



Impairment in Mitochondrial DNA Maintenance by DNA2 Mutation in Multisystemic Condition

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DESCRIPTION

Mitochondrial Disease (MTD) refers to a set of diverse disorders caused by mutations in genes involved in mitochondrial function. Nuclear and mitochondrial gene mutations can both be secondary causes of primary mitochondrial illness, and more than 350 such genes have recently been identified. Many mitochondrial disorders have been linked to this polymorphism and the interactions of genes with the environment. Mitochondrial Deoxyribonucleic Acid (mtDNA) replication machinery, nucleotide metabolism, and mitochondrial dynamics are most frequently impacted by qualitative and/or quantitative (mtDNA depletion) problems in mtDNA maintenance deficiencies, a set of diseases included under MTD.

Mitochondrial Depletion Syndrome (MDS) is one of the mtDNA maintenance abnormalities caused by nuclear gene mutations that affects the amount of mtDNA in particular tissues. Defects in the genes encoding for components of the mtDNA replication and repair machinery, such as *POLG* and *TWNK*, which impact the minimum replisome, and *MGME1* and *RNASEH1*, which affect the repair pathways, change mtDNA homeostasis. Defects in proteins such as *TK2*, *DGUOK*, *RRM2B*, *TYMP*, *SLC25A4*, and *MPV17* that is important in the delivery of mitochondrial dNTPs. MtDNA dynamics-related protein flaws, such as those in *OPA1* and *MFN2*. Even in the same patient, the aforementioned genes can result in both mtDNA depletion and deletion. The helicase/nuclease family includes DNA2, a component that controls the upkeep of mtDNA. DNA2 is also known as DNA replication helicase/nuclease2. 2.7% of his cohort's mtDNA maintenance problems are caused by DNA2 variation. DNA2 is a component of the mtDNA replication machinery, although DNA2 mutations have only been linked to numerous mtDNA deletions in skeletal muscle.

Mammals' DNA2 is crucial for cell survival, embryonic development, DNA replication, DNA repair, and the preservation of genomic stability. DNA2 variations have not been identified as the cause of MDS, despite the fact that genes that are

functionally related to and/or comparable to DNA2 have been linked to the disease. In this work, a male patient with myopathy and hearing loss, age 27, is shown to have a unique truncating variant of DNA2. Surprisingly, our findings showed that both *in vitro* and in patient muscle samples, this variation could result in mtDNA depletion. Both muscle and peripheral blood leukocyte samples were used to extract genomic DNA for Next-Generation Sequencing Analysis (NGS). The results of the functional assays mentioned below, biceps brachii biopsies, mtDNA copy number detection, muscle staining, and ultrastructural studies were carried out. To assess the quantity of mtDNA copies, quantitative PCR was used to extract the muscle mtDNA.

To determine the number of mtDNA copies, fluorescently labelled primers were utilised to find the relevant nuclear genes and mitochondrial genome fragments. In order to confirm successful translation and measure the amount of DNA2, a western blot using the antibodies anti-DNA2 and anti-GADPH was also carried out on the muscle sample. For histological analysis, samples of muscle tissue were stained. To see the morphology of muscle fibres, blood vessels, and connective tissue, many staining techniques were used, including Periodic Acid-Schiff (PAS), Oil Red O (ORO), Hematoxylin-Eosin (H/E), Modified Gomori trichrome (MGT), and Periodic Acid-Eosin (H/E).

To assess enzymatic function, enzyme histochemical investigations of ATPase processes, NADH-TR, COX-SDH, and NSE staining, were carried out. Several proteins linked to inflammatory myopathy and muscular degeneration was stained using immunohistochemistry. Using standard techniques, electron microscopy was used to analyse the ultrastructure of muscles. We came to the conclusion that the loss of ATPase and helicase function compromised mtDNA stability, causing a reduction in the number of mtDNA copies and morphological defects in the mitochondria, which ultimately caused a lack of ATP and ATPase and a drop in ROS production. These changes would be harmful to energy-consuming organs and result in seizures, hearing loss, and motor retardation. As a result, we think the patient has MDS encephalomyopathy. We also suspected

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that haploinsufficiency was the illness mechanism in this patient, and that multisystem dysfunction was caused by the insufficient availability of DNA2 protein. However, to confirm the specific underlying process, more functional investigations are required. NGS of mtDNA originating from long-range PCR amplicons of the patient's and his mother's blood samples was also carried out to further rule out its pathogenicity. The patient's heteroplasmy level was determined to be 92%, and the mother's heteroplasmy level to be 95%. As a result, we agreed that even though they had identical amounts of heteroplasmy and his mother

was asymptomatic, this mutation was not the pathogenic component in this patient. We concluded by reporting a new DNA2 variation connected to motor impairment and deafness. By using functional tests, staining, and mtDNA copy number analysis, we further demonstrated a causal connection with MDS. Decreased ROS levels, mitochondrial distortion, and insufficient ATP and ATPase were all associated with mtDNA depletion. The most recent discoveries add to our knowledge of DNA2's role as a regulator of mtDNA maintenance and the mutational spectrum of MDS.