Retinal Sensitivity Loss and Beyond in *KCNV2*-Related Retinopathy: The First Genetically Confirmed Case in Türkiye

Özlem Ural Fatihoğlu[1], Ayşe Bozkurt Oflaz[2], Özlem Özkan[1], Hande Taylan Şekeroğlu[3], Ali Osman Saatci[1]

[1]Dokuz Eylül University Faculty of Medicine, Department of Ophthalmology, İzmir, Türkiye
[2]Selçuk University Faculty of Medicine, Department of Ophthalmology, Konya, Türkiye
[3]Hacettepe University Faculty of Medicine, Department of Ophthalmology, Ankara, Türkiye

Dear Editor,

Hereditary retinal dystrophies pose significant challenges in diagnosis and monitoring because of their phenotype-genotype variability and low incidence. *KCNV2*-associated retinopathy, also known as cone dystrophy with supernormal rod response (CDSRR), was first described in the literature in 1983 as a clinical entity characterized by electroretinography (ERG) findings of attenuated and delayed cone and rod responses to low-intensity stimuli and paradoxically elevated b-wave amplitudes with high-intensity flash stimuli.[1] The genetic basis of *KCNV2*-associated retinopathy is biallelic pathogenic mutations in the *KCNV2* gene. The Kv8.2 protein encoded by this gene is a modulatory subunit of the voltage-gated potassium channel in photoreceptors.[2] The disease typically emerges in childhood or adolescence, presenting with symptoms of decreased central vision, photophobia, impaired color vision, and nyctalopia. The diagnosis can be made by evaluating specific clinical findings and ERG results, but genetic analysis is required for definitive confirmation.[1,2]

A review published in 2020 reported that a total of 114 cases of *KCNV2*-associated retinopathy had been described in the literature.[3] However, no genetically confirmed case of *KCNV2*-associated retinopathy has been reported from Türkiye to date. In this letter, we report on a female patient with a homozygous c.782C>A (p.Ala261Asp) variant in the *KCNV2* gene, presenting her detailed electrophysiological, multimodal imaging, and microperimetry findings.

A 35-year-old female patient presented to our clinic with a history of decreased vision, photophobia, and difficulty seeing at night (nyctalopia) since childhood. There was no family history of retinal disease or consanguinity between the parents. She was born at term with no perinatal complications.

Her best corrected visual acuity was 0.1 (decimal) in the right eye with a refractive error of -0.25 diopters spherical and -2.50 diopters cylindrical at 110° axis, and 0.16 (decimal) in the left eye with a refractive error of -1.25 diopters cylindrical at 65° axis. She scored 1/21 bilaterally in the Ishihara color vision test. Anterior segment examination and intraocular pressures were within normal limits.

Fundus examination revealed symmetrical, well-circumscribed circular areas of foveal retinal pigment epithelium (RPE) atrophy in both eyes. Congenital RPE hypertrophy was present in the temporal periphery of the right eye (Figure 1a, d). Autofluorescence imaging revealed hypoautofluorescence in the foveal region (Figure 1b, e). Spectral-domain optical coherence tomography (SD-OCT) demonstrated ellipsoid zone and RPE loss in the central fovea, resulting in a more prominent appearance of the choroidal capillaries (Figure 1c, f). OCT angiography showed filling defects in the foveal area in both eyes, especially in choriocapillaris sections (Figure 2).

In full-field ERG performed in accordance with the International Society for Clinical Electrophysiology of Vision

Keywords: *KCNV2* retinopathy, cone dystrophy with supernormal rod response, electroretinogram, microperimetry, genetic

Cite this article as: Ural Fatihoğlu Ö, Bozkurt Oflaz A, Özkan Ö, Taylan Şekeroğlu H, Saatci AO. Retinal Sensitivity Loss and Beyond in *KCNV2*-Related Retinopathy: The First Genetically Confirmed Case in Türkiye. Turk J Ophthalmol. 2025;55:352-356

Address for Correspondence: Özlem Ural Fatihoğlu, Dokuz Eylül University Faculty of Medicine, Department of Ophthalmology, İzmir, Türkiye
E-mail: drozlemural@gmail.com **ORCID-ID:** orcid.org/0000-0002-5682-5429

Received: 05.09.2025
Revision Requested: 18.09.2025
Last Revision Received: 23.09.2025
Accepted: 28.09.2025
Publication Date: 25.12.2025

DOI: 10.4274/tjo.galenos.2025.03491

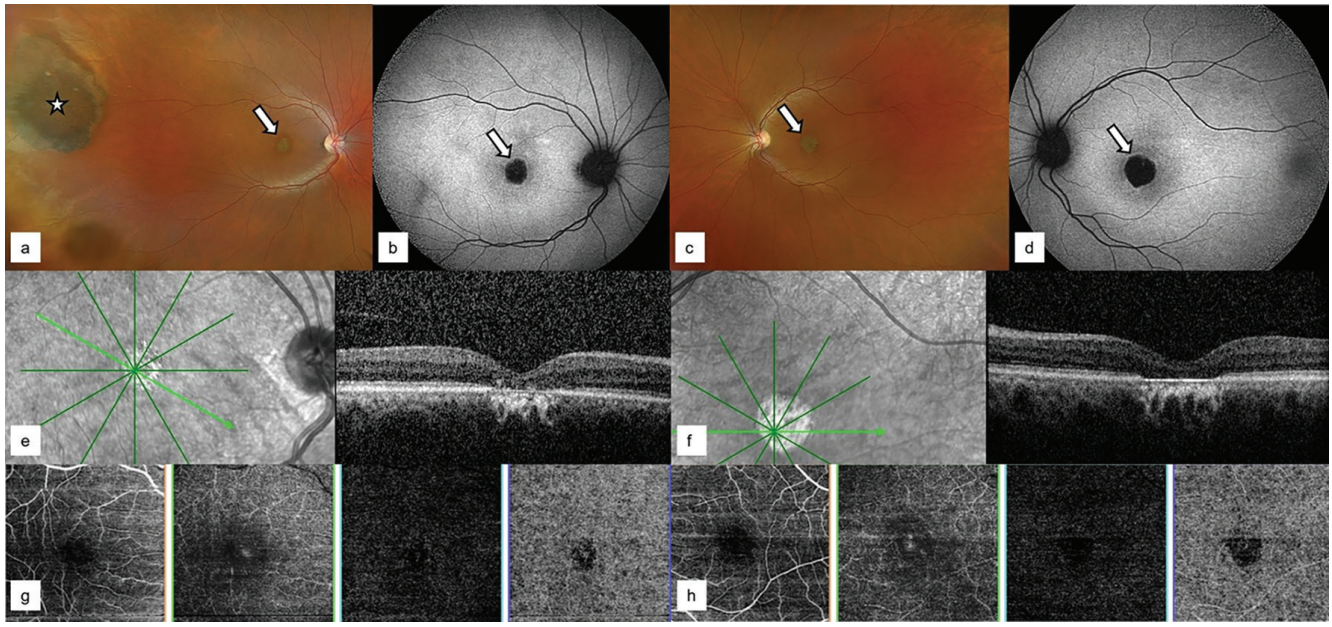

Figure 1. Right eye: a) Well-circumscribed circular foveal retinal pigment epithelium (RPE) atrophy (arrow) and prominent congenital RPE hypertrophy area (star) are observed in the temporal peripheral retina on the colored fundus image; b) Fundus autofluorescence (FAF) image shows central hypoautofluorescence (arrow); e) Spectral domain optical coherence tomography (SD-OCT) reveals increased visibility of choroidal capillaries with loss of ellipsoid zone and RPE in the central foveal region; g) Optical coherence tomography angiography (OCTA) shows filling defect in the foveal area, especially in choriocapillaris sections. Left eye: c) Circular central foveal RPE atrophy (arrow) is observed in the colored fundus image, similar to the right eye; d) FAF image shows symmetrical changes with central hypoautofluorescence (arrow); f) SD-OCT reveals loss of ellipsoid zone and RPE in the central foveal region and associated increased choroidal capillary visibility; h) OCTA shows filling defect in the foveal area, especially in choriocapillaris sections, as in the fellow eye

standards, the dark-adapted 0.01 (DA 0.01) response was delayed and subnormal (Figure 2). Increasing flash intensity (DA 3.0 and combined panel) elicited a supernormal b-wave amplitude. Light-adapted responses (LA 3.0, single flash, and 30 Hz flicker) were delayed and attenuated. On multifocal ERG, reduced amplitudes and prolonged implicit times were recorded in all rings, particularly the central ring of the right eye. These findings supported the diagnosis of CDSRR. Molecular genetic analysis revealed a homozygous c.782C>A (p.Ala261Asp) variant in the patient. One of the parents was a heterozygous carrier but had no visual complaints.

Microperimetry (MAIA, CenterVue, Padova, Italy) confirmed central vision loss and a significant reduction in retinal sensitivity (Figure 3). Mean sensitivity values were between 10 and 15 dB, with pronounced areas of central scotoma. P1 and P2 were 7% and 27% in the right eye and 13% and 49% in the left eye, respectively. According to bivariate contour ellipse area (BCEA) analysis, fixation points were more dispersed in the right eye (63% BCEA: 46.9°², 95% BCEA: 140.5°²) and more stable in the left eye (63% BCEA: 19°², 95% BCEA: 56.8°²). Fixation was in the superonasal region in the right eye and the superotemporal region in the left eye. Eccentric fixation was located 7.6° from the fovea in the right eye and 1.73° from the fovea in the left eye. Sensitivity ≥20 dB was partially preserved in the parafoveal regions.

This case reflects the characteristic clinical, electrophysiological, and genetic spectrum of *KCNV2*-associated retinopathy. The homozygous c.782C>A (p.Ala261Asp) *KCNV2* variant identified in our patient has been previously reported in the literature in patients diagnosed with *KCNV2*-associated retinopathy.[4,5] However, to the best of our knowledge, this is the first genetically confirmed case in Türkiye. Interestingly, the same variant was previously described in a consanguineous Turkish family living in Austria.[4] Two different hereditary retinal dystrophies were detected in the family, with a homozygous p.Ala261Asp variant causing *KCNV2*-associated retinopathy in the mother and a homozygous frameshift mutation in the *MFRP* gene in the son.[4]

The *KCNV2* Retinopathy Study Group identified 75 different variants in 117 patients in their multicenter retrospective series.[2] The disease was shown to have an early onset and a typically stable electrophysiological course, but is characterized structurally by progressive macular atrophy.[2] The OCT findings in our case were consistent with ellipsoid zone loss and RPE defects and corresponded to the advanced stage described in the literature. *KCNV2* Study Group reports 1 and 2 focused on electrophysiological and structural characteristics, respectively, whereas report 3 provided a detailed analysis of genotype-phenotype correlations.[2,6,7] Report 3 also demonstrated the prognostic importance of genetic diagnosis by revealing that best corrected visual acuity and retinal structure are better preserved in patients with missense variants.[7]

Our microperimetry findings showed that central function loss occurs and eccentric fixation strategies are developed in *KCNV2*-associated retinopathy. In this respect, microperimetry offers both functional and topographic information

complementary to ERG and has the potential to be a sensitive biomarker in therapeutic studies.[8]

KCNV2-associated retinopathy is considered a promising candidate for gene therapy because it is a monogenic disorder, the small gene is suitable for therapeutic delivery, and preclinical data indicate that cone cells can be preserved in the early stages of the disease.[3] Furthermore, the fact that the structural changes observed with OCT become pronounced in the later stages of the disease suggests a broad therapeutic window for treatment.[3] In addition, pharmacological approaches such as potassium channel modulators appear theoretically feasible, depending on the effect of the genetic variant on channel function.[3] However, despite these favorable biological and technical conditions, no genetic or pharmacological treatment studies for *KCNV2*-associated retinopathy have been registered in large databases such as ClinicalTrials.gov. This clearly demonstrates the need to develop translational research and clinical trials for this rare disease.

This first genetically confirmed case of *KCNV2*-associated retinopathy in Türkiye was consistent with the phenotype-genotype characteristics described in the literature. Multimodal imaging and microperimetry findings revealed both the structural and functional spectrum of the disease in detail. This case is important as it confirms the presence of *KCNV2*-associated retinopathy in our country, demonstrates the contribution of microperimetry in functional assessment, and may guide future therapeutic studies.

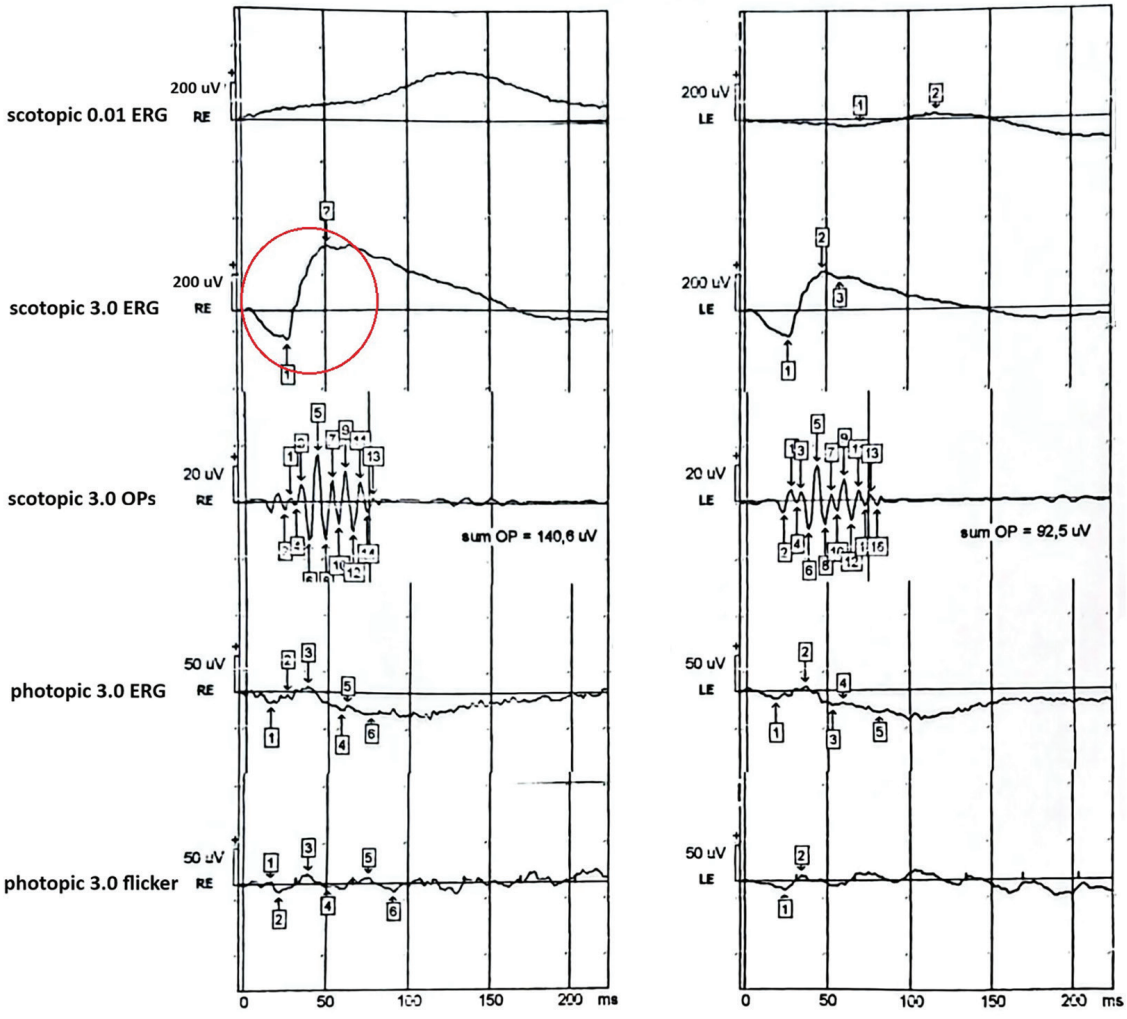

Figure 2. Full-field electroretinography (ERG) of the patient. On scotopic ERG, low intensity flash (dark-adjusted [DA] 0.01) shows delayed b-wave while DA 3.0 ERG shows a large positive b-wave followed by an enlarged negative a-wave (red circle). Photopic ERG showed marked attenuation in both single-flash and 30 Hz flicker conditions
OPs: Oscillatory potentials

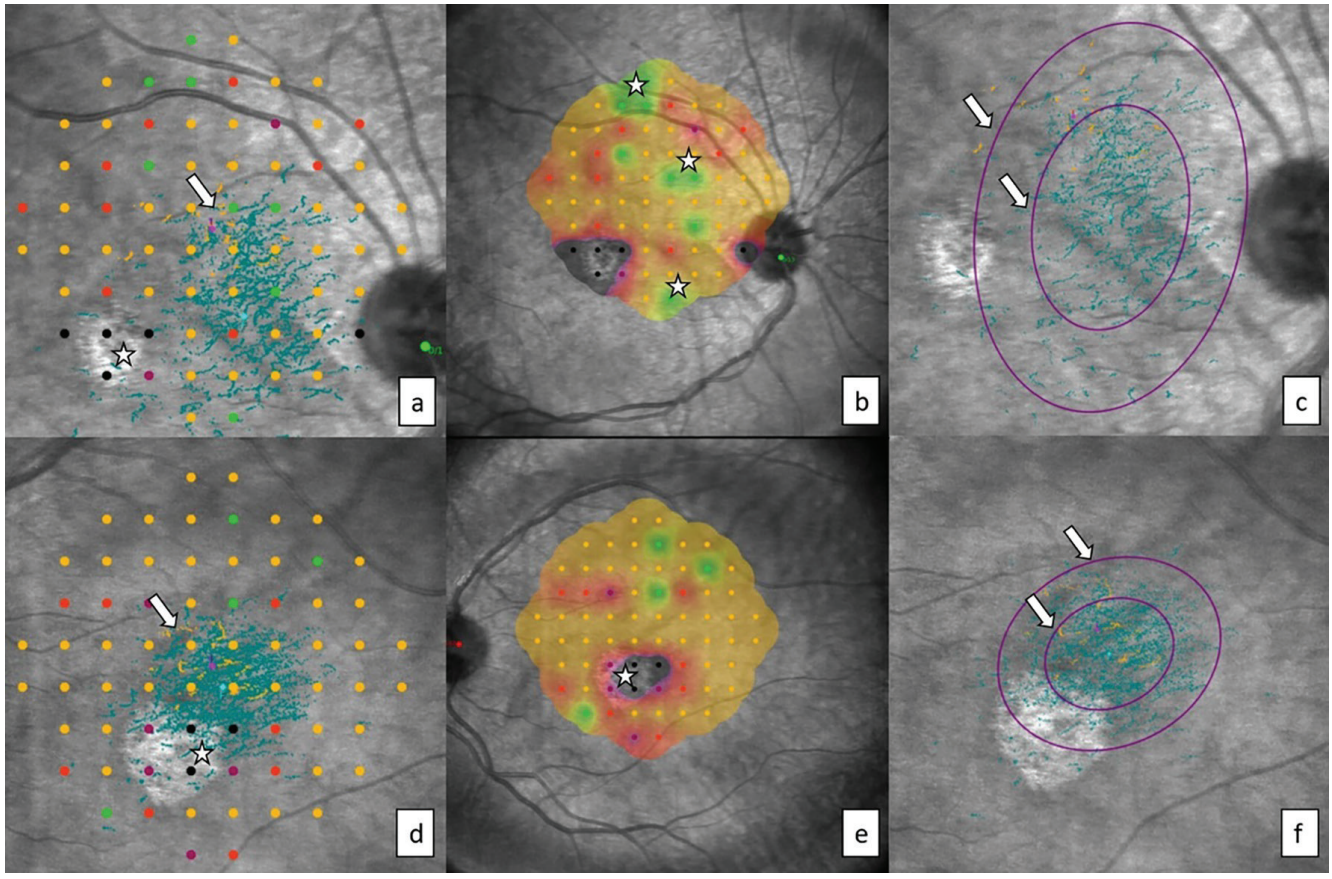

Figure 3. a) Color sensitivity values in the zoomed scanning laser ophthalmoscopy (SLO) image of the right eye show an area of absolute scotoma (star) with black dots in the central region and scattered fixation points (arrow) in the nasal region; b) Retinal sensitivity map of the right eye shows green colored retinal areas measuring ≥25 dB (stars) in the central and parafoveal regions; c) The bivariate contour ellipse area (BCEA) view of the right eye shows a large area (arrow) of scattered fixation points; d) Color retinal sensitivity values in the zoomed SLO image of the left eye show an area of absolute scotoma (star) in the central region and scattered fixation points (arrow) in the superotemporal region; e) In the color sensitivity map of the left eye, the absolute scotoma area (star) is seen in black; f) The BCEA view of the left eye shows a smaller, more limited area (arrow) compared to the right eye

Ethics

Informed Consent: Written informed consent was obtained from the patient for the publication of the clinical findings and visual materials included in this study for scientific purposes.

Declarations

Authorship Contributions

Surgical and Medical Practices: Ö.U.F., Concept: Ö.U.F., Ö.Ö., H.T.Ş., A.O.S., Design: Ö.U.F., A.B.O., Data Collection or Processing: Ö.U.F., Ö.Ö., H.T.Ş., Analysis or Interpretation: Ö.U.F., A.B.O., H.T.Ş., A.O.S., Literature Search: Ö.U.F., A.B.O., Ö.Ö., H.T.Ş., A.O.S., Writing: Ö.U.F., A.B.O., A.O.S.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Wissinger B, Dangel S, Jägle H, Hansen L, Baumann B, Rudolph G, Wolf C, Bonin M, Koeppen K, Ladewig T, Kohl S, Zrenner E, Rosenberg T. Cone dystrophy with supernormal rod response is strictly associated with mutations in KCNV2. Invest Ophthalmol Vis Sci. 2008;49:751-757.
2. Georgiou M, Robson AG, Fujinami K, Leo SM, Vincent A, Nasser F, Cabral De Guimarães TA, Khateb S, Pontikos N, Fujinami-Yokokawa Y, Liu X, Tsunoda K, Hayashi T, Vargas ME, Thiadens AAHJ, de Carvalho ER, Nguyen XT, Arno G, Mahroo OA, Martin-Merida MI, Jimenez-Rolando B, Gordo G, Carreño E, Ayuso C, Sharon D, Kohl S, Huckfeldt RM, Wissinger B, Boon CJF, Banin E, Pennesi ME, Khan AO, Webster AR, Zrenner E, Héon E, Michaelides M. KCNV2-associated retinopathy: genetics, electrophysiology, and clinical course-KCNV2 study group report 1. Am J Ophthalmol. 2021;225:95-107.
3. Guimaraes TAC, Georgiou M, Robson AG, Michaelides M. *KCNV2* retinopathy: clinical features, molecular genetics and directions for future therapy. Ophthalmic Genet. 2020;41:208-215.
4. Ritter M, Vodopiutz J, Lechner S, Moser E, Schmidt-Erfurth UM, Janecke AR. Coexistence of KCNV2 associated cone dystrophy with supernormal rod electroretinogram and MFRP related oculopathy in a Turkish family. Br J Ophthalmol. 2013;97:169-173.

5. Zelinger L, Wissinger B, Eli D, Kohl S, Sharon D, Banin E. Cone dystrophy with supernormal rod response: novel KCNV2 mutations in an underdiagnosed phenotype. Ophthalmology. 2013;120:2338-2343.
6. Georgiou M, Fujinami K, Vincent A, Nasser F, Khateb S, Vargas ME, Thiadens AAHJ, de Carvalho ER, Nguyen XT, De Guimarães TAC, Robson AG, Mahroo OA, Pontikos N, Arno G, Fujinami-Yokokawa Y, Leo SM, Liu X, Tsunoda K, Hayashi T, Jimenez-Rolando B, Martin-Merida MI, Avila-Fernandez A, Carreño E, Garcia-Sandoval B, Ayuso C, Sharon D, Kohl S, Huckfeldt RM, Boon CJF, Banin E, Pennesi ME, Wissinger B, Webster AR, Héon E, Khan AO, Zrenner E, Michaelides M. KCNV2-associated retinopathy: detailed retinal phenotype and structural endpoints-KCNV2 study group report 2. Am J Ophthalmol. 2021;230:1-11.
7. de Guimaraes TAC, Georgiou M, Robson AG, Fujinami K, Vincent A, Nasser F, Khateb S, Mahroo OA, Pontikos N, Vargas ME, Thiadens AAHJ, Carvalho ER, Nguyen XT, Arno G, Fujinami-Yokokawa Y, Liu X, Tsunoda K, Hayashi T, Jiménez-Rolando B, Martin-Merida MI, Avila-Fernandez A, Salas EC, Garcia-Sandoval B, Ayuso C, Sharon D, Kohl S, Huckfeldt RM, Banin E, Pennesi ME, Khan AO, Wissinger B, Webster AR, Heon E, Boon CJF, Zrenner E, Michaelides M. *KCNV2*-associated retinopathy: genotype-phenotype correlations - *KCNV2* study group report 3. Br J Ophthalmol. 2024;108:1137-1144.
8. de Guimaraes TAC, de Guimaraes IMC, Muthiah MN, Kalitzeos A, Michaelides M. Retinal sensitivity in KCNV2-associated retinopathy. Invest Ophthalmol Vis Sci. 2025;66:26.