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Abstract

Impaired Nuclear and Mitochondrial Cross-Talk Might Alter mtDNA Epigenetic Regulation in Maternally Inherited Diabetes- and Deafness-Affected Patients †

Luigi Donato [1,2,*], Concetta Scimone [1,2], Simona Alibrandi [1,2,3], Maria Vadalà [2,4], Massimo Castellucci [5], Domenico Mordà [1], Carmela Rinaldi [1], Rosalia D'Angelo [1] and Antonina Sidoti [1]

1 Department of Biomedical and Dental Sciences and Morphofunctional Imaging, Division of Medical Biotechnologies and Preventive Medicine, University of Messina, 98125 Messina, Italy; cscimone@unime.it (C.S.); salibrandi@unime.it (S.A.); domenico.morda@studenti.unime.it (D.M.); crinaldi@unime.it (C.R.); rdangelo@unime.it (R.D.); asidoti@unime.it (A.S.)
2 Department of Biomolecular Strategies, Genetics and Cutting-Edge Therapies, Istituto Euro-Mediterraneo di Scienza e Tecnologia (I.E.ME.S.T.), 90139 Palermo, Italy; maria.vadala@unipa.it
3 Department of Chemical, Biological, Pharmaceutical and Environmental Sciences, University of Messina, 98125 Messina, Italy
4 Department of Biomedicine, Neuroscience and Advanced Diagnostic (BIND), Ophthalmology Institute, University of Palermo, 90143 Palermo, Italy
5 Ophthalmologist Unit, University Hospital Policlinico P. Giaccone, 90127 Palermo, Italy; massimo.castellucci@gmail.com
* Correspondence: ldonato@unime.it; Tel.: +39-0902213136
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Abstract: Mitochondrial pathologies are clinically composite and show highly variable phenotypes amongst all inherited disorders, mainly due to their heteroplasmic nature. Mutations in mitochondrial DNA (mtDNA) and the nuclear genome (gDNA), or both, have been reported in mitochondrial diseases, suggesting common pathophysiological pathways. Nuclear gene mutations identified in mitochondrial diseases are mostly involved in mtDNA replication, transcription and translation, oxidative phosphorylation (OXPHOS), the biosynthesis of mtDNA, nucleoside transport, salvage or synthesis, and the homeostasis of 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 the m.3243 A>G mutation present a huge clinical heterogeneity supporting the necessity to investigate the nuclear genome to improve the knowledge on composite 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. The present study aimed to analyze the whole mitochondrial genome and the whole exome of a clinically characterized MIDD family, negative to the m.3243 A>G variant, and identify mutations in both gDNA and mtDNA, as well as their biological role in their heterogeneous phenotype. The obtained results permitted us to hypothesize that the mitochondrial defects might be due to the epigenetic deregulation of the mitochondrial and nuclear-encoded genes coding for mitochondrial structure and functions. Thus, epigenetic modifications in the context of mitochondrial dysfunctions represent an emerging area of research, possibly useful for innovative mtDNA-related disease differential analyses.

Keywords: mtDNA; WGS; WES; epigenetics; MIDD

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