• Clinical Research •

Identification of novel mutations in the *GRK1* gene in an Algerian family with Oguchi disease

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Abstract

● **AIM:** To describe novel variants in the G protein-coupled receptor kinase 1 (*GRK1*) gene associated with Oguchi disease and to analyze the different multimodal imaging results.

● **METHODS:** Five members of a single family were enrolled, including two confirmed cases of Oguchi disease and three carriers with novel variants in the *GRK1* gene. All subjects underwent a comprehensive ophthalmological examination, including color vision testing, visual field testing, wide-field retinography, fundus autofluorescence, macular optical coherence tomography (OCT), and full-field electroretinography (ERG).

● **RESULTS:** The study found that both cases of Oguchi disease showed positive Mizuo-Nakamura phenomenon, moderate retinal thickening and packing of the three outermost hyper-reflective bands in the parafoveal region. After establishing a clinical diagnosis of Oguchi disease in patients IV-II and IV-III, molecular analysis revealed a similar genotype in the patients, both carrying two heterozygous variants in the *GRK1* gene, the variants c.1055_1056delAC, p.(Tyr352CysfsTer32) and c.699+2T>C. Genetic testing also revealed that individual III-I was a heterozygous carrier of the novel variant c.1055_1056delAC in the *GRK1* gene. In addition, the novel intronic variant c.699+2T>C was detected in the same gene in the heterozygous state in individuals III-II and IV-I. Family segregation showed that Oguchi disease was transmitted in an autosomal recessive pattern in this family.

● **CONCLUSION:** Two novel variants in the *GRK1* gene are reported that are linked to Oguchi disease in a naïve Algerian family. The common findings observed on the OCT scans of our affected patients include packing of the three outer hyper-reflective bands, and thickening of the retina in the parafoveal region. These features are present not only in the affected patients but also in the carriers of the disease.

● **KEYWORDS:** Oguchi disease; *GRK1* gene; Mizuo-Nakamura phenomenon; optical coherence tomography
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INTRODUCTION

Oguchi disease (MIM# 613411) is a rare form of congenital stationary night blindness with only about 50 reported cases worldwide, most of which have been documented in Japan[1]. This autosomal recessive genetic disorder is characterized by a clinical feature known as the Mizuo-Nakamura phenomenon, which is manifested by the disappearance of the golden discoloration of the retina after adaptation to darkness[2-3]. Oguchi disease is divided into two categories depending on the gene involved; Oguchi type 1 is associated with variants in the S-Antigen Visual Arrestin

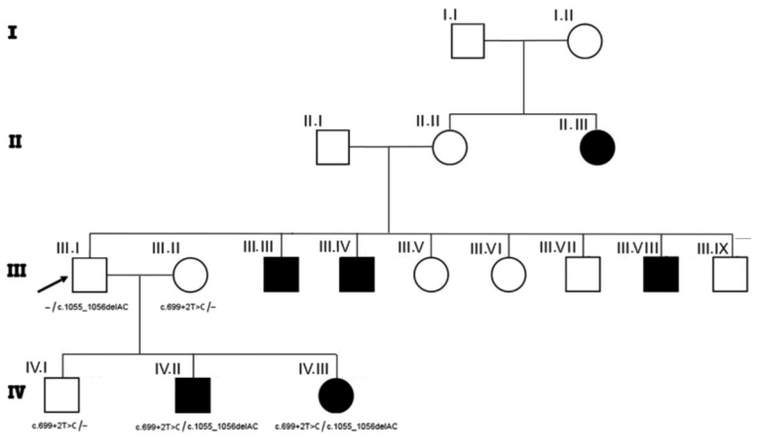


Figure 1 Pedigree of a family of Algerian patients carrying novel variants in the G protein-coupled receptor kinase 1 (*GRK1*) gene.

(*SAG*) gene which encodes arrestin-1, while Oguchi type 2 is caused by variants in the G protein-coupled receptor kinase 1 (*GRK1*) gene, which encodes a G-protein-dependent receptor kinase 1 (*GRK1,* MIM#180381, also called rhodopsin kinase), which is located on chromosome 13q34[4-5].

Both proteins play a key role in the recovery of rhodopsin after photoactivation. Patients typically present with normal visual acuity, visual field, and color vision. The dark adaptation curve may be normal for cones, but not for rods which can reach maximum sensitivity after 4 or 5h of adaptation to darkness. Electrophysiologically, Oguchi patients have normal cone function, delayed rod dark adaptation and severe rod desensitization after a bright flash[6-7]. The rod function is poorly recorded at the first flash after prolonged dark adaptation, and it disappears shortly afterwards[6,8]. Although there are few documented cases, optical coherence tomography (OCT) has revealed packing of the three outer hyper-reflective bands corresponding to the photoreceptor layer and retinal pigment epithelium in the parafoveal region of the retina in these patients[9-10]. In the present report, the clinical outcomes of a family of Algerian patients in which two members show typical clinical features of Oguchi disease confirmed by genetic testing is provided. The primary objective of this report was to describe new variants in the *GRK1* gene that underlie Oguchi disease in these patients, and to identify the different findings observed by multimodal imaging studies.

PARTICIPANTS AND METHODS

Ethical Approval A complete investigation of these cases was carried out after obtaining informed consent from patients and such study being approved by the Ethics Committee of San Juan Hospital of Alicante, Spain (approval number: 02102025).

Five members of a family of Algerian descent (Figure 1) were studied. The two probands, a 12-year-old male and an 8-year-old female (individuals IV-II and IV-III, respectively), were referred to the Ophthalmology Department of the University Hospital of San Juan in Alicante, Spain. Both complained of stationary night blindness since early childhood. Their brother, a 14-year-old asymptomatic male (Individual IV-I), was asymptomatic and had no history of ocular pathology. Individual III.I and individual III.II aged 49 and 39 years old, respectively, were the parents, both denying any general or ocular pathological history. Individuals II-III, III-III, III-IV and III-VIII also reported stationary night blindness since early childhood, but it was not possible to study them because they live in an isolated rural area of Algeria without access to clinical and genetic studies. Since this family has a high degree of inbreeding and consanguinity, we have considered these individuals to be affected and as such they have been marked in Figure 1.

Specifically, a complete ophthalmological examination was performed, including visual acuity measurement with Snellen charts, intraocular pressure measurement with Goldman applanation tonometry, anterior and posterior segment biomicroscopy with and without pupil dilation, color vision testing using Farnsworth-Munsell 100 hue test and visual field testing. For the visual field assessment, the Humphrey Field Analyzer III (Carl Zeiss Meditec, Dublin, CA, USA) was used to perform the central 30-2 Swedish Interactive Threshold.

Algorithm genetic testing was indicated for the family in accordance with the following methodology: Peripheral blood was used to extract DNA from the patients using an automated Qia symphony extractor (Qiagen, Hilden, Germany). The genetic study was performed using Illumina's next-generation sequencing technology (NextSeq 500 equipment, Illumina, Cambridge, UK). Agilent Technologies Custom Constitutional Panel 17MB (New Focused Exome v2, Agilent Technologies, Inc., Santa Clara, CA, USA) gene panel was performed. Both the exons and the flanking intronic regions of the *GRK1* gene were analyzed in detail. Finally, full-field electroretinography (ERG) was recorded using a Natus Synergy evoked potentials/electromyography electrophysiology system (four-channel configuration; Natus, Middleton, WI, USA) and performed in accordance with the standards of the International Society

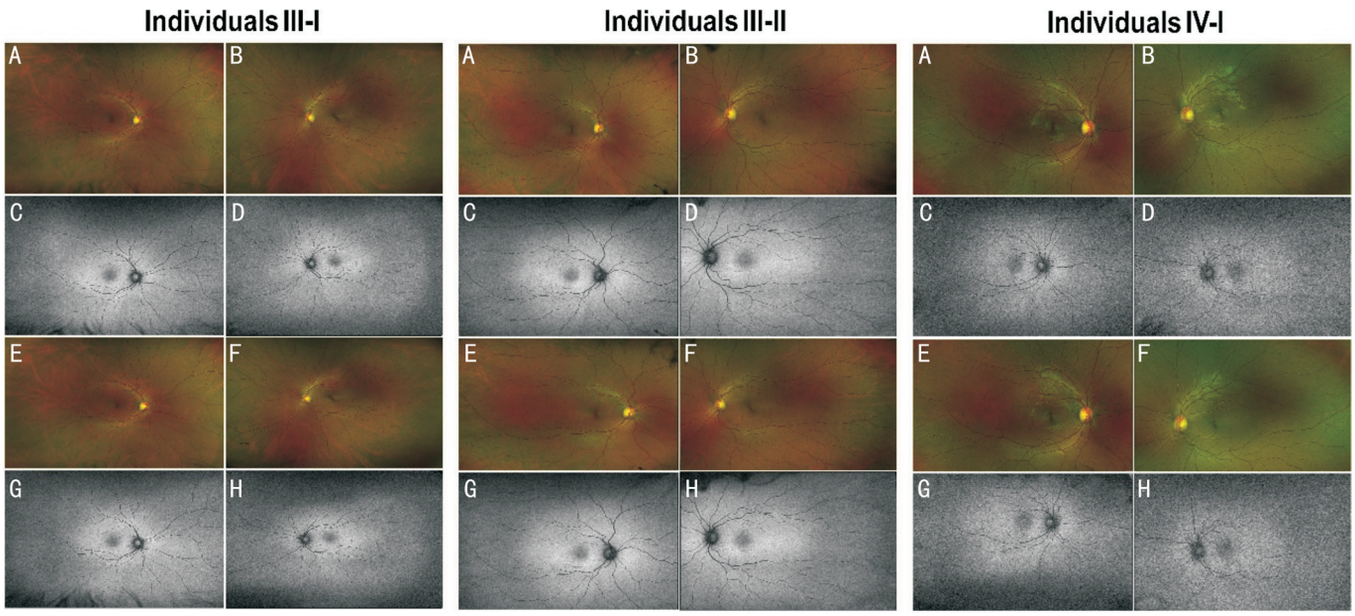


Figure 2 Multimodal retinal imaging in *GRK1* carriers (individuals III-I, III-II, IV-I) Wide-field retinography and FAF under photopic conditions and after 3-hour dark adaptation in OD and OS. Note the absence of Mizuo-Nakamura phenomenon. A, B: Photopic retinography; C, D: Photopic FAF; E, F: Post-dark adaptation retinography; G, H: Post-dark adaptation FAF. *GRK1*: G protein-coupled receptor kinase 1; FAF: Fundus autofluorescence; OD: Right eye; OS: Left eye.

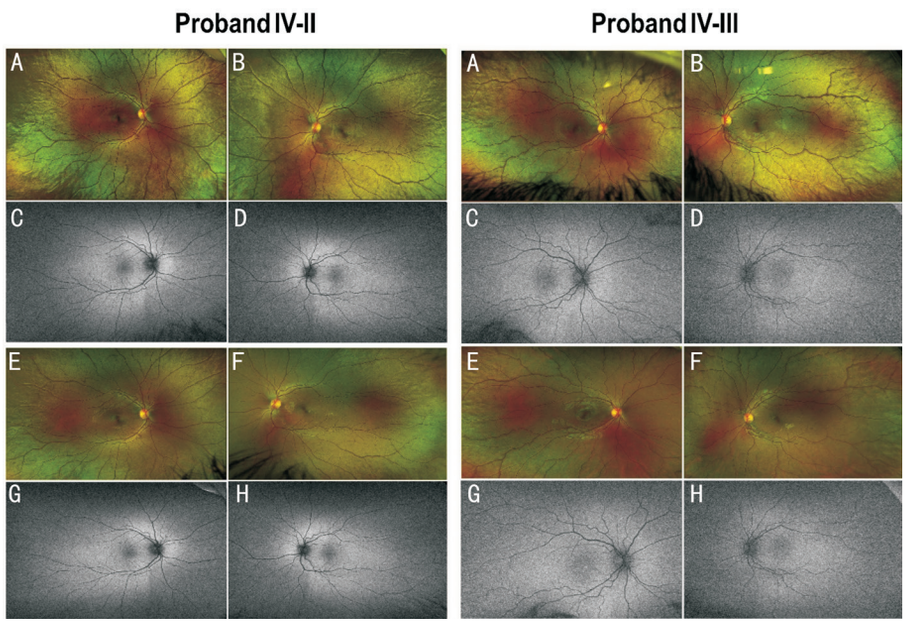


Figure 3 Multimodal retinal imaging in Oguchi disease probands (IV-II and IV-III) Wide-field retinography and FAF in OD and OS under photopic conditions and after 3-hour dark adaptation. Note the Mizuo-Nakamura phenomenon. A, B: Photopic retinography; C, D: Photopic FAF; E, F: Post-dark adaptation retinography; G, H: Post-dark adaptation FAF. FAF: Fundus autofluorescence; OD: Right eye; OS: Left eye.

for Clinical Electrophysiology of Vision[11]. The retinal analysis included the evaluation of the macular area with the OCT system Triton (Topcon Corp, Tokyo, Japan), wide-field retinography and fundus autofluorescence (California Optomap, Optos plc., Dunfermline, Scotland, UK) under photopic conditions and repeated three hours after dark adaptation.

RESULTS

The ophthalmological examination of individuals III-I, III-II, IV-I was normal, including absence of Mizuo-Nakamura sign (Figure 2). Both probands (patients IV-II and IV-III) showed a positive Mizuo-Nakamura phenomenon after three hours of dark adaptation, as observed in the ultra-widefield images (Figure 3). Moderate parafoveal retinal thickening (greater than 300 μm in all cases), with a typical “donut” shape in the color map (Figure 4), and packing of the three outermost hyper-reflective bands at the parafoveal level were observed in all the studied subjects (Figure 4), including affected individuals

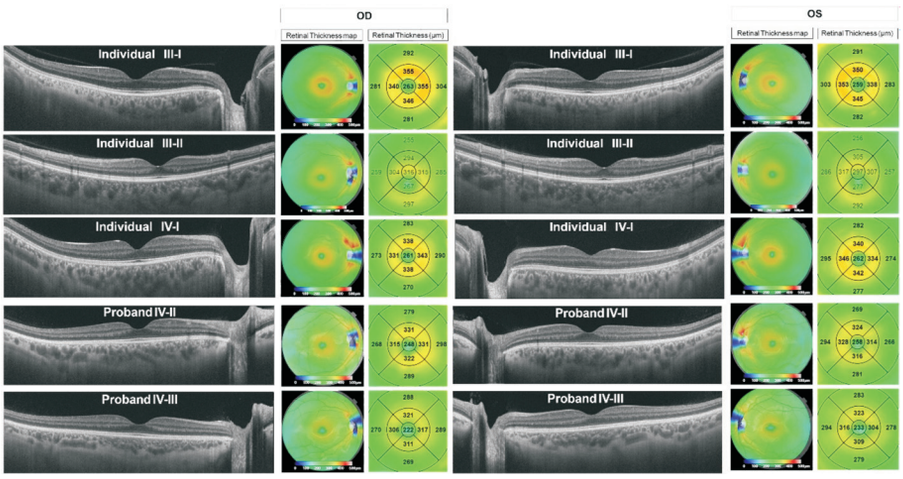


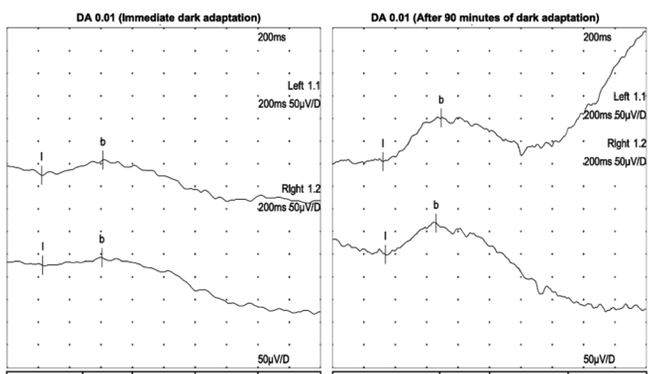
Figure 4 Structural OCT and central 9-zone retinal thickness maps of affected patients and carriers in OD and OS under photopic conditions Note parafoveal packing of outer retinal hyperreflective bands and moderate parafoveal thickening ("donut sign" on thickness maps). OCT: Optical coherence tomography; OD: Right eye; OS: Left eye.

(IV-II and IV-III) and asymptomatic patients (III-I, III-II, IV-I). Ultra-widefield autofluorescence (green) showed an increase in fundus autofluorescence in the parafoveal and peripapillary zones in all subjects (Figures 2 and 3).

Results of Visual Electrophysiological Studies Pattern visual evoked potentials (VEP), pattern ERG, and photopic full-field ERG were normal bilaterally in both individuals (IV-III, IV-II). A full-field (Ganzfeld) scotopic ERG with dark-adaptation testing (brief and 90-min**)** showed a severely reduced b-wave to dark-adapted (DA) 0.01 with only minimal improvement after 90min indicating preserved cone function with severe rod-pathway dysfunction, consistent with Oguchi disease (Figures 5 and 6).

Genetics Results After establishing a clinical diagnosis of Oguchi disease in patients IV-II and IV-III, next-generation sequencing was performed to obtain a genetic diagnosis. Molecular analysis revealed a similar genotype in the patients, both carrying two heterozygous variants in the *GRK1* gene, the variants c.1055_1056delAC, p.(Tyr352CysfsTer32) and c.699+2T>C. No variants were found in the *SAG* gene or other related genes.

The genetic segregation of the family revealed the heterozygous variant c.1055_1056delAC, p.(Tyr352CysfsTer32) in the father of the two probands (individual III-I, asymptomatic) and the heterozygous intronic change c.699+2T>C in their mother (individual III-II, asymptomatic). One brother of the probands (individual IV-I, asymptomatic) was found to be heterozygous for the intronic change c.699+2T>C variant. All these findings allowed us to confirm the diagnosis of Oguchi disease type 2 in our patients.



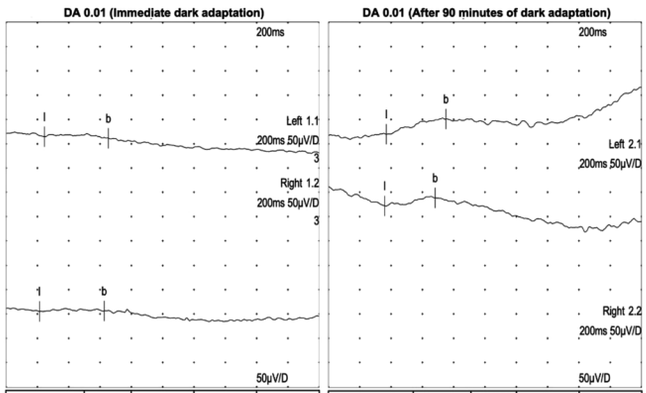
Stimulus / Protocol	Eye	b-wave implicit time (ms)	b-wave amplitude (µV)	Absence
Optic — DA 0.01	OS (Left)	61.3	33.9	—
	OD (Right)	60.6	16.6	—

Stimulus / Protocol	Eye	b-wave implicit time (ms)	b-wave amplitude (µV)
Optic — DA 0.01 (90 min dark adaptation)	OS (Left)	69.4	96.5
	OD (Right)	66.0	69.0

Figure 5 Full-field scotopic ERG recorded under dark-adapted conditions (DA 0.01) using the ISCEV standard protocol Responses correspond to rod-mediated activity recorded immediately and after 90min of dark adaptation in Individual IV-III. ERG: Electroretinogram; DA: Dark adaptation; OD: Right eye; OS: Left eye; ISCEV: International Society for Clinical Electrophysiology of Vision.

DISCUSSION

By combining genetic testing and multimodal imaging techniques, our study identified two individuals with Oguchi disease caused by biallelic *GRK1* variants, performed family segregation, and identified three asymptomatic carriers of heterozygous variants in the cited gene in a naive Algerian family. For Oguchi disease types 2 and 1, as well as for other recessive diseases, an ethnic or geographical distribution has been proposed. This is because *GRK1* variants are thought to be the most common cause of Oguchi disease in South Asian patients and worldwide, and *SAG* variants have been reported mainly in Japanese probands. To date, there are no reports in the literature of Algerian patients with congenital stationary night blindness and clinical and genetic diagnosis of Oguchi disease. To the best of our knowledge, neither the intronic c.699+2T>C variant affecting the splice donor site



Stimulus / Protocol	Eye	b-wave implicit time (ms)	b-wave amplitude (μV)	Absence
Optic — DA 0.01	OS (Left)	63.1	2.3	—
	OD (Right)	62.7	0.97	—

Stimulus / Protocol	Eye	b-wave implicit time (ms)	b-wave amplitude (μV)	Absence
Optic — DA 0.01 (90 min dark adaptation)	OS (Left)	75.0	31.3	—
	OD (Right)	68.1	16.5	—

Figure 6 Full-field scotopic ERG recorded under dark-adapted conditions (DA 0.01) using the ISCEV standard protocol Responses correspond to rod-mediated activity recorded immediately and after 90min of dark adaptation in Individual IV-II. ERG: Electroretinogram; DA: Dark adaptation; OD: Right eye; OS: Left eye; ISCEV: International Society for Clinical Electrophysiology of Vision.

on intron 1, position 2 of 1601 of the *GRK1* gene, nor the frameshift c.1055_1056del, p.Tyr352CysfsTer32 affecting exon 4 at position 70-71 of 84 detected in this family have been reported in the literature. The Mizuo-Nakamura phenomenon was observed in two patients following three hours of dark adaptation and is a characteristic clinical sign of the disease. However, it has also been observed in other retinal dystrophies such as Stargardt disease, autosomal dominant cone dystrophy, X-linked recessive cone dystrophy, and X-linked retinoschisis[3,12-13]. To emphasise the clinical specificity of our findings, it is important to incorporate multimodal imaging and electrophysiology into the differential diagnostic process. In Oguchi disease, OCT typically reveals intact outer retinal architecture without macular atrophy, while full-field ERG shows severe impairment of rod-mediated (DA) responses alongside relatively intact cone-mediated (photopic) function[14-15]. By contrast, Stargardt disease commonly presents with macular atrophy and subretinal flecks. OCT reveals disruption of the outer retina and retinal pigment epithelium at the macula, while full-field ERG is usually normal in the early stages of the disease but abnormal in the advanced stages[16-17]. Autosomal dominant cone or cone-rod dystrophy often shows outer retinal thinning in the macular region on OCT and reduced photopic responses with relatively preserved scotopic responses on ERG in the early phase[18-19]. Therefore, when an appearance similar to that observed in Mizuo-Nakamura disease is seen, it is essential to correlate the fundus phenotype with OCT morphology and ERG dysfunction patterns (rod *vs* cone predominance) to distinguish Oguchi disease from other dystrophies. Although our patients presented clear clinical characteristics of Oguchi disease and genetic testing confirmed the disease conclusively, it is important to highlight the diagnostic specificity of the electrophysiological and imaging characteristics described in this study.

The underlying cause of the Mizuo-Nakamura phenomenon is not yet known, but it is thought to be related to an excess of extracellular potassium in the retina due to a reduced potassium clearance capacity of the retinal Müller cells[12].

Our study also found that central foveal thickness was within the normal range in all patients examined using OCT. However, a slight to moderate increase in the thickness of the four central zones around the foveal center (parafoveal area) was observed in both patients with the disease and carriers. This increase in the parafoveal area produces an image resembling a “donut” in the macular thickness color map, with we refer to as the “donut sign”. Our hypothesis to explain this increase in thickness is related to a possible increase in extracellular potassium levels in the large population of rods found in this region. This alteration may be responsible for the Mizuo-Nakamura phenomenon, as other authors have previously suggested[12].

All patients examined in our study (affected individuals and carriers) showed packing of the three outermost hyperreflective bands under both photopic and scotopic conditions. This observation has been reported previously by several authors[9-10]. Tawfik *et al*[9] studied two Egyptian patients with Oguchi disease and observed a densely packed of the three outermost hyperreflective bands in the parafoveal region using OCT. Similarly, Colombo *et al*[10] described in the parafoveal area a dense packing of the inner/outer segment junction in the retinal pigment epithelium/Bruch’s membrane complex in both eyes with Oguchi disease compared to a healthy age-matched control.

In addition to affected individuals, heterozygous carriers in our series exhibited moderate parafoveal thickening and aggregation of the three outer hyper-reflective bands on OCT, despite normal ERG and absence of the Mizuo phenomenon. Comparable OCT features have been reported in Oguchi disease cohorts[1-3], raising the possibility that partial GRK1 dysfunction may induce subtle structural changes without overt clinical expression. A plausible explanation is that incomplete rhodopsin inactivation in heterozygotes disrupts ionic and osmotic homeostasis at the photoreceptor–retinal pigment epithelium interface, leading to localized extracellular volume changes or altered lamination of the outer retina[4-5]. While our carriers remained asymptomatic with normal electrophysiology, the long-term significance of these findings remains unknown. We suggest that longitudinal multimodal imaging, including quantitative OCT segmentation, OCT-angiography, DA testing, and ERG, will be necessary to determine whether these

structural changes are stable subclinical markers or potential predictors of future disease expression.

In conclusion, our study identified two novel variants in the *GRK1* gene in a family of Algerian descent. The Mizuo-Nakamura phenomenon was clearly present in both symptomatic probands. The most common findings detected by SD-OCT in our patients included packing of the three outermost hyperreflective bands and increased of retinal thickness in the parafoveal region.

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Conflicts of Interest: Molina Martín JC, None; **García GP,** None; **Campos E,** None; **García MM,** None; **Molina Martín LA,** None; **Desco C,** None; **Piñero DP,** None.

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