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Mutation analysis of *CHCHD2* and *CHCHD10* in Italian patients with mitochondrial myopathy

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ABSTRACT

Mutations in *CHCHD2* and *CHCHD10* were recently reported in a broad spectrum of neurodegenerative diseases, e.g. Parkinson's disease, amyotrophic lateral sclerosis, frontotemporal dementia or mitochondrial myopathy (MM). The aim of the study was to evaluate the prevalence of *CHCHD2* and *CHCHD10* mutations in Italian MM patients without mitochondrial DNA mutations. The coding regions of *CHCHD2* and *CHCHD10* were sequenced in 62 MM patients. None of the patients showed *CHCHD2* mutations, whereas one sporadic MM patient carried a homozygous Pro96Thr substitution in *CHCHD10*. Muscle biopsy of this patient showed intracellular glycogen accumulation with cytochrome c oxidase negative and ragged red fibers. Our study suggests that the homozygous Pro96Thr mutation in *CHCHD10* might be pathogenic, but does not support a major role for *CHCHD2* in MM pathogenesis.

KEYWORDS

Mitochondrial myopathy, *CHCHD10*, *CHCHD2*, Mitochondrial disease

Introduction

Mitochondrial myopathies (MM) can be caused by mutations in genes encoded by nuclear or mitochondrial DNA (mtDNA). A new family of mitochondrial (nuclear) proteins with a CHCH-domain and mitochondrial targeting sequence includes CHCHD2 and CHCHD10 that regulate oxidative phosphorylation, cytochrome c oxidase (COX) activity, and cristae morphology. *CHCHD10* mutations were recently reported in patients with amyotrophic lateral sclerosis (ALS) and/or frontotemporal dementia (FTD) (Bannwarth et al., 2014; Zhang et al., 2015). Intriguingly, patients from a French pedigree carrying a compound heterozygous *CHCHD10 cis*-mutation (Arg15Ser/Gly58Arg) presented with a complex phenotype, including cerebellar ataxia, parkinsonism, MM, ALS or ALS/FTD (Ajroud-Driss et al., 2015). The ALS-causing Arg15Leu mutation destabilizes the CHCHD10 protein, leading to impaired cellular respiration and an increase in the steady-state level of CHCHD2 (Straub et al., 2017). Coding mutations in *CHCHD2* were reported in Japanese patients with an autosomal dominant Parkinson's disease (PD) (Funayama et al., 2015). *CHCHD2* variants (rs10043, rs142444896) were associated with sporadic PD, but not in Caucasians (Rubino et al., 2017). Here, we conducted a mutation analysis of *CHCHD2* and *CHCHD10* in Italian MM patients.

Methods

The exons of *CHCHD2* and *CHCHD10* were analysed by Sanger sequencing in 62 MM patients without mutations in mtDNA. The frequencies of the variants were compared to public databases. Histological study included hematoxylin/eosin and Gomori modified trichrome staining, as well as COX and succinate dehydrogenase (SDH) activity. Electron microscopy results were also available.

Results

In *CHCHD2,* we detected only a non-coding variant (rs10043, c.-9 T>G) in the 5' UTR (previously implicated in PD) with a minor allele frequency (MAF) of 0.289, which is similar to that reported in the 1000 Genomes database for the European population (MAF=0.223; p=0.197). Sequencing of *CHCHD10* showed a synonymous variant (rs111527940; c.234 G>A) in one patient, which is similar to the frequency in the European population (1000 Genomes). Furthermore, we identified a homozygous Pro96Thr substitution in exon 3 (rs111677724; c.307 C>A) (Supplemental Fig. 1). The frequency of rs111677724 in our dataset

(MAF=0.016) was significantly higher than in the European population from 1000 Genomes database (MAF=0.001; p=0.012) or the Exome Aggregation Consortium database (MAF=0.006), where only one homozygote was observed among 6013 individuals of European origin. This mutation is predicted to be deleterious by SIFT or possibly damaging by Polyphen 2.

Clinical information of the Pro96Thr carrier is available in the supplemental material. A muscle biopsy showed a typical pattern of MM as dystrophic features, several ragged red fibers, glycogen accumulation and 40% COX negative fibers (Supplemental Fig. 2) with a medium quantity of blood lactate (<4 mM). Electron microscopy showed aggregates of abnormal mitochondria with paracrystalline inclusions.

Discussion

In our MM cohort, we did not find any novel pathogenic *CHCHD2* mutations or any of the rare *CHCHD2* mutations previously reported in different neurological disorders. However, the analysis of *CHCHD10* revealed one MM patient with a homozygous Pro96Thr substitution in exon 3, which is 40 amino acids away from exon 2 (a hotspot for pathogenic mutations in *CHCHD10*) (Straub et al., 2017). This patient showed several ragged-red and COX-negative fibers associated with mitochondrial deletions at muscle biopsy, similar to previous findings in *CHCHD10* patients. The homozygous Pro96Thr mutation was previously described as pathogenic in three ALS patients of European origin (Dols-Icardo et al., 2015; Teyssou et al., 2016).

In conclusion, our data suggest that the homozygous Pro96Thr mutation in *CHCHD10* might be related to MM risk in some Italian patients, but do not support a major role of *CHCHD2* in MM pathogenesis. The limitation of the current study is the modest MM cohort; however, the patients were investigated with multiple methodologies including morphological, biochemical and molecular studies of muscle biopsies. Further investigation is needed to analyze the role of *CHCHD2* and *CHCHD10* in different populations.

Conflict of Interest

None of the authors has any conflict of interest to disclose.

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