

# Phenotypic Spectrum of Autosomal Recessive Cone–Rod Dystrophies Caused by Mutations in the *ABCA4* (*ABCR*) Gene

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**PURPOSE.** To describe the phenotype of 12 patients with autosomal recessive or isolated cone-rod types of progressive retinal degeneration (CRD) caused by mutations in the *ABCA4* gene.

**METHODS.** The charts of patients who had originally received a diagnosis of isolated or autosomal recessive CRD were reviewed after molecular analysis revealed mutations in the *ABCA4* gene.

**RESULTS.** In two of the patients both the photopic and scotopic electroretinogram were nonrecordable. In the remainder, the photopic cone b-wave amplitudes appeared to be more seriously affected than the scotopic rod b-wave amplitudes. Although the clinical presentation was heterogeneous, all patients experienced visual loss early in life, impaired color vision, and a central scotoma. Fundoscopy revealed evidence of early-onset maculopathy, sometimes accompanied by involvement of the retinal periphery in the later stages of the disease.

**CONCLUSIONS.** Mutations in the *ABCA4* gene are the pathologic cause of the CRD-like dystrophy in these patients, and the resultant clinical pictures are complex and heterogeneous. Given this wide clinical spectrum of CRD-like phenotypes associated with *ABCA4* mutations, detailed clinical subclassifications are difficult and may not be very useful. (*Invest Ophthalmol Vis Sci.* 2002;43:1980–1985)

Most present classifications of retinal dystrophies are based on whether the disease is progressive or stationary and whether the retinal disease is generalized or located predominantly in the macula. Generalized retinal dystrophies are further divided according to which type of photoreceptor is mainly affected in the early stages and most severely throughout the course of the disease. Additional findings such as yellow-white fundus flecks and a dark choroid on fluorescein

angiography, as in Stargardt disease (STGD), are attributed to specific retinal disorders.

Although there are several definitions of retinitis pigmentosa (RP), “typical” RP is considered to demonstrate rod-cone patterns of retinal degeneration on the electroretinogram (ERG).<sup>1,2</sup> Patients with typical RP demonstrate progressive loss of night and peripheral vision and show ophthalmoscopic features such as attenuated retinal vessels, bone spicula in the retinal midperiphery and a waxy paleness of the optic disc. Conversely, a group of patients with a progressive retinal disorder shows cone-rod patterns on ERG testing. These retinal dystrophies, commonly described as cone-rod dystrophies (CRDs), form a clinically heterogeneous group of disorders characterized by most of the following features: early loss of visual acuity, deficits in color vision, progressive impairment of the visual field, and, sometimes, nystagmus. In time, pigmentary changes become apparent in the macular area, often followed by variable degrees of midperipheral pigmentation. The ERG is abnormal with either cone (photopic) responses more reduced than rod (scotopic) responses, or equally reduced cone and rod systems.<sup>1–8</sup>

Mutations in the adenosine triphosphate (ATP)-binding cassette transporter (*ABCA4*) gene are responsible for a spectrum of retinal dystrophies including STGD, autosomal recessive CRD and autosomal recessive RP.<sup>9–15</sup> *ABCA4* is located in the disc membrane of the rod outer segments, and it was demonstrated recently by Kelsell et al.<sup>16</sup> and Sun and Nathans<sup>17</sup> that the *ABCA4* gene is also expressed in retinal cones. In the present study we describe a group of patients with autosomal recessive or isolated CRD caused by mutations in the *ABCA4* gene.

## PATIENTS AND METHODS

The protocol of the study adhered to the provisions of the Declaration of Helsinki. After informed consent was obtained, blood samples were taken and molecular analysis on the *ABCA4* gene was performed as described by Maugeri et al.<sup>14</sup> The charts of patients with *ABCA4* mutations who originally had received diagnoses of isolated or autosomal recessive CRD were reviewed. All patients originated from the University Medical Centre Nijmegen (Nijmegen, The Netherlands) and the University of Heidelberg (Heidelberg, Germany). In this study the diagnosis of CRD was based on the following criteria: initial symptoms of blurred central vision without a history of night blindness, impairment of color vision, and fundoscopic evidence of maculopathy with or without mild peripheral retinopathy.<sup>3–5,7,8</sup> In patients with recordable ERGs a cone-rod pattern of degeneration had to be present (i.e., the photopic b-wave impairment had to be greater than or equal to the scotopic b-wave amplitude impairment). Patients 9250 and 13163, who had nonrecordable ERGs, were included because their histories and clinical features were similar to those of other patients with cone-rod degeneration and they were believed to represent advanced cases of CRD. In addition to an ophthalmic examination, Goldmann kinetic perimetry routinely was performed using III-4-e and I-4-e isopters. Color vision was tested with the Ishihara and Panel D15 tests,

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except in patients 9369, 9378, and 10125, who were tested under conditions described earlier.<sup>18</sup> Because these patients were examined in two different clinics and ERGs were recorded over a long period, the methods, instrumentation, and analysis techniques of the electroretinography varied. The ERGs in patients 9369, 9378, 10125, and 11872 were performed as described by Thijssen et al.<sup>19</sup> The ERG method used in patients 9370, 9553, 9633, and 13163 was described by Alexandridis and Krastel.<sup>20</sup> The ERGs of the remaining patients (9250, 9371, and 9650) are of a more recent date and were performed according to International Society for Clinical Electrophysiology of Vision (ISCEV) standards.<sup>21</sup> Fundus photographs were taken in most patients and some of the patients (9650, 9369, 9378, and 10125) also underwent fluorescein angiography.

## RESULTS

The characteristics of 12 patients with *ABCA4*-associated retinal dystrophy resembling CRD are summarized in Table 1. Most did not have affected family members, and therefore their retinal dystrophies could not be classified as autosomal dominant, autosomal recessive or X-linked. Four patients reported a brother or sister with subnormal vision. In view of the reputedly normal visual acuity of the parents and the molecular defects, the inheritance pattern of the gene defects in these patients (individuals 9303, 9369, 9553, and 13163) was classified as autosomal recessive.

The visual acuity of the patients did not exceed 20/200 and, on average, was much lower. With the exception of patient 9553, the age of onset was at or before the age of 12, and in each of the patients, blurred vision was the initial symptom. Night blindness did not occur except in patients 9378 and 10125, in the final stages of retinal degeneration. Evidence of maculopathy in the form of bull's eye maculopathy or pigmentary changes was present in all the patients reported in this study (Fig. 1A). The functional equivalent of the mainly centrally located retinal disease was a central scotoma, varying from 8° to more than 40°. In all but one patient, the scotoma was absolute. Only in patient 9378 was the central scotoma relative and surrounded by absolute scotomas. Fundoscopic evidence of early peripheral involvement of the retina was mild, and only in the later stages of the disease did peripheral changes characteristic of RP, such as narrowing of retinal vessels and bone spicula, occur in patients 9369 (Fig. 1B) and 10125. Similarly, mild constriction of the visual fields occurred only in two patients (9650 and 10125) and only in the advanced state. Color vision was tested in 10 patients. Six demonstrated a red-green defect, and in two of these (patients 11872 and 10125), it was accompanied by a blue-yellow defect. In the remaining four patients, color vision was so severely disturbed that the exact type of impairment could not be assessed.

The ERG recordings demonstrated degeneration of both rods and cones. When ERG responses could be elicited, the cones appeared to be affected as much as the rod photoreceptors and, in most of the patients, even more severely. The ERG responses in five patients progressively deteriorated until no photopic and scotopic responses could be recorded. In these patients, with exception of patients 9250 and 13163, ERG recordings of an earlier date were used in Table 1. This applies to patient 9369, in whom an ERG was recorded at age 12 (all ERG responses had been nondetectable since the age of 21), patient 9378 at age 33 (all ERG responses at age 46 were nondetectable), and patient 10125 at age 8 (in 1998, at age 28, the ERG responses were no longer detectable). Recent ERG findings were not available for patients 9650 and 9371. Their ERGs were recorded in 1989 and 1985, respectively. The remaining ERG data were derived from ERG recordings per-

formed in the past 4 years. Of patient 9371 only the ERG data in the left eye were available.

Two patients warrant a more detailed description, due to the unusual course of their retinal dystrophies. Patient 9378, at the age of 12, had blurred vision with fundoscopic evidence of irregular chorioretinal atrophy in the posterior pole. At that time, there were no peripheral abnormalities on ophthalmoscopy, and there was no history of night blindness. The ERG demonstrated an equal reduction of both cone- and rod-mediated responses. Later in life, however, fundoscopic changes developed that were characteristic of RP, and the patient reported a decrease in night vision. With fluorescein angiography partly confluent patches of chorioretinal atrophy were visible (Fig. 1C).

The clinical picture of patient 10125 differed from that of the other patients, despite the mutation in the *ABCA4* gene. Initially, disease in this patient was diagnosed as STGD because of the bull's eye maculopathy, the granular pigment alterations in the macular area, and the pisciform flecks surrounding the posterior pole. At age 8 his visual acuity had decreased to 20/200 in both eyes. When he was referred to our clinic in 1998 at the age of 28, peripheral degeneration in the form of narrow retinal vessels and deposition of peripheral bone spicula had developed, in addition to the earlier described disease of the central retina. A fluorescein angiogram showed typical findings: a central small hypofluorescent spot enclosed by an ellipsoid—a markedly hyperfluorescent area that in turn was surrounded by hyperfluorescent dots against a dark background, most likely caused by obscuration of choroidal background fluorescence (Fig. 1D). Early ERG recordings were not available, and the ERG tracings recorded at age 28 represent the final stage of the degenerative process, with absence of both cone and rod responses. This retinal dystrophy seemed to have evolved from STGD into more widespread retinal degeneration, resulting in loss of function of both rods and cones.

## DISCUSSION

Progressive CRD is a clinically heterogeneous retinal disorder, but typical findings include reduced visual acuity, impairment of the central visual field, color vision deficits, and fundoscopic evidence of maculopathy, with no or few midperipheral retinal pigment deposits.<sup>3,4,7,8</sup> There is some dispute about typical ERG findings in CRD. Some state that the diagnosis of CRD must be based on the reduction or absence of cone responses in the presence of quantitatively less reduction in rod responses, whereas others state that an equal impairment of both photoreceptor systems, if accompanied by the characteristic features, suffices to justify the diagnosis of CRD.<sup>3,7,8,22</sup> Several propositions have been made in the past to classify cone-rod disorders. Some classification systems have focused on individual case reports and were based on nosologic aspects; others have made a distinction according to the various patterns of inheritance.<sup>3,6,23,24</sup> In recent studies, Szlyk et al.<sup>7</sup> and Yagasaki et al.<sup>8</sup> made use of full-field ERGs, dark adaptometry, and modified perimetric techniques to identify functionally distinct subtypes of CRD. Finally, over the past few years, a molecular genetic classification of CRD has emerged.

At the moment, four genes and three loci have been implicated in autosomal dominant CRD, whereas one X-linked locus has been described.<sup>25-32</sup> Thus far, two loci and one gene (*ABCA4*) have been associated with autosomal recessive CRD.<sup>12,33,34</sup> The genetic heterogeneity seen in CRD is matched by the range of the clinical findings attributed by various investigators to this type of retinal dystrophy.

Whatever the classification system used, some patients display retinal disorders that cannot be classified satisfactorily.

TABLE 1. Patients with Cone-Rod Degeneration and ABCA4 Mutations

Patient	Sex	Current Age (ys)	ABCA4 Mutations*	Visual Acuity		Age of Onset (ys)	Fundoscopy	Color Vision	Perimetry	ERG Cone ( $\mu$ V)†			ERG Rod ( $\mu$ V)‡		
				OD	OS					OD	OS	OD	OS	OD	OS
9250	M	30	1622T→C; 3113C→T 194G→A	CF	CF	6	Pigment clumping in the macula	NP	Large central scotoma over 40°	ND‡	ND‡	ND‡	ND‡	ND‡	ND‡
9303	M	21	1622T→C; 3113C→T	20/400	20/400	7	Granular pigmentary changes in the macula	Diffusely disturbed	Central scotoma of 20°	Severely decreased§	Severely decreased§	Severely decreased§	Severely decreased§	Severely decreased§	Severely decreased§
9369	F	40	6601-6602delAG	LP	LP	8	Irregular hypopigmentation, mainly in the posterior pole. In later stages: attenuated vessels and bone spicula temporal to the macula	Red-green defect	Central scotoma varying from 10–30°	65 (65%)	80 (80%)	140 (90%)	160 (nd)	140 (90%)	160 (nd)
9370	M	15	1622T→C; 3113C→T	20/200	20/200	7	Granular aspect of the macula	NP	Concentric central scotoma of 8°	10 (13%)	9 (13%)¶	29 (29%)	29 (23%)¶	29 (29%)	29 (23%)¶
9371	M	38	1622T→C; 3113C→T	20/400	20/400	10	Bull's eye maculopathy	Red-green defect	Concentric central scotoma of 20°	NP	29 (16%)‡	NP	54 (30%)‡	NP	54 (30%)‡
9378	F	50	768G→T	CF	CF	12	Bull's eye maculopathy, narrow vessels in periphery with mild granular changes of the pigment epithelium and confluent patches of chorioretinal atrophy	Severely disturbed	Large, absolute, paracentral scotomas, relatively scotoma centrally	20 (20%)	30 (30%)	70 (47%)	90 (60%)	70 (47%)	90 (60%)
9553	F	45	2588G→C IVS35del2→+2del4	20/400	20/400	25	Bull's eye maculopathy. Peripherical diffuse mottling of RPE	Severely disturbed	Large central scotoma over 40°	14 (14%)	19 (19%)¶	41 (41%)	24 (24%)¶	41 (41%)	24 (24%)¶
9633	M	22	1622T→C; 3113C→T 4469G→A	20/400	20/200	12	Atrophy of retinal pigment epithelium in posterior pole. Early stages of bull's eye maculopathy	Red-green defect	Central scotoma of 20°	12 (16%)	12 (16%)¶	61 (62%)	39 (39%)¶	61 (62%)	39 (39%)¶
9650	F	20	3364G→A	20/400	20/400	5	Central granular aspect	Red-green defect	Large central scotoma of 30° and relative constriction of III-4	70 (39%)	106 (59%)‡	272 (nl)	115 (76%)‡	272 (nl)	115 (76%)‡
10125	M	30	IVS30+1G→T 3085C→T	20/200	20/200	8	Central hypopigmentation with dark surrounding, resembling bull's eye. Later in life: peripheral changes characteristic of RP	Severe red-green defect; mild blue-yellow defect	Central scotoma of 10–15° with mild peripheral restriction	75 (75%)	80 (80%)	130 (87%)	140 (93%)	130 (87%)	140 (93%)
11872	M	30	634C→T	20/200	20/200	10	Bull's eye pattern	Severely disturbed; blue-yellow more than red-green	Central scotoma of 25°	23 (23%)	35 (35%)	110 (73%)	95 (63%)	110 (73%)	95 (63%)
13163	M	15	1622T→C; 3113C→T IVS36+1G→A	20/400	20/200	6	Granular aspect of retinal pigment epithelium in macula. Slightly pale optic disc	Severely disturbed	Central scotoma of 10–15°, no peripheral involvement	ND¶	ND¶	ND¶	ND¶	ND¶	ND¶

CF, count fingers; LP, light perception; ND, not detectable; NP, not performed.

\* Allele 1, first line; allele 2, second line.

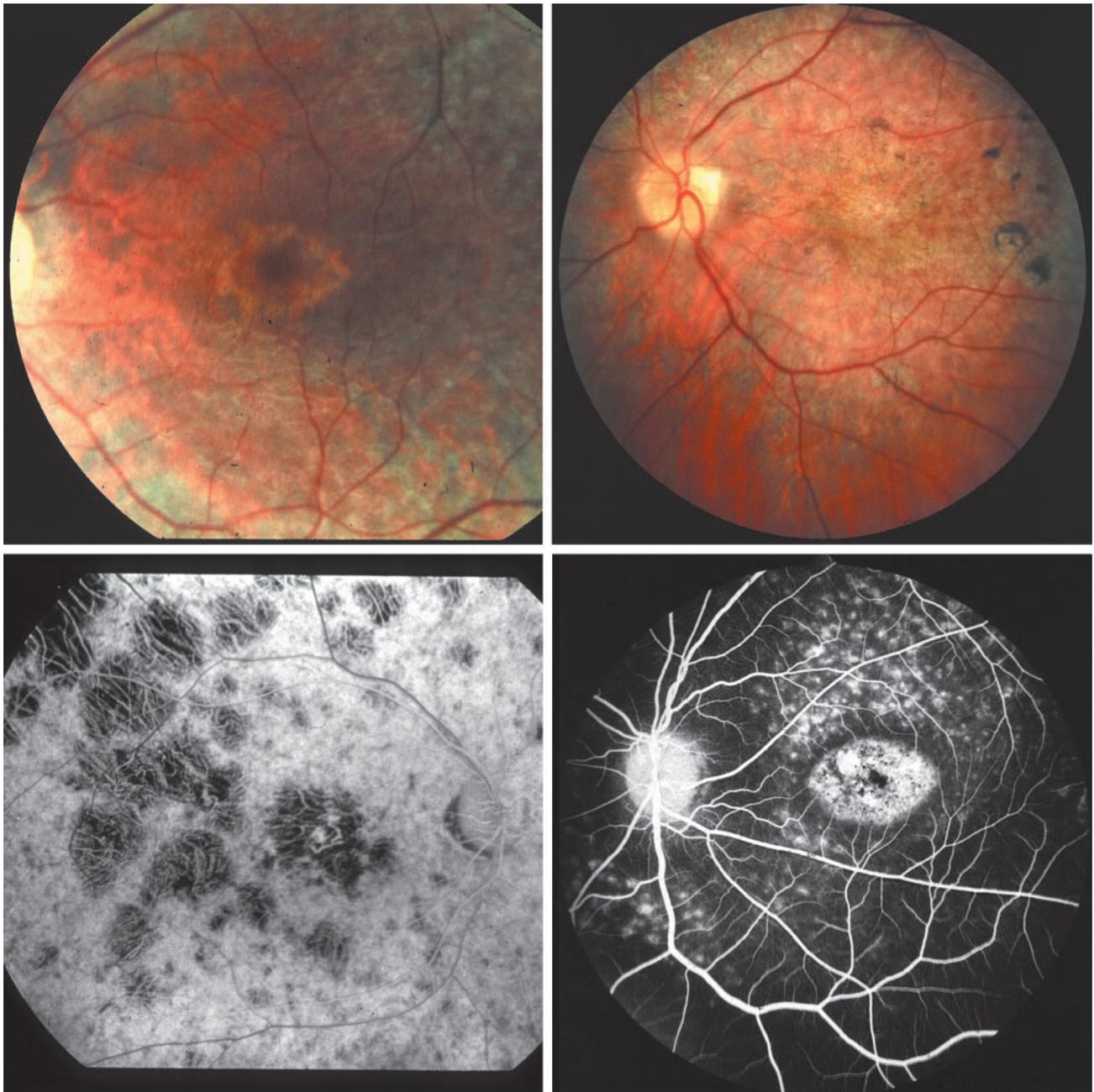
† Between parentheses: percentage of the ERG value compared to the lower limit of the normality; normal ERG values are indicated in.

‡ Minimal values for ERG recordings: 150  $\mu$ V for the photopic ERG, 180  $\mu$ V for the scotopic ERG.

§ ERG performed with skin electrodes.

|| Minimal values for ERG recordings: 100  $\mu$ V for the photopic ERG, 150  $\mu$ V for the scotopic ERG.

¶ Minimal values for ERG recordings: 99  $\mu$ V for the photopic ERG, 75  $\mu$ V for the scotopic ERG.



**FIGURE 1.** (A–D) Fundus photographs and fluorescein angiograms in eyes of patients with (atypical) CRD. (A) Patient 11872 with bull's eye maculopathy. (B) Patient 9369, demonstrating CRD in the later stages with attenuation of the retinal arterioles and irregular pigmentation temporal to the macula. (C) Fluorescein angiograms in patient 9378 showing confluent patches of chorioretinal atrophy. (D) Patient 10125 with central hypofluorescence enclosed by an ellipsoid hyperfluorescent area. In the surrounding area, hyperfluorescent flecks are visible, and the choroidal background fluorescence seems blocked, as seen in STGD.

Often, these retinal degenerations involve overlapping features. Krill et al.<sup>5</sup> reported that 9 of 45 patients with cone degenerations showed typical features associated with fundus flavimaculatus. Heckenlively<sup>2</sup> described 76 patients with cone-rod patterns on the ERG in whom retinal disease otherwise met the standard definition of RP (progressive peripheral visual field loss with ring scotoma). Alternatively, as seen in patient 10125 in this study, patients with STGD have been described who had progressive peripheral retinal degeneration with severe abnormalities in the ERG and electro-oculogram (EOG) later in life—a condition that has been described by Fishman<sup>4</sup> as secondary progressive cone-rod dysfunction.

The association of CRD and a dark choroid has also been described previously.<sup>35,36</sup> The atypical pattern of retinal degeneration with confluent patches of chorioretinal atrophy in patient 9378 resembles that in another previously described unrelated patient with CRD-like disease caused by mutations in *ABCA4*.<sup>37</sup> In the molecular genetic study by Maugeri et al.,<sup>14</sup> in which 11 of the 12 patients with autosomal recessive CRD described in this study were analyzed, *ABCA4* mutations were found in 13 of 20 unrelated patients, strongly suggesting that *ABCA4* mutations are the major cause of this disorder. If this is true, the genetic heterogeneity in autosomal recessive CRD, compared with, for example, classic RP, is surprisingly low.

Because autosomal recessive inheritance is believed to be the most frequent mode of inheritance of monogenic chorioretinal disorders, it is very possible that a large fraction of the patients with CRD who have been clinically studied previously carry *ABCA4* mutations. In that case, the explanation for the high variability of the clinical findings in autosomal recessive CRD would not be genetic heterogeneity but rather the genotype-phenotype model for *ABCA4*. According to this model, there is an inverse relationship between the presumed residual *ABCA4* function as an *N*-retinylidene-PE flippase and the severity of the disorder.<sup>12,37,38</sup> As a consequence, a continuum of phenotypes is to be expected, ranging from STGD to CRD to RP. Although this is probably a simplified representation of reality and needs corroboration by detailed biochemical studies of individual mutations, as described previously, this model explains why mutations in the *ABCA4* gene could give rise to phenotypes that do not satisfy the standard classification of retinal dystrophies.<sup>39</sup>

Two patients in this study may reflect borderline CRD phenotypes. Patient 9553 carries a combination of a mild (2588G>C) and severe *ABCA4* mutation, which, according to the genotype-phenotype model described earlier, should be associated with STGD. We have previously discussed that most likely, one of the pathologic mutations has not yet been identified in this patient.<sup>14</sup> However, the age of onset in this patient (25 years) is relatively high, and although other features such as visual acuity, perimetry, and ERG findings are typical of CRD, this may indicate a relatively mild subtype. Another more convincing example of blending of *ABCA4*-associated phenotypes is patient 10125. The molecular findings in this patient have not yet been described elsewhere. He carries a severe splice site mutation (IVS30+1G→T) in combination with a nucleotide change leading to a stop codon at Gln1029. A patient with RP who was homozygous for the IVS30+1G→T mutation has been described,<sup>12</sup> whereas the Q1029X mutation has not been described. Both mutations can be considered to be null alleles. According to the proposed *ABCA4* model, the clinical phenotype in patient 10125 should be RP. Instead, this patient exhibits a typical retinal dystrophy, which gradually progresses from STGD to a more widespread degeneration of photoreceptors in a cone-rod pattern later in life. At present, both rod and cone ERG responses are not detectable, indicative of a final stage similar to that in many patients with RP. Functional studies are necessary to clarify whether these specific *ABCA4* mutations are responsible for the particular progression of the retinal degeneration in this patient, or whether other as yet unknown modifying factors play a role.

In this study we have described 12 unrelated patients with retinal dystrophy resembling CRD caused by mutations in the *ABCA4* gene. In a previous study we described the ophthalmic features in five siblings with CRD-like retinal dystrophy who were carrying *ABCA4* mutations.<sup>37</sup> From the clinical data of these patients and previous molecular studies in patients with autosomal recessive CRD, two important conclusions can be drawn.<sup>12,14</sup> First, the genetic basis of autosomal recessive CRD is less heterogeneous than was thought, based on the variability in clinical features, because mutations in the *ABCA4* gene seems to be the major pathologic cause. Second, given the wide clinical spectrum of CRD-like phenotypes associated with *ABCA4* mutations, detailed clinical subclassifications are difficult and may not be very useful.

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