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; Müller et al., 2014; Johnson et al., 2014; Kurzwelly et al., 2015; Ronchi et al. 2015; Chiò et al., 2015). More recently, the 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 FTD patients (Zhang et al., 2015). Importantly, some of these screenings have not included neurologically healthy individuals from the same geographic origin (Bannwarth et al., 2014; Müller et al., 2014; Johnson 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 generalising 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 1,224 subjects, distributed in three clinical phenotypes: ALS (n=423), FTD (n=709) and FTD-MND (n=92) (see table 1 for clinical and demographic description). Three-
hundred nineteen neurologically healthy and unrelated elderly individuals from Spain were also included (mean age at clinical assessment 70.84 ± 9.59 years, 36.5% female). Our mutation screening of \textit{CHCHD10} disclosed two novel mutations: a nonsynonymous change (c.34 C>T, p.P12S) in a patient with ALS and a nonsense mutation that resulted in a premature stop codon (c.244 C>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 (\url{http://evs.gs.washington.edu/EVS}), the Exome Aggregation Consortium (ExAC) (\url{http://exac.broadinstitute.org}) and the 1,000 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.

The p.P12S substitution changes a conserved amino acid and is predicted, through \textit{in silico} analysis, to be “disease causing” (MutationTaster, \url{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 bradykynesia were noticed, but no resting 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 $[^{18}\text{F}]$ 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 nonsynonymous 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 (Kurzwelly et al., 2015; Müller et al., 2015; Zhang et al., 2015), thus suggesting that these may be characteristic features related to CHCHD10 mutations.
<table>
<thead>
<tr>
<th></th>
<th>ALS (n=423)</th>
<th>FTD (n=709)</th>
<th>FTD-MND (n=92)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>56.3%</td>
<td>52.14%</td>
<td>66.3%</td>
</tr>
<tr>
<td>Female</td>
<td>43.7%</td>
<td>47.86%</td>
<td>33.7%</td>
</tr>
<tr>
<td>Age at onset (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD (range)</td>
<td>59.57 ± 14.05 (23-89)</td>
<td>64.7 ± 10.25 (33-88)</td>
<td>63.42 ± 11.68 (36-83)</td>
</tr>
<tr>
<td>Family history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>78.26%</td>
<td>48.21%</td>
<td>74.29%</td>
</tr>
<tr>
<td>Positive</td>
<td>21.74%</td>
<td>51.79%</td>
<td>25.71%</td>
</tr>
<tr>
<td>FTD variant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bvFTD</td>
<td>-</td>
<td>70.23%</td>
<td>92.1%</td>
</tr>
<tr>
<td>PNFA</td>
<td>-</td>
<td>20.6%</td>
<td>6.58%</td>
</tr>
<tr>
<td>SD</td>
<td>-</td>
<td>9.17%</td>
<td>1.32%</td>
</tr>
<tr>
<td>Site of onset (ALS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bulbar</td>
<td>34.21%</td>
<td>-</td>
<td>51.9%</td>
</tr>
<tr>
<td>Limb</td>
<td>65.79%</td>
<td>-</td>
<td>49.1%</td>
</tr>
</tbody>
</table>
Table 2. Frequency of pathogenic variants within exon 2 of the \textit{CHCHD10} gene.

<table>
<thead>
<tr>
<th>Protein position</th>
<th>ALS (n=1,401) [%]</th>
<th>FTD (n=876) [%]</th>
<th>FTD-MND (n=211) [%]</th>
<th>Total (n=2,488) [%]</th>
<th>Controls (n=981) [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>p.R15L</td>
<td>7 [0.5]</td>
<td>0 [0]</td>
<td>0 [0]</td>
<td>7 [0.28]</td>
<td>0 [0]</td>
</tr>
<tr>
<td>p.P23T</td>
<td>0 [0]</td>
<td>1 [0.11]</td>
<td>0 [0]</td>
<td>1 [0.04]</td>
<td>0 [0]</td>
</tr>
<tr>
<td>p.A35D</td>
<td>0 [0]</td>
<td>1 [0.11]</td>
<td>0 [0]</td>
<td>1 [0.04]</td>
<td>0 [0]</td>
</tr>
<tr>
<td>p.S59L</td>
<td>0 [0]</td>
<td>0 [0]</td>
<td>2 [0.95]</td>
<td>2 [0.08]</td>
<td>0 [0]</td>
</tr>
<tr>
<td>p.G66V</td>
<td>1 [0.07]</td>
<td>0 [0]</td>
<td>0 [0]</td>
<td>1 [0.04]</td>
<td>0 [0]</td>
</tr>
<tr>
<td>p.P80L</td>
<td>4 [0.29]</td>
<td>0 [0]</td>
<td>0 [0]</td>
<td>4 [0.16]</td>
<td>0 [0]</td>
</tr>
<tr>
<td>p.Q82X</td>
<td>0 [0]</td>
<td>1 [0.11]</td>
<td>0 [0]</td>
<td>1 [0.04]</td>
<td>0 [0]</td>
</tr>
<tr>
<td>total</td>
<td>12 [0.86]</td>
<td>3 [0.34]</td>
<td>2 [0.95]</td>
<td>17 [0.68]</td>
<td>0 [0]</td>
</tr>
</tbody>
</table>
Table legends

Table 1

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

Table 2

In order 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 have been 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; Müller et al., 2014; Johnson et al., 2014; Kurzwelly et al., 2015; and Ronchi et al. 2015, have also been included.
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References


