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LETTER TO THE EDITOR

Mutations in the *CHCHD10* gene are a common cause of familial amyotrophic lateral sclerosis

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Sir,

A recent study by Bannwarth and colleagues has shown that variation in the *CHCHD10* gene is a cause of familial amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) (Bannwarth *et al.*, 2014). The study identified a c.176C > T (p.Ser59Leu, NM_213720.1) missense mutation in a multi-generational kindred. In the present study, we performed genome sequencing of four affected individuals from a large ALS family (USALS#5). This identified a G to T transversion at position c.44 (chr22:24,109,778, hg19) that segregated with disease within this pedigree and leads to a p.R15L amino acid change in exon two of the CHCHD10 mitochondrial protein. Previous attempts to identify the causative mutation in this family using an exome sequencing approach failed to identify this variant due to poor sequence coverage in this genomic region. The variant was not described as a human polymorphism in the Single Nucleotide Polymorphism (SNP) database (http://www.ncbi.nlm.nih.gov/SNP/, build 141) and was not found in 1158 control individuals of the Exome Sequencing Project (http://snp.gs.washington.edu/SeattleSeqAnnotation138/).

To further assess the mutation burden in patients, we Sanger sequenced all exons of *CHCHD10* in an additional series of 84 patients diagnosed with familial ALS according to the El Escorial criteria (Brooks, 1994). These samples did not carry the *C9orf72* hexanucleotide repeat expansion or known mutations in ALS genes including *SOD1*, *TARDBP*, *FUS*, *VCP*, *PFN1*, *UBQLN1*, *MATR3*, *SQSTM1*, *OPTN*, and *HNPNPA2B1* (Renton *et al.*, 2014). The ethical review boards at each institution approved the study, and all participants provided informed consent.

Our mutational screening of *CHCHD10* identified the same p.R15L mutation discovered in the USALS#5 family in two additional familial ALS cases (www.coriell.org, ND10928 and ND11809). Analysis of genome-wide SNP chip data indicates that all six patients carrying the p.R15L variant share a 6.2 Mb haplotype across the gene.

Our data demonstrate that mutations in *CHCHD10* are a relatively common cause of familial ALS and that pathogenic variants are concentrated in exon 2. This represents the first time, to our knowledge, that genome sequencing has been applied to familial ALS. The primary advantage of this methodology is improved coverage of protein-coding regions of the genome, particularly in GC-rich regions that may not be effectively captured by the oligonucleotide baits that are central to exome sequencing. It is also noteworthy that patients in the pedigree reported by Bannwarth and colleagues had reliable evidence of mitochondrial myopathy. Two other ALS genes, *VCP* and *MATR3*, have been

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associated with clinical myopathy (Johnson *et al.*, 2010, 2014), suggesting that muscle involvement may be more common in familial ALS than previously appreciated.

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