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Letter to the editor

Whole exome should be preferred over Sanger sequencing in suspected mitochondrial myopathy

Check for updates

With interest we read the article by Rubino et al. about Sanger sequencing of the genes *CHCHD2* and *CHCHD10* in 62 Italian patients with a mitochondrial myopathy without a genetic defect (Rubino et al., 2018). The authors found the previously reported variant c.307C>A in the *CHCHD10* gene (Perrone et al., 2017) in 1 of the 62 patients (Rubino et al., 2018). We have the following comments and concerns.

If no mutation was found in 61 of the 62 included myopathy patients, how can the authors be sure that these patients had indeed a mitochondrial disorder (MID). We should be informed on which criteria and by which means the diagnosis of an MID was established in the 61 patients, who did not carry a mutation in the *CHCHD2* and *CHCHD10* genes, respectively. We would like to know if all 62 patients underwent muscle biopsy and immunohistochemical, biochemical, or polarographic investigations of the muscle biopsy specimen? We would also like to know if all 62 patients presented with isolated myopathy or if some exhibited phenotypic manifestations of an MID in other organs, such as the brain, eyes, ears, endocrine organs, myocardium, intestinal organs, kidneys, lungs, blood, immune cells, cartilage, bones, or the skin? How many of the 62 patients developed multisystem disease, the most frequent presentation of an MID, during follow-up?

Because mutations in the *CHCHD2* and *CHCHD10* genes may cause familial amyotrophic lateral sclerosis and because MIDs may mimic motor neuron disease (Finsterer, 2002), we should be informed in how many of the 62 patients a needle electromyography was carried out and in how many of them the electromyography was neurogenic instead of myogenic or normal. Particularly, we should be informed if the patient with mitochondrial myopathy carrying the *CHCHD10* variant, developed features of a motor neuron disease or dementia? *CHCHD10* variants may not only be associated with motor neuron disease but also with Alzheimer's disease (Xiao et al., 2017), cerebellar ataxia (Ajroud-Driss et al., 2015), or Parkinson's disease (Rubino et al., 2017). Did the patient develop any of these features over time?

We should also know if the family history was indicative of an MID in any of the 62 patients and in how many of the 62 patients the phenotype segregated according to a maternal trait of inheritance, or an autosomal or X-linked trait of inheritance? How many of the first-degree relatives of the 62 patients were clinically affected?

Today, about 1500 nuclear genes involved in mitochondrial metabolism have been detected but only mutations in a few of these genes have been identified as the cause of an MID. Thus, in patients with mitochondrial myopathy following an autosomal or X-linked trait of inheritance, whole exome sequencing rather than Sanger sequencing of single genes is recommended to detect the underlying genetic defect. In case of a maternal trait of inheritance, however, sequencing of the mtDNA is recommended. Whole exome sequencing is preferred over Sanger sequencing as myopathies or phenotypes in general that resemble an MID are in fact due to mutations in genes not involved in mitochondrial functions, representing genotypic heterogeneity.

We do not agree that application of SIFT and polyphem 2 is sufficient to confirm pathogenicity of a variant. Confirmation of the pathogenicity requires documentation of the variant in other populations, segregation of the phenotype with the genotype through several generations, and functional studies that prove a deleterious effect of a variant on metabolic functions.

Overall, the study could be more meaningful if exome and mtDNA sequencing would have been carried out in the remaining 61 patients with mitochondrial myopathy but without a genetic cause, if long-term follow-up data and the family history would have been provided, and if the pathogenicity of the *CHCHD10* variant would have been confirmed by functional studies.

Disclosure

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