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Letter to the editor

Response to a letter to the editor

We thank Dr Finsterer for his interest in our findings (Rubino et al., 2018) and for calling attention to some aspects that may need further explanation.

We thought that it was appropriate to focus on a subgroup of patients with mitochondrial disorder (MID) who did not carry any mutations in mitochondrial DNA, to investigate also the role of the nuclear genes *CHCHD2* and *CHCHD10* in the pathogenesis of the disease, because most mitochondrial proteins are encoded by nuclear DNA. For the mutation analysis of only 2 genes it is appropriate to use the Sanger sequencing approach. Genetically unexplained patients will eventually be included in whole genome assessment. We agree with the suggestion that next generation sequencing techniques can lead to a more precise genetic diagnosis, and this strategy is currently also under investigation by our research group but was beyond the scope of this article.

The diagnosis of mitochondrial myopathies includes a multidisciplinary approach. Clinical and physical examinations are crucial in the diagnostic process, and we agree on the importance of a correct diagnosis of MID. Indeed, all the patients involved in the study and diagnosed with mitochondrial myopathy underwent a muscle biopsy with extensive histochemical, immunohistochemical, and biochemical investigations that supported the clinical diagnosis of MID. More specifically, the presence of ragged red fibers and cytochrome c oxidase-negative fibers was documented in all patients. Furthermore, all the patients underwent needle electromyography, and most of these patients presented a normal pattern or myopathic features, whereas 8% of patients showed a neurogenic pattern.

We agree with Dr Finsterer that MID may present with a vast range of symptoms. Clinically, patients with MIDs show different phenotypes, and in this data set 45.2% of patients presented with isolated myopathy at disease onset and 82.3% of subjects presented with a multisystem disorder on follow-up. Most patients without known mitochondrial gene mutations showed a negative familial history. Only 3 patients had familial disease (2 with autosomal and 1 with an X-linked mode of inheritance).

Our study did not support a major role for *CHCHD2* in the pathogenesis of disease, whereas we detected a homozygous P96T mutation in *CHCHD10*, which might be pathogenic. The carrier of this mutation showed a negative familial history, and no other samples are available for segregation analysis. Bioinformatics tools (SIFT and Polyphen-2) help characterize mutations and are commonly used by genetic studies with the understanding that they have some limitations. As we previously described (Rubino et al., 2018), this subject did not show any signs of either motor neuron disease or dementia. Notably, another article describing the homozygous P96T substitution in 1 patient with amyotrophic lateral sclerosis (ALS) reported that this substitution is predicted to activate a cryptic acceptor site, which could influence *CHCHD10* splicing and that this amino acid change could be deleterious for CHCHD10 function (Teyssou et al., 2016). Foremost, other authors reported the P96T variant in a heterozygous state in 0.22% of patients with frontotemporal dementia, in 0.23% of ALS patients, and in 1 of 703 control subjects (0.14%) (Perrone et al., 2017). Hence, we cannot exclude that in a heterozygous state this variant is insufficient to cause the disease. An independent study detected the P96T substitution in a homozygous state in 2 ALS patients (Dols-Icardo et al., 2015), further supporting the pathogenetic role of this variant. Therefore, further investigation of the *CHCHD10* gene in a larger cohort of patients with MID might be of interest.

Disclosure

The authors have no actual or potential conflicts of interest.

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