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Nuclear – mitochondrial cross-talk: Implications in mitochondrial function and disease pathophysiology

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Mitochondria are cellular organelles involved in a variety of biological functions in the cell, apart from their principal role in generation of ATP. Mitochondrion, in spite of being a compact organelle, is capable of performing complex biological functions largely because of its ability to exchange proteins, RNA, chemical metabolites and other biomolecules between cellular compartments. A close network of biomolecular interactions is known to modulate the crosstalk between the mitochondria and the nuclear genome. Apart from the small repertoire of genes encoded by the mitochondrial genome, it is now known that the functionality of the organelle is highly reliant on a number of proteins encoded by the nuclear genome, which localize to the mitochondria. However, not much is known about the functional role of the nuclear encoded proteins in the pathophysiology of the human mitochondrial disorders.

We describe a case study of a 9-month-old female who presented with global developmental delay, visual problems and regression of attained milestones since 6 months of age. On examination she had microcephaly central hypotonia and nystagmus. MRI of brain showed hyperintense symmetrical lesions in crus cerebri and brain stem tracts. Magnetic resonance spectroscopy showed lactate peaks in the involved regions. Blood lactate was elevated multiple times. A high Nijmegen score (>9) and other evidences suggested a possible mitochondrial disease.

Therefore, we attempted whole mitochondrial sequencing of mother and child. Analysis using our mitomatic pipeline ruled out any mitochondrial disease associated variations. Further, we performed whole exome analysis on the trio (mother, father and child) to identify any disease causing variations. Coverage based analysis revealed a deletion on chromosome 5, only in the proband suggesting a de novo deletion. Whole genome sequencing of the proband and parents accurately mapped the deletion boundary of ~150 kb on chromosome 5, encompassing genes responsible for mitochondrial function and DNA damage repair. The synteny of these genes is conserved in model organisms such as zebrafish and mouse, allowing us to investigate the role of this deletion in pathophysiology of the disease. Our study provides insights into a relatively unexplored layer of biomolecular pathways modulating mitochondrial-nuclear cross-talk and its role in human diseases.

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