Erratum

Inherited Chorioretinal Dystrophies

A Textbook and Atlas

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Erratum to:

Chapter 8: Isabelle Audo, Graham E. Holder, and Anthony T. Moore, *Inherited Stationary Disorders of the Retina*

Due to an unfortunate error figures and their legends were interchanged. Since the number of corrections was high, the complete chapter is included in this erratum.

Erratum to:

Chapter 9: Bernard Puech and Jean-Jacques De Laey, *Retinitis Pigmentosa and Allied Disorders*

Figure 9.2 is replaced by a new figure.

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Inherited Stationary Disorders of the Retina

8

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Inherited stationary disorders of the retina are a heterogeneous group of congenital hereditary nonprogressive conditions that may result from abnormal function of the photoreceptor cells, disordered visual signal transmission from the photoreceptor to the inner retina, or may result from abnormal retinal development. The disorders are classified clinically on the basis of whether the rod system or cone system is predominantly affected and whether the retinal appearance is normal or abnormal. The molecular defects of most of these disorders have now been identified and there is a strong genotype/phenotype correlation. Thus, a more accurate classification based on the molecular pathology is now possible. In this chapter, we will however use a classification based on the clinical phenotype as it is in common usage.

8.1 Stationary Disorders Predominantly Affecting the Rod System: Congenital Stationary Night Blindness (CSNB) and Allied Disorders

(For review, see Dryja [9], Zeitz [76], Audo et al. [5])

This group of disorders is characterised by defects in rod photoreceptor signal transmission; there is considerable genetic and phenotypic heterogeneity. The heterogeneity is evident at different levels:

- Pattern of inheritance, which can be X-linked and autosomal recessive or dominant
- The degree of night blindness and the extent of rod threshold elevation
- Refractive error (presence or absence of high myopia)
- Presence or absence of nystagmus and/or strabismus
- Fundus appearance, which can be normal or show a characteristic abnormality such as the Mizuo-Nakamura phenomenon in Oguchi disease or white dots in fundus albipunctatus
- Electrophysiological abnormalities, which can show (1) *an absence of a-wave* dark-adapted bright-flash ERG (Riggs type) [53] indicating a defect of the *rod photoreceptor* or

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(2) a *normal a-wave and a markedly decreased rod b-wave* with an electronegative waveform under the same stimulus conditions (Schubert-Bornschein type) [57], where there is *impaired signal transmission to the bipolar cells or abnormal bipolar cell function*. Schubert-Bornschein-type ERGs are further subdivided into *complete* and *incomplete* forms [44] depending whether the dysfunction is restricted to the ON-bipolar pathway or affecting both ON and OFF pathways, respectively.

8.1.1 Congenital Stationary Night Blindness (CSNB) with a Normal Fundus Examination

CSNB may be inherited as an autosomal dominant, autosomal recessive, or X-linked trait. There is genetic heterogeneity even within these subtypes. In each of these forms, the fundus appearance is normal.

Autosomal Dominant CSNB (adCSNB)

(CSNBAD1 #610445, CSNBAD2 #163500)

Patients with adCSNB typically have night blindness, no nystagmus, normal visual acuity, normal visual fields, and an unremarkable fundus examination. Typically, the ERG shows a non-recordable rod a-wave of the mixed response [53], but Schubert-Bornschein forms have also been described [21, 77]. Psychophysically, testing shows elevated dark-adapted thresholds. *RHO*, encoding rhodopsin, was the first gene implicated in adCSNB with three identified missense mutations (p.Gly90Asp, p.Thr94Ile, p.Ala292Glu) [1, 10, 60]. More recently, a p.Ala295Val change was reported in association with a Schubert-Bornschein-type ERG [77]. These missense changes are thought to induce constitutive activation of the phototransduction cascade. Affected patients are considered to have a stationary disorder although some patients may show progression [60].

Mutations in two other genes have also been reported in adCSNB: the alpha subunit of rod transducin (*GNAT1*) with a p.Gly38Asp missense mutation identified in a large pedigree (Nougaret family) originating from the south of France [11] and the beta subunit of the rod cGMP phosphodiesterase (*PDE6B*) with a p.His258Asp missense mutation reported in a large pedigree from Denmark (Rambush family) [16].

X-Linked CSNB

with Complete (CSNB1A #310500) and incomplete form (CSNB2A #300071)

Two forms of X-linked CSNB have been described on the basis of the electrophysiology phenotype [44]. Both subtypes show a Schubert-Bornschein-type ERG with an electronegative response on the bright-flash dark-adapted ERG. The terms complete CSNB (or CSNB1A, OMIM #310500) and incomplete CSNB (or CSNB2A, OMIM #300071) were first suggested by Miyake et al. In the complete form, there is no detectable rod b-wave, whereas in the incomplete form, there is a subnormal but still recordable rod b-wave (Fig. 8.1).

Patients with X-linked CSNB usually present with nystagmus in infancy. This may be accompanied by strabismus. Most patients with complete CSNB have symptomatic night vision disturbance which may become evident in later childhood. Night blindness is less constant in the incomplete form. The complete form is classically associated with moderate to high myopia whereas refractive errors in the incomplete form are more variable from myopia to hyperopia. Both forms have a variable degree of visual acuity loss. Fundus examination is usually normal apart from tilted discs and myopic changes.

The distinction between the two forms is made on the full-field ERG (Fig. 8.1) (see Audo et al. [5] for review): In the *complete form*, there is an undetectable rod-specific response and an electronegative maximum response with a normal a-wave. The 30-Hz flicker ERG, although of normal amplitude, has a broadened trough and may show very mild implicit time shift abnormality. The photopic single flash has a normal a-wave amplitude with a broadened trough and a sharply rising peak with no photopic oscillatory potentials and a reduced b/a ratio. These photopic ERG appearances are characteristic of loss of ON-pathway function with OFF-pathway preservation. This is confirmed by long-duration stimulation, which reveals an electronegative ON response but a normal OFF response. These findings are consistent with a selective loss of both rod and cone ON-pathway function. The electroretinographic abnormalities are identical to those observed in melanoma-associated retinopathy (MAR).

In the *incomplete form*, a rod-specific ERG is present but of subnormal amplitude; there is a normal a-wave in the maximal response, confirming normal phototransduction, but a reduced b-wave giving an electronegative waveform. The 30-Hz flicker is markedly subnormal in amplitude and delayed with a distinctive double peak. The single-flash photopic ERG is also markedly subnormal with a profoundly reduced b/a ratio such that the a- and b-wave are usually of similar size. Long-duration stimulation shows abnormalities in both ON and OFF responses consistent with the greater degree of cone ERG abnormality compared with the complete form.

Molecular genetic studies have confirmed that the two distinct ERG phenotypes are associated with two distinct different genetic mechanisms:

- The *complete form* of CSNB is associated with mutations in the ***NYX*** gene, on *Xp11.4*. This encodes nyctalopin, a protein thought to play a central role in protein-protein interaction with other actors essential for ON-pathway function [7].

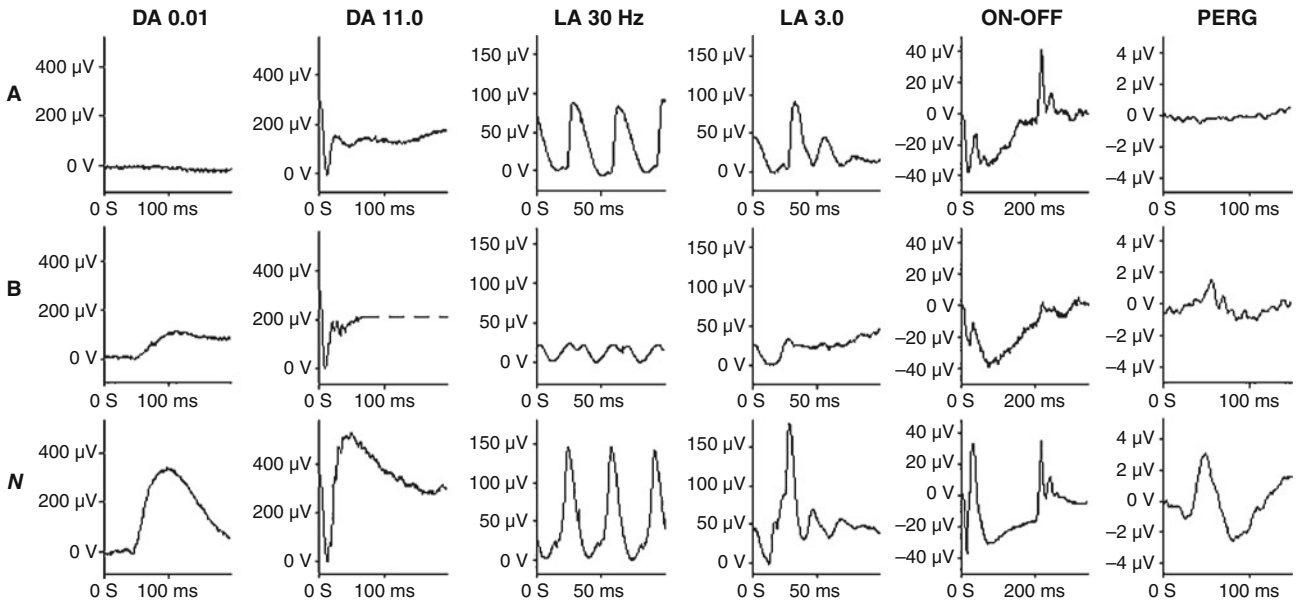


Fig. 8.1 Example of CSNB. *Patient A* has the 'complete' form of CSNB (cCSNB) relating to NYX mutation; patient B has the 'incomplete' form (iCSNB; CACNA1F mutation). The rod-specific ERG (*DA 0.01*) is undetectable in patient A in keeping with a severe disturbance of rod system function. The normal bright-flash dark-adapted ERG (DA 11.0) a-wave confirms normal photoreceptor function. The b-wave is of markedly lower amplitude than the a-wave giving a 'negative' or 'electronegative' ERG where the waveform is dominated by the negative going a-wave. The oscillatory potentials are undetectable. The cone system ERGs demonstrate sparing of the OFF pathway but involvement of the ON pathway. The flicker ERG shows slight peak time delay, a broadening of the trough and a sharply rising peak. The single-flash ERG (LA 3.0) findings are definitive; the a-wave (arising in cone photoreceptors and OFF-bipolar cells) commences normally and is of normal amplitude, but the a-wave trough is broadened and there is a sharply rising b-wave, lacking photopic oscillatory potentials, with a markedly reduced b-/a-wave amplitude ratio. The sparing of the OFF pathway is confirmed by ON-OFF-response recording. *Patient B* with iCSNB has a reduced and delayed rod-specific ERG b-wave in keeping with rod system dysfunction and a bright-flash dark-adapted ERG that is profoundly electronegative in keeping with dysfunction post-phototransduction. The oscillatory potentials are undetectable. The cone system ERGs are much more abnormal than those in the patient with cCSNB, as in iCSNB there is dysfunction in both cone ON and OFF pathways. The flicker ERG is profoundly subnormal and has a characteristic triphasic waveform, and the single-flash photopic ERG has a reduced a-wave and a profoundly reduced b-wave giving a low-amplitude simplified waveform. Long-duration stimulus ERGs (200 ms) show an electronegative ON responses and marked alteration of the OFF response

- The *incomplete form of CSNB* is associated with mutations in the ***CACNA1F*** gene, on *Xp11.23*. This encodes the retina-specific α1-subunit of a voltage-gated L-type calcium channel that contributes to the regulation of glutamate release from photoreceptors to ON- and OFF-bipolar cells. Mutations in *CACNA1F* have also been found in X-linked cone-rod dystrophies (CORDX3; [20]), and there is a suggestion that CSNB2 patients can have a more progressive disorder than initially thought.

  NYX mutation accounts for 45 % and *CACNA1F* 55 % of X-linked CSNB [76].

Autosomal Recessive CSNB (arCSNB)

(CSNB1B #257270, CSNB1C #613216, CSNB1D #613830, CSNB1E #614565, CSNB1F #615058, CSNB2B #610427)

arCSNB is genetically and phenotypically heterogeneous. Both complete (ON-bipolar dysfunction) and incomplete (both ON- and OFF-bipolar dysfunction) forms have been described. Mutations in four different genes have been identified to date underlying the complete forms. These include *GRM6*, located on 5q35, encoding the glutamate receptor mGluR6 [12] (CSNB1B #257270); *TRPM1*, located on 15q13, encoding a calcium channel [4, 31, 66] (CSNB1C #613216); *GPR179* [3] (CSNB1E #614565); and *LRIT3* [78] (CSNB1F# 615058) [3, 78] (CSNB1E #614565; ***CSNB1F #615058***). The function of the latter two proteins remains to be elucidated. In contrast, mutations in two different genes have been identified in patients with incomplete arCSNB. These include *CABP4*, localised on 11q13.1, encoding a member of the calcium-binding protein (CABP) family [79] (CSNB2B #610427), and *CACNA2D4*, an L-type calcium-channel auxiliary subunit of the alpha (2) delta type [72]. Both genes are expressed in the photoreceptor synaptic terminals.

Recently, Riazuddin et al. have reported a large consanguineous family from Pakistan with AR CSNB (CSNB1D #613830) where affected members have a Riggs-type of CSNB. Affected family members had a homozygous 2-bp deletion in the *SLC24A1* gene, a member of the solute carrier protein superfamily [52]. The role of *SLC24A1* in visual transduction remains to be elucidated.

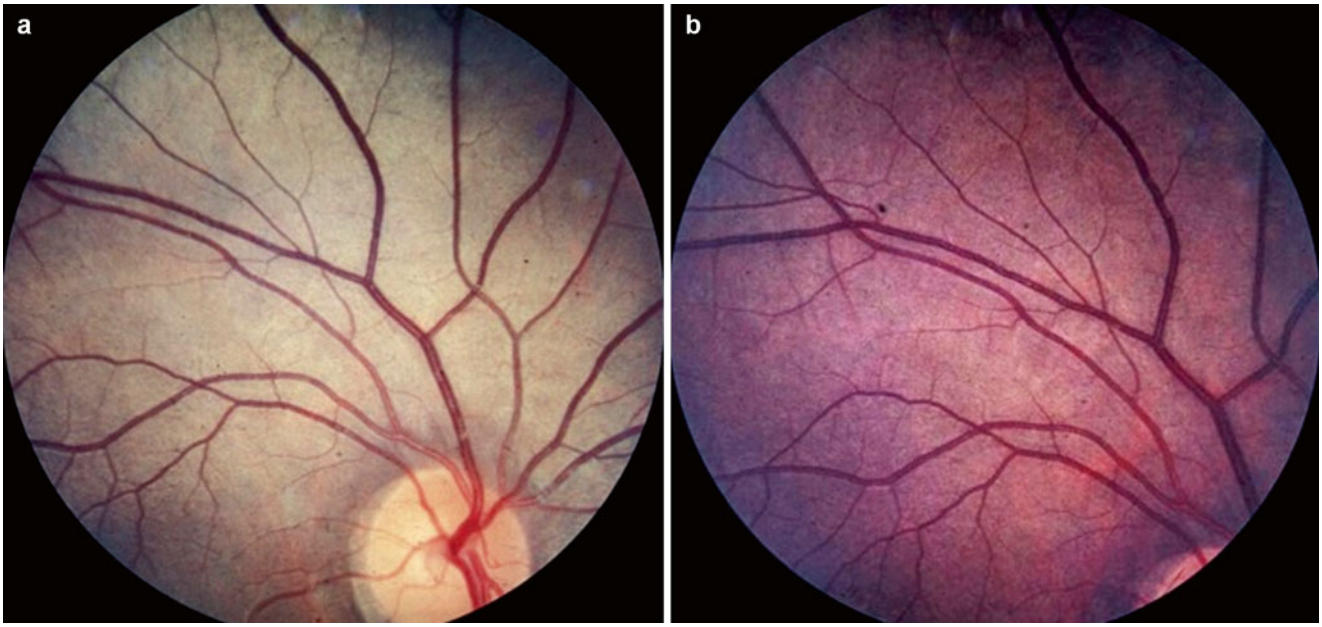


Fig. 8.2 Oguchi disease. (**a**) Light-adapted state: typical gold reflex. (**b**) After 2 h dark adaptation, disappearance of the reflex (Mizuo-Nakamura phenomenon)

Stationary Retinal Duchenne Muscular Dystrophy (DMD) (OMIM*300377)

Various authors have reported abnormal ERG responses in patients with DMD (see Audo et al. [5] for review). Interestingly, these patients do not have night blindness or other ocular symptoms. Visual acuity, colour vision, contrast sensitivity, visual fields and fundus examination are generally normal although more sophisticated tests of colour vision may show a deficit [8]. Dark-adapted sensitivity is also normal. Electrophysiology shows a reduced rod-specific response and an electronegative waveform in the dark-adapted bright-flash ERG. Photopic responses are within normal limits. These electrophysiological findings suggest a defect in post-receptoral signal transmission. The site of dysfunction may be at the level of the outer plexiform layer, as this is where dystrophin, the protein dysfunctional in DMD, has been shown to localise in the human retina. Phenotype-genotype correlation suggests that the position of the mutation in the gene determines the electrophysiological phenotype [50].

8.1.2 Congenital Stationary Night Blindness (CSNB) with Abnormal Fundus Appearance

Oguchi Disease

(1: OMIM #258100 and 2: #613411)

Oguchi disease is a very rare autosomal recessive form of CSNB in which there is normal visual acuity and visual fields but delayed dark adaptation. The disorder appears to be more common in the Japanese population. Affected patients complain of night blindness or difficulty in adjusting from bright to dim illumination. A typical clinical feature of the disorder is a golden or grey-white discolouration of the fundus upon light exposure which disappears after 2–3 h of dark adaptation (Mizuo-Nakamura phenomenon) (Fig. 8.2). If dark adaptation is performed for 20 min, prior to scotopic ERG testing (as recommended in the current ISCEV standards), no rod a-wave is detected. However, if a longer (1–2 h) dark adaptation is performed, the a-wave after stimulation with a single flash will be normal in amplitude and implicit time but a second flash will lead to a severely reduced response. Usui et al. suggested that this delayed dark adaptation was due to an abnormal deactivation of the phototransduction cascade [65].

Mutations in two genes, rhodopsin kinase (*GRK1*) [74] and arrestin (*S-ANTIGEN*, *SAG*) [15], have been described in Oguchi disease. All mutations reported to date are null alleles with no gene product or with inactive mutant proteins. Patients with *GRK1* mutations show no evidence of progression [74], while some patients with *SAG* mutations show evidence of photoreceptor cell death with time [45].

Fundus Albipunctatus

(OMIM #136880)

Fundus albipunctatus (FA) is a recessively inherited disorder characterised by night blindness, delayed dark adaptation and distinct fundus abnormalities, usually numerous small whitish-yellow subretinal spots scattered in the midperiphery and perifovea that vary with age. The first report of the disorder appears to be that of Lauber in 1910 [30]; in the

1950s, it was known as *fundus albipunctatus cum hemeralopia congenita*.

Visual acuity is usually well preserved with night blindness being the presenting symptom from early age. The disorder is probably not progressive, and some regard it as a form of congenital stationary night blindness. Miyake's group suggested that there are two groups of patients with FA: those with and without 'cone dystrophy' [43]. While there are patients with and without full-field cone system ERG abnormalities, there is little evidence that those with cone dysfunction show the progressive changes that would usually be associated with a dystrophic process affecting cone photoreceptors [32].

The characteristic white dots are present in the majority of patients (Fig. 8.3), but a patient with a normal fundus and

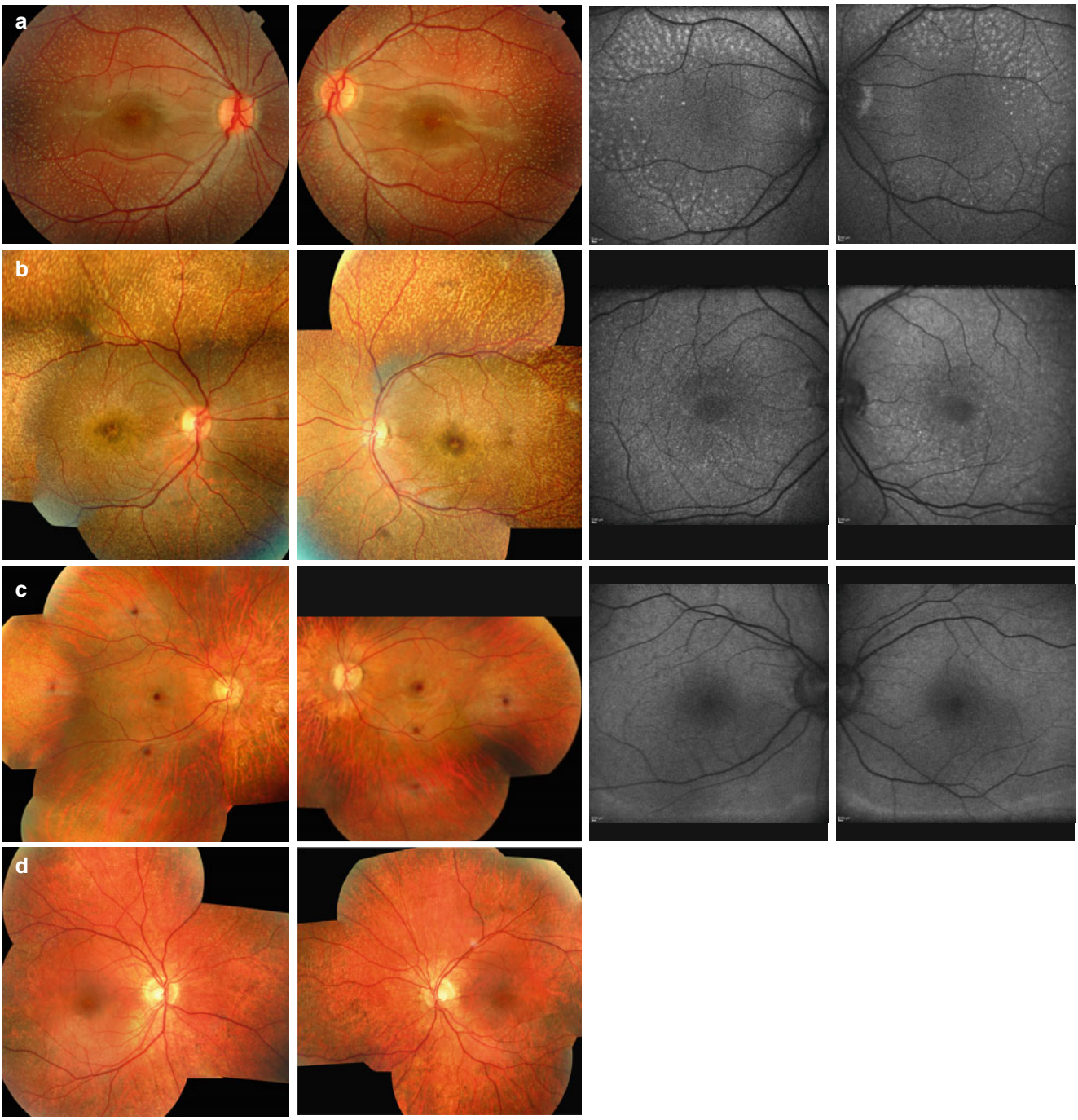


Fig. 8.3 Fundus albipunctatus. Fundus images (*left image*) and corresponding fundus autofluorescence (*right panel*) (From Sergouniotis et al. [59])

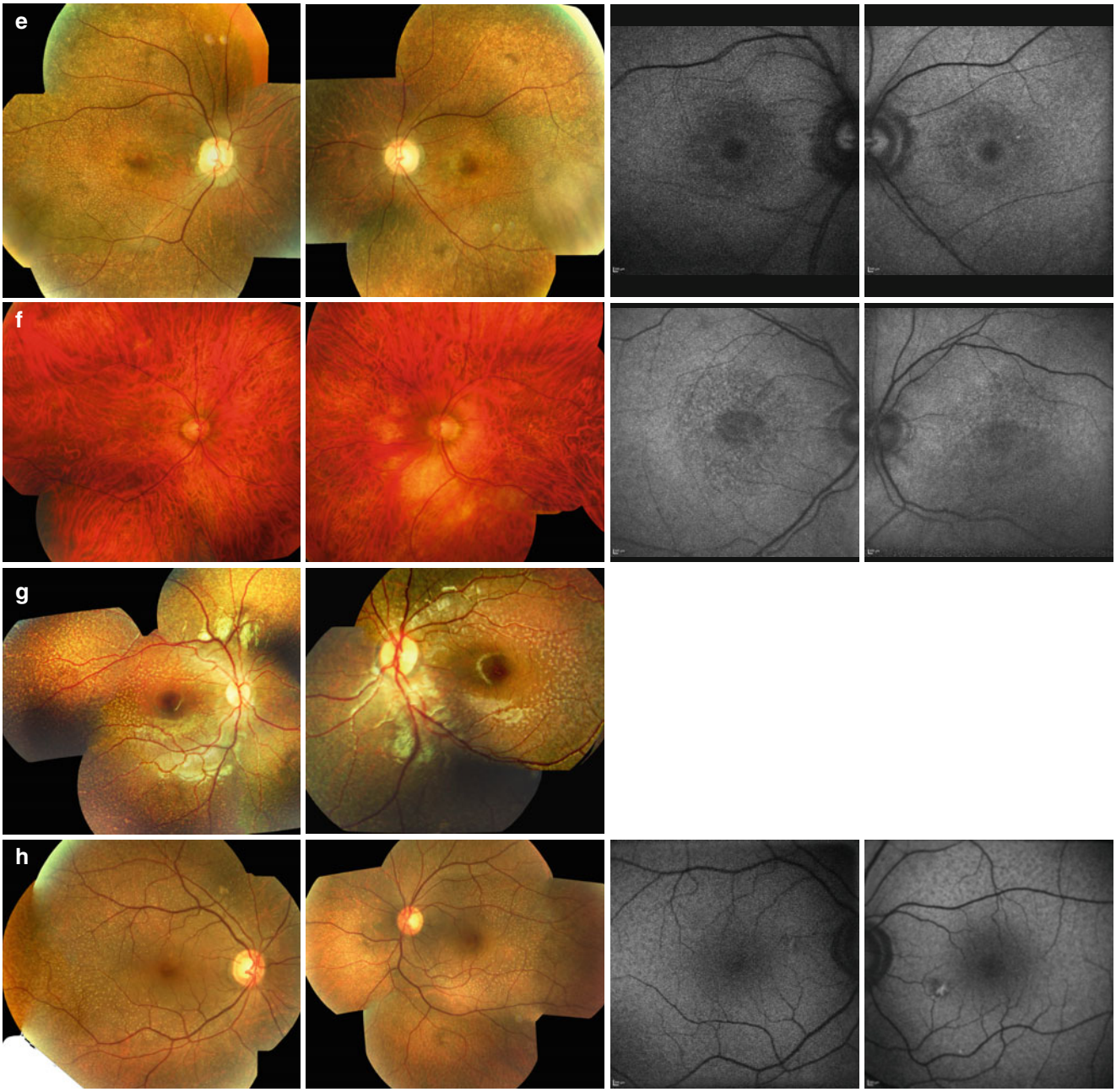


Fig. 8.3 (continued)

RDH5 mutation has been reported after characteristic electroretinographic changes directed appropriate gene screening [59]. Pigment irregularity may be present in the foveal region, but the fovea is often normal. The fundus lesions may evolve in appearance from flecks in childhood to punctate dots that increase, or decrease, in number over the years [32].

Fundus autofluorescence imaging may show a variety of different features. The white dots are associated with high-density focal increase in autofluorescence in some patients, but not in others. In general, overall the autofluorescence signal strength is low. Spectral-domain OCT reveals discrete highly reflective lesions at the level of the retinal pigment epithelium (RPE) extending into the inner segment ellipsoid band and the external limiting membrane (ELM) with focal thining of the outer nuclear layer (ONL) in location to white dots in the fundus [59, 69].

The disorder is characterised by an impaired regeneration of rhodopsin, and the retina is effectively 'bleached' for longer than would be the case in a normal subject, hence the night blindness. However, if the period of dark adaption is suitably extended, which may require many hours and differs from patient to patient, the levels of rhodopsin and dark-adapted thresholds normalise. This can be demonstrated with dark adaptometry. The changes are also reflected in the electrophysiological data, which are complex and require careful interpretation. The diagnosis cannot be established with

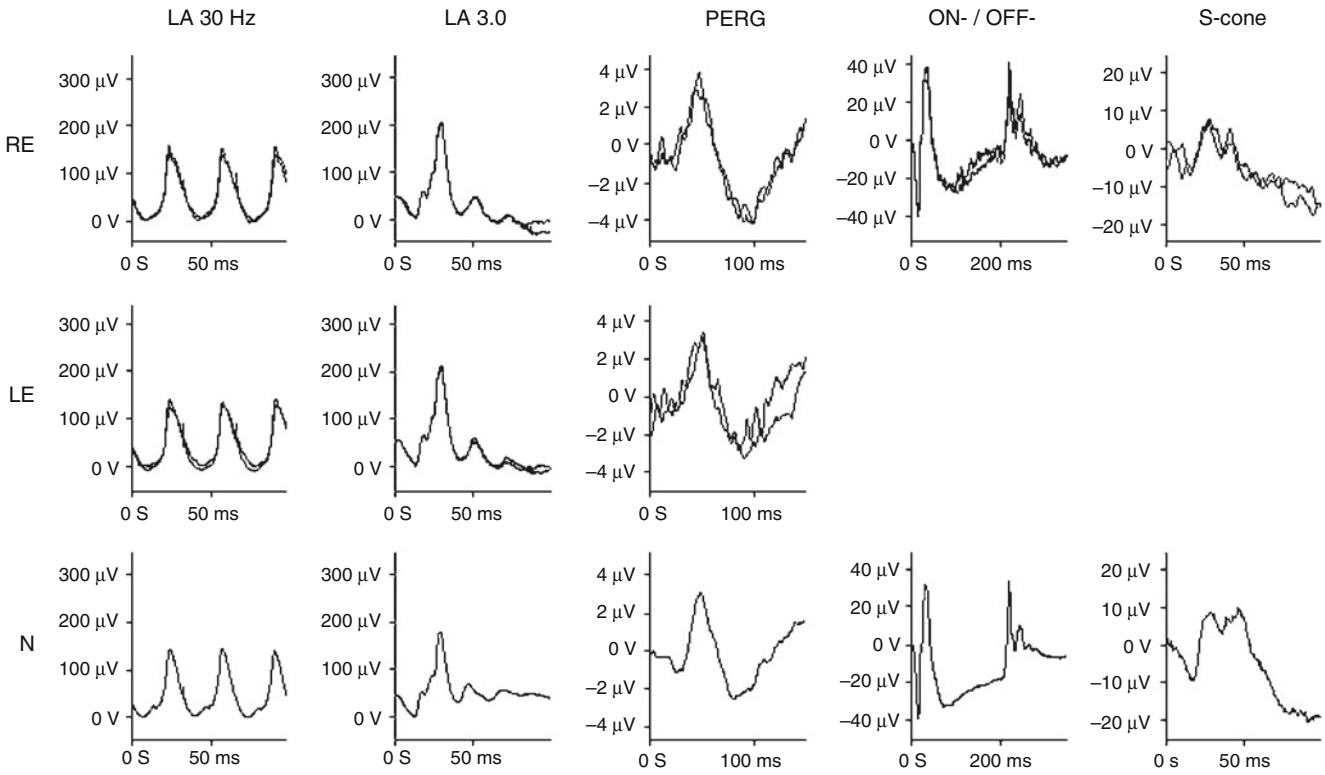


Fig. 8.4 Photopic ERGs in a patient with *RDH5* mutation and fundus albipunctatus. All cone system-derived ERGs, the 30-Hz flicker ERG, the single-flash photopic ERG (LA 3.0), pattern ERG, ON and OFF responses and S-cone ERGs are normal

certainty by the ISCEV standard ERGs alone as adequate consideration needs to be given to the underlying pathophysiology; in most patients, the dark-adapted ERGs recorded under ISCEV standard conditions will arise largely if not exclusively in dark-adapted cones. In addition, although some patients with mutation in *RDH5* have completely normal cone function, there is a subset of patients who have generalised cone system ERG abnormality where the flicker ERG is both delayed and subnormal. A few patients may have detectable, but abnormal, rod-specific ERGs.

Typical electrophysiological findings in FA appear in Figs. 8.4, 8.5 and 8.6. All cone ERGs are normal (Fig. 8.4). After a standard period of dark adaptation, the bright-flash dark-adapted DA 11.0 ERG shows a marginally subnormal a-wave accompanied by a lower amplitude b-wave giving an electronegative appearance. However, following an extended period of dark adaptation, the DA 0.01 and DA 11.0 ERGs are completely normal (Fig. 8.5). This normalisation of the dark-adapted ERGs is consistent with the delayed regeneration of rhodopsin following extended dark adaptation and establishes the diagnosis of FA. More detailed recordings under dark adaptation are shown in Fig. 8.6 where it is evident from the red flash that dark-adapted cone function is responsible for the ERGs observed. The 'negative' ERG aspect of the initial DA 11.0 response is explained by the so-called photopic hill phenomenon also occurring in dark-adapted cones, exposed in the absence of rod function. Figure 8.7 shows representative findings in 'FA with cone dystrophy'. The initial right eye findings were taken after that eye had been patched overnight, with the left eye receiving standard ISCEV dark adaptation. Note the normal dark-adapted ERGs in the right eye but the severely reduced DA 0.01 response and attenuated DA 11.0 response in the left eye. Cone ERGs from both eyes show delay, in keeping with generalised cone system dysfunction. The patients were re-dark adapted (ISCEV standard) after the photopic testing had been performed to demonstrate that the eyes are in fact symmetrical. Note the additional amplitude reductions in the left eye following the period of photopic adaptation and photopic stimulation, and thus rhodopsin bleach, during the initial ERG.

The disorder is generally assumed to be nonprogressive, but cases with progressive cone dysfunction have been reported (see for review Sergouniotis et al. [59]).

Fundus albipunctatus needs to be distinguished from other causes of flecked retina syndromes such as retinitis punctata albescens, Stargardt disease or benign fleck retina syndromes. Other differential diagnoses include long-term vitamin A deficiency, Bassen-Kornzweig syndrome or a lack of serum retinoid-binding protein that could potentially be treated with vitamin A supplementation (reviewed in Dryja et al. [9]).

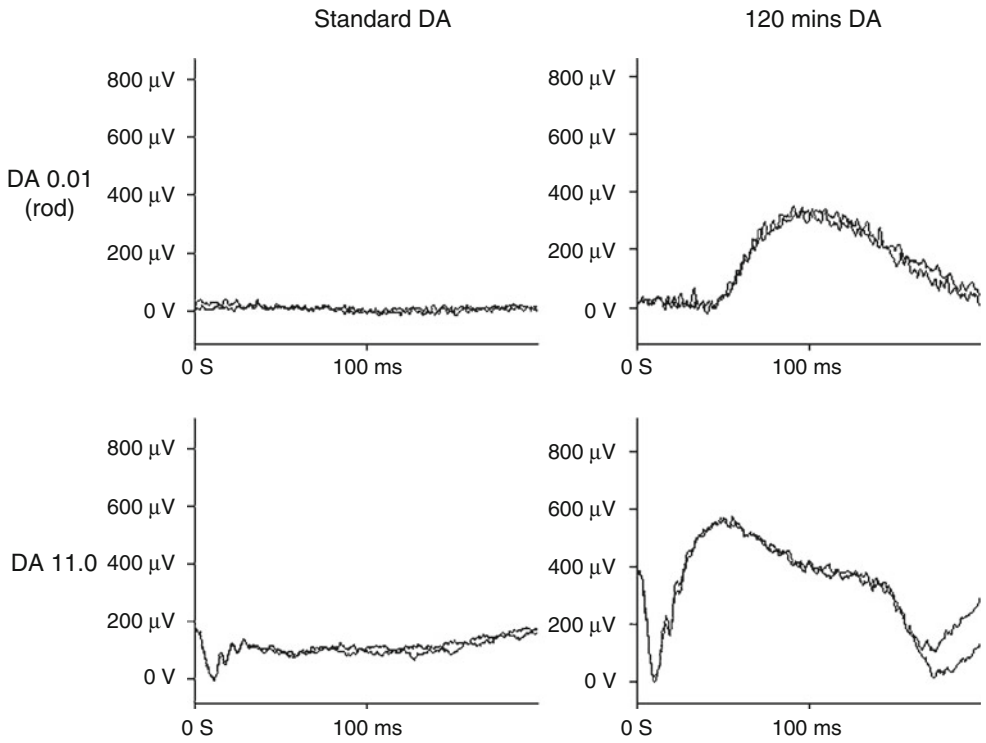


Fig. 8.5 Dark-adapted ISCEV standard dim white-flash (DA 0.01) and bright white-flash (DA 11.0) ERGs in the same patient following a standard period of dark adaptation and also following 2 h of dark adaptation. The ERGs after extended dark adaptation are normal. Following standard DA, the rod-specific ERG (DA 0.01) is undetectable and the DA 11.0 response shows an electronegative waveform (b-wave of lower amplitude than a-wave) with a mildly subnormal a-wave. Note the presence of well-defined oscillatory potentials – the small wavelets on the ascending limb of the b-wave – they would be undetectable in most cases of congenital night blindness, with which FA may be confused if consideration is not appropriately given to the need to use extended dark adaptation to allow for the delayed regeneration of rhodopsin known to be part of the pathophysiology of FA

Fundus albipunctatus is caused by mutations in *RDH5* which encodes 11-cis retinol dehydrogenase, a protein involved in the regeneration of rhodopsin as part of retinoid recycling in the retinal pigment epithelium ([73], see Dryja et al. [9] for review). It has an autosomal recessive inheritance pattern. To date, it has not proved possible to relate the presence or absence of cone dysfunction to the nature of the mutational change. Mutations in the *RLBP1* have also been reported in FA [22, 47] but also in a progressive disorder retinitis punctata albescens [33]. A case of fundus albipunctatus has also been reported in association with compound heterozygous mutations in *RPE65* [56].

8.1.3 Management

No specific treatment is currently available for any form of congenital stationary night blindness. However, it is important to make the correct diagnosis to allow the patient and family to receive accurate genetic counselling and advice about the visual prognosis. Practical management includes treatment of associated refractive errors, low vision aid assessment if appropriate and the management of any associated strabismus. A referral should be made for genetic counselling, and it is likely that molecular diagnosis will become more available in the future. Currently, a microarray-based mutation analysis is available at Asper Ophthalmics® (www.asperophthalmics.com) [80].

8.2 Cone Dysfunction Syndromes

(See for review Michaelides et al. [37])

The cone dysfunction syndromes are a group of non-progressive disorders affecting the cone photoreceptors or their post-receptoral pathways; rod function is normal. This group of disorders need to be distinguished from progressive cone dystrophies, which are usually diagnosed during childhood

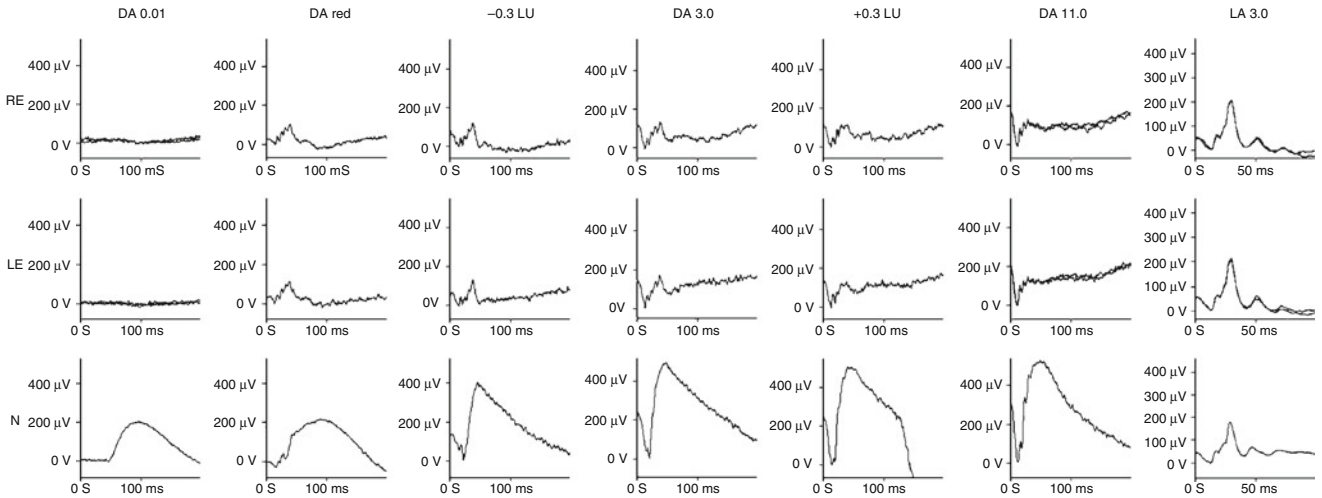


Fig. 8.6 Additional ERGs after standardised dark adaptation allow a more complete evaluation. Red stimulation in a normal subject (*N*) shows an early cone component and a later rod component. Note that only the cone component is present in the ERGs of the patient. This is predictable from what is understood of the underlying pathophysiology in FA. As stimulus intensity is increased, it is clear from the waveforms that all ERGs in the patient must be arising in dark-adapted cones. At higher stimulus strength (DA 11.0), the waveform has an electronegative appearance probably reflecting the so-called photopic hill phenomenon also being a function of dark-adapted cones, but only exposed in the absence of rod function

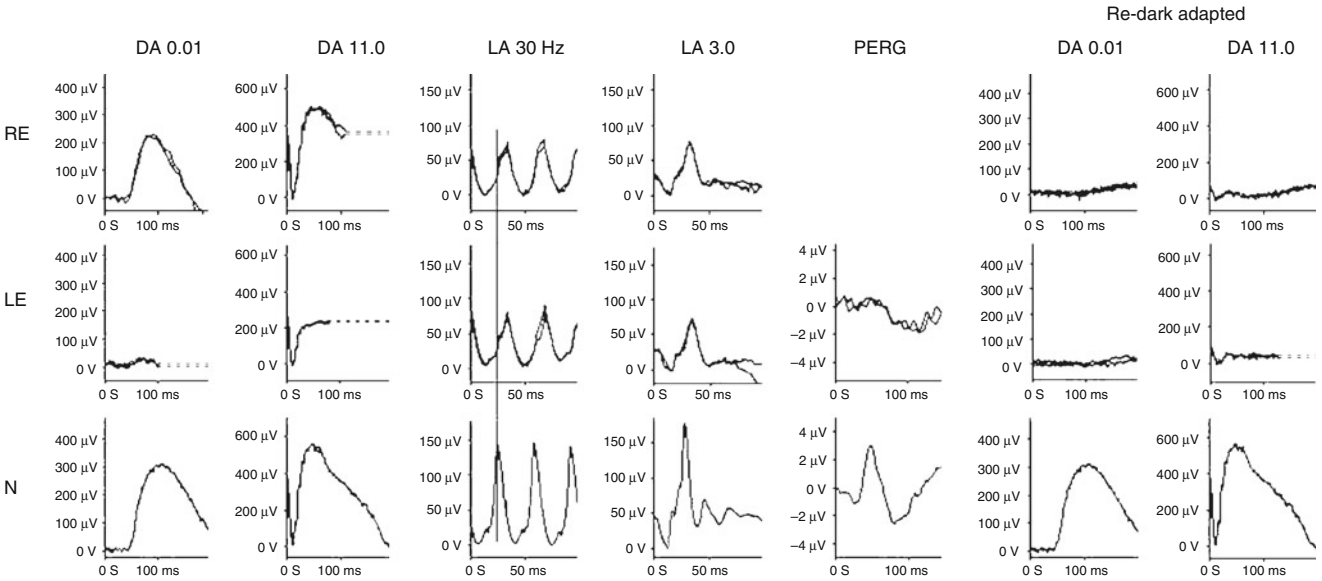


Fig. 8.7 ERGs from a patient with 'fundus albipunctatus with cone dystrophy'. Right eye findings are taken after overnight patching (approximately 13 h DA) simultaneously with left eye ERGs taken after a standard period of dark adaptation (25 min). They are presented with those from a representative normal (*N*). Note that dark-adapted ERGs from the right eye do not differ from those in the normal control subject, whereas there is profound reduction in the DA 0.01 response from the left eye and a mildly electronegative DA 11.0 ERG with mild a-wave reduction. The normal ERGs from the RE, consistent with full regeneration of rhodopsin, are in keeping with FA. Cone ERGs, best seen in the 30-Hz flicker responses, show delay in both eyes of the patient reflecting the subgroup of patients termed as 'fundus albipunctatus with cone dystrophy' by Miyake. ERGs following a further period of standardised dark adaptation following the photopic recordings show that the two eyes do in fact function in a symmetrical manner when in similar adaptive states

or early adulthood, and are often associated with rod dysfunction later in life. However, the boundary between cone dysfunction syndromes and cone dystrophies is sometimes artificial since cone stationary disorders can in some instances progress towards cone dystrophy with age, and this will need to be taken into account when advising patients.

Patients with cone dysfunction syndrome typically have reduced visual acuity, abnormal colour vision, central scotoma and a normal fundus examination. Nystagmus and photophobia are common. The full-field ERG shows abnormal single-flash photopic responses and absence or severely reduced 30-Hz flicker responses. Psychophysical testing shows absent or abnormal cone function with normal rod function.

8.2.1 Achromatopsia

ACHM

ACHM2 MIM #216900, ACHM3 MIM #262300, ACHM4 MIM #613856, ACHM5 #613093 and ACHM6 MIM # 610024

Synonyms

Rod monochromatism, Total colour blindness

Achromatopsia is a rare heterogeneous group of autosomal recessive stationary disorders characterised by an absence of functional cones (see for review Michaelides et al. [37]). The prevalence of the disorder is estimated between 1/30,000 and 1/50,000. Complete and incomplete forms exist.

8.2.2 Complete Achromatopsia

Patients usually present in infancy with nystagmus and marked photophobia; the nystagmus is often rapid and of low amplitude and may improve with age. There is usually a hyperopic refractive error and fundus examination is normal. Vision is better in dim illumination. When the child is older and formal visual assessment is possible, the visual acuity is usually around the level of 20/200 and there is no true colour vision; children may recognise primary colours by using brightness matching. There are, in some patients, paradoxical pupil responses (pupillary dilation in bright light). Electroretinography and psychophysical testing show absent cone function but normal rod sensitivity (Fig. 8.8). Although achromatopsia was thought to be a stationary cone disorder, recent studies using high-resolution imaging techniques, such as spectral-domain optical coherence tomography and adaptive optics imaging, have revealed foveal cone abnormalities [17, 64] (Figs. 8.9 and 8.10).

8.2.3 Incomplete Achromatopsia

Incomplete achromatopsia presents in a similar way to complete achromatopsia, but there is evidence of residual cone

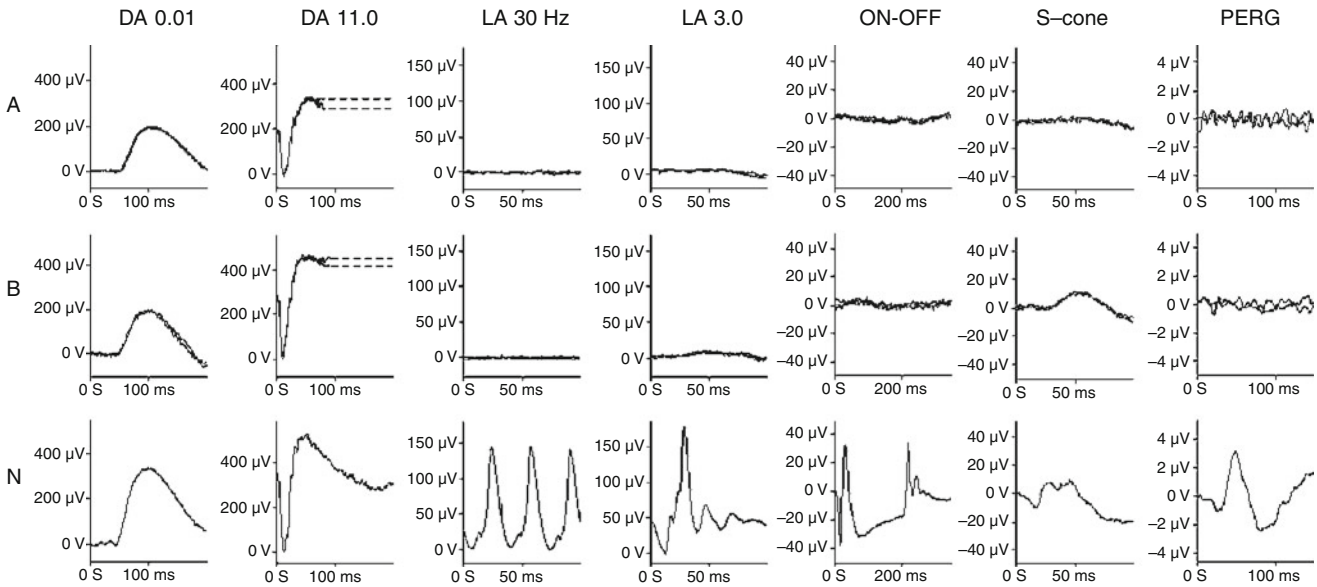


Fig. 8.8 Blue cone monochromacy and rod monochromacy. Electrophysiological findings in rod monochromacy (*patient A*) and S-cone monochromacy (*patient B*). The rod-specific (DA 0.01) and dark-adapted bright white-flash ERGs (DA 11.0) are normal in both patients. The 30-Hz flicker ERG is undetectable in both. S-cone ERGs (blue stimulus, orange background) are undetectable in patient A. There is a very low-amplitude single-flash photopic ERG (LA 3.0) in patient B, shown by S-cone-specific stimulation to be arising in S-cones. Note the b-wave at approximately 50 ms typical of an S-cone derived ERG

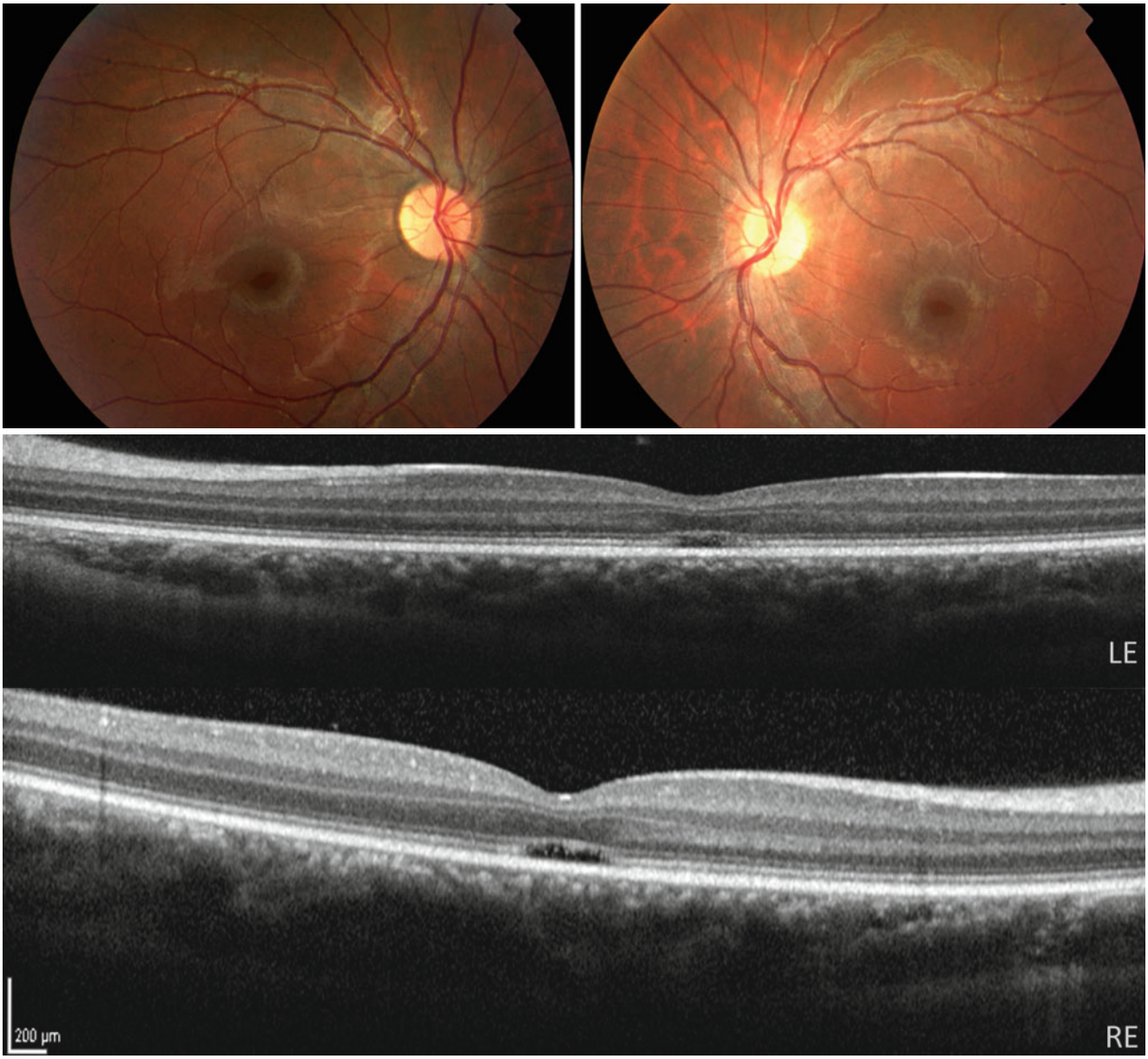


Fig. 8.9 Colour photographs and spectral-domain OCT of an 18-year-old patient with achromatopsia due to compound heterozygous *CNGB3* mutations. Visual acuity 6/60 OU. Normal fundus appearance but spectral-domain OCT shows an area of lucency at the outer segment/RPE junction (foveal cavitation)

function. The best corrected visual acuity is better between 20/80 and 20/120 with some residual colour vision. ERG recording is usually similar to complete achromatopsia, but some patients show electrophysiological evidence of residual cone function (Fig. 8.8).

Achromatopsia is a genetically heterogeneous autosomal recessive disorder. Mutations of five different genes have been identified to date including genes coding for the α and β subunits of the cyclic nucleotide-gated cation channel (*CNGA3* -MIN 600053 ACHM2 2p11- [70] and *CNGB3* -MIN 605080 ACHM3 8q21-q22- [26], respectively); the α subunit of cone photoreceptor transducin, *GNAT2* -MIM 139340 ACHM4 on 1p13.3 [27]; the cone α subunit of cyclic guanosine monophosphate (cGMP) phosphodiesterase, *PDE6C* gene on 10q24 MIM #600827 [63]; and the gamma subunit of cone cGMP phosphodiesterase, *PDE6H* gene on 12p12.3 MIM *601190 [28]. They all encode components of the cone phototransduction cascade. Mutations on *CNGA3* and *CNGB3* account for the majority of achromatopsia cases, with 20–30 and 50–60 % of patients of European origin, respectively [29, 70]. Over 50 disease-causing mutations have been identified on *CNGA3* most of which are missense

sequence variants. By contrast, about 12 mutations have been found on *CNGB3*, the majority being nonsense variants. The most common, a 1 base-pair frameshift deletion c.1148delC (p.T383fsX), is observed in more than 70 % of *CNGB3*-mutated alleles in European patients with achromatopsia [29]. Phenotypes of patients with *CNGA3* or *CNGB3* mutations are undistinguishable. *GNAT2* mutations account for less than 2 % of cases, which is probably the same for *PDE6C* and *PDE6H* mutations, although no prevalence study is available to date. Furthermore, while screening patients with achromatopsia, there are still patients with no mutation detected in none of the five known genes suggesting potential additional loci [63]. A fifth locus on chromosome 14 (ACHM1) had been suggested by the report of a case of achromatopsia who had uniparental isodisomy of chromosome 14, but this case was subsequently found to have a homozygous mutation in *CNGB3* [71].

Mutations in *CNGB3*, *GNAT2*, *PDE6C*, *CNGA3* and *CNGB3* genes have been reported in association with complete achromatopsia, whereas mutations in *CNGA3* and *PD6H* have been identified in incomplete achromatopsia.

Mutations in *CNGB3*, *GNAT2*, *PDE6C* and *PDE6H* have been associated with progressive cone dystrophies [25, 35,

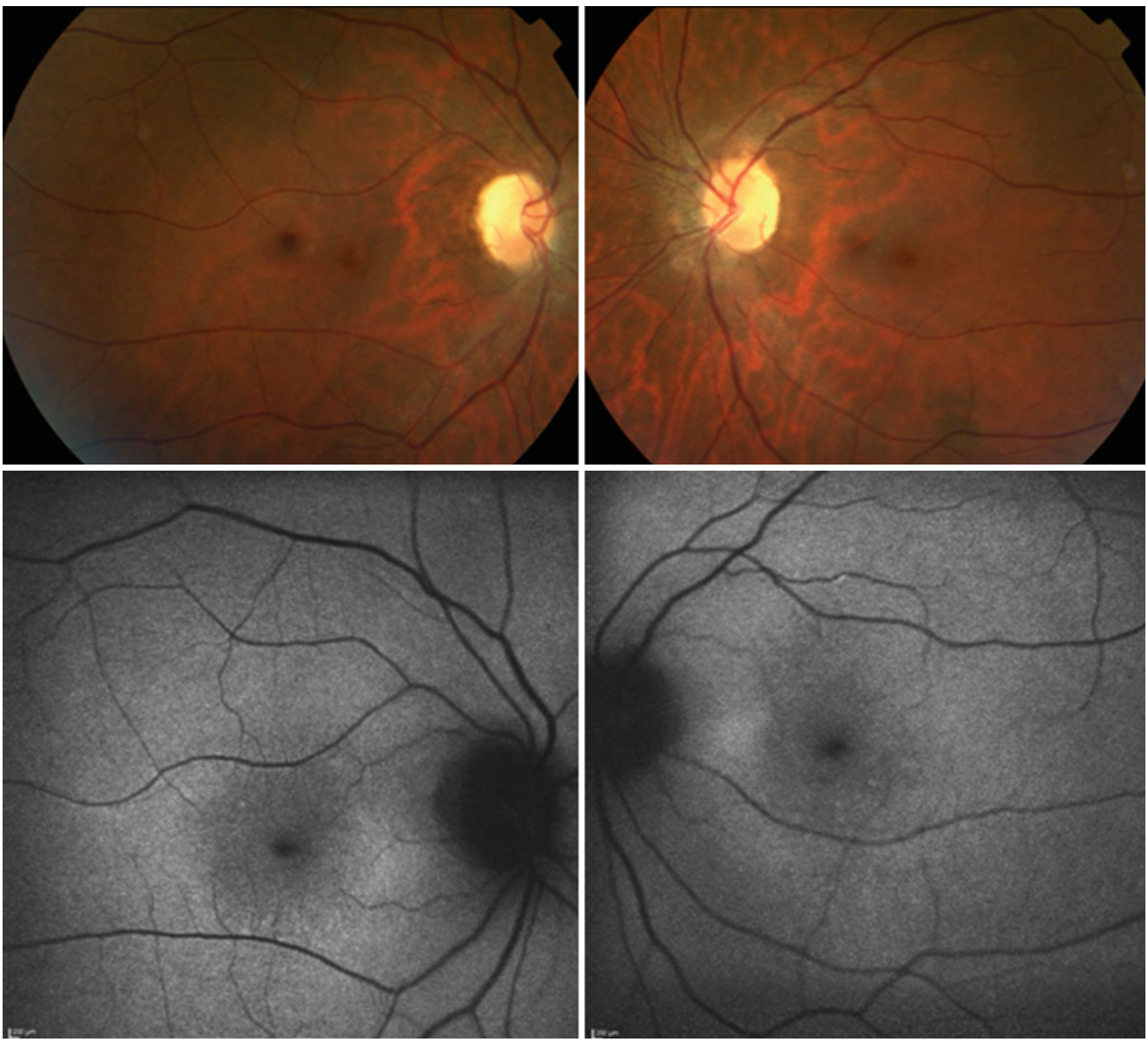
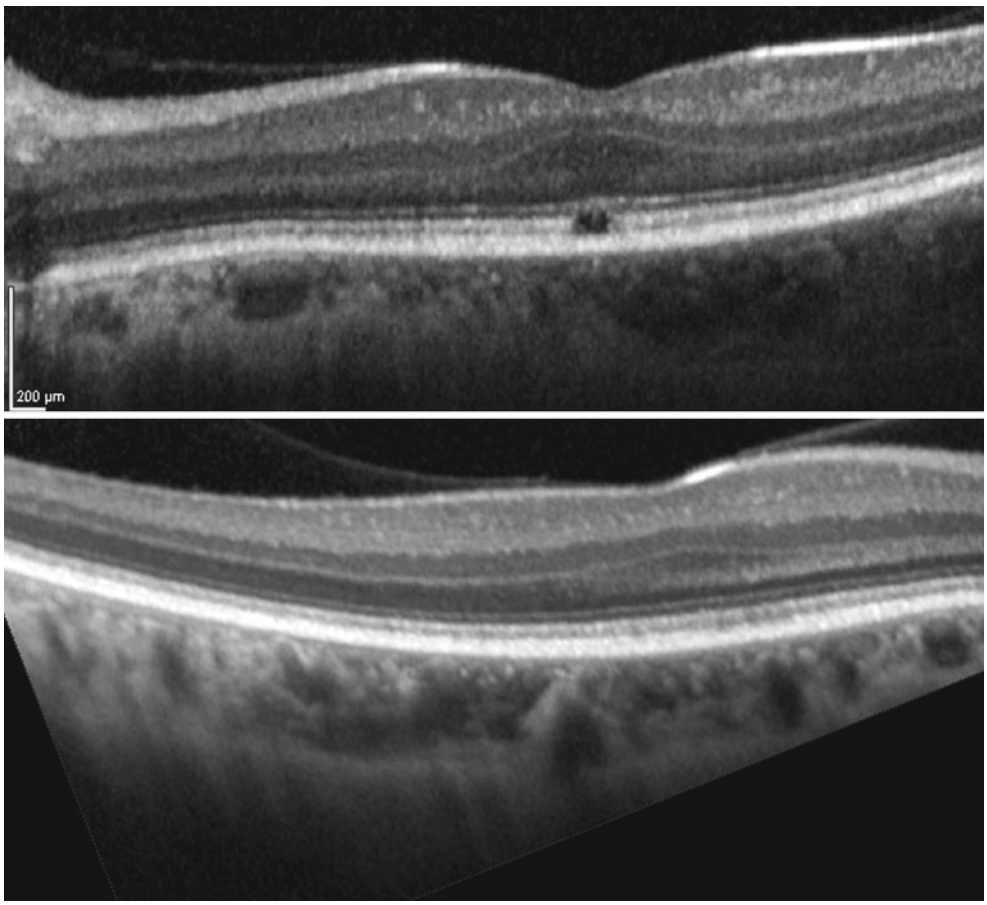


Fig. 8.10 Colour photographs, autofluorescence and spectral-domain OCT of a 30-year-old patient with achromatopsia due to homozygous *CNGB3* mutation. Normal fundus and autofluorescence but subtle focal outer segment lesion in the foveal region of the left eye

Fig. 8.10 (continued)



40, 51, 63, 64]. These findings suggest that achromatopsia is not always a stationary disorder with overlap between achromatopsia and early-onset cone dystrophy.

8.2.4 S-Cone Monochromatism

(OMIM #303700)

Synonyms

Blue cone monochromatism, X-linked incomplete achromatopsia

S-cone monochromatism is an X-linked disorder affecting 1/100,00 individuals. It is characterised by an absence of long-wavelength (L or 'red') and medium-wavelength (M or 'green') sensitive cone function and normal rod and short-wavelength (S or 'blue') sensitive cone function. The clinical presentation is similar to achromatopsia (i.e. poor central vision and colour discrimination, infantile nystagmus and nearly normal fundus appearance), but visual acuity is usually slightly better and myopia is a common finding.

S-cone monochromatism can be distinguished from achromatopsia by means of psychophysical testing and electrophysiology. On colour vision tests, S-cone monochromats show fewer errors on Farnsworth 100 Hue test (fewer tritan errors) and may display a protan-like defect on Farnsworth D-15. The Berson plates are also useful in distinguishing between achromats and S-cone monochromats, the latter being able to pass this test, in keeping with retention of the short-wavelength sensitive pigment [6].

In both achromatopsia and in S-cone monochromatism, the ERG reveals an absent or severely reduced 30-Hz flicker response, but normal rod responses (Fig. 8.8). However, in S-cone monochromatism, there is a preservation of short-wavelength stimulation ERG responses [18, 39].

S-cone monochromatism has been shown to be associated with genetic alterations affecting expression of the two genes encoding the long-wavelength (L) and middle-wavelength (M) sensitive photopigments in the cones [46]. The genetic alterations are divided into two classes: In the first class, normal L- and M-opsin gene arrays are inactivated by a deletion in the LCR (locus control region), located upstream of the L-opsin gene abolishing transcription of L and M opsins. In the second class of mutations, the LCR is preserved, but changes within the L- and M-pigment gene arrays lead to loss of functional pigment production (see Michaelides et al. [39] for more details).

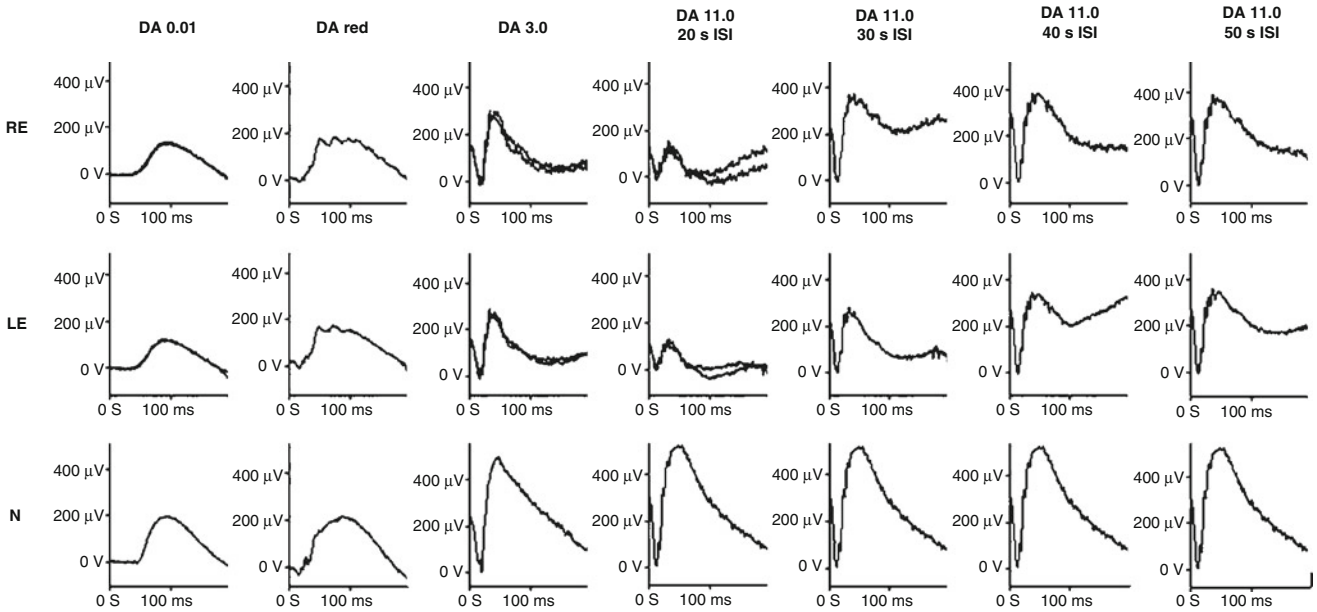


Fig. 8.11 See legend to Fig. 8.12

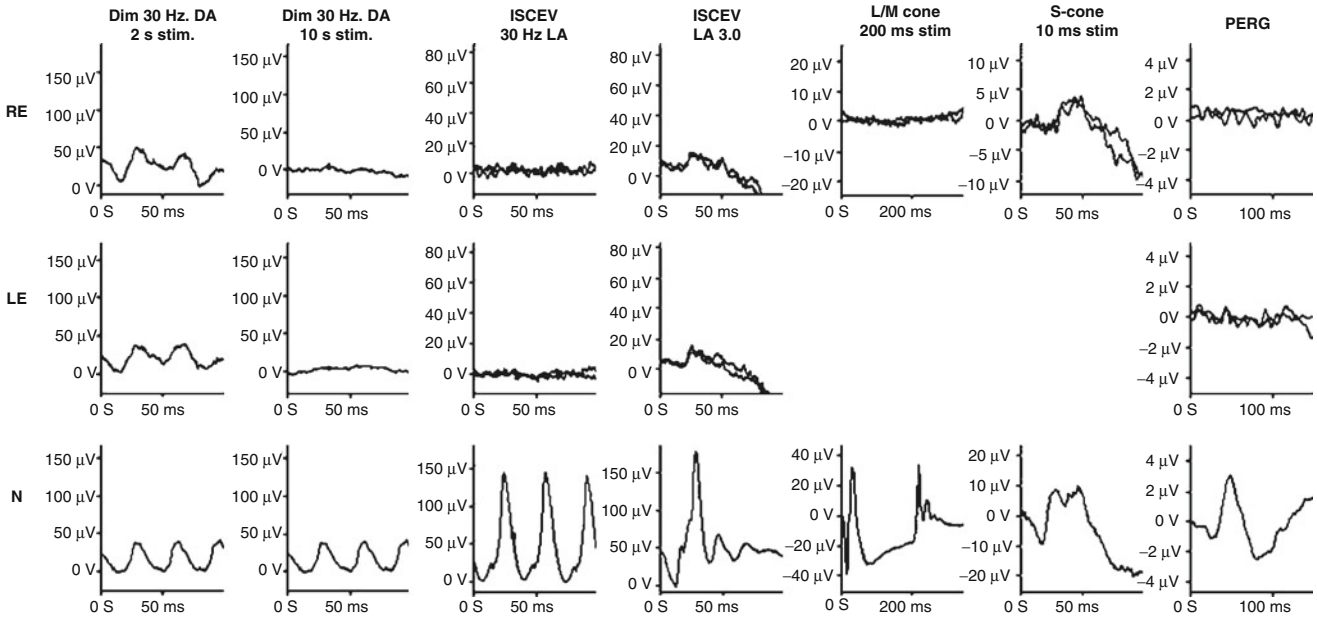


Fig. 8.12 Dark-adapted ERG in bradyopsia (*RGS9* mutation). DA 0.01 ERGs are unremarkable for age (M, 63 years). Dark-adapted red-flash ERGs (DA red) have both an early cone and later rod component. Bright-flash ERGs (DA 11.0) are attenuated after a standard interstimulus interval (ISI) of 20 s but normalise when the ISI is increased to 50 s. DA 30-Hz flicker ERGs are present 2 s after onset of the stimulus (DA 1.3 30 Hz 2 s) but are undetectable after 10 s of stimulation (DA 1.3 30 Hz 10 s). LA 3.0 30-Hz ERGs are undetectable, and there is a profoundly subnormal response to a single photopic-flash stimulus (LA 3.0) shown by blue-flash ERGs probably to have S-cone origins (S-cone). Pattern ERG (PERG) is undetectable (After Vincent et al. [68]). Note that if only the ISCEV standard ERGs are recorded, the likely diagnosis would be achromatopsia; it is the ability of the red-flash ERG under dark adaptation to reveal details of dark-adapted cone function that enables the correct diagnosis

8.2.5 Prolonged Electroretinal Response Suppression (PERRS)

(OMIM#608415)

Synonym

Bradyopsia

Bradyopsia is an unusual stationary cone dysfunction syndrome associated with normal colour vision and mild photophobia. Patients often lack nystagmus and have a normal fundus. The disease is further characterised by markedly delayed dark and light adaptation, difficulty seeing moving objects and moderately reduced visual acuity. The ISCEV standard ERGs show normal dark-adapted responses, an undetectable 30-Hz flicker ERG and a severely reduced single-flash photopic ERG, which suggest incomplete achromatopsia (Figs. 8.11 and 8.12). However, ERGs to a red flash under dark adaptation are also normal ruling out achroma-

topsia. Dark-adapted flicker responses may initially be normal but become undetectable after approximately 10 s of stimulation [41]. Bradyopsia is very similar to oligocone trichromacy, but the profound delay in adapting to varying illumination, the difficulty in tracking moving objects and the characteristic ERG findings allow the two conditions to be distinguished.

Mutations in two genes *RGS9* and *RGS9BP* have been implicated in bradyopsia. The genes encode proteins that play a critical role in the recovery phase of visual transduction [48].

8.2.6 Oligocone Trichromacy

This is a rare cone dysfunction syndrome with autosomal recessive inheritance. It was first described by Van Lith [67]. The disorder is characterised by reduced vision from infancy, mild photophobia, normal fundus, normal visual field and normal or mildly reduced colour discrimination on psychophysics. Nystagmus may be present [13, 67] or absent [36]. The condition is nonprogressive. The cone photoreceptor mosaic on high-resolution imaging shows reduced numbers of healthy cones [24, 42]. Electrophysiological testing shows various degrees of cone dysfunction with normal rod function [36]. A reduced b/a ratio has been described in some patients reflecting a possible post-receptoral processing abnormality [36] (Fig. 8.13).

Oligocone trichromacy associated with infantile-onset nystagmus may be associated with mutations in *CNGA3* [2] and *GNAT2* [54]. Mutations in *RGS9* and *RGS9BP* also account for a proportion of patients with bradyopsia and a phenotype similar to oligocone trichromacy without nystagmus [41], but careful ERG testing will distinguish the two disorders.

8.2.7 Bornholm Eye Disease

(OMIM #300843)

This rare condition was initially reported as an X-linked trait in a Danish family from Bornholm [19]. Affected individuals had high myopia, amblyopia, optic nerve hypoplasia (not always present), deuteranopia and subnormal electroretinographic (ERG) flicker function consistent with cone dysfunction. Similar associations were subsequently reported in an American family from Danish origin [75] and an English family [38] with protanopia as opposed to deuteranopia. The genetic defect was mapped by Schwartz et al. [58] and Young et al. [75] to chromosome Xq27.3-28. Recently, McClements et al. [34] have identified that mutations in the L- and M-opsin genes are responsible for this disorder.

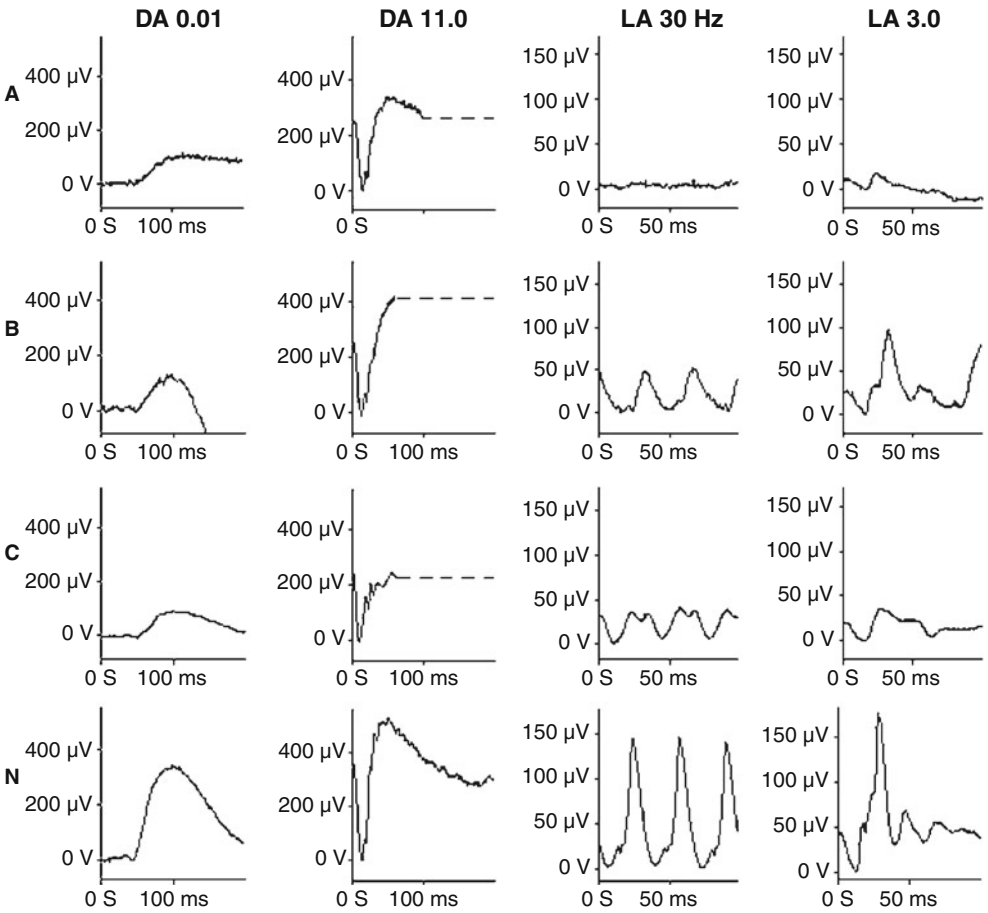


Fig. 8.13 Electrophysiological findings in three patients with oligocone trichromacy. Rod system ERGs (DA 0.01; DA 11.0) show no clinically significant abnormality. *Patient A* shows residual single-flash cone ERG (LA 3.0) with almost extinguished 30-Hz flicker ERG. *Patient B* shows a delayed and mildly subnormal flicker ERG, in keeping with generalised cone system dysfunction, but the single-flash photopic ERG shows no definite abnormality. Both are profoundly abnormal in *patient C*

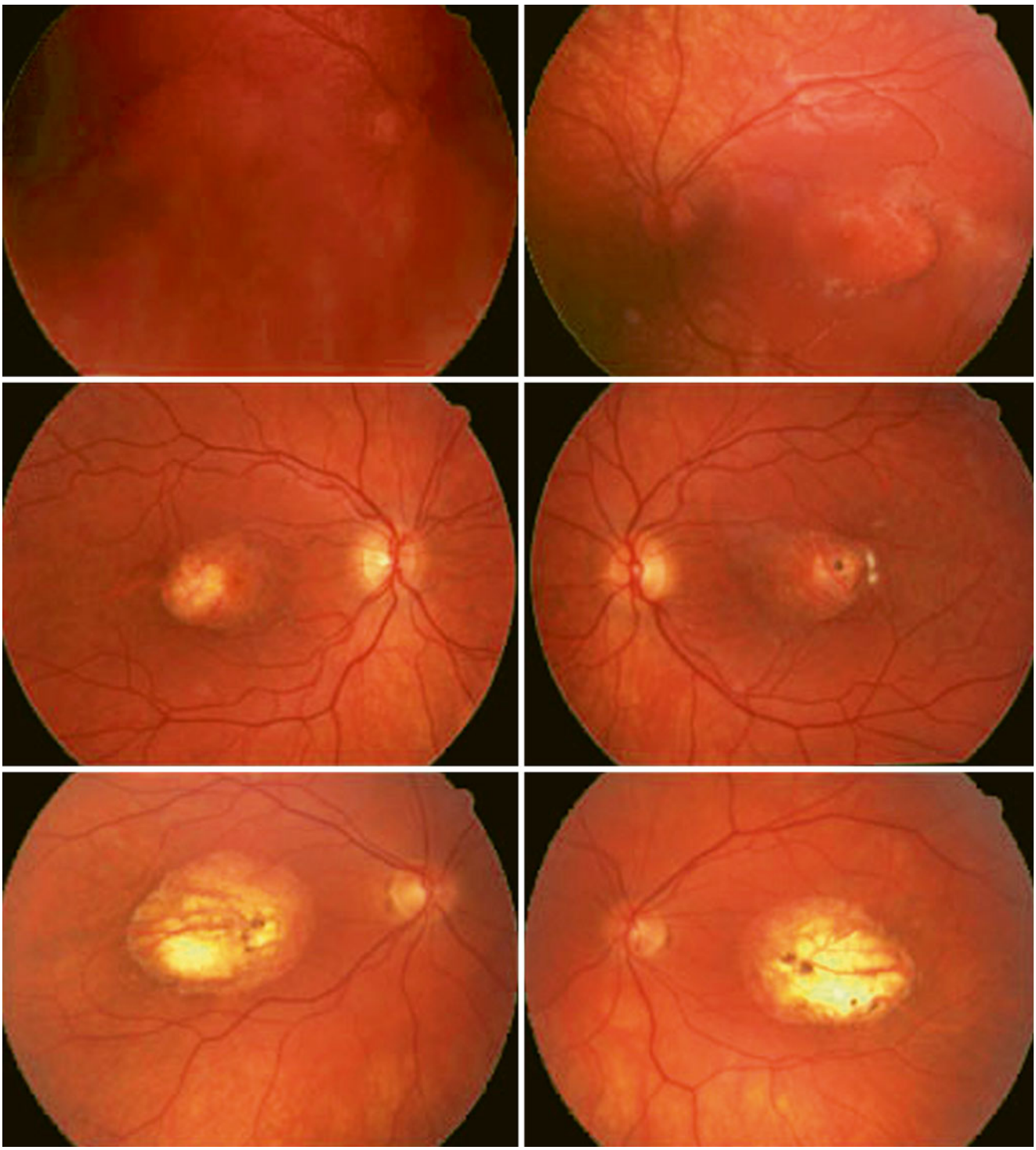


Fig. 8.14 Different aspects of North Carolina macular dystrophy (NCMD) in three generations. *Top*: 21-month-old girl. *Middle*: Mother, 20 years old. *Bottom*: Grandfather, 61 years old

8.2.8 Management

No treatment is currently available for cone dysfunction syndrome. However, correct diagnosis is necessary for accurate advice on prognosis and genetic counselling. Management includes correction of refractive errors and low vision aid. The photophobia is helped by the low light transmission tinted spectacles or contact lenses and red-tinted lenses have been recommended for achromatopsia [49].

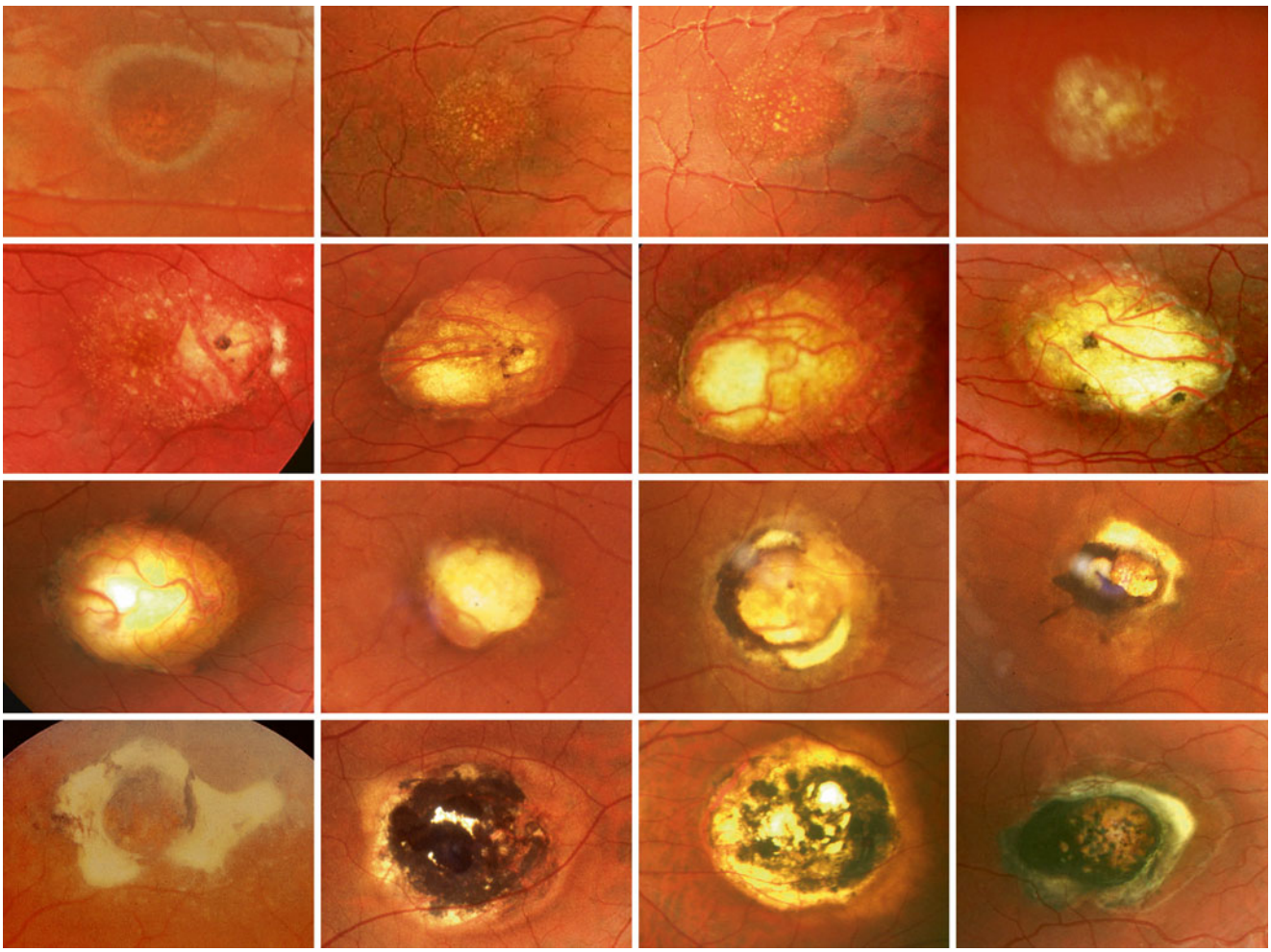


Fig. 8.15 Various aspects of NCMD. Grade 1: Drusen-like deposits. Grade 2: Confluence of the drusen-like deposits. Grade 3: Macular 'coloboma' sometimes surrounded by fibrosis. Note the marked pigmentation of the lesion in the three last cases

Patients and their families will also benefit from genetic counselling (which may include molecular diagnosis) and educational advice and support. Clinical trials of gene replacement therapy for the commoner form achromatopsia caused by mutation in *CNGB3* and *CNGA3* are likely to start soon.

8.2.9 Stationary Macular Dystrophies

8.2.9.1 North Carolina Macular Dystrophy (MCDR1)

Clinical Features

North Carolina macular dystrophy (MCDR1) (OMIM #136550) is an uncommon autosomal dominant macular dystrophy which shows a very variable phenotype. The original family reported from North Carolina was descended from three brothers who had emigrated from Southern Ireland. Since the original description, families with identical phenotype have been reported from many different countries. The fundus appearances range from multiple small drusen-like deposits in the central macular region (grade 1) which may become confluent (grade 2) to large oval areas of macular atrophy often incorrectly termed macular 'coloboma' (grade 3) (Figs. 8.14 and 8.15). The macular atrophic lesion commonly has a ring of pigmentation and fibrous tissue at its peripheral edge (Figs. 8.14 and 8.15). Rarely, there is associated choroidal neovascularisation. Some affected individuals show radial drusen-like deposits in the periphery. The drusen-like deposits seen in grade 1 disease are highly autofluorescent on fundus autofluorescence imaging (Fig. 8.16).

The visual acuity is usually normal in grade 1 and 2 disease, but there is significant central visual loss in grade 3 disease. One notable characteristic of the disorder is that in those cases with extensive macular atrophy (grade 3), the visual acuity is better than would be predicted from the fundus appearance. In grade 3 disease, there is patchy central visual field loss but with a normal peripheral visual field. Colour vision is usually well preserved. NCMD is of early

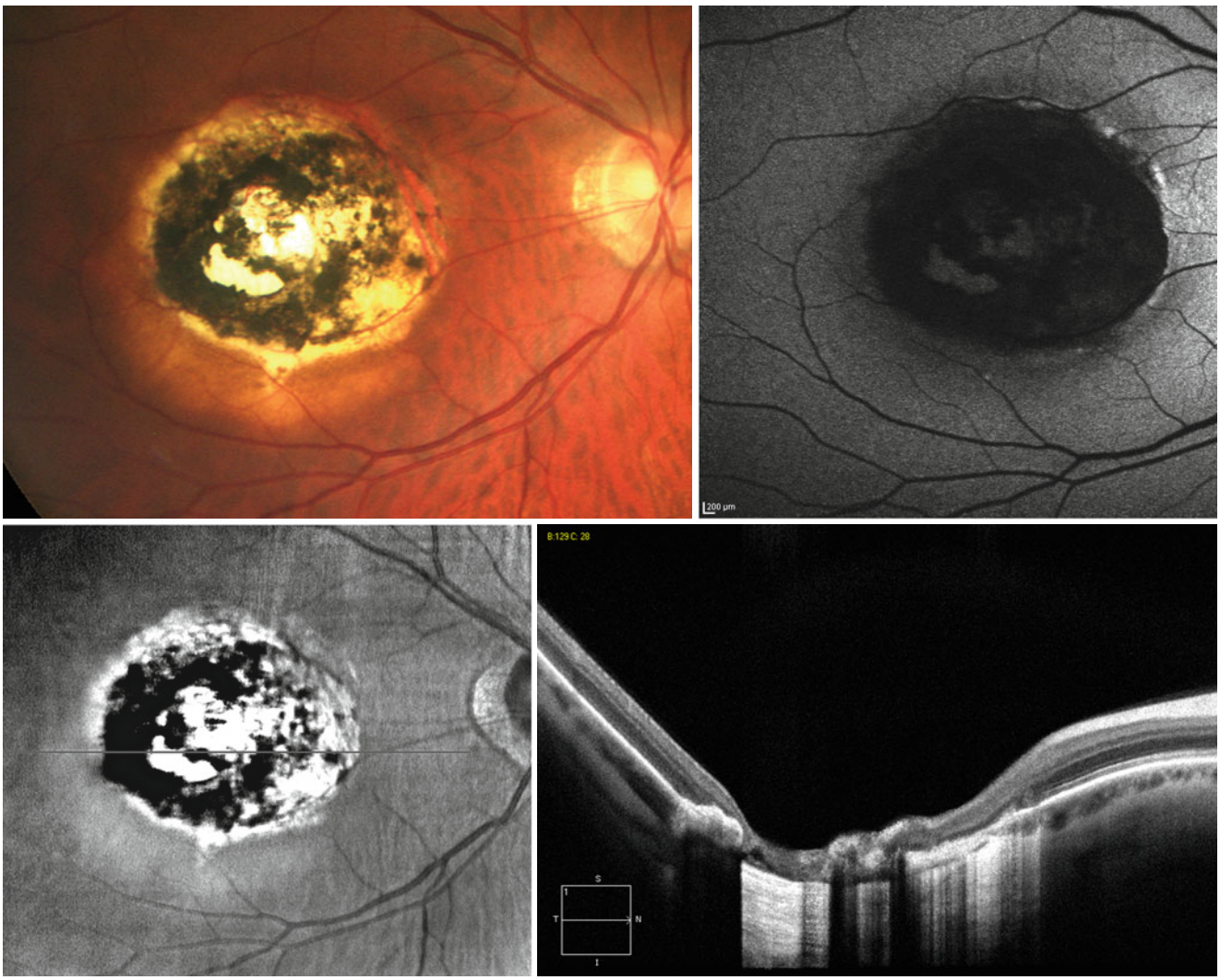


Fig. 8.16 Autofluorescence and OCT of a patient with NCMD. In autofluorescence, the coloboma remains dark. Hyperfluorescence of drusen-like deposits at the nasal margin of the lesion. OCT: Disappearance of the photoreceptors and of the RPE in the lesion and pigment hyperplasia at the temporal edge of the lesion

onset and is nonprogressive, and the finding of normal peripheral field and normal full-field ERG suggests that the retinal dysfunction is confined to the macular region.

The pattern ERG is usually normal in grade 1 and 2 diseases but abnormal where there is macular atrophy (grade 3). The full-field ERG is normal and the EOG is either normal or shows a mildly reduced Arden ratio.

Grade 3 disease may be confused with bilateral chorioretinal scarring associated with congenital toxoplasmosis, but the visual acuity is generally worse in the latter and examination of other family members will usually show other affected individuals in the former. A phenotype indistinguishable from NCMD has been reported in association with sensorineural deafness [14] and with congenital abnormalities of the hands and feet [62]. In both cases, the inheritance is autosomal dominant.

NCMD has been mapped to the chromosome 6q using linkage analysis in large families ([61]). The critical region overlaps the locus for bifocal dystrophy, another very rare developmental macular dystrophy [23] (Fig. 8.17). The causative gene has not yet been identified. Although most families show linkage to the 6q locus, two families with identical phenotype (MCDR3) have been mapped to chromosome 5q indicating that there is genetic heterogeneity in this disorder [35, 40, 55]. North Carolina macular dystrophy and deafness maps to chromosome 14q [14]; the causative genes have not yet been identified.

Summary for the Clinician

- Congenital stationary night blindness (CSNB) is a group of disorders characterised by defects in rod photoreceptor signal transmission.

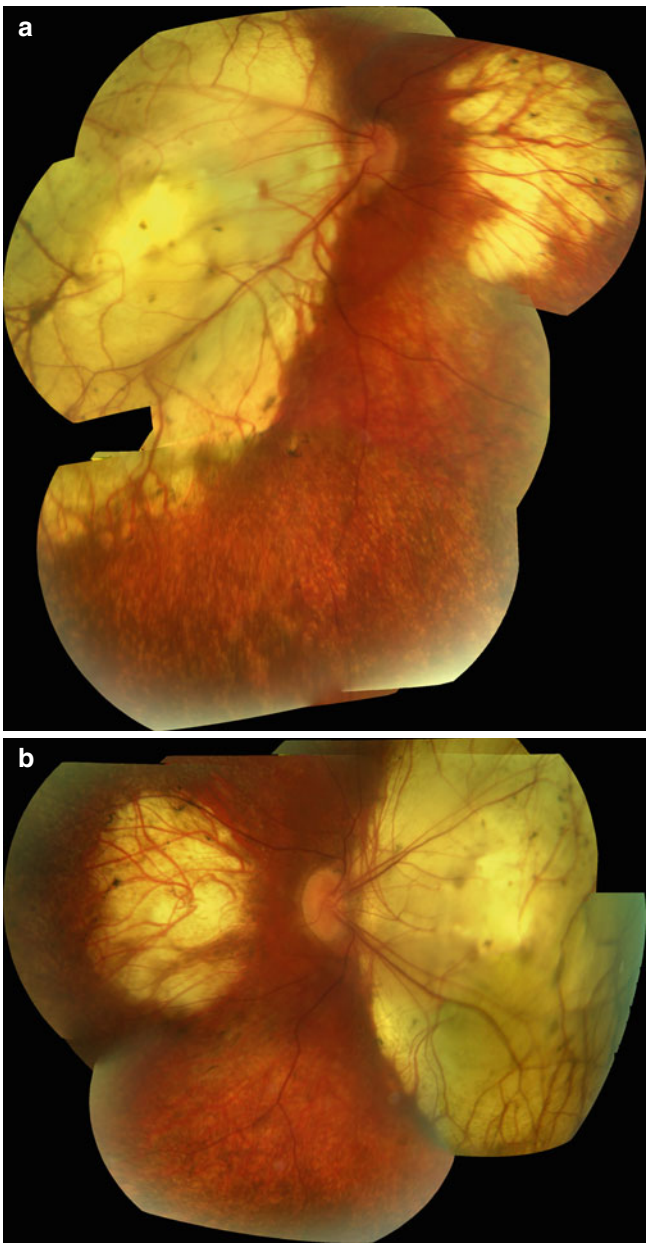


Fig. 8.17 Fundus photograph of right (**a**) and left (**b**) eyes of an affected individual from a family with progressive bifocal chorioretinal atrophy showing large areas of atrophy of retina, RPE and choriocapillaris at the macula and on the nasal side of the disc. There are mild peripheral pigmentary retinal changes more peripherally

- CSNB may be inherited as an X-linked, autosomal dominant or autosomal recessive trait.
- adCSNB patients have no nystagmus and normal visual acuity, visual fields and fundus. The ERG shows either an undetectable rod a-wave or a Schubert-Bornschein type. The genes identified to date are *RHO*, *GNAT1* and *PDE6B*.
- X-linked CSNB is associated with nystagmus. In the complete form, associated with mutations in the *NYX* gene, the rod-specific response is undetectable, whereas in the incomplete form, associated with mutation of *CACNA1F*, a rod-specific ERG is present with subnormal amplitudes.
- arCSNB may be complete or incomplete. Four genes (*GRM6*, *TRPM1*, *GPR179* and *LRIT3*) have been implicated in the complete form and two (*CAP4* and *CACNA2D4*) in the incomplete form.
- Patients with Duchenne muscular dystrophy (DMD) may have abnormal inner retinal responses on ERG but are asymptomatic.
- Oguchi disease is a rare autosomal recessive form of CSNB, typically presenting a golden discolouration of the fundus upon light exposure, which disappears after prolonged dark adaptation. Mutations in 2 genes (*GKR1* and *SAG*) have been described.
- Fundus albipunctatus is an autosomal recessive stationary disorder characterised by white dots in mid-periphery and perifoveal area. It should be distinguished from retinitis punctata albescens (RPA), which is a progressive retinal dystrophy, usually associated with greater ERG abnormalities than FA and usually with worse visual acuity. The two conditions can be distinguished by ERG testing.
- Achromatopsia (rod monochromatism) is a heterogeneous group of autosomal recessive generally stationary disorders characterised by the absence of functioning foveal cones. The presenting symptoms are nystagmus and photophobia.
- Complete achromatopsia is not always a stationary disorder and may lead to progressive foveal cone degeneration. Incomplete achromatopsia shows residual cone function. Mutations in 5 different genes have been identified in complete achromatopsia (*CNGA3*, *CNGB3*, *GNAT2*, *PDE6C*, *PDE6H*), which encode components of the cone phototransduction cascade. Mutations in *CNGA3* and *PDE6H* have been identified in incomplete achromatopsia.
- S-cone monochromatism is an X-linked disorder characterised by an absence of L- and M-sensitive cone function and normal rod and S-cone-sensitive cone function. Visual acuity is slightly better than in achromatopsia. It is associated with alterations affecting two genes encoding L and M photopigments in the cones.
- Oligocone trichromacy is a rare cone dysfunction with autosomal recessive inheritance. It is characterised by reduced vision from infancy, mild photophobia, normal fundus and visual fields and normal or mildly reduced colour discrimination.
- Bornholm disease is an X-linked-inherited disease characterised by high myopia, a characteristic colour vision disturbance (dichromacy) and evidence of abnormal cone responses on ERG. It is a nonprogressive disorder.
- North Carolina macular dystrophy is an uncommon autosomal dominant developmental macular dystrophy.

It shows a variable phenotype which has been divided into three grades: grade 1, small drusen-like deposits in the central macula; grade 2, confluent deposits; and grade 3, macular atrophy incorrectly termed 'macular coloboma'. Visual acuity is usually normal in grades 1 and 2, but reduced in grade 3. The disease is not progressive and the full-field ERG remains normal. Associations with sensorineural deafness and with congenital anomalies of hand and feet have been reported. The causative gene has not yet been identified.

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Erratum to:

Chapter 9: Bernard Puech and Jean-Jacques De Laey, *Retinitis Pigmentosa and Allied Disorders*

Figure 9.2 is replaced by a new figure.

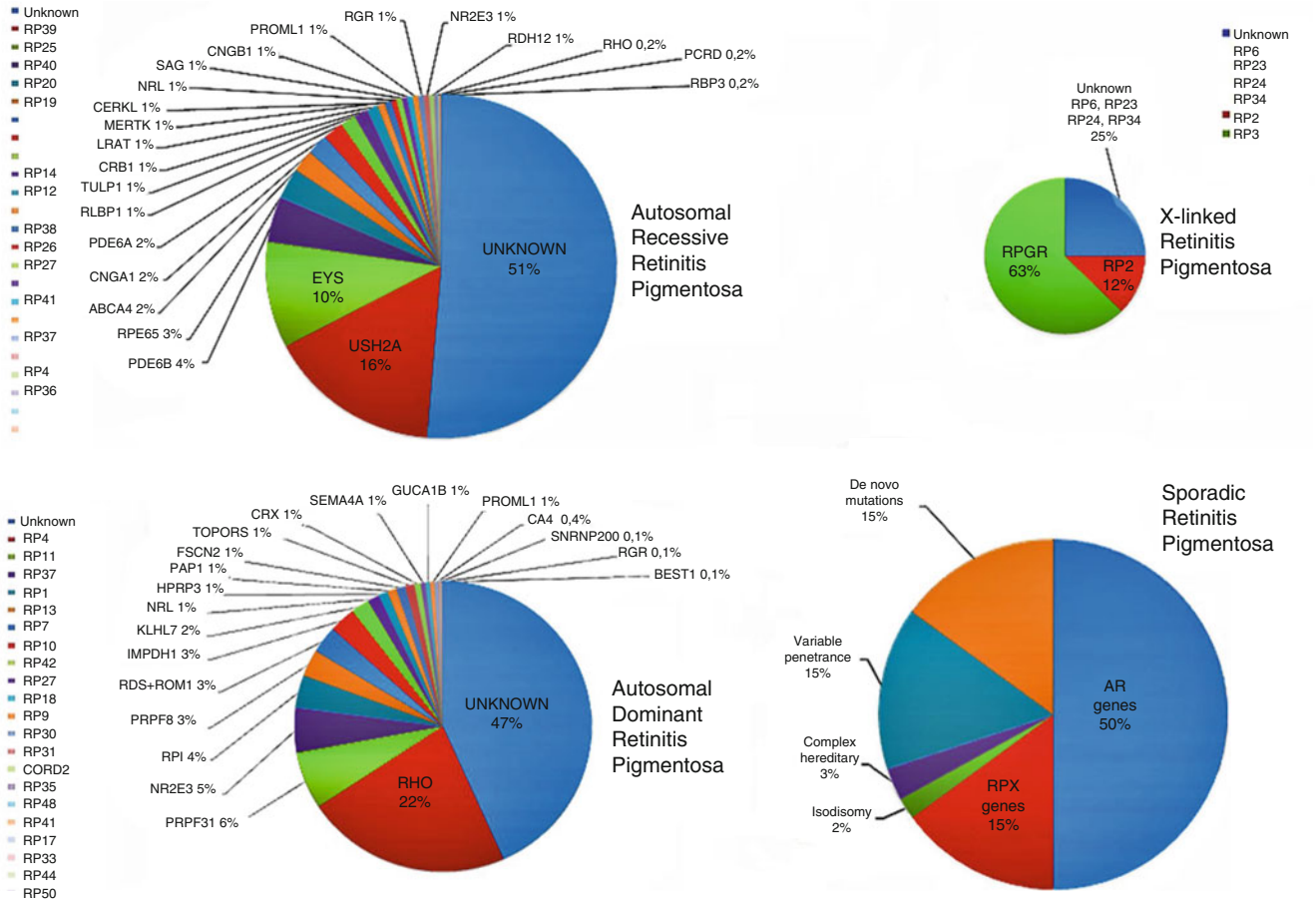

Fig. 9.2 Distribution of the genes in non-syndromic retinitis pigmentosa (Hamel 2010, personal communication). Genes with a prevalence of 1 % or less are either genes which have been recently discovered or of which the prevalence has not yet been studied. The Usher 2A gene may express RP without deafness, and possibly other more exceptional Usher 2 genes may provoke non-syndromic RP. The columns to the left indicate the colour code for the genes in the charts

The online version of the original book can be found at:
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