NEUROPSYCHOMOTOR DELAY AND MOVEMENT DISORDERS IN THE CHILD OF CONSANGUINEOUS PARENTS WITH A LIKELY PATHOGENIC VARIANT IN THE MSTO1 GENE

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INTRODUCTION

Pathogenic variants in the MSTO1 gene have been associated with mitochondrial disorders of neuromuscular and neurodegenerative presentation, such as progressive myopathy, optic atrophy, cerebellar ataxia, and neuropsychomotor developmental delay. This gene encodes a protein involved in mitochondrial dynamics, especially in the fusion process, whose dysfunction compromises the integrity and function of mitochondria, contributing to the wide range of clinical manifestations observed. Neurodevelopmental disorders with severe motor manifestations and nonspecific dysmorphisms represent important challenges for clinical diagnosis.

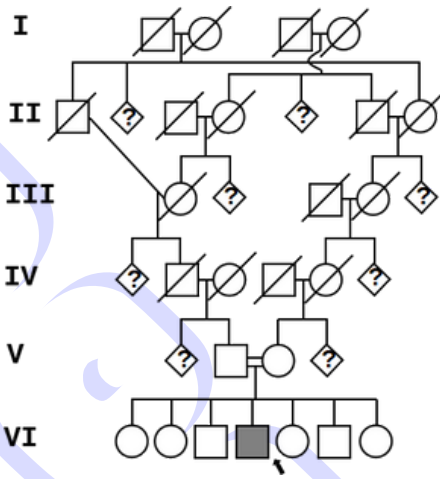
OBJECTIVE

1. To report a patient with neuropsychomotor delay associated with ataxia, presenting a rarely reported variant in the MSTO1 gene in heterozygosity;
2. To highlight the potential role in expanding the clinical spectrum related to this gene.

CASE DESCRIPTION

A 20-year-old male patient sought genetic evaluation with a syndromic condition that began in early childhood, characterized by neuropsychomotor delay, severe motor impairment, and mild dysmorphisms. He is the fourth child of seven born to a double consanguineous couple (see pedigree). Physical examination revealed short stature, an elongated face, micrognathia, high-arched palate, hyperlaxity of the large joints, mild scoliosis, pes cavus and varus, and the use of a hearing aid. A targeted neurological evaluation revealed hypotonia with mild proximal muscle weakness, hyporeflexia, cerebellar ataxia, and difficulty walking. Brain examinations and magnetic resonance imaging (MRI) (June 24, 2024; October 26, 2024) identified diacrete and diffuse cerebellar atrophy, signs of periventricular gliosis, and diffuse thinning of the optic nerves. G-banded karyotype was normal (46,XY). Genomic analysis by exome sequencing identified a heterozygous deletion in the MSTO1 gene (c.887_888delTT, p.Leu296fs), classified as pathogenic according to the ACMG criteria.

This is a frameshift mutation with high predicted functional impact, which leads to premature interruption of protein translation. The variant was not identified in population databases such as GnomAD and ClinVar, reinforcing its rare nature. The alteration found in the patient was previously reported as associated with mitochondrial myopathy syndrome with cerebellar atrophy and pigmentary retinopathy by a Brazilian group (ClinVar SCV002523976.1).



DISCUSSION

Alterations in MSTO1 have been associated with muscle weakness, cerebellar ataxia, and cognitive impairment. The convergence between clinical and molecular findings supports the diagnostic relevance of the variant and raises the hypothesis of a possible genotype-phenotype correlation, suggesting a phenotypic expansion related to the gene. Complementary exams were performed for more precise phenotypic characterization, including magnetic resonance imaging, bone age assessment, and fundus examination. The case reinforces the importance of genetic-clinical analysis in neuromuscular disorders of uncertain origin.

REFERENCES

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