C9ORF72 repeat expansion in clinical and neuropathologic frontotemporal dementia cohorts

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C9ORF72 repeat expansion in clinical and neuropathologic frontotemporal dementia cohorts

ABSTRACT

Objective: To determine the frequency of a hexanucleotide repeat expansion in C9ORF72, a gene of unknown function implicated in frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS), in Australian FTD patient cohorts and to examine the clinical and neuropathologic phenotypes associated with this expansion.

Methods: We examined a clinically ascertained FTD cohort (n = 89) and a neuropathologically ascertained cohort of frontotemporal lobar degeneration cases with TDP-43 pathology (FTLD-TDP) (n = 22) for the C9ORF72 hexanucleotide repeat expansion using a repeat primed PCR assay. All expansion-positive patients were genotyped for rs3849942, a surrogate marker for the chromosome 9p21 risk haplotype previously associated with FTD and ALS.

Results: The C9ORF72 repeat expansion was detected in 10% of patients in the clinically diagnosed cohort, rising to 29% in those with a positive family history of early-onset dementia or ALS. The prevalence of psychotic features was significantly higher in expansion-positive cases (56% vs 14%). In the pathology cohort, 41% of TDP-43-positive cases harbored the repeat expansion, and all exhibited type B pathology. One of the 17 expansion-positive probands was homozygous for the “nonrisk” G allele of rs3849942.

Conclusions: The C9ORF72 repeat expansion is a relatively common cause of FTD in Australian populations, and is especially common in those with FTD-ALS, psychotic features, and a strong family history. Detection of a repeat expansion on the 9p21 putative “nonrisk” haplotype suggests that not all mutation carriers are necessarily descended from a common founder and indicates that the expansion may have occurred on multiple haplotype backgrounds. Neurology® 2012;79:995–1001

GLOSSARY

ALS = amyotrophic lateral sclerosis; bvFTD = behavioral variant frontotemporal dementia; CBS = corticobasal syndrome; FTD = frontotemporal dementia; FTLD-TDP = frontotemporal lobar degeneration with TDP-43 pathology; LPA = logopenic aphasia; MAS = Memory and Ageing Study; PNFA = progressive nonfluent aphasia; PSP = progressive supranuclear palsy; SMD = semantic dementia.

Frontotemporal dementia (FTD) refers to a heterogeneous group of diseases characterized by personality changes, behavioral or language deficits associated with progressive loss of neurons in the frontal and temporal regions of the brain, and a range of pathologies characterized by the accumulation of intraneuronal protein inclusions.1–3 Evidence for the overlap between FTD and amyotrophic lateral sclerosis (ALS) has been strengthened by the recent finding of a hexanucleotide repeat expansion in C9ORF72, a gene of unknown function on chromosome 9p21, in Finnish and North American familial FTD and ALS cohorts.4,5 It remains unclear, however, how common this repeat expansion is in different populations, and what clinical and pathologic phenotypes are associated with this mutation. We examined the frequency of this repeat expansion in a well-characterized Australian FTD cohort according to the strength of

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reported family history of dementia or ALS and examined the clinicopathologic correlates in a pathologically defined cohort. We expected that the rate of \textit{C9ORF72} expansion would be highest in those diagnosed with both frontotemporal dementia and ALS (FTD-ALS) with a strong family history. Given the high rates of psychosis reported in people with sporadic FTD-ALS,\textsuperscript{4} we also hypothesized that psychosis might be a marker of patients with FTD carrying the repeat expansion. We genotyped all expansion-positive patients for rs3849942, a single nucleotide polymorphism used as a surrogate marker for the chromosome 9p21 risk haplotype previously associated with FTD and ALS,\textsuperscript{4,7} in order to test the hypothesis that all \textit{C9ORF72} expansion patients are descended from a common founder.

\textbf{METHODS} Subjects. We screened 2 Australian FTD cohorts: 1 clinically diagnosed cohort (n = 89) and 1 neuropathologically diagnosed cohort of frontotemporal lobar degeneration cases with TDP-43 immunopositive neuronal inclusions (FTLD-TDP) (n = 22, table 1). Three patients from the clinical cohort also had neuropathologic data, thus giving 108 independent probands in total. The number of subjects eligible for inclusion and with available DNA samples determined the sample size. Patients known to harbor a mutation in MAPT or GRN were excluded. Clinical examinations and neuropathologic analyses were performed prior to determination of \textit{C9ORF72} expansion status, thus avoiding any bias in comparison of phenotypes between expansion-positive and expansion-negative patients.

The clinical cohort was ascertained through Frontier, a multidisciplinary research clinic at Neuroscience Research Australia that assesses and follows up patients with suspected FTD and related disorders from Eastern Australia (New South Wales, Victoria, and Queensland). All patients underwent clinical, neuropsychological, behavioral, and imaging assessment between 2008 and 2011. Patients were classified according to recent internationally agreed criteria.\textsuperscript{15} Eligibility criteria were a diagnosis of behavioral variant FTD (bvFTD), corticobasal syndrome (CBS), FTD-ALS, logopenic aphasia (LPA), progressive nonfluent aphasia (PNFA), or semantic dementia (SMD). Patients with FTD-ALS were all referred with bvFTD symptoms but were discovered on clinical examination to have concurrent ALS, which was confirmed by EMG. Patients with progressive supranuclear palsy (PSP) or ALS only were not included in this study. A detailed family history was obtained in all cases and the strength of family history quantified according to the modified Goldman scale.\textsuperscript{30} Family history was scored as follows: 1 = at least 3 family members with neurologist/geriatrician-confirmed FTD or associated disorders (CBS, PSP, ALS) within 2 generations, with 1 member being a first-degree relative of the other 2; 2 = 3 or more family members with dementia or ALS but not meeting criteria for 1; 3 = 1 relative with neurologist/geriatrician-confirmed FTD or early-onset (age <65 years) dementia or ALS, or 2 relatives in same lineage with late-onset dementia; 3.5 = 1 relative with late-onset (age >65 years) or unspecified dementia; 4 = no known family history. Presence or absence of psychosis was assessed using the Cambridge Behavioral Inventory,\textsuperscript{11} asking next of kin to report frequency of 1) visual hallucinations, 2) auditory hallucinations, and 3) ideas that could not be true. Criteria for psychosis were scoring ≥2 (“a few times per week”) for at least 2 questions, or scoring ≥3 (“daily”) on any question.

We also screened healthy aged Australian Caucasian controls from the Sydney Memory and Aging Study (MAS)\textsuperscript{32} for the \textit{C9ORF72} repeat expansion (table 1). Subjects underwent detailed neuropsychiatric and medical assessments at collection (between 2005 and 2007) and have been followed up with detailed assessments biannually.

The Sydney Brain Bank neuropathologic cohort was characterized by a pathologic diagnosis of FTLD-TDP. Subjects were recruited through specialist neurologist clinics through which clinical notes were obtained. Standardized pathologic criteria were used for diagnosis and TDP-43 pathology was classified according to recent recommendations.\textsuperscript{33} We also analyzed a cohort with a pathologic diagnosis of FTLD with tau pathology (FTLD-tau), for comparison purposes (table 1).

\textbf{Standard protocol approvals, registrations, and patient consents.} The procedures in this study were approved by the University of New South Wales and South Eastern Sydney Local Health District (Northern Region) Human Research Ethics Committees. Written informed consent was collected from each participant or his or her guardian for brain donation or DNA collection.

### Table 1 Demographic information of cohorts studied

<table>
<thead>
<tr>
<th>Cohort</th>
<th>No. cases (M/F)</th>
<th>Age at onset/death, y, mean ± SD</th>
<th>Clinical/neuropathologic diagnosis</th>
<th>Family history, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>89\textsuperscript{a}(50/39)</td>
<td>O: 59.2 ± 8.7</td>
<td>28 bvFTD, 11 CBS, 11 FTD-ALS, 8 LPA, 16 PNFA, 15 SMD</td>
<td>23.6</td>
</tr>
<tr>
<td>Neuropathologic</td>
<td>22 (14/8)</td>
<td>D: 68.7 ± 9.7</td>
<td>22 FTLD-TDP43</td>
<td>36.4</td>
</tr>
<tr>
<td>Healthy aged\textsuperscript{a}</td>
<td>275 (132/143)</td>
<td>IA: 78.5 ± 4.8</td>
<td>NA</td>
<td>22.1\textsuperscript{c}</td>
</tr>
<tr>
<td>FTLD-tau\textsuperscript{a}</td>
<td>16 (9/7)</td>
<td>D: 74.7 ± 3.8</td>
<td>5 CBD, 11 PSP</td>
<td>6.3</td>
</tr>
</tbody>
</table>

Abbreviations: bvFTD = behavioral variant frontotemporal dementia; CBD = corticobasal degeneration (pathologic diagnosis); CBS = corticobasal syndrome (clinical diagnosis); D = death; FTD-ALS = frontotemporal dementia with amyotrophic lateral sclerosis; IA = age at initial assessment; LPA = logopenic aphasia; NA = not applicable; O = onset; PNFA = progressive nonfluent aphasia; PSP = progressive supranuclear palsy (pathologic diagnosis); SMD = semantic dementia.

\textsuperscript{a}Comparison cohorts.

\textsuperscript{b}Three of these cases were also present in the neuropathologically ascertained cohort.

\textsuperscript{c}Defined as any relative with early- or late-onset dementia. Family history data not available for 4 subjects.
Table 2  Clinical characteristics of C9ORF72 mutation carriersa

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age at onset, y</th>
<th>Final clinical diagnosis</th>
<th>Family history score</th>
<th>Psychosis</th>
<th>ALSb</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>F</td>
<td>53</td>
<td>bvFTD</td>
<td>4</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>25</td>
<td>M</td>
<td>60</td>
<td>FTD-ALS</td>
<td>4</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>26</td>
<td>F</td>
<td>62</td>
<td>bvFTD-ALS</td>
<td>2</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>27</td>
<td>M</td>
<td>45</td>
<td>bvFTD</td>
<td>3.5</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>28</td>
<td>M</td>
<td>49</td>
<td>bvFTD</td>
<td>3</td>
<td>No</td>
<td>(Yes)</td>
</tr>
<tr>
<td>33</td>
<td>M</td>
<td>65</td>
<td>FTD-ALS</td>
<td>3</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>78</td>
<td>M</td>
<td>48</td>
<td>bvFTD</td>
<td>2</td>
<td>No</td>
<td>(Yes)</td>
</tr>
<tr>
<td>85</td>
<td>F</td>
<td>61</td>
<td>bvFTD</td>
<td>2</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>89a</td>
<td>F</td>
<td>47</td>
<td>FTD-ALS</td>
<td>1</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Abbreviations: bvFTD = behavioural variant frontotemporal dementia; FTD-ALS = frontotemporal dementia with amyotrophic lateral sclerosis.

a Neuropathologic data detailed in table 3.

b Data in parentheses where ALS was present in a relative but absent in proband.
being 3/68 (4.4%) for scores 4 or 3.5, 2/15 (13.3%) for score 3, and 4/6 (66.7%) for scores 2 or 1.

Table 2 details the frequency of reported psychosis in expansion-positive probands and of ALS in either the proband or an affected family member. Psychosis data were available for 88/89 of the clinical cohort. There was a significant association between reported psychosis and the expansion (5/9 expansion-positive patients vs 11/79 expansion-negative patients, Fisher exact 2-tailed test $p = 0.009$). The frequency of the C9ORF72 expansion in those probands with a personal or family history of ALS was 5/17 (29.4%).

Detailed neuropathologic data from the Sydney Brain Bank were available for 9 expansion-positive patients (table 3). All cases were classified as FTLD-TDP with type B pathology. There were no significant differences between expansion-positive and expansion-negative cases (n = 13) in age at death (mean ± SEM 64.7 ± 2.5 vs 71.5 ± 2.9 years), years of disease duration (5.3 ± 1.1 vs 7.2 ± 1.2 years), or staging of atrophy (2.1 ± 0.4 vs 2.7 ± 0.3). Five of the expansion-positive patients had a positive family history of early-onset disease: of the 4 family history-negative patients, 1 reported a parent with an unspecified senile dementia, 2 reported early death of 1 or both parents, and 1 lacked sufficient family history information.

### Table 3  Neuropathologic characteristics of C9ORF72 mutation carriers

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age at death, y</th>
<th>Disease duration, y</th>
<th>Final clinical diagnosis</th>
<th>Pathologic diagnosis</th>
<th>Pathologic stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>89</td>
<td>F</td>
<td>49</td>
<td>2</td>
<td>FTD-ALS</td>
<td>FTLD-TDP type B</td>
<td>0</td>
</tr>
<tr>
<td>90</td>
<td>M</td>
<td>72</td>
<td>3</td>
<td>AD</td>
<td>FTLD-TDP type B</td>
<td>3</td>
</tr>
<tr>
<td>91</td>
<td>M</td>
<td>65</td>
<td>2</td>
<td>bvFTD</td>
<td>FTLD-TDP type B</td>
<td>2</td>
</tr>
<tr>
<td>94</td>
<td>M</td>
<td>63</td>
<td>8</td>
<td>bvFTD</td>
<td>FTLD-TDP type B</td>
<td>3</td>
</tr>
<tr>
<td>97</td>
<td>M</td>
<td>65</td>
<td>5</td>
<td>AD</td>
<td>FTLD-TDP type B</td>
<td>1</td>
</tr>
<tr>
<td>100</td>
<td>M</td>
<td>76</td>
<td>12</td>
<td>bvFTD</td>
<td>FTLD-TDP type B</td>
<td>3</td>
</tr>
<tr>
<td>101</td>
<td>F</td>
<td>65</td>
<td>5</td>
<td>FTD-ALS</td>
<td>FTLD-TDP type B</td>
<td>3</td>
</tr>
<tr>
<td>103</td>
<td>M</td>
<td>61</td>
<td>5</td>
<td>bvFTD</td>
<td>FTLD-TDP type B</td>
<td>2</td>
</tr>
<tr>
<td>107</td>
<td>M</td>
<td>66</td>
<td>6</td>
<td>AD</td>
<td>FTLD-TDP type B</td>
<td>2</td>
</tr>
</tbody>
</table>

Abbreviations: AD = Alzheimer disease; bvFTD = behavioural variant frontotemporal dementia; FTD-ALS = frontotemporal dementia with amyotrophic lateral sclerosis.

* Gross tissue atrophy scored as follows: 1, mild; 2, moderate; 3, severe; 4, maximal atrophy.14

DISCUSSION

We have confirmed, in an Australian cohort, that the C9ORF72 repeat expansion is a relatively common cause of FTD. Overall, 10.1% of clinically ascertained patients were found to harbor the expansion, but the frequency rose to 28.6% in those with a positive family history of early-onset dementia or ALS, which makes C9ORF72 a priority gene for screening in any newly identified FTD family. The clinical variant associated with the mutation was invariably bvFTD or FTD-ALS. As hypothesized, the mutation was strongly associated with the presence of psychosis. In the pathology cohort, 40.9% of TDP-43-positive cases were found to have the repeat expansion, and all exhibited type B pathology.

### Haplotype analysis of C9ORF72 expansion-positive patients

We genotyped all expansion-positive patients for rs3849942 to determine whether they shared the same haplotype as other chromosome 9-linked FTD and FTD-ALS cases reported previously.7 One patient was homozygous for the rs3849942 “nonrisk” G allele. This patient presented at age 48 with a recent history of resistant psychosis on a background of social, behavioral, and cognitive decline over several years and followed by the development of dysphagia.15 She was clinically diagnosed with FTD-ALS.

We compared the allele repeat lengths of the expansion-negative (n = 91) patients with FTD (age range 44 to 85 years) with 275 Australian cognitively assessed healthy aged controls (aged 70 to 89 years) to investigate whether allele length is associated with disease in nonexpansion FTLD cohorts. There was no significant difference in mean repeat length (cases 4.2 ± 0.2 repeats, controls 4.4 ± 0.1 repeats). One woman in the healthy aged cohort was identified with an allele corresponding to ≥38 repeats. It was not possible to accurately size this allele, either in the repeat primed PCR (due to the presence of stutter peaks) or the standard genotyping assay (due to nonamplification of extremely large alleles). This individual was last assessed at age 89 and her Mini-Mental State Examination score was found to be normal (age-adjusted score of 29/30). Both her parents died in their 70s from causes unrelated to dementia or ALS.
The discovery of the C9ORF72 mutation is a major development in the FTD and ALS fields and it is now clear that this defect accounts for a substantial proportion of cases with a strong family history of either FTD or ALS. Families with an autosomal dominant pattern of inheritance and patients with both FTD and ALS are highly likely to harbor the mutation. It should be noted, however, that the strength of family history in expansion-positive patients, as measured by the modified Goldman scale,\(^{10}\) was quite variable. In the clinical cohort, 2 of the expansion-positive patients had no affected family members and for 3 others the family history was rather weak (Goldman score 3–3.5). Screening patients with FTD-ALS but no family history may therefore be indicated, although more prevalence data from larger cohorts with family history–negative patients are required.

Phenotypic presentation of the C9ORF72 expansion appears to be predominantly the behavioral variant of FTD, while 3 of the 9 expansion-positive patients in the clinical cohort had combined FTD and ALS. Notably, none were diagnosed with a language variant of FTD. This finding is in keeping with prior observations, in that the majority of patients with PNFA show tau pathology, and in SMD the histopathologic findings are unique and distinct from those found in FTD-ALS.\(^{2}\) Moreover, ALS has been only very rarely described in association with SMD and the familial rate appears to be extremely low in this variant.\(^{16}\) Our progressive aphasia group (n = 39) included 8 with the newly recognized logopenic variant, which has been associated with underlying Alzheimer pathology.\(^{17}\) They were included because clinical differentiation from the other variants of progressive aphasia requires relatively sophisticated analysis of speech and in most centers such cases would be subsumed under the broad rubric of FTD.

Recent studies have highlighted the high rate of psychosis found in patients with familial and sporadic FTD-ALS.\(^{6,15}\) Delusions are more common than hallucinations and often take bizarre forms, such as delusions of sexual molestation and alien invasion. On the basis of this observation we hypothesized that psychotic phenomena are likely to be associated with the C9ORF72 mutation and might therefore be a clinical marker of those harboring the mutation even when a family history of FTD or ALS is absent. Overall 16 of our 89 clinically ascertained cases met criteria for psychosis, of whom 5 were found to have the expansion. Over half of patients with the expansion were psychotic compared to only 14% of expansion-negative patients. Whether this reflects the speed of progression, the distribution, or the cellular nature of the pathology remains to be established. Psychosis has also been reported as a common feature in patients with FTLD-FUS, although the latter is characterized by a young age at onset (<40 years), no family history, and caudate atrophy,\(^{2}\) all of which distinguish it from the C9ORF72 syndrome.

We identified one healthy individual who harbors an allele with ≥38 hexanucleotide repeats in C9ORF72, the longest nonexpansion allele identified so far in a cognitively normal aged control. Although it is premature to draw conclusions based on one individual, this finding indicates that the classification of all alleles >30 repeats as pathogenic, as defined by Renton et al.,\(^{3}\) may need revision. In other repeat expansion diseases, such as fragile X syndrome and Huntington disease, healthy people can harbor “premutation” alleles, which are not long enough to lead to a disease phenotype themselves but are prone to expand to a pathogenic length in the next generation.\(^{18,19}\) Large-scale longitudinal cohorts will be required to determine whether such premutation alleles exist for the C9ORF72 locus and if so, how many repeats constitutes such an allele.

One expansion-positive patient was homozygous for the “nonrisk” G allele of rs3849942, a polymorphism that has been used previously as a surrogate marker for the haplotype identified in 9p21-linked FTD-ALS families.\(^{4,7}\) Detection of a repeat expansion on the 9p21 presumed “nonrisk” haplotype suggests that mutation carriers may not all be descended from a common founder, in contrast to previous studies,\(^{4,7}\) and lends support to the hypothesis that the expansion has occurred on multiple occasions on multiple haplotype backgrounds.\(^{5}\)

Screening of the neuropathologic cohort revealed that 3 cases with a prior clinical diagnosis of Alzheimer disease (AD) were positive for the C9ORF72 repeat expansion. These patients were not systematically recruited, nor subject to an extensive standardized clinical assessment, thus the details of their clinical presentations are limited. The degree of amnesia led to a diagnosis of AD, although in each case some atypical features were present. In this context, it is of interest that recent studies have highlighted the high prevalence of episodic memory dysfunction in bvFTD that in many instances is of the severity of that seen in AD, although it is accompanied by prominent behavioral symptomatology.\(^{20,21}\) In addition, Murray et al.\(^{22}\) recently reported that 3 C9ORF72 expansion-positive patients in their neuropathologic series were clinically diagnosed with AD. On the basis of these findings it would be prudent to include C9ORF72 in mutation screens for genetic causes of clinically diagnosed AD cases.
There are a number of limitations to this study. The cohorts were determined by availability of DNA samples. Patients with a family history of FTD may have been more motivated to consent to DNA analysis. The frequency of C9ORF72 expansion in this study may therefore be higher than in unselected FTD populations. Secondly, subjects in this study were primarily of European ancestry, as to be expected in an Australian population. Future studies in non-European ancestry populations would be of use in determining the relative contribution of the C9ORF72 expansion to disease in patients with different ethnicities.

We have demonstrated that the C9ORF72 hexanucleotide repeat expansion is a common cause of FTD in Australian populations and is particularly common in patients with FTD-ALS. It is characterized clinically by a high rate of psychosis and neuropathologically by FTLD-TDP type B pathology. The pathogenic mechanism of the repeat expansion in C9ORF72 requires elucidation. It is still not certain whether neuronal loss is wholly a consequence of a pathogenic gain of function of the expansion or if loss of the normal function of C9ORF72 can contribute to disease. If the pathogenic effects are partly due to loss of C9ORF72 function, future studies would benefit from screening other regions of this gene in expansion-negative patients with FTD and ALS to determine whether null mutations are another source of disease.

AUTHOR CONTRIBUTIONS

Dr. Dobson-Stone: drafting/revising the manuscript, study concept/design, analysis/interpretation of data, acquisition of data, statistical analysis. M. Hallupp: analysis/interpretation of data, acquisition of data. L. Bartley: analysis/interpretation of data, acquisition of data. Dr. Shepherd: drafting/revising the manuscript, analysis/interpretation of data, contribution of vital reagents/tools/patents. Prof. Halliday: drafting/revising the manuscript, analysis/interpretation of data, contribution of vital reagents/tools/patents. Prof. Schofield: drafting/revising the manuscript, analysis/interpretation of data, contribution of vital reagents/tools/patents, study concept/design. Prof. Hodges: drafting/revising the manuscript, analysis/interpretation of data, contribution of vital reagents/tools/patents, study concept/design. Dr. Kwook: drafting/revising the manuscript, analysis/interpretation of data, study concept/design, study supervision/co-ordination.

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DISCLOSURE

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