Clinical Characteristics of Rod and Cone Photoreceptor Dystrophies in Patients With Mutations in the *C8orf37* Gene

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Purpose. To provide the clinical features in patients with retinal disease caused by *C8orf37* gene mutations.

Methods. Eight patients—four diagnosed with retinitis pigmentosa (RP) and four with cone-rod dystrophy (CRD), carrying causal *C8orf37* mutations—were clinically evaluated, including extensive medical history taking, slit-lamp biomicroscopy, ophthalmoscopy, kinetic perimetry, electroretinography (ERG), spectral-domain optical coherence tomography (SD-OCT), autofluorescence (AF) imaging, and fundus photography.

Results. In families A and D, respectively, one and three patients showed a classic RP phenotype with night blindness followed by concentric loss of visual field. Severe visual loss to light perception occurred early in the course of the disease. The symptoms initiated during infancy (family A) or adolescence (family D). Ophthalmoscopy revealed macular atrophy, bone spicules, attenuated vessels, and waxy pale optic discs. SD-OCT showed profound photoreceptor degeneration and AF demonstrated atrophy of the retinal pigment epithelium (RPE). ERG responses were nonrecordable in these patients. In families B and C, the patients were diagnosed with CRD. Initial symptoms were photophobia or loss of visual acuity and occurred during infancy (family B) or adolescence (family C). Ophthalmoscopy and AF revealed profound macular RPE atrophy and SD-OCT demonstrated macular photoreceptor degeneration. ERG responses were severely reduced in a cone-rod pattern or were nonrecordable. Interestingly, both patients in family B demonstrated polydactyly.

Conclusions. Mutations in *C8orf37* give rise to an early or adolescent-onset autosomal recessive CRD or RP phenotype with early macular atrophy. The occurrence of postaxial polydactyly in one family suggests a syndromic phenotype, which may indicate *C8orf37* has a ciliary function.

Keywords: clinical characteristics, C8orf37, retinitis pigmentosa, cone–rod dystrophy

Retinitis pigmentosa (RP) and cone-rod dystrophy (CRD) are inherited photoreceptor dystrophies, which are genetically and clinically highly heterogeneous. RP is the most common photoreceptor dystrophy, with a prevalence of approximately one in 4000 individuals,[1–3] whereas CRD is less frequent, with an estimated prevalence of one in 40,000 individuals.[4,5] Both conditions are characterized by progressive degeneration of photoreceptors, although in different patterns. In RP, rod photoreceptor degeneration usually starts prior to the loss of the cone photoreceptors, causing primary symptoms such as night blindness and peripheral visual field loss. Ophthalmoscopic characteristics include attenuated vessels, peripheral bone spicule pigmentation, waxy pallor of the optic disc, and peripheral chorioretinal atrophy.[3,6] In CRD, the cone photoreceptors usually degenerate prior to the rod photoreceptors, which the patient perceives as photophobia, loss of visual acuity, and central scotomas. Ophthalmoscopic features initially include macular retinal atrophy and pigment deposits, whereas in later stages mild attenuated vessels and bone spicule pigmentations in the periphery may be present, mimicking RP. These two photoreceptor degeneration patterns can be distinguished by performing an electroretinography (ERG). In RP, the rod-driven (scotopic) responses are equally or more severely reduced than cone-driven (photopic) responses,[7,8] whereas in early CRD there are normal rod responses and

substantially reduced cone responses, although rod responses will deteriorate as the disease progresses.

Mutations in many different genes have been associated with either CRD or RP. CRD and RP display all Mendelian modes of inheritance.[6] Also, digenic and mitochondrial inheritance have been described for RP.[9–11] Until now, mutations in 36 genes have been associated with nonsyndromic autosomal recessive (ar) RP.[12] Proteins of these genes are involved in phototransduction, retinoid (vitamin A) metabolism, transport along the connecting cilium, intercellular signaling or synaptic interaction, interphotoreceptor matrix, gene regulation, and phagocytosis,[6,11,13] emphasizing that RP should be defined as a spectrum of dystrophies with a similar phenotype. For CRD, mutations in six genes have been described to date.[12] Mutations in two of these genes (*ABCA4* and *CERKL*) can also cause arRP.[14,15] Taken together, it is estimated that mutations in these 40 genes are causative for approximately 50% to 60% of all arRP and CRD cases,[13] although new genes are still being discovered.

Recently, causative mutations in the *C8orf37* gene have been described in both arRP and CRD patients.[16] Sequence analysis of all six coding exons of the *C8orf37* gene led to the identification of four different pathogenic variants in these eight affected individuals.[16] *C8orf37* is ubiquitously expressed in adult human tissues, but is highly expressed in brain, heart, and retinal tissues. The function of the C8orf37 protein is not known yet, but immunolocalization studies showed that it is localized at the base of the connecting cilium, suggesting a ciliary function.[16]

Mutations in *C8orf37* are known to cause CRD or RP, but specific clinical features have not yet been described. A detailed clinical description of the patients with mutations in *C8orf37* may help to provide insight into the gene's function and improve patient counseling on the prognosis of the disease. Furthermore, this type of knowledge is crucial to the emerging new field of gene therapy, not only to select patients amenable for treatment, but also to determine the effects of the treatment they may receive.

Patients and Methods

Subjects and Genetic Analysis

Patients with inherited photoreceptor dystrophies were referred to specialized ophthalmic centers and examined at the Radboud University Nijmegen Medical Centre (by CBH and BJK), Hadassah-Hebrew University Medical Center in Jerusalem, Israel (by EB), the Goldschleger Eye Research Institute (by YR), or the Institute for Ophthalmic Research in Tuebingen, Germany (by SH).

Subsequently, genetic analysis was performed in all cases. After the discovery of a causative homozygous *C8orf37* mutation using homozygosity mapping and targeted next-generation sequencing (NGS) in a German RP patient (A-IV:1), further genetic analysis was performed in approximately 400 families with arRP, CRD, or Leber congenital amaurosis. This resulted in three more families from The Netherlands or Israel with causative mutations in *C8orf37*.[16] In total, four families including eight affected individuals were selected for this clinical study (Table).

We adhered to the tenets of the Declaration of Helsinki and informed consent was obtained from all participating patients prior to the collection of a blood sample and additional ophthalmologic examinations. Prior to this study, we obtained approval from the Institutional Ethics Committee from the Radboud University Nijmegen Medical Centre.

Clinical Analysis

Clinical data were collected from the medical records of these patients. Following the identification of causative *C8orf37* mutations, all patients were reevaluated in addition to the data accumulated over the years. Medical history was registered with a focus on age of onset, initial symptoms, and overall course of the retinal disorder. Age of onset was defined as the age at which the initial symptom was first noticed by the patient. We asked all patients about the presence of syndromic features, which are generally present in 20% to 30% of retinal dystrophy patients. These questions concerned the presence of hearing and balance abnormalities, renal failure, cardiac and respiratory anomalies, polydactyly, obesity, cognitive impairment, fertility disorders, hypogonadism, and dental anomalies. The clinical examination included best-corrected visual acuity, slit-lamp biomicroscopy, ophthalmoscopy, and fundus photography. Goldmann (kinetic) perimetry was performed insix patients. In patients A-IV:1 and D-IV:4 perimetry proved impossible due to severe visual impairment. Cross-sectional images of the central retina were obtained with a commercially available spectral-domain optical coherence tomography (SD-OCT) instrument (Spectralis; Heidelberg Engineering and Cirrus; Carl Zeiss Meditec) by performing a volume scan (15° × 20°) through the fovea. Central foveal thickness was measured at the foveola using imaging and vision software (Heidelberg Eye Explorer Software, version 1.6.4.0; Heidelberg Engineering) or vision software (Cirrus Software, version 5.1.1.6; Carl Zeiss Meditec). Fundus autofluorescence (FAF; Spectralis, Heidelberg Engineering) could be performed in six patients. A full-field ERG was performed in all patients except patient D-IV:4. ERGs were performed using Dawson-Trick-Litzkow (DTL) electrodes and a visual electrophysiology program (Espion Visual Electrophysiology System; Diagnosys LLC, Lowell, MA) in the Institute for Ophthalmic Research, Tuebingen, Germany; DTL-electrodes and the RETI-port system (Roland Consults, Stasche, & Finger GmbH, Brandenburg an der Hazel, Germany) in the Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; Bipolar Burien Allen electrodes and the UTAS SunBurst Color LED Ganzfeld (LKC Technologies, Gaithersburg, MD) in the Goldschleger Eye Research Institute, Tel Hashomer, Israel; and monopolar corneal electrodes (Henkes-type, Medical Workshop B.V., Groningen, The Netherlands) and the computerized UTAS 3000 system (LKC Technologies) in the Hadassah–Hebrew University Medical Center, Jerusalem, Israel. ERGs were assessed according to local standard values. All centers followed the guidelines of the International Society for Clinical Electrophysiology of Vision.[17]

Results

We included a total of eight patients from four families in this study. An overview of the clinical findings in these patients is provided in the Table. In families A and D, the affected individuals were diagnosed with RP, whereas in the other families (B and C) the patients were diagnosed with CRD. Additionally, both patients from family B mentioned postaxial polydactyly in their medical history, including one additional finger and toe on the right hand and foot, respectively. In the other families, no extraocular abnormalities suggesting syndromic RP or CRD were observed.

In the RP families (A and D), the mean age of onset was approximately 12 years and ranged from infancy to the age of 18 years. The initial symptom in these patients was either loss of visual acuity ($n = 2$) or night blindness ($n = 1$) in these patients, although both symptoms occurred within a year after

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Table. Clinical Features at Most Current Examination in Patients Carrying Mutations in *C8orf37*

Patient ID/ Age of Onset, y/ Age/Sex	Initial Symptom	Visual Acuity*	Lens Status	Ophthalmoscopy Results	ERG Results†	Goldmann Perimetry	OCT Results	Autofluorescence Results	Nonocular Findings	Homozygous Mutation	Dx
A-IV:1/Infancy/ 37/M	Night blindness/ loss of visual acuity	LP LP	Clear	Profound panretinal chorioretinal atrophy, waxy pallor of the optic disc, severely attenuated vessels, irregular pigment clumps, bone spicules in the midperiphery	NR‡ NR‡	UTP	Scan approximately 500 μm temporal of macula. Retinal and choroidal thinning.	Macular hypoautofluorescence and numerous hypoautofluorescent lesions in the perimacular region.	None	c.497T→ A (p.Leu166*)	RP
B-V:1/17/41/F	Photophobia	CF CF	Clear	Severe atrophy with RPE alterations and gliosis in the macula, normal aspect of the optic disc, mild attenuation of peripheral retinal vessels only, peripheral pigmentations (both bone spicule-like as well as round), chorioretinal atrophy in the midperiphery.	NR§ NR§	LE: Central scotoma RE: not reliable. Progressive constriction of VF‖	Severe thinning of retina, loss of photoreceptors with preservation of RPE peripheral of the macula. CFT: 99 μm (RE), 62 μm (LE)	Diffuse hypoautofluorescent spots in perifoveal region. Hyperautofluorecence in perimacular region with hypoautofluorescent spots.	Polydactyly on right foot and right hand	c.156-2A → G (splice defect)	CRD
B-V:7/10/26/M	Photophobia	20/125 20/125	Clear	RPE alterations, atrophy, and gliosis in the macula. Normal aspect of vasculature and optic disc. Sporadic round pigmentations in periphery.	NR NR	Unreliable. BE: Constricted VF	Severe thinning of retina, loss of photoreceptors with preservation of RPE, severe thinning of the nerve fiber layer. CFT: 105 μm (RE), 103 μm (LE)	Hypoautofluorescence in the foveal region, parafoveal hyperautofluorescence, numerous irregular hypoautofluorescent spots in the perimacular region.	Polydactyly on right foot and right hand	c.156-2A → G (splice defect)	CRD
C-II:1/Infancy/ 36/M	Loss of visual acuity	20/250 20/345	Clear	Macular atrophy with intraretinal pigment clumping, peripapillary atrophy, temporal optic disc pallor, attenuation of the retinal vessels.	SR# NR	NP	Severe thinning of the retina, hyperreflective deposits in the macula, loss of photoreceptor–RPE complex.	NP	None	c.529C→ T (p.Arg177Trp)	CRD
C-II:2/Infancy/ 30/M	Loss of visual acuity	20/60 20/400	Clear	Macular atrophy, peripapillary atrophy, temporal optic disc pallor, attenuated vessels, RPE changes in the RE following extraocular surgery for retinal detachment.	SR# NR	NP	Thinning of the retina, loss of POS in the macula, atrophy of the choriocapillaris. CFT: 68 μm (RE), 76 μm (LE).	NP	None	c.529C→ T (p.Arg177Trp)	CRD
D-IV:1/18/38/F	Night blindness/ loss of visual acuity	HM HM	Very mild PSC cataract in BE	Yellow-brown atrophic lesion in the macula with pigment clumps, waxy optic disc pallor, attenuated vessels, gray atrophy along the vascular arcades, heavy bone spicule pigmentations in mid-periphery.	NR NR	LE performed only: remaining VF of 5° with severe sensitivity loss.	Sharply demarcated hypoauto-fluorescence in macula, numerous hypoautofluorescent spots in the perimacular region. CFT: 28 μm (RE), 71 μm (LE).	Severe thinning of the retina, atrophy of the RPE and choriocapillaris.	None	c.545A→ G (p.Gln182Arg)	RP
D-IV:3/17/43/F	Loss of visual acuity	LP LP	Very mild PSC cataract in BE	Yellow-brown atrophic lesion in the macula with pigment clumps, pallor optic disc with peripapillary atrophy, attenuated vessels; gray atrophic lesions with pigmentation along the vascular arcades, heavy bone spicules pigmentation in mid-periphery.	NR NR	LE performed only: remaining VF of 5° with severe sensitivity loss.	Severe thinning of the fovea, loss of photoreceptor–RPE complex, intraretinal hyperreflective clumps, atrophy of choriocapillaris. CFT: 51 μm (RE), 63 μm (LE).	Numerous partially merged sharply demarcated hypoautofluorescent lesions in the posterior pole and peripapillary region.	None	c.545A→ G (p.Gln182Arg)	RP
D-IV:4/10/40/F	Loss of visual acuity	LP LP	Mild PSC cataract in BE	Brown atrophic lesion in the macula with pigment clumps, waxy optic disc pallor and peripapillary atrophy, attenuated vessels; grayish atrophic changes in the perimacular region, heavy bone spicule pigmentation in the mid-periphery.	NP NP	UTP	Thinning of the fovea, loss of photoreceptor–RPE complex, irregular hyperreflective intraretinal clumps, parafoveal pseudocyst in RE. CFT: 106 μm (RE), 55 μm (LE).	Numerous partially merged sharply demarcated hypoautofluorescent lesions in the posterior pole and in the perimacular region.	None	c.545A→ G (p.Gln182Arg)	RP

BE, both eyes; CFs, counting fingers; CFT, central foveal thickness; Dx, diagnosis; F, female; HMs, hand movements; LE, left eye; LP, light perception; M, male; NP, not performed; NR, nonrecordable; PIS, photoreceptor inner segment; POS, photoreceptor outer segments; PSC, posterior subcapsulary cataracts; RE, right eye; SR, severely reduced; UTP, unable to perform test, due to severe vision loss; VF, visual field.

* The upper line represents the right eye; the lower line represents the left eye. † The upper line represents the scotopic results; the lower line represents the photopic results. ‡ ERG performed at the ages of 19 and 37 years. Both rod and cone responses were nonrecordable at age of 19 years. § ERG performed at the age of 29 and 41 years. Scotopic responses were severely reduced and photopic responses were nonrecordable at age of 29. ‖ Goldmann perimetry performed at age of 29 and 41 years. At an age of 29 years, there was no constriction of the visual field. # Negative scotopic ERG.

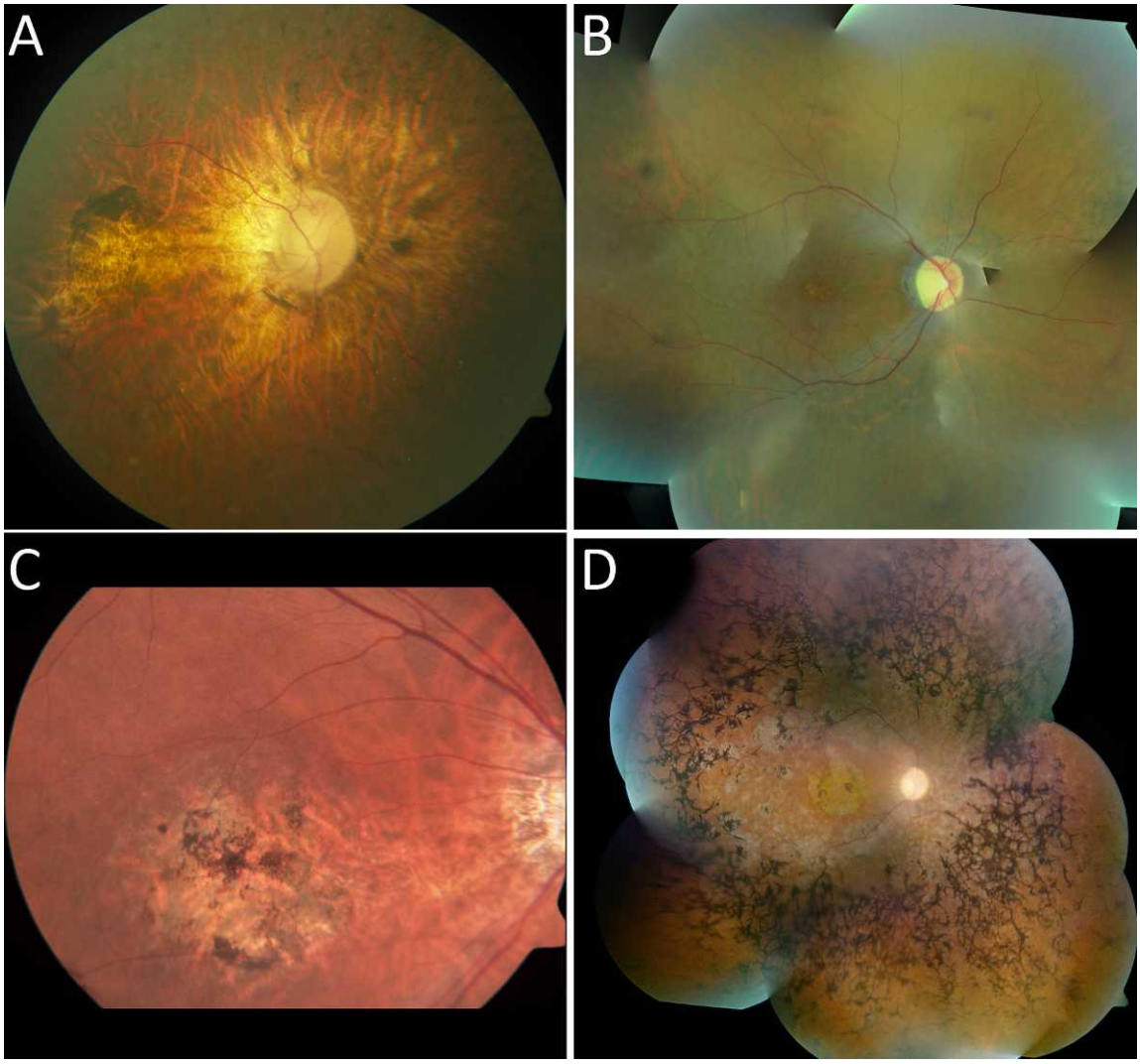

FIGURE 1. Fundus photographs of patients carrying mutations in *C8orf37*. (**A**) Fundus photograph of the central retina in the right eye of patient A-IV:1 (age 37 years) showing profound retinal degeneration, waxy pallor of the optic disc, attenuated vessels, irregular pigmentations in the macula, as well as bone spicule-like pigmentation in the midperiphery. (**B**) Fundus photograph composition of right eye of patient B-V:7 (age 26 years), revealing macular atrophy as well as slightly attenuated arterioles and areas of ongoing chorioretinal atrophy. One round pigmentation can be found along the inferior vascular arcade. (**C**) Fundus photograph of the central retina in the right eye of patient C-II:1 (age 36 years) showing profound macular atrophy and intraretinal irregular pigmentation, as well as attenuated arterioles. (**D**) Fundus photograph composition of patient D-IV:1 at age 39 years (right eye) reveals macular atrophy and pigmentation clumps, as well as pallor of the optic disc, attenuated vessels, paravascular atrophy of the retinal pigment epithelium, and abundant bone spicules.

the onset of the disease in these patients. In one patient (D-IV:1), the exact initial symptom could not be determined because night blindness and visual acuity loss occurred simultaneously. After the onset of the disease, visual acuity deteriorated to hand movements or light perception within the following two decades (range, 8–17 years). No nystagmus was observed. Early stages of posterior subcapsular cataract were present in the patients of family D, whereas the lens of patient A-IV:1 was clear. Ophthalmoscopy displayed the classic RP features of bone spicule pigmentation, attenuated vessels, and pallor of the optic disc as well as profound atrophic lesions in the macular RPE, along the vascular arcades and peripapillary region (mean age: 40 years; Figs. 1A, 1D). Correspondingly, autofluorescence imaging showed hypoautofluorescent lesions in these areas (Figs. 2A, 2G), whereas OCT examination showed a generalized loss of the photoreceptor–retinal pigment epithelium (RPE) complex (Figs. 2B, 2H). On ERG examination, both rod- and cone-driven responses were nonrecordable in all patients (mean age: 33 years). Perimetry (patients D-IV:1 and D-IV:3) showed a severely constricted visual field with approximately 5° remaining using target V-4e (mean age: 41 years).

In the two CRD families (B and C), the mean age of onset was approximately 7 years and, like that in the RP patients, ranged from infancy to the age of 18 years. Either photophobia ($n = 2$) or loss of visual acuity ($n = 2$) was mentioned as an initial symptom. In the three decades following the onset of the disease, all four CRD patients developed loss of visual acuity that gradually decreased to low vision levels of 20/60 to counting fingers. These patients showed eccentral fixation and no nystagmus or nystagmoid wandering eye movements were present. Biomicroscopy revealed no cataract was present in these patients. Ophthalmoscopy revealed macular RPE atrophy as well as (mild) attenuation of the vessels (mean age: 33 years; Figs. 1B, 1C). In patient C-II:2, pigment changes due to extraocular surgery for retinal detachment were observed.

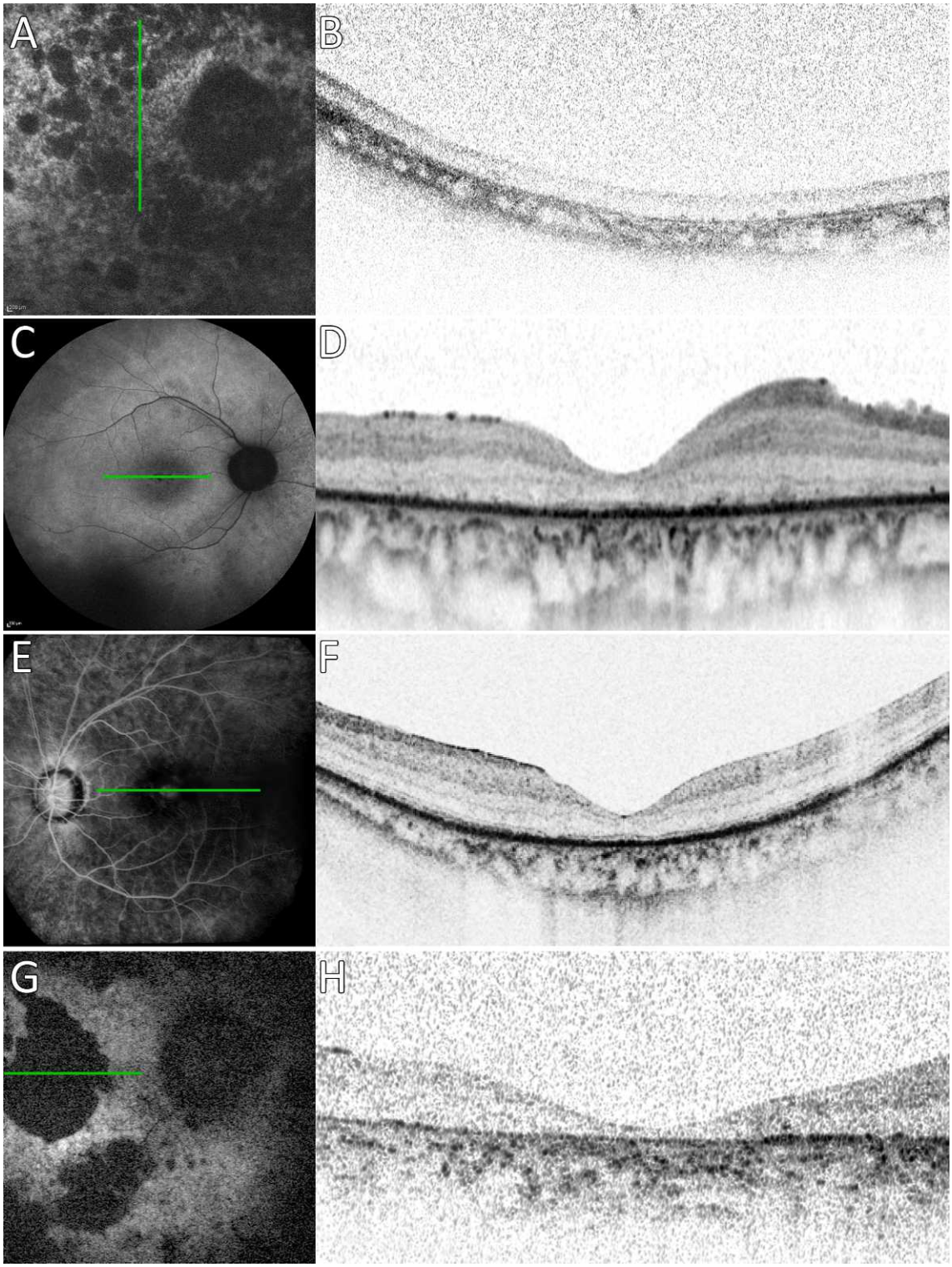

FIGURE 2. (Auto)fluorescence imaging and corresponding SD-OCT examinations in patients with mutations in *C8orf37*. (**A**, **B**) Autofluorescence (**A**) and SD-OCT (**B**) image of the right eye of patient A-IV:1 (age 37 years) showing macular hypoautofluorescence and numerous hypoautofluorescent lesions in the perimacular region (**A**), as well as severe thinning of the retina temporal of the macula (**B**). (**C, D**) Autofluorescence (**C**) and SD-OCT (**D**) imaging of the right eye of patient B-V:7 (age 26) reveals foveal hypoautofluorescence, parafoveal hyperautofluorescence, numerous irregular hypoautofluorescent spots in the perimacular region (**C**), and severe thinning of the foveal thickness and profound loss of the photoreceptor layer with preservation of the RPE cells (**D**). (**E**, **F**) Fluorescence angiography (**E**) and OCT (**F**) image of the central retina in the left eye of patient C-II:2 at the age of 30 years (no autofluorescence was performed) showing hypofluorescence in the macula (**E**), and loss of photoreceptor outer segments, thinning of the retina, and atrophy of the choriocapillaris (**F**). (**G**, **H**) Autofluorescence (**G**) and OCT (**H**) image of the central retina in the right eye of patient D-IV:1 (age 39 years) reveals hypoautofluorescence in the macula, indicating atrophy as well as atrophic lesions along the vascular arcades (**G**) and severe thinning of the retina with profound loss of the photoreceptor–RPE complex (**H**). *Green lines* indicate the location of the corresponding OCT examination. Image quality varies as result of unstable eccentric fixation.

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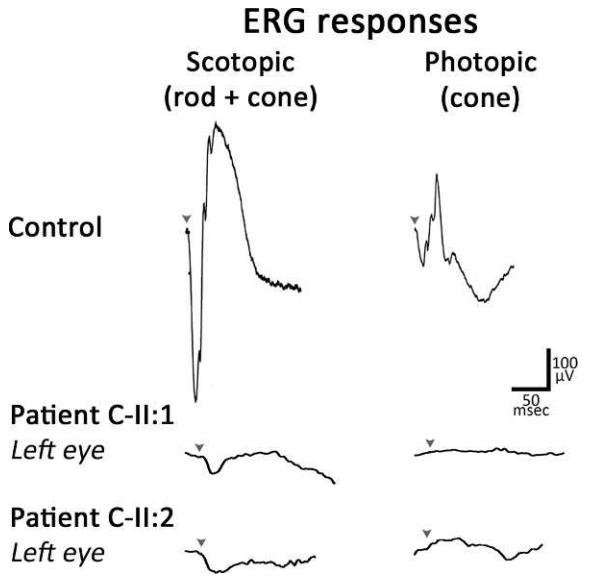

FIGURE 3. ERG recordings of all patients with recordable responses (patient C-II:1 at age 36 years and C-II:2 at age 30 years). Only scotopic mixed (rod + cone) responses and photopic (cone) responses are depicted. *Arrowheads* indicate the moment of the light flash. Control shows normal responses of individuals with healthy retinas. Both patients have severely reduced scotopic responses and nonrecordable photopic responses. The dark-adapted responses of patient C-II:1 show negative ERG waveforms. The dark-adapted responses of patient C-II:2 show only a negative ERG waveform in the left eye. ms, millisecond; µV, microvolts.

Autofluorescence imaging showed focal hypoautofluorescent lesions in the macula (Figs. 2C, 2E), whereas OCT examination showed generalized photoreceptor degeneration (Figs. 2D, 2F). Initially, cone-driven responses were more severely affected than the rod-driven responses, which were nonrecordable and severely reduced, respectively. In the affected individuals of family C, the mixed dark-adapted recordings showed negative waveforms. In later stages, rod-driven responses also became nonrecordable in the patients from family B (mean age: 34 years). Perimetry was difficult to perform, but concentric restriction of the visual field was present (mean age: 34 years). A central scotoma was found in only one patient (B-V:1).

Thinning of the central neuroretina was observed in all patients, except for A-IV:1 and C-II:1. The central foveal thickness (CFT) was 0.074 mm on average (mean age: 36 years; Table), whereas CFT generally is approximately 0.230 mm in healthy individuals as found by Tick and colleagues.[18]

DISCUSSION

Inherited retinal dystrophies are highly variable in their clinical presentation, even when more or less specific phenotypes such as RP and CRD are considered. This clinical heterogeneity is for a large part the result of the many different genes and mutations that are involved. In addition, incompletely understood genetic and environmental modifying factors influence the disease phenotype. Recently, mutations in the *C8orf37* gene have been linked to an autosomal recessive retinal dystrophy.[16] This report provides an overview of the clinical features of the *C8orf37*-associated retinal dystrophy.

The eight patients in this study presented either with a CRD phenotype or an RP phenotype with early macular involvement. Macular atrophy is an early feature of CRD. It usually does not occur in classic RP until the very end stage of disease, although it is observed in some specific forms of RP.[19–22] The RP patients in our study demonstrated a profound loss of vision in an early stage of the disease, and some even mentioned loss of visual acuity as an initial symptom, although night blindness followed visual loss by only a couple of months. Ophthalmoscopy, OCT, and FAF examination revealed profound atrophy of the photoreceptor–RPE complex in the maculae of the RP patients. Contrary to the CRD patients, RP patients developed tunnel vision. Perimetry examination in patients D-IV:1 and D-IV:3 did not show an absolute central scotoma, but a remaining central visual field residue of 5° with decreased sensitivity.

The disease progression rate was high in all patients in this study: end-stage disease was reached within two decades after the onset in the RP patients and within three decades in the CRD patients. Presently, at a mean age of 36 years, most CRD and RP patients demonstrate severely atrophic retinas as a final common end stage. In the light of gene therapy development, knowledge about the natural course of *C8orf37*-associated diseases is important. When available, early treatment before severe damage to the retinal architecture occurs and is essential in these patients.[23] The high rate of disease progression makes early evaluation of treatment effect possible. Unfortunately, gene therapy will probably not be developed in the near future, because the estimated frequency of *C8orf37* mutations as a cause of RP/CRD is low (<1%), and a suitable (animal) model is lacking.

Interestingly, *C8orf37* is one of the few genes that can cause both autosomal recessive RP and CRD. Until now, this has been described in only two other genes: *ABCA4* and *CERKL*. For *ABCA4*, it is hypothesized that the level of dysfunctional ABCA4 protein is instrumental in the degeneration pattern, causing either Stargardt disease, CRD, or RP.[24–26] Although the phenotype associated with *CERKL* mutations was originally characterized as RP,[15,27] most patients that have been described until now are diagnosed with CRD.[28–31] This is in accordance with the observation that the CERKL protein is mainly localized in cone photoreceptors of mouse retinae.[32] The *C8orf37* gene is expressed in both rod and cone photoreceptors.[16] This fits with the involvement of both types of photoreceptors, but does not explain the pattern of photoreceptor degeneration. Within the four families, we did not observe differences in degeneration patterns. This suggests a connection between the degeneration pattern and a genetic cause, given that family members carry identical *C8orf37* mutations and are likely to share modifier alleles as well. Here, the correlation between phenotype and genotype is mainly theoretical, given that the exact effects of the mutations on the C8orf37 protein and its function are not known. However, our previous study localized the protein to the ciliary rootlet of the connecting cilia in mouse photoreceptors and to the base of the primary cilia of human RPE cells, indicating a ciliary function.[16]

Ciliopathies are diseases characterized by the dysfunction of the cilium,[33] which may lead to either multiorgan syndromic phenotypes or to single-organ diseases.[34] The presence of postaxial polydactyly in patients B-V:1 and B-V:7 is interesting in view of the probable ciliary function of C8orf37, because it is one of the cardinal features of Bardet–Biedl syndrome (BBS), a ciliopathy characterized by retinal degeneration, obesity, polydactyly, hypogonadism, renal dysfunction, and cognitive impairment.[34] Retinal degeneration is a hallmark of many syndromic ciliopathies,[35,36] although mutations in retina-specific ciliary genes may also lead to nonsyndromic RP.[37,38] One third of nonsyndromic retinal dystrophies involve defects in a ciliary protein.[38] Ubiquitously expressed ciliary genes, such as *C8orf37* and, for example, *RPGR*, are more likely to cause syndromic phenotypes. Also in *RPGR*-associated disease,

most of the patients demonstrate isolated RP,[39] although systemic symptoms have been identified occasionally.[40,41]

Besides the postaxial polydactyly in individuals B-V:1 and B-V:7, we did not identify other syndromic features in these individuals. In the other patients no syndromic abnormalities were observed, although we could not perform detailed additional examinations to exclude subclinical symptoms. Polydactyly generally occurs in 5 to 19 per 10,000 live births.[42] We cannot exclude coincidental coexistence but the polydactyly in this family occurred only in the siblings affected with CRD. This strengthens the hypothesis of associations between the retinal phenotype and polydactyly. In the remaining patients, we could identify other features previously linked to ciliopathies: electronegative ERG waveforms in patients C-II:1 and C-II:2 (Fig. 3), which have been described in *BBS1*-associated BBS,[43,44] and the early occurrence of macular atrophy.[21,22,43–46] These data indicate that mutations in *C8orf37* may be able to cause both syndromic and non-syndromic phenotypes, similar to other ciliary genes such as *USH2A*,[47] *BBS1*,[48] and *RPGR*.[39–41]

In conclusion, mutations in *C8orf37* cause autosomal recessive CRD or RP with early macular involvement. The dystrophies start in the first two decades of life and progress relatively fast to a common phenotype of end-stage retinal degeneration. Although the exact function of C8orf37 is not known yet, its immunolocalization, associations, and interactions with other proteins and the presence of polydactyly in one of our families would suggest a ciliary function.

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