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C9ORF72 repeat expansions in ALS and FTD patients worldwide

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In this issue of *The Lancet Neurology*, Majounie and colleagues¹ report on the global frequency of the hexanucleotide repeat expansion in *C9ORF72*, which was recently reported as the long sought-after cause of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) on chromosome 9p.^{2,3} With a total of 4,448 ALS and 1,425 FTD patients, this is the largest study aimed at determining the frequency of this mutation performed to date, and the first study to include patients diagnosed with FTD and ALS from diverse populations.

The hunt for the chromosome 9p gene started in 2006 when linkage in families in which some patients developed pure ALS, some pure FTD, and others ALS with co-morbid FTD (ALS/FTD) was first reported^{4,5}. This locus provided strong evidence for the association between ALS and FTD, which were known to share common neuropathological features and have significant clinical overlap.⁶ Recently, the genetic defect was found to be an unusual expansion in the non-coding region of the uncharacterized gene *C9ORF72*.^{2,3} ALS and FTD patients carried 700–1600 copies of a GGGGCC hexanucleotide sequence, compared to a maximum of 23 copies in controls.²

Using a diverse population of patients, Majounie and colleagues now confirm the importance of this novel gene defect in both sporadic and familial patients.¹ In sporadic ALS, 7.0% of Caucasians and 4.1% of African American patients carried expansions, whereas no mutation carriers were identified within limited cohorts of Asian, Pacific Islander, Indian and Native American patients screened. An astonishing 37.6% of all familial ALS patients carried a pathogenic repeat expansion (including one Japanese individual). The mutation frequency in FTD patients was slightly lower, though still substantial, with 6.0% in sporadic and 25.1% in familial patients of Caucasian race. Interestingly, genome-wide genetic data on 262 mutation carriers showed that all sporadic and familial patients carried the previously defined Finnish founder haplotype⁷ with an estimated age of ~1500 years. This led the authors to suggest that the hexanucleotide repeat

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Conflict of Interest

Dr. Rademakers has a patent pending on the discovery of the hexanucleotide repeat expansion in the *C9ORF72* gene.

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expansion occurred only once in human history with current global frequencies being attributable, at least in part, to the nature and scale of past human migration. Although multiple independent expansions on a fragile predisposing haplotype present an alternative hypothesis, it is intriguing that all patients, independent of the clinical presentation or ethnic origin, carry the expansion on the same genetic background.

The frequent occurrence of *C9ORF72* repeat expansions raises the important question on whom to offer genetic testing for this mutation. Recent recommendations published in this journal suggested the use of a clinical screening algorithm in which patients should only be considered for testing in the presence of a family history of ALS or FTD or when behaviorally impaired on the frontal systems behavioral scale⁸. In contrast, Majounie and colleagues argue for genetic screening of ALS and FTD patients regardless of family history, to assist in an accurate diagnosis and improved disease management.¹ While a strict algorithm may have high sensitivity in well characterized populations, accurate and detailed information on family history is often unavailable and the 6–7% of sporadic patients carrying *C9ORF72* repeat expansions in Caucasian populations reported by Majounie and colleagues are a testament to the notion that genetic screening should be considered in all patients. Moreover, the clinical phenotype associated with these expansions extends beyond the FTD/ALS spectrum, and includes Alzheimer-type dementia as recently reported^{9,10}, suggesting that genetic testing across dementia populations could further aid in the differential diagnosis of dementia.

A note of caution is required, however, especially when considering predictive genetic testing in *C9ORF72* families. Our current understanding of the disease penetrance and range of clinical phenotypes associated with this mutation is limited and the minimal repeat-size required for pathogenicity unknown^{1–3,8,10}. In fact, accurate sizing of the GC-rich *C9ORF72* repeat is a major issue that has not yet been satisfactorily studied or discussed. As in all *C9ORF72* mutation screenings performed to date, Majounie and colleagues¹ use a repeat-primed PCR method to determine the presence of a pathogenic repeat expansion. This method is semi-quantitative at best and does not provide information on the actual repeat-size. Future studies focused on Southern blotting of large patient series will be essential to establish cut-off sizes indicative of a pathogenic mutation, to clarify the role of intermediate repeat-sizes in FTD and ALS (23–700 repeats) and to appreciate the extent of intra-individual repeat-size tissue variability.

It's still early days and many important questions related to this mutation remain. However, the implication of a single genetic defect in a substantial proportion of sporadic and familial ALS and FTD patients from diverse populations, as confirmed in this study, is expected to greatly impact FTD/ALS research priorities in the years to come.

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