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Letter to the Editor

Only pathogenic variants in protein-coding mtDNA genes cause Leigh syndrome

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With interest we read the article by Mani et al. about 165 patients with thiamin-responsive Leigh syndrome in whom 100 non-synonymous mtDNA variants in protein-coding mtDNA genes were detected [1]. We have the following comments and concerns.

The main shortcoming of the study is that it was not determined how many of the 100 non-synonymous mtDNA variants detected in the 165 patients with thiamine-responsive Leigh syndrome were truly pathogenic. A non-synonymous variant per se does not necessarily indicate pathogenicity. The strongest argument against pathogenicity of these variants is that 20 of them were also found in the 95 control subjects [1]. A further strong argument against pathogenicity of these variants is that most of them occurred in the homoplasmic state. Only 15 of the 100 non-synonymous variants detected in the 165 patients were in the heteroplasmic state. Most of the pathogenic mtDNA variants occur in the heteroplasmic state. A further argument against their pathogenicity is that many patients carried not only a single variant but several. The four variants m.8701A > G (n = 93), m.8860A > G (n = 164), m.10398A > G (n = 83), and 15326A > G (n = 114) occurred together in more than half of the patients making their pathogenicity unlikely. The described histopathological findings are no argument for pathogenicity as only 23 of 165 patients underwent muscle biopsy and as the abnormalities on muscle biopsy could be caused by completely different genetic defects as those pretended in these patients. To confirm pathogenicity of a variant it would be necessary to demonstrate that the variants occur in a highly conserved region, that the variant segregates with the phenotype in an affected family and that functional studies, such as cybrid or single fiber studies, clearly show that any of the 100 variants causes the appropriate phenotype. In silico methods for assessing the pathogenicity of a mutation are not sufficient to prove causality of a variant.

We further do not agree that the secondary LHON mutation m.4216T > C is associated with multiple sclerosis, as mentioned in the discussion [1]. In a recent study of 56 patients with multiple sclerosis and optic neuritis no association between optic neuritis and the m.4216T > C variant could be identified [2]. In another study of 100 Iranian patients with multiple sclerosis no association between the m.4216T > C variant and multiple sclerosis was detected either [3]. Andalib's study from 2015 clearly demonstrated that the m.4216T > C variant does not play a role in the pathogenesis of multiple sclerosis. Multiple sclerosis is still an immunological disorder unless it is misdiagnosed. Associations of mtDNA variants with Parkinson's disease or Alzheimer's disease often rely on overlooking the mitochondrial disorder (MID) in these patients. It is well appreciated that a number of MIDs manifest with multisystem disease, of which Parkinsonism or dementia is part of the phenotypic spectrum [4,5].

Overall, this interesting study has a number of shortcomings which need to be addressed before making final conclusions. To prove the pathogenicity of an mtDNA variant, studies other than the ones carried out the presented paper need to be conducted.

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Author contribution

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Declaration of Competing Interest

There are no conflicts of interest.

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