Molecular Vision 2013; 19:2250-2259 <http://www.molvis.org/molvis/v19/2250>
Received 15 April 2013 | Accepted 14 November 2013 | Published 16 November 2013

Clinical characteristics of early retinal disease due to *CDHR1* mutation

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Purpose: To describe the early clinical and electrophysiological features of cone-rod dystrophy due to a mutation of cadherin-related family member 1 (*CDHR1*).
Methods: Three affected siblings from a consanguineous family were ascertained. The clinical data included retinal examination, Goldmann visual fields, fundus autofluorescence imaging, optical coherence tomography (OCT), and pattern and full-field electroretinograms. Exome sequencing was performed in two siblings.
Results: The three siblings presented at age 24, 18, and 16 years, respectively. Their main symptoms were blurred central vision, dyschromatopsia, and photoaversion. All were myopic with best-corrected visual acuities of 20/60, 20/60, and 20/40, respectively. Fundoscopy revealed a range of macular appearances from mild retinal pigment epithelial changes to symmetric, subfoveal pigmented lesions. Fundus autofluorescence imaging and OCT revealed evidence of mild structural abnormalities in the two older siblings. Electroretinography findings in all three patients indicated severe generalized cone-rod dysfunction. Mutational screening in the three siblings showed them to be homozygous for a previously reported frame-shifting mutation in exon 13 of *CDHR1*, c.1463delG, p.G488fs.
Conclusions: The initial clinical signs in this specific retinopathy may be relatively subtle despite a significant functional deficit, with unusual, bilateral, subfoveal pigmented lesions in one 16-year-old patient. Lack of CDHR1 in the human retina causes symptoms related to cone photoreceptor dysfunction in the first instance. A near-normal retinal structure, at least in the first two decades, suggests that *CDHR1*-related retinopathy may be a good candidate for gene replacement or other novel stabilizing treatments.

Retinal dystrophies are a highly heterogeneous group of progressive retinal degenerations that eventually lead to significant visual loss. They can be broadly classified according to the relative severity of generalized rod or cone system dysfunction, and include cone dystrophies, cone-rod dystrophies, and rod-cone dystrophies (also known as retinitis pigmentosa) [1]. Symptoms associated with cone dysfunction include reduction of visual acuity, impaired color vision, and photophobia [2,3]. Conversely, patients with rod dysfunction complain of nyctalopia [4].

Cone-rod dystrophies can be inherited as autosomal dominant, autosomal recessive, or X-linked recessive traits [3]. Mutations in *ABCA4*, *ADAM9*, *CERKL*, *PROM1*, and *RPGRIP1* are associated with autosomal recessive cone-rod dystrophy [5-8]. Recently, mutations in cadherin-related family member 1 (*CDHR1*), a gene localized at chromosome 10q23.1, have also been associated with autosomal recessive retinal dystrophy in families of Middle Eastern, Asian, and Faroese origin [9-12]. *CDHR1* encodes the photoreceptor cadherin, a structural, transmembrane protein localized to the base of the rod and cone outer segments (OSs) and appears to be involved in maintaining the OS structure [13]. Only a few families with *CDHR1*-related retinopathy have been reported so far. There are very limited data on younger patients with the disorder; such data are important for determining the cell type first affected and to aid the clinician in making a timely diagnosis in childhood. Retinal signs are not pathognomonic and included irregular macular pigmentation, bull's eye maculopathy, metallic sheen at the macula, bone spicule pigment migration in the anterior retina, dense pigmentation, and marked outer retinal atrophic changes [9,10,12]. A mouse knockout model exists with affected animals having short, disorganized, and misaligned photoreceptor OSs leading to apoptotic photoreceptor cell death [13].

The present report describes the early phenotype in a family in which, from clinical examination and detailed investigations, the specific molecular diagnosis was not

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initially apparent. Subsequent exome sequencing determined a homozygous null mutation in *CDHR1*.

METHODS

Participants and clinical assessment: Three affected siblings from a consanguineous family of Pakistani origin were ascertained, following presentation to the inherited retinal disorders service at Moorfields Eye Hospital (family GC18832). Clinical testing and blood samples for genetic testing were obtained after informed consent by the adult patients and from the legal guardians of the younger sister. The study was endorsed by the Local Research Ethics Committee and adhered to the tenets of the Declaration of Helsinki.

Clinical assessment included Snellen visual acuity, color vision testing using Ishihara pseudo-isochromatic color plates (Kanehara Shuppan Co., Ltd., Tokyo, Japan), and slit-lamp examination after pupillary dilation. Clinical imaging included spectral-domain optical coherence tomography (SD-OCT) and fundus autofluorescence (FAF) performed on a Spectralis HRA+OCT (Heidelberg Engineering GmbH, Heidelberg, Germany), and color fundus photography on a Topcon TRC-50DX (Topcon Medical Systems, Inc., Oakland, NJ). In addition, Goldmann visual fields (Haag Streit, Bern, Switzerland) were assessed using targets that ranged from I4e to V4e. Full field electroretinograms (ERG), pattern electroretinograms (PERG) were recorded on a custom-built ERG system; multifocal electroretinograms (mfERG) were recorded on a Roland system (Roland Consult, Brandenburg, Germany) using techniques that incorporated the Standards of the International Society for Clinical Electrophysiology of Vision [14-16].

Genetic studies: Exome sequencing was performed in family members II:2 and II:3 (Figure 1) using the solution-phase Agilent SureSelect 50 Mb exome capture (SureSelect Human All Exon Kit; Agilent, Wokingham, UK) and the Illumina HiSeq2000 sequencer (Illumina, San Diego, CA). Reads were aligned to the hg19 human reference sequence using Novoalign (Novocraft, Selangor, Malaysia) version 2.05. The ANNOVAR tool (OpenBioinformatics, Beverly, MA) was used to annotate single-nucleotide polymorphisms and small insertions/deletions. To detect the likely disease-causing variant, heuristic filtering methods were used as previously described [17]. Variants were prioritized by their presence in shared regions of homozygosity, assuming the inheritance of an identical chromosomal segment from a single founder from both related parents.

RESULTS

Clinical, imaging, visual field, and electrophysiological findings are summarized in Table 1, and are detailed below for family members II:2, II:3, and II:6 (Figure 1). Parents and asymptomatic family members were not examined and parental DNA was unavailable for analysis. Exon capture and high-throughput sequencing of DNA from family members

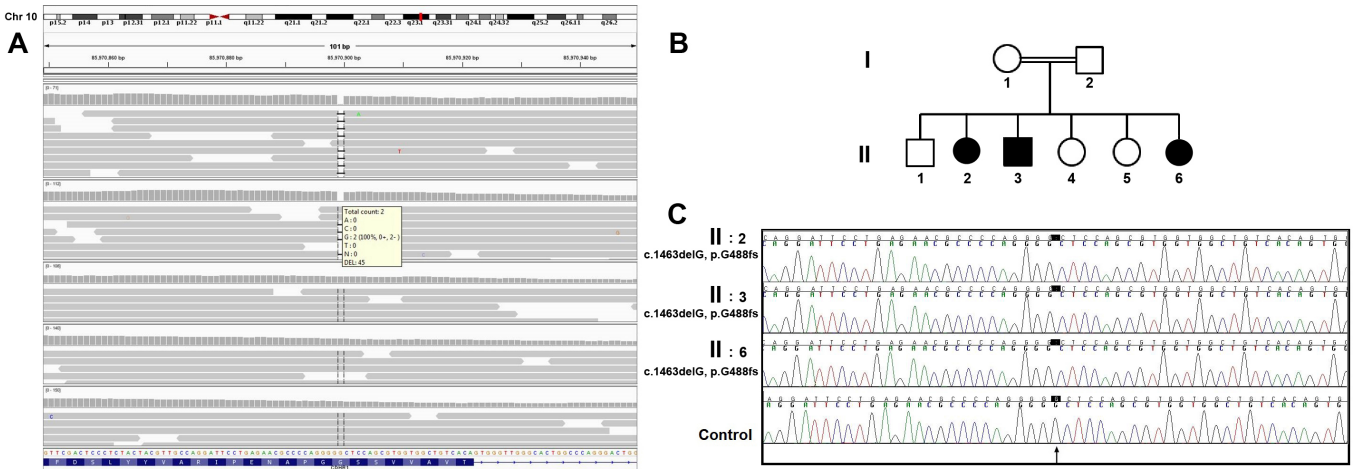

Figure 1. Identification of a CDHR1 mutation in individuals from a family with cone-rod dystrophy. **A**: An assembly of paired-end reads following Illumina HiSeq2000 sequencing and alignment with ANNOVAR 2.05, viewed using IGV2.3.0. Samples derived from patients II:2 and II:3 are shown in the top two lanes with three control samples from the same sequencing run, shown below. All 29 and 47 reads from II:2 and II:3, respectively, are consistent with deletion of a single G nucleotide in a run of 5 Gs from the wild-type sequence of exon 13 of cadherin-related family member 1 (CDHR1). **B**: Pedigree of family GC18832. The pedigree of the affected sibship. The family is an Asian, first-cousin consanguineous pedigree with three affected siblings. Open and closed symbols represent unaffected and affected individuals, respectively. **C**: Chromatograms of Sanger DNA sequencing surrounding the CDHR1 variant c.1463delG, p.G488fs are shown for patients II:2, II:3, and II:6, as well as an unrelated control sample.

II:2 and II:3, in large shared chromosomal areas of contiguous homozygosity, revealed homozygosity for a previously reported frame-shifting mutation in exon 13, c.1463delG, p.G488fs [9] in both siblings. No other likely disease-causing mutations in genes previously associated with retinal disease were identified in either sample. Direct Sanger sequencing of the DNA from members II:2 and II:3 confirmed the mutation and showed the same homozygous mutation in II:6 (Figure 1).

Case 1: Patient II:2 is a 24-year-old female who was referred with a 6-year history of worsening visual acuity and a preference for dimly lit environments. Her best-corrected visual acuity (BCVA) was 20/60 in each eye. She saw only 1 and 2 of the 17 Ishihara color plates with the right and left eye, respectively. Fundus examination revealed areas of pigment loss and hyperpigmentation at the level of the outer retina in both maculae (Figure 2A). FAF showed multiple areas of reduced macular autofluorescence (AF; Figure 2B). SD-OCT showed disruption of the photoreceptor and retinal pigment epithelium (RPE) layers at the fovea (Figure 2C). The inner segment ellipsoid line was relatively intact, suggesting a degree of preservation of macular photoreceptors, including foveal cones. Perimetry showed relatively dense central scotomata in both eyes (Figure 3). Full-field ERG showed a cone-rod pattern of generalized dysfunction (Figure 4) with severely delayed and severely reduced photopic single flash (light adapted response to a 3.0 $cd.s.m^{-2}$ stimulus) and 30 Hz flicker ERGs (light adapted response to a 3.0 $cd.s.m^{-2}$ stimulus), undetectable rod-specific ERGs (dark-adapted response to a 0.01 $cd.s.m^{-2}$ stimulus), and markedly delayed and subnormal scotopic bright flash ERGs (dark-adapted response to a 11.0 $cd.s.m^{-2}$ stimulus). PERGs (Figure 4) and multifocal ERGs (data not shown) were undetectable, in keeping with severe widespread macular involvement.

Case 2: Patient II:3 is an 18-year-old male who was referred with a 3-year history of severely reduced visual acuity and photophobia, preferring dimly lit environments. His BCVA was 20/60 in either eye. He had no detectable color vision. Retinal examination showed subtle RPE atrophic changes at the center of both maculae (Figure 2D). FAF imaging was normal (Figure 2E). OCT was not available. Visual fields were normal for the II4e, III4e, and V4e targets (Figure 3). Full-field ERGs showed a generalized cone-rod pattern of dysfunction (Figure 4) with findings similar to those described for case 1.

Case 3: Patient II:6 is a 16-year-old female who had complained of difficulty reading for the past 6 months. She denied night vision problems, and was not photophobic. Her BCVA was 20/40 in either eye. She correctly identified only the screening plate of the Ishihara test when each eye was tested. Retinal examination showed bilateral dense hyperpigmentation at the center of the macula (Figure 2F). FAF imaging showed a central region of reduced AF surrounded by alternating rings of increased and reduced AF (Figure 2G). SD-OCT showed a localized dome-shaped foveal elevation in both eyes involving the RPE layer, which also had an uneven reflectivity (Figure 2H). Localized hyporeflectivity was present in relation to the outer plexiform layer at the edges of these lesions. Visual field testing (Figure 3) showed a localized central region of reduced sensitivity to static stimuli in the left eye. The right visual field showed only a small paracentral relative scotoma. Full-field ERGs showed a cone-rod pattern of generalized dysfunction with PERG evidence of severe macular involvement (Figure 4).

DISCUSSION

This report describes the early clinical and electrophysiological features of cone-rod dystrophy arising from a mutation in *CDHR1*. All patients in the present series had visual acuity reduction starting in adolescence and rapidly developed photophobia. Color vision was severely affected in all, in keeping with previous reports, even in the youngest sibling who only had reading difficulty and relatively mild visual acuity reduction [9,11,12]. Consistent with previous studies, all patients were myopic [9,11,12]. It is not known whether this reflects an effect of the specific genetic mutation on ocular development or is a secondary response to constant blurring of the retinal image.

The present mutation has been reported previously by the same group in a different pedigree [9]. The families in both reports are unrelated, but a founder effect cannot be excluded as both families come from the Indian subcontinent. As previously reported [9], the c.1463delG mutation causes truncation of the protein in the cadherin domain through a premature stop codon, 19 codons downstream of the deletion. It may lead to nonsense-mediated decay of the transcript and loss of the whole peptide chain [9].

At presentation, despite significant symptoms and reduced acuity, fundus abnormalities can be relatively mild compared to the phenotype described previously in older subjects with mutations in *CDHR1*, including a patient with a similar mutation (Table 2) [9]. Color vision assessment was abnormal in all three individuals and may provide a useful, albeit nonspecific, early sign of this retinopathy.

The macular SD-OCT images of the youngest patient showed a novel finding, an irregular, dome-shaped lesion deep in the RPE, with some distortion of the structure of the overlying neurosensory retina. This is the first report of such lesions occurring in this retinopathy and further observation

Table 1. Summary of the clinical and electrophysiological data.

Case/age (years)/ gender	Presenting symptoms	BCVA/refractive error	Color vision	Fundoscopic features	ERG
1/24/F	Progressive loss of central vision; photophobia	OU: 20/60; OD: -4.75/-1.25x30 OS: -3.75/-1.00x160	OD:1/17 OS: 2/17	RPE changes at the macula; normally appearing peripheral retina	Undetectable PERG; Scotopic bright flash ERG is markedly delayed and subnormal; Severely delayed and reduced cone responses.
2/18/M	Reduced visual acuity, color blind-ness, photophobia	OU: 20/60; Low myopia	OU: 0/17	Subtle RPE atrophic changes at the center of both maculae	Undetectable PERG; Scotopic bright flash ERG is markedly delayed and subnormal; Severely delayed and reduced cone responses.
3/16/F	Difficulty reading	OU: 20/40; Myopia	OU: 1/17	Elevated, pigmented macular lesion; normally appearing peripheral retina	PERG: severely reduced; Scotopic bright flash ERG is moderately subnormal; Severely delayed and reduced cone responses.

BCVA: Snellen best-corrected visual acuity, ERG: electroretinogram, RPE: retinal pigment epithelium. PERG: pattern electroretinogram. Color vision was tested using Ishihara plates.

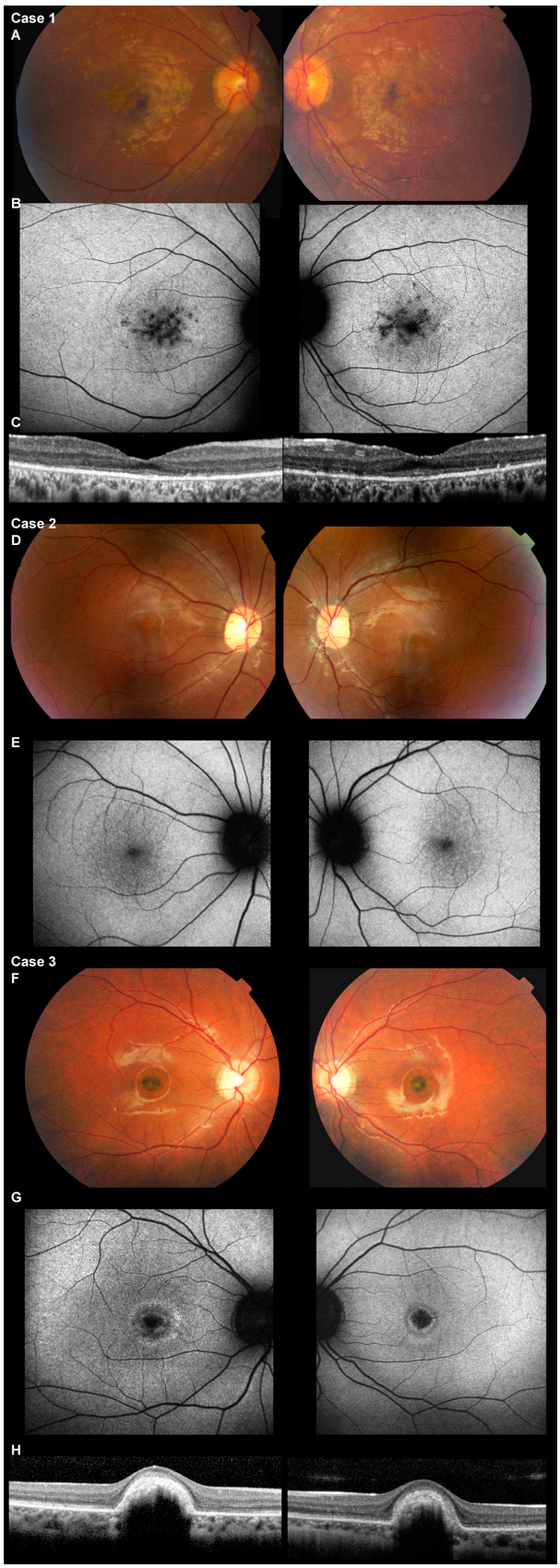

Figure 2. Color fundus photographs , fundus autofluorescence images, and optical coherence tomography images of cases 1, 2, and 3. **A**: Case 1-A mild pigment atrophy in the central macula and hyperpigmentation nasal to the fovea. **B**: Speckled hypoautofluorescence in the macular region. C: Irregular reflectivity at the level of the outer retinal layers. **D**: Case 2-Subtle pigment changes at the center of the macula. **E**: Normal fundus autofluorescence (FAF). **F**: Case 3-The retina appears normal except for a central area of dense hyperpigmentation. **G**: A ring of hyperautofluorescence surrounding a central bull's eye lesion. **H**: An elevated lesion is present at the center of the fovea. There is distortion of the retinal layers over and adjacent to the lesion.

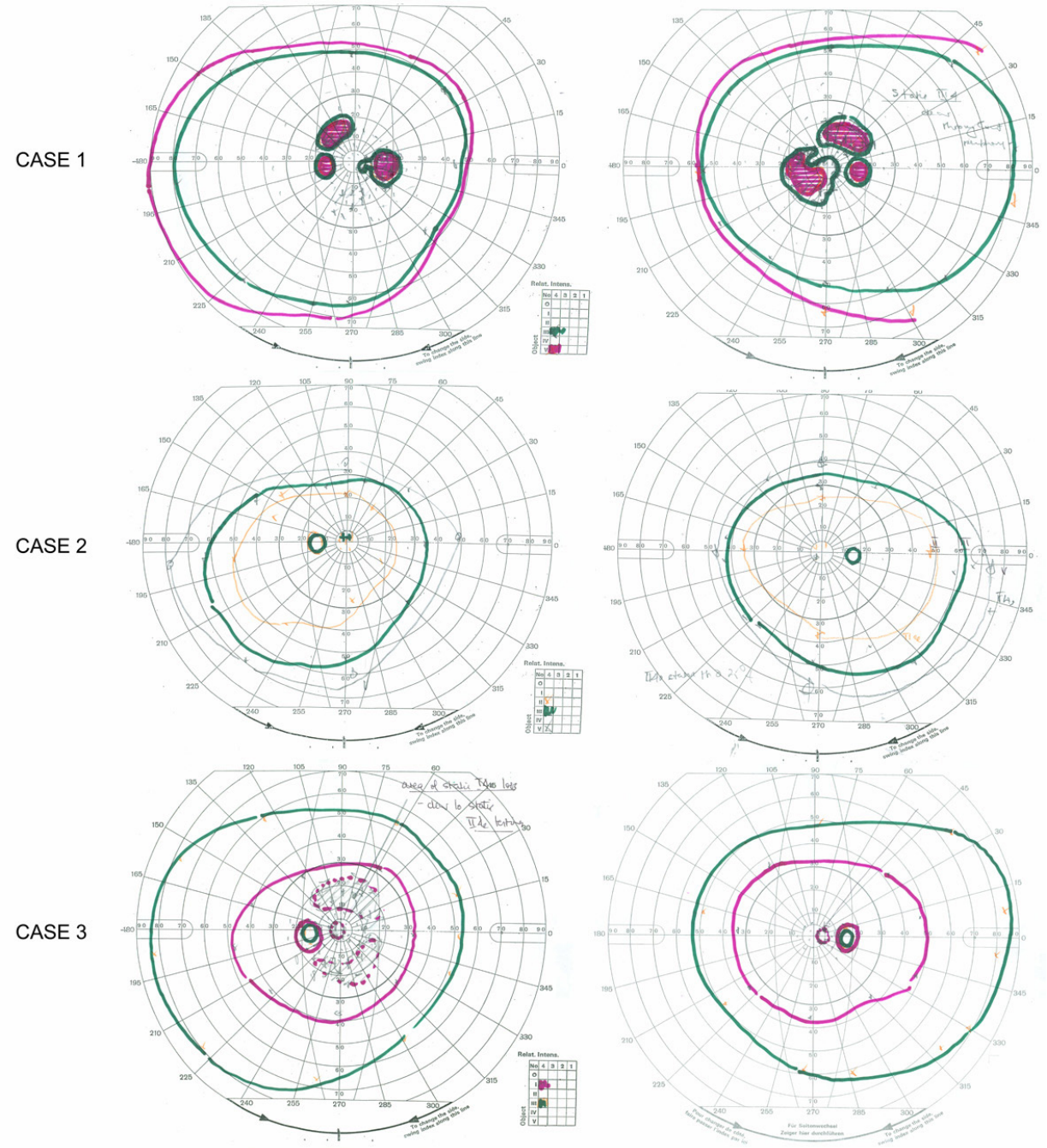

Figure 3. Goldmann visual fields of both eyes of each patient using target sizes: I4e, III4e, and V4e. The left-hand column shows the fields of the left eye, while the right-hand column illustrates the fields of the right eye. Case 1 has a relatively large central scotoma; the left eye shows smaller paracentral islands of sensitivity loss. Case 2 has normal fields. Case 3 has a left central and paracentral relative scotomata to static stimuli only. The right eye field shows a small relative scotoma.

will be necessary to determine whether this is a characteristic early feature of the disorder, or an incidental finding in this patient.

Although the retinal periphery appeared normal in all patients, the full-field cone and rod ERGs were profoundly abnormal. Electrophysiological testing is an important part of the assessment of patients with inherited retinal disorders, and can be particularly helpful in cases where the symptoms at presentation cannot be explained by the findings on ophthalmoscopy.

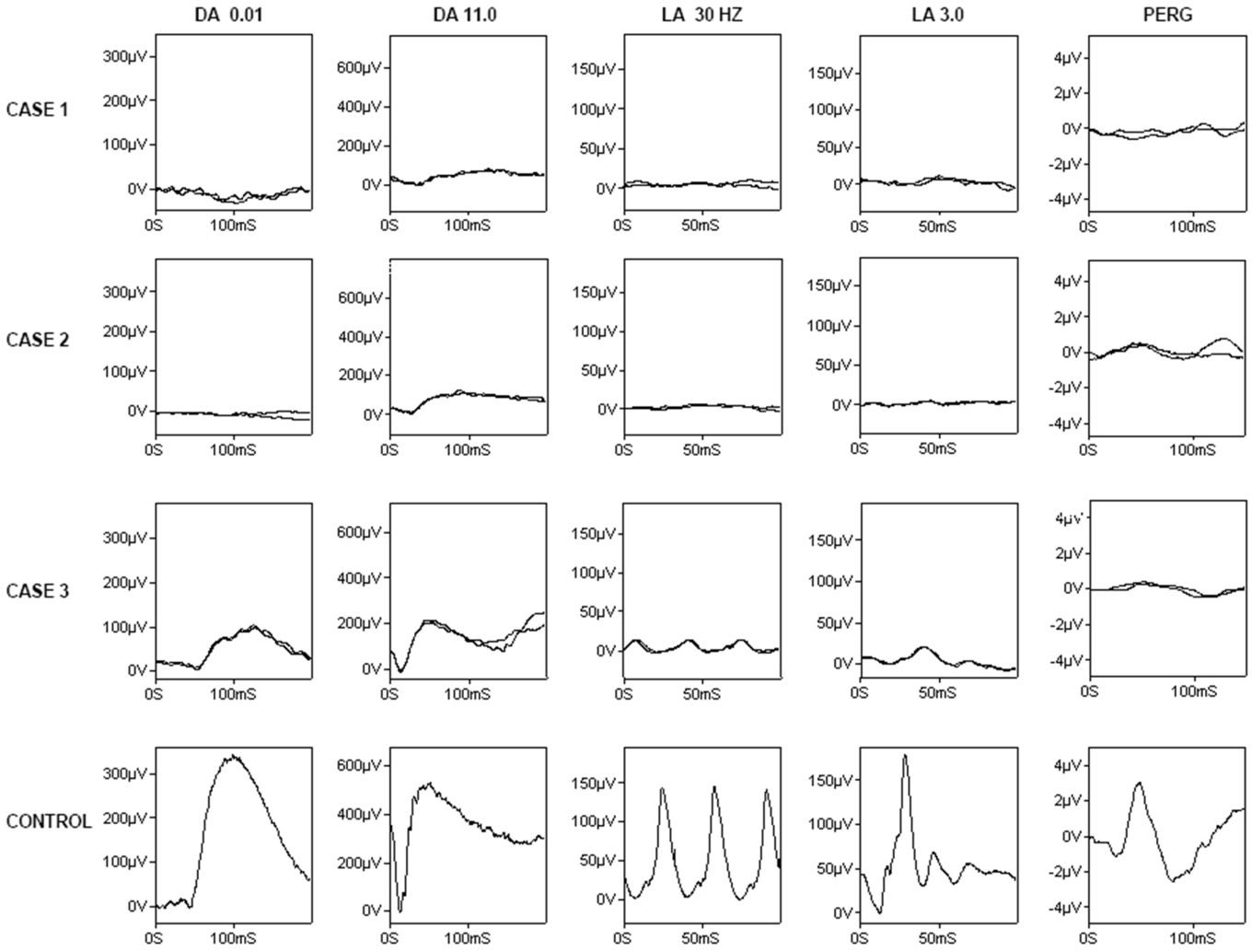

Figure 4. Electroretinograms of all cases. Bottom row: Electroretinograms (ERGs) of a control subject. No significant interocular asymmetry was present and data are only shown from one eye of each patient. DA 0.01: dark-adapted 0.01 cd.s.m^{-2}; DA 11.0: dark-adapted 11.0 cd.s.m^{-2}; LA 30 Hz: light-adapted 3.0 cd.s.m^{-2}, 30 Hz flicker; LA 3.0: light-adapted 3.0 cd.s.m^{-2}; PERG: pattern ERG.

It is clear from the symptoms, signs, and investigations, that the cone photoreceptor appears most vulnerable to an inherent lack of CDHR1. The cause of the initial vulnerability of cone photoreceptors is not suggested by the expression of these genes in both photoreceptor classes, and has yet to be determined. Moreover, the disorder, at least in the early stages, is not a form of retinitis pigmentosa, allowing it to be distinguished from the many subtypes of this class of retinal degeneration. Progressive autosomal recessive cone-rod dystrophies are rare, with only a handful of genes implicated [5-8,18]. As expected, the proteins involved in the formation and maintenance of the photoreceptor OS are critical for cell survival and any novel treatments would need to target this process [6,19]. The relative sparing of the outer retinal layers in the OCT images presented herein may suggest a period of time in the natural history of the disorder in which rescue may be successful.

In summary, a detailed description of the clinical phenotype in three siblings with a mutation in *CDHR1* corroborates other reports that the disorder initially affects the cone system rather than causing retinitis pigmentosa. The data from this family give further insights into the presentation of the disorder, facilitating early diagnosis and delivery of effective genetic counseling.

ACKNOWLEDGMENTS

The authors thank Dr. Magella M. Neveu, Moorfields Eye Hospital, for interpreting the electrophysiological data of one of the patients. We acknowledge Dr. Naushin Waseem, UCL Institute of Ophthalmology for performing Sanger

Table 2. Clinical and genetic findings in individuals with CDHR1-related retinopathy described here and elsewhere.

Genotype	Predicted amino acid sequence	Age at presentation	Symptoms	Retinal features	Electroretinography	Reference
Homozygous c.524dupA p.Asn176GlufsX48	Loss of 637 carboxyl amino acids	6 months - 37 years	Reduced visual acuity in the 2nd decade, nyctalopia and impaired color vision	Macular atrophic changes, extensive sheen, peripheral RPE atrophy and bone-spicule pigmentation	Markedly delayed and reduced rod and cone responses, undetectable in some cases	Ostergaard et al [10]
Homozygous c.338delG p.Gly113AlafsX2	Loss of 746 carboxyl amino acids	34, 36, 42 years	Nyctalopia in late teenage years , visual acuity is preserved until the 4th decade, deteriorated thereafter, impaired color vision	Macular atrophic changes, peripheral circular patches of RPE atrophy, bone-spicule pigmentation and vascular attenuation	Mild cone-rod dysfunction in the youngest, moderate-severe rod-cone dysfunction in the older 2 individuals	Henderson et al [9] (family GC16464)
Homozygous c.1381 C>T p.Gln461X	Loss of 399 carboxyl amino acids	32, 36, 45 years	Glare and photosensitivity in childhood, nyctalopia in adolescence, impaired color vision by the 3rd decade, visual acuity loss by the 4th decade	Bull's eye pattern, peripheral RPE atrophy, bone-spicule pigmentation and vascular attenuation, relative preservation of the anatomic fovea by OCT	Undetectable	Duncan et al [12]
Homozygous c.1463delG (annotated c.1459delG [9]) p.Gly488AlafsX20	Loss of 353 carboxyl amino acids	32 years 24, 18, 16 years	Nyctalopia in late teenage years, visual acuity is preserved until the 4th decade, deteriorated thereafter, impaired color vision. Lack of retinal signs led to suspected neurological cause for field loss at presentation [9]. Reduced visual acuity in the 2nd decade, impaired color vision.	Circular macular atrophic changes, peripheral circular patches of RPE atrophy, bone-spicule pigmentation and vascular attenuation [9]. Mild macular RPE changes, no peripheral retinal changes, dome-shaped subfoveal pigmented lesions, relative preservation of the anatomic fovea by OCT	Undetectable [9] Markedly delayed and reduced cone and rod responses	Henderson et al [9] (family GC3748) Present paper (family GC18832)
Homozygous c.1485+2T>G	Elimination of intron 13 donor splice site	36, 38 years	Reduced visual acuity in the 2nd decade , nyctalopia	Macular atrophic changes, peripheral RPE atrophy, few bone-spicule pigmentation, relative preservation of the anatomic fovea by OCT	Undetectable cone response, markedly reduced rod response.	Cohen et al [11]

All variants are described according to the Human Genome Variation Society guidelines based on reference sequence NM_033100.3 (*CDHR1*)

sequencing. The work was supported by grants from the National Institute for Health Research Biomedical Research Centre at Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology, Fight for Sight (including the Mercer Fund), Moorfields Eye Hospital Special Trustees, Retinitis Pigmentosa Fighting Blindness, and the Foundation Fighting Blindness (USA). MM is supported by a Foundation Fighting Blindness Career Development Award.

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