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Letter to the Editor

Pathogenicity of the Variant M.8561C>T in Pediatric Leigh Syndrome Remains Unproven

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With interest we read the article by Fragaki *et al.*, about a pediatric patient with Leigh syndrome being attributed to the novel variant m.8561C>T in *MT-ATP6* or *MT-ATP8* (Fragaki, K. *et al.*, 2019). Clinical manifestations included hypotonia, microcephaly, developmental delay, dysarthria, ataxia, bradyphrenia, learning difficulties, exercise intolerance, fatigue, retinal hypoplasia, lactic acidosis, and bilaterally symmetric basal ganglia lesions (Fragaki, K. *et al.*, 2019). The study has a number of shortcomings.

The main shortcoming of the study is that the pathogenicity of the novel variant remained unproven. When applying the Yarham score (more than one independent reports: 0; heteroplasmy: 2; segregation of the phenotype with the variant within a family: 0; respiratory chain complex dysfunction on biochemical investigations: 2; variant segregation with biochemical defect I single fiber studies: 0; pathogenicity in trans-mitochondrial cybrid studies: 0; evidence of normality on cybrid studies: 0; evolutionary conservation of nucleotide: 2; mitochondrial histopathology: 0) only 6 points were reached. Thus, the variant m.8561C>T has to be classified as neutral (Finsterer, J. *et al.*, 2018).

Heteroplasmy rate was 96% in muscle and blood but muscle histology investigations were normal. We should know how this discrepancy can be explained.

Patients with Leigh syndrome may experience epileptic seizures (Mkaouar-Rebai, E. *et al.*, 2009). We should know if the history of the index patient was positive for seizures and if the EEG was indicative of clinical or subclinical seizure activity.

Though the index patient's mother was described as asymptomatic and had a low heteroplasmy rate, we should know if she ever had hyper-CK emia or lactic acidosis.

The index patient is described with ataxia (Fragaki, K. *et al.*, 2019). We should know if ataxia was due to cerebellar involvement or due to sensory neuropathy.

Overall, this interesting case report does not convincingly demonstrate that the variant n.8561C>T is responsible for the described phenotype. Functional

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studies of affected tissues should be carried to prove causality of the detected mtDNA variant.

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