Reply: Is CHCHD10 Pro34Ser pathogenic for frontotemporal dementia and amyotrophic lateral sclerosis?

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Sir,

We and others have identified different CHCHD10 mutations responsible for mitochondrial DNA instability disorder, early-onset mitochondrial myopathy, frontotemporal dementia-amyotrophic lateral sclerosis (FTD-ALS) clinical spectrum and late-onset spinal motor neuropathy (SMAJ) (Bannwarth et al., 2014, 2015; Chaussenot et al., 2014; Johnson et al., 2014; Müller et al., 2014; Ajroud-Driss et al., 2015; Kurzwelly et al., 2015; Penttilä et al., 2015; Ronchi et al., 2015). The letter from Dobston-Stone et al., (2015) asks the question about the pathogenicity of the Pro34Ser variant that was previously identified by our group in two unrelated French patients with FTD-ALS (Chaussenot et al., 2014) and by Ronchi et al. (2015) in one Italian patient with ALS. We read with interest this study reporting the screening of CHCHD10 in several Australian cohorts that leads to the identification of the Pro34Ser variant in (i) two unrelated patients with familial FTD; (ii) five individuals with early-onset dementia among a cohort of 132 patients whereas this variant was not found in another cohort of 145 Australian patients with FTD; and (iii) 9/807 aged individuals, three of whom only showed mild cognitive impairment (MCI). In this report, several observations raise the question about the deleterious effect of the Pro34Ser variant. First, Proband 2 with familial FTD had two sisters who developed...
dementia, only one of whom carried the variant. As mentioned by the authors, it is possible that the Pro34Ser-negative patient is a phenocopy. No full clinical assessment was available for the two sisters but the phenotype of the Pro34Ser-negative patient seemed different with significant memory impairment and no frontal features. Secondly, one FTD patient from the early-onset dementia cohort also harboured the C9orf72 repeat expansion that is responsible for FTD and ALS (DeJesus-Hernandez et al., 2011; Renton et al., 2011). This patient had neuropathologically confirmed TARDBP (previously known as TDP-43) inclusions that are pathologic hallmark of both ALS and FTD (Neumann et al., 2006). We do not know yet whether TARDBP inclusions are observed in patients harbouring CHCHD10 mutations, and whether CHCHD10 protein may be found in neuronal inclusions. However, several studies suggest an oligogenic pathogenesis of ALS with the identification of patients harbouring both C9orf72 expansions and a mutation in another ALS and/or FTD associated gene (van Blitterswijk et al., 2012, 2013). Double mutation carriers generally have an early disease onset and the FTD patient carrying both C9orf72 expansion and Pro34Ser CHCHD10 variant developed the first symptoms at 43 years of age (Dobson-Stone et al., 2013). Although we can not exclude that the presence of both mutations might be coincidental, a more plausible explanation is that C9orf72 expansion and Pro34Ser CHCHD10 variant could have additive effects in disease expressivity and possibly in the early onset disorder. Lastly, the identification of the Pro34Ser variant in 9/807 aged individuals, six of whom were non-demented in their seventies and eighties is another argument against its deleterious effect. However, C9orf72 expansions that appear to account for 34% of familial ALS and 26% of familial FTD have also been identified in control individuals and several studies reported incomplete penetrance (van Blitterswijk et al., 2012). Regarding CHCHD10, Müller et al. (2014) also described incomplete penetrance in two German ALS families carrying the p.Arg15Leu mutation.

In conclusion, we agree with Dobson-Stone and colleagues that ‘none of these observations in isolation would be sufficient evidence to discount the pathogenicity of the CHCHD10 Pro34Ser variant’. Only functional studies will determine the deleterious effect of Pro34Ser and other CHCHD10 variants. We identified the CHCHD10 Ser59Leu mutation in the original family with a late-onset phenotype including motor neuron disease, FTD, cerebellar ataxia and mitochondrial myopathy (Bannwarth et al., 2014). Patient fibroblasts presented with respiratory chain deficiency, mitochondrial ultrastructural alterations and fragmentation of the mitochondrial network. Expression of the CHCHD10 Ser59Leu mutant allele in HeLa cells led to fragmentation of the mitochondrial network and ultrastructural major abnormalities including loss, disorganization and dilatation of cristae. In a submitted manuscript, we show that the expression of the CHCHD10 Pro34Ser mutant allele leads to the same alterations as those observed with the Ser59Leu mutation, demonstrating the pathogenicity of this variant that seems to predominate in Australian patients. Further studies will be necessary to clarify the intriguing hypothesis that this predominance could be due to a mutational founder effect.

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**References**


