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LETTER TO THE EDITOR

Analysis of the *CHCHD10* gene in patients with frontotemporal dementia and amyotrophic lateral sclerosis from Spain

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Sir,

Recently, a study identified a mutation (c.176C>T, p.S59L) in the *CHCHD10* gene as a cause of amyotrophic lateral sclerosis (ALS)/frontotemporal dementia (FTD) in a large pedigree with mixed phenotypes encompassing ALS, FTD, cerebellar ataxia and mitochondrial myopathy (Bannwarth *et al.*, 2014).The same mutation was also found in a second kindred suffering from ALS, FTD and/or parkinsonian signs by the same authors. Additional mutations (p.R15L, p.P34S, p.G66V and p.P80L) have been subsequently reported in ALS and FTD with motor neuron disease (FTD-MND) patients (Chaussenot *et al.*, 2014; Johnson *et al.*, 2014; Müller *et al.*, 2014; Kurzwelly *et al.*, 2015; Ronchi *et al.* 2015; Chiò *et al.*, 2015). More recently, exon 2 of the *CHCHD10* gene has been sequenced in a cohort of ALS, FTD, Parkinson's disease and Alzheimer's dementia, revealing two novel mutations (p.P23T and p.A35D) in two patients with FTD (Zhang *et al.*, 2015). Importantly, some of these screenings have not included neurologically healthy individuals from the same geographic origin (Bannwarth *et al.*, 2014; Johnson *et al.*, 2014; Müller *et al.*, 2014; Kurzwelly *et al.*, 2015) and therefore, the real allele diversity within *CHCHD10* might have been missed. This could have important consequences in terms of establishing firm conclusions on the genetic effects of rare alleles that have been identified in patients with ALS and/or FTD, and caution should be taken when generalizing the outcomes to other populations and/or phenotypes.

To further investigate the role of *CHCHD10* in ALS/FTD disease spectrum, we Sanger sequenced its entire coding region in a comprehensive cohort of Spanish patients of 1224 subjects, distributed in three clinical phenotypes: ALS ($n = 423$), FTD ($n = 709$) and FTD-MND ($n = 92$) (Table 1). Three hundred and nineteen neurologically healthy and unrelated elderly individuals from Spain were also included (mean age at clinical assessment 70.84 ± 9.59 years, 36.5% females).

Our mutation screening of *CHCHD10* disclosed two novel mutations: a non-synonymous change (c.34C>T, p.P12S) in a patient with ALS and a nonsense mutation that resulted in a premature stop codon (c.244C>T, p.Q82X) in a patient from the FTD cohort. None of these variants were present in our neurologically healthy control series nor in European samples from public databases, including the NHLBI Exome Sequencing Project (http://evs.gs.washington.edu/EVS), the Exome Aggregation Consortium (ExAC) (http://exac.broadinstitute.org) and the 1000 Genome (1KG) Project Consortium (Abecasis *et al.*, 2012), thus discarding the p.P12S and the Q82X mutations in a total of 35 470 and 61 386 chromosomes, respectively.

Table 1 Demographic and clinical characteristics of patients included in this study

	ALS ($n = 423$)	FTD ($n = 709$)	FTD-MND ($n = 92$)
Gender			
Male	56.3%	52.14%	66.3%
Female	43.7%	47.86%	33.7%
Age at onset (years)			
Mean ± SD (range)	59.57 ± 14.05 (23–89)	64.7 ± 10.25 (33–88)	63.42 ± 11.68 (36–83)
Family history			
Negative	78.26%	48.21%	74.29%
Positive	21.74%	51.79%	25.71%
FTD variant			
bvFTD	–	70.23%	92.1%
PNFA	–	20.6%	6.58%
SD	–	9.17%	1.32%
Site of onset (ALS)			
Bulbar	34.21%	–	51.9%
Limb	65.79%	–	49.1%

bvFTD = behavioural variant of FTD; PNFA = progressive non-fluent aphasia; SD = semantic dementia.

The p.P12S substitution changes a conserved amino acid and is predicted, through *in silico* analysis, to be 'disease causing' (MutationTaster, http://mutationtaster.org). The variant was identified in a male who developed a classical ALS phenotype of spinal onset at 58 years of age. The disease progression was slow and the patient died after 11 years from a non-related cause, with no cognitive impairment. His father developed dementia of unknown aetiology at 70 years of age.

The p.Q82X nonsense mutation, which would result in the loss of the entire CHCH domain of CHCHD10, was found in a female who, at age 58 years, started with short-term memory problems, spatial disorientation and marked language difficulties. In particular she had reduced spontaneous speech, word finding difficulties and impairment in language comprehension. Formal neuropsychological evaluation revealed global and diffuse impairment. In the neurological exam 2 years after symptoms onset, asymmetrical rigidity and bradykinesia were noticed, but no resting

Table 2 Frequency of pathogenic variants within exon 2 of the *CHCHD10* gene

Protein position	ALS (*n* = 1401) [%]	FTD (*n* = 876) [%]	FTD-MND (*n* = 211) [%]	Total (*n* = 2488) [%]	Controls (*n* = 981) [%]
p.R15L	7 [0.5]	0 [0]	0 [0]	7 [0.28]	0 [0]
p.P23T	0 [0]	1 [0.11]	0 [0]	1 [0.04]	0 [0]
p.A35D	0 [0]	1 [0.11]	0 [0]	1 [0.04]	0 [0]
p.S59L	0 [0]	0 [0]	2 [0.95]	2 [0.08]	0 [0]
p.G66V	1 [0.07]	0 [0]	0 [0]	1 [0.04]	0 [0]
p.P80L	4 [0.29]	0 [0]	0 [0]	4 [0.16]	0 [0]
p.Q82X	0 [0]	1 [0.11]	0 [0]	1 [0.04]	0 [0]
Total	12 [0.86]	3 [0.34]	2 [0.95]	17 [0.68]	0 [0]

To eliminate any possible bias due to genetic testing approaches (genotyping of a particular variant versus full sequencing of the coding exon), only control subjects from studies in which the entire exon 2 has been analysed were included (Chiò *et al.*, 2015; Zhang *et al.*, 2015, and the present study). For the rest of phenotypes, data from Bannwarth *et al.* (2014), Chaussenot *et al.* (2014), Johnson *et al.* (2014), Müller *et al.* (2014), Kurzwelly *et al.* (2015), and Ronchi *et al.* (2015), have also been included.

tremor was detected. She scored 12 out of 30 in the Mini-Mental State Examination. Brain MRI revealed cortico-subcortical atrophy, more pronounced in the left fronto-insular region. After 3 years of onset, brain ^{18}F-fluorodeoxyglucose-PET imaging showed left fronto-temporo-parietal hypometabolism. Her mother died from an accident at 28 years of age and her father at 50 years old due to hepatic cirrhosis, with no signs of neurological disorders.

Our analysis also revealed two previously reported non-synonymous variants: p.P34S (rs551521196) and p.P96T (rs111677724). The p.P34S was identified in two ALS and four FTD patients, and the p.P96T was carried by four ALS and five FTD individuals. Interestingly, the p.P96T variant was presented in two ALS patients in a homozygous state. These two variants were also found in our control series (two control individuals presented the p.P34S and three harboured the p.P96T), and have been reported at low frequencies (<0.003) in European individuals from the 1KG Project Consortium and the ExAC databases. The fact that the p.P34S has been recently encountered in control subjects from USA/UK, Canada and Italy (Zhang *et al.*, 2015), strongly indicates that this variant is not likely to be pathogenic.

Including our two novel mutations, there are eight pathogenic variants in the *CHCHD10* gene that have been implicated in the ALS/FTD spectrum, seven of them within exon 2. These data suggest that mutations located in the exon 2 of *CHCHD10* gene might be responsible for 0.86% of ALS, 0.34% of FTD and 0.95% of FTD-MND cases (Table 2).

To our knowledge, this is the largest study performed to date aimed at evaluating the role of *CHCHD10* in the ALS/FTD disease continuum. We report the first mutation in exon 1 and the first nonsense variant in this gene. Interestingly, the p.Q82X mutation was found in a patient presenting with atypical FTD with clinical features of progressive non-fluent aphasia together with parkinsonian signs and no motor neuron involvement. This complex phenotype reinforces the idea that mutations in *CHCHD10* might cause a broader range of clinical presentations, and strengthens the hypothesis that mitochondrial functional impairment is implicated in several neurodegenerative disorders (Mattson *et al.*, 2008). The second novel mutation (p.P12S) was found in a patient who suffered from ALS and died after 11 years of disease onset from an unrelated cause. Long disease duration and slow progression have been previously reported in other *CHCHD10* mutation carriers (Müller *et al.*, 2014; Kurzwelly *et al.*, 2015; Zhang *et al.*, 2015), thus suggesting that these may be characteristic features related to *CHCHD10* mutations.

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