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Phenotypic and genotypic characterization of Palestinian patients with neuronal ceroid lipofuscinosis: A report of 5 new individuals and novel pathogenic variant

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Background: Neuronal ceroid lipofuscinoses (NCLs) are a group of ultrarare inherited neurodegenerative disorders characterized by consistent clinical features and pathophysiology. Pathogenic variants in several genes were established to be causative for NCL. These genes encode various types of proteins, including lysosomal, cytoplasmic, and transmembrane proteins involved in lipid and protein trafficking, endocytosis, and lysosomal transport. Loss of function variants in NCL genes result in the buildup of autofluorescent lipoprotein aggregates, known as ceroid lipofuscin, in neurons and other cells. This accumulation leads to progressive psychomotor decline, visual impairment, and ultimately, premature death.

Methods: DNA from buccal swabs and/or blood samples underwent whole exome/ genome sequencing, followed by bioinformatics analysis and variant prioritization. Sanger sequencing was employed to confirm carrier status in patients and their parents, facilitating segregation analysis. Detailed clinical and neuroimaging phenotyping was conducted to explore genotype-phenotype correlations.

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Results: In this study, data from five patients belonging to three consanguineous unrelated parents is presented. NCL is diagnosed between the age of 2 to 6 years due to newly onset symptoms of seizures, progressive psychomotor decline, and visual loss. The clinical, neuroimaging, and molecular data are reviewed. In the first family, a novel homozygous frameshift variant (p.Leu58Trpfs*58) in *CLN6* gene is detected in a 4 year old male patient who presented with new onset seizure, hyperactivity, and T2 hyperintense bilateral symmetrical periventricular white matter abnormalities. Presymptomatic detection of this variant in the younger female sibling was possible. In the second family, urgent genomic studies in a 4-year old female child who presented with rapidly progressive visual loss, speech regression, and ataxia revealed a recurrent pathogenic inframe deletion (p.Ser265del) in *CLN3*. In the third family, a 5 year old female child presented progressive visual impairment was homozygous for the common intragenic deletion in exons 8 and 9 of *CLN3* gene, resulting in frameshift and premature termination. Segregation analysis in family members identified a presymptomatic two year old brother with the pathogenic variant.

Conclusion: NCL is a hereditary ultra-rare severe neurodevelopmental condition. The inheritance pattern, often autosomal recessive, renders offspring of consanguineous unions particularly vulnerable to this condition. Identifying carriers not only facilitates comprehensive counseling but also enables proactive prevention strategies. Moreover, early detection proves crucial for timely intervention, ensuring affected individuals can benefit from the latest advancements in management protocols.

Keywords: Neuronal ceroid lipofuscinosis, NCLs, neurodegenerative disorder, gene.

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