CLN3 pathogenic variants: Brazilian's first case report of non-syndromic retinal degeneration

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INTRODUCTION

CLN3 is a gene located in 16p12.1 and encodes battenin, a transmembrane protein containing 438 aminoacids. The exact cellular function of battenin is still unclear but appears to be linked with vesicular addressing and trafficking, posttranslational protein modification, autophagy, and overall lysosomal function.[1]

Variants in CLN3 are known to lead to the juvenile form of neuronal ceroid lipofuscinosis (NCL), also known as Batten disease (MIM #204200), a severe neurometabolic disease that leads to neurodegeneration. NCL is a genetically heterogeneous group of metabolic disorders with lysosomal involvement and accumulation of ceroid material. However, variants in this gene have recently been associated with non-syndromic inherited retinal degeneration (IRD).[2]

CASE REPORT

A male patient from Salvador, Bahia, currently in his sixth decade of life, developed progressive visual loss at the age of thirty. During this same period, he was diagnosed with retinitis pigmentosa. Exome sequencing of the patient identified biallelic compound heterozygotic variants in CLN3 classified as pathogenic and probably pathogenic, respectively: c.1000C>T and c.868G>T. Although this gene is associated with severe early-onset neurodegenerative condition, on clinical examination, the patient does not present any signs or symptoms of neurologic abnormalities. Four of his seven siblings had similar visual impairment, initiated in the third decade of life without neurologic symptoms associated. The patient's children, now 39 years old each, had no visual symptoms, until date.

DISCUSSION AND CLOSING COMMENTS

Several genes associated at first with syndromic pathologies were later found to cause isolated retinal disease without syndromic features. Alongside CLN3, other examples include BBS1, which can cause either Bardet-Biedl syndrome or non-syndromic retinitis pigmentosa when mutated.[3] CEP290, associated with Joubert syndrome or isolated Leber Congenital Amaurosis,[4] also, pathogenic variants in a major ciliopathy associated gene, USH2A, account for about 20% of cases of isolated autosomal-recessive retinitis pigmentosa.[5-7]

Despite being the first brazilian IRD due to CLN3 pathogenic variants reported, both variants are not novel in the literature. The first variant was found reported in compound heterozygosity with Ex8_9del as an allele, associated with delayed-onset JNCL (neurological symptoms occurring years after initial visual involvement) in a family originating from Netherlands, while the latest variant was found in biallelic compound heterozygosity with a nonsense variant (c.966C>G, p.Y322*) in a Sicilian patient in the fourth decade of life with disease restricted to retina. A more prolonged course of ceroid lipofuscinosis, consistent with the diagnosis of Kufs disease (adult-onset ceroid lipofuscinosis), is in the spectrum of clinical manifestations of biallelic variants in CLN3. To conclude, it is necessary to be cautious about the potential neurological outcome if a pathogenic variant in CLN3 is detected in a case of presumed isolated retinal degeneration, as neurological symptoms may be delayed, making it hard to predict. Testing family members to determine the segregation of variants and functional studies of novel CLN3 variants could be beneficial for deciphering the retinal degeneration pathophysiological mechanism.

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