DOI:10.14744/bej.2024.90235
Beyoglu Eye J 2024; 9(4): 235-240

Case Report

A Case of Autosomal Recessive Retinitis Pigmentosa with Vitelliform-Like Appearance at the Macula Associated with Novel *MYO7A* Variant P.Ser383TrpfsTer64

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Abstract

Retinitis pigmentosa (RP) is an inherited disease involving progressive degeneration of rod and cone photoreceptors. It is highly heterogeneous and the resulting clinical phenotypes may differ in age at onset, progression, and severity. Mutations in the myosin VIIA (MYO7A) gene have been known to cause Usher syndrome, a condition characterized by RP and deafness. In this report, we present a rare case of RP without hearing loss associated with a novel MYO7A variant, p.Ser383TrpfsTer64. With this case, we also wanted to draw attention to the rare vitelliform-like appearance in the macula in patients with RP.

Keywords: MYO7A, retinitis pigmentosa, vitelliform-like macula

Introduction

Retinitis pigmentosa (RP) is the most common hereditary retinal degenerative disease and is characterized by nyctalopia, tunnel vision, and progressive visual loss. The condition is highly heterogeneous, with more than 90 associated genes identified to date (1). Common inheritance patterns include autosomal dominant, autosomal recessive, and X-linked. The enormous heterogeneity of the disease complicates the genetics of RP, and the resulting clinical phenotypes may vary in terms of age at onset, progression, and severity (2,3). Moreover, in addition to the diversity of mutations, different mutations in the same gene can also cause different diseases (4,5). Although RP is usually limited to the eye, it can also occur as part of a syndrome, as in Usher syndrome and Bardet-Biedl syndrome (6,7).

The myosin VIIA (MYO7A) gene is located on chromosome 11 and encodes MYO7A, which is estimated to consist of 2215 amino acids (8,9). MYO7A is primarily expressed in the retinal pigment epithelium (RPE) and photoreceptors and the cochlear and vestibular neuroepithelia of the inner ear. In the retina, MYO7A is involved in the migration of RPE melanosomes, phagocytosis of photoreceptor outer segment tips, and opsin transport through the cilium of these photoreceptors (10).

How to cite this article: Yaman C, Sekeryapan Gediz B, Bahsi T, Teke MY. A Case of Autosomal Recessive Retinitis Pigmentosa with Vitelliform-Like Appearance at the Macula Associated with Novel *MYO7A* Variant P.Ser383TrpfsTer64. Beyoglu Eye J 2024; 9(4): 235-240.

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Submitted Date: July 23, 2024 **Revised Date:** September 08, 2024 **Accepted Date:** September 24, 2024 **Available Online Date:** December 11, 2024

Beyoglu Eye Training and Research Hospital - Available online at www.beyoglueye.com

Although mutations in MYO7A have been known to cause Usher syndrome, a disorder characterized by RP and deafness, here, we present for the 1st time a case of RP without hearing loss and with vitelliform-like appearance in the macula associated with a novel MYO7A variant, p.Ser383TrpfsTer64.

Case Report

A 12-year-old boy presented with complaints of decreased vision in both eyes. He had no known diseases and his parents are not related (negative consanguinity). His best-corrected visual acuity was 20/120 with −0.75 diopter (D) spherical and −1.75 D cylindrical error in the right eye and 20/40 with −0.50 D spherical and −2.00 D cylindrical error in the left eye. Intraocular pressures and anterior segment findings were normal in both eyes. Fundus examination revealed well-circumscribed, yellowish, and lobulated round lesions in the fovea and mild RPE changes in the mid-peripheral and peripheral areas bilaterally (Fig. 1). The macular lesions appeared hyperautofluorescent on fundus autofluorescence (FAF) imaging (VISUCAM 524; Carl Zeiss, Jena, Germany) (Fig. 2a). On fluorescein angiography (FA) (VISUCAM 524; Carl Zeiss, Jena, Germany), there were window defects in the fovea and granular hyper-and hypofluorescence corresponding to the RPE changes in the mid-peripheral and peripheral regions (Fig. 2b). On optical coherence tomography (OCT) (Cirrus HD-OCT 5000; Carl Zeiss, Jena, Germany), sections passing through the fovea revealed no vitelliform material, but there was an increase in thickness in the ellipsoid zone and interdigitation zone in both eyes (Fig. 3). OCT sections passing superior to the macula showed defects in the external limiting membrane and ellipsoid zone (Fig. 4). Full-field electroretinography (ERG) demonstrated decreased rod and cone amplitudes in isolated rod and combined rod/cone responses (Fig. 5). Electro-oculography revealed a normal ratio (Arden ratio) of 1.86 right eye and a subnormal ratio of 1.69 left eye (Fig. 6). Genetic analysis using a RP panel of 41 genes or more, including the BEST1 gene, detected heterozygous MYO7A gene variants c.1135_1147dup (p.ser383TrpfsTer64) and c.3695C > T (p.Pro1220Leu), which are classified as likely pathogenic and of uncertain clinical significance, respectively (Fig. 7). If these variants are found in the compound heterozygous state (transposition), the result can be considered compatible with MYO7A-related autosomal recessive

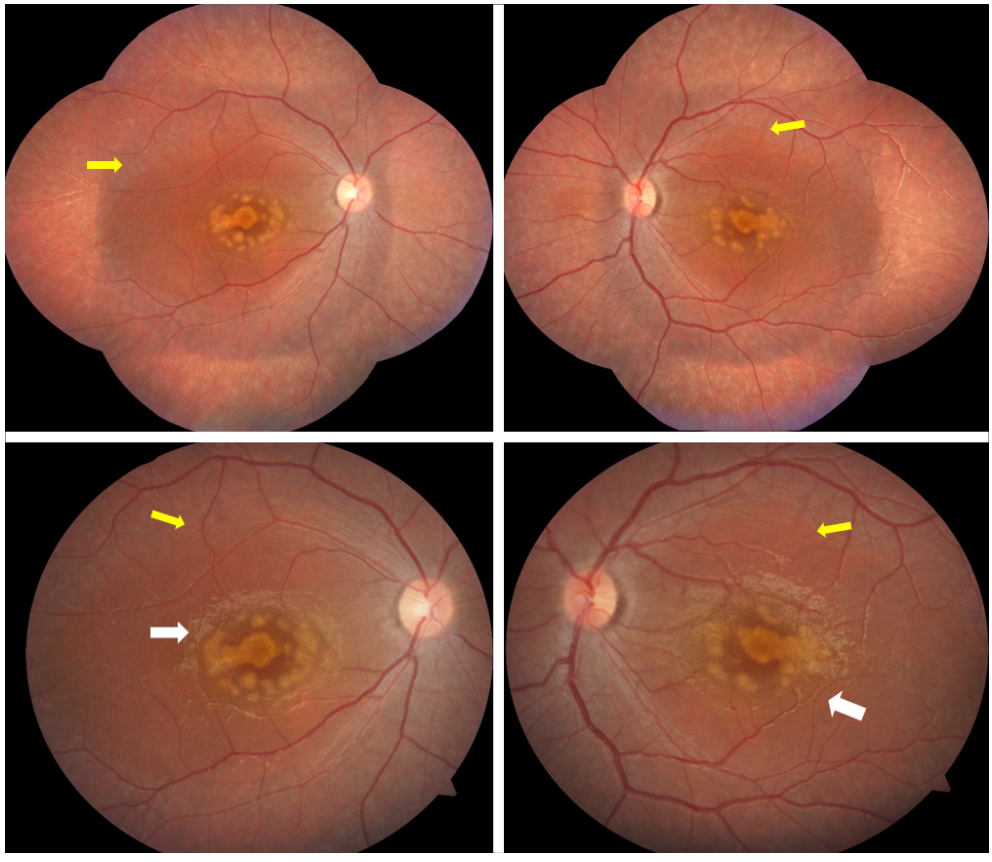

Figure 1. Color fundus photograph covering 7 quadrants (top panel) shows retinal pigment epithelial (RPE) changes (yellow arrow) at the transition from the posterior pole to the peripheral area in the right and left eyes. The image in the bottom panel shows the mid-peripheral RPE changes (yellow arrow) and the vitelliform-like appearance in the fovea (white arrow) in the right and left eyes.

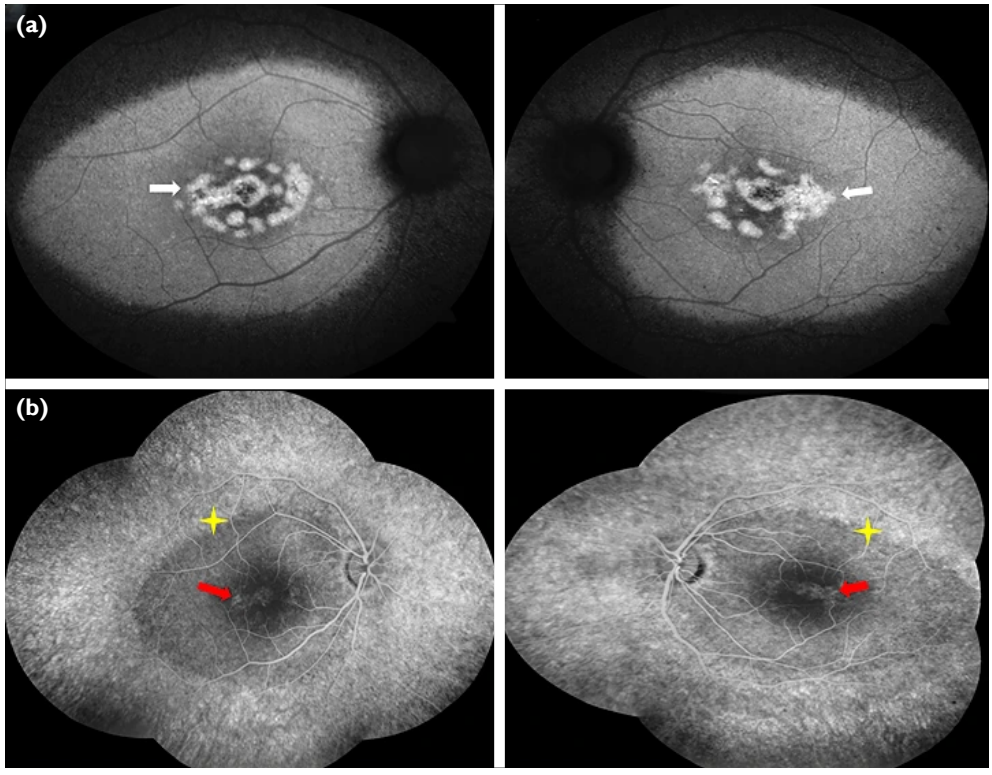

Figure 2. (a) Fundus autofluorescence imaging of the right and left eyes showed a hyperreflective change in the fovea (white arrow). **(b)** Fundus fluorescein angiography of the right and left eyes showed a window defect in the fovea (red arrow) and hypo- and hypergranularity changes (yellow asterisk) in the periphery.

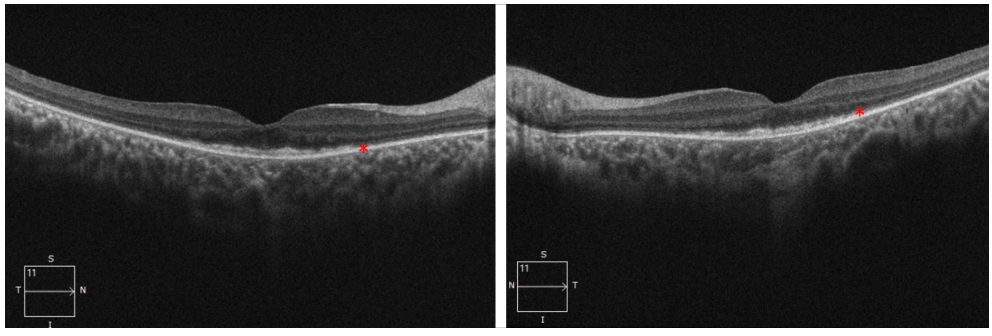

Figure 3. Optical coherence tomography sections passing through the right and left fovea showed no vitelliform-like material but revealed thickening (asterisk) in the ellipsoid and interdigital zones.

inherited diseases. Upon referral to the otolaryngology department, no neuronal hearing loss was detected. Systemic examination performed in the pediatric department was also unremarkable.

Discussion

RP is a clinically and genetically diverse group of retinal dystrophies affecting primarily the rods and subsequently the cones. Progressive degeneration of the retina typically starts in the mid-periphery and advances toward the macula. Regardless of the underlying genetic defect in RP, the common pathogenetic process involves apoptotic photoreceptor cell death. In all forms of RP, the genetic mutation is expressed only in the rods, but cones are also affected. Cone degeneration has been described in all genetic forms of the disease and was suggested to be a result of the release of free radicals into the environment after rod apoptosis (11). Another proposed mechanism is decreased interphotoreceptor retinoid-binding protein (IRBP) immunoreactivity. IRBP is the protein involved in retinoid transport between photoreceptors and the RPE. IRBP was shown to be involved in cone function especially (12).

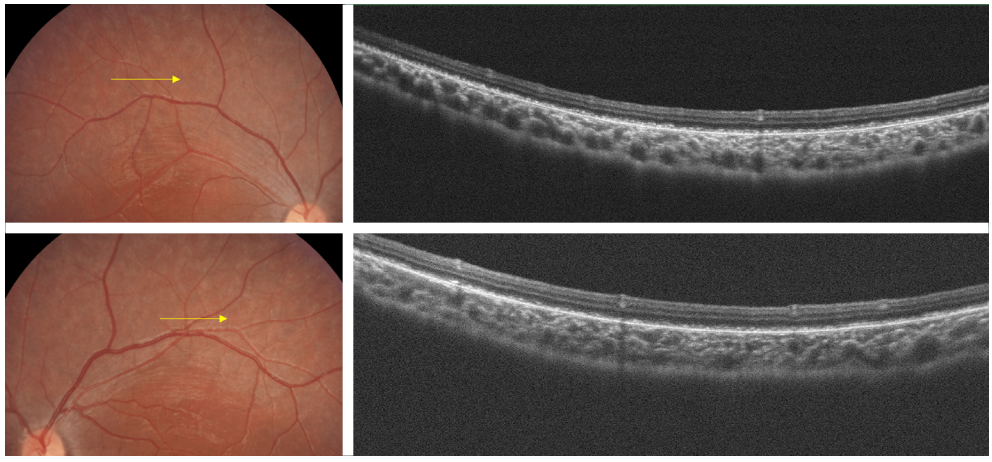

Figure 4. OCT sections passing through the right and left eye superior to the macula (yellow arrow) showed defects in the external limiting membrane and ellipsoid zone.

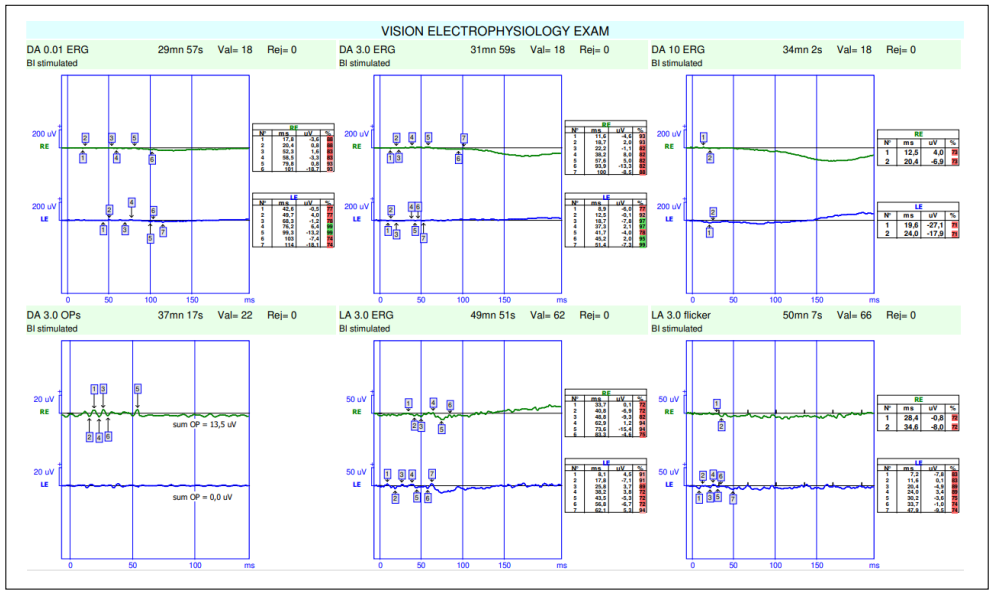

Figure 5. Depressed cone and rod amplitudes were observed on full-field electroretinography.

The most remarkable finding in the fundus examination of our patient was the vitelliform-like appearance in the fovea. This appearance corresponded to OCT findings of increased thickness of the ellipsoid zone and interdigitation zone in both eyes. Although this finding has not yet been described in the literature to our knowledge, it is one of the OCT findings encountered in RP (13). This finding may be caused by material accumulated as a result of disruption of the transport systems between the inner and outer segments of cone photoreceptors. The hyperfluorescence observed on FAF and FA imaging in our patient may also be explained by probable structural changes such as fluorophore accumulation in the subretinal space and a defect in the RPE. Moreover, OCT sections passing through the midperiphery revealed defects in the external limiting membrane and ellipsoid zone. Bone spicules are typical features of the fundus in RP and they have been identified as Muller cells that have phagocytosed melanin granules or translocated RPE cells in response to photoreceptor cell death. Bone spicules may not be seen in early phases and in some forms of RP (14). Fundoscopic findings such as the absence of bone spicules and OCT images of the midperipheral retina may suggest early signs of RP in our case. The patient's full-field ERG findings are also consistent with this explanation.

However, OCT findings and genetic analysis do not support it; our case presents clinical findings of bestrophinopathy-related RP. Bestrophinopathies are five clinically distinct retinal degenerative diseases associated with BEST1 gene mutations (15). Although bestrophinopathy-related RP is a rare disorder, it should come first in the differential diagnosis of our case due to vitelliform-like appearance in the macula. Nevertheless, the absence of vitelliform material in the OCT sections pass-

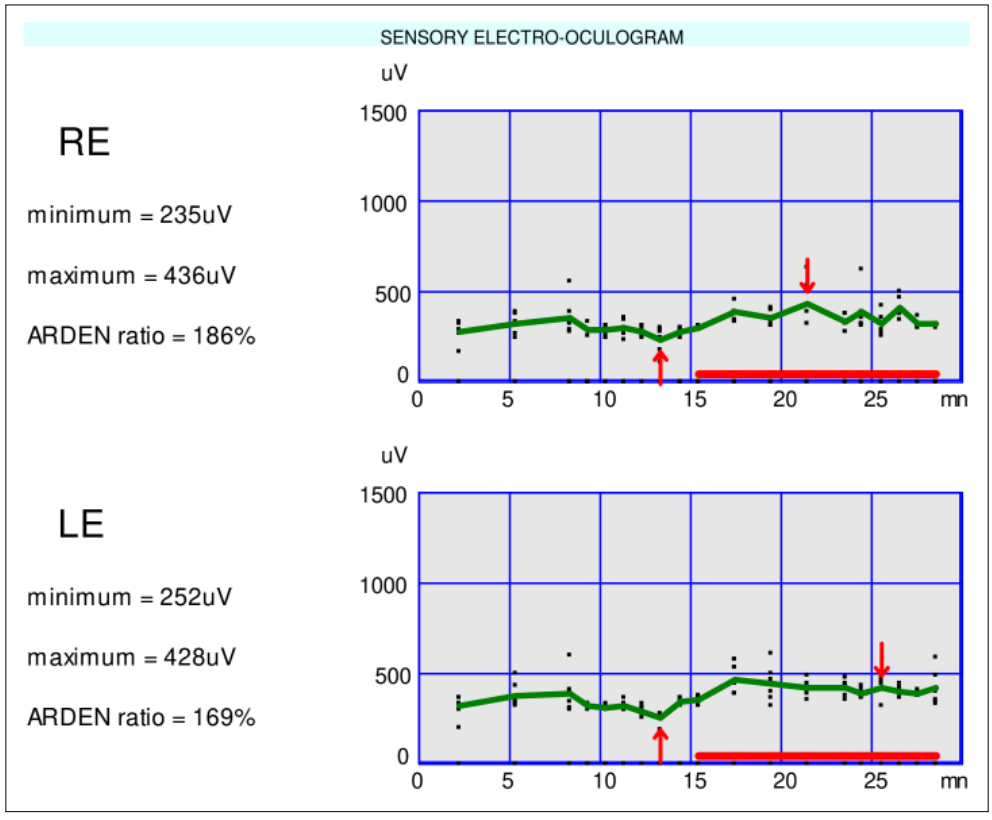

Figure 6. Electro-oculography (EOG) showed that the Arden radio was compromised by 1.86 and 1.69 of the right and left eye, respectively.

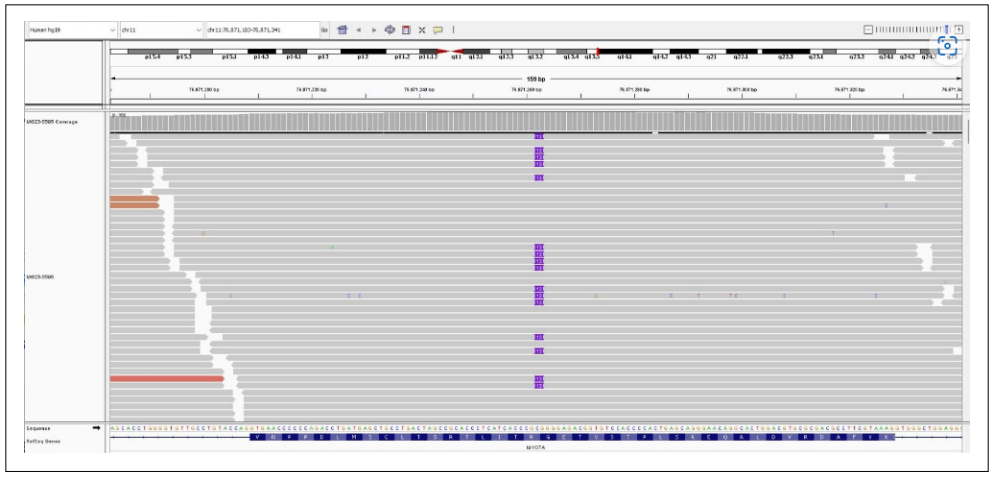

Figure 7. Changes in the myosin VIIA (MYO7A) gene were detected in next-generation DNA sequencing.

ing through the fovea, the absence of mutation in the BEST1 gene, and the fact that the Arden ratio is normal in the right eye and subnormal in the left eye exclude our case from the diagnosis of bestrophinopathy-related RP (16).

Although the MYO7A gene has so far been associated with Usher syndrome, our case is compatible with non-syndromic RP. It is also possible that hearing symptoms have not yet appeared, but considering the patient's age, non-syndromic RP seems more likely. Likewise, the variants in Usherin 2A gene, located on chromosome 1, have been reported to cause Usher syndrome, as well as non-syndromic RP (4). For instance, the c.2299delG variant causes Usher syndrome, while the c.2276G > T variant has been associated with non-syndromic RP (5). However, the reason behind the phenomenon of some variants in Usherin 2A leading to Usher syndrome and others leading to non-syn-

dromic RP remains unknown. Based on these findings, we can propose that our patient with a novel MYO7A variant, p.Ser383TrpfsTer64, has a phenotype of non-syndromic RP.

Conclusion

With this report, we aimed to draw attention to a very rare case of RP with vitelliform-like appearance in the macula. The patient should continue to be followed up for possible future findings and genetic counseling. Further, genotype-phenotype studies are required to identify the difference in MYO7A variants in Usher syndrome and non-syndromic RP.

Disclosures

Informed consent: Written, informed consent was obtained from the patient's family for the publication of thís case report and the accompanying images.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Use of AI for Writing Assistance: Not declared.

Authorship Contributions: Concept – B.S.G.; Design – C.Y., B.S.G.; Supervision – B.S.G., M.Y.T., T.B.; Materials – C.Y., B.S.G., M.Y.T., T.B.; Data collection and/or processing – B.S.G., C.Y.; Analysis and/or interpretation – B.S.G., C.Y.; Literature search – C.Y., B.S.G., M.Y.T., T.B.; Writing – C.Y., B.S.G.; Critical review – B.S.G.

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