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Letter to the Editor

Pathogenicity of the M.5667G>A Variant in Chronic Progressive External Ophthalmoplegia

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In a recent article, Schlapakow *et al.*, reported about a 14yo Turkish male with pure chronic progressive external ophthalmoplegia (CPEO), in whom the tRNA(Asp) (MT-TN) variant m.5667G>A was made responsible for the phenotype after investigation of the skeletal muscle (SKM) and an extraocular muscle (EOM) by histological (SKM, EOM), histochemical (SKM, EOM), biochemical (SKM), and genetic studies (SKM, EOM) (Schlapakow, E. *et al.*, 2019). The study raises the following comments and concerns.

We disagree with the assessment of the m.5667G>A variant as definitively pathogenic (Schlapakow, E. *et al.*, 2019). According to the modified Yarham score (Finsterer, J. *et al.*, 2018), the pathogenicity of a variant relies on the validation of the items number of publications (0 or 2), heteroplasmy (0 or 2), disease segregation with the variant (0 or 2), biochemical respiratory chain defect 0 or 2, variant segregation with biochemical defect in single fiber studies (0 or 3), evidence of pathogenicity on cybrid studies 0 or 5, evolutionary conservation of variant (0, 1 or 2), and histopathological findings (0, 1, or 2) (Finsterer, J. *et al.*, 2018). Missing in the report is the confirmation of the segregation of the disease with the variant in an affected family, cybrid studies, and the evolutionary conservation. Based on the presented studies, the maximal score is 10 and thus, not fulfilling the criteria of a definite variant, which needs to be >10 in case of single-fiber, steady state-level studies or cybrid studies (Finsterer, J. *et al.*, 2018). Another argument against the pathogenicity of the variant is that mutation loads in COX-negative fibers were not different in the SKM and the EOM (Schlapakow, E. *et al.*, 2019).

We also disagree with the notion that CPEO is the most frequent mitochondrial disorder (MID) (Schlapakow, E. *et al.*, 2019). More frequent than any of the >50 mitochondrial syndromes tagged with an acronym are the nonspecific MIDs, which do not fit with one of these acronyms.

Missing in this report is the information whether the parents were consanguineous or not and from which region of Turkey they originated from. It is well known that consanguinity is highly prevalent in certain rural areas in Turkey (Koç, İ., & Eryurt, M.A. 2017). We should know if other children of the couple were normal or presented also with features of hereditary disease.

Furthermore, MIDs may not only manifest in the brain, ears, endocrine organs, myocardium, bone marrow, peripheral nerves, and muscle, but also in the lungs, liver, intestines, kidneys, immune cells, cartilage, and skin (Finsterer, J. 2018). Thus, we should be informed if the index patient was prospectively investigated for clinical or subclinical involvement of the lungs, liver, intestines, kidneys, immune cells, cartilage, or skin.

Another shortcoming of the study is that the mother of the index patient was neither clinically nor genetically investigated. Since mtDNA mutations are transmitted via the maternal line in 75% of the cases (Poulton, J. *et al.*, 2017), it is quite likely that the variant was maternally inherited and that the mother

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was clinically or subclinically affected. To assess the pathogenicity of the variant it is crucial to study not only a single family member but several affected and unaffected siblings.

Overall, this interesting study does not convincingly provide evidence that the m.5667G>A variant is definitively pathogenic and that family studies are crucial for the assessment of the pathogenicity and genotype phenotype correlations.

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