Check for updates

Original research article

EJO European Journal of Ophthalmology

Cone dystrophy with supernormal rod responses: A rare KCNV2 gene variant

European Journal of Ophthalmology
1–9
© The Author(s) 2021
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/11206721211000000
journals.sagepub.com/home/ejo
SAGE

João Esteves-Leandro[1]*, Sónia Torres-Costa[1]*, Sérgio Estrela-Silva[1,2], Renato Santos-Silva[1,2], Elisete Brandão[1], Ana Grangeia[3], Susana Fernandes[3,4], Renata Oliveira[3], Fernando Falcão-Reis[1,2] and Amândio Rocha-Sousa[1,2]

Abstract

Purpose: To describe the clinical, electrophysiological, and genetic findings of three Portuguese families with a rare variant in the *KCNV2* gene resulting in "cone dystrophy with supernormal rod responses" (CDSRR).

Methods: Retrospective clinical revision of five individuals from three unrelated families with CDSRR. Ophthalmological examination was described in all patients and included color vision testing, fundus photography, fundus autofluorescence (FAF) imaging, spectral domain-optical coherence tomography (SD-OCT), pattern electroretinogram (ERG), and full-field ERG. The mutational screening of the *KCNV2* gene was performed with Sanger and Next Generation Sequencing.

Results: All patients showed childhood-onset photophobia and progressive visual acuity loss with varying degrees of severity. In multimodal imaging, various degrees of retinal pigment epithelium disturbances and outer retinal atrophy, which tend to be worst with advancing age, were observed. Molecular screening identified a rare presumed truncating variant (p.Glu209Ter) in homozygosity in two families and in compound heterozygosity in a third family. Three patients showed ERG changes characteristic of CDSRR, however, two patients presented with incomplete electrophysiological features of the disease.

Conclusion: A rare variant in the *KCNV2* gene was identified in five patients from three Portuguese families. This variant often leads to a severe and progressive form of retinopathy. Considerable variability in the ERG responses among patients with this *KCNV2* variant was observed.

Keywords

Retinal dystrophy, KCNV2, pathogenic variant, electroretinogram, cone dystrophy, retinal degeneration

Date received: 25 December 2020; accepted: 2 February 2021

Introduction

Recessive pathogenic variants in the potassium channel *KCNV2* gene, located on chromosome 9p24, are known to cause "cone dystrophy and supernormal rod electroretinogram" (CDSRR), a rare retinal dystrophy associated with progressive loss of cone photoreceptors and rod system anomalies.[1,2]

KCNV2 gene encodes a silent voltage-gated potassium channel subunit (Kv8.2) expressed in the inner segment of rods and cones. Kv8.2 interacts with members of the Kv2.1 subfamily to form heteromeric channels that produce a voltage-dependent potassium current.[3–5] These channels allow transient hyperpolarization overshoots,

[1]Department of Ophthalmology, Centro Hospitalar Universitário de São João, Porto, Portugal
[2]Department of Surgery and Physiology, Faculty of Medicine, University of Porto, Porto, Portugal
[3]Department of Genetics, Centro Hospitalar Universitário de São João, Porto, Portugal
[4]Institute for Innovation and Health Research (I3S), University of Porto, Porto, Portugal

*These authors contributed equally to this work and should be considered as equal first authors.

Corresponding author:
Sónia Torres-Costa, Department of Ophthalmology, Centro Hospitalar Universitário de São João, Alameda Prof Hernâni Monteiro, Porto 4200-319, Portugal.
Email: sonia.torres.costa@gmail.com

regulating photoreceptor responses to light flashes.[4] Variants in the *KCNV2* gene result in absent potassium channels or pure homomeric Kv2.1 channels with abnormal functional properties, affecting phototransduction, and visual function.[6]

Clinically, CDSRR is characterized by photophobia, visual acuity loss and dyschromatopsia affecting mainly the red-green axis which typically manifests in the first two decades of life.[7–10] Nyctalopia usually presents later in the course of the disease.[8,9] The fundus appearance is variable, often with pigmentary changes at the macula. Fundus autofluorescence (FAF) imaging findings include hyperautofluorescent parafoveal ring encircling areas of hypoautofluorescence that can progressively enlarge.[7,11,12] Spectral-domain optical coherence tomography (SD-OCT) usually demonstrates variable outer retina defects.[12] Notably, the clinical findings are limited to the central macular area and the periphery remains normal.[6,9,12]

Diagnostic features of CDSRR are found in the full-field electroretinogram (ERG) and are exclusively linked to *KCNV2* gene variants.[1,9,10,13–15] The dim light scotopic ERG is either undetectable or subnormal and delayed with a disproportionate increment of rod b-wave amplitude with small increments in stimulus luminance. Also, the rod a-wave shows late squaring with bright flash strengths and cone ERGs are reduced and delayed.[8–10]

More than 90 disease-causing variants in *KCNV2* gene have been reported so far,[2] mainly small insertion and deletion variants.[6,7] However, as far as we know, there are no studies reporting cases of CDSRR in the Portuguese population. The purpose of this study is to describe the clinical and electrophysiological characteristics of a novel variant in the *KCNV2* gene observed in five Portuguese patients from three different families.

Methods

Subjects

Five subjects from three different families from North of Portugal, previously diagnosed with a stationary retinal disorder who carried *KCNV2* gene variants, either in homozygosity or compound heterozygosity were evaluated at the Ocular Genetic Unit of the Ophthalmology Department of Centro Hospitalar Universitário de São João. The procedures used were in accordance with the tenets of the Declaration of Helsinki and received Institutional Review Board approval. Informed consent was obtained from all subjects before each procedure.

Molecular genetics

Following informed consent, genomic DNA was extracted from venous EDTA-blood samples according to standard procedures. In two patients (1 and 2), the coding exons and flanking intronic sequences of the *KCNV2* gene were PCR amplified and sequenced according to methods previously described.[3] Large genomic rearrangements were evaluated by quantitative PCR assay by using three gene-specific amplicons encompassing the coding exons of the *KCNV2* gene.

Next Generation Sequencing (NGS) was performed in patient 3. This consisted in capturing DNA of the described regions with DNA hybridization probes and sequencing it using Illumina's Reversible Dye Terminator (RDT) (Illumina, San Diego, CA, USA). The same variants detected by this method were confirmed in the two siblings of the same family (patients 4 and 5) by Sanger sequencing.

Classification and description of the identified variants were performed according to the international recommendations.[16] Therefore, variants were classified as pathogenic, probably pathogenic and of unknown clinical significance.[16]

Human Genome Variation Society (HGVS) recommendations are used to describe sequence variants. The missense variant identified was analyzed using software prediction programs: BayesDel_addAF, DANN, DEOGEN2, EIGEN, FATHMM-MKL, M-CAP, MVP, MutationAssessor, MutationTaster, PolyPhen2, REVEL, and SIFT.[17,18]

The frequency of the allele variants in general population was estimated according to the Genome Aggregation Database (gnomAD).

Clinical assessment

Clinical assessment in all patients included detailed history, best-corrected visual acuity (BCVA) in logMAR scale, complete ophthalmological evaluation, multimodal imaging including color fundus photography, FAF, SD-OCT, and also electrophysiological study.

FAF images of central $30° \times 30°$ square field were obtained with the Spectralis HRA+OCT with viewing module version *5.1.2.0* (Heidelberg Engineering, Heidelberg, Germany; excitation light, 488 nm, barrier filter, 500 nm).

SD-OCT scans were acquired with the Spectralis HRA+OCT with viewing module version *5.1.2.0* (Heidelberg Engineering, Heidelberg, Germany), including a linear, horizontal scan, centered on the fovea and a volume scan (19 B-scans) for each eye.

Electrophysiological assessments

Electrophysiological tests were performed with Moniteur Ophtalmologique produced by Metrovision. Electrophysiological assessment included full-field ERGs and Pattern-ERG (PERG) performed according to the recommendations of the International Society of Clinical Electrophysiology of Vision (ISCEV).[19,20] Our ERG protocol included (1) Dark-adapted (DA) 0.01, 0.1, and 1 ERG (rod ERG); (2) DA 3 ERG (combined rod-cone standard flash ERG); (3) Light-adapted (LA) 3 ERG (standard flash

"cone" ERG); and (4) LA 30 Hz flicker ERG. The available Ganzfeld stimulator did not support the standard strong flash stimulus of 10 cd s m^2 (strong flash ERG). The ERG was performed with gold-foil electrodes.

Case series description

Clinical findings

The clinical features of the five individuals with *KCNV2* gene variants are summarized in Tables 1 and 2. Patients 3–5 belonged to the same family. No history of consanguineous marriage or familiar history of stationary retinal disorder was documented in the three families. The patient's age at the time of the examination ranged from 25 to 47 years. The first recorded logMAR BCVA ranged from 0.5 to 1.0 while the last recorded logMAR BCVA was between 0.6 and 1.5 (Table 1). All patients complained of color vision problems and photophobia at examination, patient 5 had also nyctalopia complaints. A mild pendular nystagmus was present in two patients (patients 2 and 5). Patient 5 had also a right eye endotropia of 40 PD (Table 2).

Table 1. Demographics and best-corrected visual acuity (BCVA) in logMAR scale of the five cases with *KCNV2* gene variants at presentation and at last examination.

Case	Sex	First recorded BCVA		Last recorded BCVA	
		Age	BCVA OD/OS	Age	BCVA OD/OS
1	F	18	0.5/0.5	25	1/1
2	F	26	1/1	30	1.2/1.2
3	M	7	0.4/0.4	32	0.6/0.6
4	F	9	0.3/0.3	34	1/1
5	F	20	1/1	47	1.5/1.5

F: female; M: male; BCVA: best-corrected visual acuity; OD: right eye; OS: left eye.

Color fundus photographs, FAF and SD-OCT findings are summarized in Figure 1 and Table 3. Fundus appearance ranged from a dull foveal reflex (patient 3), macular mottling of RPE with scattered areas of atrophy (patients 1, 2, and 4) to severe central atrophy (patient 5). FAF images mainly demonstrated decreased central autofluorescence surrounded by a hyperautofluorescent ring (which was barely noticeable in patient 3) and complete central atrophy in patient 5. SD-OCT showed variable loss of the photoreceptor layer in all patients which correlated with the FAF findings. In patient 5, the degree of atrophy was more severe and also included loss of the interdigitation zone.

Electrophysiological findings

Pattern ERGs and full-field ERGs of all five patients are shown in Figure 2 and Table 4. In PERG the P50 waves were undetectable in all patients. In the DA 0.01 ERG, the b-wave amplitude was reduced in patient 1, it was reduced and delayed in patients 3 and 4, and it was not detected in patients 2 and 5. In the DA 0.1 and 1 ERG, a rapid increase in b-wave amplitude was observed. The DA 3 ERG showed a broadened and delayed a-wave trough and a b-wave of supernormal amplitude. LA 3.0 ERG showed an amplitude reduction of the a and b-wave with a more prominent decrease in the b-wave. The 30 Hz flicker amplitude was reduced and delayed. These features were less remarkable in patients 1 and 3. In both these patients, the DA 3 ERG demonstrated a broadened a-wave through, which was also delayed and of higher amplitude, however the b-wave amplitude was within normal values. In patient 1, the b-wave in the LA3 ERG was slightly delayed, but the amplitude was normal.

Molecular genetics

The probably pathogenic variant in *KCNV2* gene was identified in all patients (Table 3) and consisted in a

Table 2. Refraction and symptoms of the five cases with *KCNV2* gene variants.

Case	Refraction	Dischromatopsia	Photophobia	Nyctalopia	Nystagmus	Other
1	Emmetropic Emmetropic	+	+	−	No	
2	−3.75 −0.75 × 90° −3.75 −2.00 × 75°	+	+	−	Present	
3	Emmetropic Emmetropic	+	+	−	No	
4	Emmetropic Emmetropic	+	+	−	No	
5	−1.00 −0.50	+	+	+	Present	ET OD

ET: esotropia.

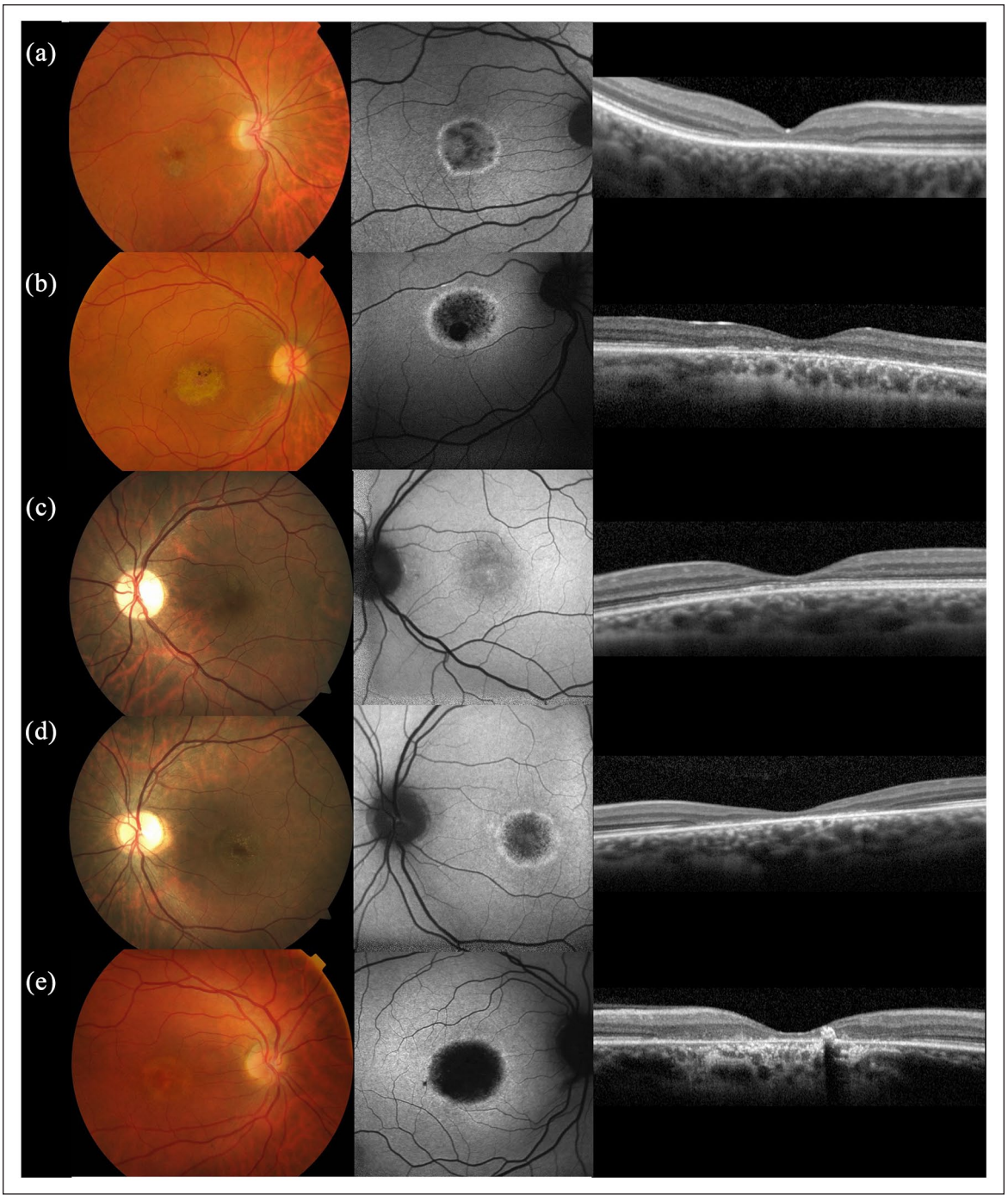

Figure 1. Fundus photographs, fundus autofluorescence images, and SD-OCT of patients with KCNV2 gene variants described in Table 2: (a) case 1, (b) case 2, (c) case 3, (d) case 4, and (e) case 5.

substitution of a G–T in cDNA position 625 (reference sequence NM_133497). The aberrant transcript would lead, if translated, to a premature termination codon p.Glu209Ter in the first extracellular domain (EC1) of the protein. Patients 1 and 2 were homozygous and patients 3–5 (from the same family) were heterozygous for this variant. This variant was previously reported in heterozygosity in one individual from South Asia in the population gnomAD exomes, although it has not been previously reported in disease database (ClinVar) or in the literature. This variant was classified as likely pathogenic according to the recommendations of the American College of Medical Genetics and Genomics (ACMG), based on the extremely low frequency (1:217184 alleles, 0.0000046) in the population database (GnomAD exomes, homozygous allele count = 0); it is a null variant affecting gene

Table 3. Molecular status and retinal findings in the five cases with *KCNV2* gene variants.

Case	Age	*KCNV2* gene variant status	Macular appearance on fundoscopy	FAF imaging	SD-OCT imaging
1	25	c.625G > T (p.Glu209Ter)*	RPE changes with areas of atrophy	Patchy decreased AF surrounded by a ring of increased AF	Loss of the ellipsoid and ELM layers in the fovea, with preservation of the ONL
2	30	c.625G > T (p.Glu209Ter)*	RPE changes with atrophy and pigmentation	Patchy decreased AF and central atrophy surrounded by a ring of increased AF	Epiretinal membrane, Discontinuous loss of the photoreceptor layers in the fovea;
3	32	c.625G > T (p.Glu209Ter)‡ c.457C > G (p.Arg153Gly)‡	Dull foveal reflex	Faint perifoveal ring of increased AF	Discontinuous loss of photoreceptor layers in the fovea
4	34	c.625G > T (p.Glu209Ter)‡ c.457C > G (p.Arg153Gly)‡	Bull's eye type maculopathy	Patchy decreased AF surrounded by ring of increased AF	Mild and discontinuous loss of the ellipsoid layer in the fovea
5	47	c.625G > T (p.Glu209Ter)‡ c.457C > G (p.Arg153Gly)‡	Macular atrophy	Central loss of AF	Complete photoreceptor layers loss; loss of the interdigitation zone

RPE: retinal pigment epithelium; FAF: fundus autofluorescence; AF: autofluorescence; SD-OCT: spectral domain-optical coherence tomography.
*Homozygous state.
‡Heterozygous state.

KCNV2, which is a known mechanism of disease associated with Retinal cone dystrophy 3B; pathogenic computational verdict based on five pathogenic predictions from BayesDel_addAF, DANN, EIGEN, FATHMM-MKL, and MutationTaster; and patient's phenotype highly specific for a disease with a single genetic etiology).[16] Quantitative PCR analysis likely excluded multiexonic and whole-gene deletions/duplications within or encompassing the *KCNV2* gene.

Patients 3–5 (same family) were also heterozygous for a sequence variant designated c.457C > G which is predicted to result in the amino acid substitution p.Arg153Gly, located in the cytoplasmic domain N-terminal A and B box. This variant seems to be rare in the general population, detected in heterozygosity in two subjects (allele frequency of 0.00000809; gnomAD exomes). The amino acid residue Arg in 153 protein position has been highly conserved in the *KCNV2* gene during evolution according to MutationTaster. Also, multiple lines of computational evidence support a deleterious effect of the p.Arg153Gly variant on the *KCNV2* gene (BayesDel_addAF, DANN, DEOGEN2, EIGEN, FATHMM-MKL, M-CAP, MVP, MutationAssessor, MutationTaster, PolyPhen, REVEL, and SIFT). Segregation analysis was not performed since parents were not available. However, analysis of the next-gen sequence data revealed that the *KCNV2* c.625G > T and c.457C > G variants in this patient were localized on opposite chromosomes (*trans*phase).

Discussion

To the best of our knowledge, the present work is the first to describe the clinical and genetic features CDSRR in the Portuguese population. All patients from three different families harbored the same likely disease-causing variant in *KCNV2* gene which was not previously reported in the literature or in the disease database ClinVar. Three patients from the same family also presented a rare variant in heterozygosity in *KCNV2* gene. Although it was not possible to identify a common ancestor to the three families, all patients are from the North of Portugal, indicating a common origin.

All patients presented with photophobia, colour vision abnormalities and central scotomata from the first or second decade and myopia was present in two of them which is consisted with previous reported data.[1,7–9,15] CDSRR is often considered a relatively mild form of cone dystrophy, as most patients have been reported not to progress[6] or at least to maintain a stable BCVA in middle age.[9,21] However, most patients in this series showed a decline in BCVA, with the exception being patient 3, which showed a relatively stable BCVA for more than 20 years of follow-up (decreased from 0.4 to 0.6 logMAR). To noticed that the oldest patient (patient 5) had the poorest BCVA (1.5 logMAR), being the only patient with complaints of nyctalopia, which is known to occur later in the course of the disease.[8]

RPE defects in macular region were evident in all five patients. FAF findings included hyperautofluorescent rings that encircle areas of RPE atrophy. These changes seem to correlate with patient age, as the older patient had a more pronounced area of absent fluorescence (Figure 1). This was also reported in previous studies with KCNV2 retinopathy and other cone-rod dystrophies.[9,22–24] Increased autofluorescence represents the progressive accumulation of lipofuscin in the central macula being a result of the RPE incapacity to metabolize outer segment debris. These changes precede photoreceptor cell death.[9,23,24] In

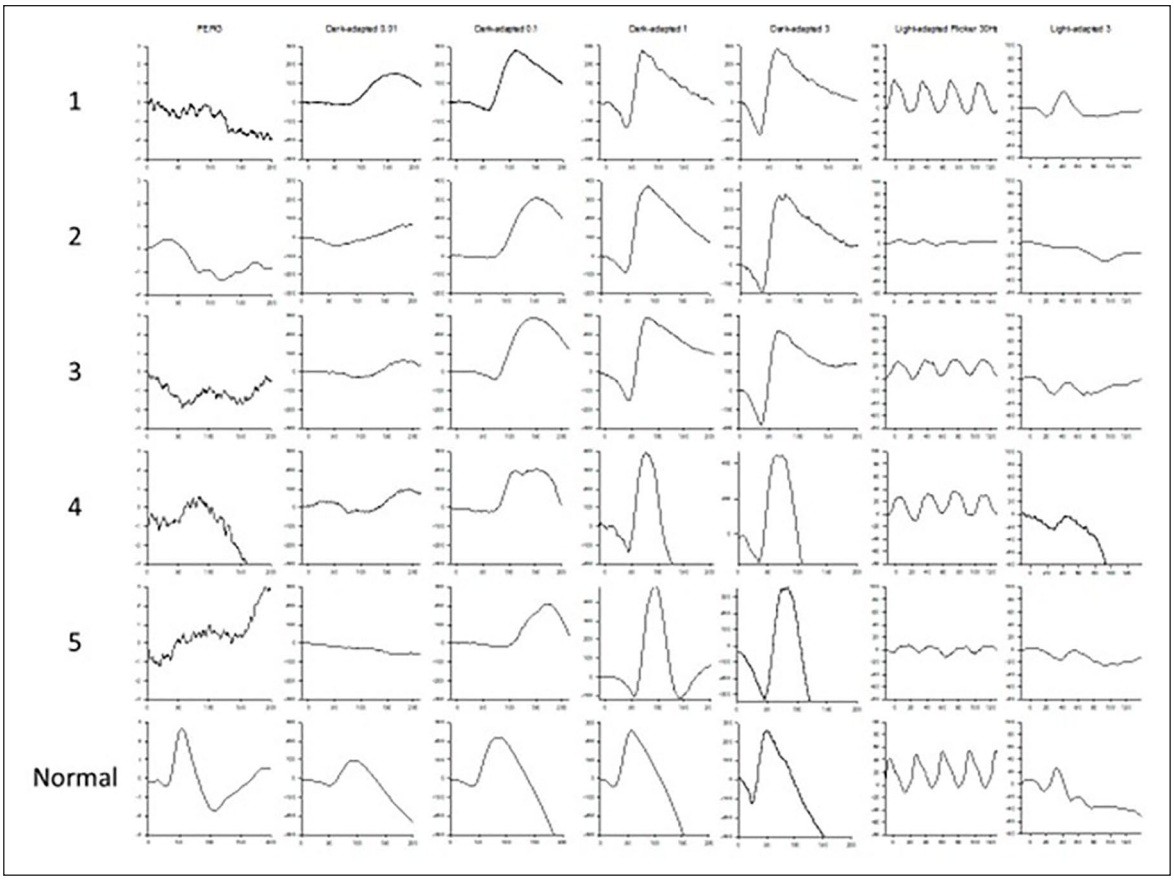

Figure 2. Electrophysiological findings of each patient with KCNV2 mutations. Pattern (PERG) and Full-field electroretinograms (ERGs) of patients 1–5 are shown. The ERGs from a normal control are shown for comparison. Protocol included: Dark-adapted 0.01, 0.1, and 1 ERG; dark-adapted 3 ERG; Light-adapted 30 Hz flicker ERG and Light-adapted 3 ERG. In PERG the P50 waves were undetectable in all patients expect for patient 1 who preserve residual amplitude. In the DA 0.01 ERG, the b-wave amplitude was reduced in patient 1, it was reduced and delayed in patients 3 and 4, and it was not detected in patients 2 and 5. In the DA 0.1 and 1 ERG, a rapid increase in b-wave amplitude was observed. The DA 3 ERG showed a broadened and delayed a-wave trough and a b-wave of supernormal amplitude. LA 3.0 ERG showed an amplitude reduction of the a and b-wave with a more prominent decrease in the b-wave. The 30 Hz flicker amplitude was reduced and delayed. These features were less remarkable in patients 1 and 3. In both these patients, the DA 3 ERG demonstrated a broadened a-wave through, which was also delayed and of higher amplitude, however the b-wave amplitude was within normal values. In patient 1, the b-wave in the LA3 ERG was slightly delayed, but amplitude was normal.

addition, as expected, SD-OCT showed foveal outer retinal layer defects in all patients, also explaining the FAF findings.

KCNV2 gene is expressed in both cone and rod photoreceptors.[3] Fundoscopic, FAF and OCT abnormalities suggest that cones are more vulnerable to the deleterious effects of genetic variants than rods as they did not show unequivocal signs of rod degeneration, such as peripheral loss of RPE.[6,9] PERG abnormalities are indicative of severe macular involvement. On the other hand, full-field ERG revealed a panretinal dysfunction in all affected patients (Figure 2). These findings could suggest that rod dysfunction may not be accompanied by rod degeneration as opposed to what occurs with foveal cones.[25] It was proposed that the retinal distribution of Muller cells could be an important factor, as their regulatory and buffering effect on the extracellular potassium is missing in the cone-rich or foveal area, thereby making cones more vulnerable.[6]

A rare variant (p.Glu209Ter) was found in all studied patients, being in homozygosity (in patients 1 and 2 and in heterozygosity in the remaining patients (from the same family). The aberrant transcript would lead, if translated, to a premature termination codon, resulting in a severely truncated KCNV2 protein and thus, in a nonfunctional channel. The other variant (p.Arg153Gly) found was previously reported as a missense variant which may lead to a KCNV2 protein with residual function, resulting in a milder clinical phenotype. Unfortunately, our findings do not allow us to establish correlations between genomic data and prognosis, since patients 3 and 5 (siblings from this family) showed, respectively, the more benign and severe clinical abnormalities of our cohort. One study

Table 4. Full-field electroretinograms (ERGs) peak times and amplitudes of patients 1–5.

	DA 0.01 ERG		DA 3 ERG				LA flicker 30 Hz ERG		LA 3 ERG	
	b-wave		a-wave		b-wave		b-wave		b-wave	
	Implicit time (ms)	Amplitude (μV)	Implicit time (ms)	Amplitude (μV)	Implicit time (ms)	Amplitude (μV)	Implicit time (ms)	Amplitude (μV)	Implicit time (ms)	Amplitude (μV)
Normal	[80,111]	[123,328]	[20,26]	[−262,−106]	[42,52]	[291,516]	[25,29]	[61,160]	[30–35]	[41,98]
1	153	150	31.4	−170	57.9	454	30.5	44.9	41.1	42.2
2	Not identified	Not identified	42	−163	73	588	39.9	8.7	Not identified	Not identified
3	173	82	34	−186	60.6	507	35.2	29.5	41.1	19.6
4	182	91	31.4	−160	61.5	606	37.6	43	43.8	22.3
5	Not identified	Not identified	41.1	−330	78.3	693	39.9	10.1	51.8	17.5

DA: dark-adapted; ERG: electroretinogram; LA: light-adapted.
The ERGs values from normal control are shown for comparison.

reported slightly better BCVA in cases with homozygous missense mutations compared with homozygous nonsense mutations carriers,[1] however, other studies also could not stablish reliable genotypic-phenotypic correlations.[6,21]

Most of our patients had a relatively fast clinical progression with poor visual outcomes which seem to contradict some reports that describe CDSRR as a slowly progressive disease.[9,21] In fact, some studies reported that a considerable proportion of patients do not demonstrate an evident clinical progression over several years despite the early onset of disease.[21,26,27] However, in our cohort, even the patient showing the mildest form of CDSRR had a documented deterioration of BCVA during the follow-up period.

In our patients, the pathognomonic electrophysiological features of CDSRR presented in the study were evident in three patients (patients 2–5) and included (1) disproportionate b-wave increase with small rises in stimulus intensity; (2) late squaring of the a-wave with b-wave of supernormal amplitude in the mixed rod-cone response ERG (Figure 2). The changes in the a-wave suggest that the dysfunction occurs after phototransduction.[9] The rapid increase in the b-wave amplitude is thought to be caused by a "gated" mechanism, in which an abnormally high stimulus is required to activate the post-transduction reaction.[8–10] Though, the youngest (patient 1) and the patient presenting with the more benign course (patient 3) had less remarkable ERG findings, as the b-wave increment was not so pronounced and the b-wave in the 3.0 DA rod-cone response was of normal amplitude (Figure 2). It should be mentioned that our protocol did not include dark-adapted 10 ERG, which can highlight some features that could be help to diagnose of this condition. Nevertheless, we confirmed that the term "supernormal rod ERG" may be misleading[9] as the amplitude of b-wave with high intensity flashes can be within normal values and ERG testing can show remarkable variations between patients with the same genetic variant. Some studies reported that full-field ERG parameters do not worsen or correlate with age,[9,21] while there was a previous report of mild progression of the rod-cone ERG abnormalities.[25] It should be interesting to assess if the mild full-ERG abnormalities in patients 1 and 3 will progress with time and, if they will acquire more characteristic features of the CDSRR, including the supernormal b-wave amplitude with high intensity flashes. On the other hand, it may also be possible that worsening maculopathy may occur in association with stable peripheral retinal dysfunction, as previously suggested.[9]

In addition, the present study highlights that the electrophysiological characteristics of the CDSRR may not be so evident. To overcome this difficulty, some authors recommend a small increment in the intensity of flashes in the dark-adapted patient to improve sensibility.[9] Some authors also recommend evaluating with caution the elevated b/a-wave ratios in the mixed rod-cone response.[14,25] A previous

study demonstrated that 10 patients with homozygous or compound heterozygous *KCNV2* gene variants were initially diagnosed with another cone disease.[28] Nine of these 10 patients were reclassified with CDSRR after reevaluation. Initial misdiagnosis was a result of unawareness of CDSRR and overlooking of typical features that could be not present or be so evident as we demonstrated in our study. It is important for the clinician to be fully familiarized with the clinical and ERG characteristics of this disease, including the possibility of more subtle presentations, in order to correctly refer cases for *KCNV2* gene screening and abbreviate more extensive sequencing panels.

Conclusion

This study describes the clinical features and the molecular genetic findings of a rare variant in the *KCNV2* gene in five Portuguese patients with retinal dysfunction. All patients showed clinical progression of the disease, often with severe central vision loss. The pathognomonic ERG findings of CDSRR were not evident in all patients and this study highlights the importance of a high degree of clinical suspicion to establish the correct diagnosis. Moreover, the confirmation of a molecular diagnosis allows for a better genetic counseling and in the future maybe could be the target of new therapies.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

João Esteves-Leandro https://orcid.org/0000-0001-9093-1455
Sónia Torres-Costa https://orcid.org/0000-0002-7079-9554
Renato Santos-Silva https://orcid.org/0000-0003-0932-8398
Amândio Rocha-Sousa https://orcid.org/0000-0001-8374-0298

References

1. Wissinger B, Dangel S, Jagle H, et al. Cone dystrophy with supernormal rod response is strictly associated with mutations in KCNV2. *Investig Ophthalmol Vis Sci* 2008; 49(2): 751–757.
2. Guimaraes TAC, Georgiou M, Robson AG, et al. KCNV2 retinopathy: clinical features, molecular genetics and directions for future therapy. *Ophthalmic Genet* 2020; 41(3): 208–215.
3. Wu H, Cowing JA, Michaelides M, et al. Mutations in the gene KCNV2 encoding a voltage-gated potassium channel subunit cause "cone dystrophy with supernormal rod electroretinogram" in humans. *Am J Hum Genet* 2006; 79(3): 574–579.
4. Czirjak G, Toth ZE and Enyedi P. Characterization of the heteromeric potassium channel formed by kv2.1 and the retinal subunit kv8.2 in Xenopus oocytes. *J Neurophysiol* 2007; 98(3): 1213–1222.
5. Mohapatra DP, Park KS and Trimmer JS. Dynamic regulation of the voltage-gated Kv2.1 potassium channel by multisite phosphorylation. *Biochem Soc Trans* 2007; 35(Pt 5): 1064–1068.
6. Zobor D, Kohl S, Wissinger B, et al. Rod and cone function in patients with KCNV2 retinopathy. *PLoS One* 2012; 7(10): e46762.
7. Fujinami K, Tsunoda K, Nakamura N, et al. Molecular characteristics of four Japanese cases with KCNV2 retinopathy: report of novel disease-causing variants. *Mol Vision* 2013; 19: 1580–1590.
8. Michaelides M, Holder GE, Webster AR, et al. A detailed phenotypic study of "cone dystrophy with supernormal rod ERG". *Br J Ophthalmol* 2005; 89(3): 332–339.
9. Robson AG, Webster AR, Michaelides M, et al. "Cone dystrophy with supernormal rod electroretinogram": a comprehensive genotype/phenotype study including fundus autofluorescence and extensive electrophysiology. *Retina (Philadelphia, Pa)* 2010; 30(1): 51–62.
10. Vincent A, Robson AG and Holder GE. Pathognomonic (diagnostic) ERGs. A review and update. *Retina (Philadelphia, Pa)* 2013; 33(1): 5–12.
11. Khan AO, Alrashed M and Alkuraya FS. 'Cone dystrophy with supranormal rod response' in children. *Br J Ophthalmol* 2012; 96(3): 422–426.
12. Sergouniotis PI, Holder GE, Robson AG, et al. High-resolution optical coherence tomography imaging in KCNV2 retinopathy. *Br J Ophthalmol* 2012; 96(2): 213–217.
13. Ben Salah S, Kamei S, Senechal A, et al. Novel KCNV2 mutations in cone dystrophy with supernormal rod electroretinogram. *Am J Ophthalmol* 2008; 145(6): 1099–1106.
14. Nagy D, Kohl S, Zrenner E, et al. Detailed functional and morphological analysis in patients with cone dystrophy with supernormal rod response due to mutations in the Kcnv2 Gene. *Investig Ophthalmol Vis Sci* 2009; 50(13): 4757.
15. Thiagalingam S, McGee TL, Weleber RG, et al. Novel mutations in the KCNV2 gene in patients with cone dystrophy and a supernormal rod electroretinogram. *Ophthalmic Genet* 2007; 28(3): 135–142.
16. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015; 17(5): 405–424.
17. Schwarz JM, Rodelsperger C, Schuelke M, et al. MutationTaster evaluates disease-causing potential of sequence alterations. *Nat Methods* 2010; 7(8): 575–576.
18. Flanagan SE, Patch AM and Ellard S. Using SIFT and PolyPhen to predict loss-of-function and gain-of-function mutations. *Genet Test Mol Biomark* 2010; 14(4): 533–537.
19. Bach M, Brigell MG, Hawlina M, et al. ISCEV standard for clinical pattern electroretinography (PERG): 2012 update. *Doc Ophthalmol* 2013; 126(1): 1–7.

20. McCulloch DL, Marmor MF, Brigell MG, et al. ISCEV standard for full-field clinical electroretinography (2015 update). *Doc Ophthalmol* 2015; 130(1): 1–12.
21. Vincent A, Wright T, Garcia-Sanchez Y, et al. Phenotypic characteristics including in vivo cone photoreceptor mosaic in KCNV2-related "cone dystrophy with supernormal rod electroretinogram". *Investig Ophthalmol Vis Sci* 2013; 54(1): 898–908.
22. Wabbels B, Demmler A, Paunescu K, et al. Fundus autofluorescence in children and teenagers with hereditary retinal diseases. *Graefe's Arch Clin Exp Ophthalmol* 2006; 244(1): 36–45.
23. Robson AG, Michaelides M, Saihan Z, et al. Functional characteristics of patients with retinal dystrophy that manifest abnormal parafoveal annuli of high density fundus autofluorescence; a review and update. *Doc Ophthalmol* 2008; 116(2): 79–89.
24. Robson AG, Michaelides M, Luong VA, et al. Functional correlates of fundus autofluorescence abnormalities in patients with RPGR or RIMS1 mutations causing cone or cone rod dystrophy. *Br J Ophthalmol* 2008; 92(1): 95–102.
25. Friedburg C, Wissinger B, Schambeck M, et al. Long-term follow-up of the human phenotype in three siblings with cone dystrophy associated with a homozygous p.G461R mutation of KCNV2. *Investig Ophthalmol Vis Sci* 2011; 52(12): 8621–8629.
26. Foerster MH, Kellner U and Wessing A. Cone dystrophy and supernormal dark-adapted b-waves in the electroretinogram. *Graefe's Arch Clin Exp Ophthalmol* 1990; 228(2): 116–119.
27. Rosenberg T and Simonsen SE. Retinal cone dysfunction of supernormal rod ERG type. Five new cases. *Acta Ophthalmol (Copenh)* 1993; 71(2): 246–255.
28. Wissinger B, Schaich S, Baumann B, et al. Large deletions of the KCNV2 gene are common in patients with cone dystrophy with supernormal rod response. *Hum Mutat* 2011; 32(12): 1398–1406.