LETTER TO THE EDITOR

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

Samir Abdelkarim,1,* Sarah Morgan,2,* Vincent Plagnol,3 Ching-Hua Lu,4,5 Gary Adamson,6 Robin Howard,7 Andrea Malaspina,5 Richard Orrell,4 Nikhil Sharma,4 Katie Sidle,2 Jan Clarke,7 Nick C. Fox,8 Martin N. Rossor,8 Jason D. Warren,8 Camilla N. Clark,8 Jonathan D. Rohrer,8 Elizabeth M. C. Fisher,1 Simon Mead,6 Alan Pittman2 and Pietro Fratta1,4

*These authors contributed equally to this work.
1 Department of Neurodegenerative Disease, University College London Institute of Neurology, Queen Square, London WC1N 3BG, UK
2 Department of Molecular Neuroscience, University College London Institute of Neurology, Queen Square, London WC1N 3BG, UK
3 UCL Genetics Institute, Department of Genetics, Environment and Evolution, UCL, London WC1E 6BT, UK
4 Sobell Department of Motor Neuroscience and Movement Disorders, Queen Square, London, WC1N 3BG, UK
5 Centre for Neuroscience and Trauma, Blizard Institute, Queen Mary University of London, North-East London and Essex Regional MND Care Centre, E1 2AT, UK
6 Medical Research Council Prion Unit, Department of Neurodegenerative Disease, University College London Institute of Neurology, Queen Square, London, WC1N 3BG, UK
7 National Hospital for Neurology and Neurosurgery, Queen Square, London, WC1N 3BG, UK
8 Dementia Research Centre, Department of Neurodegenerative Disease, University College London Institute of Neurology, Queen Square, London WC1N 3BG, UK

Correspondence to: Pietro Fratta,
Sobell Department of Motor Neuroscience and Movement Disorders,
Institute of Neurology,
University College London
Queen Square
London WC1N 3BG, UK
E-mail: p.fratta@ucl.ac.uk

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; Kurzweily 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).
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 (rs3707872556) 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 multi-ethnic 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.

**Acknowledgements**

We are grateful to all patients and family members who agreed to DNA donation, without which these studies would have been impossible. We are grateful the UK10K Project (http://www.uk10k.org).

**Funding**

P.F. is recipient of a Lady Edith Wolfson Medical Research Council/Motor Neurone Disease Association Clinician Scientist Fellowship and is funded by the National Institute for Health Research University College London Hospitals Biomedical Research Centre. J.D.R., J.D.W., N.C.F., C.N.C. and M.N.R acknowledge the support of the NIHR Queen Square Dementia Biomedical Research Unit, Leonard Wolfson Experimental Neurology Centre, and the University College London Hospitals NHS Trust Biomedical Research Centre. The Dementia Research Centre at UCL is an Alzheimer’s Research UK coordinating centre and has also received equipment funded by Alzheimer’s Research UK and Brain Research Trust. J.D.R. is funded by an NIHR Rare Disease TRC Fellowship. J.D.W. is funded by a Wellcome Trust Senior Clinical Fellowship (091673/Z/10/Z). N.C.F. and M.N.R. are NIHR Senior Investigators.

**References**


