FTD/ALS families are no longer orphaned

The *C9ORF72* story

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The frontotemporal degenerations (FTD) are, as a group, considered as orphan diseases. A variety of clinical syndromes are encompassed by FTD, including behavioral variant FTD (bvFTD), and semantic and nonfluent/agrammatic variants of primary progressive aphasia (PPA). Motor neuron disease or amyotrophic lateral sclerosis (ALS) may co-occur in small percentages of sporadic cases, and within families with or without FTD.

Very recently, hexanucleotide repeat expansions in the chromosome 9 open reading frame 72 (*C9ORF72*) have been indentified in families with FTD with or without ALS.[1,2] This is a notable discovery in neurodegenerative disease research of FTD over the last 14 years, along with the identification of microtubule-associated protein tau (MAPT) mutations, progranulin (PGRN) gene mutations, and the discovery of the TDP-43 protein as major component of ubiquitin-positive inclusions in FTD and ALS. The presence of the latter inclusions in both FTD and ALS has already lent strong support to the hypothesis that both FTD and ALS are part of a disease continuum, uniting FTD and ALS researchers in their goals.

The discovery of the *C9ORF72* repeat expansion has extraordinary importance for clinical practice in neurodegenerative diseases. This is due in part to its very high frequency, varying between 10% and 30% in familial FTD, and 20%–50% of familial ALS, and its broad range of clinical manifestations, including an anterograde amnestic dementia easily mislabeled as Alzheimer disease (AD) dementia, and its apparent occurrence in sporadic cases. These and other aspects of *C9ORF72* expansion repeats are emphasized in 2 studies published in this issue of *Neurology*®.[3,4]

There is considerable variation in age at onset and clinical presentation among and within families with *C9ORF72* repeat expansions.[3–5] For cohorts of patients with pure ALS, a younger onset age, comorbid FTD, and apathy or dysexecutive behavior are more common in carriers with expanded repeats.[6] Motor neuron disease occurs in approximately 20%–40% of FTD cases with expanded repeats. The behavioral variant, predominantly with apathy and loss of initiative, is the most common clinical manifestation of FTD in the studies of Sha et al.[4] and Dobson-Stone et al.[3], as well as in other series. Both of these studies also report the occurrence of psychotic symptoms. Delusions, often with bizarre content, are more common than hallucinations, and sometimes lead to an initial psychiatric diagnosis.[7] The idea that psychosis may be a clinical marker even in cases with a negative family history seems to be somewhat premature, as hallucinations or hallucinosis are reported much less frequently in other studies.[8,9]

PPA may occur as the presenting clinical manifestation of *C9ORF72* repeat expansion,[7–9] but was not encountered in the studies of Dobson-Stone et al.[3] and Sha et al.[4] Although the small sample may explain the absence of PPA size in the first,[3] the second study should have been large enough to detect such cases.[4] Also a few cases of semantic variant PPA, rarely associated with a family history, have been reported.[7,8] Parkinsonism and akinetic-rigid syndromes without resting tremor frequently occur, but are rarely the dominant presentations in patients with *C9ORF72* repeat expansions.[9,10] Some cases in Dobson-Stone et al. have the clinical diagnosis of AD dementia, and this merits special attention as it has important implications for clinical practice. The diagnosis AD dementia, also reported in other series, can be partly ascribed to the frequent occurrence of impaired episodic memory found in carriers with repeat expansions.[9,11] Despite the clinical diagnosis of AD, most of these actually were pathologically proven cases of amnestic FTD.[9,11] In the future, anterograde amnestic dementia patients with a strong family history but amyloid imaging or CSF not diagnostic of AD could be considered candidates for screening for *C9ORF72* expansions.

Another possible distinctive feature is the pattern of cerebral atrophy on MRI in patients with

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C9ORF72 repeat expansions. Sha et al. reported more parietal and bilateral thalamic atrophy in patients with FTD with expansions compared to those without. Apart from frontal, anterior temporal, and parietal atrophy, cerebellar atrophy and changes in diffusivity and fractional anisotropy in thalamic radiations have been reported.[9,10] However, the value of these distinct anatomic profiles must be interpreted cautiously in these small studies, and should be confirmed in larger studies. Finally, the presence of p62-positive, TDP-43 negative inclusions in cerebellar granular cells, and extensive ubiquilin pathology in the hippocampal molecular layer and CA regions, may neuropathologically differentiate, although not completely, FTD and ALS cases with and without repeat expansions.[7,12,13]

Every patient with FTD or ALS carrying the GGGGCC repeat expansion has proven to share the Finnish founder risk haplotype, or at least a part.[5] As apparently sporadic cases also carry the risk allele, this suggests that these cases are in fact cryptically familial cases. Incomplete penetrance is sometimes observed in families with FTD/ALS,[8] and may partly explain the occurrence of these sporadic cases. The study of Dobson-Stone et al. reports homozygosity of the "non"-risk G allele at the rs3849942 locus in a single patient carrying the repeat expansion. The authors suggest that the presence of this nonrisk allele supports the hypothesis that the expansion has occurred on multiple occasions. However, as not all patients in other studies carry the full haplotype, the authors should have tested neighboring markers before affirming this conclusion.

Genetic counseling and genetic testing for *C9ORF72* in apparently sporadic cases is an important clinical issue and should be carefully considered as tests for the repeat expansion become increasingly available. The high frequency of expanded repeats (14%) in sporadic FTD in the study of Dobson et al. may be due to some unrecognized recruitment bias in this small sample size, as larger studies have reported 5% or less. As incomplete penetrance occurs, detailed information on second- and third-degree relatives may contribute to decision-making of genetic testing in apparently sporadic cases. It would be interesting to follow-up families with apparently sporadic cases to examine whether they remain truly sporadic or other relatives become affected. Byrne et al.[14] believed that genetic testing should be restricted to patients with ALS with a family history for ALS or FTD or cognitive/behavioral impairment, while Majounie et al. believed that testing should be considered in every patient as a technique for accurate diagnosis.[5,14] Bearing in mind the huge implications for offspring, caution should also be exercised in the interpretation of *C9ORF72* expansion repeat testing in sporadic cases. Repeat expansions are occasionally found in apparent controls, and it is difficult to know whether these individuals will eventually manifest clinical features of ALS or FTD. Finally, the exact cutoff indicating a pathologic repeat expansion is still unknown. From a biological perspective, the discovery of hexanucleotide repeat expansions brings FTD and ALS into the same sphere of research as other repeat expansions, like dystrophia myotonia, spinocerebellar ataxias, fragile X syndrome/FXTAS, and Huntington disease. The location of the GGGGCC repeat in a noncoding region, and the finding of nuclear RNA foci, suggest a toxic effect of mutant RNA itself. However, the presence of RNA foci could not be confirmed in another recent study,[8] and therefore it awaits final interpretation. Future work with transgenic mice and cellular models will hopefully elucidate the pathogenic mechanisms.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. **Go to Neurology.org for full disclosures.**

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