The m.13513 G>A Variant Is Pathogenic and Phenotypically Heterogeneous

**Keywords:** mtDNA, Leigh syndrome, arrhythmias, cardiomyopathy, heteroplasmy.

**INTRODUCTION**

With interest we read the article by Liang et al., (2021) about a 15 months old male with Leigh syndrome due to the variant m.13513G>A with a heteroplasy rate of 86% in blood lymphocytes (Wei, Y. et al., 2021). Leigh syndrome manifested as developmental delay (poor body weight gain, delayed gross motor development), ptosis, exaggerated patella tendon reflexes, Wolff-Parkinson-White (WPW) syndrome, left bundle branch block (LBBB), bilaterally symmetric T2-hyperintensities in the midbrain and thalamus, and lactic acidosis (Wei, Y. et al., 2021). The patient developed respiratory failure at age 23 months, required intubation and mechanical ventilation, and died shortly afterwards (Wei, Y. et al., 2021). It was concluded that the m.13513G>A variant can manifest as Leigh syndrome and WPW syndrome, and that particularly Chinese patients should be investigated for this variant (Wei, Y. et al., 2021). The case report is appealing but raises the following comments and concerns.

**DISCUSSION**

The m.13513G>A variant has been reported in more patients than mentioned in the discussion. At least 33 patients carrying the m.13513G>A variant have been reported. Age in this cohort ranged between 0 and 45 years. Male gender was reported in 20 and female gender in 12 of these patients. The phenotype was highly variable. The most common phenotypes were LS (n=16), Leigh-like syndrome (n=3), MELAS (n=5), MELAS/LS (n=3), MELAS/LHON (n=1), and LHON (n=1). More rarely, patients manifested with PEO and non-syndromic phenotypes, such as optic atrophy (OA), myopathy (MP), cardiomyopathy (CMP), strabism, seizures, or ataxia. Heteroplasy rates were highly variable ranging from 0% to 86% depending on the investigated tissue.

A further limitation of the study is that the description of the phenotype lacks essential information. We should be told why the patient experienced respiratory insufficiency, particularly if it was due to pulmonary infection, heart failure, ventricular arrhythmias, brainstem involvement, electrolyte disturbance, involvement of the respiratory muscles, or lactic acidosis. We should be told if also creatine-kinase, troponin, and pro-brain natriuretic peptide (proBNP) were elevated, the results of long-term ECG recordings, and which type treatment was applied for WPW (antiarrhythmic drugs, ablation). Missing is the information if organs other than the brain and the heart were affected. As mitochondrial disorders are usually multisystem disease, in the majority of cases (Rahman, S. 2020), we should be told if other than these organs were prospectively investigated for clinical or subclinical involvement. Of particular interest is the skeletal muscle, as affection of the muscle could explain lactic acidosis.

A further limitation is that no biochemical investigations for assessing respiratory chain functions had been carried out. We should be told if there was involvement of the skeletal muscle, if the patient had undergone muscle biopsy, and if biochemical investigations for a respiratory chain defects had been carried out. In light of the ND5 mutation one would expect complex-I deficiency in the index patient depending on the degree of tissue affection.

We do not agree with the notion that in patients with Leigh syndrome and WPW syndrome one should look specifically for the m.13513G>A variant. Patients with suspected mitochondrial disorder (MID), particularly Leigh syndrome, should undergo a more extensive work-up, including sequencing of the entire mtDNA, and if negative whole
Exome sequencing to eventually detect a nuclear defect. Extensive work-up for Leigh syndrome is crucial in the light of the broad genetic heterogeneity and the wide phenotypic heterogeneity of MIDs.

Overall, the interesting report has several limitations which challenge the results and their interpretation. The points raised above should be addressed to strengthen the conclusions.

DECLARATIONS
Acknowledgement: none
Statement of ethics: was in accordance if ethical guidelines
Conflicts of interest: none
Funding sources: no funding was received
Author contribution: JF: design, literature search, discussion, first draft, critical comments, final approval,
Informed consent: was obtained
The study was approved by the institutional review board

REFERENCES