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Novel Compound Heterozygous USH2A Splice-Site Genotype Associated with Nonsyndromic Retinitis Pigmentosa: A Case Report

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Abstract

Retinitis pigmentosa (RP) is an inherited retinal disorder characterized by progressive photoreceptor degeneration and vision loss. We report a 67-year-old Chinese male with nonsyndromic RP presenting with nyctalopia and peripheral vision loss since mid-adulthood, and progressively developed a visual acuity of 20/50 in the right eye and light perception in the left eye. Fundus examination revealed typical bilateral RP features, with the left eye more severe. Retinal imaging demonstrated ellipsoid zone loss, outer retinal tubulations, and diffuse thinning of both outer and inner retinal layers. Audiologic evaluation was normal. Genetic testing identified compound heterozygous splice-site variants in USH2A (c.3812-2A>G and c.8559-2A>G), both affecting conserved splice acceptor sites and classified as pathogenic or likely pathogenic. Although each variant has been reported individually, clinical characterization of c.3812-2A>G is limited, and this genotype has not been previously described. This case adds to the understanding of USH2A-associated RP and highlights the importance of genetic testing, particularly for identifying splice-site variants that may inform future therapeutic approaches.

Abbreviations

RP: Retinitis Pigmentosa; USH2A: Usher Syndrome Type 2A; USH2: Usher Syndrome Type II; RPE: Retinal Pigment Epithelium; OCT: Optical Coherence Tomography; EZ: Ellipsoid Zone; RNFL: Retinal Nerve Fiber Layer; GCL: Ganglion Cell Layer; CDR: Cup-to-Disc Ratio

Introduction

Retinitis Pigmentosa (RP) is a genetically and clinically diverse group of inherited retinal disorders characterized by progressive degeneration of photoreceptor cells, starting with rods and eventually cones, resulting in severe visual impairment. More than 150 genes contain causative mutations in RP patients [1–3]. Among these genes, USH2A is one of the most common causative genes in patients with autosomal recessive RP [4,5].

The USH2A gene product, usherin, is a large extracellular matrix protein found in the connecting cilium and periciliary region of the retina's photoreceptor cells and is essential for maintaining normal structure and function in these cells [6,7]. Mutations in this gene may cause nonsyndromic RP or Usher syndrome type II (USH2), depending on the degree of residual usherin protein function [8,9].

Splice-site mutations constitute one of the major categories of pathogenic USH2A variants. These mutations involve abnormal

RNA splicing, including exon skipping, intron retention, and the creation of cryptic splice sites [10–12]. These abnormal RNA splicing events lead to the production of a nonfunctional usherin protein, which is associated with retinal degeneration. Notably, abnormal RNA splicing variants, particularly those affecting the USH2A gene, are now considered potential candidates for RNA-based therapeutic interventions [13,14].

The splice-site mutation c.8559-2A>G has been identified as a causative mutation for RP and USH2 in East Asian populations [15–17]. This mutation has been found to cause a loss of function through exon skipping. In contrast, the splice-site mutation c.3812-2A>G has been identified as a causative mutation in USH2A-related retinopathy and has been associated with RP and USH2 [18–20]. However, there has been a lack of phenotypic characterization of this mutation. Therefore, the current study denotes a novel presentation of these two variants occurring together in a compound heterozygous state, specifically c.3812-2A>G/c.8559-2A>G for USH2A-related retinopathy.

Case Presentation

A 67-year-old Chinese male presented with a longstanding history of progressive visual decline. The patient reported nyctalopia and peripheral visual field loss since mid-adulthood, followed by gradual deterioration of central vision. His visual symptoms were highly asymmetric, with near-complete vision loss in the left eye and reduced best-corrected visual acuity in the right eye. There was no family history of inherited retinal disease.

The best-corrected visual acuity was 20/50 in the right eye (OD) and light perception in the left eye (OS). Examination of the anterior segment showed age-related changes in both eyes, with anterior cortical, nuclear sclerotic, and posterior subcapsular cataracts. Funduscopic examination showed classic signs of RP. The right eye exhibited moderate mid-peripheral bone spicule pigmentation, vascular attenuation, and relative macular preservation. In the left eye, there was extensive pigment deposition, severe vascular attenuation, and waxy optic disc pallor, indicative of advanced degeneration. Multimodal imaging further delineated the extent of disease and revealed marked interocular asymmetry. In the right eye, color and red-free fundus photographs revealed attenuated retinal vessels and moderate Retinal Pigment Epithelium (RPE) atrophy, suggestive of intermediate disease (Figure 1). Spectral domain Optical Coherence Tomography (OCT) revealed partial preservation of the central Ellipsoid Zone (EZ), with disruption of the parafoveal EZ, outer nuclear layer thinning, and early outer retinal tubulations (Figure 1,Figure 3). Vertical scan series revealed patchy, asymmetric outer retinal degeneration across the macula. Because of the partial preservation of the inner retinal layer in the central fovea region with mild choroidal hypertransmission, he retained adequate central vision in the right eye. In contrast, multimodal imaging of the left eye demonstrated advanced disease (Figure 2). Fundus photographs showed diffuse RPE atrophy, attenuated retinal vessels, and intensive pigmentary changes. OCT revealed complete loss of the EZ across the entire macula, severe outer nuclear layer thinning, extensive outer retinal tubulations, and marked choroidal hypertransmission, suggesting full-thickness outer retinal and RPE loss. Vertical scan series revealed pan-macular outer retinal collapse with no preserved EZ, suggestive of end-stage disease (Figure 2,Figure 4).

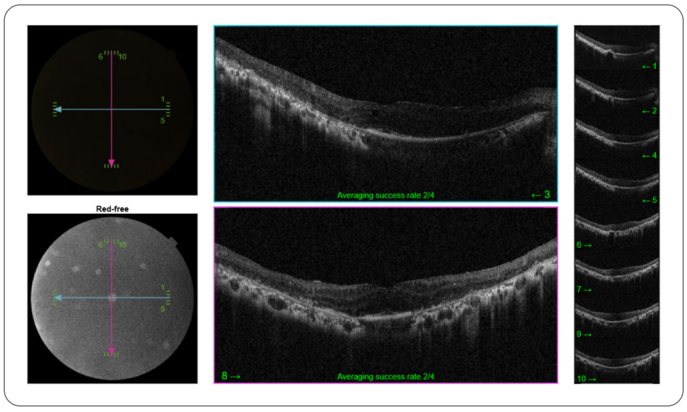

Figure 1: Spectral domain optical coherence tomography of the right eye (OD). Multimodal imaging indicated moderate macular involvement. Color and red-free fundus images showed retinal vascular attenuation and retinal pigment epithelium (RPE) changes (left panel). Central B-scan showed partial preservation of the central ellipsoid zone (EZ) with parafoveal changes, outer nuclear layer thinning, and early outer retinal tubulations (middle panel). A series of parallel line scans confirmed moderate macular degeneration (right panel).

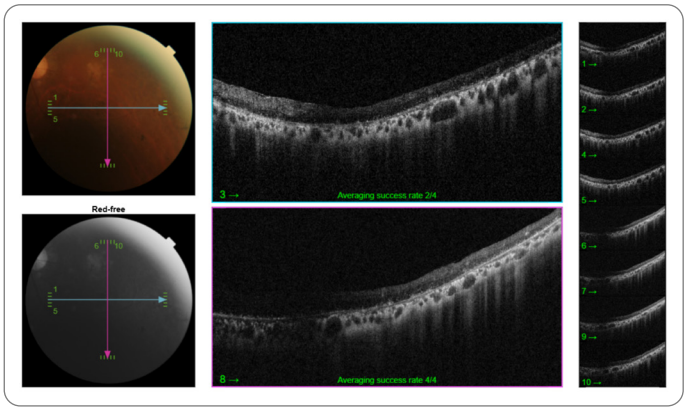

Figure 2: Spectraldomain optical coherence tomography of the left eye (OS). Multimodal imaging indicated advanced macular degeneration. Fundus images displayed diffuse vascular attenuation, widespread retinal pigment epithelium (RPE) atrophy, and pigmentary abnormalities (left panel). Central B-scans showed complete loss of the ellipsoid zone (EZ), severe outer nuclear layer thinning, extensive outer retinal tubulations, and significant choroidal hypertransmission (middle panel). The parallel vertical line scans indicated generalized macular degeneration with uniform EZ loss and near-complete disruption of the outer retinal architecture (right panel). In comparison with the right eye, the left eye displayed much more advanced degeneration, consistent with marked interocular asymmetry in USH2A-associated retinitis pigmentosa.

Quantitative retinal thickness analysis further supported these findings. In the right eye, macular thickness maps showed diffuse thinning, most prominently in the inferior and temporal regions (Figure 3). Retinal Nerve Fiber Layer (RNFL) and Ganglion Cell Layer (GCL) analyses showed significant thinning across multiple quadrants, with an average RNFL thickness of 38 µm, well below the first percentile for his age group, indicating advanced neuroaxonal

loss. The left eye exhibited more severe, diffuse thinning across all macular quadrants than the right eye, consistent with advanced retinal and optic nerve degeneration (Figure 4). Visual field testing using the Humphrey 30-2 and 10-2 SITA-Standard protocol was attempted, but the results were unreliable due to the severity of the patient's nyctalopia, fixation instability, and false-response issues. Despite the lack of reliability, all the results showed significant concentric visual field constrictions, indicative of advanced RP.

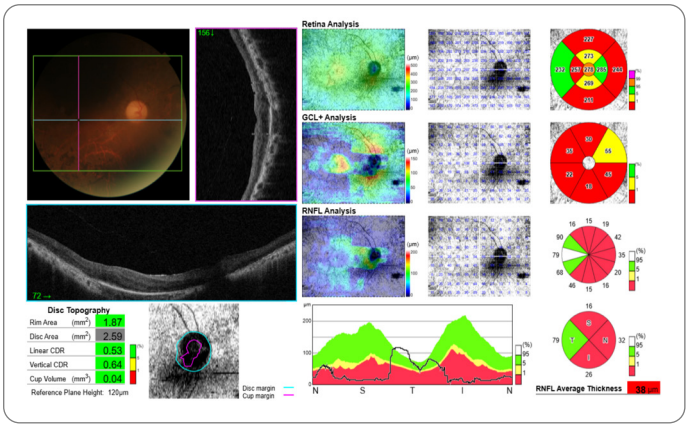

Figure 3: Retinal thickness analysis of the right eye (OD). Retinal thickness maps indicated an intermediate stage pattern of macular and peripapillary degeneration. The color fundus image (top left) showed vascular attenuation and retinal pigment epithelium (RPE) granularity. The cross-sectional images (middle and lower left) demonstrated ellipsoid zone (EZ) disruption, outer nuclear layer thinning, and early signs of outer retinal tubulations, with relative preservation of the fovea. The macular thickness maps (right three panels) showed diffuse thinning, most prominently in the inferior and temporal regions. The retinal nerve fiber layer (RNFL) analysis revealed significant thinning in the superior, nasal, and inferior quadrants, with an average thickness of 38 µm. CDR = cup-to-disc ratio; GCL = ganglion cell layer.

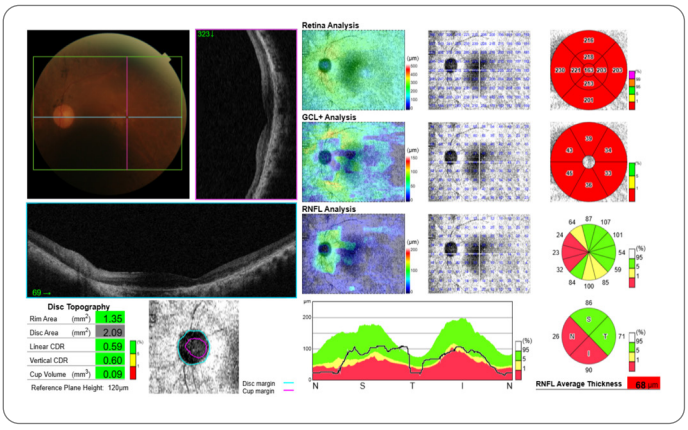

Figure 4: Retinal thickness analysis of the left eye (OS). Retinal thickness maps revealed significant macular and peripapillary degeneration. The color fundus image (top left) showed reduced retinal vasculature, diffuse retinal pigment epithelium (RPE) granularity, and widespread pigmentary changes. The vertical and horizontal B-scan images (middle and lower left) revealed complete loss of the ellipsoid zone (EZ), severe outer nuclear layer thinning, and extensive outer retinal tubulations, consistent with significant photoreceptor degeneration. Macular thickness map, ganglion cell layer (GCL), and retinal nerve fiber layer (RNFL) analysis (right panels) revealed severe diffuse thinning across all quadrants, with measurements below the 1st percentile for age-matched normative values. The average RNFL thickness is reduced to 68 µm, consistent with significant neurodegeneration and correlating with optic disc pallor observed on fundus examination. CDR = cup-to-disc ratio.

Audiologic testing results showed normal bilateral hearing, with no history of congenital or progressive hearing loss or vestibular system dysfunction, consistent with nonsyndromic RP.

Genetic testing identified compound heterozygous variants in USH2A: c.8559-2A>G (pathogenic) and c.3812-2A>G (likely pathogenic). Both mutations affect canonical splice-acceptor sites and are predicted to disrupt normal RNA splicing, resulting in loss of function. Together, these variants form a compound heterozygous genotype consistent with autosomal recessive USH2A-associated RP.

Overall, the patient demonstrated advanced retinitis pigmentosa with significant asymmetric visual loss, diffuse retinal degeneration, optic disc pallor, and severe visual field constriction. The clinical phenotype is consistent with that expected for USH2A-related disorders and supports the pathogenicity of both splice-site variants.

Discussion

This case represents a typical, though advanced, form of USH2A-associated autosomal recessive RP with progressive nyctalopia, peripheral visual field loss, and severe photoreceptor cell degeneration [1,3]. The multimodal imaging findings, including EZ disruption, outer retinal tubulations, and inner retinal thinning, support established structural hallmarks of advanced RP and reflect both primary photoreceptor loss and secondary retinal remodeling [4,18].

The noteworthy aspect of this case is the significant interocular asymmetry: the left eye shows extensive degenerative changes, whereas the right eye retains some macular structural components. Interocular asymmetry in USH2A-related RP has also been documented in other cases [5,21].

From a genetic standpoint, mutations affecting splice sites are a key etiological event in USH2A-related RP. Disruption of canonical splice acceptor sites generally leads to a predictable functional deterioration phenotype, making them of particular interest from both biological and therapeutic standpoints [10–12]. The c.8559-2A>G variant is well documented in the literature, with well-characterized effects on splicing that lead to aberrant protein production [15–17]. On the contrary, the c.3812-2A>G variant has remained poorly studied, with limited clinical data available.

The identification of c.3812-2A>G in trans with a well-known pathogenic variant is strong evidence for its pathogenicity. In autosomal recessive conditions such as USH2A RP, biallelic pathogenic variants are required for disease expression. A severe phenotype in this patient, together with the functional predictions for these variants, supports a loss-of-function mechanism and demonstrates the clinical validity of c.3812-2A>G.

In addition to its implications in diagnosis, this case has significant translational importance. In inherited retinal disease, therapeutic advances are rapidly being realized, with an increasing focus on

precision medicine. Splice-site variants are of particular interest for RNA-based therapeutic intervention, such as antisense oligonucleotide-based treatments to restore normal splicing [11,13,19]. As these treatments move forward in clinical trials, variant-level characterization will be critical for patient selection and treatment eligibility.

This case report contributes to refining genotype-phenotype correlations in USH2A disease through detailed phenotypic and genetic characterization of an underreported variant. This is an important aspect of improving variant interpretation and facilitating therapeutic advances.

Conclusion

This case report presents a novel compound-heterozygous USH2A splice-site variant associated with nonsyndromic retinitis pigmentosa. The findings provide the first detailed clinical characterization of the c.3812-2A>G variant and document the compound heterozygosity with the c.8559-2A>G variant. This report expands the mutational and phenotypic spectrum of USH2A-associated disease and reinforces the value of genetic evaluation in inherited retinal disease. As RNA-based therapies continue to emerge, a precise understanding of splice variants will be essential for advancing personalized treatment strategies.

Key Clinical Message

Rare USH2A splice-site variants may be underrecognized in inherited retinal disease; detailed genotype-phenotype correlation is essential for accurate diagnosis, genetic counseling, and emerging RNA-based therapeutic strategies.

Author Contributions

Claire Xiao: Conceptualization, data collection, data analysis, manuscript drafting, and revision.

Fei Fu: Conceptualization, clinical supervision, data interpretation, and critical revision of the manuscript.

All authors have read and approved the final manuscript.

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Consent

The patient provided written informed consent for the publication of this case report, in accordance with the journal's consent policy.

Data Availability Statement

Data will be made available upon request from the corresponding author.

Conflict of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. Informed consent was obtained for this publication.

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