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Letter to the Editor

Pathogenicity of the *MT-TL1* variant m.3274_3275delAC remains so far unproven

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We read with interest the article by Domenico *et al*. reported on a 49 years old female who was diagnosed with multisystem mitochondrial disorder (MID) based on the clinical presentation and the heteroplasmic mtDNA variant m.3274_3275delAC in *MT-TL1* [1]. The patient manifested phenotypically with migraine, basal ganglia calcification, cerebral atrophy, progressive sensory-neural hearing loss, cataracts, pigmentary retinopathy, Wolff-Parkinson-White syndrome, renal tubulopathy, myopathy, and lactic acidosis [1]. Heteroplasmy of the mtDNA variant was 59% in skeletal muscle and 40% in kidneys. No other first-degree family member was tested for the variant considered pathogenic by in silico assessment using MitoTip [1]. The study is appealing but raises concerns that warrant further discussion.

The main shortcoming of the study is that the pathogenicity of the variant m.3274 3275delAC in *MT-TL1* remained unproven. In silico methods such as MitoTip to prove or disprove the pathogenicity of an mtDNA variant are insufficient and unreliable. No other first degree family member was tested for the variant, so it is not possible to assess whether the variant was sporadic or inherited. Furthermore, it remains unknown whether or not the variant segregated with the phenotype within the family. Another argument against pathogenicity of the variant is the low heteroplasmy rate in clinically affected tissues. In addition, the variant accused of being responsible for the phenotype has not been previously reported. No biochemical studies of the muscle homogenate were performed: There is no mention of the results of single fibre studies and whether the variant segregated with the level of involvement in single muscle fibers. No cybrid studies have been conducted. The pathogenicity of mtDNA encoded tRNA variants can be assessed by the modified Yarham score [2]. Definite pathogenicity is only given if the score is ≥11 [2]. According to the provided data, the m.3274_3275delAC variant achieved a score of 2 and is therefore clearly not pathogenic.

Mitochondrial disorders (MIDs) commonly manifest with multisystem disease [3], why it is mandatory that MID patients are prospectively investigated for multisystem involvement. In addition to the brain and skeletal muscles, MIDs manifest commonly in the eyes, ears, endocrine system, heart, liver, guts kidneys, muscle, nerve, bone marrow, and skin, We should know which organs/system other than the brain, eyes, ears, heart, muscle, and kidneys were affected in the index patient. Surprisingly, none of the endocrine organs was affected.

Some essential data are missing. We should know if lactate was elevated also in the serum. We also should know if creatine-kinase was elevated or not. Since peripheral nerves can be also affected in MIDs, it is crucial to know the results of nerve conduction studies (NCSs). No information was provided if the electroencephalogram (EEG) was normal or not. MID patients commonly manifest with epilepsy. There is no information provided whether the patient ever experienced a stroke-like episode (SLE) which is pathognomonic for mitochondrial encephalopathy lactic acidosis and stroke-like episodes (MELAS) syndrome, but can occur in other MIDs as well [4]. The term "woman married with no sons" should be explained. Since the patient obviously had Wolff-Parkinson-White syndrome or at least PQ shortening, we should know if long-term ECG recordings showed supra-ventricular or ventricular arrhythmias or not.

Overall, the study carries obvious limitations that require re-evaluation and discussion. Clarifying these weaknesses would strengthen the conclusions and could improve the study. Pathogenicity of mitochondrial tRNA variants should not be assessed by in silico methods but rather by the application of biochemical, functional, and cybrid studies. According to the Yarham score, the mtDNA variant made responsible for the phenotype of the index case was not pathogenic.

Declarations

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