LETTER TO THE EDITOR

Reply: Are CHCHD10 mutations indeed associated with familial amyotrophic lateral sclerosis?

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Sir,

In a Letter to the Editor submitted to Brain, van Rheenen and colleagues (2014) critically appraise the involvement of the CHCHD10 gene in familial amyotrophic lateral sclerosis (ALS). They also question the involvement of CHCHD10 in frontotemporal dementia (FTD)-ALS when they state that ‘the assumption that the novel variants indeed cause ALS/FTD in these families is derived from the fact that these variants are well conserved across different species’. The authors outline a number of methodological concerns in their letter and we welcome this opportunity to clarify some of the points that were raised. In our original article published in Brain, we described a novel heterozygous CHCHD10 mutation (c.176C>T; p.Ser59Leu) in a large French family with a late-onset phenotype including cognitive decline resembling FTD, motor neuron disease, cerebellar ataxia and mitochondrial myopathy with multiple mtDNA deletions (Bannwarth et al., 2014). We found the same pathogenic mutation in one family among a cohort of 21 families with pathologically proven FTD-ALS. These results provide solid evidence that CHCHD10 is a novel gene responsible for FTD-ALS and it is not correct to say that the pathogenicity of p.Ser59Leu variant is based on the conservation of the serine residue at position 59. Indeed, the segregation within the large French family is the major evidence for the pathogenicity of this mutation that was present in the eight patients tested and absent in two healthy individuals with normal neurological examination at 79 and 69 years of age, respectively (Bannwarth et al., 2014). Cristae alterations and fragmentation of the mitochondrial network found in HeLa cells overexpressing the CHCHD10599R mutant are similar to those observed in patient fibroblasts and these results also provide...
strong arguments for the deleterious effect of the p.Ser59Leu variant (Bannwarth et al., 2014). Secondarily, we sequenced CHCHD10 in a cohort of 94 FTD-ALS patients and found a novel heterozygous missense variant (c.100C>T; p.Pro34Ser) in two unrelated individuals (Chaussenot et al., 2014). We fully agree that putative pathogenicity of this novel substitution in this second article, which van Rheenen and colleagues do not mention, was based on the conservation of the proline residue at position 34 and on the absence of this variant in public single-nucleotide polymorphism databases and in 200 ethnically and geographically matched control alleles (Chaussenot et al., 2014). To further elucidate the deleterious consequences of these reported CHCHD10 variants, we have performed a number of functional tests and the pathophysiological pathways that we have uncovered clearly indicate a biologically plausible link with neurodegeneration (unpublished data).

Following the involvement of CHCHD10 in FTD-ALS, Mueller et al. (2014) analysed 102 German and 26 Nordic patients with pure ALS. Whole-exome sequencing had been previously performed in this cohort and screening for CHCHD10 mutations led to the identification of two novel variants in three families (Mueller et al., 2014). The first variant (c.44C>A; p.Arg15Leu) was found in two families and the second one (c.197C>A; p.Gly66Val) was found once. We agree with van Rheenen and colleagues that this study does not provide genetic evidence of CHCHD10 involvement in pure familial ALS. Both variants affect highly conserved amino acid residues and were not found in public and in-house databases. However, no functional studies were available and the segregation of the p.Arg15Leu variant in both families suggested an autosomal dominant mode of inheritance with incomplete penetrance, based on healthy individuals transmitting the disease. It should nevertheless be noted that the age of unaffected individuals, who are still alive or not, is not mentioned. In our reply to this letter, we clearly precised that functional studies and further analyses of larger series are needed to confirm the association of CHCHD10 with ALS. More recently, Johnson and colleagues analysed a cohort of 85 patients with familial ALS from different geographical backgrounds (Johnson et al., 2014). They found the p.Arg15Leu variant in a large family and in two unrelated cases with familial ALS.

Genetic approaches that combine linkage analysis with whole exome or targeted sequencing remain the most successful strategy for finding genes responsible for ALS, but they are strongly dependent on family size and on the number of individuals available for analysis. To our knowledge, the 22q11.23 locus encompassing CHCHD10 has not been identified as a potential locus for either FTD or ALS (Ferrari et al., 2014; Leblond et al., 2014), but it must be noted that genome-wide association studies have so far failed to identify common variants contributing to the aetiology of these diseases (Leblond et al. 2014). To date, both the association of CHCHD10 with FTD-ALS and the identification of recurrent variants in ALS families from different geographical origins are solid observations that substantiate a causal genetic link between CHCHD10 mutations and the development of ALS, at least in a subset of patients. Elucidating the cellular pathways disrupted by the expression of CHCHD10 mutant alleles will be crucial in clarifying the role of mitochondrial dysfunction, not only in ALS, but also more broadly in other more complex neurodegenerative disorders.

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**References**


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