LETTER TO THE EDITOR

Reply: High prevalence of CHCHD10 mutations in patients with frontotemporal dementia from China

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Sir,

In 2014, we provided a genetic basis to support the conclusion that mitochondrial dysfunction can have a causative effect in motor neuron degeneration. We reported a large family with a mitochondrial myopathy associated with motor neuron disease and cognitive decline looking like frontotemporal dementia (FTD). Since the identification of the p.Ser59Leu mutation in the CHCHD10 gene in this family, more than a dozen publications have reported CHCHD10 variants in patient cohorts from different geographic origins. CHCHD10-related clinical spectrum is continuously expanding and includes FTD, familial or sporadic amyotrophic lateral sclerosis (ALS), FTD-ALS, late-onset spinal motor neuropathy and Charcot-Marie-Tooth disease type 2 (Bannwarth et al., 2014; Chaussenot et al., 2014; Johnson et al., 2014; Müller et al., 2014; Auranen et al., 2015; Chiò et al., 2015; Dols-Icardo et al., 2015; Kurzwelly et al., 2015; Penttilä et al., 2015; Ronchi et al., 2015; Zhang et al., 2015).

We read with interest the Letter to the Editor from Bin et al. (2016) suggesting that CHCHD10 is the most important gene linked to FTD in the Chinese population. Among a cohort of 165 patients with ALS and 65 patients with FTD, they identified five novel CHCHD10 variants in five individuals with pure FTD (7.7%). No variant was detected in the ALS population. The putative pathogenicity of these variants...
was based not only on their absence both in control subjects and in different databases, but also in the in silico predictions. Among the different variants reported in the published studies, these criteria led to the selection of ~15 of them which are probably deleterious (Table 1). However, they are clearly insufficient to confirm pathogenicity and help determine the actual frequency of CHCHD10 mutations in the FTD-ALS clinical spectrum. Several studies have recently questioned the pathogenicity of the p.Pro34Ser substitution (Abdelkarim et al., 2015; Dobson-Stone et al., 2015; Dols-Icardo et al., 2015; Marroquin et al., 2015; Wong et al., 2015; Zhang et al., 2015). The p.Pro34Ser variant was found neither in ALS nor in FTD Chinese cohorts reported by Bin and colleagues but it is one that has been most commonly found in Caucasian populations. The observations that raise deservedly the question about its deleterious effect are (i) its identification in one FTD patient who carries a deleterious mutation in another FTD gene (Dobson-Stone et al., 2015); (ii) a non-segregation with the disease in a FTD family with only one of the two affected sisters of the index case carrying the p.P34S variant (Dobson-Stone et al., 2015); and (iii) its presence in non-affected subjects recently reported by several groups (Abdelkarim et al., 2015; Dobson-Stone et al., 2015; Dols-Icardo et al., 2015; Marroquin et al., 2015; Wong et al., 2015; Zhang et al., 2015). None of these results allow us to formally eliminate the deleterious role of this variant in the FTD-ALS clinical spectrum. Indeed, several studies have reported double mutations in ALS- or FTD-associated genes, suggesting an oligogenic model (van Blitterswijk et al., 2012, 2013; King et al., 2013) and it is possible that the Pro34Ser-negative patient in the FTD family reported by Dobson-Stone and colleagues (2015) is a phenocopy. Regarding the recent publications reporting the detection of the p.Pro34Ser variant in control populations, it should be noted that the late-onset of the disease can explain the detection of asymptomatic carriers who have not yet developed symptoms. Incomplete penetrance may also partly explain the presence of deleterious mutations in the general population and an incomplete penetrance in two families of German descent with ALS carrying the p.Arg15Leu mutation in CHCHD10 has been reported by Müller and colleagues (2014). C9orf72 expansions responsible for ALS and FTD have also been identified in control individuals with several studies reporting incomplete penetrance (van Blitterswijk et al., 2012).

Functional tests are needed to elucidate the role of the variants identified in clinical studies. We do not have fibroblasts from patients carrying the p.Pro34Ser substitution. We therefore expressed the CHCHD10Pro34Ser mutant allele in HeLa cells and compared the effects of the mutation to those observed with the CHCHD10Ser59Leu mutant. The pathogenicity of the p.Ser59Leu mutation is clearly demonstrated and mainly based on its co-segregation with the disease in a large family and on the mitochondrial dysfunction observed.

<table>
<thead>
<tr>
<th>CHCHD10 variants</th>
<th>Found in control population</th>
<th>Found in association with another FTD-ALS gene</th>
<th>Incomplete penetration</th>
<th>Co-segregation with the disease</th>
<th>Mitochondrial dysfunction in vitro</th>
</tr>
</thead>
<tbody>
<tr>
<td>p.P12S</td>
<td>Yes</td>
<td>No</td>
<td>Not described</td>
<td>Not described</td>
<td>No</td>
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<tr>
<td>p.R15L</td>
<td>Yes</td>
<td>No</td>
<td>Not described</td>
<td>Not described</td>
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<tr>
<td>p.H22Y</td>
<td>No</td>
<td>No</td>
<td>Not described</td>
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<tr>
<td>p.P23T</td>
<td>No</td>
<td>No</td>
<td>Not described</td>
<td>Not described</td>
<td>No</td>
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<tr>
<td>p.P23S</td>
<td>No</td>
<td>No</td>
<td>Not described</td>
<td>Not described</td>
<td>No</td>
</tr>
<tr>
<td>p.P23L</td>
<td>No</td>
<td>No</td>
<td>Not described</td>
<td>Not described</td>
<td>No</td>
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<tr>
<td>p.A32D</td>
<td>No</td>
<td>No</td>
<td>Not described</td>
<td>Not described</td>
<td>No</td>
</tr>
<tr>
<td>p.P34S</td>
<td>Yes</td>
<td>One patient with FTD (Dobson-Stone et al., 2015)</td>
<td>Not described</td>
<td>One CHCHD10-negative affected sister in a family with FTD (Dobson-Stone et al., 2015)</td>
<td>Yes (Genin et al., 2016).</td>
</tr>
<tr>
<td>p.A35D</td>
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<td>No</td>
<td>Not described</td>
<td>Not described</td>
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<tr>
<td>p.V57E</td>
<td>No</td>
<td>No</td>
<td>Not described</td>
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<td>p.GS9R with p.R15S in cis</td>
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<td>No</td>
<td>Not described</td>
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<tr>
<td>p.S59L</td>
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<td>No</td>
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<tr>
<td>p.G66V</td>
<td>No</td>
<td>No</td>
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<td>p.P80L</td>
<td>No</td>
<td>No</td>
<td>Not described</td>
<td>One CHCHD10-negative affected sister in a family with FTD (Dobson-Stone et al., 2015)</td>
<td>Yes (Genin et al., 2016).</td>
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<td>p.Q82X</td>
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<td>No</td>
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<td>Not described</td>
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</tr>
</tbody>
</table>

*Responsible for an early-onset mitochondrial myopathy without symptoms of FTD or motor neuron disease.
both in patient fibroblasts and in HeLa cells overexpressing the mutant allele (Table 1) (Bannwarth et al., 2014). Overexpression of mutant CHCHD10P34S led to a significant fragmentation of the mitochondrial network contrary to overexpression of the wild-type allele. Electron microscopy confirmed that CHCHD10P34S expression alters mitochondrial morphology with loss and disorganization of mitochondrial cristae. Furthermore, the expression of either CHCHD10S59L or CHCHD10P34S mutant has the same deleterious effects on nucleoid organization and apoptosis (Genin et al., 2016). These results are strikingly similar to those observed both in fibroblasts of patients carrying the p.Ser59Leu mutation and in HeLa cells overexpressing the CHCHD10S59L mutant allele. They confirm the pathogenic effect of the p.Pro34Ser mutation.

The identification of variants in disease-associated genes has significant implications for the determination of frequency of pathogenic variants but also for genetic diagnostics and counselling. Our results show the difficulty in confirming the pathogenicity of a variant in the absence of functional and clinical evidence. Particularly in late-onset dominant diseases with incomplete penetrance. Zhang and colleagues (2015) also identified the p.Pro34Ser mutation in one individual with Charcot-Marie-Tooth disease. Neurol Genet 2015; 1: e1. 

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References


