Frontotemporal Dementia Associated With the C9ORF72 Mutation
A Unique Clinical Profile

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IMPORTANCE While advances have been made in characterizing the C9ORF72 clinical phenotype, the hallmark features that discriminate between carriers and noncarriers remain unclear.

OBJECTIVES To determine the frequency of the C9ORF72 mutation in a frontotemporal dementia (FTD) cohort and to define the clinical, neuropsychological, behavioral, and imaging features of C9ORF72 mutation carriers in comparison with noncarriers in a well-defined behavioral-variant (bv)-FTD cohort.

DESIGN, SETTING, AND PARTICIPANTS A prospective cohort study of patients assessed during a 5-year period from January 1, 2008, to December 31, 2012, at an FTD specialist referral center (FRONTIER). A total of 114 consecutive patients with FTD, FTD-amyotrophic lateral sclerosis (ALS), and corticobasal syndrome were assessed at FRONTIER. Patients with bvFTD who carried the C9ORF72 mutation (n = 10) were compared with noncarriers (n = 19) and a healthy control group (n = 35). These were matched for age, sex, and education history. Blood sampling for gene analysis was performed after informed consent was obtained.

MAIN OUTCOMES AND MEASURES Clinical, behavioral, cognitive, and neuropsychological deficits, cortical atrophy on a magnetic resonance imaging visual rating scale, and family history as quantified by the Goldman Scale.

RESULTS In a cohort of 114 FTD cases, 14 patients expressed the C9ORF72 mutation, representing a frequency rate of 34% in bvFTD and 17% in FTD-ALS. Family histories of ALS (P = .001) and psychiatric disorders (P = .02) were significantly more common in mutation carriers. The C9ORF72 carriers were also more likely to experience psychotic symptoms (P = .03). The degree of brain atrophy was significantly less in the C9ORF72 cohort, and in many the progression was slow. Presenting features of C9ORF72 carriers were compared against International Consensus Diagnostic Criteria for bvFTD, and most cases failed to satisfy criteria for probable bvFTD.

CONCLUSIONS AND RELEVANCE The C9ORF72 mutation appears to be a common cause of bvFTD. Many of the C9ORF72 carriers have a family history of ALS or psychiatric illness. Psychotic features emerged as the most discriminating clinical feature between mutation carriers and noncarriers. Progression is often slow and brain atrophy is less pronounced than in nonmutation cases of bvFTD. These findings have clinical relevance for both diagnosis and selection of patients for genetic testing.
The C9ORF72 mutation accounts for approximately one-third of cases of familial frontotemporal dementia (FTD) and familial amyotrophic lateral sclerosis (ALS). Notably, it is also positive in a percentage (4%-21%) of patients with apparently sporadic disease. Given the relatively high rate of mutations in apparently sporadic cases, it is important to delineate the clinical profile of C9ORF72 carriers.

Across the clinical spectrum of FTD, the predominant phenotype associated with the C9ORF72 mutation is behavioral-variant (bv) FTD, often occurring with features of ALS. Although primary progressive aphasia has been reported to varying degrees, additional features that characterize C9ORF72 carriers have been suggested by previous studies and include family history of ALS, parkinsonism, psychosis at presentation, a distinctive neuroanatomical signature with posterior and subcortical atrophy, and the typical frontal and temporal atrophy of FTD. However, these results have not always been consistent across studies, and with these inconsistencies come diagnostic challenges. As such, our study aimed to establish the frequency of the C9ORF72 mutation in a well-defined cohort of patients with FTD and to clarify the clinical, behavioral, neuropsychological, and imaging profile of patients with bvFTD who harbor this mutation by comparing mutation carriers with non-carriers. In contrast to previous studies, which often included historical data from numerous sources, our study has the advantage of prospectively collected comprehensive data during a 5-year period (2008-2012 inclusive) using standardized instruments. As such, this study seeks to provide a coherent description of the clinical phenotype of patients with bvFTD who have the C9ORF72 mutation.

Methods

Participants
To establish the frequency of the C9ORF72 mutation, we adopted an inclusive approach and screened consecutive patients in whom a diagnosis of bvFTD was considered as well as those with a clinical diagnosis of bvFTD, semantic dementia, nonfluent-variant primary progressive aphasia, FTD-ALS, and corticobasal syndrome as per current diagnostic guidelines. Each patient was assessed at FRONTIER, the Frontotemporal Dementia Research Group, at Neuroscience Research Australia, between January 1, 2008, and December 31, 2012. Ethical approval for this study was obtained from the ethics committees of the South Eastern Sydney and Illawarra Area Health Service and the University of New South Wales. Participants, or their person responsible, provided written informed consent in accordance with the Declaration of Helsinki. Participants did not receive a stipend.

A detailed family history was obtained and the Goldman Scale score was calculated. A score of 1 indicates at least 3 family members with FTD and/or ALS over 2 generations with 1 person being a first-degree relative of the other; score of 2, 3 or more family members with dementia and/or ALS but do not meet criteria for a score of 1; score of 3, at least 1 family member with confirmed FTD and/or ALS or early-onset dementia; score of 3.5, 1 relative with unspecified or late-onset dementia; and score of 4, no family history of FTD, ALS, or dementia. All patients completed a detailed family history questionnaire that asked about neurological and psychiatric illnesses in first-degree relatives.

In a second phase, we compared demographic, clinical, behavioral, neuropsychological, and imaging data in C9ORF72 carriers with bvFTD, noncarriers, and a healthy control group selected from a volunteer panel at FRONTIER who were matched case by case for age, sex, and education history. The bvFTD comparison group comprised those who had previously tested negative for other available genetic mutations and subsequently tested negative for the C9ORF72 mutation.

Global cognitive function at first presentation was measured using Addenbrooke’s Cognitive Examination–Revised. Disease staging was assessed with the FTD Functional Rating Scale.

Genetic Analysis
Blood sampling for genetic analysis was collected after informed consent was obtained. Genomic DNA was extracted from peripheral blood lymphocytes or frozen brain tissue according to standard procedures. Proband DNA was screened for the hexanucleotide repeat expansion in C9ORF72 by repeat-primed polymerase chain reaction based on the protocol of Renton et al. Samples were scored as expansion positive if they harbored more than 30 repeats. The C9ORF72 hexanucleotide repeat nonexpansion alleles were detected by polymerase chain reaction amplification and capillary electrophoresis.

Clinical and Behavioral Features
All patients were assessed by an experienced behavioral neurologist (J.R.H.). Core behavioral symptoms of FTD were systematically explored during the carer interview and recorded on a standardized inventory based on the Cambridge Behavioural Inventory as present or absent. Features on neurological examination of ALS, aphasia, parkinsonism, apraxia, ataxia, and eye movement abnormalities were documented.

A longitudinal approach was favored for the analysis of the clinical data as it was crucial to establish whether these features developed as the disease progressed.

Neuropsychological Assessments
The copy component of the Rey-Osterrieth Complex Figure Test and the Visual Object and Space Perception Battery assessed visuospatial abilities. The Rey Auditory Verbal Learning Test and the recall component of the Rey-Osterrieth Complex Figure Test assessed episodic memory. Tests of executive function included the Hayling Test, the FAS Verbal Fluency test, and the Trail Making Test. Semantic and phonological processing was assessed using the Sydney Language Battery. The Test for Reception of Grammar, version 2, assessed syntactic comprehension.

Neuroimaging
Patients underwent a 3T T1- and T2-weighted magnetic resonance imaging (MRI) scan. When the MRI findings were not typical for bvFTD, fludeoxyglucose F 18 positron emission to-
mography (FDG-PET) was performed. Previously validated MRI visual rating scales based on coronal T1 images were used for 5 areas: orbitofrontal cortex, anterior cingulate, temporal lobe, insula, and basal ganglia.38-40 This method was extended to include precentral and cerebellar regions. Areas of atrophy were rated on a Likert scale by a rater (E.D.) blinded to the diagnosis after appropriate training on an independent data set. Inter-rater reliability was assessed using intraclass correlation coefficient and was found to be very high (Cronbach α = 0.9). The scale ranged from 0 (no atrophy) to 4 (severe atrophy) for all of the areas except the cerebellum, which was rated on a 4-point Likert scale.

Statistical Analysis
Data were analyzed using SPSS version 20.0 statistical software (SPSS Inc). Kolmogorov-Smirnov tests determined whether variables were normally distributed. Parametric variables were compared across the groups via independent t tests. Nonparametric data were analyzed using Mann-Whitney U tests, and categorical data were compared with χ² tests. For MRI data, P < .01 was regarded as statistically significant, which allowed for multiple comparisons.

Results

Frequency of C9ORF72 Mutations
In total, 114 subjects were included in this study and screened for the C9ORF72 mutation. These included patients with FTD (n = 84), FTD-ALS (n = 23), and corticobasal syndrome (n = 7). The mutation was found in 14 patients (12%): 10 with bvFTD (n = 84), FTD-ALS (n = 23), and corticobasal syndrome (n = 7).

In the overall bvFTD cohort of 29 patients, 10 cases (34%) were mutation positive. Of the 29 patients with bvFTD, 13 (45%) had a Goldman Scale score of 3.0 or lower (indicating a strong family history), while 16 (55%) had a Goldman Scale score of 3.5 or higher (indicating a weak or absent family history). Of patients with a Goldman Scale score of 3.0 or lower, 7 (54%) were mutation positive; of those with a Goldman Scale score of 3.5 or higher, 3 (19%) were mutation positive. Of 23 patients with FTD-ALS, 4 (17%) expressed the C9ORF72 mutation. Of these 23 patients, 6 (26%) had a Goldman Scale score of 3.0 or lower, while 17 (74%) had a Goldman Scale score of 3.5 or higher. Of patients with a Goldman Score of 3.0 or lower, 3 (50%) harbored the mutation; of those with a Goldman Scale score of 3.5 or higher, 1 (6%) was mutation positive. To put this another way and as illustrated in Figure 1, 70% of mutation carriers with bvFTD and 75% of mutation carriers with FTD-ALS had a Goldman Scale score of 3.0 or lower.

Clinical and Behavioral Features
A comparison of the 10 C9ORF72 mutation carriers with bvFTD and 19 matched noncarriers revealed no significant difference between the groups across age at disease onset, disease duration at presentation, sex, education history, Addenbrooke’s Cognitive Examination–Revised score at onset, or disease severity on the FTD Functional Rating Scale score at onset (Table 1).

The behavioral and imaging features of the C9ORF72 mutation carriers were compared against the International Consensus Diagnostic Criteria for bvFTD.41 In this comparison, 4 mutation carriers (40%) did not meet diagnostic criteria for possible bvFTD (Table 2). In 1 instance, this was due to lack of a sufficient number of core features; in the other cases, the presence of exclusion features was a factor, most notably strong indicators of psychiatric disease in 1 case, prominent episodic memory impairment and visuospatial deficits in 1 case, and the likelihood of autoimmune or prion disease in another. Of the cases in which imaging was possible (8 cases [80%]), it was striking that only 3 (38%) of these fulfilled criteria for probable bvFTD. This was due almost entirely to the absence of typical imaging changes on MRI or FDG-PET. Typically abnormal MRI findings with unequivocal frontal or temporal atrophy were found in only 1 patient with the C9ORF72 mutation.

The flowchart demonstrates the frequency of C9ORF72 mutation positivity in a frontotemporal dementia cohort. Patients with frontotemporal dementia are categorized according to subtype, and mutation-positive patients are further categorized by Goldman Scale (GS) score. Twenty-eight additional patients were screened but deemed not suitable for inclusion in the study, so they were excluded. bvFTD indicates behavioral-variant frontotemporal dementia; CBS, corticobasal syndrome; FTD-MND, frontotemporal dementia with motor neuron disease; PPA-nf, nonfluent-variant primary progressive aphasia; and PPA-sv, semantic-variant primary progressive aphasia.
mutation. Imaging with FDG-PET was undertaken in 6 patients who had normal findings on MRI, and it showed a pattern typical of bvFTD in 3 cases.

Patients harboring the C9ORF72 mutation were more likely to have a family member with ALS than nonmutation carriers (6 vs 0, respectively; P = .001). Psychiatric illness in family members was also significantly more common in mutation carriers than in nonmutation carriers (4 vs 1, respectively; P = .02). Psychiatric illnesses comprised schizophrenia in 1 family member, significant depression in 2, and suicide in another.

Psychotic symptoms were more common in patients with the mutation (n = 4) than in those without, a finding that remained consistent for delusions (P = .02) and hallucinations (P = .02). By contrast, apathy in the very early stage of disease was more common in C9ORF72 noncarriers (n = 9) compared with mutation carriers (n = 1) (P = .002). As the illness progressed, apathy in the mutation carriers increased; at presentation, there was no significant difference between the groups (P = .63). Disease progression in general was slow in 5 carriers; 1 patient exhibited symptoms for 10 years prior to presentation.

The C9ORF72 mutation carriers had a higher likelihood of developing parkinsonism throughout their illness than noncarriers (P = .02). There were no significant differences in groups at presentation for the following features: aphasia (P = .48), parkinsonism (P = .67), apraxia (P = .65), or eye movement abnormalities (P > .99). Ataxia was not present in either C9ORF72 carriers or noncarriers at presentation. No C9ORF72 mutation-positive patients with pure bvFTD had developed ALS at follow-up.

**Neuropsychological Assessments**

Performance on memory, executive, and language tests failed to discriminate between C9ORF72 mutation carriers and non-mutation carriers.

### Table 1. Baseline Demographic Characteristics of Patients With Behavioral-Variant Frontotemporal Dementia, Comparing C9ORF72 Mutation Carriers, Noncarriers, and Controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Carriers (n = 10)</th>
<th>Noncarriers (n = 19)</th>
<th>Controls (n = 35)</th>
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</thead>
<tbody>
<tr>
<td>Age at onset, mean (SD), y</td>
<td>54.1 (9.4)</td>
<td>57.2 (7.8)</td>
<td>NA</td>
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<tr>
<td>Duration of symptoms at presentation, mean (SD), y</td>
<td>4.7 (3.5)</td>
<td>2.6 (1.4)</td>
<td>NA</td>
</tr>
<tr>
<td>Education history, mean (SD), y</td>
<td>10.6 (1.6)</td>
<td>11.3 (3.2)</td>
<td>11.8 (2.3)</td>
</tr>
<tr>
<td>Sex, No.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6</td>
<td>13</td>
<td>17</td>
</tr>
<tr>
<td>Female</td>
<td>4</td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td>ACE-R score, mean (SD)*</td>
<td>75.7 (8.4)</td>
<td>67.3 (22.1)</td>
<td>94.2 (3.1)</td>
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<tr>
<td>FTDFS Rasch score, mean (SD)*</td>
<td>−0.8 (1.8)</td>
<td>−1.1 (1.5)</td>
<td>NA</td>
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### Table 2. Characteristics of C9ORF72 Mutation Carriers Compared With the International Consensus Diagnostic Criteria for Behavioral-Variant Frontotemporal Dementia

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Neurodegenerative, Appropriate Progression</th>
<th>Possible bvFTD</th>
<th>bvFTD</th>
<th>Probable a</th>
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<td>Behavioral Features, No.</td>
<td>Exclusion Features b</td>
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<td>Functional Decline c</td>
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<tr>
<td>1</td>
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<td>10</td>
<td>+</td>
<td>3/6</td>
<td>+</td>
<td>−</td>
</tr>
</tbody>
</table>

**Abbreviations:** bvFTD, behavioral-variant frontotemporal dementia; MRI, magnetic resonance imaging; NA, not assessed; PET, positron emission tomography; +, present; −, absent.

* Most cases failed to meet criteria for probable bvFTD.

* Elusion criteria for bvFTD were according to the International Consensus Diagnostic Criteria. Criteria A and B must be answered negatively for any bvFTD diagnosis; criterion C can be positive for possible bvFTD but must be negative for probable bvFTD. The exclusion criteria were as follows: criterion A, pattern of deficit is better accounted for by other neurodegenerative disease or medical disorder; criterion B, behavioral disturbance is better accounted for by a psychiatric diagnosis; and criterion C, biomarkers are strongly indicative of Alzheimer disease or other neurodegenerative process.

* Impaired activities of daily living.

* Patients met exclusion criterion A. In patient 7, autoimmune or prion disease was initially thought to be most likely owing to rapidity of onset and normal imaging findings. In patient 10, prominent memory and visuospatial dysfunction made Alzheimer disease the most likely diagnosis.

* Patient met exclusion criterion B. Late-onset psychiatric illness was the primary consideration in this case because of severe delusions, hallucinations, and mood disorder.
carriers, with both groups showing comparable performance. The C9ORF72 mutation carriers scored significantly more poorly than the noncarriers on the Rey-Osterrieth Complex Figure Test copy subscale (P = .09), but the Visual Object and Space Perception Battery did not discriminate between the groups.

Neuroimaging

Patterns of Gray Matter Atrophy

Two patients were unable to undergo MRI or FDG-PET. The visual rating scores revealed variability across the groups with significant differences in each of the 7 areas assessed (Figure 2). Compared with controls, there was a trend toward more significant atrophy of the precuneus in the C9ORF72 mutation carriers (P = .02). By contrast, the C9ORF72 noncarriers had more atrophy than controls in each of the 7 areas (all P < .01). Notably, the C9ORF72 carriers showed an absence of significant atrophy of the orbitofrontal cortex, anterior cingulate, insula, and temporal pole, regions all typically involved in bvFTD. A comparison of the 2 bvFTD groups confirmed no significant difference in the precuneus region between C9ORF72 carriers and noncarriers. Significant differences were found in the orbitofrontal cortex (P = .001), anterior temporal lobe (P = .001), insula (P = .001), and anterior cingulate (P < .001), with noncarriers showing greater atrophy across these regions. Illustrative examples of MRI scans from C9ORF72 carriers and noncarriers are shown in Figure 3.

Patterns of Regional Hypometabolism

Imaging with FDG-PET was performed in 6 mutation carriers and showed an unequivocal pattern of hypometabolism in the frontal and/or temporal regions, as seen in typical bvFTD, in 3 cases. In 1 of these typical cases, hypometabolism was also present in the parietal region. In contrast, 1 atypical case revealed abnormal perfusion globally, including the parietal region, thalamus, and cerebellum. The second atypical case showed mild hypometabolism in the temporal and parietal regions, while the findings in the third were equivocal.

Discussion

This study has highlighted a constellation of characteristics that may be used to identify patients with bvFTD who have the C9ORF72 mutation. Initial indications include a high rate of psychosis in mutation carriers combined with an increased frequency of ALS in family members. The clinical course was frequently atypical with slow disease progression in one-half of patients and lack of brain atrophy on MRI in the majority, potentially leading to misdiagnosis. Our results also suggest that 2 novel clues to the presence of the mutation are lack of apathy early in the disease course and psychiatric illness in family members.

A high frequency of the C9ORF72 mutation in patients with familial bvFTD and familial FTD-ALS was identified in this study and corroborated previous reports. By contrast, the frequency rate in apparent sporadic bvFTD was considerably higher than previously reported. This high frequency in apparently sporadic disease raises the question of whether genetic mutations in sporadic cases are due to expansion instability in patients without family history or simply represent low penetrance. On a practical level, the presence of the mutation in sporadic disease has significant implications for genetic counseling, highlighting the need to establish clear markers of carrier status.

Most of our mutation carriers with bvFTD had a family history of ALS in a first-degree relative, often in conjunction with an increased frequency of psychiatric illness in family members, suggesting that the phenotype might extend beyond FTD and ALS to psychiatric disease. A recent study reported a high prevalence of mental health disorders in first-degree relatives of patients with ALS who harbored the C9ORF72 mutation. More recently, additional evidence for an expansion in genotype-phenotype correlation has emerged, with reports of the C9ORF72 mutation in other common diseases such as Alzheimer disease, Huntington disease-like syndromes, and forms of parkinsonism.

The prominence of psychotic symptoms may not be unexpected given that earlier studies have linked this feature to FTD-ALS. In this study, delusions were more frequently present than hallucinations and were mainly persecutory, negative, and paranoid, often involving the health or relationships of the patient. In 1 case, previously reported in the literature, the patient with the C9ORF72 mutation exhibited bizarre and complex delusions and hallucinations similar to those described by other groups. This was an extreme case in our cohort; in most instances, the delusions and hallucinations were more prosaic. The high frequency of psychosis contrasts with a low frequency of apathy in mutation carriers. This dissociation has not been previously described in C9ORF72 mutation carriers. Hence, the neural substrates underlying this remain unexplored.

Most C9ORF72 mutation carriers in this study lacked the typical imaging features associated with bvFTD. Comparison of C9ORF72 mutation carriers with controls showed a trend toward greater precuneus atrophy in the former group with other regions lacking significant atrophy. Other studies have highlighted differences in the degree of precuneus atrophy, in which precuneus atrophy accurately discriminated between C9ORF72 mutation and sporadic FTD. At a clinical level, an apparently normal MRI lacking overt frontal or temporal atrophy does not exclude a diagnosis of bvFTD related to the C9ORF72 mutation.

A study of 2 mutation carriers has linked bvFTD phenocopy syndrome with the C9ORF72 mutation. The most reliable features that distinguish true bvFTD cases from phenocopy cases are frontal and/or temporal atrophy on imaging, deterioration in activities of daily living, poor performance on global cognitive tests, and impairment on executive tasks. Considering our cohort of C9ORF72 mutation carriers in this context, most had functional decline in activities of daily living, all scored below the cutoff level on Addenbrooke’s Cognitive Examination-Revised, and at a group level they were impaired on tests of executive function. In brief, while this cohort of C9ORF72 mutation carriers has imaging findings similar to those of phenocopy cases, it is evident that
distinguishing features that differentiate them from the phenocopy syndrome are present.

Taken together, our findings suggest that C9ORF72 mutation carriers represent a distinct group not typical of patients with bvFTD. This finding is exemplified by the failure of most
to satisfy the International Consensus Diagnostic Criteria for bvFTD for probable, and in almost half of cases even possible, bvFTD. Given the complexity of accurate diagnosis in this cohort coupled with the high frequency of this mutation in sporadic disease, it seems paramount that the key characteristics

Box plots (whiskers indicate minimum and maximum scores) demonstrate atrophy ratings for C9ORF72 mutation carriers, noncarriers, and controls. A magnetic resonance imaging visual rating scale assessed 7 cortical regions: the orbitofrontal cortex (A), anterior cingulate (B), anterior temporal lobe (C), insula (D), basal ganglia (E), precuneus (F), and cerebellum (G). There was a statistical trend for more precuneus atrophy in the C9ORF72 mutation carriers compared with controls (P = .02). For all other regions, no statistical differences were found between C9ORF72 mutation carriers and controls. The horizontal lines represent the median (ie, 50% of the data are greater than this value). The top and bottom lines of the box represent the 75th and 25th percentiles, respectively. In some cases, the median is the same value as the 25th or 75th percentile and therefore is not shown.
of C9ORF72 mutation carriers identified in this study are used as a complement to current diagnostic criteria. Our study has clear limitations that temper the conclusions that can be drawn. Recruitment through specialist centers may introduce bias, future prospective studies would benefit from larger sample sizes, and replication of our findings in a population-based cohort would be desirable. Larger studies should include patients with other neurodegenerative and psychiatric disorders in addition to FTD. Consequently, the non-FTD phenotype of the C9ORF72 mutation may be uncovered. Collection of detailed family history data with particular emphasis on psychiatric disease would be an interesting addition to future studies. The imaging findings clearly need to be replicated with quantification of the FDG-PET abnormalities.

Conclusions

We have confirmed several characteristic features of C9ORF72 mutation carriers. We have also identified a number of novel
features in this group, including links with a family history of psychiatric illness and lack of apathy early in the disease course. These results have important clinical implications. First, this mutation is prevalent in sporadic FTLD cases, raising challenging issues for physicians in the selection of patients for genetic testing. Second, a significant number of mutation carriers do not satisfy current diagnostic criteria for bvFTD, mainly owing to lack of cortical atrophy on visual inspection. With this in mind, we propose that clinicians should consider this mutation in patients with bvFTD in the presence of the key markers identified in this study and, in particular, psychosis. Atypical MRI findings should raise suspicion of the C9ORF72 syndrome, and clinicians are advised to check for precuneus atrophy.

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Study concept and design: All authors.
Acquisition of data: Burrell, Hodges.
Analysis and interpretation of data: Devenney, Hornberger, Irish, Mioshi.

Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Devenney.

Study supervision: Kiernan, Hodges.

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REFERENCES


