Novel *KCNV2* Mutations in Cone Dystrophy with Supernormal Rod Electroretinogram

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• PURPOSE: To describe patients with cone dystrophy and supernormal rod electroretinogram (ERG) and search for mutations in the recently described *KCNV2* gene.

• DESIGN: Clinical and molecular study.

• METHODS: Patients from three families originating from France, Morocco, and Algeria had standard ophthalmologic examination and color vision analysis, Goldmann perimetry, International Society for Clinical Electrophysiology of Vision (ISCEV) protocol in accordance with ERG testing, autofluorescence evaluation, and optical coherence tomography 3 scanning. The two coding exons of KCNV2 were polymerase chain reaction amplified and sequenced.

• RESULTS: All patients had the characteristic features of supernormal, delayed rod ERG responses at the highest levels of stimulation and markedly reduced cone responses. In the French family, two affected sisters were compound heterozygotes for the recurrent c.1381G>A (Gly461Arg) mutation and for a novel c.442G>T (Glu148Stop) mutation. In the Moroccan family, affected members were homozygotes for the novel c.1404delC mutation (His468fsX503) and in the Algerian family, the proband was homozygote for the novel c.1001delC mutation (Ala334fsX453). In the three families, parents were unaffected heterozygote carriers. None of the mutations were present in 50 control chromosomes.

• CONCLUSIONS: The three novel truncative mutations are likely to be null mutations leading to loss of function, with no difference in the phenotype presentation. Amino acid changes are found exclusively in the N-terminal fragment of the protein and in the P-loop, indicating the importance of those regions for the function of the KCNV2 protein. (Am J Ophthalmol 2008;145:1099–1106. © 2008 by Elsevier Inc. All rights reserved.)

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THE CONE DYSTROPHIES ARE PROGRESSIVE HEREDITARY retinal disorders with electrophysiologic or psychophysical evidence of cone dysfunction and degeneration.[1] There is considerable clinical and genetic heterogeneity and various phenotypes have been described including an unusual cone disorder associated with supernormal and delayed rod electroretinogram (ERG) b-waves.[2–8] This rare form of retinal dystrophy (OMIM no. 610356) is characterized by autosomal recessive inheritance, onset in the first or second decade of life with poor visual acuity (VA), marked photophobia, myopia, dyschromatopsia in the red-green axis, central scotoma, and, later in the course of the disease, night blindness. There is often disturbance of the retinal pigment epithelium (RPE) with increased autofluorescence in perifoveal or central macula areas and no apparent retinal degeneration in the periphery.[8] A characteristic hallmark of the disease is the decreased and delayed dark-adapted response to dim flashes, which contrasts with the supernormal response at the highest levels of stimulation. In addition, light-adapted responses to a bright flash or to 30-Hz flickers are delayed and markedly decreased.

Elevation in retinal cyclic guanosine monophosphate (cGMP) has been considered as a possible pathophysiologic mechanism leading to photoreceptor cell degeneration in these patients, based on the similarities of the ERG features observed between the patients and animal retinas showing increased cGMP. However, no convincing mutation was found in the cone cGMP-phosphodiesterase (PDE) gamma subunit gene (*PDE6H*).[9] Mutation screening of NR2E3, whose mutations cause the enhanced S-cone syndrome (ESCS),[10] featuring a large b-wave amplitude to stimulation with blue light, was also negative.[8]

By linkage analysis of a consanguineous family originating from the Middle East, a group led by Webster and associates[11] recently showed that this disorder is a result of mutations in *KCNV2*, a gene mapping on chromosome 9p24, and coding for a voltage-gated potassium channel subunit.[12] KCNV2 is strongly expressed in heart and photoreceptors.[11,13] In photoreceptors, its gene product, Kv8.2, forms heterotetrameres with Kv2.1, producing a permanent outward potassium current characteristic for the photoreceptor cells.[13,14] We describe here three additional families with the same condition whose affected members carry novel mutations in KCNV2.

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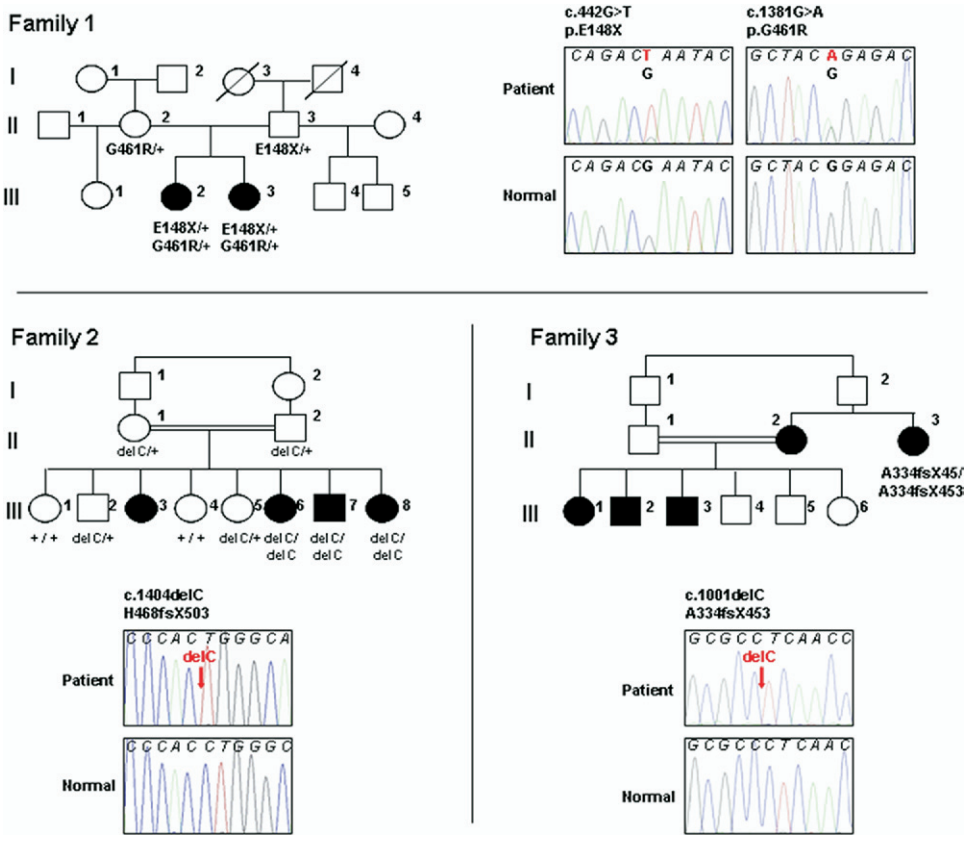

FIGURE 1. Pedigrees and genotypic findings in three families segregating cone dystrophy with supernormal rod electroretinogram (ERG). In pedigrees, squares indicate males, circles indicate females, filled symbols show affected individuals, and a double horizontal line between a mating pair indicates consanguinity. The mutation information ("+" means a wild-type allele) was indicated only for those individuals whose deoxyribonucleic acid (DNA) samples were available for the study. Note that for family 2, delC corresponds to the His468fsX503 mutation. For each family, the electropherograms for the mutated (patient) and wild-type (normal) sequence are shown. The normal sequence is shown in italics and the mutated nucleotides are in red. The nucleotide mutation and the protein sequence are indicated on top of each electropherogram.

TABLE 1. Primers for KCNV2

Primer Name	Sequence (5′→3′)	Product Size (bp)	Annealing Temperature (C)	Amplified Fragment
1AF	GGAGGAAATGGGCTAAGAGG	641	60.2	exon 1, fragment A
1AR	CCAGCTCGCAGTAGTCCAG			
1BF	GAGGTCACCACCGCCAAG	794	67.0	exon 1, fragment B
1BR	GATGGCCACCAGGTCCAC			
1CF	GGCTTCTTCACGCTCGAGTA	532	58.3	exon 1, fragment C
1CR	GACGAGGATCAGAAGCCAAA			
2F	CTCCGTGGGAAGCCATTAC	555	59.9	exon 2
2R	TTCTAGAGGCAGTACTTTGTGAACG			

bp = base pairs.

METHODS

• **FAMILIES AND CLINICAL EXAMINATION:** Three families, originating from Southern France (family 1), Morocco (family 2), and Algeria (family 3), were recruited for this study. The families from Morocco and Algeria were identified as being consanguineous (Figure 1). There was no evidence of extraocular signs of disease. Blood was obtained from family members with their informed consent.

TABLE 2. Clinical Features in Members from the Three Families with Cone Dystrophy with Supernormal Rod Electroretinogram

	KCNV2 Protein	Functional Signs	Age at Exam	Refraction Visual Acuity, OD/OS	Fundus	Color Vision	Goldmann Perimetry	Electroretinogram of Right Eye*: Dark-Adapted Maximum at 0 dB (rod cone); Light-Adapted 30-Hz Flickers (cone)
Family 1								
III-2	G461R/(E148X)	Nystagmus at age 2; photophobia; mild night blindness	11	−1.75 (−2.25; 115 degrees): 5/10 −0.50 (−1.25; 65 degrees): 4/10	Loss of foveal reflex; fine granular pigmentation of the macula	Subnormal	Six-degrees central scotoma at I4	Supernormal at 634 μV; severely decreased at 43 μV
III-3	G461R/E148X	No nystagmus; photophobia; mild night blindness	8	−1.75 (−1.25;160 degrees): 3/10 −1.75 (−1.00;10 degrees): 3/10	Loss of foveal reflex	Red-green axis of dyschromatopsia	15-degrees central scotoma at I4	Supernormal at 662 μV; severely decreased at 47 μV
Family 2								
II-1	H468fsX503/+	None	56	+1.00 (−0.75;105 degrees): 10/10 +2.25 (−3.00;150 degrees): 10/10	Normal	Mild tritanopia	Not done	Normal at 352 μV; normal at 111 μV
II-1	H468fsX503/+	None	54	+1.00 (−0.75;115 degrees): 10/10 +1.50 (−0.75;155 degrees): 10/10	Normal	Mild tritanopia	Not done	Normal at 304 μV; moderately decreased at 60 μV
III-1	+/+	None	38	Emmetropic: 10/10 Emmetropic: 10/10	Normal	Subnormal	Not done	Normal at 359 μV; subnormal at 89 μV
III-2	H468fsX503/+	None	33	+0.25 (−0.75;165 degrees): 10/10 +0.50 (−1.75;140 degrees): 10/10	Few depigmented areas in mid periphery; posterior pole normal	Mild tritanopia	Not done	Normal at 339 μV; moderately decreased at 83 μV
III-4	+/+	None	31	Emmetropic: 10/10 Emmetropic: 10/10	Normal	Subnormal	Not done	Moderately decreased at 275 μV; moderately decreased at 69 μV
III-5	H468fsX503/+	None	25	Emmetropic: 10/10 Emmetropic: 10/10	Normal	Subnormal	Not done	Normal at 408 μV; normal at 107 μV
III-6	H468fsX503/ H468fsX503	No nystagmus; intense photophobia; no night blindness	22	+1.00 (−1.50;160 degrees): 1.5/10 −2.00 (−1.25;175 degrees): 1.5/10	Loss of foveal reflex	Red-green axis of dyschromatopsia	Five-degrees central scotoma at I4	Supernormal at 690 μV; highly decreased at 27 μV
III-7	H468fsX503/ H468fsX503	No nystagmus; photophobia; mild night blindness	17	−7.00 (−1.25;170 degrees): 1.5/10 −7.50 (−1.00; 30 degrees): 1.5/10	Loss of foveal reflex; atrophy of peripapillary and inferior retina (myopia)	Red-green axis of dyschromatopsia	20- to 30-degrees central scotoma at I4	Supernormal at 560 μV; severely decreased at 37 μV
III-8	H468fsX503/ H468fsX503	Nystagmus at age 2	9	−15.75 (−1.75; 5 degrees): 1/20 −16.00 (−1.25;140 degrees): 1/20	Foveal depigmentation; atrophy of retina (myopia)	Scotopic axis of dyschromatopsia	Not done	Not done

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TABLE 2. Clinical Features in Members from the Three Families with Cone Dystrophy with Supernormal Rod Electroretinogram (*Continued*)

	KCNV2 Protein	Functional Signs	Age at Exam	Refraction Visual Acuity, OD/OS	Fundus	Color Vision	Goldmann Perimetry	Electroretinogram of Right Eye*: Dark-Adapted Maximum at 0 dB (rod cone); Light-Adapted 30-Hz Flickers (cone)
Family 3								
II-2	Affected; not tested	No nystagmus; photophobia; no night blindness	54	+0.75 (−2.25; 80 degrees): 1/10 +0.50 (−2.00; 20 degrees): LP	Round-shaped foveal atrophy	Red-green axis of dyschromatopsia	Not done	Supernormal at 650 μV; moderately decreased at 54 μV
II-3	A334fsX453/ A334fsX453	No nystagmus; photophobia; no night blindness	38	−8.00 (−0.75; 5 degrees): 1/10 −8.00 (−1.25;170 degrees): 1/10	Round-shaped foveal atrophy	Red-green axis of dyschromatopsia	Central relative scotoma	Supernormal at 588 μV; highly decreased at 15 μV
III-2	Affected; not tested	No nystagmus; photophobia; no night blindness	23	−7.00 (−1.00; 90 degrees): 2/10 −10.50 (−0.25;165 degrees): 1/20	Round-shaped foveal atrophy	Red-green scotopic axis of dyschromatopsia	No central scotoma on right eye	Supernormal at 469 μV; highly decreased at 28 μV

dB = decibels; LP = light perception; OD = right eye; OS = left eye.
*Normal values are: dark-adapted maximum at 0 dB = 300–450 μV; light-adapted 30-Hz flickers = >105 μV.

A standard ophthalmic exam (refractometry, VA, slit-lamp examination, applanation tonometry, and funduscopy) was performed. Color vision was evaluated with the Lanthony Desaturated 15-Hue test. Kinetic visual fields were determined with a Goldmann perimeter using targets V_{4e}, II_{4e}, and I_{4e}. Optical coherence tomography (OCT) measurement of the macula was performed using an OCT-3 system (Stratus model 3000; Carl Zeiss Meditec, Dublin, California, USA) with version 3.0 software. Autofluorescence (AF) measurements were obtained with the Heidelberg Retinal Angiograph (HRA2) confocal angiograph (Heidelberg Engineering, Dossenheim, Germany) and fundus pictures were taken. Full-field ERG was recorded using a ganzfeld apparatus (Métrovision, Pérenchies, France) with a bipolar contact lens electrode on maximally dilated pupils, according to International Society for Clinical Electrophysiology of Vision (ISCEV) protocol.[15]

• **DNA ANALYSIS:** *Polymerase Chain Reaction*. Genomic DNA was extracted from 10-ml peripheral blood samples by a standard salting-out procedure.[16] For the two coding exons of KCNV2, primers were designed to include flanking intronic sequences (Table 1). Polymerase chain reactions (PCR) contained 10 pmoles of forward and reverse primers, 100 to 150 ng of genomic DNA, 3 mM $MgCl_2$, 200 μM of each dNTP, and 1 U of *Taq* DNA polymerase (AmpliTaq Gold; Applied Biosystems, Foster City, California, USA) in a 50-μl volume with the appropriate buffer. Following the denaturation step at 95 C for nine minutes, the amplification was carried out for 35 cycles at 95 C for 30 seconds, the appropriate annealing temperature for 30 seconds (Table 1), and 72 C for one minute, ending with a final extension step at 72 C for 10 minutes. Amplicons were run on 2% agarose gels in 1× TAE buffer to verify the quality and specificity of the PCR.

Sequencing. The purified PCR products (QIAquick PCR purification kit; QIAGEN, Hilden, Germany) were sequenced in both directions using the BigDye Terminator Cycle Sequencing Ready Reaction kit V1.1 (Applied Biosystems) on an ABI PRISM 3130 capillary sequencer (Applied Biosystems). Sample sequences were aligned to the wild-type ones and to those of 50 control chromosomes originating from France and North Africa. They were analyzed with the Collection and Sequence Analysis software package (Applied Biosystems).

RESULTS

• **CLINICAL FINDINGS:** Members from the three families had typical cone dystrophy with supernormal rod ERG (Table 2). In all families, the parents of affected patients were clinically normal. Photophobia was a constant finding and was associated with a decreased VA ranging from 5/10 to 1/20. The oldest patient (54 years; II-2 from family

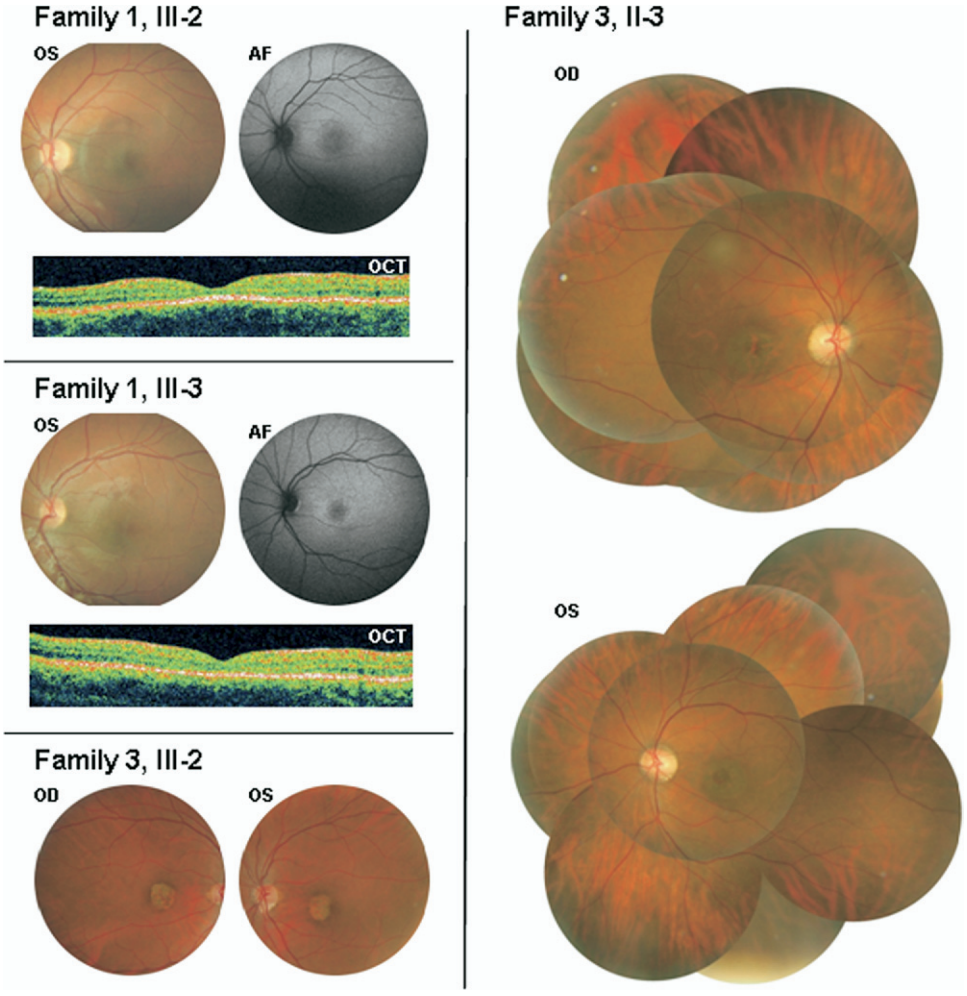

FIGURE 2. Fundus photographs, autofluorescence (AF), and optical coherence tomography-3 (OCT-3) scans in patients having cone dystrophy with supernormal rod ERG from families 1 and 3. In both sisters (III-2 and III-3) from family 1, the fundus shows a loss of the foveal reflex (left eye; [OS]) with a slightly decreased AF and with a thinned foveal photoreceptor layer at the OCT-3 scan. Fundus examination of both eyes (right [OD] and left OS eyes) of the proband (II-3) and of her affected nephew (III-2) from family 3 shows a foveomacular atrophy that was more prominent in III-2.

3) had light perception in one eye. An early-onset nystagmus was often observed, and a few patients complained of mild night blindness. Fundus examination disclosed a loss of the foveal reflex (Figure 2; family 1), fine granular pigmentations of the fovea, and in oldest patients, a round-shaped foveal atrophy (Figure 2; family 3), suggesting that the disease slowly progresses toward the death of foveal photoreceptors and RPE cells. In the two young affected sisters from family 1, fundus AF in the foveal area appeared slightly decreased and the OCT-3 scan already showed a significant thinning of the retina at the foveal pit (114 ± 23 μm vs 161 ± 19 μm in age-matched controls) (Figure 2, family 1). Goldmann perimetry revealed a slight constriction of the peripheral isopter and various degrees of central relative scotomas (Table 2). Dyschromatopsia was an almost constant finding, showing a red-green axis in most patients that tended to be scotopic in severe cases (III-2 from family 3). ERG findings were characteristic of the cone dystrophy with supernormal rod ERG (Figure 3). All patients had decreased light-adapted responses, with 30-Hz flicker amplitudes ranging from 54 to 15 μV (normal, >105 μV). In dark-adapted conditions, the amplitudes of the response at the highest level of stimulation (318 cd.s/m^2) were constantly supernormal, ranging from 469 to 690 μV (normal value, 300 to 450 μV), in contrast with decreased amplitudes at the lowest level of stimulation (1 cd.s/m^2), ranging from zero to 70 μV (normal value, 100 to 200 μV), with a remarkable delay in the b-wave peak, ranging from 171 to 180 ms (normal value, <130 ms). The intermediate level of stimulations at 3.2 cd.s/m^2 showed no significant difference in amplitudes between affected and nonaffected patients (Table 3).

• **GENOTYPIC FINDINGS:** KCNV2 mutations were found in the three families. In family 1 (Figure 1), both affected sisters (III-2 and III-3) were compound heterozygotes for

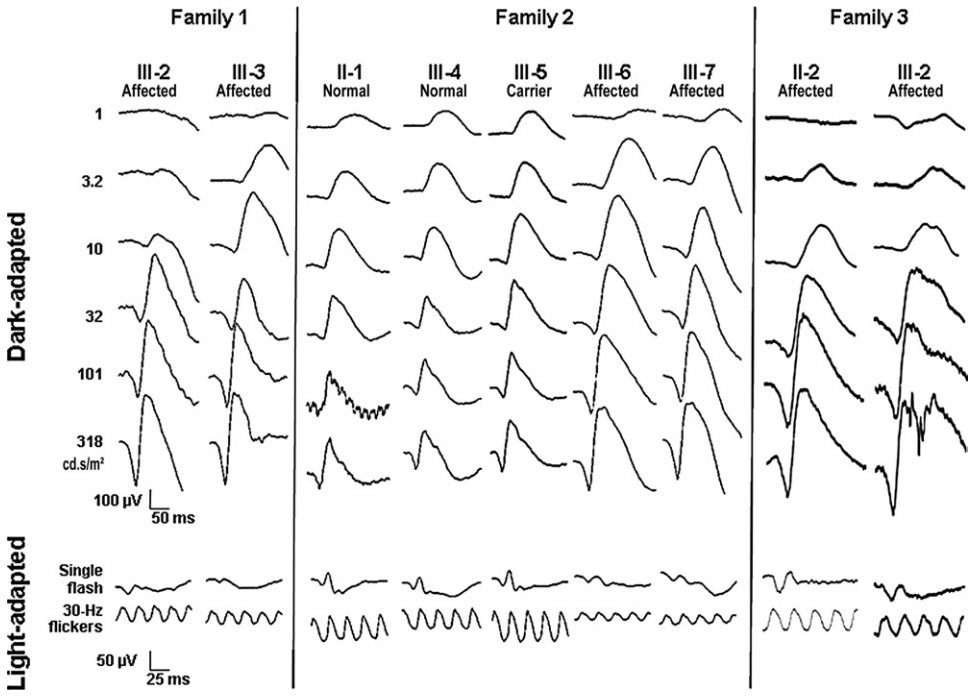

FIGURE 3. International Society for Clinical Electrophysiology of Vision (ISCEV) ERG in patients having cone dystrophy with supernormal rod ERG from families 1, 2, and 3. ERGs were recorded in affected members from families 1 (III-2, III-3), 2 (III-6, III-7), and 3 (II-2, III-2) and in nonaffected members (normal or carriers) from family 2 (II-1, III-4, III-5). In affected individuals, the low-intensity response in dark-adapted conditions (1 cd.s/m^2) is decreased and delayed while at higher intensities (101 to 318 cd.s/m^2) the response is supernormal. In light-adapted conditions, the cone responses to single flash (cone) and to 30-Hz flickers are notably reduced in affected individuals compared with normal individuals.

TABLE 3. Electroretinogram Values for Unaffected and Affected Patients with Cone Dystrophy and Supernormal Rod Electroretinogram

Patients	1 cd.s/m^2	3.2 cd.s/m^2	10 cd.s/m^2	32 cd.s/m^2	101 cd.s/m^2	318 cd.s/m^2	30-Hz Flicker
b-wave amplitude							
Affected (n = 6)	39 ± 36 µV	204 ± 111 µV	389 ± 90 µV	471 ± 87 µV	544 ± 81 µV	596 ± 74 µV	40 ± 12 µV
Unaffected (n = 5)	127 ± 35 µV	216 ± 41 µV	266 ± 24 µV	285 ± 21 µV	295 ± 54 µV	334 ± 39 µV	82 ± 10 µV
Student *t* test	$P < 10^{-2}$	$P = .81$*	$P < 10^{-1}$*	$P < 10^{-2}$	$P < 10^{-3}$	$P < 10^{-4}$	$P < 10^{-13}$
b-wave implicit time							
Affected (n = 6)	171 ± 9 ms	142 ± 11 ms	120 ± 5 ms	96 ± 4 ms	81 ± 4 ms	70 ± 4 ms	
Unaffected (n = 5)	121 ± 4 ms	103 ± 5 ms	88 ± 3 ms	68 ± 1 ms	64 ± 1 ms	60 ± 3 ms	
Student *t* test	$P < 10^{-5}$	$P < 10^{-4}$	$P < 10^{-5}$	$P < 10^{-6}$	$P < 10^{-4}$	$P < 10^{-3}$	

Cut-off *P* value for significance was .05.
*Indicates unsignificant results.

the c.442G>T nonsense mutation in exon 1 that leads to a stop codon (p.Glu148Stop), and for the c.1381G>A missense mutation in exon 2 leading to an amino acid change (p.Gly461Arg) (Figure 1). The presence of only one heterozygous mutation in each unaffected parent indicated that they were carriers and confirmed the autosomal recessive inheritance of the disease. In family 2, the affected brother (III-7) and sisters (III-6 and III-8) were homozygotes for a c.1404delC mutation in exon 2 leading to a frameshift and a premature stop (His468fsX503) (Figure 1); DNA from affected sister III-3 was not available. Unaffected brother III-2 and sisters III-1, III-4, and III-5 either were heterozygote carriers or had a wild-type genotype (Figure 1). Both parents, who were first cousins, were heterozygote carriers. In family 3, only the DNA from the proband (II-3) was available. We found that she was homozygotic for a c.1001delC mutation in exon 1 leading to a frameshift and a premature stop (Ala334fsX453)

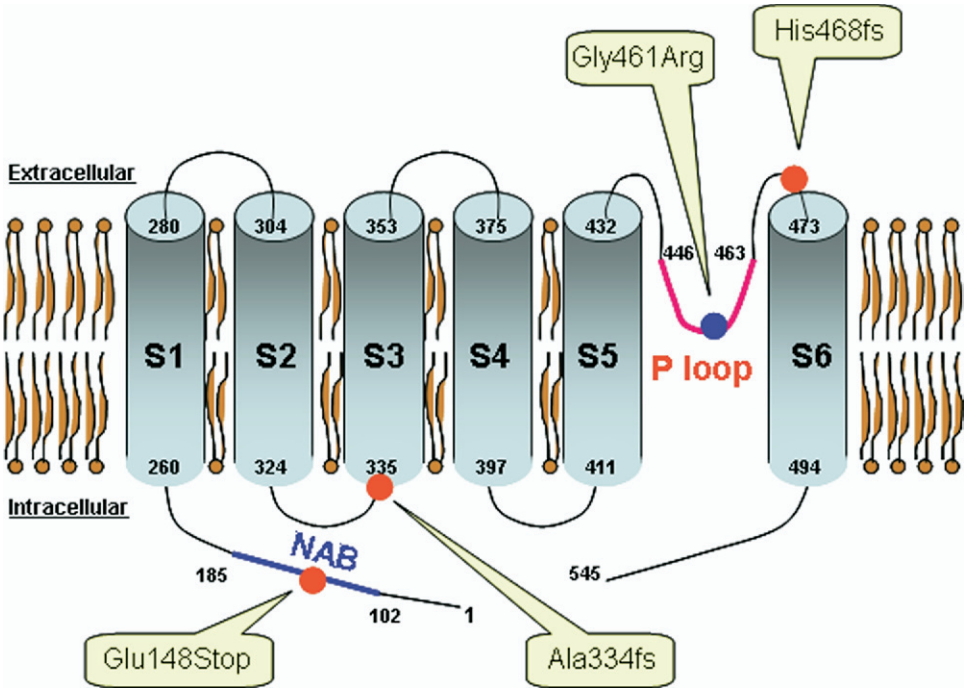

FIGURE 4. Schematic representation of the KCNV2 subunit of the K^+ channel, drawn from the KCNV2 sequence deposited in GenBank #NM133497 and from the structure of Kv channels (reference 14), showing the N-terminal A and B boxes (NAB, in blue), the six transmembrane segments of the protein (S1 through S6), and the P-loop (in red), which forms the channel pore. Small numbers indicate the amino acid positions. The position and sequence of the four mutations found are indicated, in blue for the amino acid change and in red for truncating mutations.

(Figure 1). Her parents were not known to be related but her affected sister (II-2) made a consanguineous marriage with an unaffected male and had three of six affected children, suggesting that the proband inherited both alleles from a common ancestor. None of these mutations were present in 50 control chromosomes.

DISCUSSION

WE REPORT HERE PATIENTS FROM THREE FAMILIES SHOWING cone dystrophy with supernormal rod ERG. They all carry mutations in KCNV2. Most patients from the 22 published families (including ours) have been found mutated in KCNV2,[11,17] except for one in which no mutation was found[11] and two for which only one allele was mutated.[11,17]

All four mutations that we found presumably inactivate the function of KCNV2 (Figure 4). Three of them are novel and truncate the protein either inside the N-terminal A and B boxes (Glu148Stop), before the third transmembrane segment with the addition of 119 novel amino acids (Ala334fsX453), or before the sixth transmembrane segment with the addition of 35 novel amino acids (His468fsX503). The fourth mutation is recurrent and changes the third amino acid (Gly461Arg) of the highly conserved GlyTyrGly K^+ selective motif in the P-loop, which forms with other subunits the pore of the channel.[13,14]

To date, there have been 24 published mutations,[11,17] of which 13 are truncating (with the two mutations p.Gly143X and p.Lys260X being recurrent) and 11 are amino acid changes (with the p.Gly461Arg mutation being reported in five families). Amino acid changes are found exclusively in the N-terminal fragment of the protein, which includes the A and B boxes, and in the P-loop, indicating the importance of those regions for the function of KCNV2.

The description of the disease in our patients is well in accordance with what has been found before, showing a slow and progressive degeneration of the macular area and a relatively mild impairment of VA in young patients. A red-green axis of dyschromatopsia is frequently observed, as usually found in cone dystrophies. Differences in the amplitude of the dark-adapted b-wave are remarkable. It is decreased at low levels of stimulation and increased at high levels of stimulation, implicating, as previously shown,[3] that there is an intermediate level where there is no difference. We found this point at 3.2 cd.s/m^2 (Table 3). However, the b-wave implicit time still remains highly augmented. Thus, the highly delayed b-wave, even if the amplitude is normal, is a major criterion for recognition of this condition.

The slow progression of the disease, and the fact that the condition is probably linked to one gene with probable loss-of-function mutations, make this disease an attractive choice for gene therapy, which will have to be tested on knockout animal models.

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