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LETTER TO THE EDITOR

CHCHD10 Pro34Ser is not a highly penetrant pathogenic variant for amyotrophic lateral sclerosis and frontotemporal dementia

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Sir,

Recently, Bannwarth and colleagues reported that mutations in *CHCHD10* were causative of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), with compelling segregation data and functional investigations well supporting these findings (Bannwarth *et al.*, 2014).

In a number of follow-up studies, *CHCHD10* was screened in ALS, FTD and other neurodegenerative disorder cohorts—including autosomal dominant mitochondrial myopathy and late-onset spinal motor neuronopathy—and novel putative disease-causing variants were identified (Chaussenot *et al.*, 2014; Johnson *et al.*, 2014; Müller *et al.*, 2014; Ajroud-Driss *et al.*, 2015; Chiò *et al.*, 2015; Kurzwelly *et al.*, 2015; Penttilä *et al.*, 2015; Ronchi *et al.*, 2015; Zhang *et al.*, 2015). In particular, one variant, the Pro34Ser in exon 2, was reported by three studies to be present in >1% of ALS and FTD cases in Caucasian populations (Chaussenot *et al.*, 2014; Chiò *et al.*, 2015; Ronchi *et al.*, 2015). In the context of ALS, this is a remarkable finding and would make the *CHCHD10* Pro34Ser variant the second most frequent known disease-causing variant of Caucasian ALS, after the hexanucleotide expansion in *C9orf72* (DeJesus-Hernandez *et al.*, 2011; Renton *et al.*, 2011).

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We screened our cohort of 547 UK patients (452 ALS and 95 FTD) for mutations in the four exons of *CHCHD10* by Sanger sequencing. We identified no novel variants, but did find the Ser77Gly variant (rs370872556) in a case of ALS, the Tyr135His variant (rs145649831) in a case of ALS-FTD and the Pro34Ser variant in five individuals (four ALS, one FTD), the latter representing 0.91% of cases. None of the five cases had a positive family history of ALS or FTD, all were Caucasian and one was also carrier of a *C9orf72* expansion (with over 1500 hexanucleotide repeats, as measured by Southern blot). As our UK cohort was composed of > 90% Caucasian individuals, in order to compare these results to population-matched controls, we used data from the UK10K Project (http://www.uk10k.org), finding the Pro34Ser variant to be present in 29 of 4777 individuals (0.61%). Statistical analysis confers the Pro34Ser an odds ratio of 1.51 (95% confidence interval: 0.58, 3.9; $P = 0.3965$). The Tyr135His variant was present in 4 of 5232 individuals (0.076%) from the UK10K, and the Ser77Gly, which was found in an individual with Cuban origin in our cohort, was absent from UK10K, but present in 0.2–0.8% of cases in African samples reported in Exome Variant Server and ExAC databases.

The Pro34Ser variant has previously been considered pathogenic, yet it is present in 0.19% of ExAC multiethnic controls, and, when considering only European-origin controls, the frequency increases to 0.6%, which matches the data reported here from the UK control population. This, and lack of segregation data, has recently led Dobson-Stone and colleagues to question this variant's pathogenicity (Dobson-Stone *et al.*, 2015; Zhang *et al.*, 2015). Our results do not support the Pro34Ser as being a penetrant pathogenic variant.

The Tyr135His and Ser77Gly variants have not previously been reported to be associated with ALS and FTD and further data will help clarify their role in disease, which currently remains uncertain.

Specific variants in known pathogenic genes for neurodegenerative disorders have been found to not be penetrant or sufficient for development of disease, but to act as risk factors (Coppola *et al.*, 2012; Fratta *et al.*, 2014). Although our data do not currently support a role for Pro34Ser as a risk factor, larger numbers will be necessary to understand whether this variant does confer a mild increase in risk. Functional data, as proposed by Bannwarth and colleagues (2015), will be extremely valuable, and have previously been able to support the role of certain variants as risk factors for ALS (Coppola *et al.*, 2012; Wu *et al.*, 2012; Figley *et al.*, 2014; Boopathy *et al.*, 2015).

It is important to note that exon 2 of *CHCHD10* has very poor coverage in exome sequencing, a factor that has likely contributed to the absence of common variants in this region from some of the major public databases. Whole genome sequencing data on the other hand appears to be more reliable in our analyses.

In conclusion, our data do not support a highly penetrant pathogenicity of the *CHCHD10* Pro34Ser variant. This finding has significant implications for genetic diagnostics and counselling, given the frequency of Pro34Ser and the increasingly extensive use of genetic sequencing in the clinical context.

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