Retinitis Pigmentosa

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Introduction

Retinitis pigmentosa (RP) is a heterogeneous group of disorders characterized by the degeneration of photoreceptor cells and the retinal pigment epithelium (RPE), leading to profound vision loss or blindness. The prevalence of RP is approximately one in every 4000 individuals worldwide (Hartong et al. 2006). In 1836, Bernhard von Langenbeck used the term *melanosis retinae* to describe the pigmented condition of the retina during a postmortem examination (Langenbeck 1836). Later, in 1838, Friedrich von Ammon published drawings of widespread pigmentation based on pathological studies of the eye but did not correlate the condition to night blindness (Ammon 1838) (Fig. 1.1). After Helmholtz invented the ophthalmoscope in 1851, van Trigt in 1853 and Ruete in 1854 identified this disease in living subjects and linked it to visual symptoms (van Trigt 1853; Ruete 1855) (Fig. 1.2), which was ultimately named *retinitis pigmentosa* in 1857 by Franciscus Donders (Donders 1857). Even though there are no inflammatory processes in RP, the same name is still used today. To date, over a hundred years later, several treatment options have been proposed for patients with RP such as gene therapy, stem cells, and retinal prosthesis. However, long-term outcomes still need further investigation.

Fig. 1.1 A pathology illustration of retina pigmentation, recreated from the original work by Friedrich von Ammon in 1838 (smaller image). At the time, the condition was not thought to be linked to the clinical symptom of night blindness

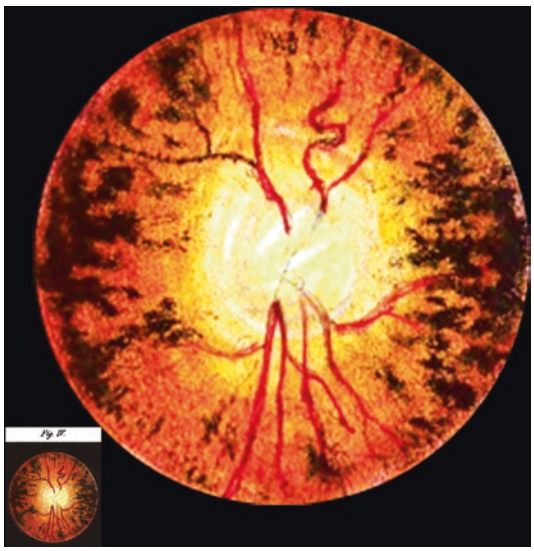

Fig. 1.2 Recreated image of the first illustration of RP under an ophthalmoscope by von Trigt where he described the pigmentation on the upper left blood vessel in 1853 (lower left image)

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Genetics and Inheritance Patterns

RP can be inherited as an autosomal-dominant (AD) (30–40%), autosomal-recessive (AR) (50–60%), X-linked (XL) (5–15%), or mitochondrial trait (Hartong et al. 2006). It is a highly heterogeneous disorder with more than 50 culprit genes reported (RetNet 2017), and with various phenotypes and variants. One genotype can lead to different phenotypes, and a certain phenotype can be related to several different gene mutations.

RP can be divided into two main categories: *Non-syndromic RP,* where only the eyes are affected, and *syndromic RP,* where other neurosensory or systemic organs are also involved in addition to the eyes.

Non-syndromic Retinitis Pigmentosa

Typical Retinitis Pigmentosa

The initial presentation of RP is most commonly night blindness, which begins before adolescence. Peripheral vision usually starts to be affected from young adulthood, with the visual field gradually constricting as the disease progresses, resulting in central tunnel vision. Depending on the gene involved, some patients may completely lose their vision during their 60s (Hartong et al. 2006).

The classic triad of the fundus's appearance in RP consists of retinal blood vessel attenuation, waxy pallor optic disc, and retinal pigment epithelium (RPE) cell alteration, resulting in bone-spicule intraretinal hyperpigmentation, especially in the mid-peripheral of the retina (Fig. 1.3). It is often a bilateral disease with a highly symmetrical fundus appearance (Fig. 1.4). However, despite the remarkable fundus features, central visual acuity may not be affected due to the preservation of the central retinal function. Several examinations and imaging modalities can help determine and document the severity and progression of RP.

Clinical Assessment

Fundus photography is a basic documentation modality. However, this technique can only capture a limited view of the fundus with one film. Recently, the development of ultrawide field retinal imaging technique has allowed a more convenient way to record a wider view of the fundus without the need of montage. Therefore, it is especially useful in RP (Fig. 1.5).

The Goldmann perimetry is the main functional assessment tool for monitoring RP severity and progression. The classic pattern of visual field (VF) deterioration in RP is concentric VF loss (Fig. 1.6). There are also different patterns, including mid-peripheral arcuate or ring scotoma (Grover et al. 1998) (Fig.1.7). However, all patients eventually end up with a residual central island and finally general depression of the VFs.

The full-field electroretinogram (ERG) demonstrates a reduced rod and cone response amplitude, and a delayed implicit time in RP (Fig. 1.8). ERG aids differential diagnosis and provides objective measurements of visual function and

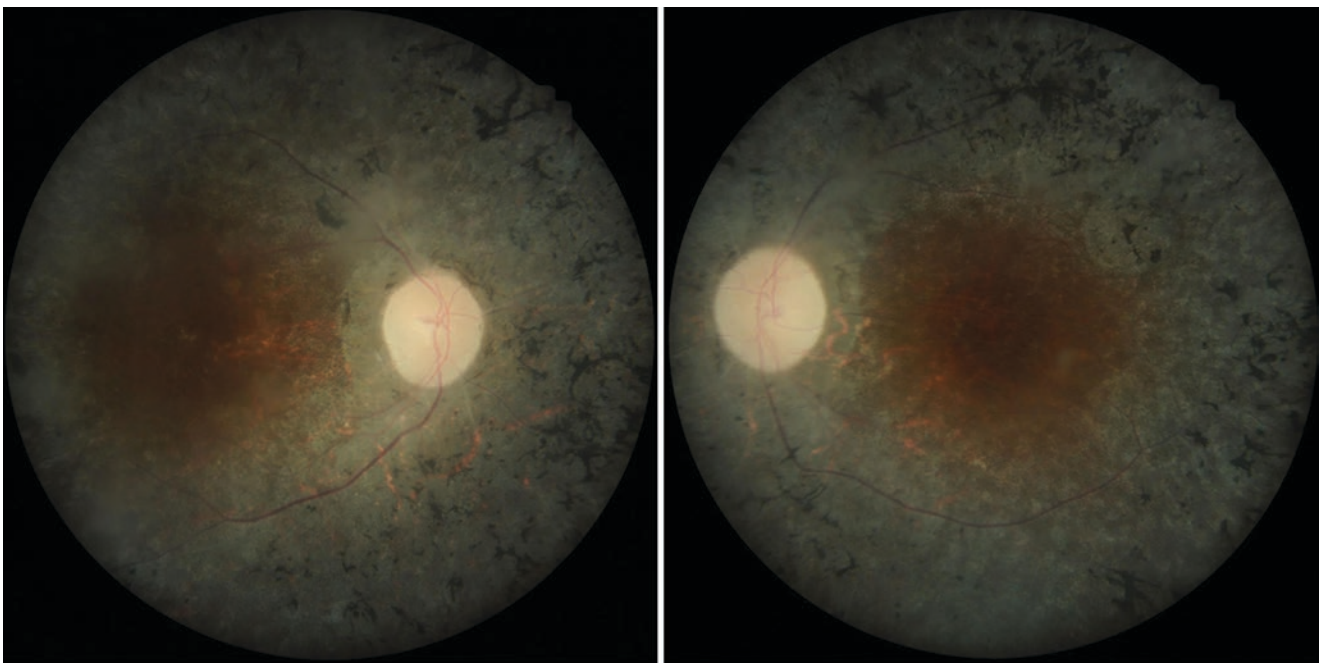


Fig. 1.3 The classic triad of retinitis pigmentosa fundus: waxy pallor disc, attenuated vessels, and mid-peripheral bone-spicule pigmentation. The macula is not yet involved and appears more orange in color

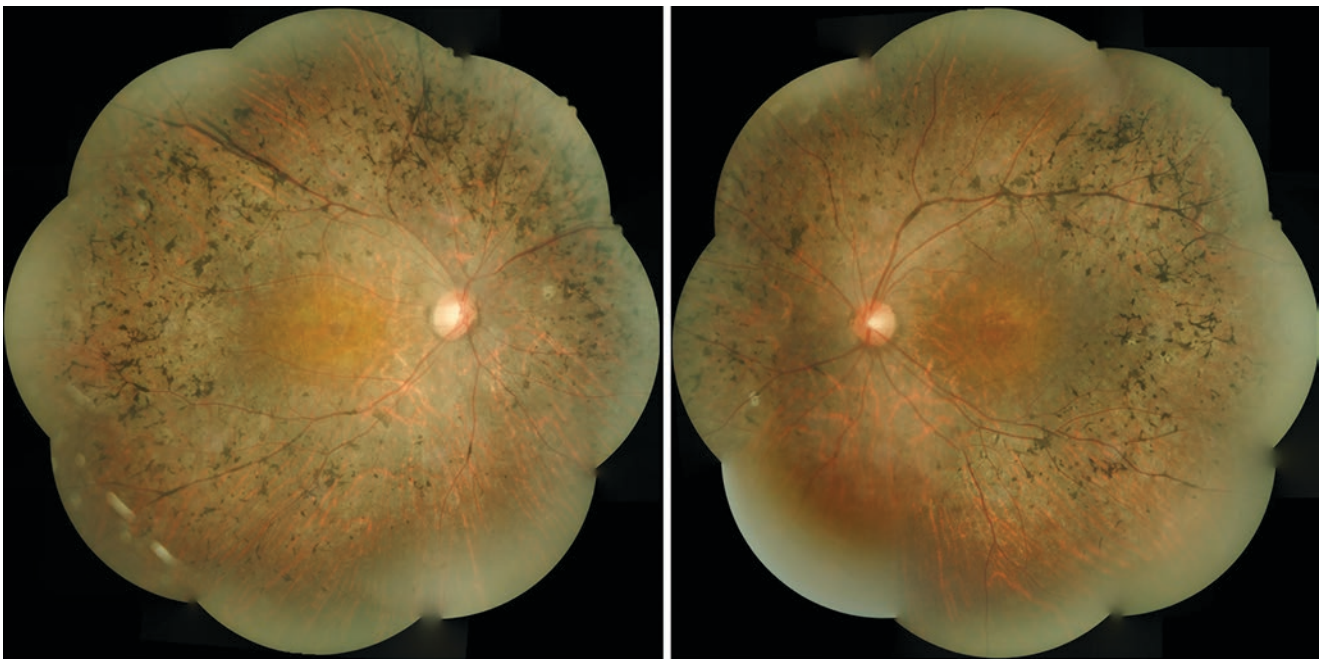


Fig. 1.4 Color fundus photograph showing attenuated retinal vessels and bone-spicule hyperpigmentation in the mid-peripheral of the retina. Note the symmetric fundus appearance between the two eyes

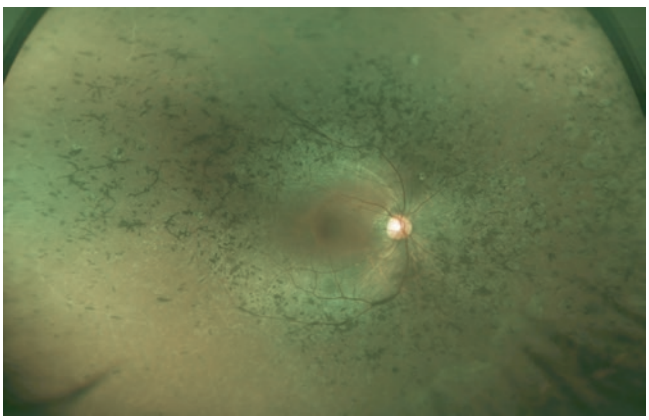


Fig. 1.5 Ultra-wide field retinal image of a patient with retinitis pigmentosa. The image clearly demonstrates the dense accumulation of hyperpigmentation, mainly distributed in the mid-peripheral of the retina. Note the round and patchy atrophic areas of the retina, which is more obvious with fundus autofluorescence imaging (Fig. 1.10). The linear shadow in the inferior were artifacts caused by eyelashes

correlates well with the VF study (Iannaccone et al. 1995; Sandberg et al. 1996).

Optical coherence tomography (OCT) provides structural measurements of the posterior pole. The transitional zone between the reserved central retina and the peripheral abnormal retina show outer retinal structural changes in the OCT (Jacobson et al. 2009; Hood et al. 2011) (Fig. 1.9). Functional studies have found that these structural changes include the thinning of the outer nuclear layer (ONL) and disruption of the ellipsoid zone (EZ) and external limiting membrane (ELM) (Witkin et al. 2006; Sandberg et al. 2005; Matsuo and Morimoto 2007; Jacobson et al. 2010; Wolsley et al. 2009).

Fundus autofluorescence (FAF) imaging is also a useful and non-invasive assessment tool. Excessive accumulation of lipofuscin in RPE cells is related to photoreceptor cell degeneration and can lead to hyper-autofluorescence (AF) (Katz et al. 1986). A hyper-AF ring surrounding the macula was reported as being present in 59% of RP patients (Murakami et al. 2008) (Figs. 1.10 and 1.11). The ring may serve as a precursor of apoptosis of the RPE cells and indicate the transition area between reserved healthy central retina and the degenerated peripheral retina (Lenassi et al. 2012; Greenstein et al. 2012). The hyper-AF ring is related to structural changes of the retina on OCT (Greenstein et al. 2012; Lima et al. 2009), and the diameter of the ring is well correlated with the preserved EZ area (Wakabayashi et al. 2010). The ring diameter is also correlated with functional studies such as perimetry, pattern ERG, and multifocal ERG (Ogura et al. 2014; Oishi et al. 2013; Robson et al. 2003; Robson et al. 2006), representing the size and function of the reserved retina and indicates disease severity. FAF imaging is non-invasive and offers an objective structural parameter, which is ideal for the documentation of progression (Lima et al. 2012; Robson et al. 2006). Together with OCT, it has been proposed that FAF should be performed upon RP patients annually as an assessment and follow-up tool (Sujirakul et al. 2015) (Fig. 1.12).

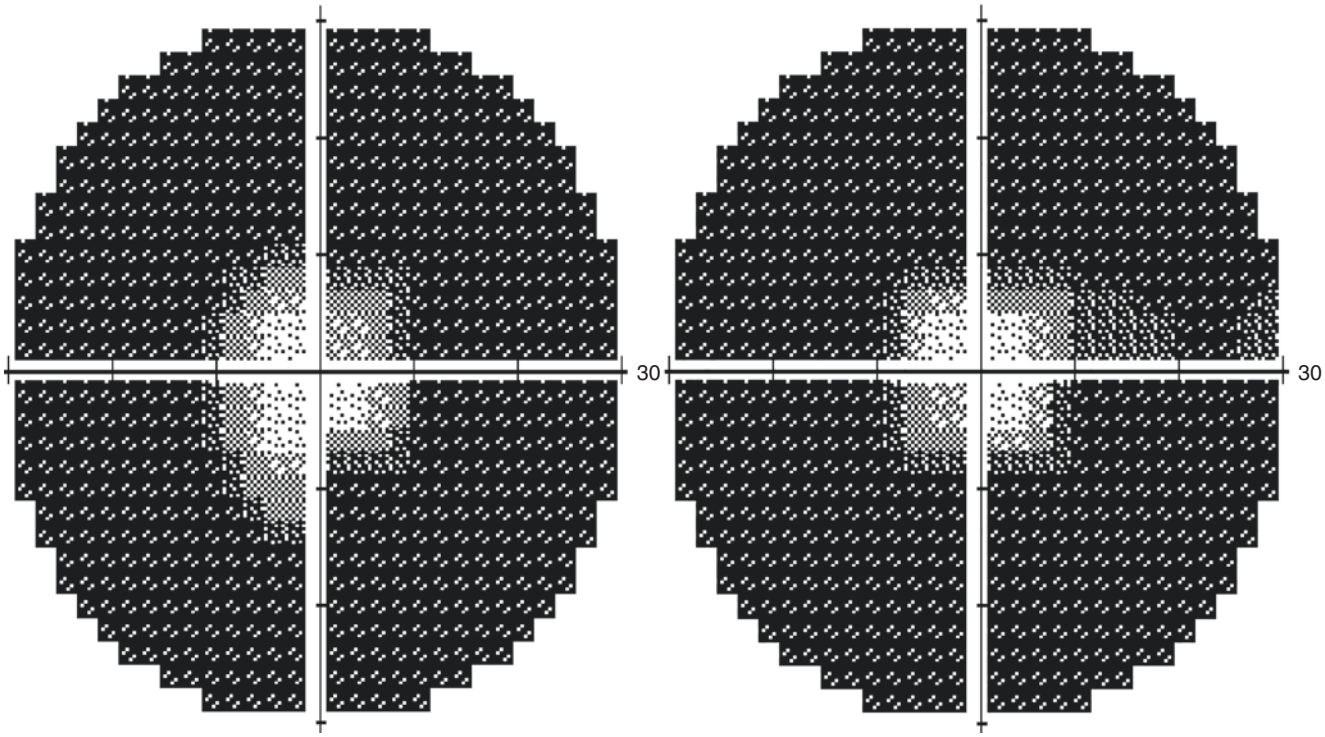


Fig. 1.6 Constricted visual fields in a retinitis pigmentosa patient. The two eyes are symmetric with the macula spared

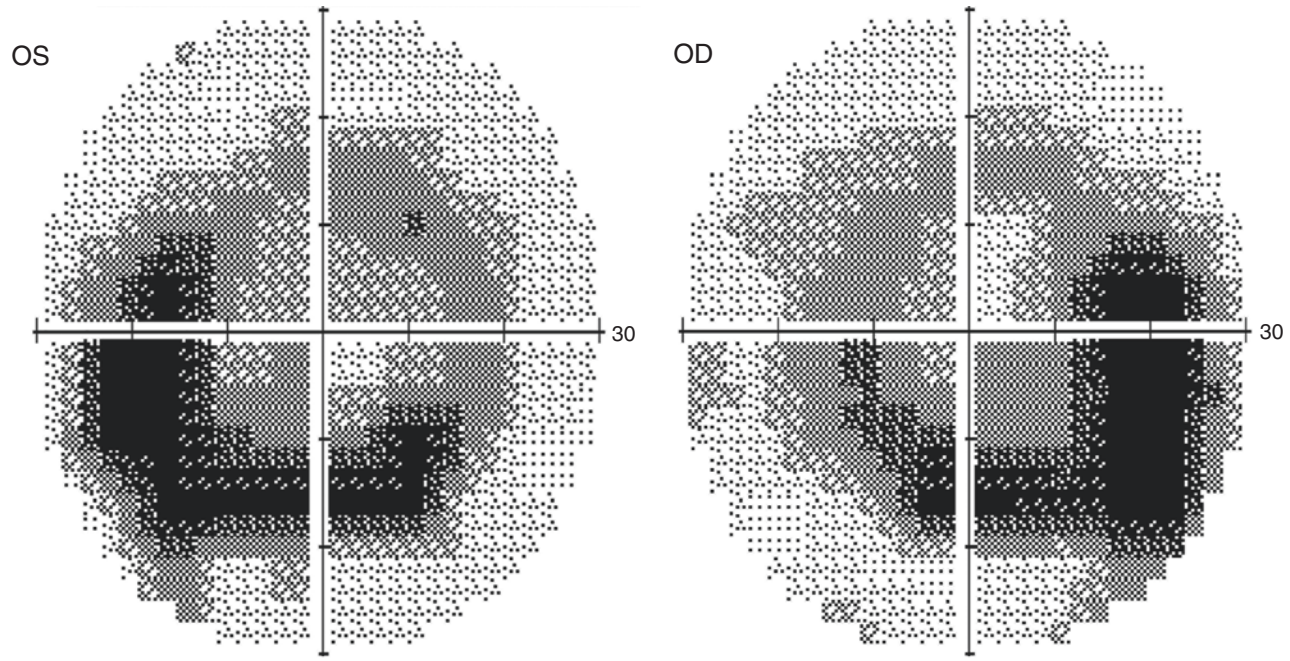
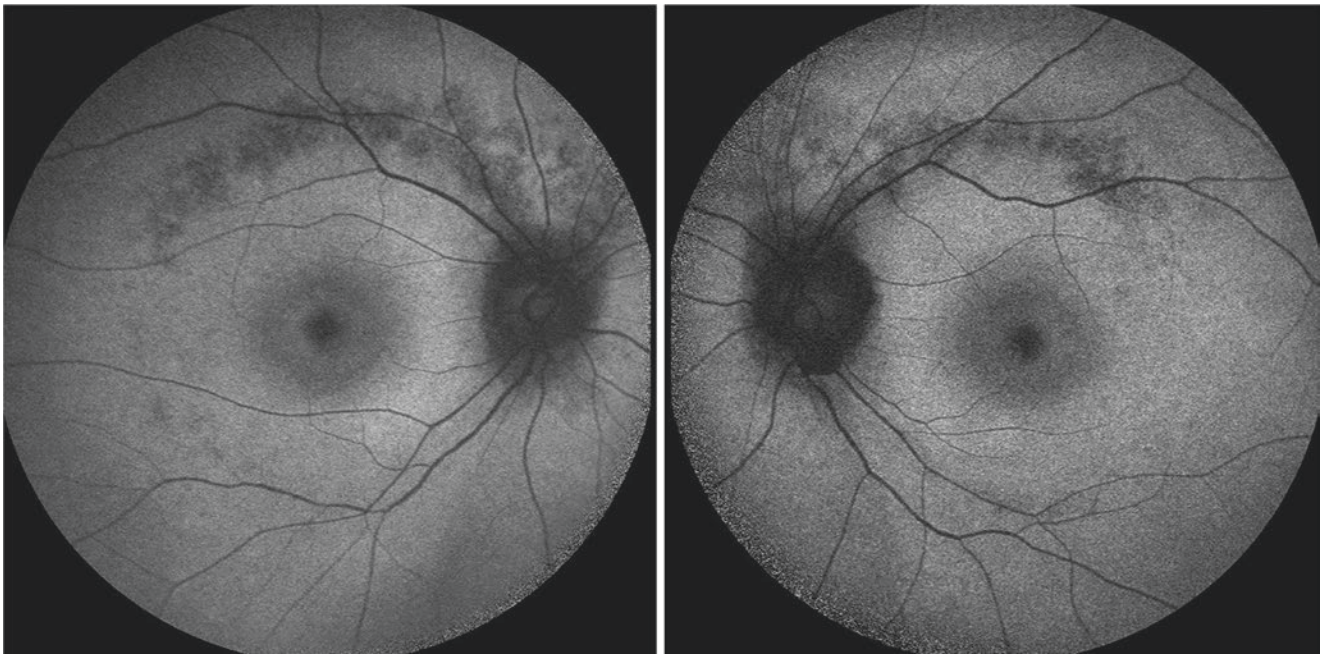


Fig. 1.7 Perifoveal arcuate scotoma is shown in the visual field exam. The arcuate scotoma corresponds well to the hypo-autofluorescent area in the fundus autofluorescence study



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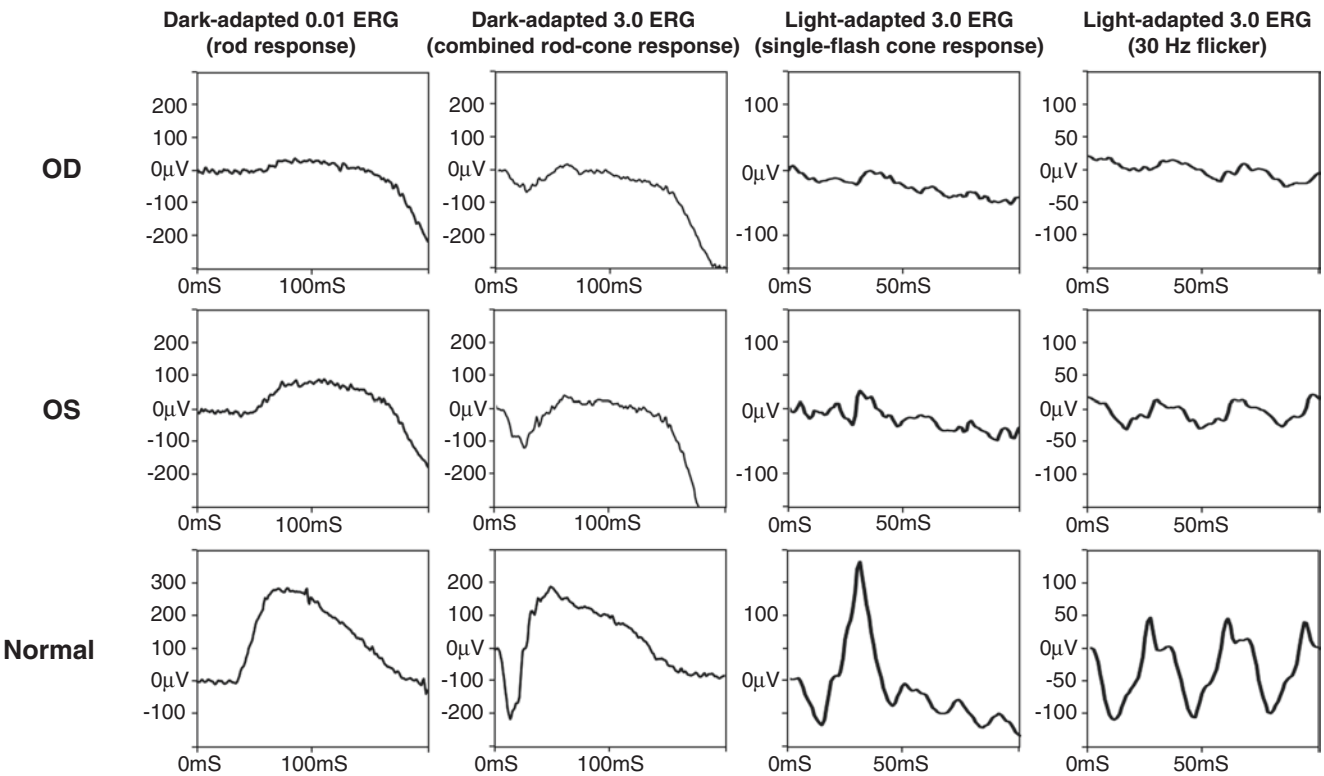


Fig. 1.8 Electroretinogram (ERG) of a patient with retinitis pigmentosa (RP) (upper two rows) compared to a normal subject (lower row). The full-field ERG shows a decrease in rod and cone amplitude in rod response and combined rod-cone response, as well as a delayed implicit time. The single-flash cone response also shows a decreased amplitude. In more advanced RP cases, the ERG is extinguished

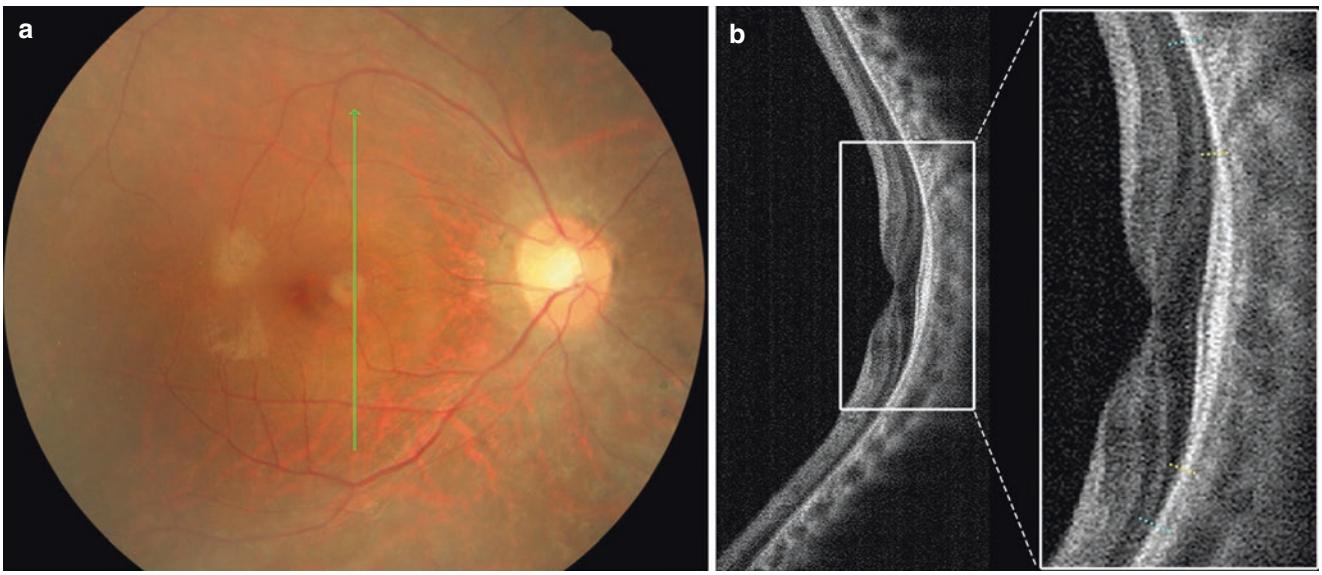


Fig. 1.9 Optical coherence tomography (OCT) images showing structural changes in retinitis pigmentosa. (**a**) The retinal alterations are not obvious in the fundus photograph. The green line indicates the orientation of the OCT. (**b**) The fovea was preserved with normal retinal lamination. The enlarged image demonstrates the transition from a normal retinal lamination in the fovea to a peripheral degenerated retina. These changes include the loss of the external limiting membrane (ELM) and the ellipsoid zone, and the thinning of the outer nuclear layer (ONL). The yellow dotted lines indicate the termination point of the ELM, and the blue dotted lines indicate the termination point of the ONL

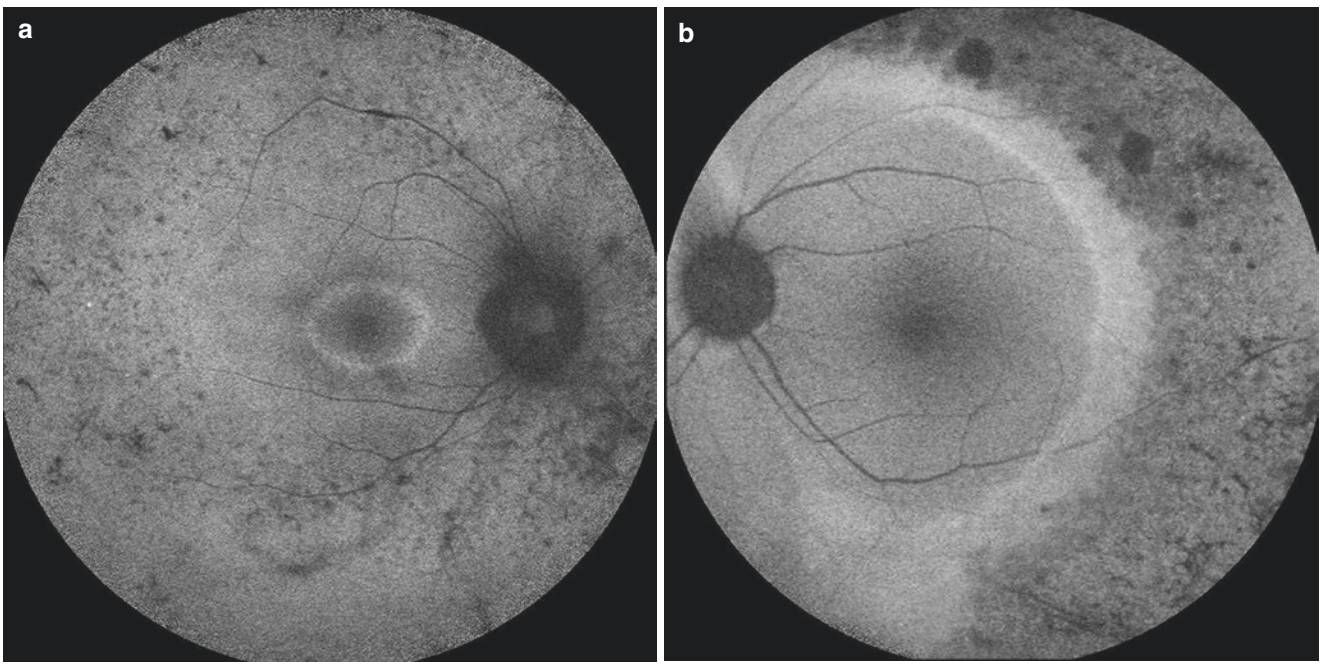
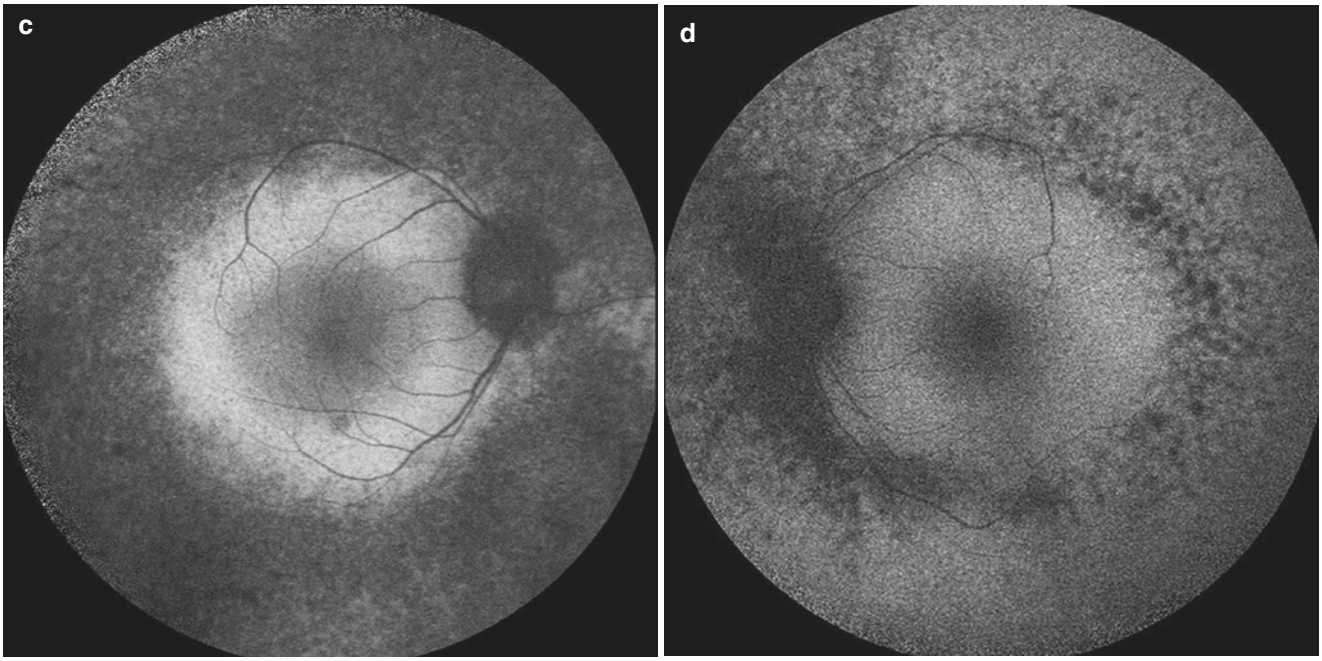


Fig. 1.10 Fundus autofluorescence images displaying variations of hyper-autofluorescent (AF) rings. The diameter of the hyper-AF ring correlated with the size of the preserved retinal structures and also the function of the retina (**a**, **b**). The transitional zone itself (i.e., the hyper-AF area between the inner and outer border of the ring) can be a thin (**a**, **b**) or wide ring (**c**). Some patients have no apparent ring in FAF images (**d**)



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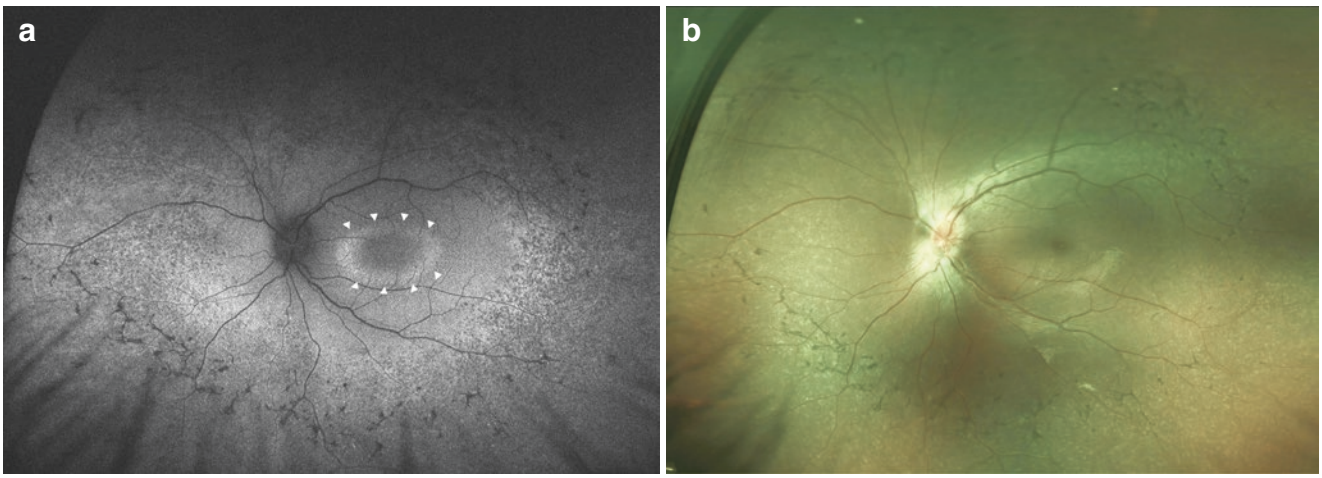


Fig. 1.11 Hyper-autofluorescent ring in retinitis pigmentosa. (**a**) An ultra-wide field fundus autofluorescence (FAF) image showing a hyper-autofluorescent ring surrounding the fovea (white arrowheads). Hyperpigmentation and retinal round or patchy atrophic areas are easily observed by the FAF study. (**b**) The corresponding ultra-wide field color fundus photograph

Macular Abnormalities in Retinitis Pigmentosa

Compared to the general population, macular abnormalities are more frequent in patients with RP (Testa et al. 2014). These abnormalities include cystoid macular edema (CME), epiretinal membrane (ERM), macular hole, macular atrophy, and vitreoretinal interface disorders. An OCT examination is useful for detecting these changes in the posterior pole, and functional studies such as microperimetry offer objective measurements (Lupo et al. 2011; Battu et al. 2015).

CME could compromise the central vision in RP patients earlier in the disease course. CME was reported to be present in approximately 10–50% of RP cases (Strong et al. 2017). Clinical diagnosis of CME is challenging by sole slit-lamp biomicroscopy. In fluorescein angiography (FA) and FAF, CME demonstrates a perifoveal petalloid pattern of hyper-fluorescence and hyper-AF, respectively (McBain et al. 2008) (Fig. 1.13). Various treatment methods have been used. Topical dorzolamide and oral carbonic anhydrase inhibitors (acetazolamide) have been used most widely, but

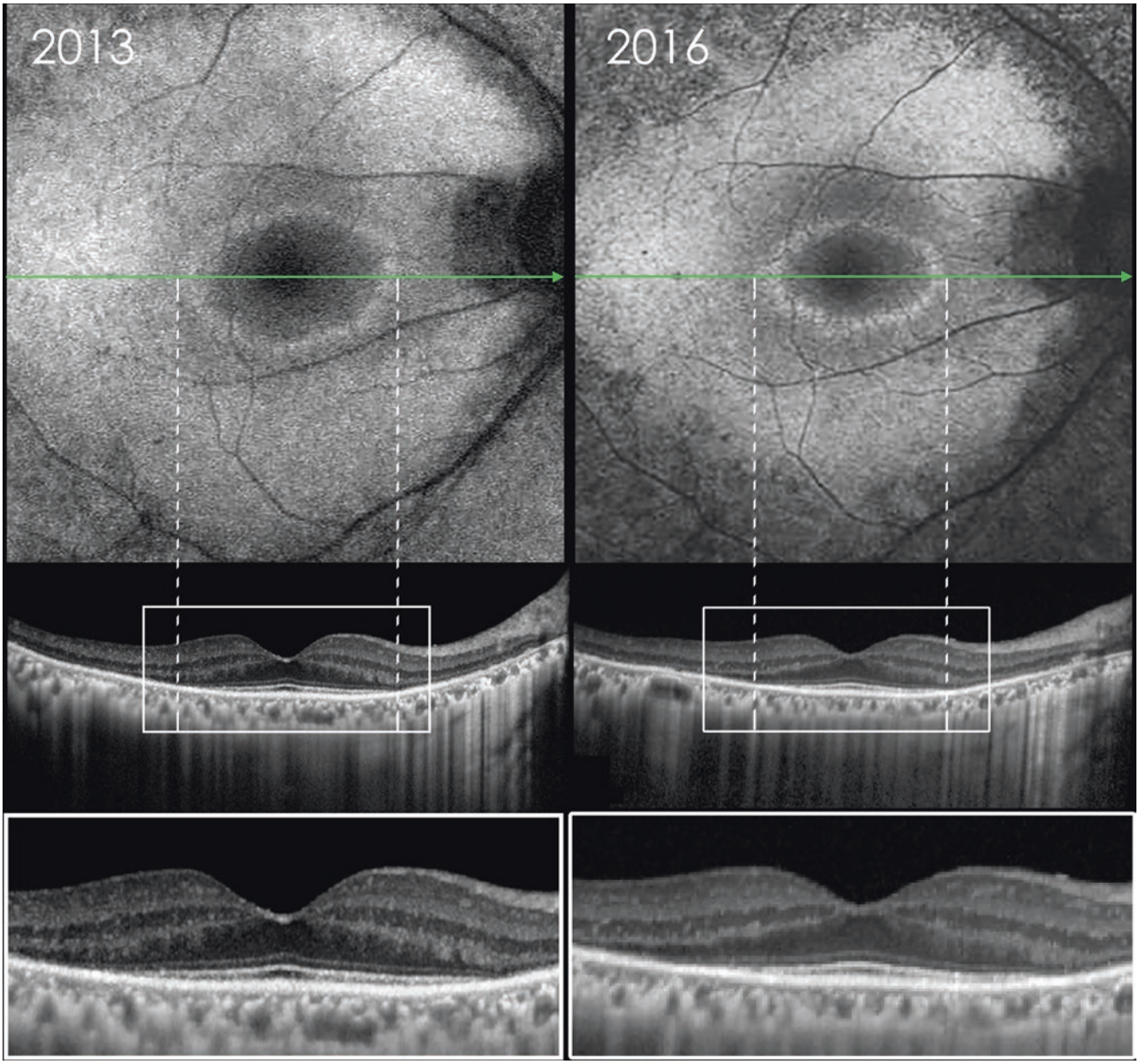


Fig. 1.12 Progression of fundus autofluorescence and optical coherence tomography (OCT) of the same patient 3 years apart. Note the constriction of the ring and the marching of the atrophic areas of retina toward the fovea. The hyper-autofluorescent ring corresponds to the structural alterations on the OCT (white dashed line). The enlarged OCT image showing the disruption of the ellipsoid zone and the external limiting membrane and thinning of the outer nuclear layer. The green lines indicate the orientation of the OCT

the response has been inconsistent. Other options of treating CME have been reported, which include intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) agents, steroids, and laser photocoagulation (Huckfeldt and Comander 2017).

ERM and macular hole can also interfere with central vision (Figs. 1.14 and 1.15). The prevalence of ERM or vitreomacular traction syndrome was 1.4–20.3%, and 0.5–10% for macular hole (Ikeda et al. 2015). Surgical outcomes for these conditions have been reported, but visual function improvement was limited (Hagiwara et al. 2011; Ikeda et al. 2015).

Macular atrophy and thinning are not rare in RP and have been reported in over 45% of patients (Sayman Muslubas et al. 2017; Thobani et al. 2011; Flynn et al. 2001). Different patterns of macular atrophy can be observed, including bull's eye, cystic, or geographic atrophy (Flynn et al. 2001) (Figs. 1.16, 1.17, and 1.18). Structural assessment by OCT demonstrates a reduction of foveal and ONL thickness, as well as the disruption of the ELM and the EZ (Fig. 1.18).

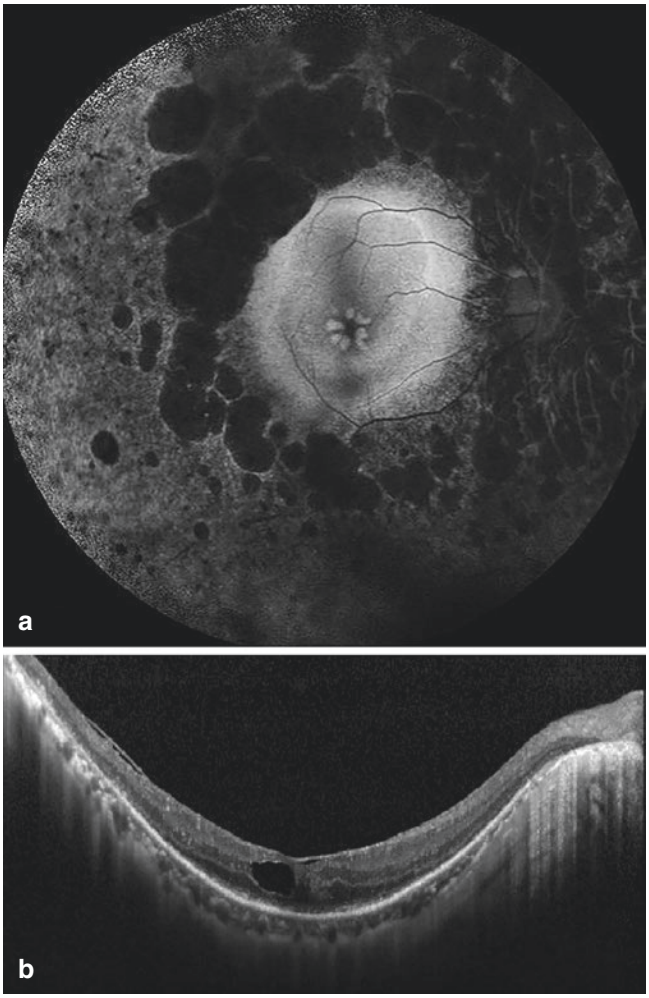


Fig. 1.13 Cystoid macular edema (CME) imaged by fundus autofluorescence (AF). (**a**) The perifoveal petalloid hyper-AF is a characteristic of CME. There are also features of retinitis pigmentosa, including a macula hyper-AF ring and mid-peripheral patchy atrophic areas, which are well demonstrated by hypo-AF. (**b**) The corresponding optical coherence tomography image reveals the thickening and accumulation of cystoid fluid in the fovea

Functional studies such as visual acuity and microperimetry correlated with the above structural alterations (Battu et al. 2015; Aizawa et al. 2009).

A few cases of central serous chorioretinopathy (CSC) have been reported in RP (Dorenboim et al. 2004; Meunier et al. 2008). Fluorescein angiography (FA) study has demonstrated the characteristics of typical CSC including a hyperfluorescent smoke-stack leaking point in the macular area and pooling of fluorescein dye in the subretinal space (Fig. 1.19). Bone-spicule hyperpigmentation blocks fluorescence in both FA and indocyanine green studies. RPE atrophic areas result in window defects in the mid-periphery.

A few other macular abnormalities can be seen in combination with RP, such as macular retinoschisis and posterior staphyloma (Figs. 1.20 and 1.21). These conditions are commonly related to pathological myopia (Steidl and Pruett 1997; Benhamou et al. 2002) but are rarely associated with RP in the literature.

Optic Disc Drusen in Retinitis Pigmentosa

The largest series to date showed that the incidence of nerve fiber layer drusen involving the optic disc or parapapillary regions in RP was approximately 10% (Grover et al. 1997), which is higher than the incidence of 0.34–2.4% in the general population (Auw-Haedrich et al. 2002). In a specific subgroup of RP with preserved para-arteriolar RPE, the incidence was even higher (39%) (van den Born et al. 1994). Optic disc drusen (ODD) was also found in some syndromic RP such as Usher syndrome and nanophthalmos-retinitis pigmentosa-foveoschisis-ODD syndrome (Edwards et al. 1996; Ayala-Ramirez et al. 2006) and was related to mutations in the membrane-type frizzled-related protein (*MFRP*) gene and the crumbs homolog 1 (*CRB1*) gene (Crespi et al. 2008; Paun et al. 2012).

Differentiating ODD from papilledema via funduscopic examination can be difficult, because both situations appear as swollen optic discs. B-scan echography can readily detect ODD, but only if the drusen become calcified. On FAF imaging, if the ODD is superficially located, it appears as a marked hyper-AF spot in the optic disc (Fig. 1.22). On FA imaging, ODD displays staining without leakage, whereas true papilledema shows leakage in the early or late phases (Chang and Pineles 2016).

Other Abnormalities in Retinitis Pigmentosa

Although rare, retinal exudation, retinal hemorrhage, telangiectasia, retinal angioma, and exudative retinal detachment can also be found in RP. These retinal changes have a resemblance with Coats' disease and are referred to as *Coats-like RP* (see Coats-like Retinitis Pigmentosa). The condition is related to the *CRB1* gene mutation (de Hollander et al. 2001; Bujakowska et al. 2012) but has been also reported in Usher syndrome and other RP variants (Fig. 1.23) (Murthy and Honavar 2009; Kiratli and Ozturkmen 2004; Osman et al. 2007). Retinal angioma is a secondary vasoproliferative tumor caused by benign vascular and glia proliferations. It is usually small, remains stable, and requires no treatment.

Differential Diagnosis

Many retinopathies with pigmentary changes can mimic RP and lead to misdiagnosis or diagnostic confusion. We should be especially aware of the three treatable RP-like conditions: abetalipoproteinemia (Bassen–Kornzweig syndrome), phytanic acid oxidase deficiency (Refsum disease), and familial isolated vitamin E deficiency (Grant and Berson 2001). Early diagnosis and treatment of these abnormalities could reverse the disease's impact on vision.

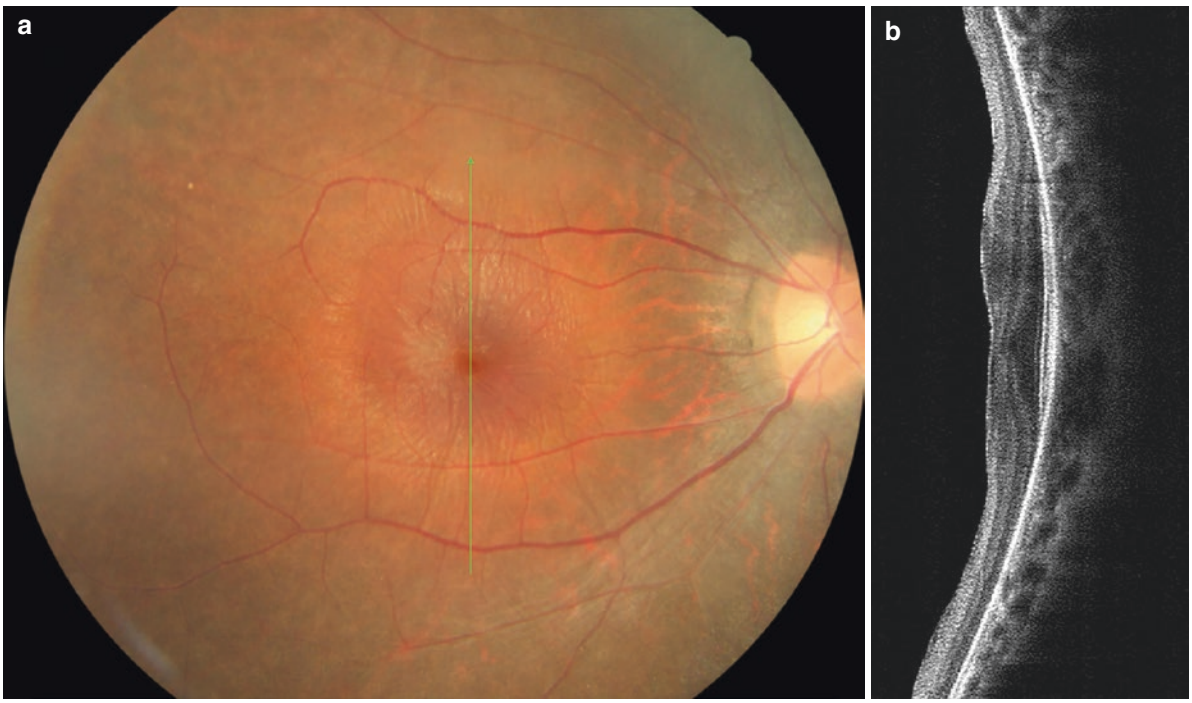


Fig. 1.14 Retinitis pigmentosa with epiretinal membrane (ERM). (**a**) The color fundus photography shows puckering of the macula. There are some atrophic areas outside the macular area, but the typical pigmentary changes in the mid-peripheral retina are not well demonstrated in this picture. The more recent technique of ultra-wide field retinal imaging can more readily document changes outside the posterior pole (Fig. 1.5). The green line indicates the orientation of the OCT. (**b**) An optical coherence tomography examination was used to detect macular changes, revealing a thin whitish epiretinal membrane

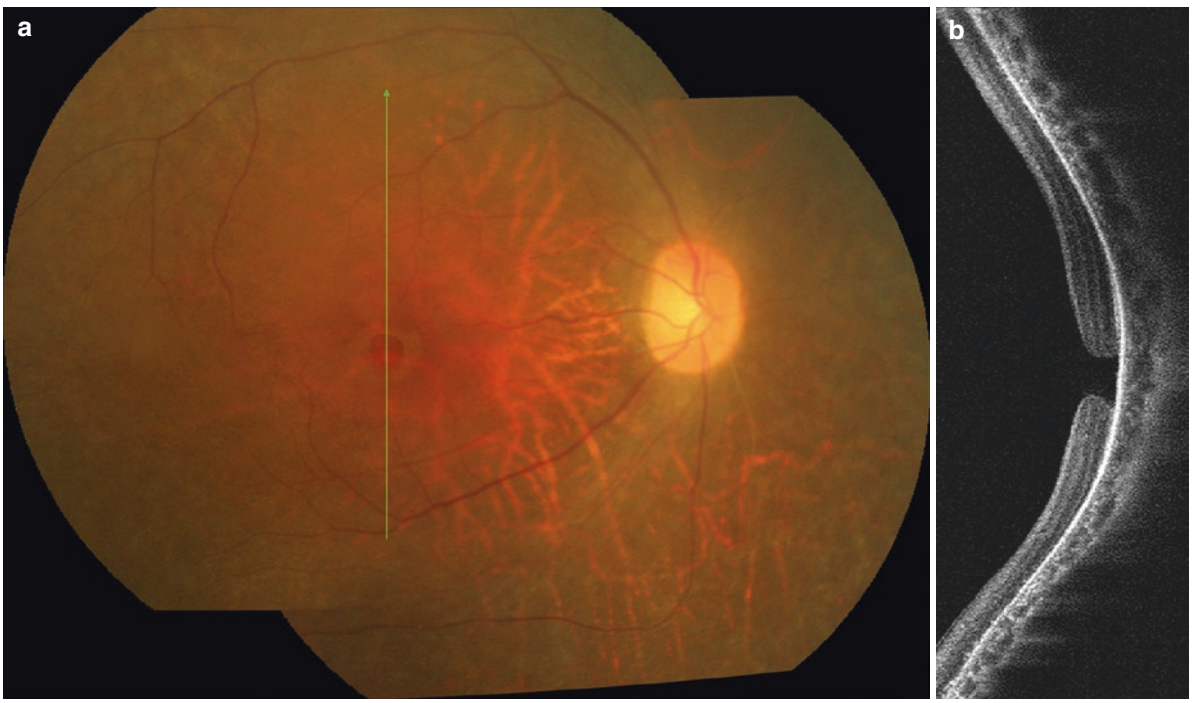


Fig. 1.15 Usher syndrome with macular hole. (**a**) A middle-aged woman had attenuated retinal vessels, mid-peripheral hyperpigmentation (not visible on this posterior pole picture), macular hole, and hearing impairment. The green line indicates the orientation of the OCT. (**b**) Optical coherence tomography image shows a full-thickness macular hole formation. Her older brother had similar fundus appearance except for the macular hole and had hearing problems. Their parents were first cousins without similar ocular or hearing abnormalities. Based on the symptoms and family history, the impression was Usher Syndrome with macular hole formation

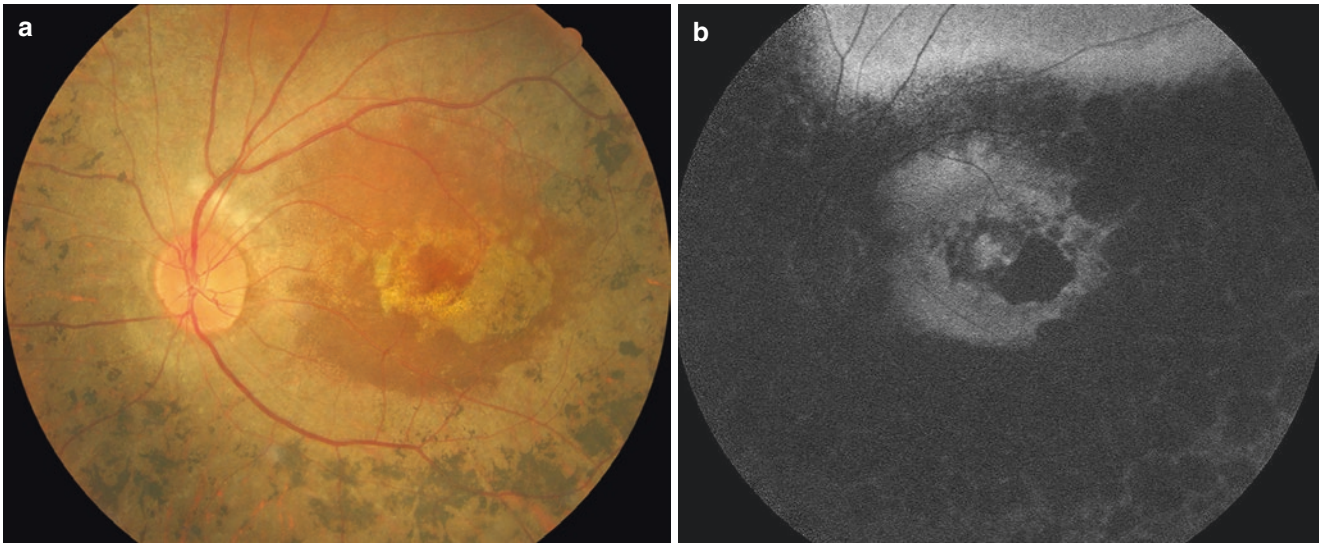


Fig. 1.16 "Bull's eye" macular atrophy in retinitis pigmentosa (RP). There are typical changes of RP in the mid-periphery (**a**) with the superior sector spared. (**b**) The macular atrophy is apparent with a remaining perifoveal ring and a foveal island, forming a "bull's eye" configuration

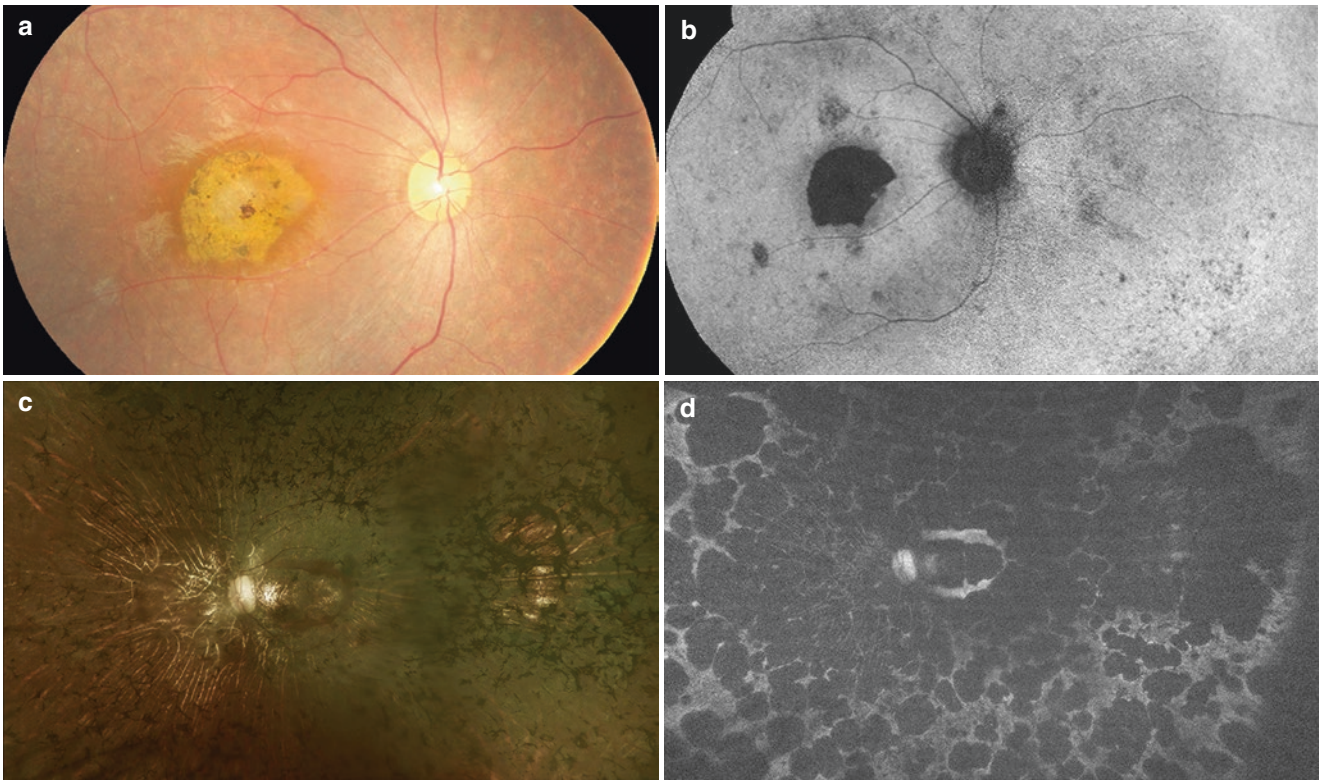


Fig. 1.17 Geographic macular atrophy in retinitis pigmentosa. The well-demarcated macular atrophic area is seen in the fundus photos (**a**, **c**) and is more apparent in the fundus autofluorescence images (**b**, **d**). The fovea was affected

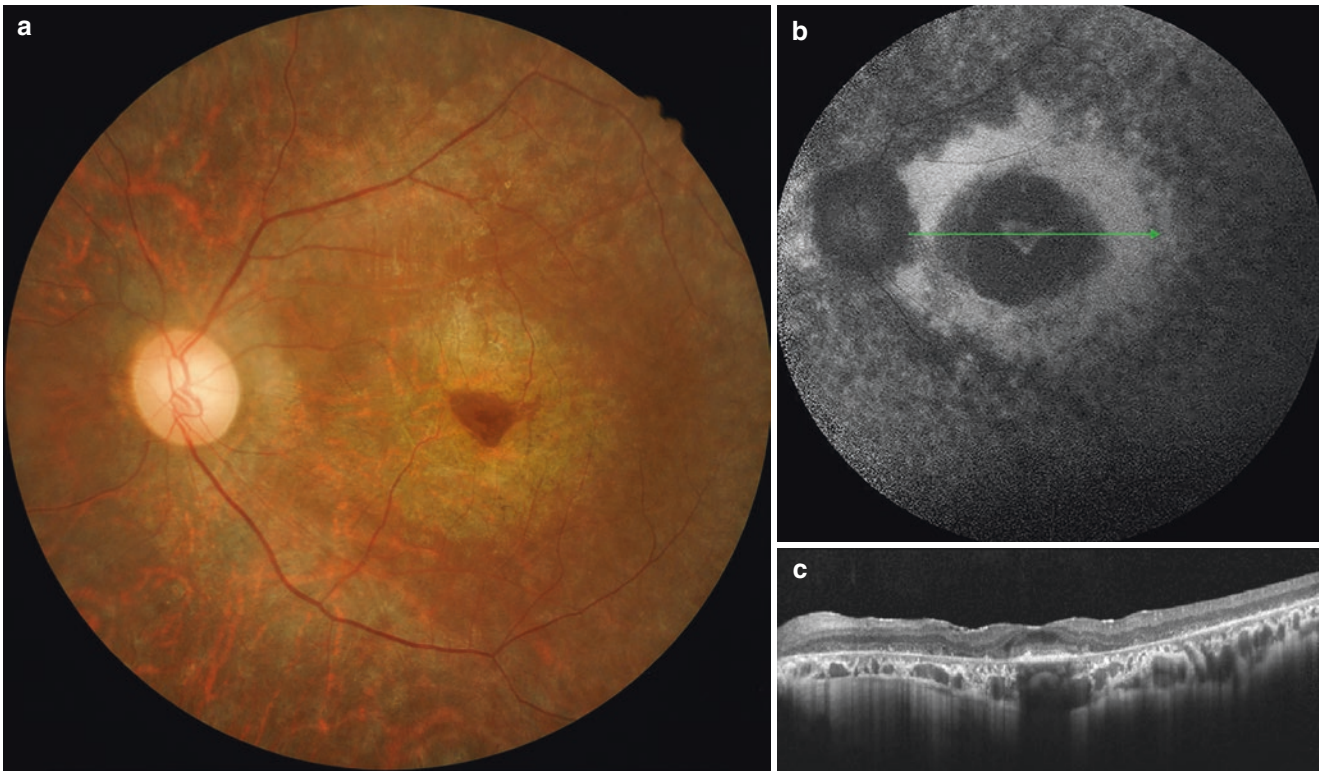


Fig. 1.18 A 32-year-old patient with retinitis pigmentosa with "bull's eye" macular atrophy and peripapillary atrophy. (**a**) Only a perifoveal ring and a small central foveal island are left. (**b**) However, the perifoveal ring and the foveal island both show hyper-autofluorescence, indicating that retinal pigment epithelial cell function was already altered in these areas. The green line indicates the orientation of the optical coherence tomography cross section. (**c**) Outside the central island, the outer retinal structures are lost. The vision was counting fingers

Many inherited retinal diseases can also be difficult to distinguish from RP. Cone/cone-rod dystrophy (CRD) is a form of retinal dystrophy, involving macular cone cells initially, and can have RP-like peripheral bone-spicule pigmentation in later stages. Leber's congenital amaurosis (LCA) is featured by severe visual impairment since infancy, often accompanied with nystagmus and oculo-digital sign. The fundus appearance in LCA could range anywhere from normal to RP-like. Other conditions such as Bietti's crystalline dystrophy, choroideremia, Sorsby fundus dystrophy, and Stargardt macular dystrophy can also be confused with RP in advanced stages.

Some acquired conditions can cause diffuse chorioretinal atrophy and *pseudoretintis pigmentosa*. Syphilis, congenital rubella, drug toxicity (thioridazine, chloroquine, hydroxychloroquine, quinine, chlorpromazine), acute zonal occult outer retinopathy (AZOOR), or cancer-associated retinopathy (CAR) should all be listed as RP differentials. Traumatic retinopathy and diffuse unilateral subacute neuroretinitis (DUSN) cause unilateral pigment clumping and *unilateral RP*. Careful ophthalmic examinations and systemic investigations in the patient and family members are the key to a final diagnosis.

Treatment

Although a definitive cure for RP has not yet been discovered, ophthalmologists, armed with new knowledge regarding the disease, are now even more able to offer aid to patients. These *treatments* include careful refraction, low vision aids, and genetic consultations. Managing RP complications, such as cataract and CME, is also an important measure.

Whether to use nutritional supplements is a question frequently asked in clinics. These supplements include vitamin A, vitamin E, docosahexaenoic acid (DHA), lutein, and β-carotene, but the effectiveness of these drugs remain controversial (Rayapudi et al. 2013; Brito-Garcia et al. 2017; Berson et al. 1993, 2004, 2010).

Several new treatment approaches are under investigation in clinical trials or animal studies (Jacobson and Cideciyan 2010). Electronic retinal implants are already available commercially and could offer limited vision for end-stage RP patients (Luo and da Cruz 2016; Chuang et al. 2014). An innovative method for LCA, which is caused by an *RPE65* gene mutation, is gene therapy (see Treatment section in Leber's Congenital Amaurosis). Inspired by success in LCA, *optogenetic therapy* involves the introduction of genetically encoded light sensors via adeno-associated viral (AAV)

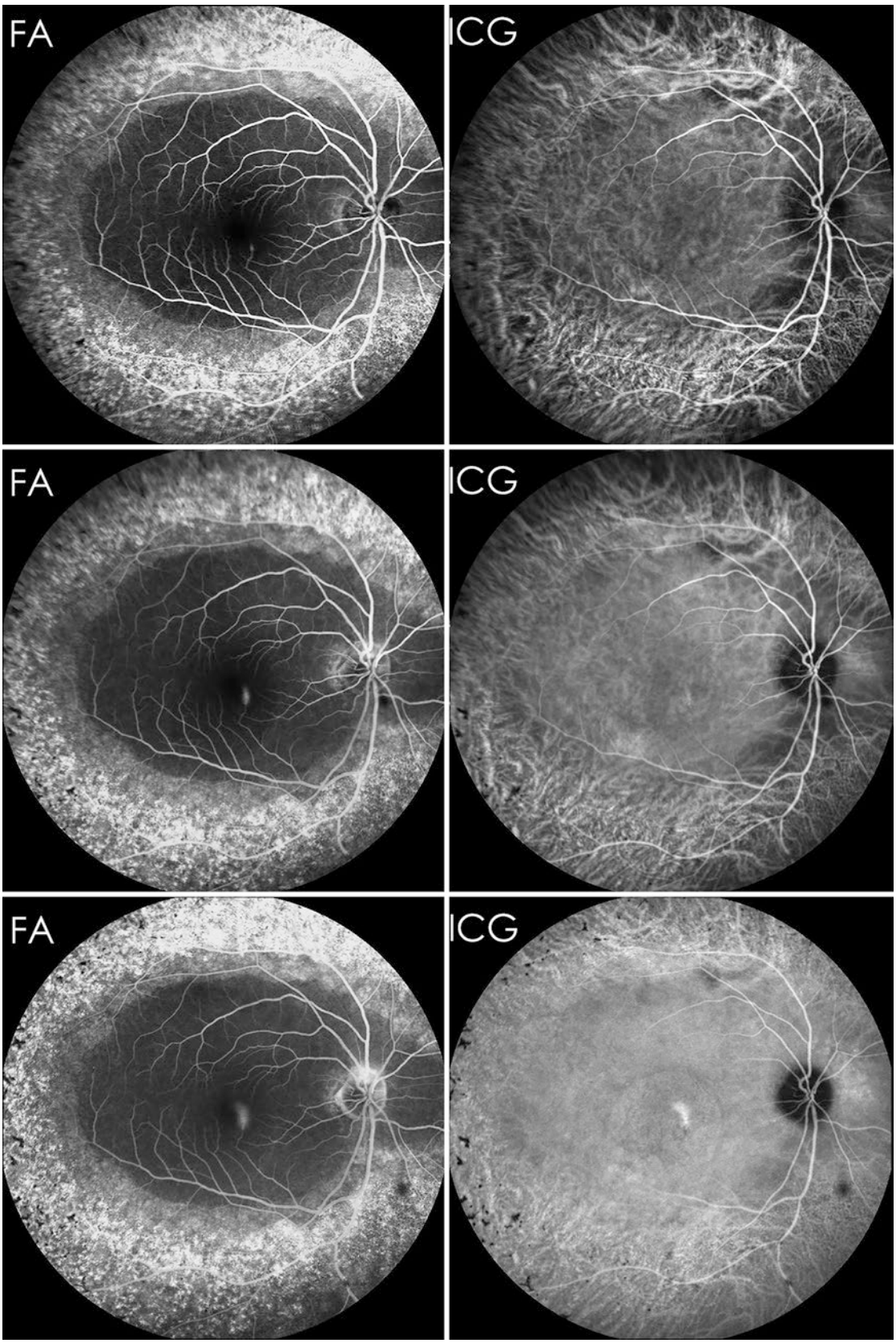


Fig. 1.19 Retinitis pigmentosa with central serous chorioretinopathy. The typical smoke-stack leakage is well demonstrated by the serial fluorescein angiography (FA) images. In the mid-periphery, bone-spicule hyperpigmentation blocks fluorescence in both FA and indocyanine green (ICG) images, and the hyperfluorescent spots clearly demarcate the atrophic areas

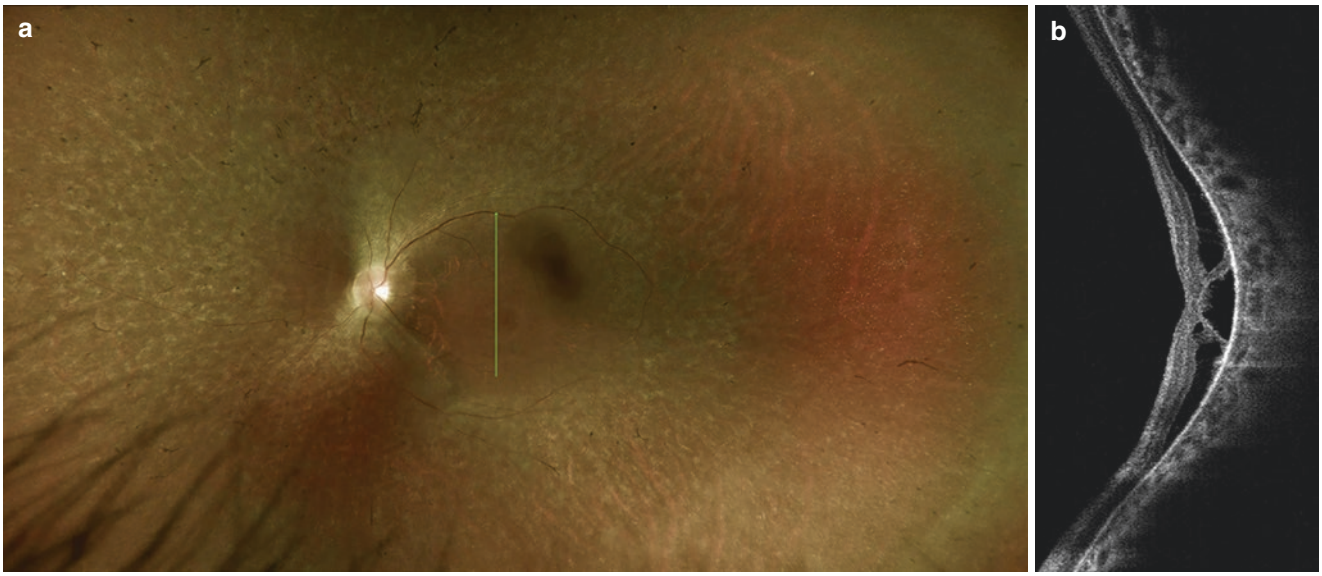


Fig. 1.20 Macular retinoschisis in retinitis pigmentosa. The 31-year-old woman has myopia −3.0 diopter in the left eye, and she reported to have distorted vision. (**a**) It is hard to appreciate the schisis change in the macula in the ultra-wide field fundus photograph. Some scattered pigmentation and atrophic areas are seen in the periphery. The green line marks the orientation of the optical coherence tomography (OCT). (**b**) The OCT image reveals schisis in the outer plexiform layer, compatible with outer retinoschisis

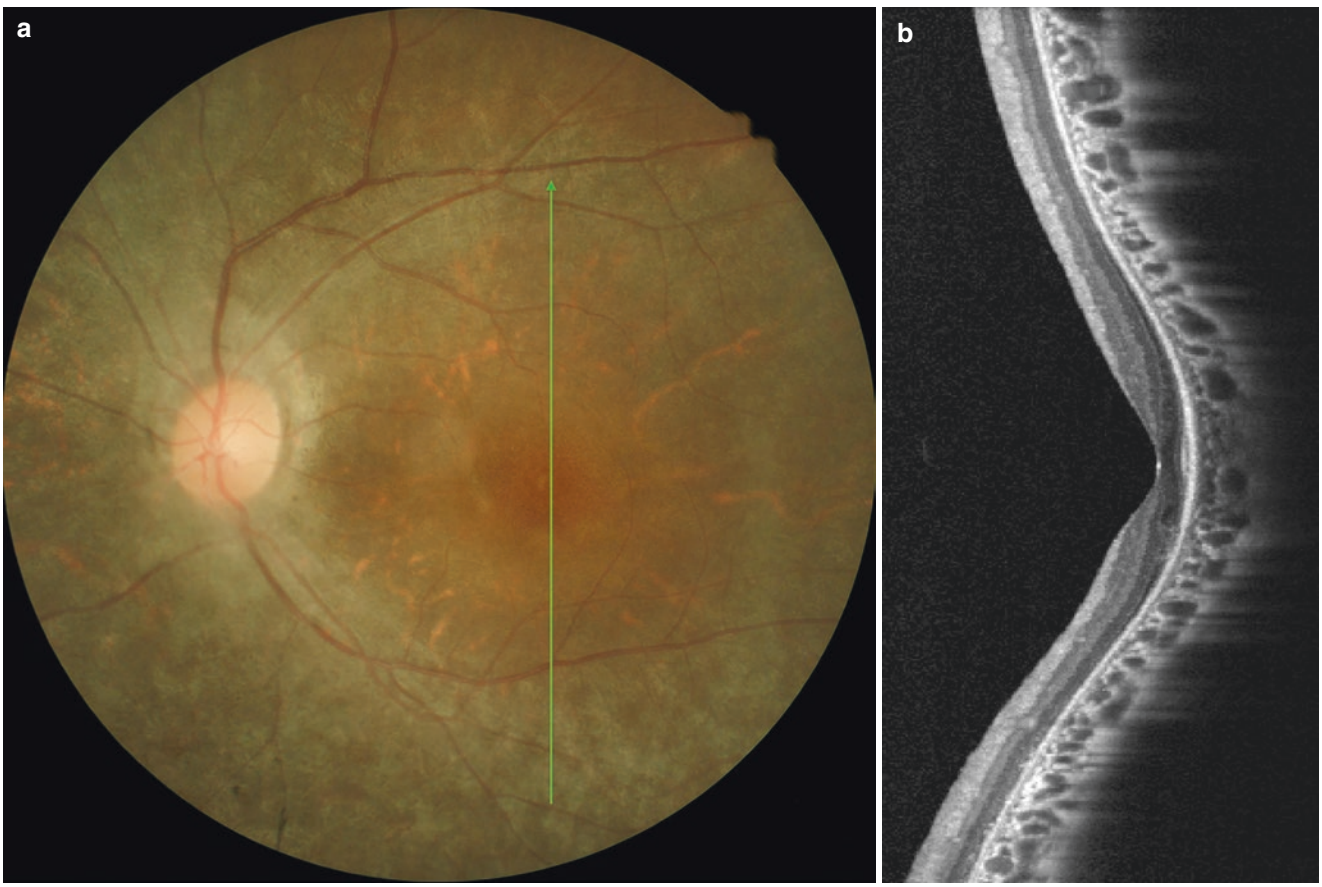


Fig. 1.21 A 28-year-old woman with retinitis pigmentosa and posterior staphyloma. She has no myopia (+0.25 diopter by both autorefraction and subjective refraction). (**a**) The fundus photography shows chorioretinal atrophy with macular sparing. The green line marks the orientation of the SD-optical coherence tomography (OCT). (**b**) The SD-OCT image displays posterior staphyloma at the macular area. There are also outer retinal structural changes, including thinning of the outer retinal layer and disrupted external limiting membrane and ellipsoid zone

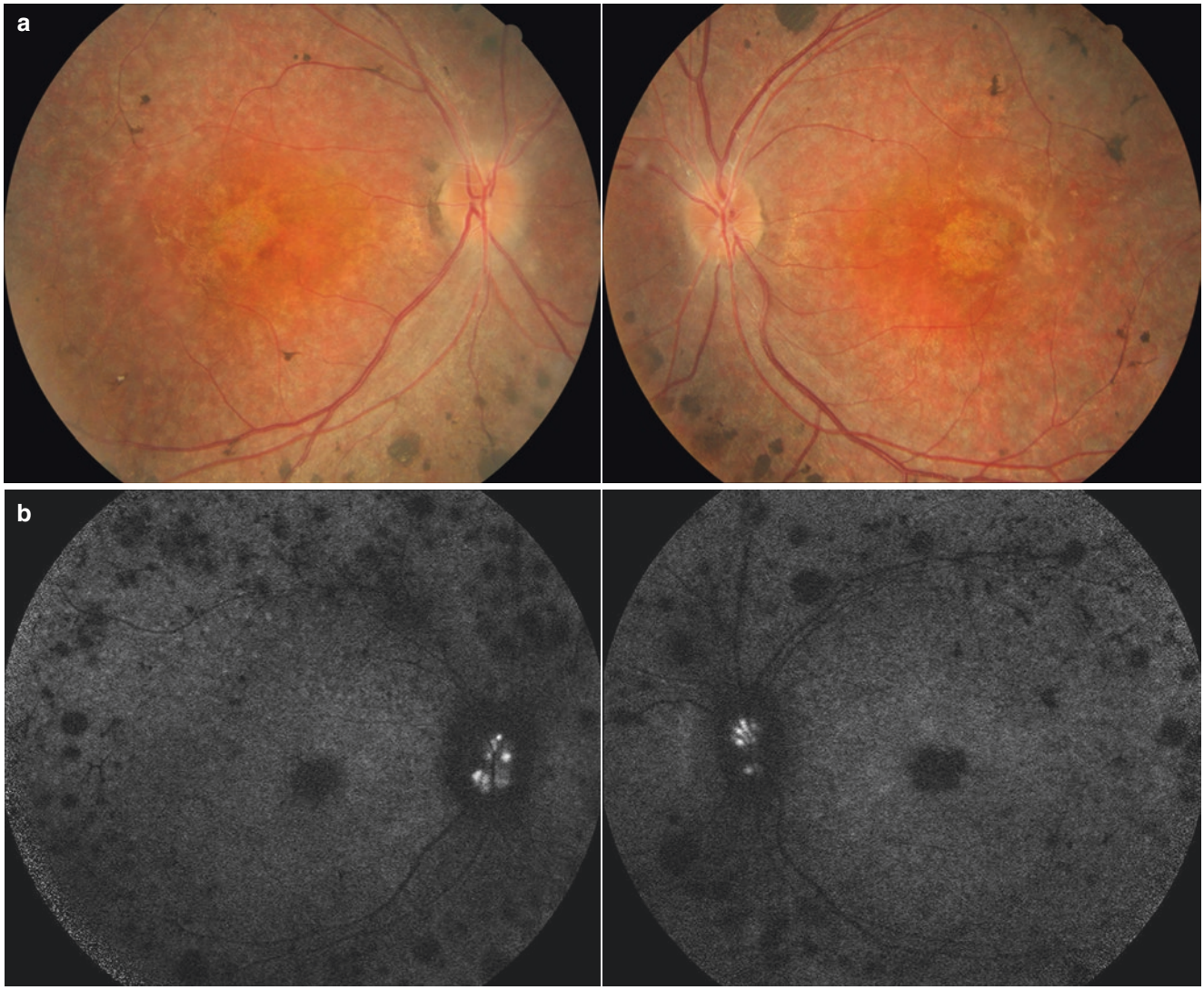


Fig. 1.22 Bilateral optic disc drusen (ODD) in a patient with retinitis pigmentosa (RP). The ODD could be an isolated feature or found in some syndromic RP such as Usher syndrome and nanophthalmos-RP-foveoschisis-optic disc drusen syndrome. (**a**) Fundus images display blurred optic disc margins. (**b**) ODD appears as a well-defined hyper-autofluorescent lesion on the fundus autofluorescence examination

vectors, making retinal cells responsive to light stimuli in animal studies (Busskamp et al. 2010; Bi et al. 2006; Lagali et al. 2008). It is hoped that these experimental approaches could assist RP patients, as well as patients with other inherited retinal dystrophy, in the near future.

X-Linked Retinitis Pigmentosa

Introduction

X-linked retinitis pigmentosa (XLRP) is an inherited condition that accounts for 6~17% of RP cases, but generally results in more severe phenotypes (Boughman et al. 1980; Boughman and Fishman 1983; Fishman 1978; Haim 1993). Although several XLRP pedigrees were reported in the early 1900s, Usher was recognized as the first author who described an X-linked recessive RP pedigree in 1935 (Usher 1935). Affected men (Fig. 1.24) show early onset of visual symptoms with night blindness followed by progressive constriction of the field of vision before the first two decades of life, which often leads to legal blindness in the fourth or fifth decade (Fishman et al. 1988). XLRP is a genetically heterogeneous disorder. Mutations in the genes *RP GTPase regulator* (*RPGR*) located at Xp21.1 and *RP2* located at Xp11.23 are responsible for most cases of XLRP (Breuer et al. 2002). The *RPGR* gene sequence variants account for more than 70% of XLRP (Pelletier et al. 2007; Sharon et al. 2003) and the *RP2* gene mutation is responsible for a further 5–20% (Breuer et al. 2002; Pelletier et al. 2007; Sharon et al. 2003).

In contrast, female carriers are usually asymptomatic, and their fundus appearance is variable (Wu et al. 2018). The

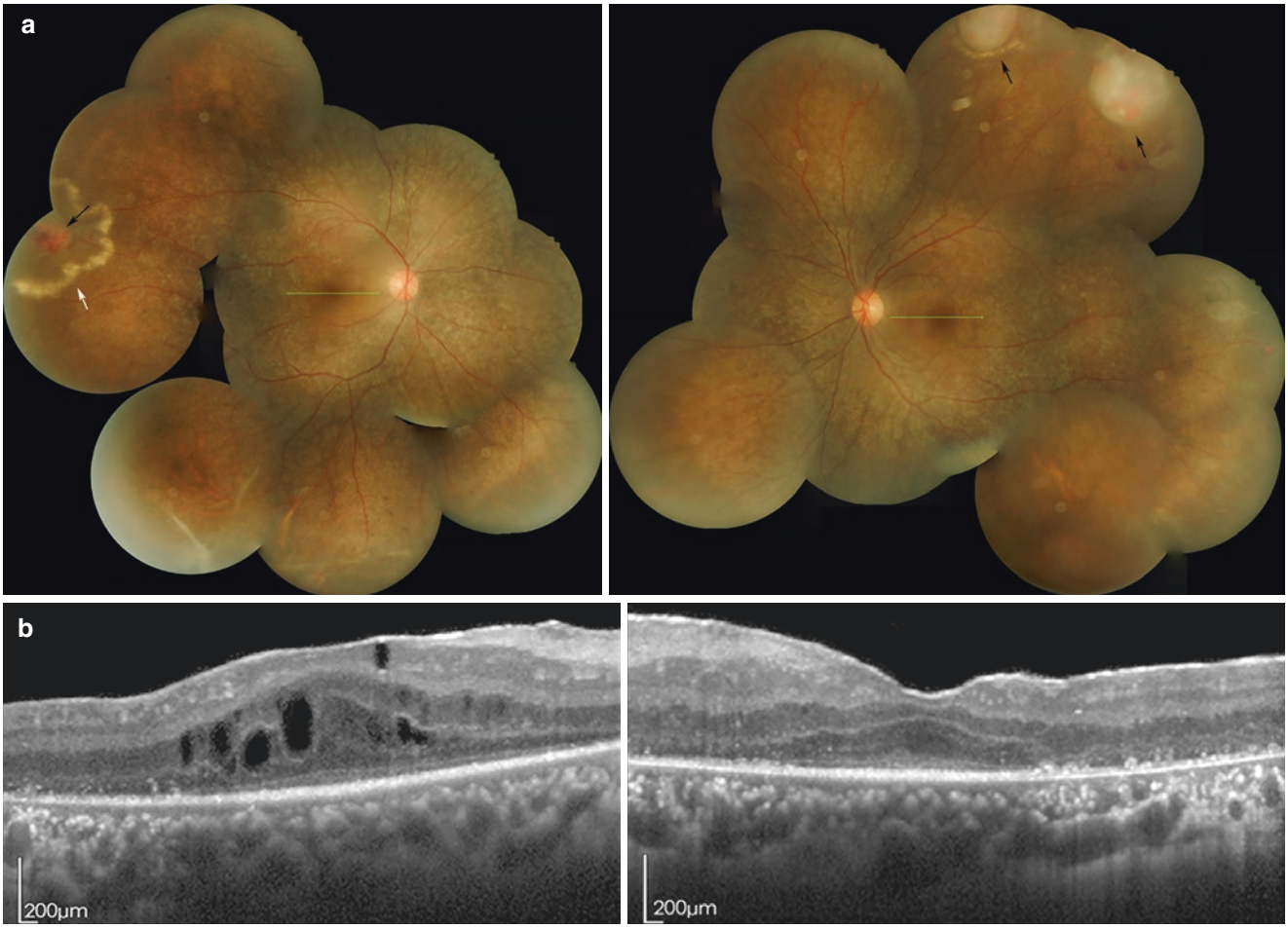


Fig. 1.23 A 25-year-old man with retinitis pigmentosa and Coats-like exudative vasculopathy. (**a**) Fundus examination showed peripheral multiple macroaneurysms (black arrows) with exudations (white arrow). His visual fields were severely constricted and electroretinogram was extinguished. The green lines indicate the orientation of the OCT. (**b**) SD-OCT revealed "thickened" and abnormally laminated retina. The foveal thickness was 446 μm in the right eye and 428 μm in the left eye. The patient also had hearing impairment since adolescence. *USH2A* mutation was confirmed and the final diagnosis was Usher syndrome with Coats-like exudative vasculopathy

pathogenic mechanisms of XLRP carriers are not well understood. However, histopathological studies in affected female carriers with different mutations in *RPGR* genes have shown some loss of photoreceptor cell nuclei and RPE abnormalities (Ben-Arie-Weintrob et al. 2005). A combination of adaptive optics with scanning laser ophthalmoscopy was used to demonstrate the mosaic pattern of cone disruption, although carriers had normal visual acuity and no visual symptoms (Pyo Park et al. 2013). Furthermore, the radial pattern of locally increased FAF was described as a bright radial reflex extending to the periphery against a dark background and was further investigated in carriers of XLRP (Wegscheider et al. 2004; Wu et al. 2018) (Fig. 1.30). These results suggested that in XLRP carriers, random X-inactivation may aid in early embryogenesis during clonal expansion in photoreceptor cell differentiation and peripheral migration in the developing retina. Correct identification of XLRP in female carriers can lead to an accurate diagnosis and confirm the nature of an unrecognizable entity in an affected male relative. Early diagnosis of XLRP carriers and their sons is essential for genetic counseling and for identifying patients who may benefit from future experimental therapy.

Clinical Features

Fundus appearance of affected men with XLRP may often show typical RP with or without the early onset of macular atrophy, including the characteristic bone-spicule clumping of intraretinal pigment located in the mid-periphery (Fig. 1.25), retinal arteriolar attenuation and a generalized hypopigmentation of RPE (Fig. 1.26). Waxy pallor of the disc and macular atrophy are usually signs of a more advanced disease (Fig. 1.27). FAF may show the presence of variably sized perifoveal rings and an arc of hyper-AF, which is not apparent on funduscopic photography, representing an area of an abnormal accumulation of lipofuscin in the RPE around a preserved sub-foveal region (Figs. 1.24, 1.25, and

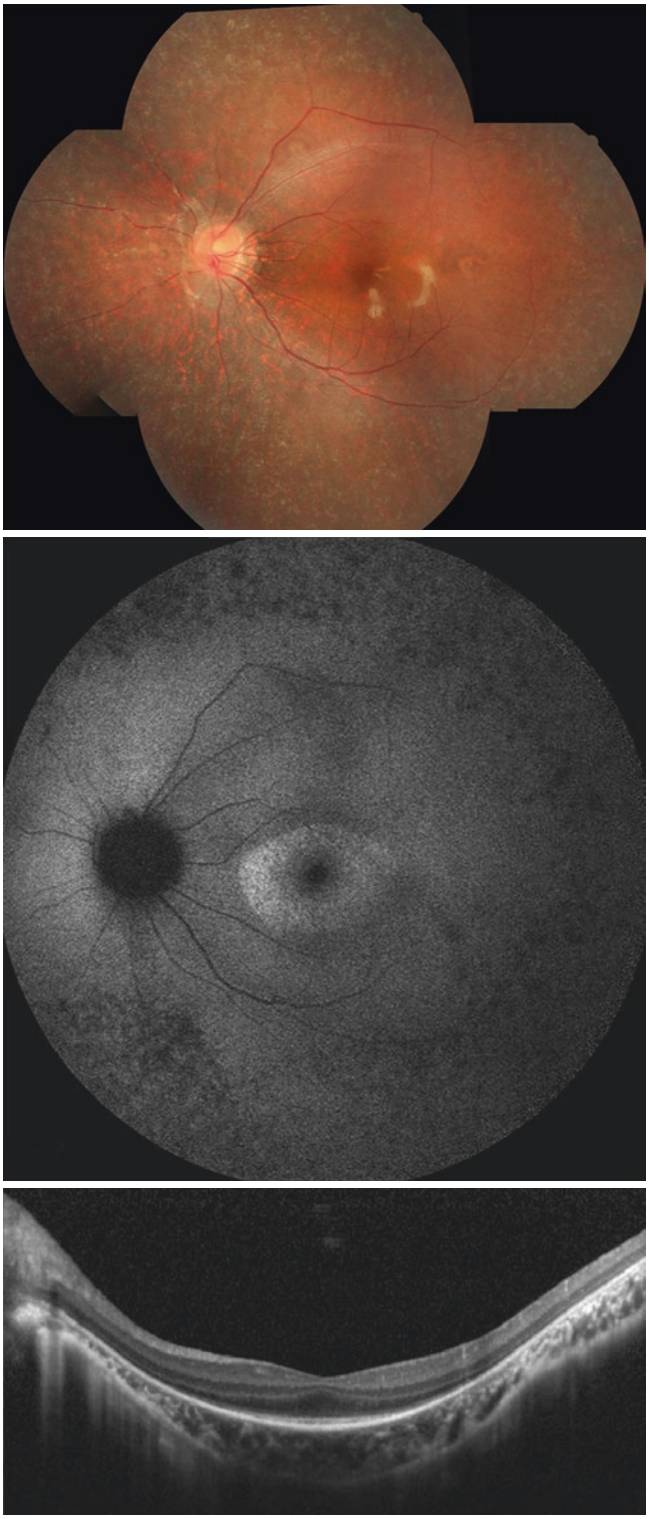


Fig. 1.24 This 11-year-old boy with X-linked retinitis pigmentosa had a history of poor visual acuity since his childhood. The visual acuity was 20/60 in the right eye and 20/30 in the left eye. The fundus is remarkable for hypopigmentation over the mid and extending into the far peripheral of the fundus. The fundus autofluorescence shows the presence of the perifoveal hyper-autofluorescence ring, which cannot be seen when using funduscopic photography. The optical coherence tomography illustrates the preserved ellipsoid layer in the fovea

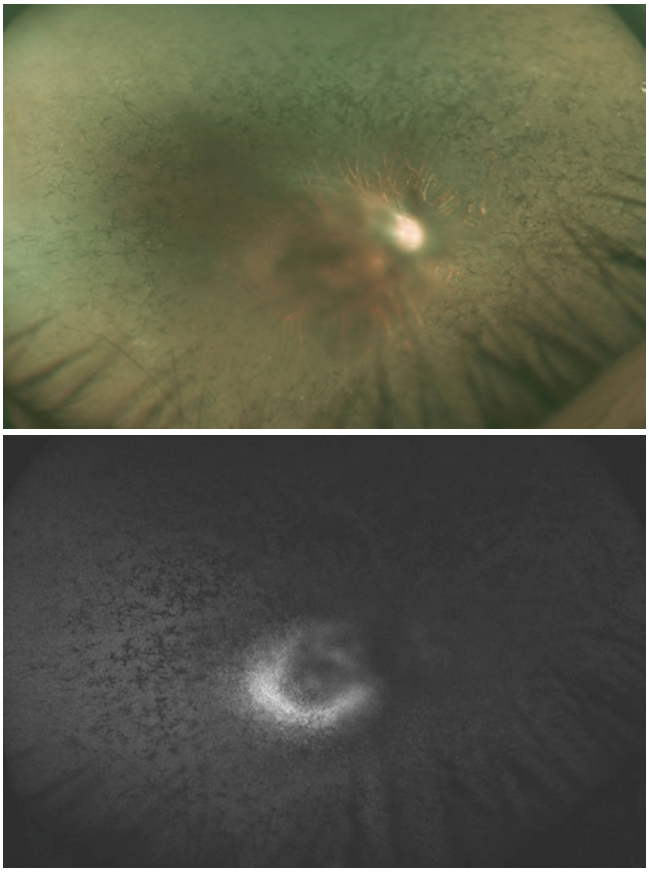


Fig. 1.25 An ultra-wide field color fundus photograph of a patient with X-linked retinitis pigmentosa (XLRP), confirmed by genetic testing for mutation in *RP2*, which showed lacy-like spicules of pigment epithelial hyperplasia over the mid and far peripheral fundus. The fundus autofluorescence image shows the presence of the perifoveal hyper-autofluorescence ring. We differentiated the correct diagnosis from a typical diagnosis of retinitis pigmentosa clinically by identifying the presence of XLRP in the female carrier of his sister in Fig. 1.30

1.26). The increased central hyper-AF ring is associated with the disruption of the EZ and a decrease in outer retinal thickness on OCT (Figs. 1.26 and 1.27) (Lima et al. 2009). EZ width might be considered a structural surrogate for the VF in RP (Birch et al. 2013). An ERG result may reveal absent or subnormal amplitudes.

In carriers of XLRP, fundus appearance is variable, ranging from unremarkable (Fig. 1.29) to the presence of pigmentary change and tapetal-like reflex (TLR), which is a golden metallic-luster sheen on the retinal surface, usually within the perimacular area (Fig. 1.28). FAF imaging may show striking findings of TLR with hyper-AF (Figs. 1.28, 1.29, and 1.30), even though TLR was not evident by color fundus examinations (Fig. 1.29). Wide-field AF may exhibit radial hyper-AF-orientated lines extending from the fovea to the periphery, with AF appearing as a characteristic bright reflex against a dark background (Fig. 1.30). Abnormal retinal structure such as EZ irregularities, EZ loss outside

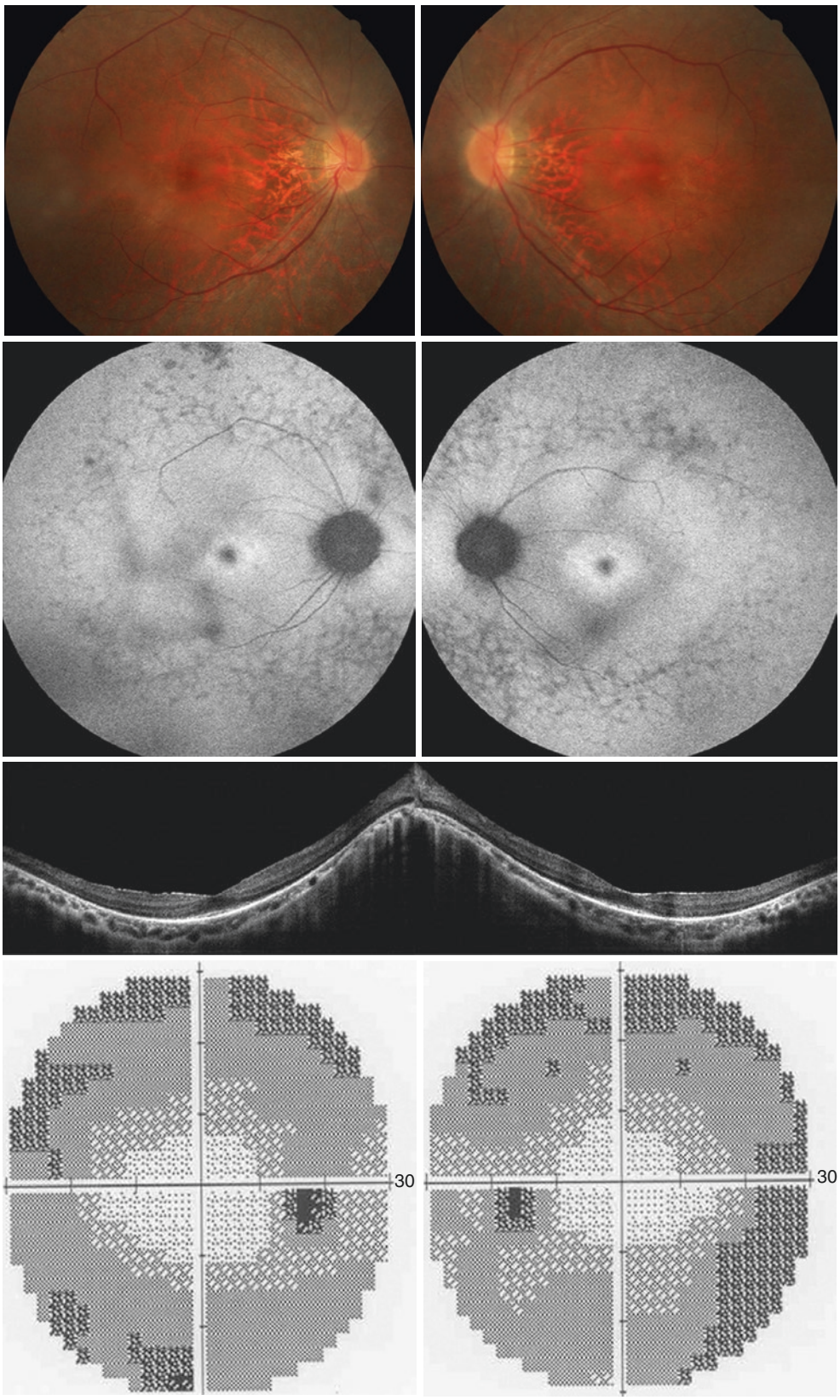


Fig. 1.26 This patient is a 23-year-old man with X-linked retinitis pigmentosa. Note the tessellated fundus change despite the lack of any myopia history. Fundus autofluorescence shows the perifoveal hyper-autofluorescence ring with hypo-fundus autofluorescence flecks. The optical coherence tomography reveals loss of the nerve fiber layer and photoreceptors outside the fovea. A visual field test confirmed peripheral constriction with tunnel vision only. Non-recordable electroretinogram was used to confirm the extinction of all rod and cone responses

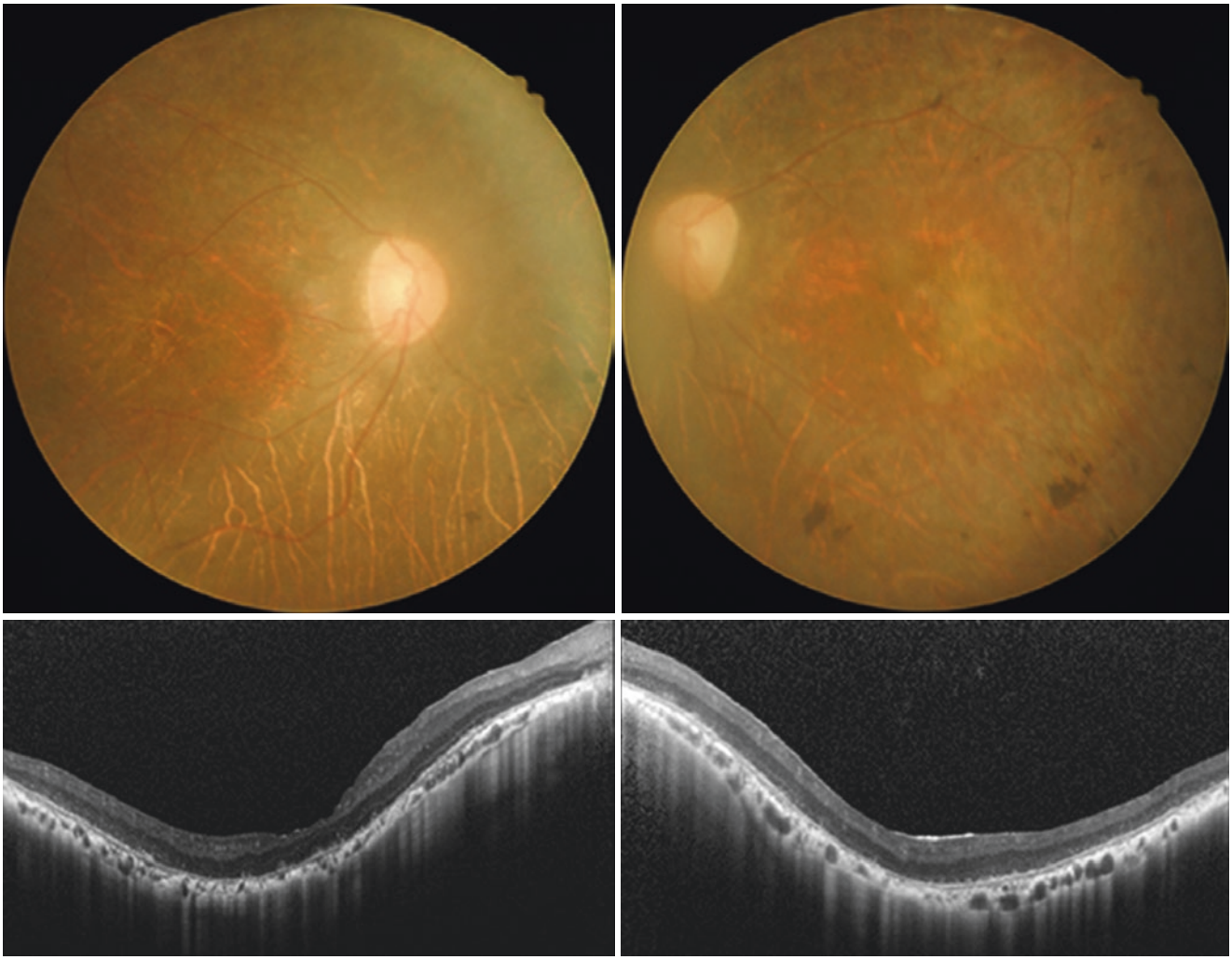


Fig. 1.27 This 59-year-old man with night blindness since high school was found to have retinal arteriolar attenuation and waxy pallor of the disc in both eyes. The optical coherence tomography shows atrophic change of the macula. Genetic testing revealed the presence of the RPGR mutation, confirming the diagnosis of X-linked retinitis pigmentosa

the fovea, increased reflectivity from the RPE–photoreceptor layer complex can be observed (Figs. 1.29 and 1.30). Hyper-AF might be related to the damage of photoreceptor cells, and the abnormal retinal structure with loss of the EZ seen on OCT was localized to areas of enhanced reflectance on FAF images (Fig. 1.30). ERG may show abnormalities of reduced amplitude or delayed cone-wave implicit time. This mosaicism and variability has been ascribed to lyonization (Wuthisiri et al. 2013), a phenomenon characterized by random X-inactivation.

Leber's Congenital Amaurosis

Introduction and Genetics

LCA (Leber congenital tapetoretinal degeneration, heredoretinopathia congenitalis, hereditary retinal aplasia, hereditary epithelial dysplasia of retina, dysgenesis neuroepithelial retinae) is an early onset and severe form of inherited retinal dystrophy responsible for congenital blindness. The estimated prevalence of LCA is 1–3 per 100,000, and it accounts for around 5% of all retinal dystrophies (Alkharashi and Fulton 2017; Chacon-Camacho and Zenteno 2015; Fazzi et al. 2003; Coussa et al. 2017). In 1869, German ophthalmologist Theodor von Leber first described the disease as a disorder characterized by profound visual loss at or near birth, wandering nystagmus, sluggish pupillary response, and a normal appearing fundus that progressed to pigmentary retinopathy (Leber 1869). Franceschetti and Deiterlé later added severely reduced ERG and altered visual evoked potentials (VEP) (Franceschetti 1954). Other associated clinical appearances included oculo-digital sign, cataract, keratoconus, high hyperopia, high myopia, and nyctalopia (Lambert et al. 1989).

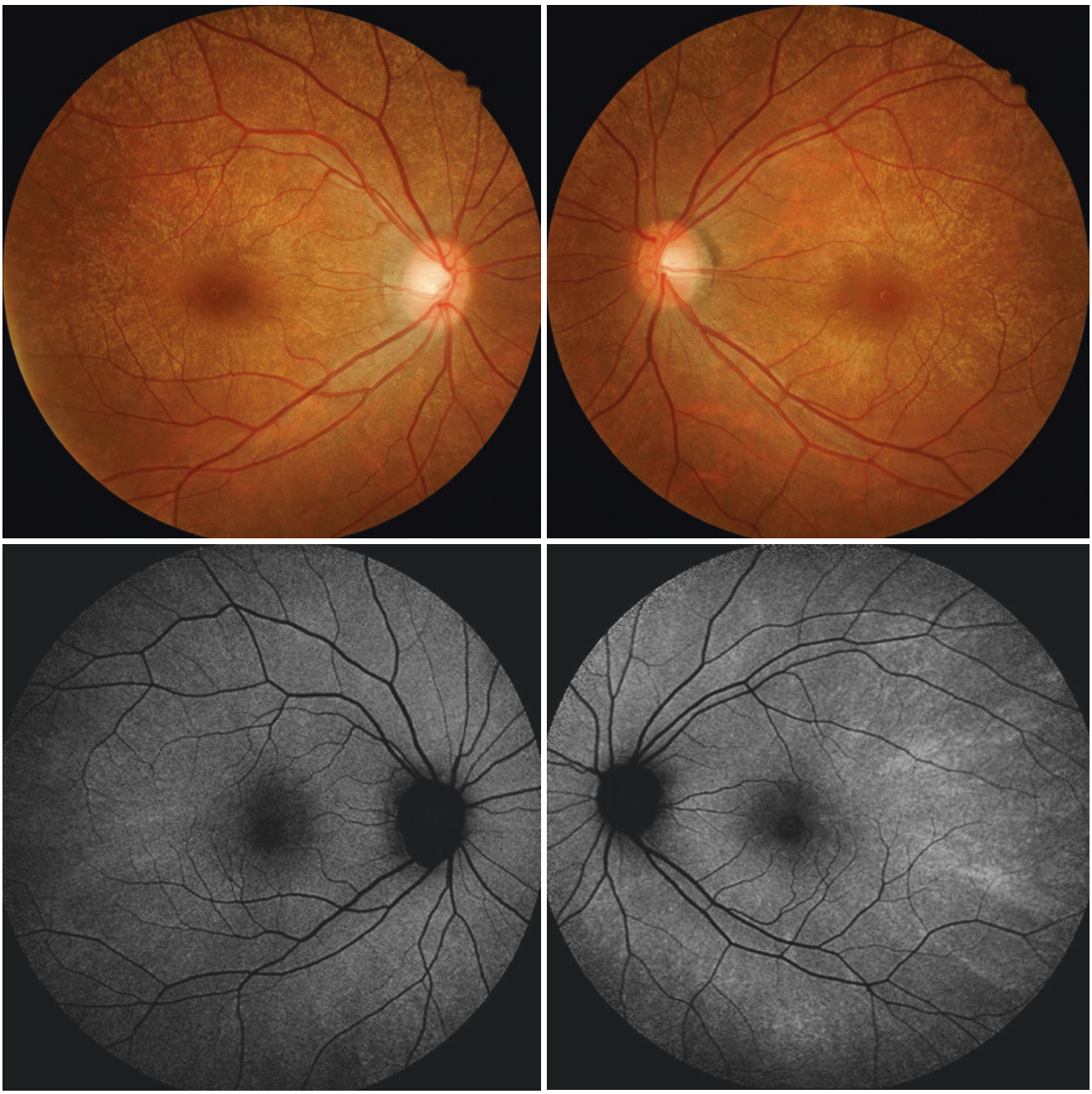


Fig. 1.28 This carrier with X-linked retinitis pigmentosa has a tapetal-like reflex (TLR) and a golden metallic-luster sheen on the retinal surface located within the perimacular area in both eyes. Note that the striking findings of TLR with hyper-autofluorescence are also evident in autofluorescence images

LCA is mostly inherited in an autosomal recessive pattern, with 23 causative genes identified as affecting the developmental and physiological pathway of either photoreceptors or RPE (Chacon-Camacho and Zenteno 2015).

Clinical Features

The diagnosis of LCA is made according to clinical signs. De Laey proposed the diagnostic criteria of LCA in 1991, including (1) early onset of poor vision (mostly before 6 months of age), (2) sluggish pupillary response, (3) nystagmus, (4) oculo-digital sign, (5) extinguished or severely reduced ERG, (6) abnormal VEP, and (7) variable fundus (De Laey 1991).

LCA differs from typical RP in the age of visual impairment and early development of retinopathy. Some inherited retinal dystrophies share similar presentation with LCA. Patients with achromatopsia, congenital stationary night blindness and albinism may all present with nystagmus.

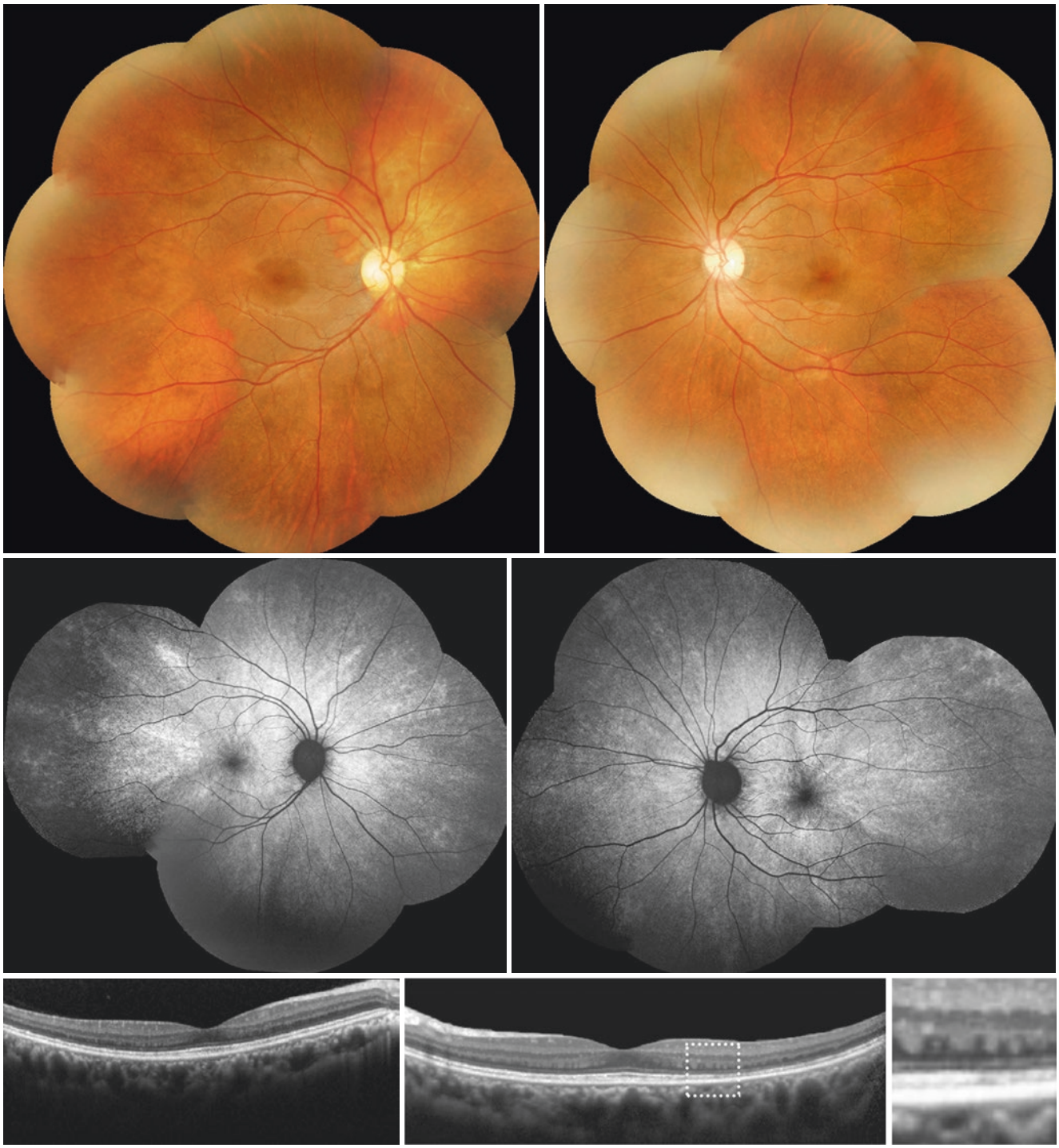


Fig. 1.29 This carrier with X-linked retinitis pigmentosa has a tapetal-like reflex (TLR) with hyper-autofluorescence in the autofluorescence image even though TLR was not evident in the color fundus photo. The optical coherence tomography scan shows irregularities in the ellipsoid zone involving the macula. Higher magnification (right lower) of the area outlined by white dots shows the thinning of the outer nuclear layer (ONL) and a dentate appearance of the outer plexiform layer (OPL)

In comparison, patients with achromatopsia are unable to differentiate between different colors but have an improved contrast sensitivity at dimmer light. In addition, they have an absence of obvious fundus pigmentary changes and abnormal cone but preserved rod function on ERG. On the other hand, patients with congenital stationary night blindness have stationary impaired night vision, a normal fundus appearance, abnormal rod response, and

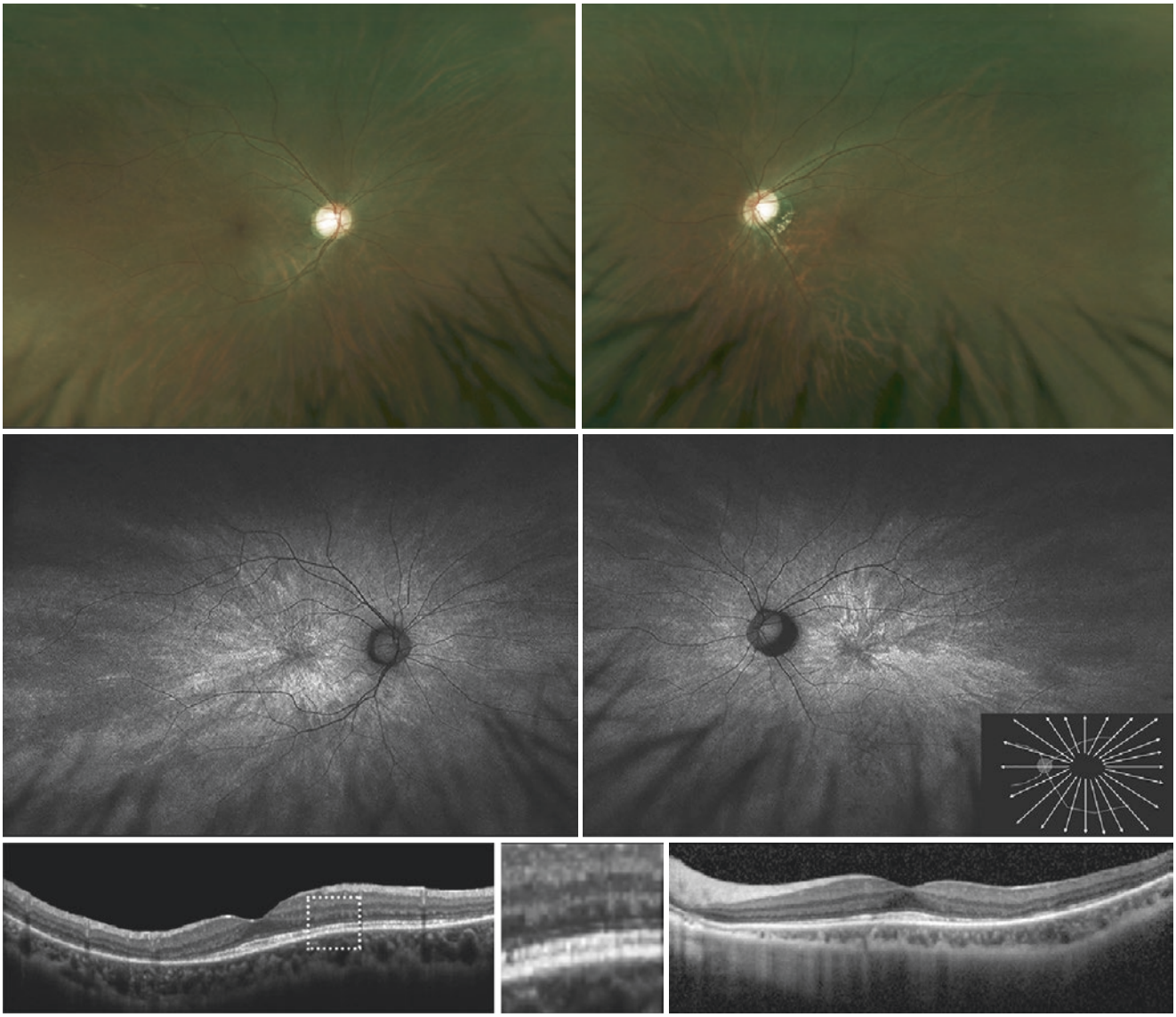


Fig. 1.30 This carrier with X-linked retinitis pigmentosa has tessellated fundus changes of the retina in both eyes. Wide-field fundus autofluorescence exhibit radial hyper-autofluorescence (AF) orientated lines extending from the fovea to the periphery as a characteristic bright reflex against a dark background. The detection of the peripheral radial hyper-AF pattern shown on the ultra-wide field image provided superior visibility. The optical coherence tomography shows ellipsoid zone loss in the macula corresponding to the areas of enhanced reflectance on the autofluorescence image

electronegative ERG. Albinism has generalized fundus depigmentation and foveal hypoplasia (den Hollander et al. 2008; Koenekoop 2004).

The fundus appearance of LCA patients is highly variable, ranging from normal to findings similar to that of typical RP, maculopathy, and macular colobomas (Figs. 1.31 and 1.32). Some genotypes of LCA are associated with certain phenotypes (Table 1.1) (Alkharashi and Fulton 2017; Chacon-Camacho and Zenteno 2015; Coussa et al. 2017). The *RPE65* (LCA2) and *LRAT* (LCA14) genes are both involved in the retinoid cycle, which is responsible for the isomerization of vitamin A and production of lipofuscin (Takahashi et al. 2011). Disruption of the cycle causes a diminished amount of lipofuscin, the source of AF. Therefore, patients with *RPE65* or *LRAT* mutations have a loss of AF (Scholl et al. 2004; Lorenz et al. 2004) (Fig. 1.33). The *CRB1* (LCA8) gene is responsible for the polarization of photoreceptors. The phenotypic particularity of the *CRB1* mutation in LCA patients is an unlaminated thickened retina (Tosi et al. 2009). The *GUCY2D* (LCA1), *AIPL1* (LCA4), and *RD3* (LCA12) genes are part of the photo-transduction cascade (Pasadhika et al. 2010). Mutation in the *AIPL1* (LCA4) and *RD3* (LCA12) genes presents with early maculopathy (Alkharashi and Fulton 2017; Dharmaraj et al.

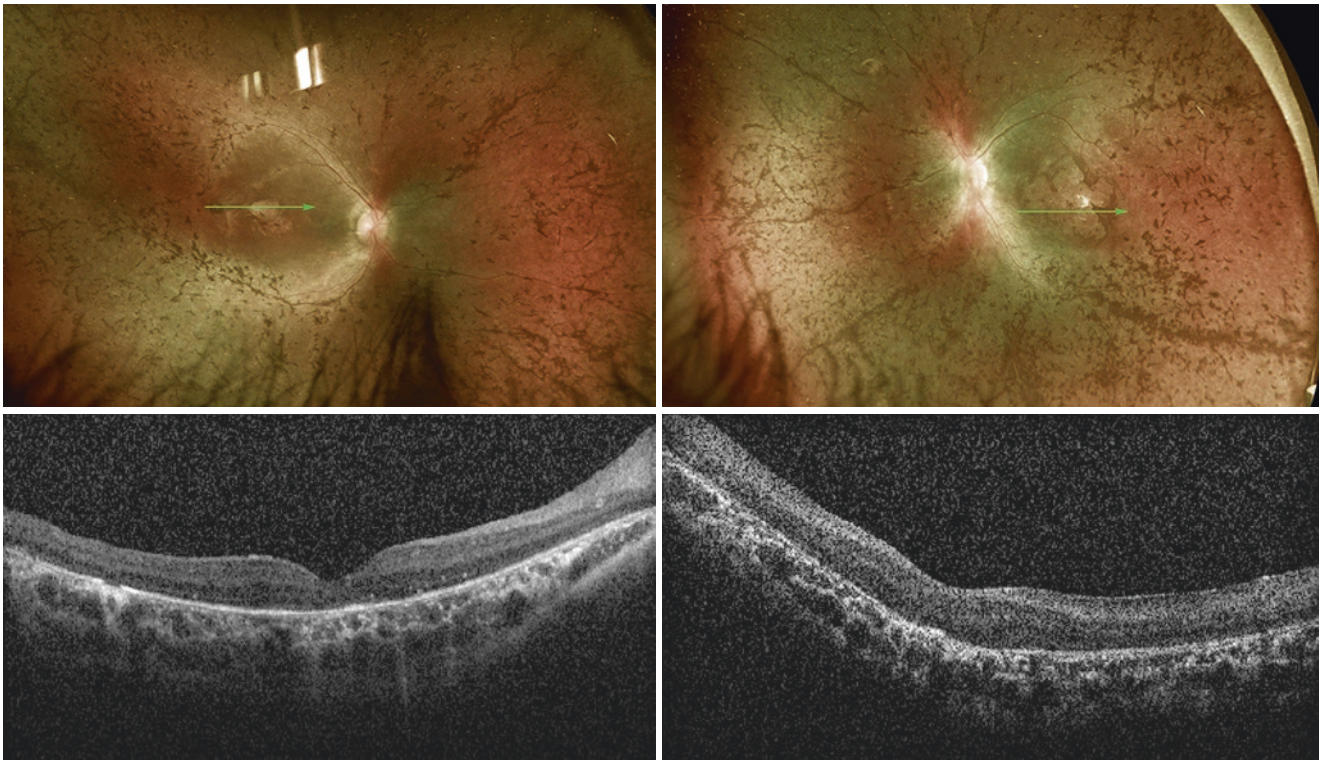


Fig. 1.31 These are the images of a 3-year-old patient with Leber's congenital amaurosis (LCA). The Fundus photo reveals bone-spicule pigmentation at mid-peripheral retina, vessel attenuation, and diffused retinal pigment epithelium (RPE) alteration, which are typical findings of retinitis pigmentosa. Noted the early macula involvement in the LCA and the RPE change are marked. The optical coherence tomography of the macular shows loss of the ellipsoid zone

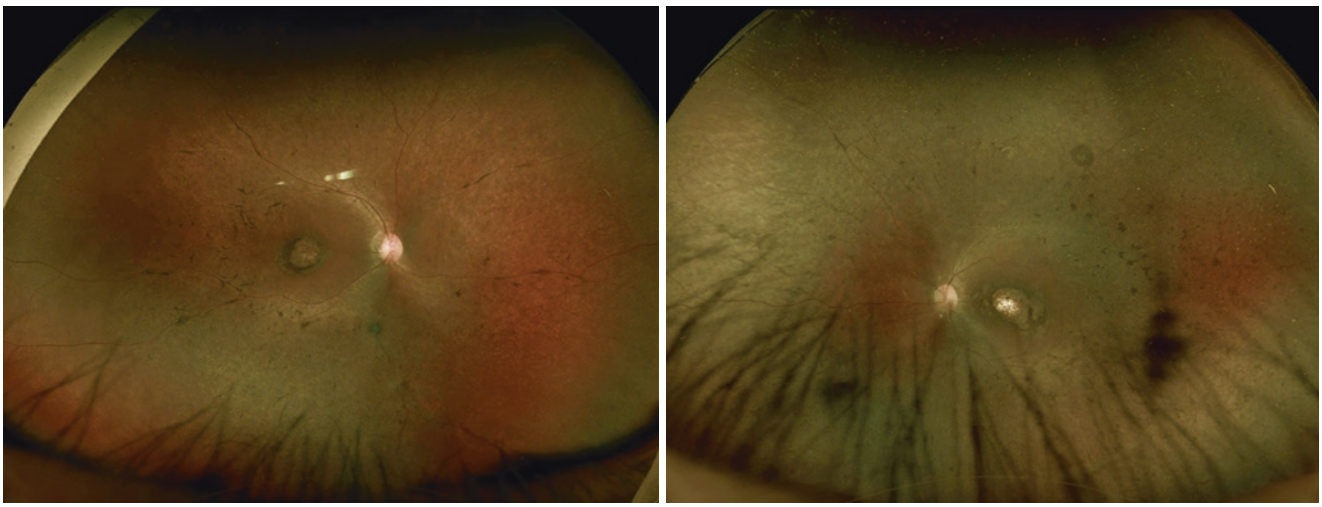


Fig. 1.32 Fundus photo of a 12-year-old boy with Leber's congenital amaurosis, which shows bilateral macula chorioretinal change, and some pigmentation at the mid-peripheral retina. This patient is the elder brother of the patient in Fig. 1.31

2004) (Fig. 1.34). Patients with *CEP290* (LCA10) may present with Coats-like RP (Yzer et al. 2012) (Fig. 1.35). 6q14.1 (LCA5), *CRX* (LCA7), and *NMNAT1* (LCA9) gene mutations are associated with macula-coloboma like fundus (Mohamed et al. 2003; Swaroop et al. 1999; Koenekoop et al. 2012).

Treatment

With notable genetic heterogeneity, LCA was considered incurable previously. Until 2008, with the advances in genome studies, three independent clinical trials have described the phase I-II outcome of gene therapy for RPE65 mutation (LCA 2) (Bainbridge et al. 2008; Maguire et al.

Table 1.1 Reported clinical features of LCA subtypes

Subtype	Gene	Clinical features
LCA1	*GUCY2D*	Normal appearing fundus
LCA2	*RPE65*	Lack of autofluorescence
LCA3	*SPATA7*	Retinal atrophy
LCA4	*AIPL1*	Maculopathy, reduced macula thickness
LCA5	6q 14.1	Macula coloboma-like picture
LCA6	*RPGRIP1*	Normal then pigmentary change
LCA7	*CRX*	Macula coloboma-like picture
LCA8	*CRB1*	Coats-like exudative vasculopathy, thick retina
LCA9	*NMNAT1*	Macula coloboma-like picture
LCA10	*CEP290*	Fundus pigmentation
LCA11	*IMPDH1*	Diffuse RPE mottling
LCA12	*RD3*	Macula atrophy
LCA13	*RDH12*	Bone spicules
LCA14	*LRAT*	Lack of autofluorescence
LCA15	*TULP1*	Salt and pepper retinopathy

2008; Hauswirth et al. 2008). Mutation of RPE65 gene affects vitamin A metabolism, photoreceptor response, and thus vision. In addition, the mutation results in degeneration of RPE and photoreceptor cells. LCA caused by mutated RPE65 has a disproportionately preserved outer retinal structure, giving it a window of opportunity for gene-replacement therapy. The three clinical trials used subretinal delivery of recombinant adeno-associated virus vector during standardized 23 gauge vitrectomy (Wright 2015). The FDA approved 2 potential therapies for RP: a retinal prosthesis, approved only for patients with end-stage RP and RPE65 gene therapy, approved only for patients carrying the RPE65 mutation (Duncan et al. 2018).

All studies have demonstrated an initial improvement with subsequent decline in visual sensitivity after gene therapy, with a possible dose–response effect (Bainbridge

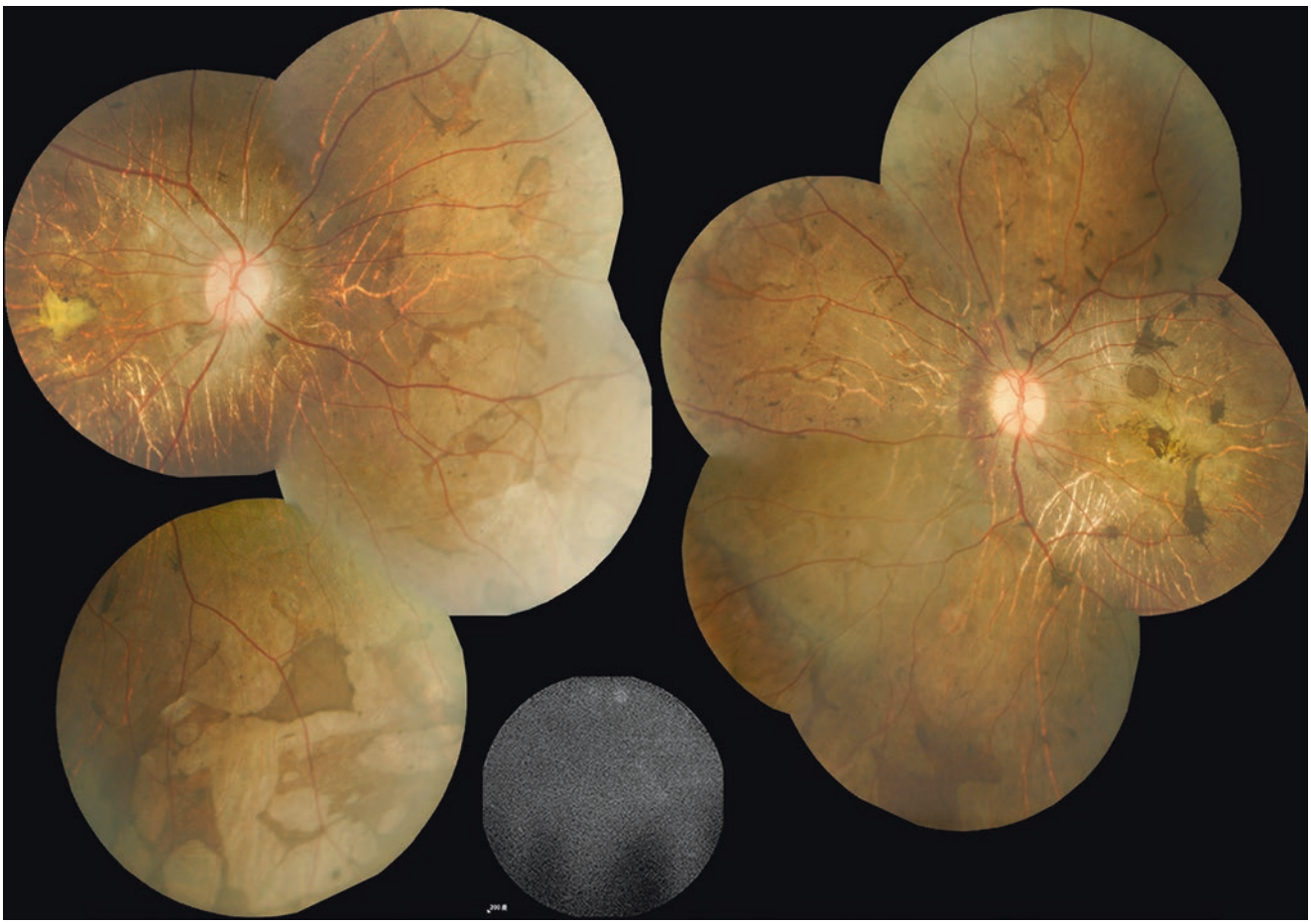


Fig. 1.33 A 9-year-old patient with Leber's congenital amaurosis. The fundus photo reveals diffuse retinal pigment epithelium (RPE) alteration, some bone-spicule pigmentation at the mid-peripheral retina, slight vessel attenuation, and chorioretinal change at the posterior pole. Note the loss of autofluorescence

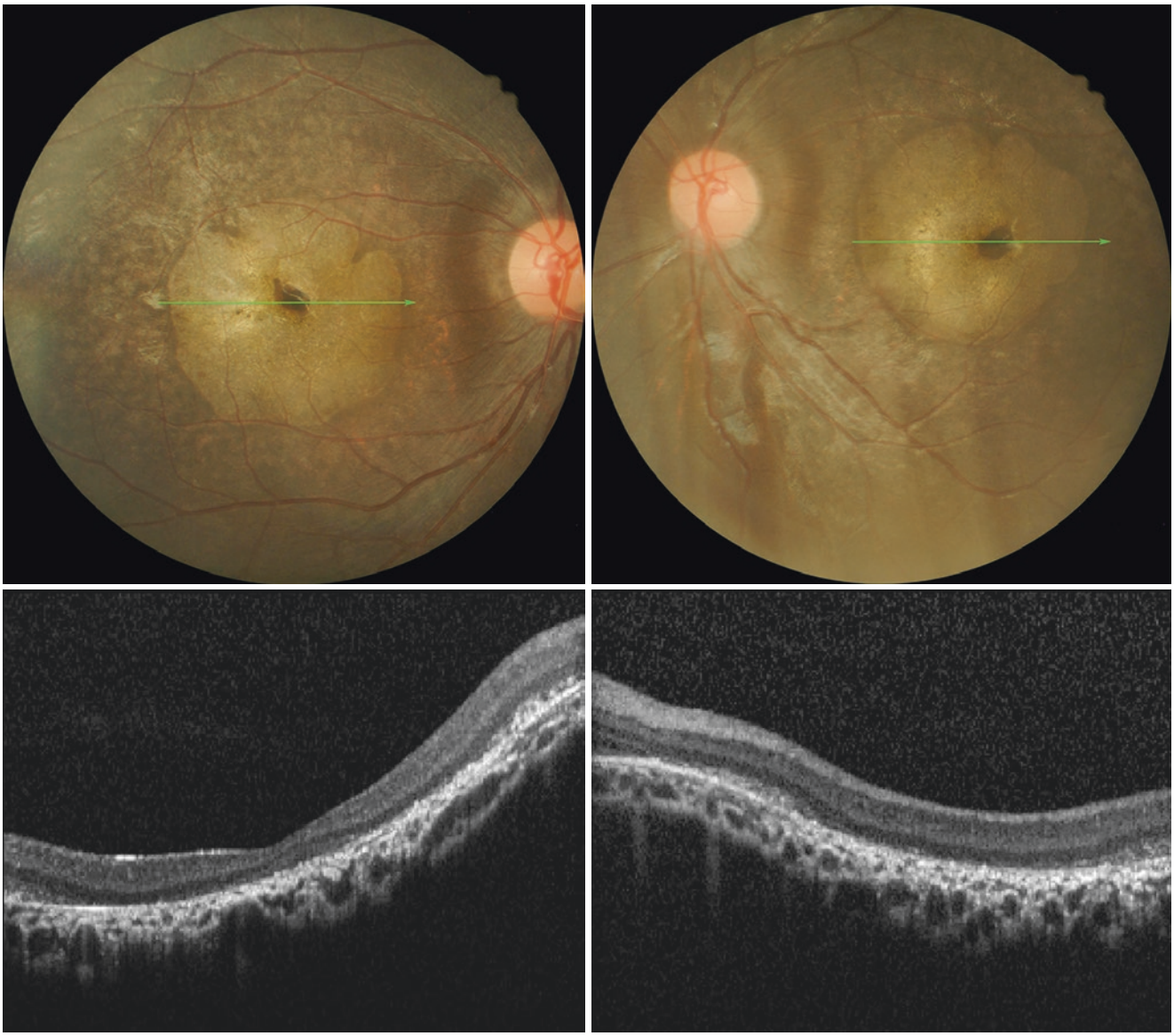


Fig. 1.34 A 2-year-old patient with Leber's congenital amaurosis (LCA) 4 (*AIPL1* gene mutation). The fundus photo demonstrates diffused retinal pigment epithelium (RPE) alteration, especially at the macula with prominent xanthophyll. The optical coherence tomography shows thinning of the macula in the right eye

et al. 2015). Despite functional response, continuous loss of photoreceptors was observed, indicating an ongoing retinal degeneration during the process. The results disclosed that RPE65 gene therapy provided temporary and incomplete restoration of retinal function, prompting further study and the need for a vector delivery system with higher efficiency in the future (Bainbridge et al. 2015; Jacobson et al. 2015).

Sector Retinitis Pigmentosa and Retinitis Pigmentosa Inversa

Sector retinitis pigmentosa is a rare variant of RP, usually involving the inferior nasal quadrant and is often bilaterally symmetric (Omphroy 1984). The affected areas demonstrate the features of typical RP, including retinal vessel attenuation and retinal pigment epithelial cell changes with hyperpigmentation (Figs. 1.36 and 1.37). The central vision is generally maintained, with peripheral VF defects corresponding with the affected areas. The condition is stationary or only slowly progressive. Mutations in the *rhodopsin (RHO)* gene have been associated with sector RP and transmit usually in an AD trait (Krill et al. 1970; Heckenlively et al. 1991).

Retinitis pigmentosa inversa (or inverse RP) is another rare RP variant (Ferrucci et al. 1998; Sheth et al. 2011). Pigmentation and chorioretinal atrophy link this condition to RP, but retinal changes occur in the macula initially and compromise the central vision in the very early phase

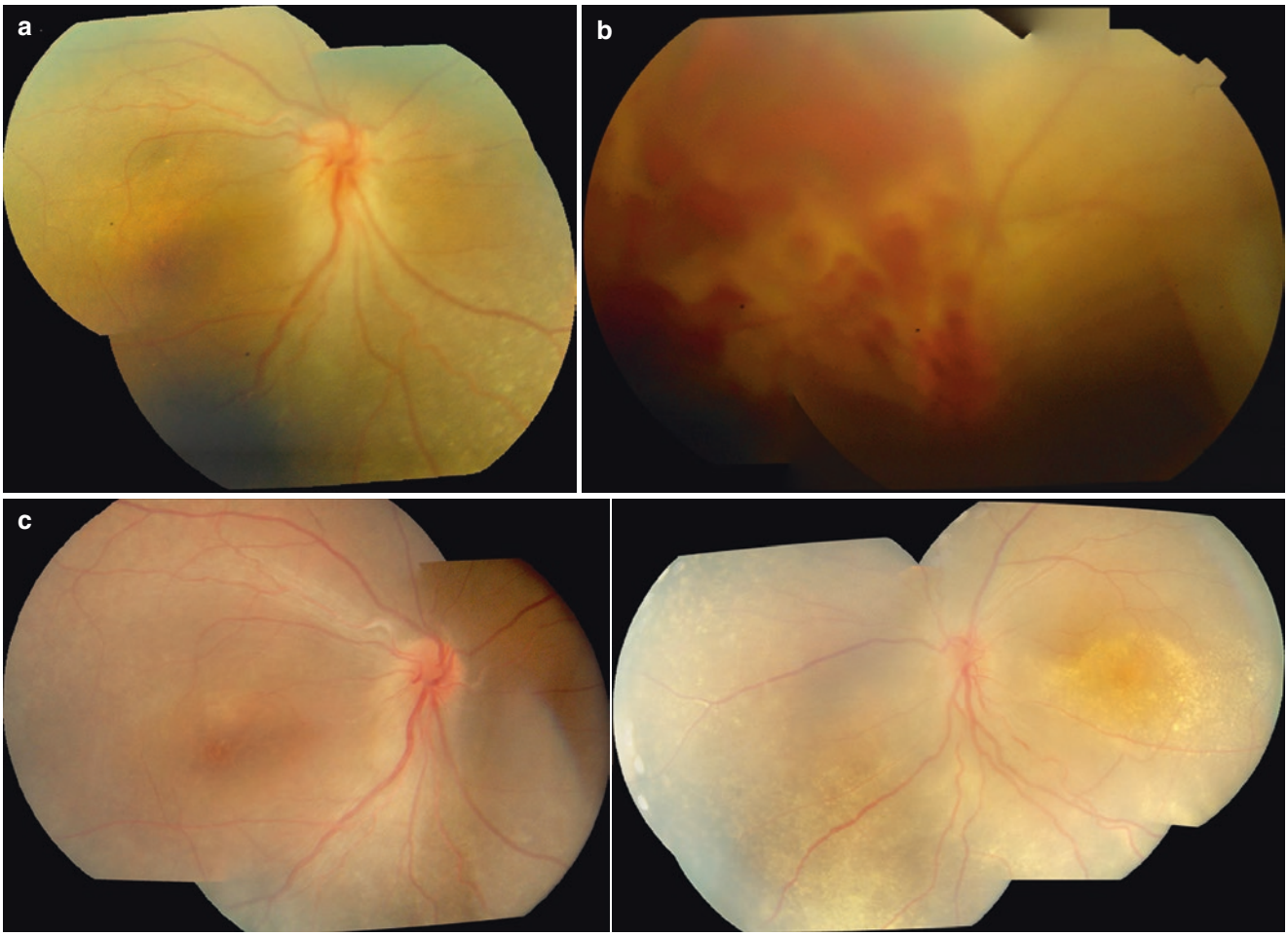
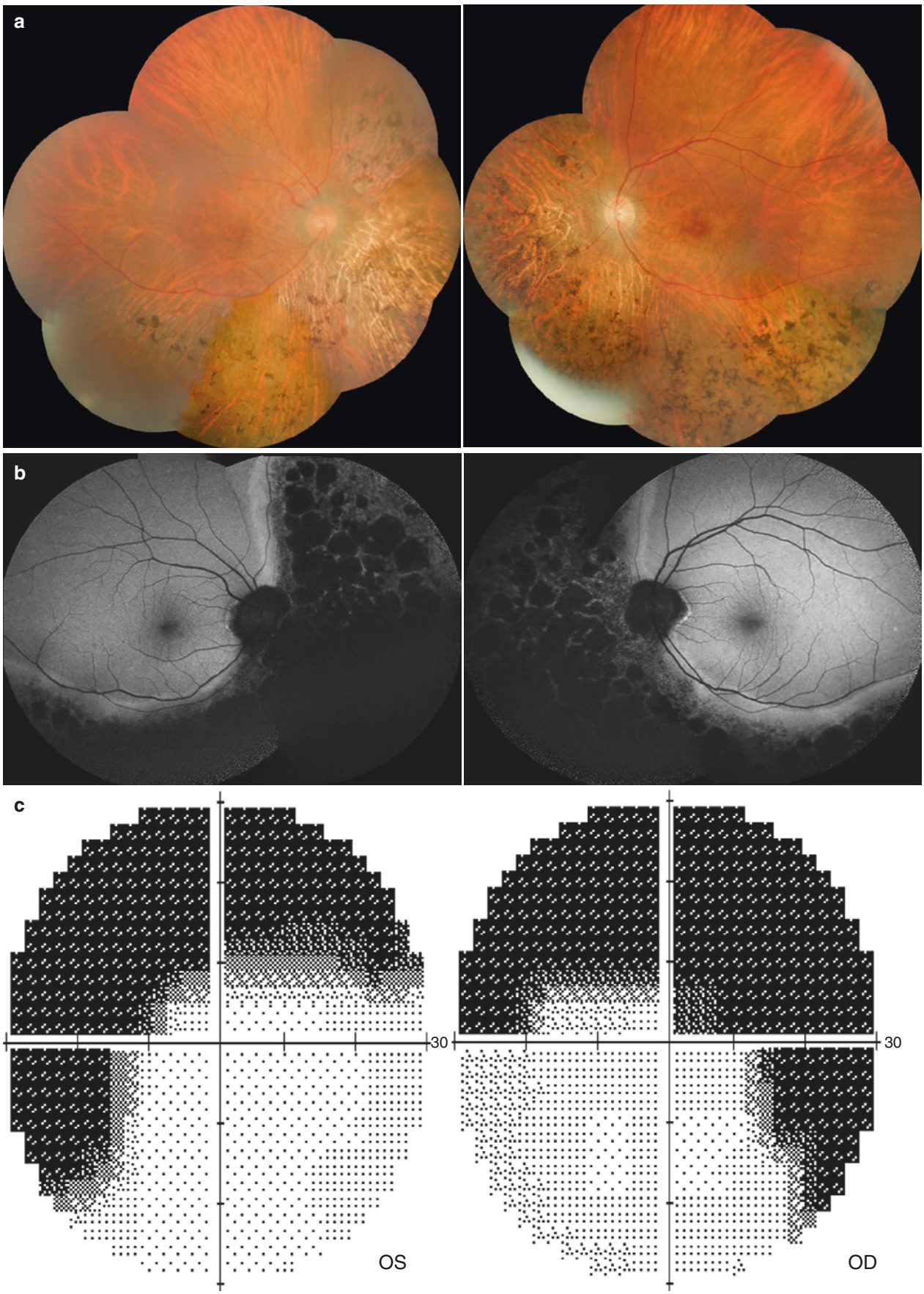


Fig. 1.35 A 9-year-old patient with Leber's congenital amaurosis (LCA) 10 (*CEP290* mutation). (**a**) The fundus photo reveals diffuse white dots in the right eye. (**b**) Coats-like exudation at the inferotemporal and superonasal quadrants with fresh hemorrhage was found in the left eye. The patient underwent cryotherapy and retinal laser photocoagulation. (**c**) Three years later, the fundus photo shows diffuse white dots and marked retinal pigment epithelium (RPE) alteration at the macula

Fig. 1.36 A case with sector retinitis pigmentosa. (**a**) The fundus appearances in the two eyes are highly symmetric. (**b**) Instead of forming a perifoveal hyper-autofluorescent ring, the hyper-autofluorescent area is along the posterior border of the affected retina, designating the area with retinal pigment epithelial cell changes. (**c**) The visual fields corresponded well with the area with hyperpigmentation and chorioretinal atrophy. (**d**) The full-field electroretinogram shows decreased rod and cone response amplitude. The lower row is from a normal subject, for comparison. Despite the ERG changes, the visual acuity was still relatively preserved at 20/30 in both eyes due to macula preservation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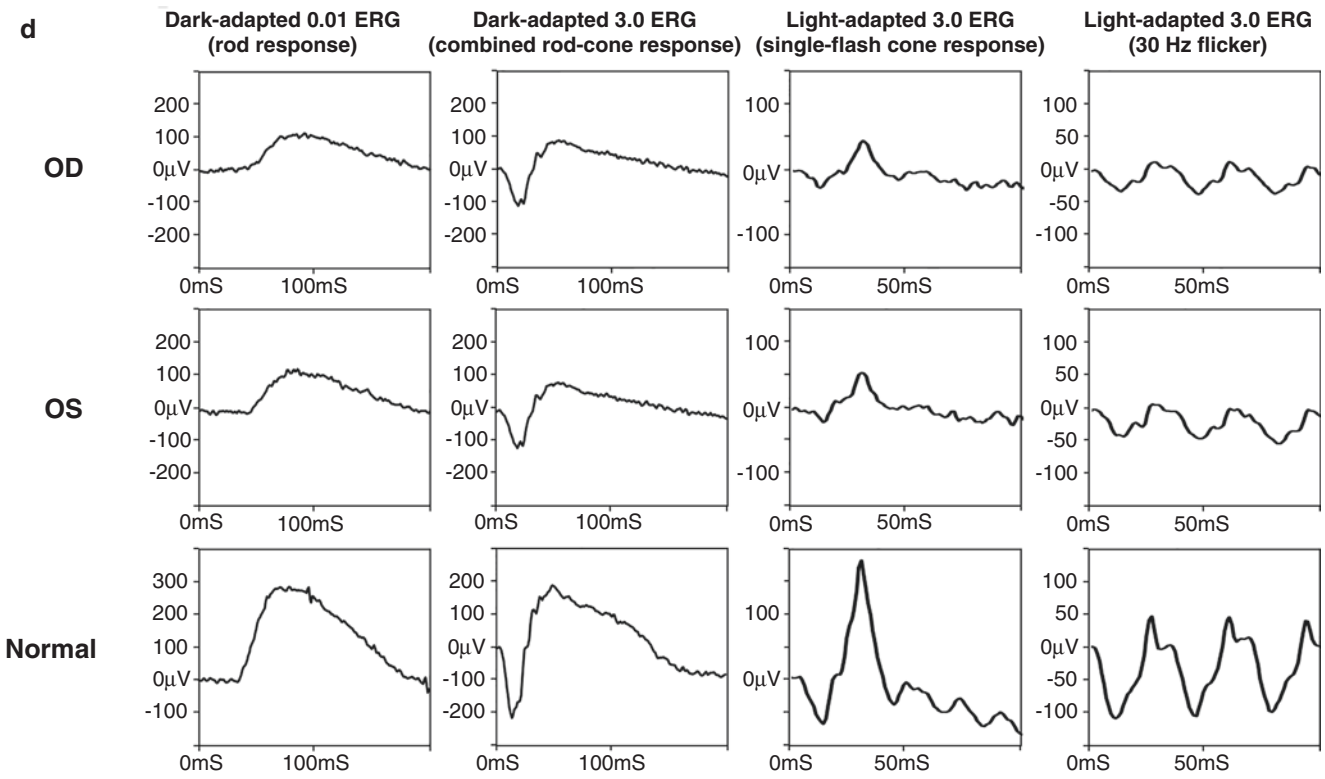

Fig. 1.36 (continued)

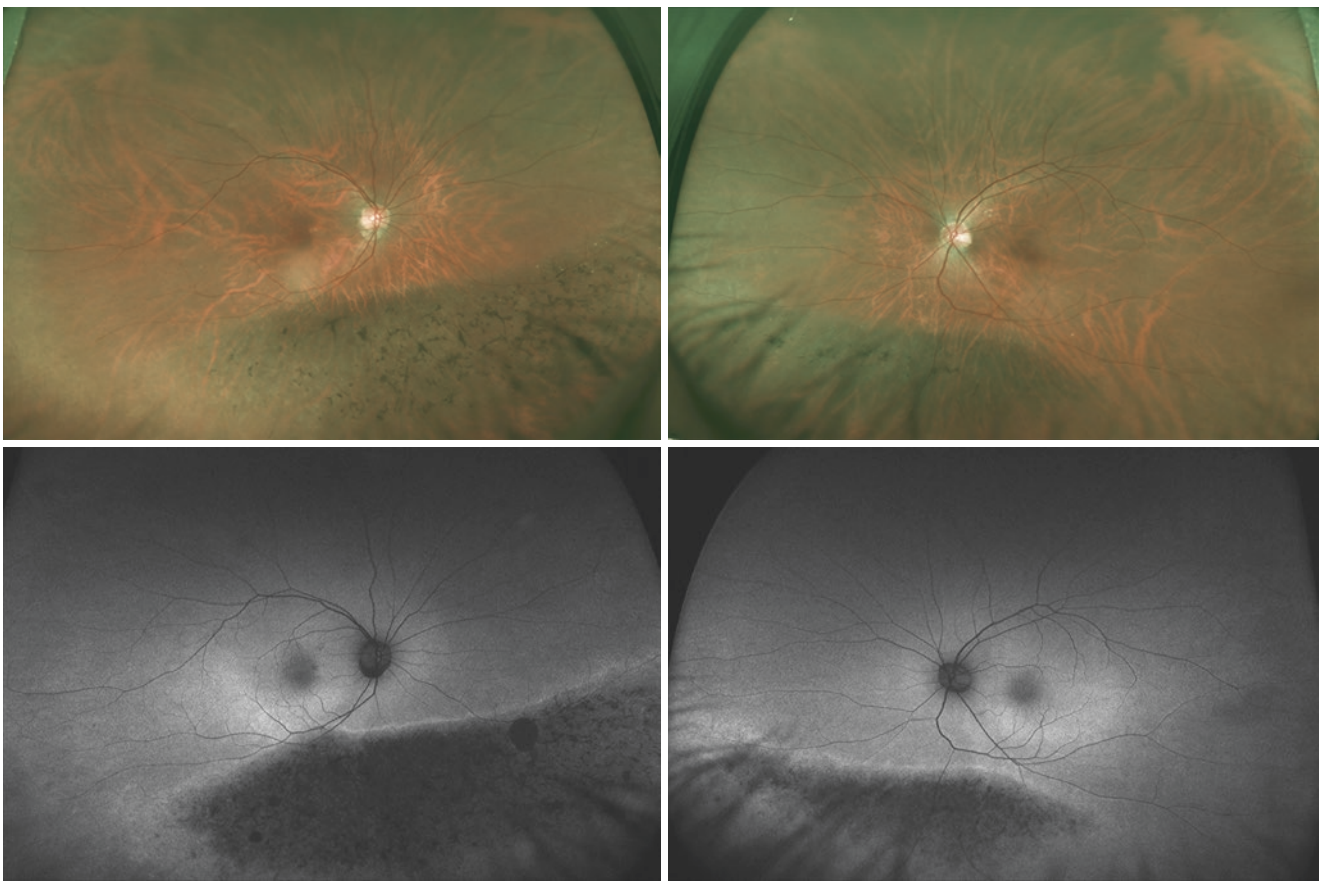

Fig. 1.37 Sector retinitis pigmentosa. The ultra-wide field retinal imaging displays symmetric fundus appearances. Apart from the typical retinitis pigmentosa changes in the inferonasal quadrant, the rest of the unaffected retina appears normal

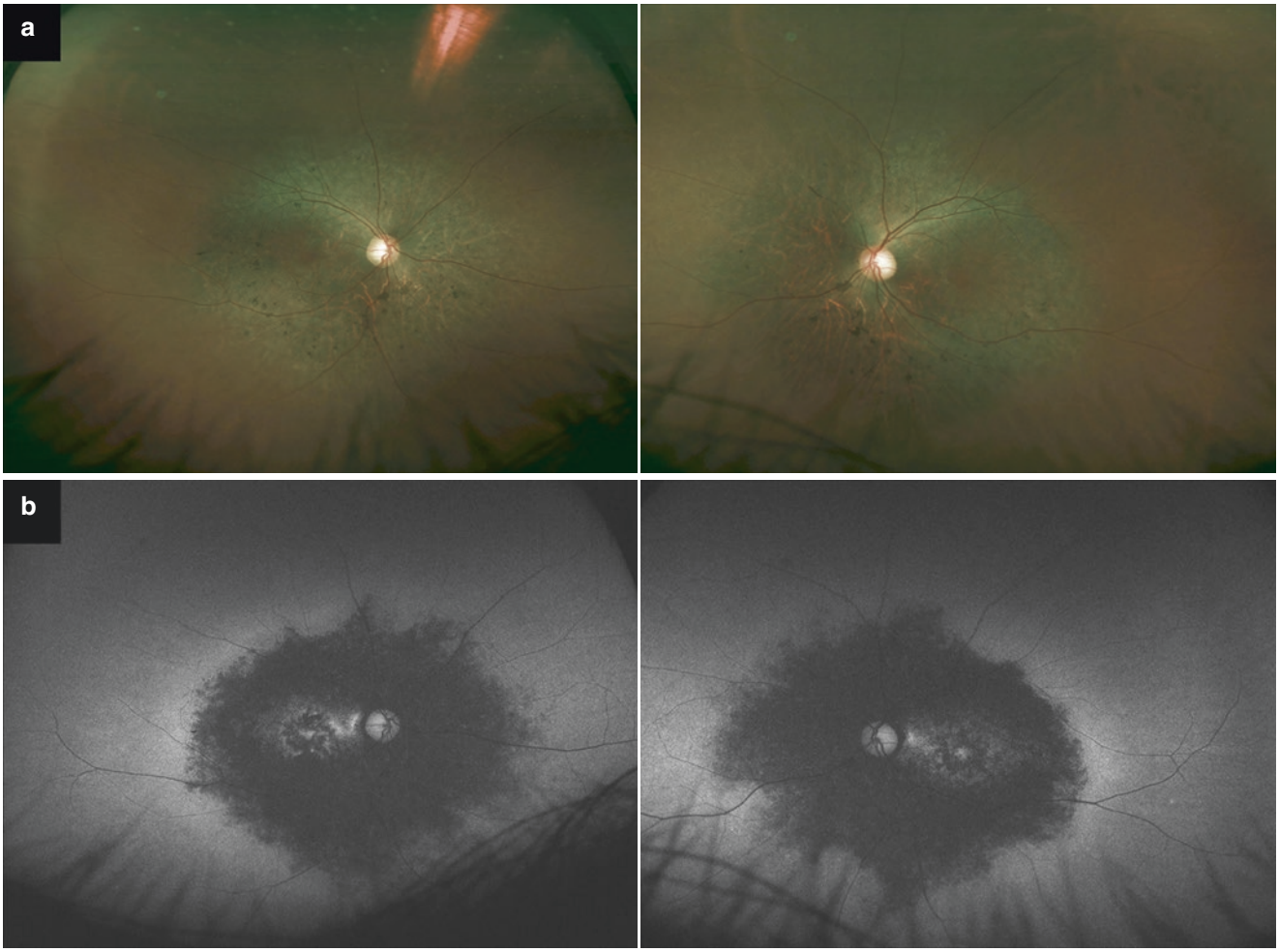

Fig. 1.38 Images of a 59-year-old patient with retinitis pigmentosa inversa. (**a**) Fundus photograph showing accumulated symmetrical pigments and retinal atrophy in the macula. (**b**) The fundus autofluorescence images clearly demonstrate the atrophic area in the posterior pole with some preserved retina in the fovea. The peripheral retina is also intact

(Fig. 1.38). Peripheral vision remains intact. Other differential diagnoses should be ruled out, including LCA, progressive CRD, central areolar choroidal sclerosis, as well as syphilitic retinopathy, retinal toxicity from phenothiazine use, and chloroquine retinopathy.

CRB1 Retinopathy and Related Features

Mutations in the crumbs homolog 1 (*CRB1*) gene have been reported in multiple inherited retinal degeneration (IRD) phenotypes, including LCA8 , early onset rod-cone dystrophy, CRD, autosomal recessive retinitis pigmentosa, retinitis pigmentosa with preserved para-arteriole retinal pigment epithelium (PPRPE), pigmented paravenous chorioretinal atrophy (PPCRA), and retinal telangiectasia with exudation (also referred to as Coats-like vasculopathy or Coats-like RP) (Slavotinek 2016). Other *CRB1*-associated ocular conditions include keratoconus and nanophthalmos. To date, more than 150 mutation variants have been reported on the *CRB1* gene (Slavotinek 2016), but genotype–phenotype correlations are yet difficult to establish.

The *CRB1* gene encodes the CRB1 protein. The CRB1 protein is located in the subapical region of the photoreceptors and abuts the adherens junctions, which form the ELM in the mammalian retina (Bulgakova and Knust 2009). Alterations in the CRB1 protein affect photoreceptor morphogenesis and homeostasis and influence the polarity of epithelial cells (Pocha and Knust 2013).

Unlike in other IRDs, the retina in patients with mutations in *CRB1* is usually thickened and coarsely laminated. The abnormal retinal structure resembles normal human fetal retina and suggests that *CRB1* mutations affect the maturing process of normal retina lamination (Jacobson 2003). This feature is most apparent in OCT studies (Fig. 1.39).

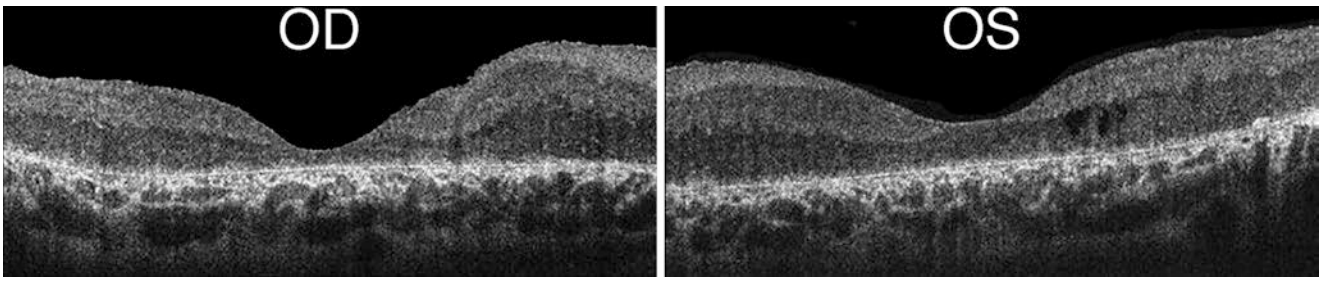

Fig. 1.39 A 17-year-old girl with early-onset retinal dystrophy and confirmed to have the *CRB1* mutation. Fourier domain optical coherence tomography reveals a coarsely laminated and thickened retina, which is a key feature of *CRB1* retinopathy. (Reproduced from Tosi et al. 2009)

Retinitis Pigmentosa with Preserved Para-Arteriole Retinal Pigment Epithelium (PPRPE)

The fundus appearance is unique in RP with PPRPE. Despite diffuse RPE degeneration, the RPE along the retinal arterioles is relatively preserved (Fig. 1.40). *CRB1* mutations have been reported in approximately 74.1% of RP cases with PPRPE (Bujakowska et al. 2012).

Coats-Like Retinitis Pigmentosa (Coats-Like Exudative Vasculopathy)

Coats' disease is a rare idiopathic exudative retinal disease that features by aneurysmal dilation and telangiectatic retinal veins, yellow extravascular lipid depositions, and retinal detachment. It has male predominance and is usually unilateral. The association between RP and exudative retinopathy was first presented by Zamoranin in 1956 and has been termed *Coats-like retinitis pigmentosa* due to the resemblance. It affects 1–4% of RP cases (Pruett 1983) and has been reported to be associated with *CRB1* gene mutations in approximately 53.3% of affected individuals (de Hollander et al. 2001; Bujakowska et al. 2012).

Coats-like RP has different demographic characteristics that relate classic Coats' disease with older age, slight female predominance, and family history. The clinical presentation combines both the features of RP and Coats' disease. Dilated, telangiectatic, or aneurysmal retinal veins are accompanied with lipid depositions and exudative retinal detachment (Fig. 1.41). In the areas not affected by Coats-like changes, typical changes found in RP are displayed (Khan et al. 1988).

Pigmented Paravenous Chorioretinal Atrophy (PPCRA)

RP with PPCRA is a rare phenotype of RP characterized by bilaterally symmetric paravenous distribution of RPE atrophy and pigment clumping. The subjects are often asymptomatic and are diagnosed incidentally during routine eye examination (Fig. 1.42). However, variable clinical presentations do exist, and symptoms of night blindness and ERG abnormalities have been reported (Fig. 1.43). Most documented cases were sporadic, but there was also an association with the *CRB1* gene (McKay et al. 2005). FAF is a useful and noninvasive examination to demonstrate the distribution of RPE alterations (Hashimoto et al. 2012) (Figs. 1.42 and 1.44).

Enhanced S-Cone Syndrome (Goldmann–Favre Syndrome)

Introduction

Enhanced S-cone syndrome (ESCS), also known as Goldmann–Favre syndrome, is a slowly progressive autosomal recessive retinal dystrophy caused by an *NR2E3* (photoreceptor-specific nuclear receptor, PNR) gene mutation. *NR2E3*, located on chromosome 15q23, encodes a ligand-dependent transcription repressor of cone-specific genes in rod photoreceptors and determines the differentiation of retinal progenitor cells. Mutations of *NR2E3* disturb normal photoreceptor differentiation, possibly by encouraging a default from the rod photoreceptor pathway to the S-cone pathway, leading to decreased rod numbers and increased proportion of S-cones (Chen et al. 2005; Bernal et al. 2008; Bumsted O'Brien et al. 2004).

Clinical Features

ESCS was first described by Marmor et al. (1990) as a disease characterized by night blindness, maculopathy, and increased S-cone sensitivity. The fundus appearance is highly variable, with the most classical phenotype being nummular pigment clumping at the level of RPE along the vascular arcades in adult ESCS patients (Yzer et al. 2013; Audo et al. 2008) (Figs. 1.45 and 1.46). Whereas in younger patients, multiple whitish spots, whitish subretinal deposit and maculopathy are found (Wang et al. 2009). Compared to typical RP, the distribution of pigment in ESCS confines to the mid-peripheral retina without peripheral involvement, and in a clumping pattern rather than dispersed. FAF images can present in a similar way to RP or as hyper-AF spots in younger patients. Wang et al. (2013) studied the origin of these hyper-AF spots and found that these hyper-AF spots are not from RPE but microglia cells that phagocytose

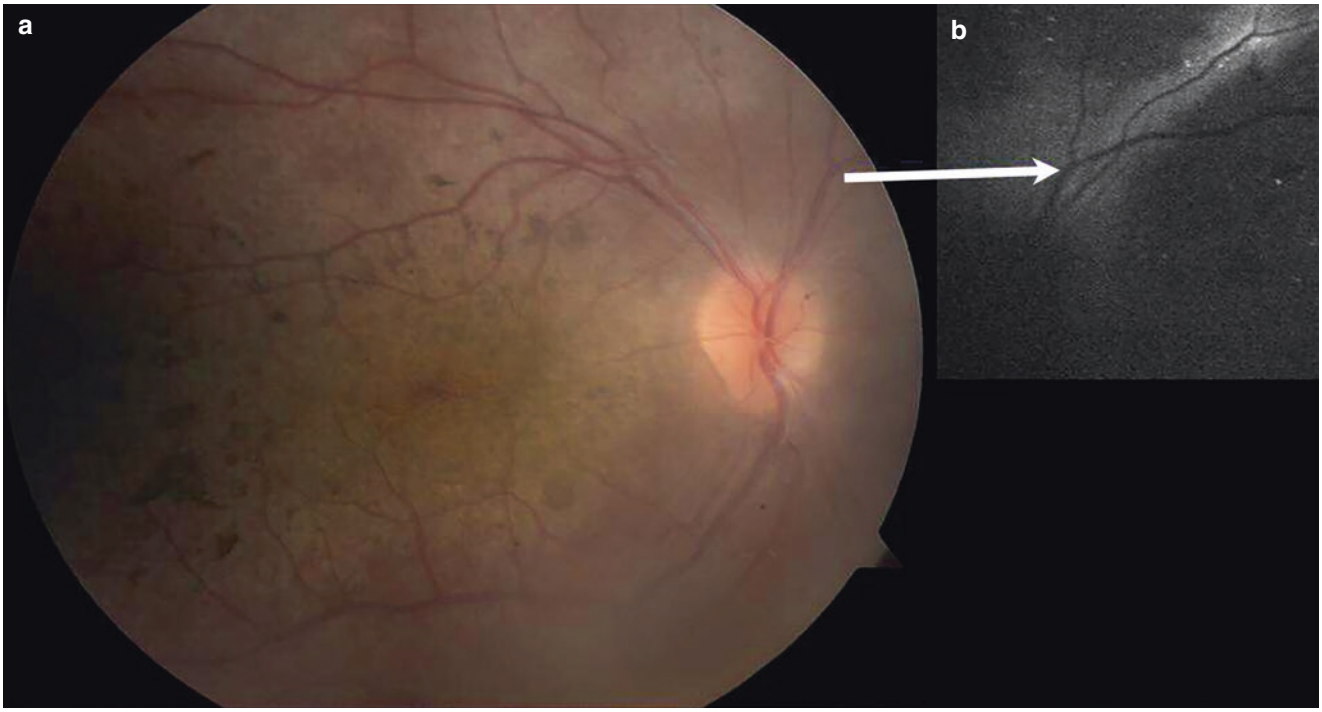

Fig. 1.40 Color fundus photograph and fundus autofluorescence (FAF) image of the same patient in Fig. 1.39. (**a**) There are retinal pigment epithelium (RPE) alterations, RPE atrophy, and hyperpigmentation on color fundus photograph. (**b**) The preserved RPE along the arterioles is easily identified on the FAF study. The diagnosis was *CRB1*-related retinitis pigmentosa with preserved para-arteriole of the retinal pigment epithelium. (Reproduced from Tosi et al. 2009)

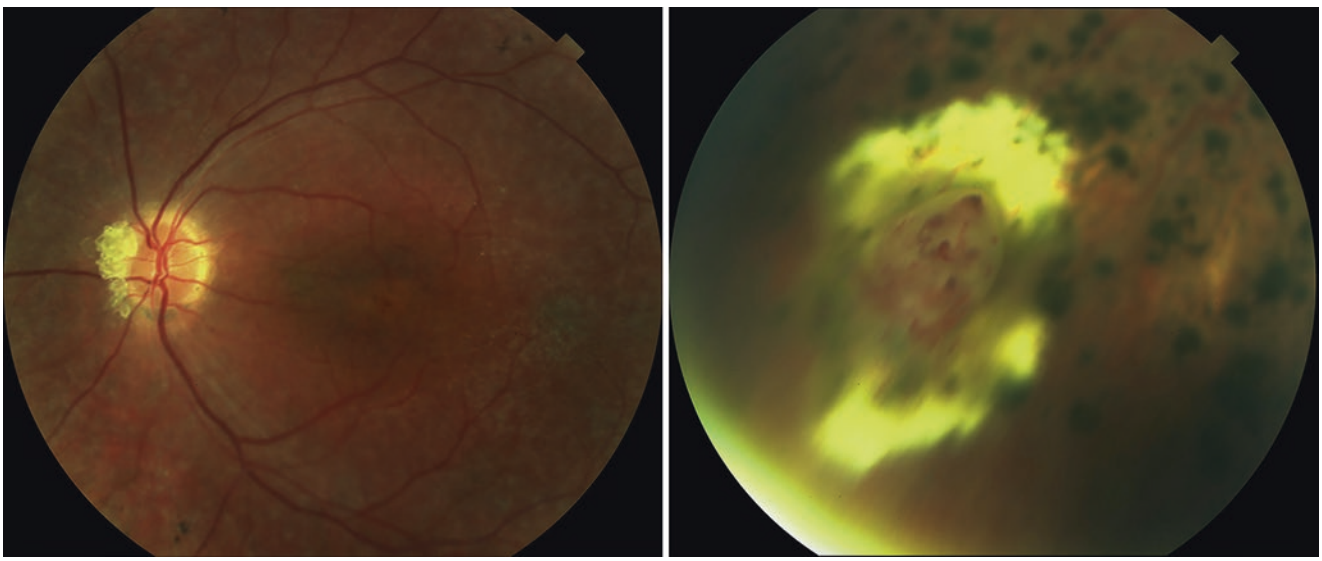

Fig. 1.41 A 23-year-old patient with Coats-like exudative vasculopathy. Fundus photographs showing multiple optic disc drusens, chorioretinal atrophy, lipid depositions, and vessel telangiectasia. (Reproduced from Talib et al. 2017)

photoreceptor outer segments. OCT of macula may show CME, macula scar, or ONL foldings that correspond to the hyper-AF. FA reveals hyper-AF spots corresponding to the white spots, but no fluorescence leakage despite the presence of CME (Wang et al. 2009) (Fig. 1.47). CME without obvious angiographic leakage can also be found in niacin-related maculopathy (Domanico et al. 2013), X-linked retinoschisis, and optic pit (Moisseiev et al. 2015).

ERG plays a key role in diagnosis. Classic ERG findings include (1) no rod response, (2) the waveforms of scotopic maximal response identical to the transient photopic responses except for size, (3) and the amplitude of a wave in

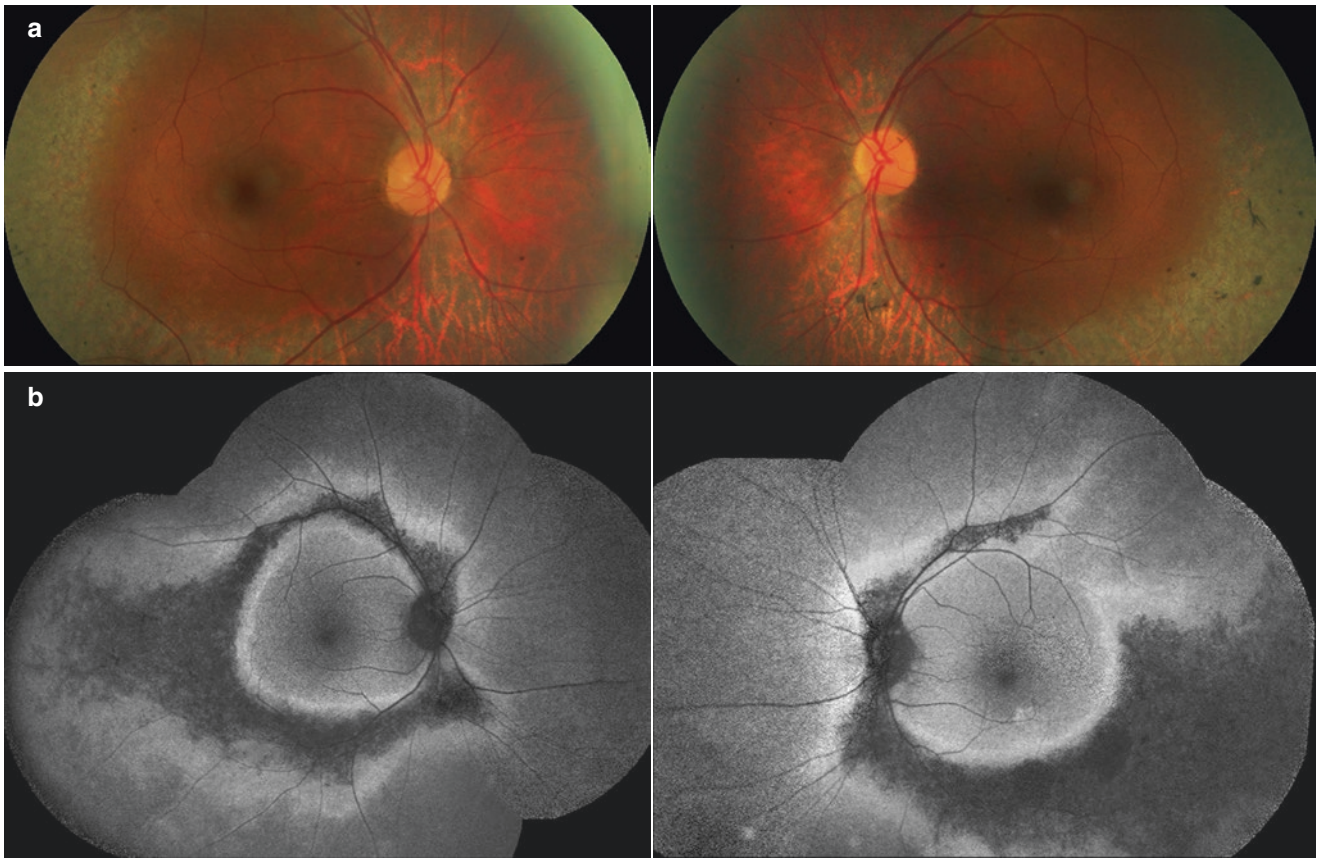

Fig. 1.42 A 59-year-old man with retinitis pigmentosa and pigmented paravenous chorioretinal atrophy. He has ankylosing spondylosis and a history of recurrent acute anterior uveitis in both eyes. He does not have night blindness, and his best-corrected visual acuity was 20/20. (**a**) The fundus appearances are bilaterally symmetric. There is mainly retinal pigment epithelium (RPE) atrophy along the retinal veins, and only some pigment clumping is visible. (**b**) FAF study shows paravenous hypo-autofluorescent areas. Adjacent hyper-autofluorescent borders indicate possible RPE alterations in the future

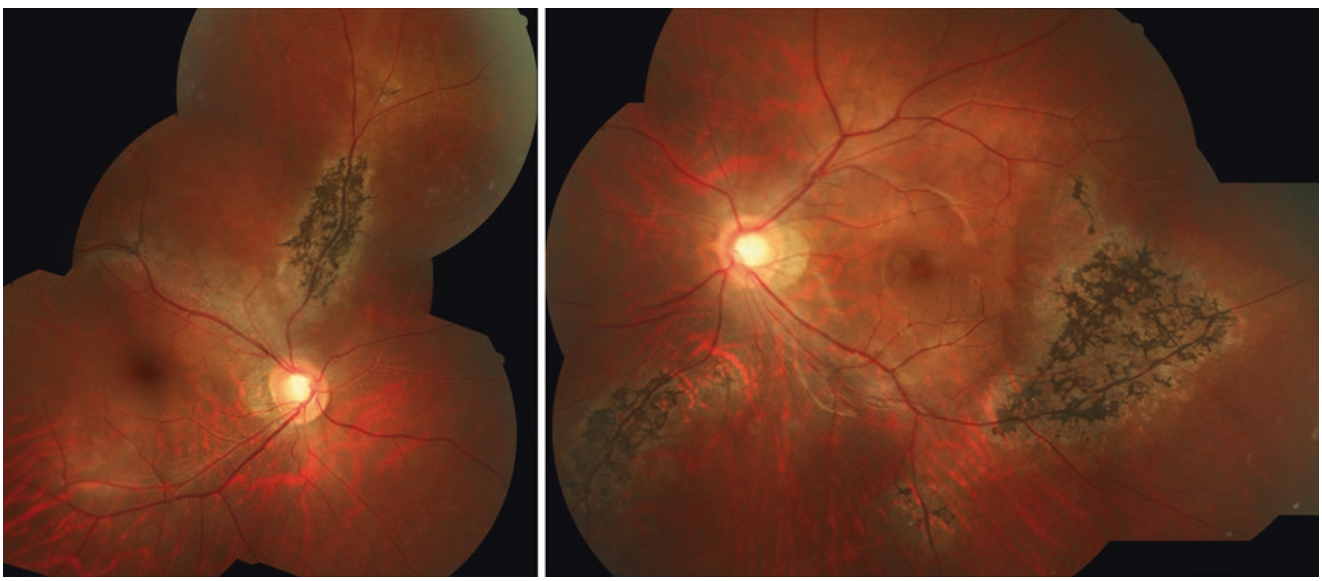

Fig. 1.43 A 26-year-old man with retinitis pigmentosa and pigmented paravenous chorioretinal atrophy. He presented with blurred vision in the right eye. The best-corrected vision was 8/20 in the right eye and 20/20 in the left eye. Both eyes display pigmentation and chorioretinal atrophy along some parts of the retinal veins, but they are not symmetrical. The scotomas on visual field examination corresponded well with the affected areas

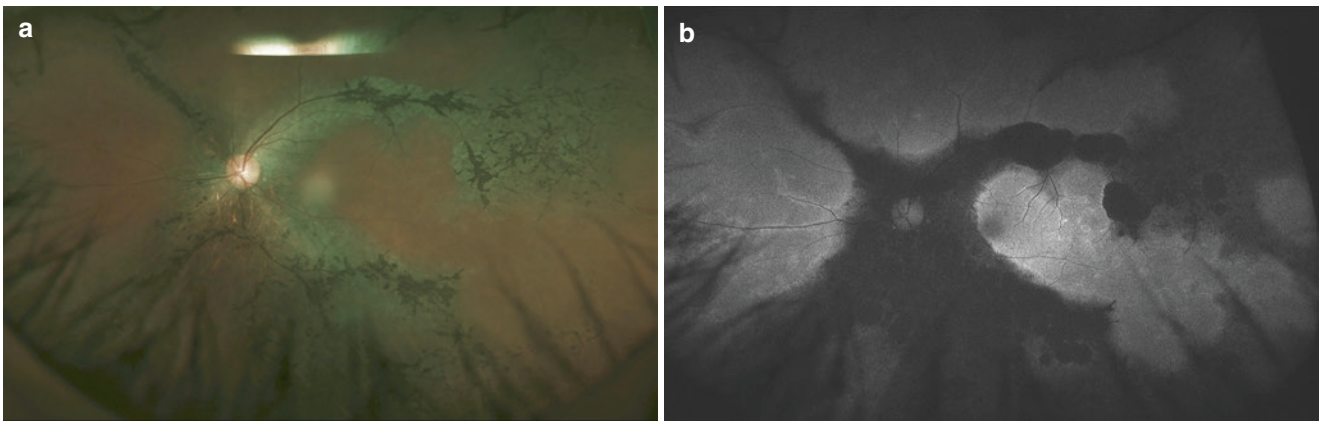

Fig. 1.44 A 52-year-old woman with retinitis pigmentosa and pigmented paravenous chorioretinal atrophy. (**a**) Ultra-wide field color fundus photograph showing pigmentation and retinal pigment epithelium atrophy distributed along the retinal veins. The macula was preserved and she had 8/20 vision in her left eye. (**b**) Ultra-wide field fundus autofluorescence clearly demonstrates the atrophic areas, compatible with the paravenous distribution on the color photograph

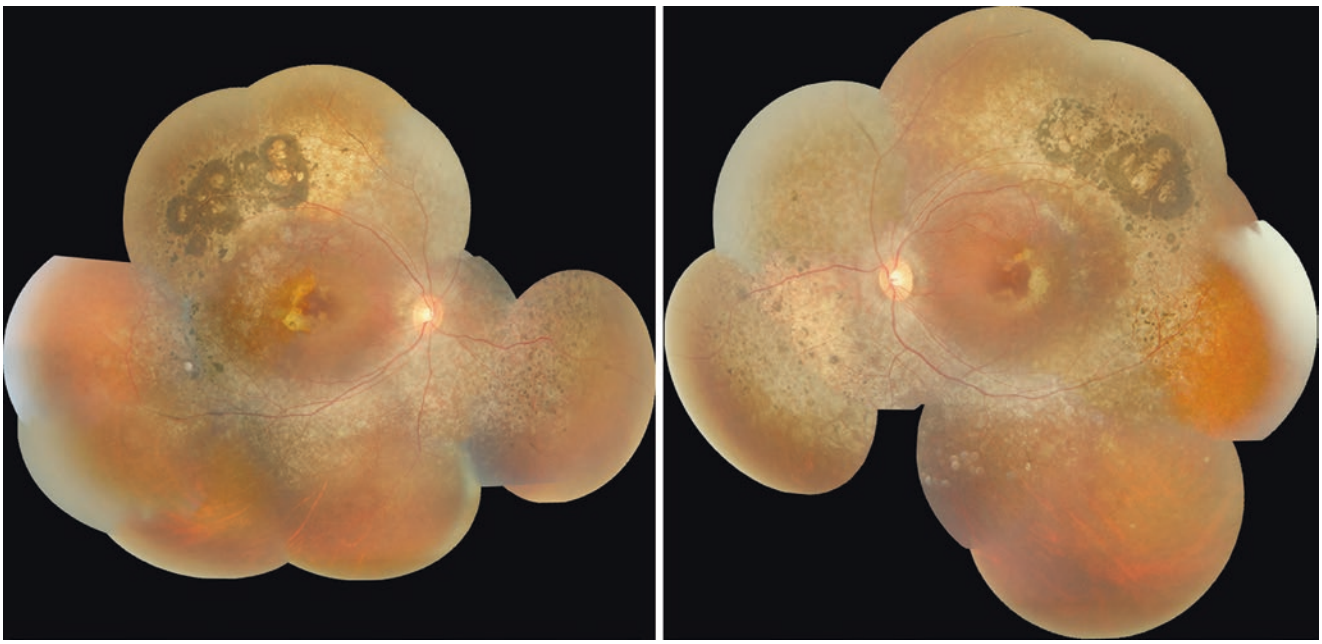

Fig. 1.45 Photograph of the fundus of a 26-year-old patient with enhanced S-cone syndrome (ESCS) revealing multiple white dots with focal hyperpigmentation at mid-peripheral retina and some yellowish pigmentation in the macula

the transient photopic response larger than amplitude of photopic 30 Hz flicker (Wang et al. 2009) (Fig. 1.48).

Syndromic Retinitis Pigmentosa

Usher Syndrome

Usher syndrome (USH) is an autosomal recessive disorder affecting both retina and inner ear. The prevalence is 1–4 per 25,000 people and is the leading cause of deaf-blindness worldwide (Mathur and Yang 2015). Over 10 USH genes have been identified as causative genes. The USH proteins encoded by these genes can be found in several different organs and interact with one another. In the inner ear, USH proteins are related to the functioning and maintenance of inner ear hair cells, whereas the function of these proteins in the retina are still not well understood.

USH has been classified into three subtypes. Each subtype has a variable degree of visual impairment, hearing impairment, or vestibular dysfunction. It is among the most common forms of syndromic RP, and the fundus appearances of USH patients are identical to typical RP (Figs. 1.15 and 1.49).

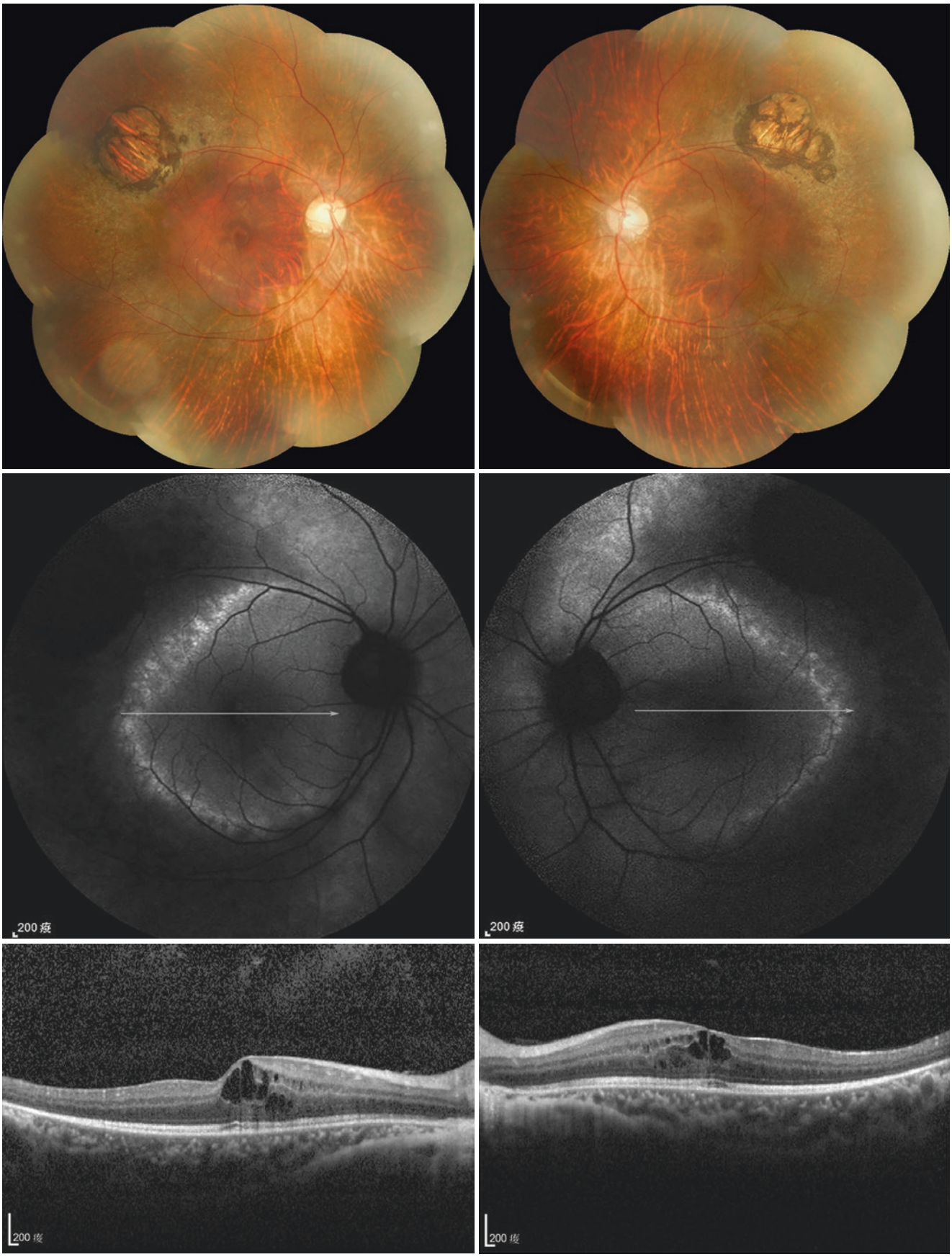

Fig. 1.46 A 22-year-old patient with enhanced S-cone syndrome (ESCS). The photo of the fundus revealed multiple white dots along the vascular arcade with focal hyperpigmentation. Optical coherence tomography revealed the presence of cystoid macula edema. FA found a ring of increased autofluorescence of the white dots

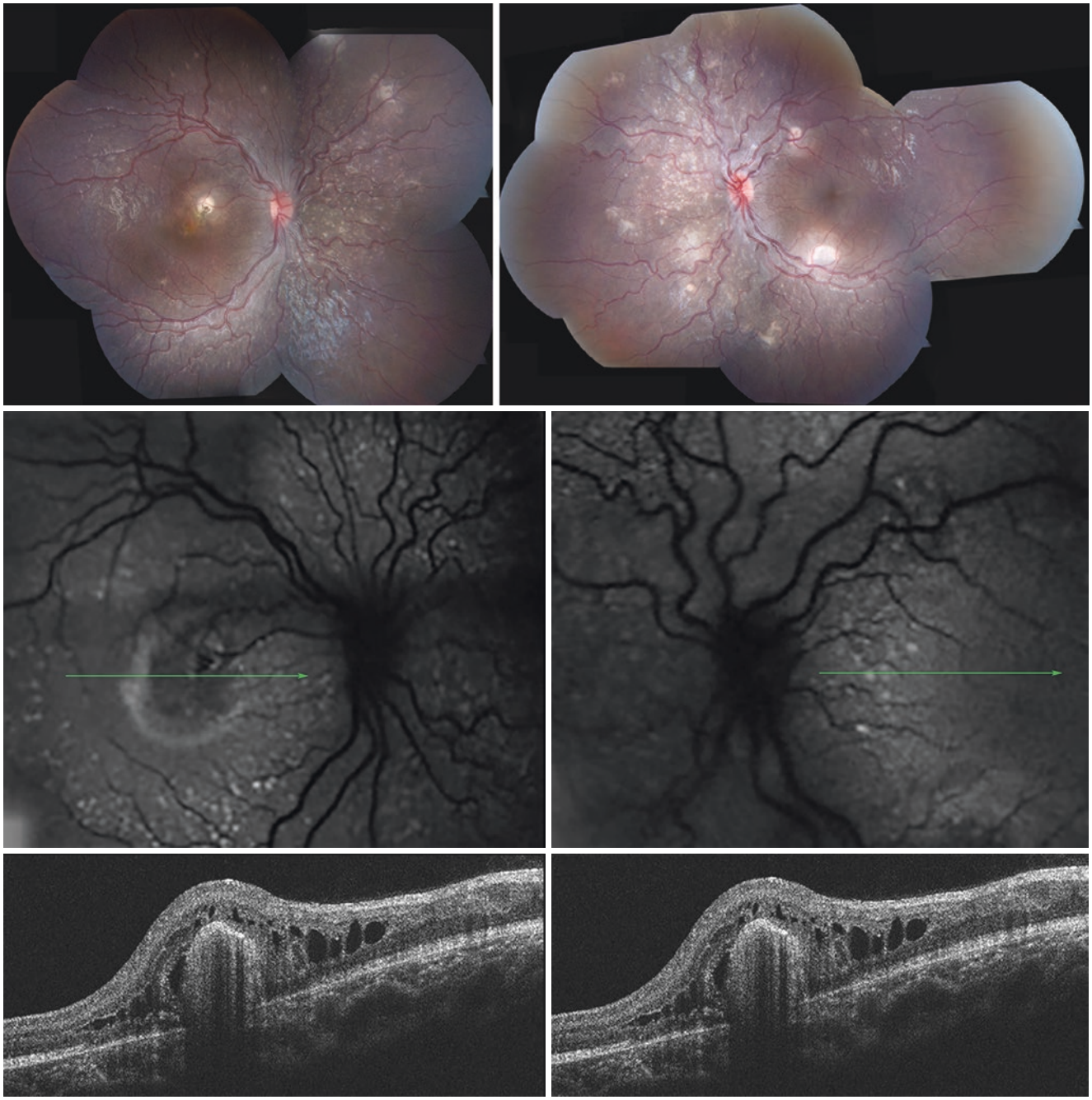

Fig. 1.47 Enhanced S-cone syndrome with cystoid macular edema. Fundus photographs showing multiple white dots at mid-periphery, subretinal whitish deposits at the macula in the right eye, and focal subretinal whitish deposits near the vascular arcade in the left eye. Fundus autofluorescent exam disclosed hyper-autofluorescent spots in the macular and mid-peripheral retina. The hyper-autofluorescence at the mid-periphery corresponds to the whitish spots on the fundus, whereas hyper-autofluorescence within the macula does not. Optical coherence tomography demonstrates intraretinal cystic change at the macula in the right eye. Note the rosette-like intraretinal lesions corresponding to the hyper-autofluorescent spots and loss of retinal lamination

Bardet–Biedl Syndrome

Bardet–Biedl syndrome (BBS) is a rare autosomal recessive multiorgan disorder related to ciliopathy. The cardinal features include retinal degeneration, polydactyly, early obesity, renal dysfunction, genital abnormalities, and learning difficulties (Forsythe and Beales 2013). Rod-cone dystrophy was reported in >90% of cases and is the most common feature (Beales et al. 1999) (Fig. 1.50). RP usually presents in the first decade, and central vision is severely affected before 20 years of age (Klein and Ammann 1969).

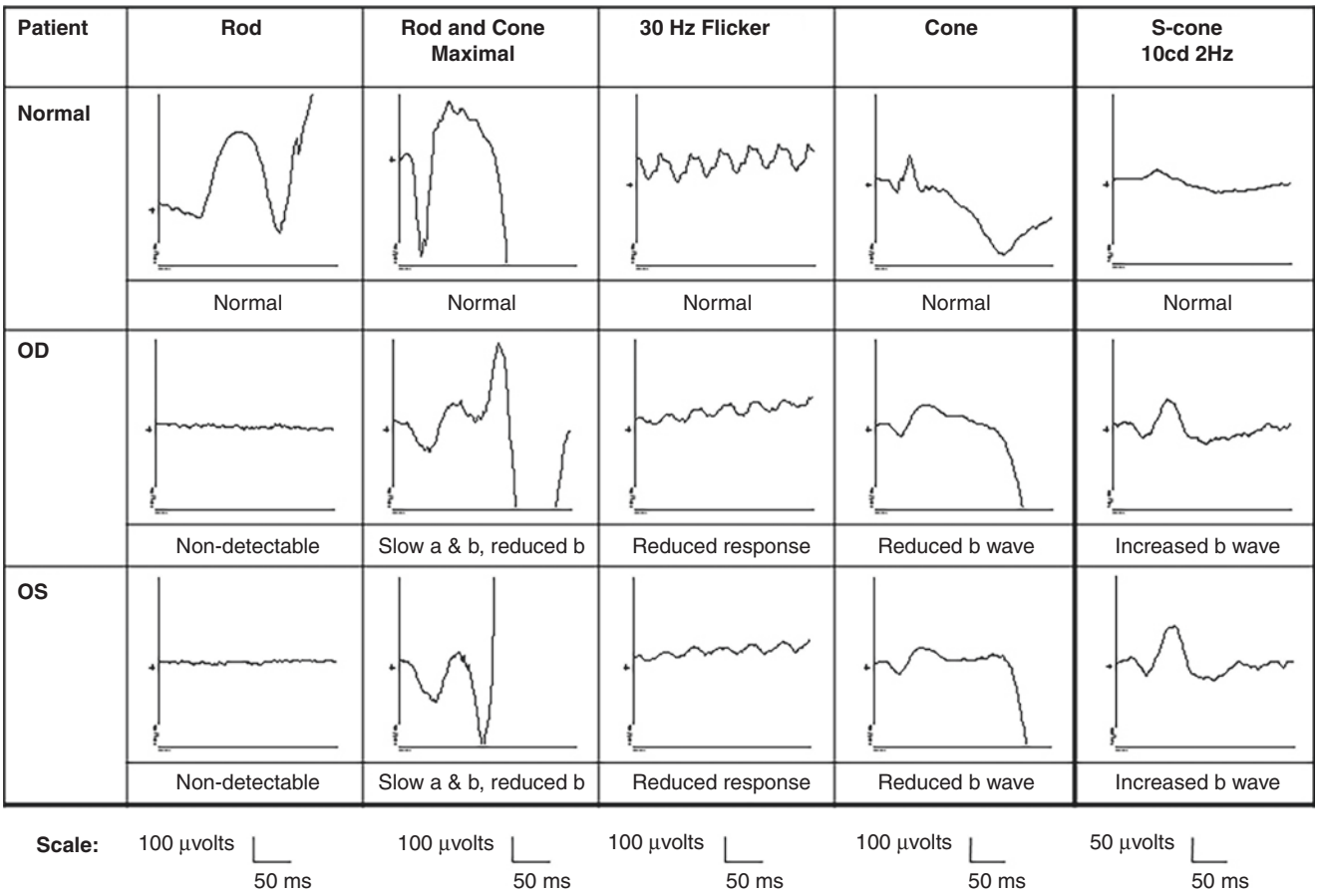

Fig. 1.48 Electroretinogram (ERG) showing classic findings of enhanced S-cone syndrome (ESCS). (1) No rod response, (2) the waveforms of scotopic maximal response identical to the transient photopic responses except for size, and (3) amplitude of a wave in the transient photopic response larger than the amplitude of the photopic 30 Hz flicker. Note the remarkably high amplitude of S-cone specific ERG

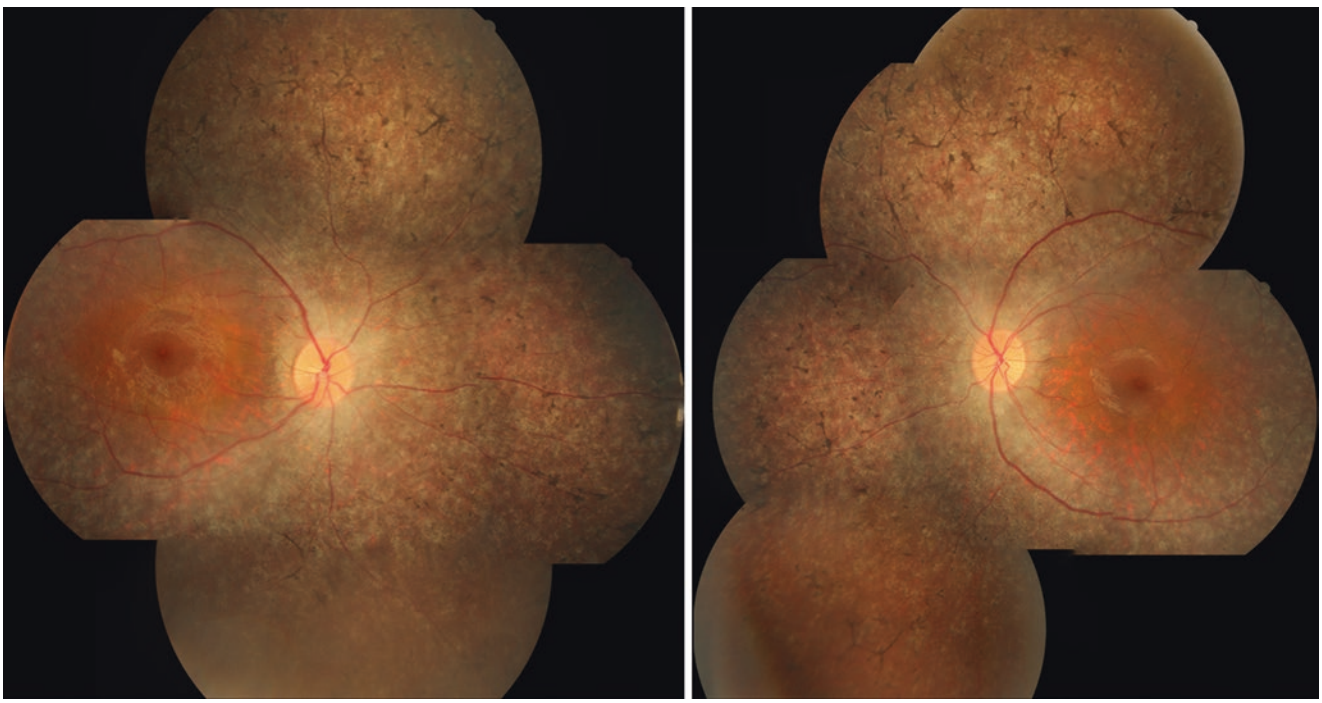

Fig. 1.49 A 23-year-old woman with night blindness since her early teens and hearing impairment since childhood. A fundus exam showed a typical retinitis pigmentosa appearance with preservation of the macula. Her parents and one brother have no ophthalmic or hearing-related problems. The clinical diagnosis was Usher Syndrome type II

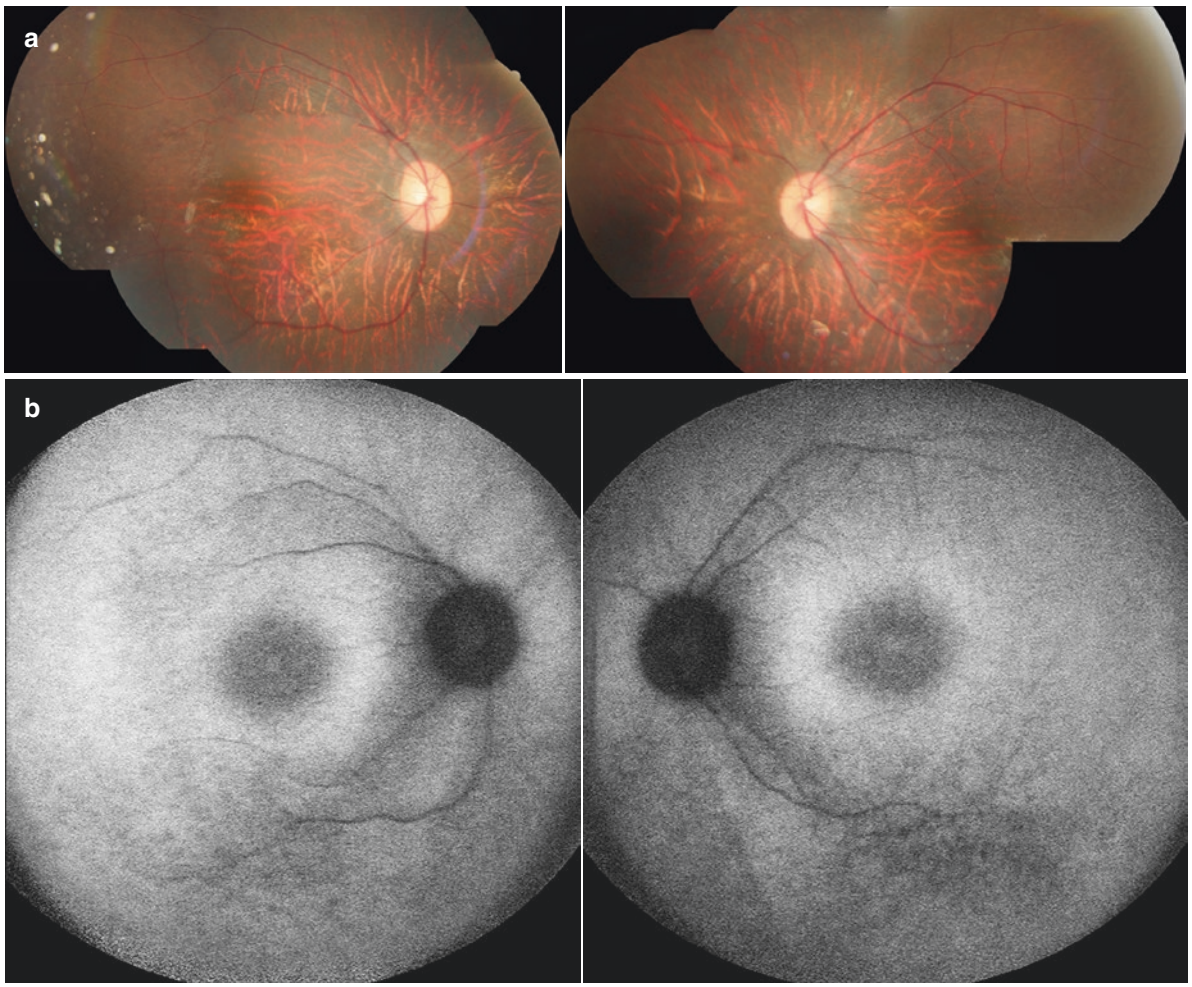

Fig. 1.50 A 17-year-old girl with Bardet–Biedl syndrome. She has diabetes mellitus, impaired renal function, vaginal atresia, and polydactyly in both feet. (**a**) Fundus photographs showing vessel attenuation, retinal hypopigmentation, and chorioretinal atrophy. The macula was preserved. (**b**) Fundus autofluorescence images display features of retinitis pigmentosa including mid-peripheral hypo-autofluorescence and perifoveal hyper-autofluorescent ring. The ERG study revealed severe rod and cone degeneration

Senior–Loken Syndrome

Senior–Loken syndrome is a rare autosomal recessive disorder affecting the eyes and the kidneys. The disease belongs to the spectrum of ciliopathy and causes RP- or LCA-like degenerative retinopathies and nephronophthisis, a cystic kidney disease which can lead to end-stage renal disease. The ocular findings consist of early onset night blindness or vision loss, nystagmus, and clinical features of RP (Ronquillo et al. 2012) (Fig. 1.51).

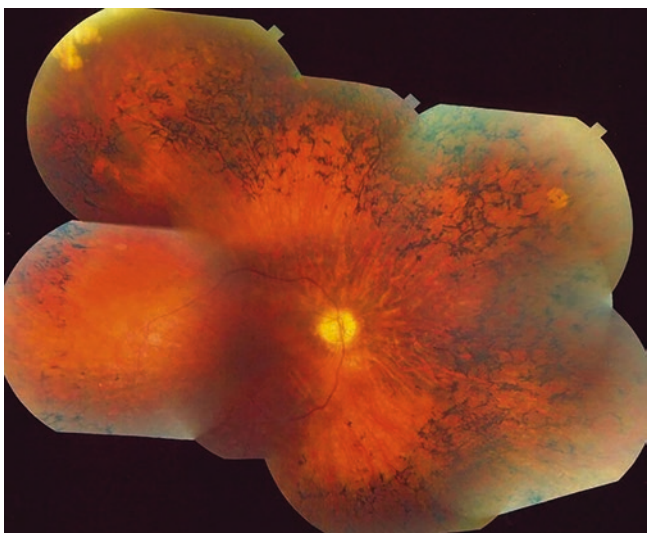

Fig. 1.51 The color fundus image of a patient with Senior–Loken syndrome demonstrates features of retinitis pigmentosa. (Reproduced from Ronquillo et al. 2012)

Kearns–Sayre Syndrome

Kearns–Sayre syndrome (KSS) is a group of rare mitochondrial diseases. Most patients initially present with ophthalmic abnormalities. The classic KSS triad includes progressive external ophthalmoplegia, pigmentary retinopathy, and onset age younger than 20 years. Additional diagnostic features

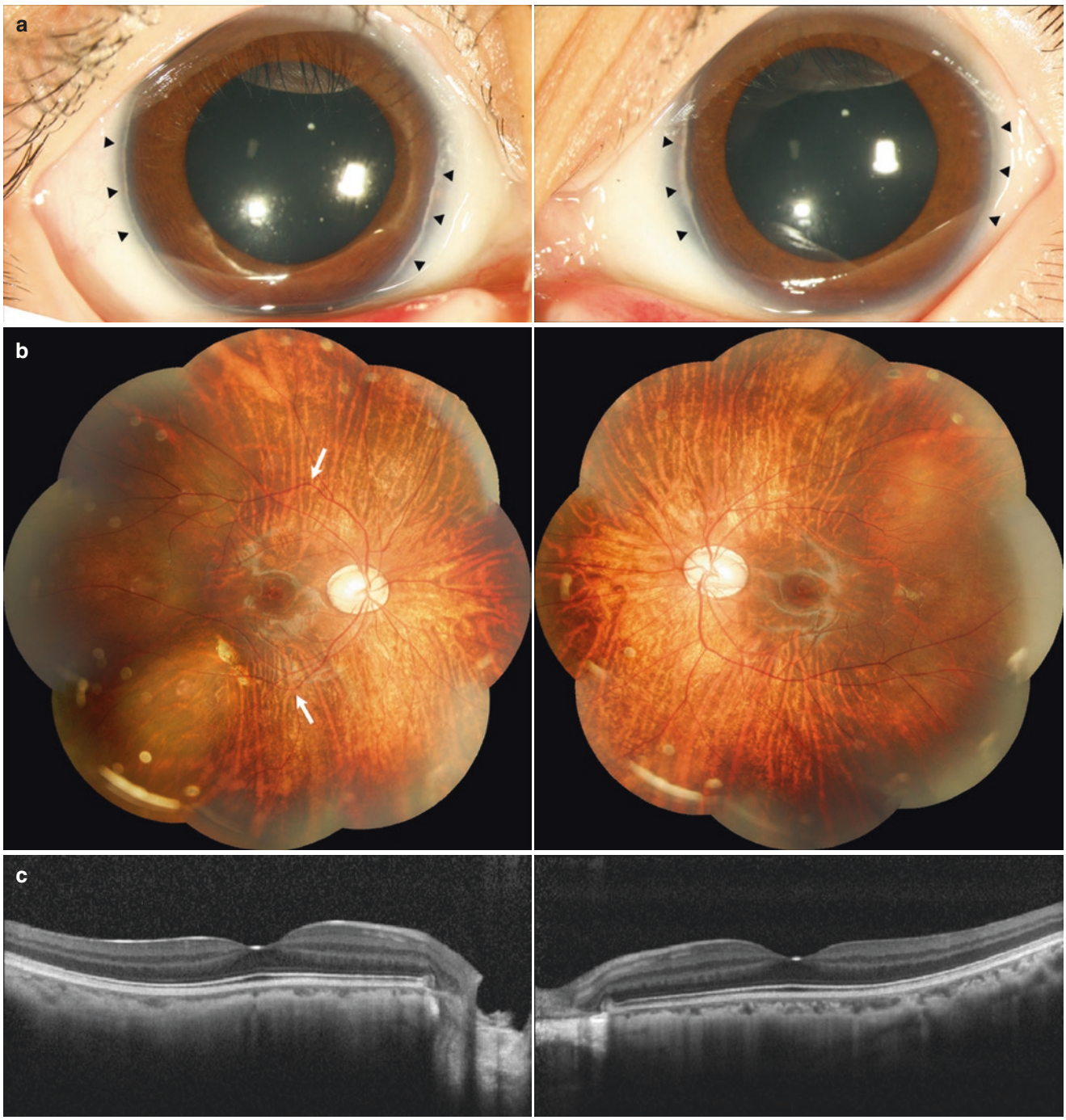

Fig. 1.52 A 9-year-old boy with Alagille syndrome and confirmed *human Jagged 1* (*JAG1*) gene mutation. His vision was 20/20 in both eyes. (**a**) Posterior embryotoxon (black arrowhead) is a key ophthalmic feature in Alagille syndrome. (**b**) Fundus photographs showing diffused hypopigmentation, retinal pigment epithelium alterations, oval-shaped optic nerve head anomaly with large cupping, and angulated retinal vessels (white arrow). (**c**) The optical coherence tomography images display decreased choroidal thickness for both eyes. (Reproduced from Shen et al. 2017)

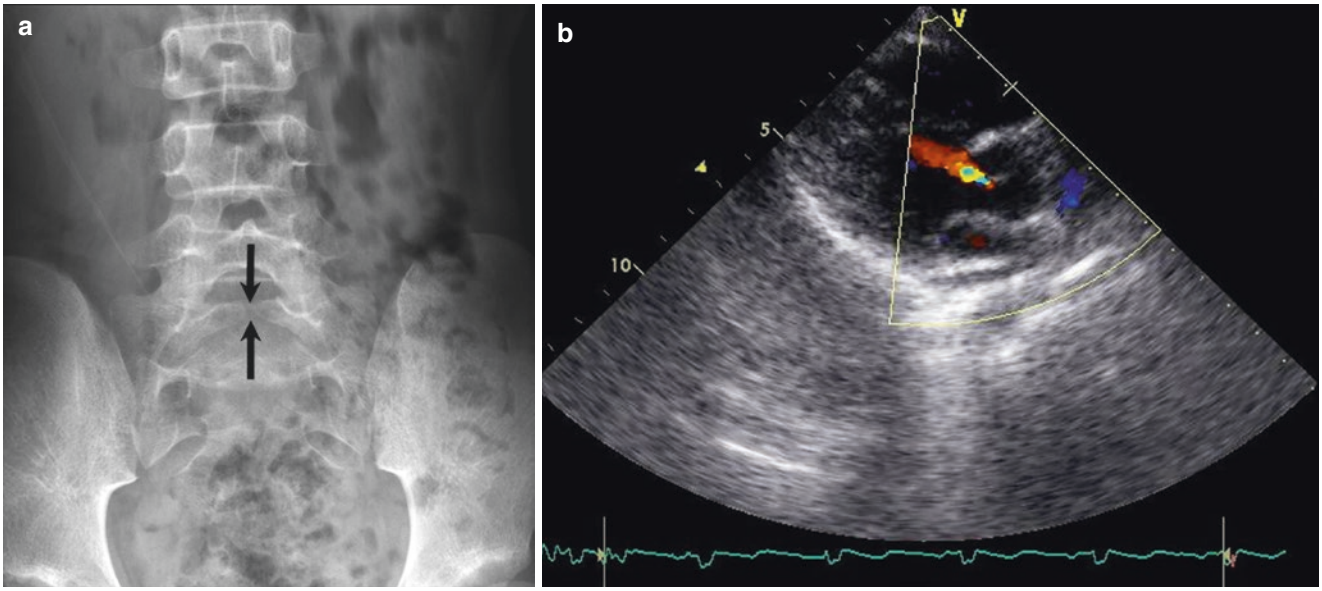

Fig. 1.53 The same Alagille syndrome patient in Fig. 1.52. (**a**) Lumbar X-ray showing inferior endplate depression and irregularity of the L5 body, and S1 spinal bifida (black arrows). No butterfly vertebrae were noted. (**b**) Cardiac echography showed mild aortic valve regurgitation, trivial tricuspid valve regurgitation, and equivocal mitral valve prolapse

include heart block, cerebellar ataxia, and increased cerebrospinal fluid protein level. The diagnosis is confirmed by muscle biopsy and genetic testing.

For ophthalmic disorders, 89% present with progressive external ophthalmoplegia, 86% with ptosis, and 71% with pigmentary retinopathy (Khambatta et al. 2014). The retinal pigments usually show a "salt and pepper" appearance instead of typical bone-spicules in RP.

Alagille Syndrome

Alagille syndrome (ALGS) is a rare multisystem disorder involving the eye. The primary manifestations are cholestasis, decreased bile duct numbers in a liver biopsy, congenital heart disease, butterfly vertebrae, characteristic facial features, and ocular abnormalities (Kim and Fulton 2007) (Figs. 1.52 and 1.53). The inheritance pattern is an autosomal dominant mutation that has been identified to be associated with the *human Jagged 1* (*JAG1*) gene.

Ophthalmologists can contribute to the early diagnosis of ALGS, especially in the circumstance of unexplained neonatal cholestasis. Over 90% of ALGS have been reported to have posterior embryotoxon (Hingorani et al. 1999) (Fig. 1.52). Other common ocular findings include microcornea, iris abnormalities, optic nerve head anomalies, retinal vessel changes, and retinopathies such as fundus hypopigmentation and RPE pigmentary changes (Fig. 1.52). Despite these ocular findings, ALGS patients usually have good visual acuity.

References

Aizawa S, Mitamura Y, Baba T, Hagiwara A, Ogata K, Yamamoto S. Correlation between visual function and photoreceptor inner/outer segment junction in patients with retinitis pigmentosa. Eye. 2009;23(2):304–8.

Alkharashi M, Fulton AB. Available evidence on Leber congenital amaurosis and gene therapy. Seminars in Ophthalmology. 2017;32(1):14–21.

Ammon FA. Klinische Darstellungen der Krankheiten und Bildungsfehler des menschlichen Auges. Berlin; 1838.

Audo I, Michaelides M, Robson AG, Hawlina M, Vaclavik V, Sandbach JM, Neveu MM, Hogg CR, Hunt DM, Moore AT, Bird AC, Webster AR, Holder GE. Phenotypic variation in enhanced S-cone syndrome. Investigative Ophthalmology & Visual Science. 2008;49(5):2082–93.

Auw-Haedrich C, Staubach F, Witschel H. Optic disk drusen. Surv Ophthalmol. 2002;47(6):515–32.

Ayala-Ramirez R, Graue-Wiechers F, Robredo V, Amato-Almanza M, Horta-Diez I, Zenteno JC. A new autosomal recessive syndrome consisting of posterior microphthalmos, retinitis pigmentosa, foveoschisis, and optic disc drusen is caused by a MFRP gene mutation. Mol Vis. 2006;12:1483–9.

Bainbridge JW, Smith AJ, Barker SS, Robbie S, Henderson R, Balaggan K, Viswanathan A, Holder GE, Stockman A, Tyler N, Petersen-Jones S, Bhattacharya SS, Thrasher AJ, Fitzke FW, Carter BJ, Rubin GS, Moore AT, Ali RR. Effect of gene therapy on visual function in Leber's congenital amaurosis. The New England Journal of Medicine. 2008;358(21):2231–9.

Bainbridge JW, Mehat MS, Sundaram V, Robbie SJ, Barker SE, Ripamonti C, Georgiadis A, Mowat FM, Beattie SG, Gardner PJ, Feathers KL, Luong VA, Yzer S, Balaggan K, Viswanathan A, de Ravel TJ, Casteels I, Holder GE, Tyler N, Fitzke FW, Weleber RG, Nardini M, Moore AT, Thompson DA, Petersen-Jones SM, Michaelides M, van den Born LI, Stockman A, Smith AJ, Rubin G,

Ali RR. Long-term effect of gene therapy on Leber's congenital amaurosis. The New England Journal of Medicine. 2015;372(20):1887–97.
Battu R, Khanna A, Hegde B, Berendschot TT, Grover S, Schouten JS. Correlation of structure and function of the macula in patients with retinitis pigmentosa. Eye. 2015;29(7):895–901.
Beales PL, Elcioglu N, Woolf AS, Parker D, Flinter FA. New criteria for improved diagnosis of Bardet-Biedl syndrome: results of a population survey. J Med Genet. 1999;36(6):437–46.
Ben-Arie-Weintrob Y, Berson EL, Dryja TP. Histopathologic-genotypic correlations in retinitis pigmentosa and allied diseases. Ophthalmic Genetics. 2005;26(2):91–100.
Benhamou N, Massin P, Haouchine B, Erginay A, Gaudric A. Macular retinoschisis in highly myopic eyes. Am J Ophthalmol. 2002;133(6):794–800.
Bernal S, Solans T, Gamundi MJ, Hernan I, de Jorge L, Carballo M, Navarro R, Tizzano E, Ayuso C, Baiget M. Analysis of the involvement of the NR2E3 gene in autosomal recessive retinal dystrophies. Clinical Genetics. 2008;73(4):360–6.
Berson EL, Rosner B, Sandberg MA, Hayes KC, Nicholson BW, Weigel-DiFranco C, Willett W. A randomized trial of vitamin A and vitamin E supplementation for retinitis pigmentosa. Arch Ophthalmol. 1993;111(6):761–72.
Berson EL, Rosner B, Sandberg MA, Weigel-DiFranco C, Moser A, Brockhurst RJ, Hayes KC, Johnson CA, Anderson EJ, Gaudio AR, Willett WC, Schaefer EJ. Clinical trial of docosahexaenoic acid in patients with retinitis pigmentosa receiving vitamin A treatment. Archives of Ophthalmology. 2004;122(9):1297–305.
Berson EL, Rosner B, Sandberg MA, Weigel-DiFranco C, Brockhurst RJ, Hayes KC, Johnson EJ, Anderson EJ, Johnson CA, Gaudio AR, Willett WC, Schaefer EJ. Clinical trial of lutein in patients with retinitis pigmentosa receiving vitamin A. Archives of Ophthalmology. 2010;128(4):403–11.
Bi A, Cui J, Ma YP, Olshevskaya E, Pu M, Dizhoor AM, Pan ZH. Ectopic expression of a microbial-type rhodopsin restores visual responses in mice with photoreceptor degeneration. Neuron. 2006;50(1):23–33.
Birch DG, Locke KG, Wen Y, Locke KI, Hoffman DR, Hood DC. Spectral-domain optical coherence tomography measures of outer segment layer progression in patients with X-linked retinitis pigmentosa. JAMA Ophthalmology. 2013;131(9):1143–50.
Boughman JA, Fishman GA. A genetic analysis of retinitis pigmentosa. Br J Ophthalmol. 1983;67(7):449–54.
Boughman JA, Conneally PM, Nance WE. Population genetic studies of retinitis pigmentosa. Am J Hum Genet. 1980;32(2):223–35.
Breuer DK, Yashar BM, Filippova E, Hiriyanna S, Lyons RH, Mears AJ, Asaye B, Acar C, Vervoort R, Wright AF, Musarella MA, Wheeler P, MacDonald I, Iannaccone A, Birch D, Hoffman DR, Fishman GA, Heckenlively JR, Jacobson SG, Sieving PA, Swaroop A. A comprehensive mutation analysis of RP2 and RPGR in a North American cohort of families with X-linked retinitis pigmentosa. American Journal of Human Genetics. 2002;70(6):1545–54.
Brito-Garcia N, Del Pino-Sedeno T, Trujillo-Martin MM, Coco RM, Rodriguez de la Rua E, Del Cura-Gonzalez I, Serrano-Aguilar P. Effectiveness and safety of nutritional supplements in the treatment of hereditary retinal dystrophies: A systematic review. Eye. 2017;31(2):273–85.
Bujakowska K, Audo I, Mohand-Said S, Lancelot ME, Antonio A, Germain A, Leveillard T, Letexier M, Saraiva JP, Lonjou C, Carpentier W, Sahel JA, Bhattacharya SS, Zeitz C. CRB1 mutations in inherited retinal dystrophies. Human Mutation. 2012;33(2):306–15.
Bulgakova NA, Knust E. The crumbs complex: From epithelial-cell polarity to retinal degeneration. Journal of Cell Science. 2009;122(Pt 15):2587–96.
Bumsted O'Brien KM, Cheng H, Jiang Y, Schulte D, Swaroop A, Hendrickson AE. Expression of photoreceptor-specific nuclear receptor NR2E3 in rod photoreceptors of fetal human retina. Investigative Ophthalmology & Visual Science. 2004;45(8):2807–12.
Busskamp V, Duebel J, Balya D, Fradot M, Viney TJ, Siegert S, Groner AC, Cabuy E, Forster V, Seeliger M, Biel M, Humphries P, Paques M, Mohand-Said S, Trono D, Deisseroth K, Sahel JA, Picaud S, Roska B. Genetic reactivation of cone photoreceptors restores visual responses in retinitis pigmentosa. Science. 2010;329(5990):413–7.
Chacon-Camacho OF, Zenteno JC. Review and update on the molecular basis of Leber congenital amaurosis. World Journal of Clinical Cases. 2015;3(2):112–24.
Chang MY, Pineles SL. Optic disk drusen in children. Survey of Ophthalmology. 2016;61(6):745–58.
Chen J, Rattner A, Nathans J. The rod photoreceptor-specific nuclear receptor Nr2e3 represses transcription of multiple cone-specific genes. The Journal of Neuroscience. 2005;25(1):118–29.
Chuang AT, Margo CE, Greenberg PB. Retinal implants: a systematic review. Br J Ophthalmol. 2014;98(7):852–6. https://doi.org/10.1136/bjophthalmol-2013-303708.
Coussa RG, Lopez Solache I, Koenekoop RK. Leber congenital amaurosis, from darkness to light: an ode to Irene Maumenee. Ophthalmic Genet. 2017;38(1):7–15. https://doi.org/10.1080/13816810.2016.1275021.
Crespi J, Buil JA, Bassaganyas F, Vela-Segarra JI, Diaz-Cascajosa J, Ayala-Ramirez R, Zenteno JC. A novel mutation confirms MFRP as the gene causing the syndrome of nanophthalmos-renititis pigmentosa-foveoschisis-optic disk drusen. Am J Ophthalmol. 2008;146(2):323–8. https://doi.org/10.1016/j.ajo.2008.04.029.
de Hollander AI, Heckenlively JR, van den Born LI, de Kok YJ, van der Velde-Visser SD, Kellner U, Jurklies B, van Schooneveld MJ, Blankenagel A, Rohrschneider K, Wissinger B, Cruysberg JR, Deutman AF, Brunner HG, Apfelstedt-Sylla E, Hoyng CB, Cremers FP. Leber congenital amaurosis and retinitis pigmentosa with coats-like exudative vasculopathy are associated with mutations in the crumbs homologue 1 (CRB1) gene. Am J Hum Genet. 2001;69(1):198–203. https://doi.org/10.1086/321263.
De Laey JJ. Leber's congenital amaurosis. Bull Soc Belge Ophtalmol. 1991;241:41–50.
den Hollander AI, Roepman R, Koenekoop RK, Cremers FP. Leber congenital amaurosis: genes, proteins and disease mechanisms. Prog Retin Eye Res. 2008;27(4):391–419. https://doi.org/10.1016/j.preteyeres.2008.05.003.
Dharmaraj S, Leroy BP, Sohocki MM, Koenekoop RK, Perrault I, Anwar K, Khaliq S, Devi RS, Birch DG, De Pool E, Izquierdo N, Van Maldergem L, Ismail M, Payne AM, Holder GE, Bhattacharya SS, Bird AC, Kaplan J, Maumenee IH. The phenotype of Leber congenital amaurosis in patients with AIPL1 mutations. Arch Ophthalmol. 2004;122(7):1029–37. https://doi.org/10.1001/archopht.122.7.1029.
Domanico D, Carnevale C, Fragiotta S, Verboschi F, Altimari S, Vingolo EM. Cystoid macular edema induced by low doses of nicotinic acid. Case Rep Ophthalmol Med. 2013;2013:713061. https://doi.org/10.1155/2013/713061.
Donders FC. Beitrage zur pathologischen Anatomie des Auges. II Pigmentbildung in der Netzhaut. Albrecht Von Graefes Arch Ophthalmol. 1857;3(1):139–50.
Dorenboim Y, Rehany U, Rumelt S. Central serous chorioretinopathy associated with retinitis pigmentosa. Graefes Arch Clin Exp Ophthalmol. 2004;242(4):346–9. https://doi.org/10.1007/s00417-003-0819-1.
Duncan JL, Pierce EA, Laster AM, Daiger SP, Birch DG, Ash JD, Iannaccone A, Flannery JG, Sahel JA, Zack DJ, Zarbin MA, the Foundation Fight Blindness Scientific Advisory Board. Inherited

retinal degenerations: Current landscape and knowledge gaps. Translational Vision Science & Technology. 2018;7(4):6.
Edwards A, Grover S, Fishman GA. Frequency of photographically apparent optic disc and parapapillary nerve fiber layer drusen in Usher syndrome. Retina. 1996;16(5):388–92.
Fazzi E, Signorini SG, Scelsa B, Bova SM, Lanzi G. Leber's congenital amaurosis: an update. Eur J Paediatr Neurol. 2003;7(1):13–22.
Ferrucci S, Anderson SF, Townsend JC. Retinitis pigmentosa inversa. Optom Vis Sci. 1998;75(8):560–70.
Fishman GA. Retinitis pigmentosa. Genetic percentages. Arch Ophthalmol. 1978;96(5):822–6.
Fishman GA, Farber MD, Derlacki DJ. X-linked retinitis pigmentosa. Profile of clinical findings. Arch Ophthalmol. 1988;106(3):369–75.
Flynn MF, Fishman GA, Anderson RJ, Roberts DK. Retrospective longitudinal study of visual acuity change in patients with retinitis pigmentosa. Retina. 2001;21(6):639–46.
Forsythe E, Beales PL. Bardet-Biedl syndrome. Eur J Hum Genet. 2013;21(1):8–13. https://doi.org/10.1038/ejhg.2012.115.
Franceschetti D. Importance diagnostique et prognostique de l'é lectroré tinogramme (ERG). dans les dé gé né rescences ré tré cissement du champ. Confin Neurol. 1954;14:184–6.
Grant CA, Berson EL. Treatable forms of retinitis pigmentosa associated with systemic neurological disorders. Int Ophthalmol Clin. 2001;41(1):103–10.
Greenstein VC, Duncker T, Holopigian K, Carr RE, Greenberg JP, Tsang SH, Hood DC. Structural and functional changes associated with normal and abnormal fundus autofluorescence in patients with retinitis pigmentosa. Retina. 2012;32(2):349–57. https://doi.org/10.1097/IAE.0b013e31821dfc17.
Grover S, Fishman GA, Brown J Jr. Frequency of optic disc or parapapillary nerve fiber layer drusen in retinitis pigmentosa. Ophthalmology. 1997;104(2):295–8.
Grover S, Fishman GA, Brown J Jr. Patterns of visual field progression in patients with retinitis pigmentosa. Ophthalmology. 1998;105(6):1069–75. https://doi.org/10.1016/s0161-6420(98)96009-2.
Hagiwara A, Yamamoto S, Ogata K, Sugawara T, Hiramatsu A, Shibata M, Mitamura Y. Macular abnormalities in patients with retinitis pigmentosa: prevalence on OCT examination and outcomes of vitreoretinal surgery. Acta Ophthalmol. 2011;89(2):e122–5. https://doi.org/10.1111/j.1755-3768.2010.01866.x.
Haim M. Retinitis pigmentosa: problems associated with genetic classification. Clin Genet. 1993;44(2):62–70.
Hartong DT, Berson EL, Dryja TP. Retinitis pigmentosa. Lancet. 2006;368(9549):1795–809. https://doi.org/10.1016/s0140-6736(06)69740-7.
Hashimoto Y, Kase S, Saito W, Ishida S. Abnormalities of fundus autofluorescence in pigmented paravenous chorioretinal atrophy. Open Ophthalmol J. 2012;6:125–8. https://doi.org/10.2174/1874364101206010125.
Hauswirth WW, Aleman TS, Kaushal S, Cideciyan AV, Schwartz SB, Wang L, Conlon TJ, Boye SL, Flotte TR, Byrne BJ, Jacobson SG. Treatment of leber congenital amaurosis due to RPE65 mutations by ocular subretinal injection of adeno-associated virus gene vector: short-term results of a phase I trial. Hum Gene Ther. 2008;19(10):979–90. https://doi.org/10.1089/hum.2008.107.
Heckenlively JR, Rodriguez JA, Daiger SP. Autosomal dominant sectoral retinitis pigmentosa. Two families with transversion mutation in codon 23 of rhodopsin. Arch Ophthalmol. 1991;109(1):84–91.
Hingorani M, Nischal KK, Davies A, Bentley C, Vivian A, Baker AJ, Mieli-Vergani G, Bird AC, Aclimandos WA. Ocular abnormalities in Alagille syndrome. Ophthalmology. 1999;106(2):330–7. https://doi.org/10.1016/s0161-6420(99)90072-6.
Hood DC, Lazow MA, Locke KG, Greenstein VC, Birch DG. The transition zone between healthy and diseased retina in patients with retinitis pigmentosa. Invest Ophthalmol Vis Sci. 2011;52(1):101–8. https://doi.org/10.1167/iovs.10-5799.
Huckfeldt RM, Comander J. Management of cystoid macular edema in retinitis pigmentosa. Semin Ophthalmol. 2017;32(1):43–51. https://doi.org/10.1080/08820538.2016.1228404.
Iannaccone A, Rispoli E, Vingolo EM, Onori P, Steindl K, Rispoli D, Pannarale MR. Correlation between Goldmann perimetry and maximal electroretinogram response in retinitis pigmentosa. Doc Ophthalmol. 1995;90(2):129–42.
Ikeda Y, Yoshida N, Murakami Y, Nakatake S, Notomi S, Hisatomi T, Enaida H, Ishibashi T. Long-term surgical outcomes of epiretinal membrane in patients with retinitis pigmentosa. Sci Rep. 2015;5:13078. https://doi.org/10.1038/srep13078.
Jacobson SG. Crumbs homolog 1 (CRB1) mutations result in a thick human retina with abnormal lamination. Hum Mol Genet. 2003;12(9):1073–8. https://doi.org/10.1093/hmg/ddg117.
Jacobson SG, Cideciyan AV. Treatment possibilities for retinitis pigmentosa. N Engl J Med. 2010;363(17):1669–71. https://doi.org/10.1056/NEJMcibr1007685.
Jacobson SG, Aleman TS, Sumaroka A, Cideciyan AV, Roman AJ, Windsor EA, Schwartz SB, Rehm HL, Kimberling WJ. Disease boundaries in the retina of patients with Usher syndrome caused by MYO7A gene mutations. Invest Ophthalmol Vis Sci. 2009;50(4):1886–94. https://doi.org/10.1167/iovs.08-3122.
Jacobson SG, Roman AJ, Aleman TS, Sumaroka A, Herrera W, Windsor EA, Atkinson LA, Schwartz SB, Steinberg JD, Cideciyan AV. Normal central retinal function and structure preserved in retinitis pigmentosa. Invest Ophthalmol Vis Sci. 2010;51(2):1079–85. https://doi.org/10.1167/iovs.09-4372.
Jacobson SG, Cideciyan AV, Roman AJ, Sumaroka A, Schwartz SB, Heon E, Hauswirth WW. Improvement and decline in vision with gene therapy in childhood blindness. N Engl J Med. 2015;372(20):1920–6. https://doi.org/10.1056/NEJMoa1412965.
Katz ML, Drea CM, Eldred GE, Hess HH, Robison WG Jr. Influence of early photoreceptor degeneration on lipofuscin in the retinal pigment epithelium. Exp Eye Res. 1986;43(4):561–73.
Khambatta S, Nguyen DL, Beckman TJ, Wittich CM. Kearns-Sayre syndrome: a case series of 35 adults and children. Int J Gen Med. 2014;7:325–32. https://doi.org/10.2147/ijgm.s65560.
Khan JA, Ide CH, Strickland MP. Coats'-type retinitis pigmentosa. Surv Ophthalmol. 1988;32(5):317–32.
Kim BJ, Fulton AB. The genetics and ocular findings of Alagille syndrome. Semin Ophthalmol. 2007;22(4):205–10. https://doi.org/10.1080/08820530701745108.
Kiratli H, Ozturkmen C. Coats-like lesions in Usher syndrome type II. Graefes Arch Clin Exp Ophthalmol. 2004;242(3):265–7. https://doi.org/10.1007/s00417-003-0818-2.
Klein D, Ammann F. The syndrome of Laurence-Moon-Bardet-Biedl and allied diseases in Switzerland. Clinical, genetic and epidemiological studies. J Neurol Sci. 1969;9(3):479–513.
Koenekoop RK. An overview of Leber congenital amaurosis: a model to understand human retinal development. Surv Ophthalmol. 2004;49(4):379–98. https://doi.org/10.1016/j.survophthal.2004.04.003.
Koenekoop RK, Wang H, Majewski J, Wang X, Lopez I, Ren H, Chen Y, Li Y, Fishman GA, Genead M, Schwartzentruber J, Solanki N, Traboulsi EI, Cheng J, Logan CV, McKibbin M, Hayward BE, Parry DA, Johnson CA, Nageeb M, Poulter JA, Mohamed MD, Jafri H, Rashid Y, Taylor GR, Keser V, Mardon G, Xu H, Inglehearn CF, Fu Q, Toomes C, Chen R. Mutations in NMNAT1 cause Leber congenital amaurosis and identify a new disease pathway for retinal degeneration. Nat Genet. 2012;44(9):1035–9. https://doi.org/10.1038/ng.2356.
Krill AE, Archer D, Martin D. Sector retinitis pigmentosa. Am J Ophthalmol. 1970;69(6):977–87.

Lagali PS, Balya D, Awatramani GB, Munch TA, Kim DS, Busskamp V, Cepko CL, Roska B. Light-activated channels targeted to ON bipolar cells restore visual function in retinal degeneration. Nat Neurosci. 2008;11(6):667–75. https://doi.org/10.1038/nn.2117.

Lambert SR, Kriss A, Taylor D, Coffey R, Pembrey M. Follow-up and diagnostic reappraisal of 75 patients with Leber's congenital amaurosis. Am J Ophthalmol. 1989;107(6):624–31.

Langenbeck BCR. De retina. Observations anatomico-pathologica. Göttingen: Sumptibus; 1836.

Leber TV. Uber retinitis pigmentosa und angeborene amaurose. Graefes Arch Clin Exp Ophthalmol. 1869;15(3):1–25.

Lenassi E, Troeger E, Wilke R, Hawlina M. Correlation between macular morphology and sensitivity in patients with retinitis pigmentosa and hyperautofluorescent ring. Invest Ophthalmol Vis Sci. 2012;53(1):47–52. https://doi.org/10.1167/iovs.11-8048.

Lima LH, Cella W, Greenstein VC, Wang NK, Busuioc M, Smith RT, Yannuzzi LA, Tsang SH. Structural assessment of hyperautofluorescent ring in patients with retinitis pigmentosa. Retina. 2009;29(7):1025–31. https://doi.org/10.1097/IAE.0b013e3181ac2418.

Lima LH, Burke T, Greenstein VC, Chou CL, Cella W, Yannuzzi LA, Tsang SH. Progressive constriction of the hyperautofluorescent ring in retinitis pigmentosa. Am J Ophthalmol. 2012;153(4):718–27, 727.e711–712. https://doi.org/10.1016/j.ajo.2011.08.043.

Lorenz B, Wabbels B, Wegscheider E, Hamel CP, Drexler W, Preising MN. Lack of fundus autofluorescence to 488 nanometers from childhood on in patients with early-onset severe retinal dystrophy associated with mutations in RPE65. Ophthalmology. 2004;111(8):1585–94. https://doi.org/10.1016/j.ophtha.2004.01.033.

Luo YH, da Cruz L. The Argus((R)) II retinal prosthesis system. Prog Retin Eye Res. 2016;50:89–107. https://doi.org/10.1016/j.preteyeres.2015.09.003.

Lupo S, Grenga PL, Vingolo EM. Fourier-domain optical coherence tomography and microperimetry findings in retinitis pigmentosa. Am J Ophthalmol. 2011;151(1):106–11. https://doi.org/10.1016/j.ajo.2010.07.026.

Maguire AM, Simonelli F, Pierce EA, Pugh EN Jr, Mingozzi F, Bennicelli J, Banfi S, Marshall KA, Testa F, Surace EM, Rossi S, Lyubarsky A, Arruda VR, Konkle B, Stone E, Sun J, Jacobs J, Dell'Osso L, Hertle R, Ma JX, Redmond TM, Zhu X, Hauck B, Zelenaia O, Shindler KS, Maguire MG, Wright JF, Volpe NJ, McDonnell JW, Auricchio A, High KA, Bennett J. Safety and efficacy of gene transfer for Leber's congenital amaurosis. N Engl J Med. 2008;358(21):2240–8. https://doi.org/10.1056/NEJMoa0802315.

Mathur P, Yang J. Usher syndrome: hearing loss, retinal degeneration and associated abnormalities. Biochim Biophys Acta. 2015;1852(3):406–20. https://doi.org/10.1016/j.bbadis.2014.11.020.

Matsuo T, Morimoto N. Visual acuity and perimacular retinal layers detected by optical coherence tomography in patients with retinitis pigmentosa. Br J Ophthalmol. 2007;91(7):888–90. https://doi.org/10.1136/bjo.2007.114538.

Marmor MF, Jacobson SG, Foerster MH, Kellner U, Weleber RG. Diagnostic clinical findings of a new syndrome with night blindness, maculopathy, and enhanced S cone sensitivity. American Journal of Ophthalmology. 1990;110(2):124–34.

McBain VA, Forrester JV, Lois N. Fundus autofluorescence in the diagnosis of cystoid macular oedema. Br J Ophthalmol. 2008;92(7):946–9. https://doi.org/10.1136/bjo.2007.129957.

McKay GJ, Clarke S, Davis JA, Simpson DA, Silvestri G. Pigmented paravenous chorioretinal atrophy is associated with a mutation within the crumbs homolog 1 (CRB1) gene. Invest Ophthalmol Vis Sci. 2005;46(1):322–8. https://doi.org/10.1167/iovs.04-0734.

Meunier I, Ben Salah S, Arndt C, Hamel C. [Retinitis pigmentosa and central serous choroiditis. Retinal imaging and optical coherence tomography views]. J Fr Ophtalmol. 2008;31(7):735.

Mohamed MD, Topping NC, Jafri H, Raashed Y, McKibbin MA, Inglehearn CF. Progression of phenotype in Leber's congenital amaurosis with a mutation at the LCA5 locus. Br J Ophthalmol. 2003;87(4):473–5.

Moisseiev E, Moisseiev J, Loewenstein A. Optic disc pit maculopathy: when and how to treat? A review of the pathogenesis and treatment options. Int J Retina Vitreous. 2015;1:13. https://doi.org/10.1186/s40942-015-0013-8.

Murakami T, Akimoto M, Ooto S, Suzuki T, Ikeda H, Kawagoe N, Takahashi M, Yoshimura N. Association between abnormal autofluorescence and photoreceptor disorganization in retinitis pigmentosa. Am J Ophthalmol. 2008;145(4):687–94. https://doi.org/10.1016/j.ajo.2007.11.018.

Murthy R, Honavar SG. Secondary vasoproliferative retinal tumor associated with Usher syndrome type 1. J AAPOS. 2009;13(1):97–8. https://doi.org/10.1016/j.jaapos.2008.07.012.

Ogura S, Yasukawa T, Kato A, Usui H, Hirano Y, Yoshida M, Ogura Y. Wide-field fundus autofluorescence imaging to evaluate retinal function in patients with retinitis pigmentosa. Am J Ophthalmol. 2014;158(5):1093–8. https://doi.org/10.1016/j.ajo.2014.07.021.

Oishi A, Ogino K, Makiyama Y, Nakagawa S, Kurimoto M, Yoshimura N. Wide-field fundus autofluorescence imaging of retinitis pigmentosa. Ophthalmology. 2013;120(9):1827–34. https://doi.org/10.1016/j.ophtha.2013.01.050.

Omphroy CA. Sector retinitis pigmentosa and chronic angle-closure glaucoma: a new association. Ophthalmologica. 1984;189(1–2):12–20.

Osman SA, Aylin Y, Arikan G, Celikel H. Photodynamic treatment of a secondary vasoproliferative tumour associated with sector retinitis pigmentosa and Usher syndrome type I. Clin Exp Ophthalmol. 2007;35(2):191–3. https://doi.org/10.1111/j.1442-9071.2007.01440.x.

Pasadhika S, Fishman GA, Stone EM, Lindeman M, Zelkha R, Lopez I, Koenekoop RK, Shahidi M. Differential macular morphology in patients with RPE65-, CEP290-, GUCY2D-, and AIPL1-related Leber congenital amaurosis. Invest Ophthalmol Vis Sci. 2010;51(5):2608–14. https://doi.org/10.1167/iovs.09-3734.

Paun CC, Pijl BJ, Siemiatkowska AM, Collin RW, Cremers FP, Hoyng CB, den Hollander AI. A novel crumbs homolog 1 mutation in a family with retinitis pigmentosa, nanophthalmos, and optic disc drusen. Mol Vis. 2012;18:2447–53.

Pelletier V, Jambou M, Delphin N, Zinovieva E, Stum M, Gigarel N, Dollfus H, Hamel C, Toutain A, Dufier JL, Roche O, Munnich A, Bonnefont JP, Kaplan J, Rozet JM. Comprehensive survey of mutations in RP2 and RPGR in patients affected with distinct retinal dystrophies: genotype-phenotype correlations and impact on genetic counseling. Hum Mutat. 2007;28(1):81–91. https://doi.org/10.1002/humu.20417.

Pocha SM, Knust E. Complexities of crumbs function and regulation in tissue morphogenesis. Curr Biol. 2013;23(7):R289–93. https://doi.org/10.1016/j.cub.2013.03.001.

Pruett R. Retinitis pigmentosa: clinical observations and correlations. Trans Am Ophthalmol Soc. 1983;81:693–735.

Pyo Park S, Hwan Hong I, Tsang SH, Chang S. Cellular imaging demonstrates genetic mosaicism in heterozygous carriers of an X-linked ciliopathy gene. Eur J Hum Genet. 2013;21(11):1240–8. https://doi.org/10.1038/ejhg.2013.21.

Rayapudi S, Schwartz SG, Wang X, Chavis P. Vitamin A and fish oils for retinitis pigmentosa. Cochrane Database Syst Rev. 2013;(12):CD008428. https://doi.org/10.1002/14651858.CD008428.pub2.

RetNet. https://sph.uth.edu/retnet/. Accessed 4 Nov 2019.

Robson AG, El-Amir A, Bailey C, Egan CA, Fitzke FW, Webster AR, Bird AC, Holder GE. Pattern ERG correlates of abnormal fundus autofluorescence in patients with retinitis pigmentosa and normal visual acuity. Invest Ophthalmol Vis Sci. 2003;44(8):3544–50.

Robson AG, Saihan Z, Jenkins SA, Fitzke FW, Bird AC, Webster AR, Holder GE. Functional characterisation and serial imaging of abnormal fundus autofluorescence in patients with retinitis pigmentosa and normal visual acuity. Br J Ophthalmol. 2006;90(4):472–9. https://doi.org/10.1136/bjo.2005.082487.

Ronquillo CC, Bernstein PS, Baehr W. Senior-Loken syndrome: a syndromic form of retinal dystrophy associated with nephronophthisis. Vis Res. 2012;75:88–97. https://doi.org/10.1016/j.visres.2012.07.003.

Ruete C. Bildliche Darstellung der Krankheiten des Menschlichen Auges. Teubner, Leipzig: Druck und Verlag von B.G; 1855.

Sandberg MA, Weigel-DiFranco C, Rosner B, Berson EL. The relationship between visual field size and electroretinogram amplitude in retinitis pigmentosa. Invest Ophthalmol Vis Sci. 1996;37(8):1693–8.

Sandberg MA, Brockhurst RJ, Gaudio AR, Berson EL. The association between visual acuity and central retinal thickness in retinitis pigmentosa. Invest Ophthalmol Vis Sci. 2005;46(9):3349–54. https://doi.org/10.1167/iovs.04-1383.

Sayman Muslubas I, Karacorlu M, Arf S, Hocaoglu M, Ersoz MG. Features of the macula and central visual field and fixation pattern in patients with retinitis pigmentosa. Retina. 2017;38:424–31. https://doi.org/10.1097/iae.0000000000001532.

Scholl HP, Chong NH, Robson AG, Holder GE, Moore AT, Bird AC. Fundus autofluorescence in patients with Leber congenital amaurosis. Invest Ophthalmol Vis Sci. 2004;45(8):2747–52. https://doi.org/10.1167/iovs.03-1208.

Sharon D, Sandberg MA, Rabe VW, Stillberger M, Dryja TP, Berson EL. RP2 and RPGR mutations and clinical correlations in patients with X-linked retinitis pigmentosa. Am J Hum Genet. 2003;73(5):1131–46. https://doi.org/10.1086/379379.

Shen JH, Chen KJ, Wang NK. Leptochoroid in a case of alagille syndrome (arteriohepatic dysplasia). Ophthalmology. 2017;124(8):1135.

Sheth S, Rush R, Narayanan R. Retinitis pigmentosa inversa with unilateral high myopia with fellow eye optic disc pitting. Eur J Ophthalmol. 2011;21(4):509–12. https://doi.org/10.5301/ejo.2011.6264.

Slavotinek AM. The family of crumbs genes and human disease. Mol Syndromol. 2016;7(5):274–81. https://doi.org/10.1159/000448109.

Steidl SM, Pruett RC. Macular complications associated with posterior staphyloma. Am J Ophthalmol. 1997;123(2):181–7.

Strong S, Liew G, Michaelides M. Retinitis pigmentosa-associated cystoid macular oedema: pathogenesis and avenues of intervention. Br J Ophthalmol. 2017;101(1):31–7. https://doi.org/10.1136/bjophthalmol-2016-309376.

Sujirakul T, Lin MK, Duong J, Wei Y, Lopez-Pintado S, Tsang SH. Multimodal imaging of central retinal disease progression in a 2-year mean follow-up of retinitis pigmentosa. Am J Ophthalmol. 2015;160(4):786–798.e784. https://doi.org/10.1016/j.ajo.2015.06.032.

Swaroop A, Wang QL, Wu W, Cook J, Coats C, Xu S, Chen S, Zack DJ, Sieving PA. Leber congenital amaurosis caused by a homozygous mutation (R90W) in the homeodomain of the retinal transcription factor CRX: direct evidence for the involvement of CRX in the development of photoreceptor function. Hum Mol Genet. 1999;8(2):299–305.

Takahashi Y, Moiseyev G, Chen Y, Nikolaeva O, Ma JX. An alternative isomerohydrolase in the retinal Muller cells of a cone-dominant species. FEBS J. 2011;278(16):2913–26. https://doi.org/10.1111/j.1742-4658.2011.08216.x.

Talib M, van Schooneveld MJ, van Genderen MM, Wijnholds J, Florijn RJ, Ten Brink JB, Schalij-Delfos NE, Dagnelie G, Cremers FPM, Wolterbeek R, Fiocco M, Thiadens AA, Hoyng CB, Klaver CC, Bergen AA, Boon CJF. Genotypic and phenotypic characteristics of CRB1-associated retinal dystrophies: A long-term follow-up study. Ophthalmology. 2017;124(6):884–95.

Testa F, Rossi S, Colucci R, Gallo B, Di Iorio V, della Corte M, Azzolini C, Melillo P, Simonelli F. Macular abnormalities in Italian patients with retinitis pigmentosa. Br J Ophthalmol. 2014;98(7):946–50. https://doi.org/10.1136/bjophthalmol-2013-304082.

Thobani A, Fishman GA, Genead M, Anastasakis A. Visual acuity loss in recessive retinitis pigmentosa and its correlation with macular lesions. Retina. 2011;31(5):967–72. https://doi.org/10.1097/IAE.0b013e3181f441e1.

Tosi J, Tsui I, Lima LH, Wang NK, Tsang SH. Case report: Autofluorescence imaging and phenotypic variance in a sibling pair with early-onset retinal dystrophy due to defective CRB1 function. Current Eye Research. 2009;34(5):395–400.

Usher C. On a few hereditary eye affections. Trans Ophthal Soc U K. 1935;55:164–245.

van den Born LI, van Soest S, van Schooneveld MJ, Riemslag FC, de Jong PT, Bleeker-Wagemakers EM. Autosomal recessive retinitis pigmentosa with preserved para-arteriolar retinal pigment epithelium. Am J Ophthalmol. 1994;118(4):430–9.

Trigt ACV. Dissertatio ophthalmologica inauguralis de speculo oculi. Utrecht: Utrecht University Library; 1853.

Wakabayashi T, Sawa M, Gomi F, Tsujikawa M. Correlation of fundus autofluorescence with photoreceptor morphology and functional changes in eyes with retinitis pigmentosa. Acta Ophthalmologica. 2010;88(5):e177–83.

Wang NK, Fine HF, Chang S, Chou CL, Cella W, Tosi J, Lin CS, Nagasaki T, Tsang SH. Cellular origin of fundus autofluorescence in patients and mice with a defective NR2E3 gene. The British Journal of Ophthalmology. 2009;93(9):1234–40.

Wang NK, Lai CC, Liu CH, Yeh LK, Chou CL, Kong J, Nagasaki T, Tsang SH, Chien CL. Origin of fundus hyperautofluorescent spots and their role in retinal degeneration in a mouse model of Goldmann-Favre syndrome. Disease Models & Mechanisms. 2013;6(5):1113–22.

Wegscheider E, Preising MN, Lorenz B. Fundus autofluorescence in carriers of X-linked recessive retinitis pigmentosa associated with mutations in RPGR, and correlation with electrophysiological and psychophysical data. Graefes Archive for Clinical and Experimental Ophthalmology. 2004;242(6):501–11.

Witkin AJ, Ko TH, Fujimoto JG, Chan A, Drexler W, Schuman JS, Reichel E, Duker JS. Ultra-high resolution optical coherence tomography assessment of photoreceptors in retinitis pigmentosa and related diseases. American Journal of Ophthalmology. 2006;142(6):945–52.

Wolsley CJ, Silvestri G, O'Neill J, Saunders KJ, Anderson RS. The association between multifocal electroretinograms and OCT retinal thickness in retinitis pigmentosa patients with good visual acuity. Eye. 2009;23(7):1524–31.

Wright AF. Long-term effects of retinal gene therapy in childhood blindness. The New England Journal of Medicine. 2015;372(20):1954–5.

Wu AL, Wang JP, Tseng YJ, Liu L, Kang YC, Chen KJ, Chao AN, Yeh LK, Chen TL, Hwang YS, Wu WC, Lai CC, Wang NK. Multimodal imaging of mosaic retinopathy in carriers of hereditary X-linked recessive diseases. Retina. 2018;38(5):1047–57.

Wuthisiri W, Lingao MD, Capasso JE, Levin AV. Lyonization in ophthalmology. Current Opinion in Ophthalmology. 2013;24(5):389–97.

Yzer S, Hollander AI, Lopez I, Pott JW, de Faber JT, Cremers FP, Koenekoop RK, van den Born LI. Ocular and extra-ocular features of patients with Leber congenital amaurosis and mutations in CEP290. Mol Vis. 2012;18:412–25.

Yzer S, Barbazetto I, Allikmets R, van Schooneveld MJ, Bergen A, Tsang SH, Jacobson SG, Yannuzzi LA. Expanded clinical spectrum of enhanced S-cone syndrome. JAMA Ophthalmology. 2013;131(10):1324–30.