LETTER TO THE EDITOR

Reply: CHCHD10 mutations in Italian patients with sporadic amyotrophic lateral sclerosis

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Sir,

The work from Giacomo Comi's group in Milan confirms that CHCHD10 is associated with motor neuron disease (Ronchi et al., 2015). Firstly, this group identified two individuals who carried a CHCHD10 mutation among a cohort of 218 Italian patients with sporadic amyotrophic lateral sclerosis (ALS) (1.4%). A female, who developed bulbar ALS at 75 years of age, carried the p.Pro34Ser mutation that we previously identified in two unrelated frontotemporal dementia-amyotrophic lateral sclerosis (FTD-ALS) patients (Chaussenot et al., 2014). A novel missense mutation (p.Pro80Leu) was also found in two unrelated males who developed the disease at 25 and 59 years of age, respectively. After the identification of CHCHD10 mutations in FTD-ALS and familial pure ALS cohorts, this novel study supports the involvement of this gene in sporadic ALS (Chaussenot et al., 2014; Johnson et al., 2014; Müller et al., 2014; Ronchi et al., 2015). Secondly, this report confirms that mitochondrial dysfunction can be at the origin of ALS in a subset of patients. Pure motor neuron disorders are seen infrequently in mitochondrial diseases. On the other hand, although several reports describe mitochondrial dysfunction both in human and mouse ALS models, its pathogenic significance remains unclear and controversial. The idea that mutations in primary mitochondrial genes can cause motor neuron disease was only based on a few reported cases in the literature (Hirano et al., 2008). To assess the prevalence of mitochondrial...
dysfunction in this disease, 50 patients with typical sporadic ALS underwent systematic muscle biopsies (Crugnola et al., 2010). It is of interest to note that 23/50 patients (46%) had COX-negative fibres. A severe mitochondrial myopathy (>10 COX-negative fibres per 100) was observed in 7 cases out of 23, including the Italian patient who developed ALS symptoms at age 25 and who carried the p.Pro80Leu CHCHD10 mutation (Ronchi et al., 2015). This case is reminiscent to the one of Patient V-2 from the French family, carrying the p.Ser59Leu mutation, that was at the origin of the association of French family, carrying the p.Ser59Leu mutation (Ronchi et al., 2015). This case is reminiscent to the one of Patient V-2 from the French family, carrying the p.Ser59Leu mutation, that was at the origin of the association of CHCHD10 with FTDALS (Bannwarth et al., 2014). Both had isolated ALS symptoms and a combined respiratory chain deficiency with numerous COX-negative fibres in muscle. Contrary to Patient V-2, the Italian patient had no multiple mtDNA deletions. Such alterations of mitochondrial genome accumulate in post-mitotic tissue during ageing. The absence of mtDNA instability can be explained by the age of this patient who was 27 years old when he underwent the muscle biopsy, whereas Patient V-2 was 50 years of age. This report is the second to demonstrate that a mutation in the CHCHD10 gene is associated with a primary mitochondrial disorder leading to ALS phenotype. Among the other six patients with severe mitochondrial myopathy, causative mutations in two ALS-related genes had also been identified (SOD1: p.Gln22Arg and TARDBP: p.Arg382Thr) by Crugnola and colleagues (2010). Both patients presented a secondary mitochondrial myopathy, with numerous COX-negative fibres but without mtDNA deletions, indistinguishable from that associated with the p.Pro80Leu mutation in the CHCHD10 gene. Secondary respiratory chain deficiency has been described in many disorders and it may specifically affect their pathological evolution and their clinical prognosis. In metabolic diseases, for example, quinone deficiency secondary to propionic acidemia can lead to fatal cardiac complications (Fragaki et al., 2011). Mitochondria are multifunctional ubiquitous organelles, and dysfunction in this key cellular compartment can lead to bioenergetics failure, oxidative stress or apoptosis resulting ultimately in cell death. In secondary mitochondrial disorders, elucidating the respective role and contribution of these different deleterious consequences in the development of overt clinical symptoms remains a challenging task. Dissecting the cellular pathways disrupted by the expression of CHCHD10 mutant alleles represents, therefore, a golden opportunity to gain powerful insight into the sequence of events that link mitochondrial dysfunction with neuronal death in patients with ALS spectrum disorders.

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**References**


