HHS Public Access

Author manuscript

*Nat Rev Neurol*. Author manuscript; available in PMC 2015 June 01.

Published in final edited form as:

*Nat Rev Neurol*. ; 8(5): 249–250. doi:10.1038/nrneurol.2012.58.

# The *C9orf72* hexanucleotide repeat expansion in FTD and ALS

**Eileen H. Bigio**

Department of Pathology and Northwestern University Alzheimer Disease Center, Northwestern University Feinberg School of Medicine, 710 North Fairbanks Court, Olson 2-458, Chicago, IL 60611, USA.

Eileen H. Bigio: e-bigio@northwestern.edu

## Abstract

Two new studies provide strong evidence for the link between mutations in the *C9orf72* gene and familial frontotemporal dementia or amyotrophic lateral sclerosis. One of the papers presents some unique associations between clinical features and *C9orf72* mutation, and raises questions regarding the specificity of some previously reported pathological findings.

The clinical overlap between amyotrophic lateral sclerosis (ALS), or motor neuron disease (MND), and frontotemporal dementia (FTD) has been known for many years. The long-sought mutation in FTD and ALS cases linked to chromosome 9p was reported in two *Neuron* papers in September 2011.[1,2] The mutation comprises expansion of a unique hexanucleotide repeat in a noncoding region of the chromosome 9 open reading frame 72 (*C9orf72*) gene, which encodes a protein of unknown function. Two new publications[3,4] join several recently published studies that describe the clinical and pathological phenotype of frontotemporal lobar degeneration (FTLD) with or without ALS, or ALS alone, associated with *C9orf72* repeat expansion.

The syndromes resulting from the overlapping diseases are referred to clinically as FTD–ALS or FTD–MND, and are designated pathologically as FTLD with MND (FTLD–MND). Most cases are linked pathologically by inclusions composed of aggregates of abnormal TAR DNA-binding protein 43 (TDP 43). The distribution of TDP pathology varies, usually with specific clinical and genetic associations.[5,6] Patients with TDP type A may have granulin (*GRN*) mutations, are equally likely to present with behavioural variant FTD (bvFTD) or primary progressive aphasia (PPA), rarely have ALS, and have TDP 43-positive cytoplasmic and intranuclear inclusions, predominantly in the upper cortex. Patients with TDP type B sometimes have linkage to chromosome 9p, most often present with bvFTD with or without ALS, and have TDP 43-positive cytoplasmic inclusions in all layers of the cortex. Patients with TDP type C most often present with PPA (but up to one-third present with bvFTD), do not usually have ALS, and have TDP 43-positive long neurites in the upper cortex.[6]



**Competing interests**

The author declares no competing interests.

The two most recent studies to shed light on the link between the above disorders and *C9orf72* mutations were conducted in the Netherlands and the UK.[3,4] In the Netherlands study, Simon-Sanchez *et al.* screened 353 patients with bvFTD or PPA, with or without ALS, and 522 controls.[3] Patients with FTLD-tau pathology with or without microtubule-associated protein tau (*MAPT*) mutations, and patients with *GRN* mutations, were assumed not to harbour *C9orf72* mutations and were, therefore, excluded. In the UK study, Snowden *et al.* screened for *C9orf72* mutations in 398 patients with bvFTD or PPA (progressive nonfluent aphasia or semantic dementia), 55 of whom also had MND.[4]

Simon-Sanchez *et al.* found *C9orf72* mutations in 42 patients (12%) in the FTD cohort; among these patients, 34 had bvFTD, eight had PPA, and seven had ALS. *C9orf72* repeat expansion was also detected in three of the 522 controls.[3] On the basis of these results, 53.8% of cases of familial FTD in the Netherlands are now explained: 17.8% have *C9orf72* mutations, 22.1% have *MAPT* mutations, and 13.9% have *GRN* mutations.[3] Snowden *et al.* found *C9orf72* mutations in 32 patients (8%) in their cohort, which included 19 FTD cases, nine FTD–MND cases, three progressive nonfluent aphasia cases, and one semantic dementia case.[4]

In both studies, bvFTD predominated over PPA in mutation carriers with cognitive impairment.[3,4] In the UK study, 38% of mutation carriers presented with psychosis.[4] With a few exceptions, most other studies have noted delusions only occasionally or not at all in patients with *C9orf72* mutations. Whether this feature is unique to the UK cohort, or whether psychiatric signs, delusions or psychosis will be found in more patients with *C9orf72* mutations if more specifically sought, remains to be seen.

The *C9orf72* mutation seems to be inherited in an autosomal dominant manner, but reduced penetrance is evident, in that some obligate carriers do not develop ALS or dementia.[3,7] In both of the new studies, the *C9orf72* mutation was more common in patients with ALS and in those with a family history of ALS or FTD than in individuals without these characteristics,[3,4] similar to another recent report.[7] Should screening for the *C9orf72* mutation be considered, targeting of individuals with ALS plus dementia who have a family history of ALS or FTD would, therefore, be a reasonable approach.

All previous studies of patients with *C9orf72* mutations or chromosome 9p linkage have reported FTLD-TDP or ALS pathology.[8,9] Some studies found a predominance of TDP type B pathology, the type most often associated with ALS, whereas others reported a heterogeneity of TDP types including some apparently type A, the type most often associated with *GRN* mutations. Conversely, in the UK study, a brain autopsy on one patient with a *C9orf72* mutation revealed FTLD-tau with corticobasal degeneration (CBD),[4] representing the only report of a diagnosis other than FTLD-TDP or ALS with this mutation. This finding, if correct, calls into question the specificity of the *C9orf72* mutation for FTLD-TDP. Chromosome 9p linkage and a subsequent finding of *C9orf72* hexanucleotide repeat expansion has previously only been reported in cases of ALS, with or without dementia. However, exclusion of patients with *MAPT* and *GRN* mutations or FTLD-tau pathology, as in the Netherlands study,[3] might cause ‘outliers’ as seen in the UK study to be missed.

Both studies report the results of immunostaining using an antibody to the C9orf72 protein. The two groups found diffuse and granular cytoplasmic labelling of neurons in areas affected by pathology in FTLD-TDP and ALS, but this feature was present in all cases, including controls, and was considered to be physiological.[3,4] C9orf72-positive hippocampal CA4 synaptic arborizations extending into areas CA2–3 were also observed. The Netherlands group found this labelling in cases of FTD with and without the repeat expansion.[3] By contrast, the UK group found this labelling to be strong in healthy controls, variably preserved in cases of MND, but decreased or absent in some patients with FTLD and not markedly different in those with *C9orf72* mutations.[4]

Both groups found p62-positive TDP 43-negative inclusions in cerebellar granular neurons,[3,4] as has previously been reported.[8,9] These inclusions were not labelled with the C9orf72-specific antibody; the identity and significance of the inclusion protein, therefore, remain unknown. Although previously thought to be specific for *C9orf72* cases, these inclusions were not found by Snowden *et al.* in the *C9orf72* mutation carrier with FTLD-tau (CBD) pathology, and were detected in three cases of FTLD-TDP seemingly without a *C9orf72* mutation.[4] If the absence of a repeat expansion in these three cases proves to be true, the inclusions may not be specific to cases with *C9orf72* repeat expansion, as has been previously reported.[8,9]

RNA misprocessing might be the pathophysiological link between *C9orf72* mutation and FTD–ALS, as intranuclear RNA foci have been observed in cases with *C9orf72* repeat expansion.[1] Simon-Sanchez *et al.* were unable to confirm this finding,[3] possibly owing to use of a different RNA probe from that employed in previous studies. Other disorders with repeat expansion are associated with RNA misprocessing, which has provided researchers with testable potential therapeutic targets.

These two new reports confirm that *C9orf72* repeat expansion is common in familial cases of FTD–ALS.[3,4] Unique findings from the UK study, such as the association of the mutation with psychosis, remain to be confirmed by others.[4] As more is learned about the clinical and pathological characteristics of this genetic FTLD subtype, it is hoped that the threads linking ALS and FTD will be better understood, ultimately enabling the design of a targeted therapy for these disorders.

## References

1. DeJesus-Hernandez M, et al. Expanded GGGGCC hexanucleotide repeat in non-coding region of *C9ORF72* causes chromosome 9p-linked FTD and ALS. Neuron. 2011; 72:245–256. [PubMed: 21944778]
2. Renton AE, et al. A nexanucleotide repeat expansion in *C9ORF72* is the cause of chromosome 9p21-linked ALS–FTD. Neuron. 2011; 71:257–268. [PubMed: 21944779]
3. Simon-Sanchez J, et al. The clinical and pathological phenotype of *C9orf72* hexanucleotide repeat expansions. Brain. http://dx.doi.org/10.1093/brain/awr353.
4. Snowden JS, et al. Distinct clinical and pathological characteristics of frontotemporal dementia associated with *C9ORF72* mutations. Brain. http://dx.doi.org/10.1093/brain/awr355.
5. Mackenzie IR, et al. Heterogeneity of ubiquitin pathology in frontotemporal lobar degeneration: classification and relation to clinical phenotype. Acta Neuropathol. 2006; 112:539–549. [PubMed: 17021754]

6. Mackenzie IR, et al. A harmonized classification system for FTLD-TDP pathology. Acta Neuropathol. 2011; 122:111–113. [PubMed: 21644037]

7. Byrne S, et al. Cognitive and clinical characteristics of patients with amyotrophic lateral sclerosis carrying a *C9orf72* repeat expansion: a population-based cohort study. Lancet Neurol. 2012; 11:232–240. [PubMed: 22305801]

8. Murray ME, et al. Clinical and neuropathologic heterogeneity of c9FTD/ALS associated with hexanucleotide repeat expansion in *C9ORF72*. Acta Neuropathol. 2011; 122:673–690. [PubMed: 22083254]

9. Stewart H, et al. Clinical and pathological features of amyotrophic lateral sclerosis caused by mutation in the *C9ORF72* gene of chromosome 9p. Acta Neuropathol. 2012; 123:409–417. [PubMed: 22228244]