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Letter to the Editor

Pathogenicity of the *MT-ND1* variant m.3685T>C remains currently unproven

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We read with interest the article by Jean *et al*. about a 4 years-old female with maternally inherited Leigh syndrome (MILS) for which the mtDNA variant m.3685T>C in *MT-ND1* was made causally responsible [1]. The variant occurred with a heteroplasmy rate of 62.3% [1]. The patient manifested phenotypically with developmental delay, generalised tonic-conic seizures, hypotonia, asymmetric putaminal lesions, left hemiparesis, intoeing, dystonia, tremor, fatigue, and constipation [1]. The patient did not profit from a mitochondrial cocktail administered during a period of 2 years [1]. The study is appealing but raises concerns that need to be discussed.

We do not agree with classification of the variant m.3685T>C as "likely pathogenic" [1]. When applying the Marham scoring system, developed for classifying tRNA variants of the mtDNA, the m.3685T>C variant reached a score of 6 (>1 independent report (0), heteroplasmy (2), segregation with variant (0), biochemical defect in complexes I, III, or IV (2), variant segregation with the biochemical defect in single fibres studies (0), evidence of pathogenicity in trans-mitochondrial cybrid studies (0), evidence of normality in trans-mitochondrial cybrid studies (0), evolutionary conservation (2), mitochondrial histopathology (0)). A score of ≤6 means that the variant has to be classified as "neutral" [2].

The presented MRI figures do not explain the left-sided hemiparesis. We should be told if the patient ever experienced a stroke-like lesion (SLL), the hallmark of mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome or if the brainstem was concomitantly affected.

Dystonia is a general term but we should be told if the patient presented with focal dystonia, regional dystonia, or generalised dystonia. Furthermore, we should be informed which type of treatment was applied to alleviate dystonia respectively tremor.

Missing is a muscle biopsy and immune histochemical investigations of the biopsy material. It would be interesting to know if not only the brain (epilepsy, epilepsy, cognitive impairment), and the guts (obstipation) were affected but also the eyes, ears, heart, the endocrine system, or the kidneys. We should be told in which tissue the heteroplasmy rate was determined.

Missing is the information about the type and dosage of the antiepileptic drug (AED) regimen in the index patient. Since some of the AEDs are potentially mitochondrion-toxic [3], it is crucial to apply only AEDs that are well tolerated do not to deteriorate the phenotype.

We do not agree that ophthalmoparesis in MILS is due to degeneration of the eye muscles, as mentioned in the introduction [1]. Ophthalmoparesis is usually due myopathy affecting the eye muscles. This is why myopathy can be diagnosed by biopsy of extra-ocular eye muscles.

Overall, the interesting study has several limitations which challenge the results and their interpretation. The pathogenicity of the variant m.3685T>C remains unproven. Relatives with clinical manifestations suggesting a mitochondrial disorder, particularly the one sister of the index patient's father, should undergo genetic testing. Variants pretended to be novel require extensive investigations to confirm causality and responsibility for the phenotype.

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Consent for publication: was obtained from the patient.

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Code availability: not applicable.

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