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LETTER TO EDITOR

Extensive clinical and genetic workup is worthwhile in patients with Leigh-like syndrome due to the *TSFM* variant c.547G>A

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Letter to the Editor,

We read with interest the article by Scala et al. about a 7-year-old male with encephalocardiomyopathy due to the novel, homozygous *TSFM* variant c.547G>A [1]. The patient presented with a Leigh-like syndrome (LLS), and his mother carried the variant in the heterozygous form and was asymptomatic. We have the following comments and concerns.

A shortcoming of the study is that the results of the genetic workup of first-degree relatives other than the mother were not provided. Thus, the trait of inheritance remains unclear. An argument for an autosomal recessive trait is that no other family member was clinically affected and that the index case carried the variant in the homozygous form.

A further shortcoming of the study is that the workup for cardiac involvement was insufficient. Since MIDs are frequently associated with left ventricular hypertrabeculation/noncompaction (LVHT) [2], we should know if the available echocardiographic or cardiac MRI investigations were revised for LVHT. Additionally, we should know the results of long-term ECG recordings. This is crucial as arrhythmias, including atrial fibrillations and ventricular arrhythmias may be subclinical but nonetheless may determine the outcome. Sudden cardiac death (SCD) is frequently associated with hypertrophic cardiomyopathy [3]. proBNP and troponin serum values should be provided.

Concerning the bilaterally symmetric putaminal lesions on cerebral imaging [1], we should be informed if the corresponding apparent diffusion coefficient (ADC) maps were iso-, hyper-, or hypointens. This is of particular relevance for assessing if the diffusion weighted imaging (DWI) hyperintens lesions represent a cytotoxic or vasogenic oedema. The putaminal lesions may represent stroke-like lesions (SLLs), if the corresponding ADC maps were hyperintens. If the corresponding ADC maps were hypointens, the patient might have experienced an ischemic stroke, or the lesions represent necrosis.

Childhood-onset ataxia, dystonia, and tremor have been previously reported as manifestations of *TSFM* variants [4, 5]. Additionally, a *TSFM* variant has been described in association with a hyperkinetic movement disorder [6]. The 20-year-old male responded favourably to cannabis [6]. However, the index patient presented neither with ataxia or dystonia, nor with tremor. It should be discussed why the index patient did not present with hyperkinesia, ataxia, dystonia, or tremor, given the cerebellar and basal ganglia affection and previous reports about these phenotypic features in patients carrying *TSFM* variants [7]. Presence of a movement disorder in the index patient is conceivable given the bilaterally symmetric lesions of the putamina [1].

The index patient is described with speech delay [1]. Was speech delay attributable to cerebellar atrophy, to basal ganglia involvement or to hypotonia? Was there cortical atrophy on subsequent MRIs?

The patient had generalised hypotonia [1]. Was hypotonia attributed to involvement of the brainstem, due to neuropathy of peripheral nerves, or due to myopathy?

Epicanthus is an infrequent phenotypic feature in mitochondrial disorders (MIDs), which has not been reported in patients with Leigh syndrome or LLS so far. Did the authors exclude an additional chromosomal defect? Did any other first degree relative present with epicanthus?

Overall, the report could be more meaningful if more first-degree relatives were clinically and genetically investigated, if workup for cardiac involvement was more extensive, if the cause of epicanthus was discovered, and if the pathogenesis of various phenotypic features, such as hypotonia or speech delay was clarified.

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Author contribution JF: design, literature search, discussion, and first draft

Compliance with ethical standards

Conflict of Interest The author declare that he has no conflict of interest.

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