Mitochondrial tRNA Glutamic Acid Variant 14709T>C Manifesting as Myoclonic Epilepsy with Ragged Red Fibers

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We read with interest the case report by Ban *et al*.[1] about a 17-year-old male with myoclonic epilepsy with ragged red fibers (MERRF) syndrome being attributed to the mitochondrial tRNA glutamic acid (*tRNA [Glu]*) variant mitochondrial 14709T>C. The authors claimed that the variant occurred sporadically and has not been reported in association with a MERRF phenotype so far.[1] We have the following comments and concerns.

A main shortcoming of the report is that the authors do not provide the heteroplasmy rate of the variant in various tissues. Since the phenotype strongly depends on the heteroplasmy rate in various tissues, it is essential to know these values in hair follicles, skin fibroblasts, buccal epithelial cells, muscle cells, or urinary epithelial cells. Knowing the heteroplasmy rates is crucial, since low heteroplasmy rates would exclude the variant as being causative.

Another shortcoming is that the authors describe the variant as being located in the *tRNA (Glu)* gene on the one hand and on the other hand as being located in the mitochondrial NADH dehydrogenase subunit 6 gene. The variant is definitely located in the *tRNA (Glu)* gene and this should be kept throughout the manuscript. It is ruled out that a particular variant occurs in two genes simultaneously.

The next shortcoming is that the onset of epilepsy is not well delineated. On the one side, the authors described that the patient experienced "recurrent episodes of loss of consciousness (in the absence of seizures)." In the next sentence, they state that "the duration of these episodes was about 1 min while the seizure frequency was around 5–6 times per year." These statements are contradictory and it remains unclear when the first seizures truly occurred in the index case. What do the authors mean with "in the absence of seizures?" According to the case description, it is conceivable that the onset of seizures was at the age 8 years, but this issue requires further specification.

We should know if recurrent syncopes at that time could be attributed to supra-ventricular or ventricular arrhythmias, conduction block, arterial hypotension, heart failure, or involvement of the autonomic nervous system. Which were the results of the electroencephalography or the carotid ultrasound at that time? Did the patient present with cognitive decline or intellectual disability? The patient had developed dysarthria.[1] Was there also dysphagia, frequently associated with dysarthria? Was cerebrospinal fluid (CSF) lactate elevated on magnetic resonance spectroscopy or investigation of the CSF?

Incomprehensibly, the antiepileptic regimen applied in the index case is not provided.[1] Since myoclonic epilepsy may be a challenge to treat, it would be interesting to know if the patient responded to any of the available antiepileptic drugs (AEDs) in monotherapy or to any of the AEDs in combination. In addition, we should know if any of the potentially mitochondrion-toxic AEDs were applied.[2]

We do not agree with the statement that scoliosis is rare in mitochondrial disorders (MIDs).[1] Scoliosis has been reported as a phenotypic feature in specific and nonspecific MIDs and is most frequently due to affection of the axial muscles. Occasionally, scoliosis may be associated with head drop or camptocormia. Did the patient also present with weakness of ante- and retro-flexion of the head or weakness of the erector spinae muscles? Occasionally, scoliosis may be caused by osteoporosis.[3] Was there any indication of impaired mineralization of the bones in the index case?

Based on the information provided, it is not justified to classify the variant as sporadic. Despite absence of clinical features indicative of an MID in the mother, the mother was not prospectively investigated for subclinical involvement and was not checked for the variant of her son. However, it is conceivable that she had subclinical involvement and that she carried the variant at a low heteroplasmy rate. Since mtDNA variants are transmitted via the maternal line in about two-thirds of the cases,[4] the probability is greater that the variant had been inherited than sporadic.

MIDs are usually multi-system diseases.[5] The presented patient manifested in the brain and the muscles. However, with progression of the disease, more and more organs become affected. Thus, it is desirable that the patient would have been prospectively investigated

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for involvement of the endocrine system, heart, guts, the eyes, ears, kidneys, hematological system, skin, optic nerve, lungs, bones, or cartilage. MIDs manifest also frequently in the extra-ocular muscles and the facial muscles. Did the patient ever develop ptosis or osteoporosis? Was there a myopathic face or dysmorphism?

In summary, this interesting case requires clarification concerning the sporadic occurrence of the variant, concerning subclinical affection of the heart or other organs, concerning the AED treatment, and concerning the phenotype and genotype of the mother.

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Conflicts of interest

There are no conflicts of interest.

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