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Disease Progression in Autosomal Dominant Cone-Rod Dystrophy Caused by a Novel Mutation (D100G) in the *GUCA1A* Gene

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Abstract

Purpose—To document longitudinal fundus autofluorescence (FAF) and electroretinogram (ERG) findings in a family with cone-rod dystrophy (CRD) caused by a novel missense mutation (D100G) in the *GUCA1A* gene.

Methods—Observational case series.

Results—Three family members 26 to 49 years old underwent complete clinical examinations. In all patients, funduscopic findings showed intraretinal pigment migration, loss of neurosensory retinal pigment epithelium (RPE), and macular atrophy. Fundus autofluorescence (FAF) imaging revealed the presence of a progressive hyperautofluorescent ring around a hypoautofluorescent center corresponding to macular atrophy. Full-field electroretinograms (ERG) showed a more severe loss of cone than rod function in each patient. 30 Hz flicker responses fell far below normal limits. Longitudinal FAF and ERG findings in one patient suggested progressive cone-rod dystrophy. Two more advanced patients exhibited reduced rod response consistent with disease stage. Direct sequencing of the *GUCA1A* gene revealed a new missense mutation, p.Asp100Gly (D100G), in each patient.

Conclusion—Patients with autosomal dominant CRD caused by a D100G mutation in *GUCA1A* exhibit progressive vision loss early within the first decade of life identifiable by distinct ERG characteristics and subsequent genetic testing.

Keywords

Autosomal dominant; autofluorescence; cone dystrophy; cone-rod dystrophy; electroretinogram; *GUCA1A*; D100G

Introduction

Hereditary cone and cone-rod dystrophies (CRD) are a group of heterogeneous photoreceptor degenerations characterized by reduced central visual acuity, visual field loss, variable photophobia, and nystagmus [1–3]. In cone dystrophy, the cone responses are markedly diminished on electroretinography (ERG), whereas in cone-rod dystrophy, patients present with additional rod abnormalities as part of the initial presentation or disease progression [4]. Funduscopically, the retinal pigment epithelium (RPE) can present with

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granular RPE changes followed by the formation of a central bull's-eye lesion [5]. Other forms of cone-rod dystrophy present with diffuse atrophy of the posterior pole with pigment clumping [5], with varying degrees of intraretinal pigment and vessel attenuation [6]. Cone-rod dystrophies are genetically heterogeneous and may present with sporadic, autosomal recessive, autosomal dominant, or X-linked recessive inheritance [3, 4]. Candidate genes in which mutations may cause dominantly inherited CRD include *AIPL1, CRX, GUCA1A, GUCY2D, PITPNM3, PRPH2, PROM1, RIMS1,* and *UNC119* [7–20].

Of the mutations that associate with dominant CRD, *GUCA1A and GUCY2D* selectively affect cones over rods, with *GUCA1A* usually accompanied by amplitudinal reductions in cones with sparing of waveform morphology on ERG. *GUCA1A* encodes the guanylate cyclase-activating protein 1 (GCAP1), a calcium-sensitive regulator of phototransduction [7]. GCAP1 activates RETGC1, a guanylate cyclase located in the photoreceptor outer segments that regenerate cGMP [21–23]. GCAP1 is inhibited by intracellular calcium, which increases in the dark-adapted state [24, 25]. Two prior missense mutations, Y99C and E155G, have been shown to reduce the calcium-dependent inhibition of GCAP1, resulting in constitutive RETGC1 activity and continuously high levels of cGMP [13]. Excess levels of cGMP have been shown to cause retinal degeneration and conditions such as retinitis pigmentosa, Leber congenital amaurosis, and congenital stationary night blindness [26–30].

This report documents the phenotypic progression of CRD in a 2-generation family using fundus autofluorescence (FAF) imaging and ERG testing, which assisted in making the diagnosis of CRD [31, 32] Direct sequencing of *GUCA1A* exons identified a new missense (D100G) mutation in all affected subjects. In contrast to some previously described mutations in the *GUCA1A* gene causing CD, the more severely affected members exhibited a mixed cone-rod phenotype consistent with the known expression of GCAP1 in both cone and rod photoreceptors [4, 34].

Materials and Methods

Approval was obtained from the Institutional Review Board of Columbia University, and all research procedures adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all subjects in this prospective study, and Health Insurance Portability and Accountability Act (HIPAA) compliance was maintained. Pupils were dilated using tropicamide 1% and phenylephrine hydrochloride 2.5% prior to clinical examinations. Each patient received a full genetic history and dilated ophthalmic examination by a retina attending (SHT). Earlier medical records were retroactively reviewed when indicated. Clinical testing was performed in each patient and included the collection of fundus autofluorescence using a scanning laser ophthalmoscope (HRA2, Heidelberg Engineering, Heidelberg, Germany) and the acquisition of electroretinograms (Diagnosys LLC, Lowell, Massachusetts, USA). Fundus autofluorescence images were computed and aligned by the Heidelberg Eye Explorer software. Ganzfeld full-field scotopic and photopic ERGs were recorded after pupil dilation. ERG traces from patient 1 (P1) were obtained with DTL electrodes; patients 2 and 3 (P2 and P3) were obtained with Burian-Allen contact lens. Rod-specific ERGs were elicited with a white stimulus after 20 minutes of dark adaptation followed by maximal response ERG elicitation. Transient cone and 30 Hz flicker ERGs were recorded following a 10 minute light adaptation period. Amplitudes and implicit times recorded in each patient were compared to values measured in age-matched normal controls. Stimulus conditions were performed in compliance with International Society for Clinical Electrophysiology of Vision standards [35].

Deoxyribonucleic acid (DNA) was extracted from blood samples of three affected family members. The entire open reading frame of the *GUCA1A* gene (OMIM # 600364) was

sequenced in the proband. Genetic screening was performed with bi-directional direct sequencing of the entire open reading frame of the candidate gene *GUCA1A*, including all exons and 50bp adjacent intronic sequences. Primers for the *GUCA1A* exons (5′-3′) are as follows: exon 1, ggcctgtccatctcagacgt (forward), ccccagctggtcaggcttccag (reverse); exon 2, gcctgaggctggagtgagcg (forward), ctaaccctgggctctcagttcc (reverse); exon 3, cctgagataggataaggatgg (forward), acccacatccatggtgacc (reverse); exon 4, ctggactgcagaaatgaacaccctc (forward), ggcgagctaagcctctgagttc (reverse).

Results

This current report describes the genetic and clinical phenotype of an affected family with CRD resulting from a c.299 A>G single base pair substitution in the *GUCA1A* gene, which results in a substitution of aspartic acid for glycine at the 100th position (p.D100G). The presence of this mutation was confirmed in all affected family members, and the clinical characteristics of each patient are presented (Table 1). A dilated fundus exam showed intraretinal pigment migration without arterial attenuation in all patients and a loss of neurosensory retina and RPE in P1 (Fig 1a, 2b) and P2 (Fig 1c), presenting the appearance of underlying choroidal vessels in the macula. The macula of P3 showed bull's-eye maculopathy, uneven RPE hyperpigmentation, and hypopigmentation (Fig 1d). Autofluorescence imaging revealed dark annular lesions corresponding to macular atrophy and RPE loss. Patterns of increased autofluorescence circumscribed dark areas of atrophy and extended temporally in each patient. Pigmented autofluorescent deposits were also noted in areas inferior to the macula in the more advanced P1 (Fig 1e, 1f) and P2 (Fig 1g) but were absent in the younger P3 (Fig 1h). No abnormalities were observed in peripheral areas of the retina in any patient. Figure 2 shows the progression of autofluorescence patterns for P3 over three years. P3 exhibited a pattern of temporal-superior (OD) and temporal-inferior increases in hyperautofluorescence (OS) along with infero-superior widening of the atrophied areas (OU).

Figure 3 shows full-field ERGs collected in each patient in 2009 as well as two groups of 10 age-matched controls. Normal ranges for waveform amplitude and implicit time were established for the age groups 20–29 and 50–59 years of age. The more advanced P1 and P2 exhibited reduced rod amplitudes without implicit time shift (Fig 4 rod response). Additionally, there was a reduced b/a ratio on the maximal response although not electronegative (Fig 4 maximal response). Generalized cone function appeared to be nearly extinguished for all patients. In all patients, the a- and b-waves of the transient cone responses were undetectable; implicit time delays were evident in P3 but were not observable in P1 and P2 due to signal noise; 30 Hz flicker was nearly extinguished, ranging from 1.78 μV to 4.96 μV, and cone responses were markedly reduced (Fig. 4 30 Hz flicker and cone response).

Furthermore, longitudinal ERGs in P3 over three years demonstrated disease progression: 30 Hz flicker amplitudes decreasing from 5 μV to 1.5 μV with implicit time delays (Fig 5). Amplitude decreases in rod-specific and maximal responses were also observed (Fig 5). These observations are consistent with the characteristics of cone-rod dystrophy [4].

Discussion

This report describes a family of patients affected by a previously unreported dominantly inherited mutation in the *GUCA1A* gene who presented with predominant cone deficiency and subsequent rod dysfunction on ERG, most consistent with dominant cone-rod dystrophy. The two more severely affected members also progressed to rod dysfunction consistent with disease severity. Serial ERG and FAF of the youngest patient, P3, over a

three year period showed the disease worsening over time. Our findings indicate that, despite the early age of onset, the D100G GCAP1 mutation results in progression throughout the second decade. Mutations in the *GUCY2D* gene may also selectively affect cones more than rods on ERG, but *GUCY2D* retinopathy is most commonly associated the congenital retinal blinding disease Leber congenital amaurosis. In contrast, the age of onset in childhood to teens and the progressive disease progression in adulthood seen in this family is more in concordance with *GUCA1A* retinopathy. For example, correlation between rod waveform amplitude and disease-stage was observed in our patients, resulting in reduced scotopic responses in more advanced patients. This is consistent with prior studies that observed the progression of cone to cone-rod dystrophy in the later stages of disease [5, 13]. This is also consistent with phenotypes of a previously described GCAP1 mutation, Y99C, that has been attributed to both cone dystrophy and cone-rod dystrophy, demonstrating the intrafamilial variability of the mutation [4].

Another possible etiological explanation of inevitable rod involvement is the possibility that cones affect rod-specific signaling [33]. Immunolabeling studies have shown that GCAP1 is expressed at higher levels in cones than rods, which may explain the greater cone involvement than rods [33, 36]. An analogous study in retinitis pigmentosa, a rod-cone dystrophy, found that the absence of rods, over time, results in loss of neurotrophic support of cones, resulting in their eventual deterioration [37]. The particular mutation found in the presented patients may have a more immediate effect on rods in the aforementioned mechanisms. Further genotype-phenotype studies will be necessary to better understand the time scale of rod involvement in cone-rod dystrophies.

The presented family experienced an earlier age of onset and more severe visual impairment than typical clinical presentations [4, 13]. While early age of onset may provide a longer window for progression, the severe functional impairment in the family is likely attributable to biochemical consequences of this particular substitution. In a related study, Kitiratschky and colleagues described the clinical phenotype of another GCAP1 mutation of aspartic acid to glutamic acid at the 100th position (D100E) [38]. Although the age of onset was unknown, a clinical examination at the age of 60 revealed a visual acuity of hand motion (OD) and 20/40 (OS) and normal ERG findings. The comparatively milder phenotype of the D100E mutation may be explained by the amino acid substitution. Both aspartic acid (D) and glutamic acid (E) are negatively charged residues, which suggests that their substitution is less deleterious than the substitution to glycine (G), a non-polar residue. Such differences could give rise to immediate structural consequences affecting the high affinity calcium EF-hand binding motif in the GCAP1 protein. Different amino acid substitutions at the same position can result in phenotypically different degrees of severity in functional retinal impairment, as also seen in dominant retinitis pigmentosa [27].

Another clue to the disease etiology comes from serial FAF imaging. In P3, enlarging hypo-autofluorescent lesions over three years are consistent with macular atrophy, suggesting disease progression over time. FAF shows widespread pigmentary changes commensurate with evidence showing rod compromise in the more severely affected members of the family. This is consistent with the ERG observations. In the two older patients, the macular atrophy is circumscribed by a hyperautofluorescent annulus of FAF. High-density autofluorescence in the fundus suggests localized accumulation of lipofuscin, a waste product of photoreceptor outer segment dysgenesis and RPE metabolism. The resulting disruption in RPE metabolism and consequential accumulation of lipofuscin has been histologically correlated with a reduction of photoreceptor cells suggesting the intrinsic toxicity of lipofuscin on photoreceptor cells [5, 39].

In summary, this report describes a heterogeneous presentation of phenotypes in a family with a D100G mutation in the *GUCA1A* gene responsible for macular atrophy, pure cone, and cone-rod dysfunction on ERG. The affected patients showed an earlier age of onset and more severe visual impairment than those with currently reported cone dystrophies. Direct sequencing of the *GUCA1A* gene confirmed the clinical diagnosis of CRD, as supported by FAF and ERG testing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

CD	cone dystrophy
CRD	cone-rod dystrophy

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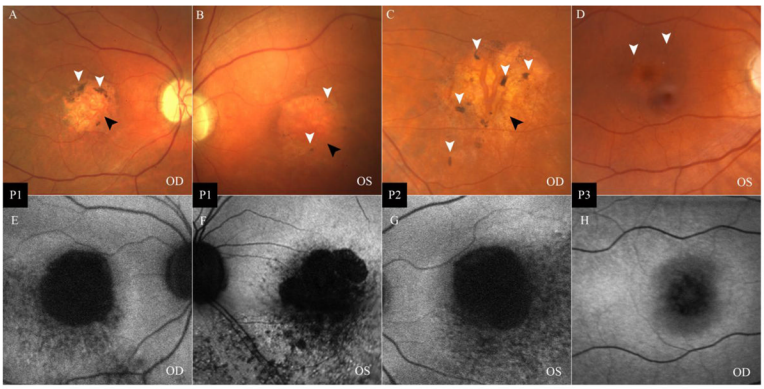

Figure 1.

(a) Atrophic macula in P1, the proband, age 49, (OD) with normal surrounding retina. Migrated retinal pigment epithelium (white arrows) localized around areas of exposed choroidal vessels. (b) Similar atrophic findings (OS) in P1. (e, f) Corresponding fundus autofluorescence (FAF) images in the eyes (OU) of P1. Dark central atrophy is enclosed within a ring of high density autofluorescence. Massive depositions of hyperautofluorescent material is observed in the infero-temporal region of the lesions in both eyes. (c) P2, age 51, exhibiting similar features including RPE migration and abnormally extensive choroidal vessel visibility. (g) An increased signal of AF surrounds a lesion of dark atrophy resembling that of the proband, P1, along with a granular RPE appearance in the infero-temporal region of the macula. (d) P3, age 26, exhibited milder symptoms when compared to the more advanced P1 and P2. Early RPE migration (white arrows) and pigmentation was detected along darkening area of retinal thinning. (h) A band of AF, extending temporally is observed surrounding an area of early atrophy and hypoautofluorescence.

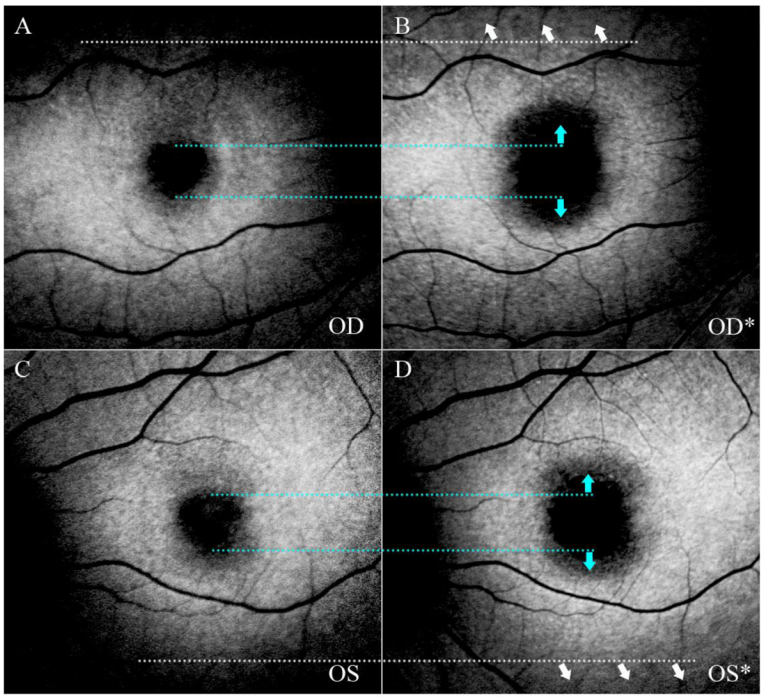

Figure 2.
Serial fundus autofluorescence imaging in P3. A three-year follow-up visit shows the expansion of early atrophy (turquoise arrows) in the macula as well as spatial increases in autofluorescence (white arrows). Images taken at the first visit (a, c for RE and LE, respectively) were compared to images taken three year later (b, d for RE and LE respectively) to document disease progression.

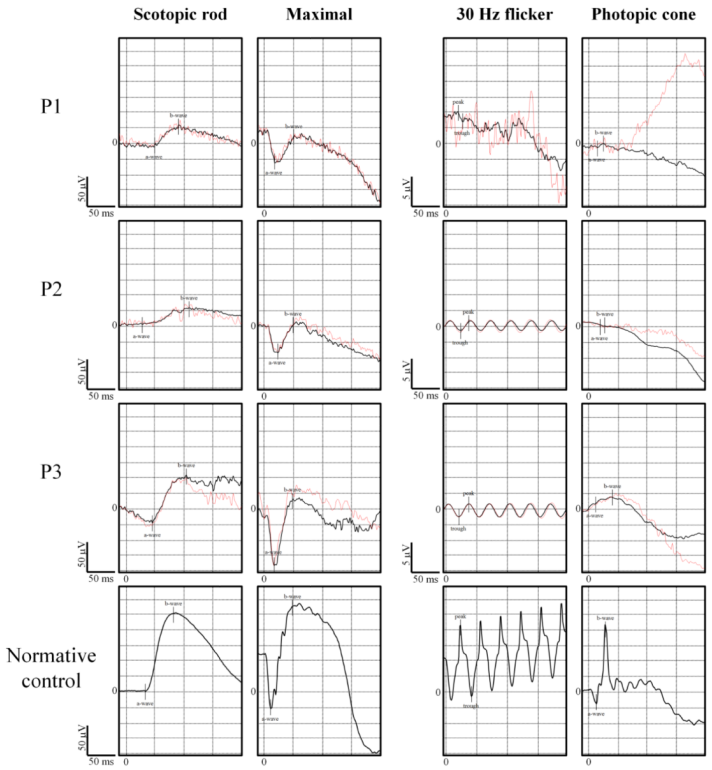

Figure 3.

The International Society for Clinical Electrophysiology of Vision (ISCEV)-standardized scotopic rod, maximal, 30 Hz flicker, and photopic cone responses of the rights eyes of P1, P2, and P3. An average scan (black), along with a successive typical responses (red), is shown for each stimulus condition. Normal waveforms for a subject (age 20–50) are provided in the bottom row for each condition. Note the adjustment in the amplitude scale for the 30 Hz flicker and photopic cone stimuli in P1, P2, and P3, revealing severe waveform and amplitude attenuation.

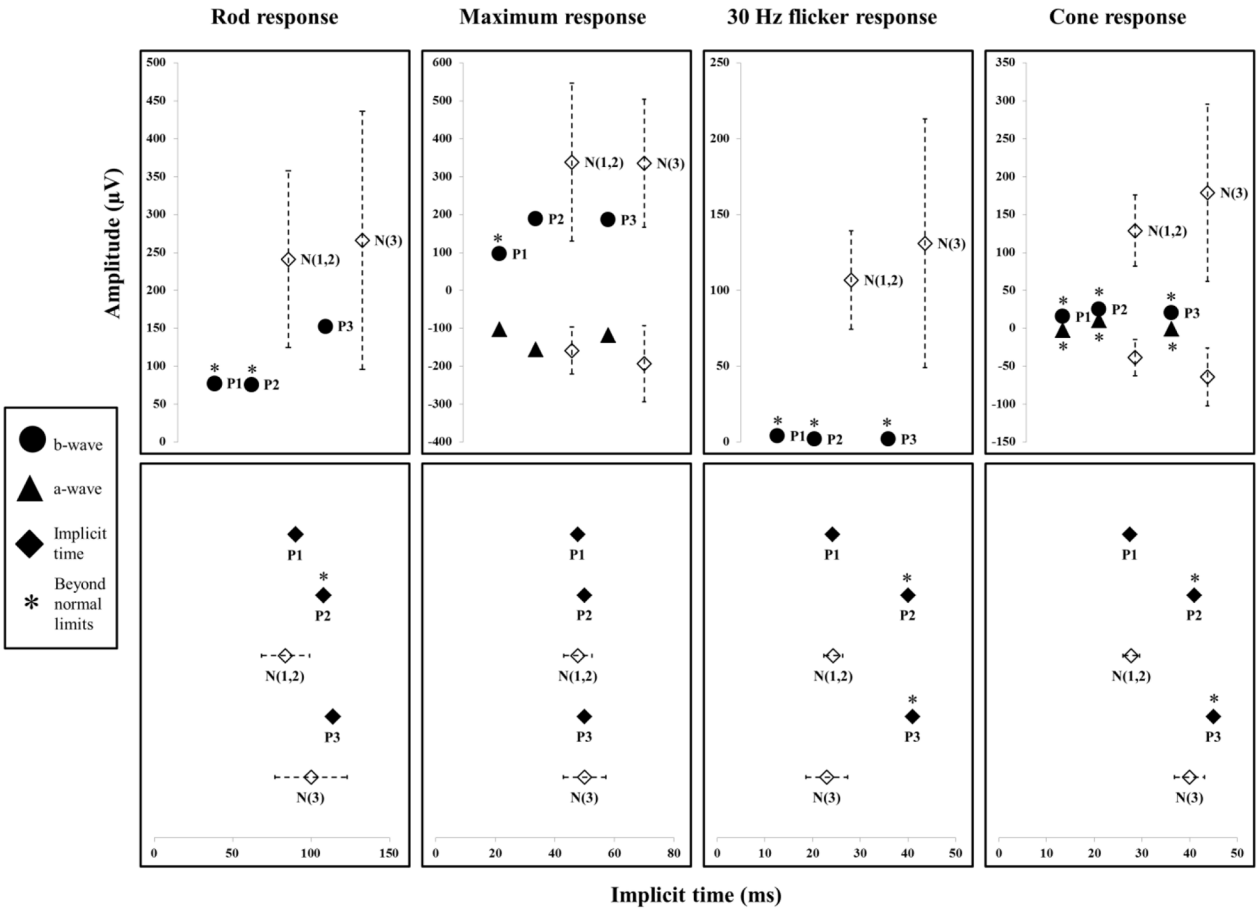

Figure 4.

Quantitative ERG results for each patient and their respective age-match normal ranges are plotted to show relative measurements in amplitude and implicit time differences. N(1,2) represents the normative age range for P1 and P2 (age 50–60) and N(3) for P3 (age 20–30) – asterisks (*) mark significant deviations from normal ranges in each plot. All patients exhibited extinguished b- and a-wave forms of the 30 Hz flicker and photopic cone responses; however, only P2 and P3 exhibited implicit time delays for these stimuli while P1 showed relative sparing of photopic implicit time. Scotopic rod responses were borderline normal in amplitude for both P1 and P2, but the implicit time was prolonged only for P2.

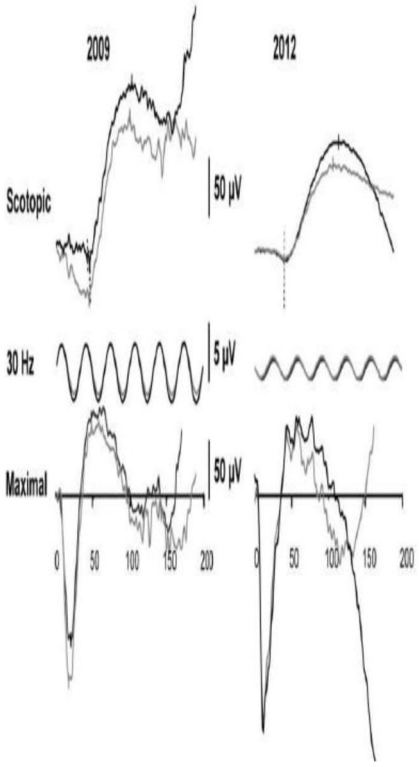

Figure 5.
ERG responses for patient 3 from 2009 (left panel) and 2012 (right panel) (RE: dark gray, LE: light gray lines) showing the disease progression.

Table 1

Patient Demographic and Clinical Characteristics[a]

Family member	Age	Age of Onset	BCVA (OD)	BCVA (OS)	Symptoms
Patient 1 (Proband)	49	4	20/400	20/300	Nystagmus Vision Decline
Patient 2 (Sister)	51	5	20/400	20/400	Vision Decline
Patient 3 (Niece)	26	9	20/400	20/150	Vision Decline

[a]Deterioration of visual acuity began during the first decade of life in each patient. Slit lamp examinations of each patient showed quiet anterior segments and no nuclear sclerosis in the lens (OU). Intraocular pressures were within normal limits.

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