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*Abstract*

# Impaired nuclear and mitochondrial cross-talk might alter mtDNA epigenetic regulation in maternally inherited diabetes and deafness affected patients †

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**Abstract:** Mitochondrial pathologies are clinically complex and show highly variable phenotypes among all inherited disorders, mainly due to their heteroplasmic nature. Mutations in mitochondrial DNA (mtDNA) and nuclear genome (gDNA) or both have been reported in mitochondrial diseases, suggesting common pathophysiological pathways. Nuclear gene defects identified in mitochondrial alterations are primarily responsible for mtDNA replication, transcription and translation, oxidative phosphorylation (OXPHOS), biogenesis of mtDNA, nucleoside transport, salvage or synthesis, maintenance of balanced mitochondrial deoxyribonucleoside triphosphates (dNTP) pool. The m.3243 A>G mtDNA mutation in the MT-TL1 gene coding for the tRNALeu (UUR) is one of the most common mitochondrial disease-causing mutations, with a carrier rate as high as 1:400. Recent studies suggest that patients with m.3243 A>G mutation exhibiting a huge clinical heterogeneity underpinning the necessity to investigate nuclear genome for a better understanding of complex mitochondrial disorders, such as mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS), maternally inherited diabetes and deafness (MIDD) and myopathy. MIDD is a multi-system disorder characterized by diabetes, hearing impairment and maculopathy but can present several other clinical manifestations. This study aimed to sequence the whole mitochondrial genome and the whole exome of a clinically characterized MIDD family, negative to m.3243 A>G variant, and identify mutations in both nuclear and mitochondrial genome and their biological contribution to its heterogeneous phenotype. Obtained results permitted us to hypothesize that the mitochondrial abnormalities might be due to epigenetic deregulation of mitochondrial and nuclear-encoded genes that code for mitochondrial structure and functions. Thus, epigenetic modifications in the context of mitochondrial dysfunctions represent an emerging area of research, possibly useful to innovative mtDNA-related disease differential analyses.

**Keywords:** mtDNA; WGS; WES; epigenetics; MIDD.

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