COMPOUND HETEROZYGOSITY IN THE USH2A GENE: JUST RETINITIS PIGMENTOSA OR AN ATYPICAL FORM OF USHER SYNDROME?

João Ivanildo da Costa Ferreira Neri; José Eduardo Kroll; Tayna da Silva Fiuza; Rafaella Sousa Ferraz; Gisele Guiçardi Tomazella; Sandro José de Souza.

Liga de Mossoró de Estudos e Combate ao Câncer; DNA GTx Bioinformatics; Bioinformatics Multidisciplinary Environment (BioME UFRN); Federal University of Rio Grande do Norte (UFRN).

INTRODUCTION

Usher syndrome (USH) is a rare disease involving progressive vision loss, beginning in childhood and associated with retinitis pigmentosa (RP) and sensorineural deafness. The severity of this disease, together with vestibular function, classifies USH into three types: type 1 is the most severe, with profound hearing loss and absence of vestibular function, while type 2 has moderate to severe congenital deafness and normal vestibular function, and type 3 begins between the second and third decades of life and vestibular function ranges from mild to normal. However, there is a large overlap in clinical signs and symptoms between the different subtypes.

OBJECTIVE

1. To present a patient with compound heterozygosity in USH2A (Chr1q41) presenting only late-onset RP without hearing loss and a history of similar symptoms on both sides of the family;
2. To discuss the possibility that the variants found are determinants of late-onset USH or only RP.

CASE DESCRIPTION

A 43-year-old female patient sought genetic evaluation due to RP that began in her forties, and progressed relatively rapidly, with no other complaints. She is the eldest of two children born to a non-consanguineous couple. Only her brother reports a similar condition in the family, but he shows no interest in investigating his condition. Genomic analysis by exome sequencing identified two heterozygous variants in the USH2A gene: the first, c.15089C>A (p.Ser5030), a gain-of-stop mutation, classified as pathogenic, with high functional impact; the second, c.907C>A (p.Arg303Ser), a missense variant, classified as likely pathogenic.

Both variants are associated with Usher syndrome type 2A and syndromic RP, with autosomal recessive inheritance. The pure tone and vocal impedance audiometry tests (August 19, 2025) were normal in both ears. The brainstem evoked auditory potentials test (August 19, 2025) identified the absence of wave I in the right ear at an intensity of 80 DBNHL, which confers hearing loss for high tones. The CLRN1 (Usher 3A) and HARS1 (Usher 3B) genes do not present significant variants.

DISCUSSION

The variants found in this patient are associated with Usher syndrome type 2A and syndromic RP, with autosomal recessive inheritance. However, there are reports of compound heterozygosity for these variants in combination with other variants. The p.Ser5030 variant was previously identified as one of the most frequent in RP patients in South America, while p.Arg303Ser has been reported in Portuguese patients with visual and hearing impairment. The identification of these two variants in a single individual raises the question of whether this is isolated retinitis pigmentosa or atypical USH type 2A. The clinical and laboratory data from this case reinforce the importance of understanding the genotype-phenotype correlation of conditions with genetic etiologies and highlight the importance of detailed analysis and follow-up of each case.

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CONTACT US

www.dnagtxbioinfo.com | contact@dnagtxbioinfo.com | (84) 3113 5085