician's decision to recommend genetic testing. Earlier versions of the criteria included early age at onset (<45 years) as a criterion. However, we found that age at onset alone did not predict C9orf72, GRN, or MAPT mutation. Fourteen individuals in our cohort had age at onset before 45 years, and 5 of these (mutation rate, 35.7%) were mutation positive. All 5 mutation-positive cases were categorized as high (n = 2) or medium (n = 3) because of family history. Conversely, the clinical diagnosis of combined FTLD with ALS is likely reason enough to recommend testing of C9orf72. Of 25 FTLD with ALS probands, 7 tested positive for C9orf72 (mutation rate, 28.0%); 3 were categorized as high, 1 as low, 1 as the sole mutation-positive apparent sporadic case, and 2 as unknown significance. In addition, because mutations were found in multiple races and ethnicities, all pedigrees should be evaluated without race or ethnicity factoring into the criteria.

Although the purpose of the criteria is to help identify the likelihood of a gene mutation, none of the proposed criteria guarantee genetic status. A previous study reported a 3.2% rate of GRN mutations in apparently sporadic FTLD cases, but only FDRs were used in that study to ascertain FTLD family history. Using our criteria, which consider both FDRs and SDRs, we found no GRN mutations in cases that met the criteria for the apparent sporadic category, and the single GRN-positive case in unknown significance was categorized as such because of family-reported information that questioned the neurologic health of an SDR. On the basis of our analysis, genetic risk in FTLD cannot be determined only by FDRs; classification of apparently sporadic FTLD must include information on SDRs.

Strengths of our study include the large number of serially analyzed pedigrees, review of each pedigree independently by 2 genetic counselors (E.M.W. and D.F.), and ascertainment of genetic status in the entire cohort. A selection bias toward individuals with a strong family history is unlikely because all individuals with an FTLD spectrum disorder seen serially by a University of Pennsylvania neurologist were in-
vited to participate, and individuals referred by neurologists outside the University of Pennsylvania system because of a positive family history were excluded. Some probands in our clinical cohort do not have FTLD because the clinical diagnosis of FTLD has a reported accuracy of approximately 80%.

Although this study focuses on a clinical approach to assessing risk, in which the patient’s condition would be unknown, consideration of autopsy-based diagnosis did not change our findings. In addition, pedigrees were collected during 10 years, and some older pedigrees did not contain as detailed information as currently collected. Therefore, many of these pedigrees had to be classified as unknown significance. Because families were ascertained at a tertiary referral clinic, the cohort may not be representative of the population as a whole. With these caveats in mind, the criteria developed here seem to provide a high detection rate for known genetic causes of FTLD and thus are likely to offer useful information to help guide genetic testing decisions by clinicians.

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Acquisition of data: Wood, Falcone, Suh, Irwin, Lee, Van Deering, Grossman.
Analysis and interpretation of data: All authors.
Drafting of the manuscript: Wood, Falcone, Van Deering, Grossman.
Critical revision of the manuscript for important intellectual content: Wood, Suh, Irwin, Chen-Plotkin, Lee, Xie, Van Deering, Grossman.
Obtained funding: Van Deering, Grossman.
Study supervision: Van Deering, Grossman.

Conflict of Interest Disclosures:
None reported.

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REFERENCES


