

Non-syndromic retinitis pigmentosa

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ABSTRACT

Retinitis pigmentosa (RP) encompasses a group of inherited retinal dystrophies characterized by the primary degeneration of rod and cone photoreceptors. RP is a leading cause of visual disability, with a worldwide prevalence of 1:4000. Although the majority of RP cases are non-syndromic, 20–30% of patients with RP also have an associated non-ocular condition. RP typically manifests with night blindness in adolescence, followed by concentric visual field loss, reflecting the principal dysfunction of rod photoreceptors; central vision loss occurs later in life due to cone dysfunction. Photoreceptor function measured with an electroretinogram is markedly reduced or even absent. Optical coherence tomography (OCT) and fundus autofluorescence (FAF) imaging show a progressive loss of outer retinal layers and altered lipofuscin distribution in a characteristic pattern. Over the past three decades, a vast number of disease-causing variants in more than 80 genes have been associated with non-syndromic RP. The wide heterogeneity of RP makes it challenging to describe the clinical findings and pathogenesis. In this review, we provide a comprehensive overview of the clinical characteristics of RP specific to genetically defined patient subsets. We supply a unique atlas with color fundus photographs of most RP subtypes, and we discuss the relevant considerations with respect to differential diagnoses. In addition, we discuss the genes involved in the pathogenesis of RP, as well as the retinal processes that are affected by pathogenic mutations in these genes. Finally, we review management strategies for patients with RP, including counseling, visual rehabilitation, and current and emerging therapeutic options.

1. Introduction

Retinitis pigmentosa (RP) is a major cause of visual disability and blindness, affecting more than 1.5 million patients worldwide. RP is the most common inherited retinal dystrophy (IRD), with a worldwide prevalence of approximately 1:4000 (Pagon, 1988), although reports vary from 1:9000 (Na et al., 2017) to as high as 1:750 (Nangia et al., 2012), depending on the geographic location. The term “retinitis pigmentosa” was first coined by the famous Dutch ophthalmologist F.C. Donders in 1857 (Donders, 1857), although his colleague A.C. van Trigt provided the first description of RP viewed through an ophthalmoscope

four years earlier (Van Trigt, 1853). Even in those early days, certain forms of retinal degenerations had already been reported. For example, in 1744 R.F. Ovelgün described a form of familial night blindness closely resembling RP (Ovelgün, 1744). In the early 19th century, both M. Schon and F.A. von Ammon reported patients with poor vision and pigmented retinal lesions (Schon, 1828; Von Ammon, 1838).

RP encompasses a group of progressive IRDs characterized by the primary degeneration of rod photoreceptors, followed by the loss of cone photoreceptors. The initial symptom is reduced night vision, which is followed by a progressive loss of the visual field in a concentric pattern. Function at the macula is usually relatively well preserved until

Abbreviations: BBS, Bardet-Biedl syndrome; cGMP, cyclic guanosine monophosphate; CSNB, congenital stationary night blindness; ESCs, embryonic stem cells; GTP, guanosine triphosphate; IFT, interflagellar transport; iPSCs, induced pluripotent stem cells; IRD, inherited retinal dystrophy; PPR, pericentral pigmentary retinopathy; PPRCA, pigmented paravenous retinochoroidal atrophy; RP, retinitis pigmentosa; RPCs, retinal progenitor cells

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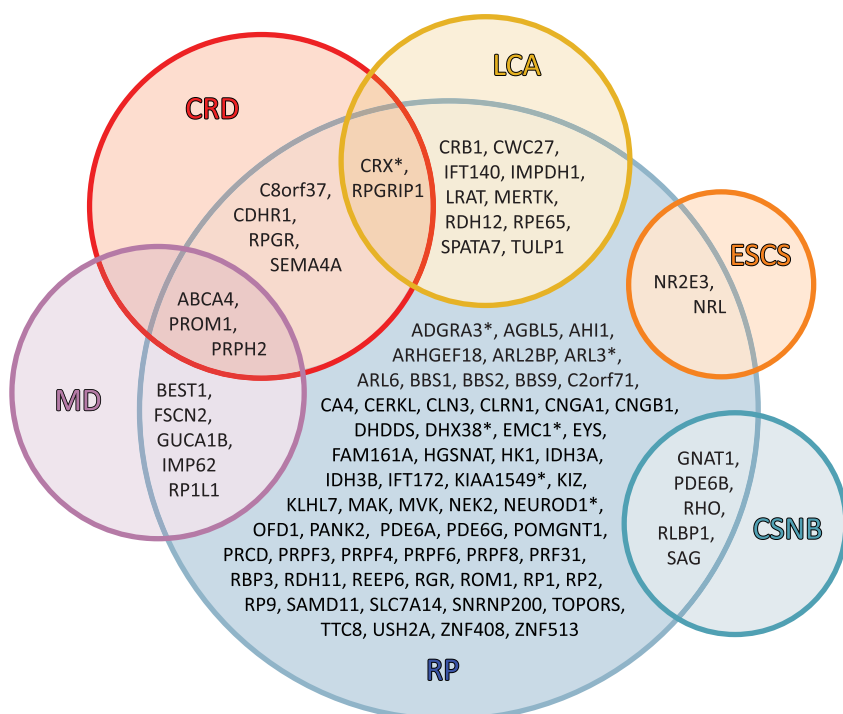


Fig. 1. Venn diagram summarizing the genetic overlap between RP and other inherited retinal dystrophies. Each circle represents a specific clinical diagnosis. The gene names listed in the overlapping areas indicate that mutations in these genes can lead to different phenotypes. Genes marked with an asterisk are candidate genes for non-syndromic RP.; Abbreviations: CRD: cone-rod dystrophy, CSNB: congenital stationary night blindness, ESCS: enhanced S-cone syndrome, LCA: Leber congenital amaurosis, MD: macular dystrophy, RP: retinitis pigmentosa.

later stages of the disease. Fundus abnormalities typically include bone spicule pigmentation predominantly in the periphery and/or mid-periphery, attenuation of retinal vessels, and a waxy pallor of the optic nerve head. An electroretinogram can help in the diagnosis and reveals the characteristic loss of photoreceptor function, primarily among rod photoreceptors rather than cones in early stages of the disease.

RP is clinically distinct from other IRDs, including IRDs that manifest at birth or within the first few months of life (e.g., Leber congenital amaurosis, or LCA), dystrophies in which cone degeneration precedes rod degeneration (e.g., cone-rod dystrophy), macular dystrophies, and disorders that are generally not progressive such as achromatopsia and congenital stationary night blindness (CSNB). In addition, 20–30% of patients with RP present with a syndromic form of RP associated with extra-ocular abnormalities. Together, all of these disorders form a continuum of retinal dystrophies with partially overlapping clinical and/or genetic findings (Fig. 1). This overlap can complicate the classification of an individual IRD and is subject to discussion. Moreover, few therapeutic options are currently available in daily clinical practice. Therefore, the practitioner's focus should be to provide the patient with the best possible information regarding the expected clinical course and inheritance pattern. In this respect, developing a classification system that combines the clinical diagnosis with the underlying genetic factors can provide valuable prognostic information regarding the rate of progression and long-term outcome.

The wide heterogeneity among RP patients is best illustrated by the large number of genetic defects associated with RP. In 1990, Dryja et al. reported the first identified gene involved in autosomal dominant RP: the rhodopsin (*RHO*) gene (Dryja et al., 1990). Since then, mutations in more than 80 genes have been implicated in non-syndromic RP (Daiger et al., 2016), and each year new genes are added to this list. Each of these genes corresponds to a gene-specific subtype of RP with a specific age of onset, visual impairment, retinal appearance, and/or rate of progression. Moreover, several factors can vary widely within each of

these gene-specific subtypes, even between affected family members, suggesting the presence of unidentified genetic and/or environmental factors that can influence the RP phenotype.

Information regarding the clinical course of various RP subtypes is spread across numerous reports that often describe only limited numbers of patients. In this review, we provide a comprehensive overview of the clinical features associated with the various genetic subtypes of non-syndromic RP. A related—yet equally complicated—subject is the functional role of the many proteins encoded by their respective RP genes. To better appreciate the effect of mutations in RP genes, we also discuss the role of these proteins in the structure and function of the retina. Finally, we discuss the current therapeutic options and future perspectives for non-syndromic RP.

2. Clinical findings in RP

RP is characterized by the progressive degeneration of photoreceptors and retinal pigment epithelium (RPE), leading to night blindness, tunnel vision, and a gradual reduction of central vision. However, the clinical findings in RP vary widely due to the large number of genes involved, each of which can have several alleles. In this chapter, we discuss the clinical features that are generally considered to be characteristic of RP. A comprehensive overview of the features specific to the various genetic subtypes of RP is provided in Chapter 4.

2.1. Age of onset and rate of progression

In the “classic” presentation of RP, difficulty with dark adaptation begins in adolescence, and visual loss in the mid-peripheral field becomes apparent in young adulthood. However, the age at onset among patients with RP varies widely; thus, some patients develop symptomatic visual loss in early childhood, whereas others can remain

relatively asymptomatic until mid-adulthood. The exact age of onset is often difficult to determine, as many patients—particularly children—are able to compensate for peripheral visual loss. In addition, difficulties with dark adaptation can remain unnoticed by the patient due to our artificially illuminated nighttime environment.

In general, RP subtypes that manifest early in life tend to progress more rapidly. Moreover, the severity of the disease is correlated with the disease's Mendelian pattern of inheritance. In general, patients with X-linked RP (5–15% of RP patients) have a more severe disease course compared to patients with autosomal recessive RP (50–60% of RP patients), whereas patients with an autosomal dominant form of RP (30–40% of RP patients) (Bunker et al., 1984; Novak-Lauš et al., 2002) have the best long-term prognosis with respect to retaining central vision (Grover et al., 1996; Hamel, 2006).

2.2. Symptoms

The initial symptoms of RP include night blindness (nyctalopia) and difficulty with dark adaptation. In some cases, RP can also present with loss of the mid-peripheral visual field, although this is rarely reported as an early symptom. The central retina remains relatively preserved until the final stages of the disease, although anatomical abnormalities in the central retina can appear early in the course of the disease. Eventually, and typically when the patient reaches middle age, central cone degeneration leads to a decline in visual acuity. Most patients with RP retain the ability to perceive light due to residual macular function and/or the presence of a preserved peripheral temporal retinal island (Hamel, 2006). Photopsia is a common but often-neglected symptom (Heckenlively et al., 1988) that can be highly disturbing to patients. This phenomenon may be caused by a lack of afferent nerve impulses in response to photoreceptor degeneration (Kolmel, 1993) or spontaneous self-signaling activity as a result of inner retina remodeling (Marc et al., 2003). Photopsia can occur in the early stages of RP (Bittner et al., 2009), but is most striking—and particularly disturbing—in patients with more advanced stages of the disease (Bittner et al., 2011). In advanced RP, the visual hallucinations can take animate forms, which corresponds with the diagnosis Charles Bonnet syndrome (O'Hare et al., 2015). Patients with RP can also experience photophobia and dyschromatopsia (Hamel, 2006; Pinckers et al., 1993).

2.3. Family history

A thorough family history is very important in any patient suspected for RP and we recommend drawing a pedigree for each proband. A pedigree is useful in several ways, it helps assessing the mode of inheritance and may also have diagnostic consequences. For example, if an X-linked inheritance is suspected, the *RPGR* gene should be sequenced prior to whole exome sequencing (see section 6.1). A pedigree may also illustrate which family members are at risk for developing RP and/or indicate subjects where non-penetrance should be suspected, for instance when mutations in *PRPF31* and *HK1* are involved (see Chapter 4).

2.4. Ophthalmic examination

2.4.1. The classic RP triad

Three clinical features—bone spicule pigmentation, attenuation of retinal vessels, and a waxy pallor of the optic nerve—are the hallmark signs of RP. In the early stages of RP, a fundus examination may appear normal, as bone spicule-shaped pigment deposits are either absent or sparse, vascular attenuation is minimal, and the optic disc is normal in

appearance. Prior to the typical RP abnormalities, some patients may present with aspecific abnormalities such as irregular reflexes from the internal limiting membrane, broadening of the foveal reflex, and discrete local whitish lesions at the level of the RPE. Not all RP patients develop typical bone spicules; some develop dust-like pigmentation, whereas others develop nummular hyperpigmentation. The degree of hyperpigmentation can vary among patients and does not necessarily reflect the severity of the disease. Bone spicule pigmentation consists of RPE cells that detach from Bruch membrane following photoreceptor degeneration and migrate to intraretinal perivascular sites, where they form melanin pigment deposits (Li et al., 1995). These bone spicules often arise in the mid-periphery, where the concentration of rod cells is highest (Berson, 1993). Precisely what triggers RPE migration is unknown, given the high level of interdependence between the choriocapillaris, RPE, and photoreceptors. However, the RPE migration might be triggered by the reduced distance between the inner retinal vessels and the RPE, due to the degeneration of photoreceptors in *RHO* knock-out mice (Jaissle et al., 2010).

The etiology underlying the attenuation of retinal vessels in RP remains unclear. Initially, this clinical feature was attributed to reduced metabolic demand following ganglion cell degeneration secondary to photoreceptor cell loss. An alternative hypothesis attributes the loss of oxygen-consuming photoreceptors to a hyperoxic state of the remaining inner retina, which leads to vasoconstriction and reduced blood flow in retinal vessels (Grunwald et al., 1996; Padnick-Silver et al., 2006; Penn et al., 2000; Yu and Cringle, 2005). Additionally, Li et al. found that thickening of the extracellular matrix between the retinal vessels and the migrated RPE cells causes narrowing of the vessels (Li et al., 1995). Finally, Stone et al. suggested that a loss of synaptic input secondary to photoreceptor cell death—and the resulting decline in trophic factors—causes reduced metabolism of the inner retinal layers, which may induce vascular remodeling and subsequent vessel attenuation (Stone et al., 1992). On the other hand, Cellini et al. found that ocular blood flow was reduced more than would be expected due to retinal atrophy, which raises the question of whether vascular changes in RP patients are merely secondary to neuroretinal remodeling, or whether they play a more pivotal role in the development of RP (Cellini et al., 2010). In addition, a role for the vasoconstrictor endothelin-1 has been suggested, although both increased and decreased plasma levels of endothelin-1 have been reported among RP patients, thus indicating the need for further study (Cellini et al., 2010; Ohguro et al., 2010; Sorrentino et al., 2015; Strobbe et al., 2015). Given that most of the genes linked to RP play a role in either the photoreceptor-RPE complex or the interphotoreceptor matrix, a secondary cause of these vascular changes is likely.

The optic disc typically develops a waxy pallor as the disease progresses; this feature is likely caused by the formation of glial cells both on the surface and inside the optic disc, resulting in increased light reflectance (Hwang et al., 2012; Szamier, 1981).

2.4.2. Ocular findings associated with RP

Several other ocular conditions—some of which are amenable to treatment—are often associated with RP. For example, patients with early-onset RP can also present with nystagmus, and disease-associated refractive error is also common. Macular complications can include cystoid macular edema (CME), macular hole, and epiretinal membrane formation. CME has been reported to occur in up to 50% of patients with RP (Strong et al., 2017). Although the etiology remains unknown, Strong et al. recently proposed several mechanisms that may contribute to the formation of CME, including *i*) breakdown of the blood-retina barrier, *ii*) impaired function of the RPE pumping mechanism, *iii*)

Müller cell edema and dysfunction, iv) anti-retinal antibodies, and v) vitreomacular traction (Strong et al., 2017). Up to 36% of RP patients present with epiretinal membrane formation (Chebil et al., 2016; Fujiwara et al., 2016; Hagiwara et al., 2011; Testa et al., 2014; Triolo et al., 2013), which may be the result of idiopathic preretinal glial cell proliferation (Szamier, 1981) or—as suggested recently—may occur secondary to an inflammatory process (Fujiwara et al., 2016). The notion of an inflammatory component in RP is not new, as evidenced by the word “retinitis” in the name, and is generally believed to be secondary to photoreceptor cell death. Recent evidence, however, suggests that inflammatory cells contribute to retinal degeneration via their cytotoxic effect on bystander cells such as photoreceptors (Peng et al., 2014; Zhao et al., 2015). Posterior subcapsular cataract may significantly affect vision and occurs in approximately 45% of RP patients (Auffarth et al., 1997; Heckenlively, 1982; Pruett, 1983); visually significant cataract can be removed even when there is macular involvement. The underlying mechanism in posterior subcapsular cataract is currently unknown, although a possible association with inflammation was recently suggested (Fujiwara et al., 2017). Another vitreous abnormality that can occur in RP is the presence of vitreous cysts, which have been reported to occur in 6% of RP patients (Yoshida et al., 2015b). In addition, optic nerve head drusen and/or optic nerve fiber layer drusen were reported in 9% of a cohort of 262 RP patients (Grover et al., 1997), and later studies were able to link these drusen to specific subtypes of RP (see section 4.9). Finally, RP appears to be one of the most commonly underlying diseases in patients with secondary retinal vasoproliferative tumors (Shields et al., 2013).

2.5. Retinal function

2.5.1. Perimetry

Progressive loss of the visual field is a characteristic feature of RP. This visual field loss has high bilateral symmetry (Massof et al., 1979) and typically begins with isolated scotomas in the mid-peripheral areas, which gradually coalesce to form a partial or complete ring scotoma. As the disease progresses, this annular scotoma extends both outward and—albeit more slowly—inward. In addition to ring scotomas, other patterns of visual field progression have been reported, including concentric visual field loss without a preceding ring scotoma and visual field loss progressing from the superior to inferior retina in an arcuate pattern (Grover et al., 1998). Kinetic perimetry is best suitable for assessment of peripheral visual field loss; the annual rate of decline for target V4e of the Goldmann perimeter ranges from 2 to 12% and varies among gene-specific subtypes (Berson et al., 2002; Hafler et al., 2016; Holopigian et al., 1996; Sandberg et al., 2007, 2008b; Talib et al., 2017). Progression of central visual field loss is usually determined using static perimetry. A relatively novel technique to assess the central visual field is fundus-driven perimetry (i.e., microperimetry), which uses precise eye tracking throughout the examination, and enables direct structure-function correlations by providing an annotated en face image of the posterior pole.

2.5.2. Color vision

Initially, color vision may be normal; however, dyschromatopsia—particularly blue-yellow color vision defects where patients principally experience difficulty distinguishing shades of blue from green and yellow-green from violet—can occur in advanced stages of the disease. These so-called type III (blue) acquired color vision defects are more prevalent than type I (red-green) color vision defects (Pinckers et al., 1993). Blue cone dysfunction has been attributed to the scarcity of these short-wavelength cones at the fovea (Kolb, 1995). Due to this

uneven distribution, loss of pericentral retinal function may lead to tritanopia (blue-yellow color blindness). Loss of visual acuity—together with the associated degeneration of central photoreceptors—increases the likelihood of developing a type I color defect (Pokorny et al., 1979). On the other hand, vision loss due to CME seems to have little effect on color vision (Pinckers et al., 1993).

2.5.3. Dark adaptometry

An abnormal dark-adapted threshold is a hallmark feature of RP. Rod threshold is often increased due to decreased rod sensitivity and prolonged recovery of rod sensitivity (Alexander and Fishman, 1984). Studies regarding dark adaptation in RP revealed increases in both cone and rod thresholds, a delay in reaching the asymptotic rod threshold, or the complete loss of rod photoreceptor function (Mantyjärvi and Tuppurainen, 1994).

2.5.4. Electroretinography

Full-field electrophysiological testing—according to the ISCEV guidelines (<http://www.iscev.org/standards>)—helps in the diagnosis and is essential in the quantitative assessment of the severity of the disease, as well as monitoring disease progression (McCulloch et al., 2015). Electroretinogram (ERG) abnormalities occur early and precede the night blindness symptoms and fundus abnormalities (Fig. 2.). On the dark-adapted, bright flash (combined rod-cone) ERG, the a-wave is subnormal. In addition, isolated rod responses to a dark-adapted (scotopic) dim flash are delayed, diminished, or absent in a full-field ERG recording. Cone responses may also be affected in the early phases of RP, but this typically lags behind the onset of rod dysfunction. When present, cone dysfunction manifests in the light-adapted (photopic) ERG as a delayed and reduced response to a bright flash and 30-Hz flicker stimuli (Berson, 1981). Oscillatory potentials may also be reduced in RP patients (Wachtmeister, 1998). The annual rate of decay in the full-field ERG among RP patients ranges from 9 to 11% (Berson et al., 1993). The decay in central cone function is slower (Berson et al., 1985; Nagy et al., 2008); in a heterogeneous patient cohort including all three inheritance patterns (autosomal dominant, autosomal recessive, and X-linked) and syndromic subtypes, the annual rate of decay in central cone function was estimated at 4–7% (Falsini et al., 2012). As the disease progresses, the full-field ERG may become non-recordable despite a residual visual field. Under these circumstances, full-field stimulus threshold (FST), a fast test that does not require patients' fixation, or a multifocal ERG (mfERG) may still be able to elicit responses and may therefore be used to follow the disease progression (Messias et al., 2013; Nagy et al., 2008). Delayed responses in the mfERG may be used to predict visual field loss in a healthy-appearing retina (Hood, 2000).

2.6. Retinal imaging

2.6.1. Fundus imaging

In a single capture, conventional fundus photography covers a field of view of 30–50 degrees of the retina. The peripheral retina is generally covered rather poorly, even with 7-field fundus photography. Conventional color fundus photography is limited by media opacities and inadequate pupillary dilation, and patient cooperation is important. A better alternative may be found in ultra-wide field imaging, which uses confocal scanning laser ophthalmoscopy (cSLO) with green and red laser light. Ultra-wide field imaging depicts up to 200 degrees of retina in a single capture (Shoughy et al., 2015; Witmer and Kiss, 2013). This technique, however, also has its disadvantages: the colors are artificial, the peripheral image is distorted caused by the two

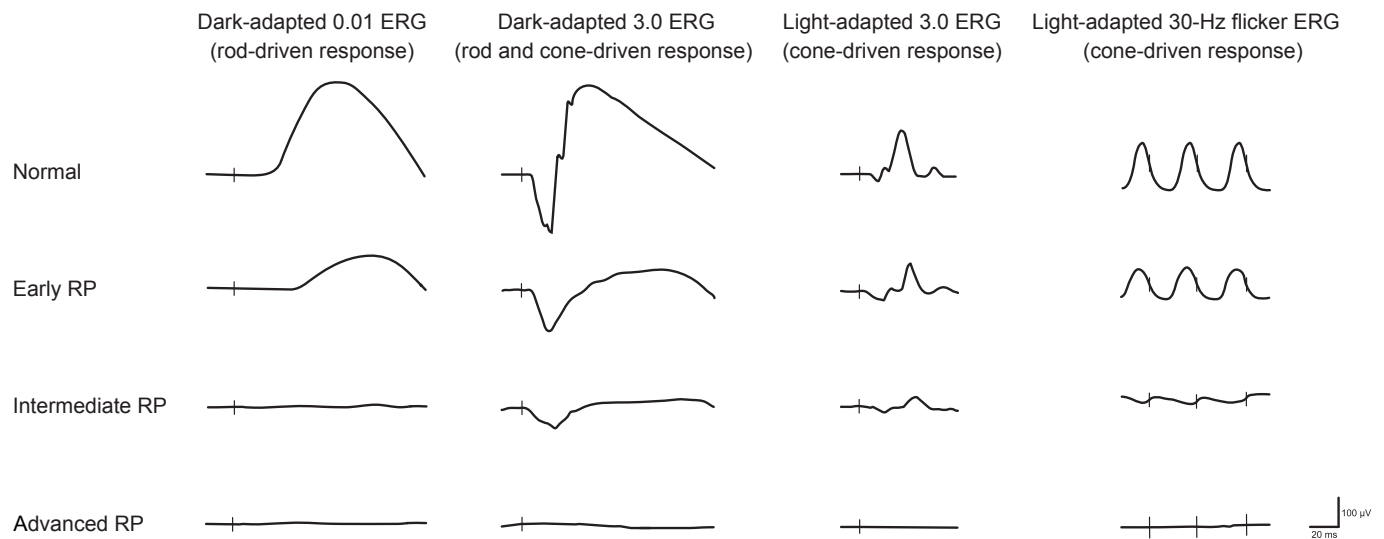


Fig. 2. Schematic representation of ERG recordings in different stages of RP (i.e. early, intermediate and advanced RP). Vertical lines indicate the moment of stimulus flash. As the RP progresses, the amplitude of responses decreases, and the implicit time may increase. Cone dysfunction typically lags behind the onset of rod dysfunction. Eventually, the ERG—under both scotopic and photopic conditions—is extinguished.

dimensional image of the three dimensional globe, and structures anterior to the retina (e.g. eyelashes and vitreous opacities) can cause artefacts (Witmer and Kiss, 2013). Multicolor imaging is a technique that uses the reflectance of three lasers with a particular wavelength, to provide information about different layers of the retina (Sergott, 2014). The eventual multicolor image is composed of the reflectance images from the individual lasers, and the coloring is also artificial. In patients with RP, multicolor imaging is better at defining the borders of the intact macular area compared to conventional fundus photography (Liu et al., 2017).

2.6.2. Optical coherence tomography

The earliest histopathological change in RP is shortening of the photoreceptor outer segments (Milam et al., 1998). This change is reflected in a spectral-domain optical coherence tomography (SD-OCT) image as disorganization of the outer retinal layers, initially at the interdigitation zone, followed by the ellipsoid zone, and finally at the external limiting membrane (Liu et al., 2016) (Fig. 3 and Fig. 4). As RP progresses, thinning of the outer segments is accompanied by a decrease in the thickness of the outer nuclear layer, which contains the nuclei of the photoreceptor cells. The late stages of RP are characterized by the complete loss of both the outer segment and the outer nuclear layer (Hood et al., 2011). In contrast, the inner retinal layers—including the inner nuclear layer and the ganglion cell layer—remain relatively well preserved. In fact, a decrease in the thickness of the photoreceptor outer segments may even be accompanied by thickening of the inner retinal layers; although the underlying cause of this thickening is not entirely clear, it may be related to edema formation in the retinal nerve fiber layer and/or neuronal-glial retinal remodeling in response to thinning of the outer retina (Aleman et al., 2007). In patients with advanced disease and atrophy of the outer retinal layers, SD-OCT imaging may reveal outer retinal tubulations (Goldberg et al., 2013). Hyperreflective foci are a common finding in the inner nuclear layer, the outer nuclear layer, and/or the subretinal space. These

hyperreflective foci may represent migrating RPE cells and seem to be correlated with the condition of the RPE layer, the condition of the ellipsoid zone, and—in some cases—fundoscopically visible hyperpigmentation. Interestingly, an absence of hyperreflective foci in the outer nuclear layer has been associated with better visual acuity (Kuroda et al., 2014). Several studies also revealed a correlation between the visual acuity in RP patients and the condition of the ellipsoid zone line (Aizawa et al., 2009; Tamaki and Matsuo, 2011; Witkin et al., 2006). In addition, the width of the ellipsoid zone line is associated with a decrease in visual field sensitivity. Another study found a linear correlation between a decrease in the visual field and thinning of the outer segments (Liu et al., 2016).

OCT imaging may also be valuable in diagnosing other macular abnormalities present in up to half of all RP patients (Makiyama et al., 2014). For example, CME is the most common finding, followed by epiretinal membrane formation, vitreomacular traction syndrome, and macular hole (Liu et al., 2016). In RP patients with CME, cystoid spaces are found primarily in the inner nuclear layer, but they can also occur in the outer nuclear layer, the outer plexiform layer, and/or the ganglion cell layer (Makiyama et al., 2014).

2.6.3. Fundus autofluorescence imaging

Fundus autofluorescence (FAF) can reveal an otherwise undetectable disruption in RPE metabolism. With short-wavelength (SW)-FAF, using blue or green light, the signal emanates principally from lipofuscin molecules present in the RPE (Delori et al., 1995). In contrast, near-infrared (NIR)-FAF displays the autofluorescence signal that originates from RPE and—to a lesser extent—choroidal melanin or related fluorophores (Keilhauer and Delori, 2006). FAF is increasingly used in evaluating and monitoring the progression of RP; however, sufficient data is lacking regarding the increased susceptibility to light toxicity of retinas with retinal dystrophies characterized by the accumulation of photosensitizers such as lipofuscin (Hunter et al., 2012; Teussink et al., 2017).

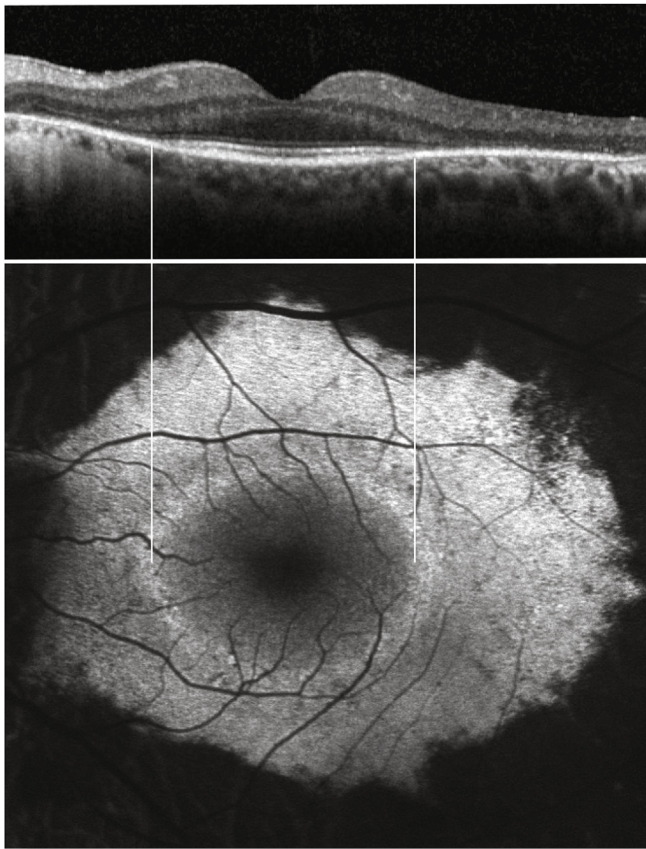


Fig. 3. Horizontal spectral-domain optical coherence tomography (SD-OCT; top panel) and fundus autofluorescence (FAF) images of the left eye of a patient with RP. The OCT image shows the perifoveal loss of the outer retinal layers. The central preservation of the ellipsoid zone corresponds to the internal edges of the hyperautofluorescent ring visible on FAF.

An abnormal foveal ring or curvilinear arc of increased autofluorescence (Fig. 3), not visible on ophthalmoscopy, is present in 50–60% of RP patients (Lois and Forrester, 2015). This ring can be visualized using both SW-FAF and NIR-FAF. The diameter of the ring ranges from 3 to 20° and usually has a relatively high level of interocular symmetry (Sujirakul et al., 2015). This hyperautofluorescent ring represents a transition zone between abnormal and normal retinal function; thus, function is relatively normal within the ring and absent

outside of the ring. The level of autofluorescence immediately outside of the ring is relatively preserved, despite severely impaired retinal function. Moreover, the degeneration of photoreceptor cells outside of the ring is reflected in a loss of the ellipsoid zone and the external limiting membrane, as well as a thinning or absence of the outer nuclear layer in an SD-OCT scan (Lima et al., 2009). The autofluorescent ring itself corresponds to an area of outer segment dysgenesis and lipofuscin production, with progressive retinal thinning, usually accompanied by loss of the ellipsoid zone at—or close to—the internal edge of the ring (Greenstein et al., 2012; Lenassi et al., 2012; Lima et al., 2009; Murakami et al., 2008). In the majority of patients, the autofluorescence measured inside the ring is quantitatively similar to autofluorescence in a healthy eye (Schuerch et al., 2017). Over time, the diameter of the hyperautofluorescent ring grows smaller; although the rate of this reduction in diameter varies, relatively large rings tend to reduce in size more rapidly than small rings. The inner edge of the constricting ring generally matches the progression of cone system dysfunction; in contrast, the loss of rod sensitivity is more widespread and includes the parafoveal area within the ring (Robson et al., 2012). Eventually, the ring may disperse, and this phenomenon is correlated with a widespread loss of sensitivity and visual acuity (Robson et al., 2011, 2012; Wakabayashi et al., 2010). Microperimetry in RP patients shows that visual sensitivity is relatively preserved within the ring, reduced in the ring zone itself, and decreased or non-recordable in the region outside of the ring (Duncker et al., 2013).

Besides the hyperautofluorescent ring, other autofluorescence patterns can be observed (see Fig. 5, and section 4.9). In nearly all adult patients with RP, wide-field FAF imaging shows patchy and/or reduced autofluorescence in the mid-periphery, which appears to be related to a loss of peripheral vision (Oishi et al., 2013). In addition, an abnormal pattern of increased autofluorescence maybe observed at the central macula and is associated with central visual impairment (Robson et al., 2011; von Ruckmann et al., 1999; Wakabayashi et al., 2010).

2.6.4. Fluorescein angiography

These days, fluorescein angiography is not commonly used in RP. On the angiogram, chorioretinal atrophy can be readily observed, initially in the periphery and/or mid-periphery, and later at the posterior pole. Although there is usually no delay in the filling of the retinal vessels, the vessels themselves are attenuated, and some leakage of dye may be present. The presence and extent of CME is also easily depicted with fluorescein angiography. Choroidal neovascularization—although not common in RP—can be visualized with fluorescein angiography and, more recently, with optical coherence tomography angiography (OCTA), a non-invasive alternative (Kashani et al., 2017; Sayadi et al., 2017).

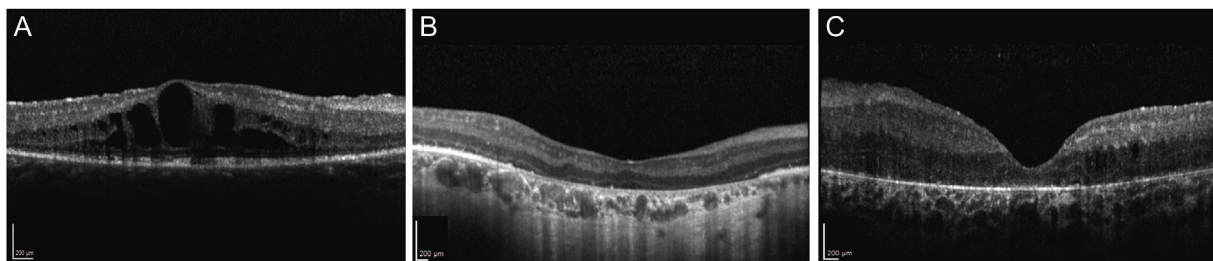


Fig. 4. Horizontal spectral-domain optical coherence tomography (SD-OCT) images of three patients with RP. (A) SD-OCT image of a 27-year-old female with *PDE6B*-associated RP, showing cystoid macular edema and central loss of the ellipsoid zone band (B) SD-OCT image of a 46-year-old male with *CDHR1*-associated RP, showing profound loss of photoreceptor outer segments, with central loss of the RPE and increased visibility of the choroidal vasculature. (C) SD-OCT image of a 9-year-old female with *CRB1*-associated RP, showing minimal intraretinal cysts, irregular foveal architecture and an increased retinal thickness—despite a generalized loss of the outer retinal layers—with loss of the retinal laminations.

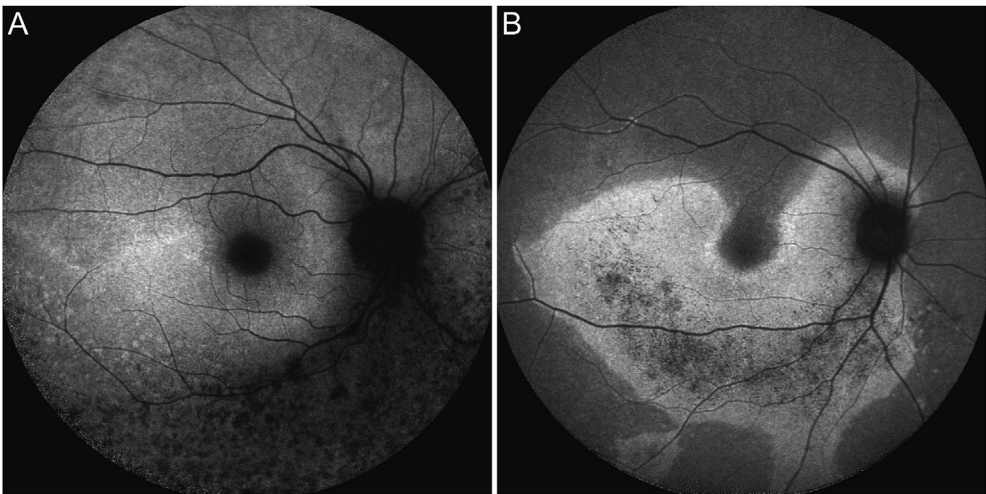


Fig. 5. Fifty-five-degree fundus autofluorescence (FAF) images of two RP patients that illustrate the diversity of autofluorescence patterns in RP. (A) FAF image of 27-year-old female with *FAM161A*-associated RP, showing a curvilinear arc of hyperautofluorescence surrounding the macula, in combination with sectoral peripheral hypoautofluorescence in the inferior quadrants. (B) FAF image of a 55-year-old female with *EYS*-associated RP, showing a well demarcated hyperautofluorescent area along the inferior vascular arcade, partially surrounding the fovea.

2.6.5. Adaptive optics scanning laser ophthalmoscopy

Adaptive optics scanning laser ophthalmoscopy (AOSLO) is a relatively new, non-invasive imaging modality that enables the visualization of photoreceptors at a microscopic level by correcting for ocular aberrations (Georgiou et al., 2017). In patients with RP, the high resolution of AOSLO allows early detection of photoreceptor damage, even when the outer retinal architecture on OCT appears intact (Sun et al., 2016). In addition, it can reveal a decrease in cone density before the visual acuity is reduced, since a significant cone reduction is possible before the visual acuity becomes affected (Ratnam et al., 2013). AOSLO is a highly sensitive imaging modality that may be of additional

value in monitoring disease progression, and evaluating treatment safety and efficacy in clinical trials.

3. Differential diagnosis for non-syndromic retinitis pigmentosa

The spectrum of IRDs is broad and includes disorders that primarily affect the macula (e.g., Stargardt disease and Best vitelliform macular dystrophy) and stationary disorders such as achromatopsia and CSNB. Precisely where RP lies within this spectrum is based on both relatively objective criteria such as symptoms, fundus abnormalities, and ERG findings, as well as seemingly arbitrary criteria such as the patient's age

Table 1
Differential diagnoses for non-syndromic retinitis pigmentosa.

Inherited retinal dystrophies	Syndromic forms of retinitis pigmentosa	Pseudoretinitis pigmentosa
Progressive retinal disease - Cone-rod dystrophy - Cone dystrophy - Leber congenital amaurosis - Bietti crystalline corneoretinal dystrophy - Late-onset retinal degeneration - Macular dystrophy (Stargardt disease, Sorsby fundus dystrophy)	Ciliopathies - Usher syndrome - Bardet-Biedl syndrome - Cohen syndrome - Joubert syndrome - Senior-Løken syndrome - Sensenbrenner syndrome (cranioectodermal dysplasia) - Short-rib thoracic dysplasia with or without polydactyly (includes Jeune, Mainzer-Saldino, Ellis-van Creveld, and short-rib polydactyly syndrome)	Drug-induced - Thioridazine and chlorpromazine - Quinolines (e.g. (Hydroxy)chloroquine)
Stationary retinal disease - Congenital stationary night blindness (including fundus albipunctatus and Oguchi disease)	Metabolic disorders - Alfa-tocopherol transfer protein deficiency (familial isolated vitamin E deficiency) - Bassen-Kornzweig syndrome (abetalipoproteinemia) - Mucopolysaccharidoses - Neuronal ceroid-lipofuscinoses, childhood onset (Batten disease) - Refsum disease (phytanic acid oxidase deficiency) - Mevalonate kinase deficiency - HARP syndrome (hypoprebetalipoproteinemia, acanthocytosis, RP and pallidal degeneration) - PHARC syndrome (polyneuropathy, hearing loss, ataxia, RP, and cataract)	Chorioretinal infections - Syphilis, Lyme disease, acute retinal necrosis and other viral infections (rubella, chicken pox, measles, cytomegalovirus)
Inherited vitreoretinopathies - X-linked juvenile retinoschisis - Enhanced S-cone syndrome/Goldmann-Favre syndrome - Wagner syndrome/erosive vitreoretinopathy - Snowflake vitreoretinopathy	Mitochondrial disorders - Kearns-Sayre syndrome - NARP syndrome (neuropathy, ataxia, and RP)	Sequela of inflammatory disease - Sarcoidosis - Acute posterior multifocal placoid pigment epitheliopathy - Birdshot chorioretinopathy - Serpiginous choroidopathy - Diffuse unilateral subacute neuroretinitis - Systemic lupus erythematosus
Chorioretinal dystrophies - Choroideremia - Gyrate atrophy - Helicoid peripapillary chorioretinal degeneration (Sveinsson chorioretinal atrophy) - Progressive bifocal chorioretinal atrophy		Miscellaneous - Vitamin A deficiency - Paraneoplastic - Trauma - Siderosis bulbi - Old retinal detachment - Pigmented paravenous retinochoroidal atrophy - Acute zonal occult outer retinopathy
Female carriers of inherited retinal dystrophies - Retinitis pigmentosa - Choroideremia - Ocular albinism		

A more extensive overview of the differential diagnoses of non-syndromic retinitis pigmentosa, including clinical features and references, is provided in [Supplementary Table S1](#).

at onset and even historical factors. Finally, when classifying an IRD, it is important to take the entire disease course into consideration, as some phenotypes tend to overlap in late stages. An overview of the considerations for differential diagnoses in RP is given in [Table 1](#) (See [Supplementary Table S1](#) for a more comprehensive overview, including clinical features).

3.1. Other inherited retinal dystrophies

Early-onset RP has both clinical and genetic overlap with LCA, and both disorders represent a continuum of retinal dystrophies divided by indistinct criteria based on the age of onset. Most often, patients who present at birth or within the first few months of life are classified as having LCA ([Kumaran et al., 2017](#)). The lower age limit for diagnosing RP has been set by some after infancy (variably defined as age one or two), resulting in a gray area where both disorders overlap ([Kumaran et al., 2017](#)). In LCA, the extremely early loss of visual function leads to a set of symptoms that include nystagmus, sluggish or near-absent pupillary response, photophobia, and oculo-digital signs such as poking, pressing, and rubbing the eyes. Visual acuity is rarely better than 20/400, and the aspect of the fundus can range from normal to an extensive atrophic RP-like pigmentary retinopathy. Scotopic and photopic ERG recordings are generally non-recordable or—at the very least—severely reduced. Early-onset RP can present with many of these symptoms, and this overlap with LCA is clearly reflected in the number of genes associated with both disorders (see [Fig. 1](#)).

Cone-rod dystrophy is another IRD that has both clinical and genetic overlap with RP. An ERG recording is not always conclusive with respect to determining which photoreceptors are primarily affected, particularly in the later stages of the disease. However, the early symptoms of cone-rod dystrophy, which include early loss of visual acuity, intense photophobia, variable achromatopsia, and the initial absence of night blindness, can help the practitioner differentiate between cone-rod dystrophy and RP ([Hamel, 2007](#)).

Certain retinal dystrophies demonstrate degeneration in a rod-cone pattern; however, based on their highly specific phenotype, they have historically been differentiated from RP. Examples are choroideremia (patchy chorioretinal atrophy and normal appearing retinal vessels), gyrate atrophy (well demarcated circular chorioretinal atrophy with elevated ornithine levels), and late-onset retinal degeneration (perimacular drusen-like lesions and long anterior lens zonules) ([Borooah et al., 2009](#); [Mauthner, 1872](#)). Retinitis punctata albescens also has a very specific phenotype; nevertheless, this entity has been considered an RP subtype throughout most of the literature.

CSNB is an example of a stationary disorder characterized predominantly by rod dysfunction. With the exception of two subtypes of CSNB—namely, Oguchi disease and fundus albipunctatus—CSNB patients generally have a normal fundus. However, CSNB has considerable overlap with RP with respect to the genes involved; thus mutations in the *PDE6B*, *RDH5*, *RHO*, *RLBP1*, and *SAG* genes can lead to either RP or CSNB ([Zeitz et al., 2015](#)).

3.2. Syndromic RP

Mutations in genes involved in ciliary function often—but not always—result in a syndromic form of RP. Arguably, the most common ciliopathy is Usher syndrome, which presents with a variable degree of neurosensory hearing loss ([Boughman et al., 1983](#)). Another well recognized syndromic form of RP is Bardet-Biedl syndrome; in addition to retinopathy, patients with this syndrome can also present with obesity, postaxial polydactyly, hypogonadism, renal dysfunction, and/or cognitive impairment ([Mockel et al., 2011](#)). The type and extent of these

extra-ocular features in Bardet-Biedl can vary widely and depend—for the most part—on the specific gene involved and the specific mutation within that gene. Syndromic RP is also associated with systemic metabolic and mitochondrial disorders. The extra-ocular features in syndromic RP can be extremely subtle (for example, an impaired sense of smell) and/or easily overlooked by the examining ophthalmologist (for example, in the case of cardiovascular and/or renal disease); on the other hand, some features can be surgically corrected at an early age (e.g., polydactyly). Therefore, obtaining a careful, thorough history that includes these various extra-ocular abnormalities is extremely important for obtaining a diagnosis. However, genetic analysis may reveal mutations in a gene that is associated with syndromic forms of RP, when the initial clinical assessment did not indicate extra-ocular abnormalities. In such cases, it is important to reexamine the patient for the presence of systemic manifestations. For example, patients with *TRNT1*-associated RP all demonstrate a mild erythrocytic microcytosis that is only discovered after analysis of the blood count parameters ([DeLuca et al., 2016](#)). Keep in mind, however, that not all extra-ocular abnormalities indicate syndromic disease; these abnormalities should match with the gene involved. A number of genes associated with non-syndromic RP (e.g. *BBS1*, *CLRN1* and *USH2A*) may also cause syndromic RP (see [Table 2](#)). Correctly diagnosing a patient with syndromic RP can have sight-saving—or even life-saving—implications, particularly in patients with a metabolic disorder such as Refsum disease or Kearns-Sayre syndrome, a mitochondrial disorder that often includes cardiac dysfunction.

3.3. Pseudoretinitis pigmentosa

Several conditions can mimic the clinical features of RP (phenocopy) and are classified as pseudoretinitis pigmentosa ([Table 1](#), [Fig. S1](#)). It is important to distinguish these entities from RP, as several forms of pseudoretinitis pigmentosa are treatable and do not have an underlying genetic component. A thorough history, including current and past medications, lack of interocular symmetry, and lack of disease progression, may indicate a diagnosis other than RP. Indeed, many patients who were diagnosed with “unilateral RP” fall in this category, although a germline mutation in the *RP1* gene was reported in a patient with strictly unilateral RP ([Mukhopadhyay et al., 2011](#)).

4. Clinical findings in genetic subtypes of RP

In Chapter 2, we discussed the typical features attributed to RP in general. However, the heterogeneous presentation of these conditions warrants a closer look at the clinical findings that have been reported for genetic subtypes of RP. Many early studies used non-genotyped RP cohorts and occasionally subdivided the patients according to their inheritance pattern. More recently, however, the phenotype for a specific causative gene is described, albeit with limited numbers of patients and/or a lack of clinical details. Obtaining a clear picture regarding the phenotypes associated with genetic subtypes of RP is therefore challenging. In [Tables 2 and 3](#) and [Fig. 6](#), we provide a comprehensive overview of the specific clinical features attributed to various subtypes in order to help the clinician identify the subtype and predict the clinical course. In addition, a unique atlas containing color fundus photographs of most RP subtypes is available in [Supplementary Fig. S2](#). Nevertheless, it is important to realize that even within a specific subtype, considerable phenotypic variation can occur due to the variable effects of mutations, genetic modifiers, and—in some cases—environmental factors.

Table 2
Genetic subtypes and specific characteristics of non-syndromic RP.

Gene	RP type	IP	Decade of onset	Visual function	Ophthalmic features	Syndromic associations	Other IRD phenotypes
<i>ABCA4</i> ^{1a}	19	AR	1	VA is severely affected: FC to NLP at higher age.	Bone spicule-like pigmentation may reach into the macular region. Severe chorioretinal atrophy.	–	CRD, STGD
<i>AGBL3</i> ^{2b}	75	AR	1–2	VA loss is highly variable. At 40–50 years, VA may range from 20/40 to NLP.	Macular involvement: macular atrophy, CME, PSC.	Mental retardation	–
<i>AHI1</i> ^{2a}	NA	AR	3–4	VA in 3 rd decade can range from 20/32 to HM or even LP.	Macular involvement, PSC.	JS type 3	–
<i>ARHGAP18</i> ^{2a}	78	AR	3–4	VA: 20/30–20/60 in 4 th decade, but may decrease to CF in the 6 th decade. Photopsias.	Nummular pigment clumping, CME. Vitreous opacities (in 1 patient)	–	–
<i>ARL2BP</i> ^{2b}	66 ^d	AR	3	Relative early loss of VA: HM (or even LP) in the 4 th decade of life. Yet, other patients may retain a VA of 20/40 up to the 6 th decade of life.	Marked macular atrophy, PSC, ERM.	Situs inversus, otitis media, primary ciliary dyskinesia	–
<i>ARL6</i> ^{2a}	55	AR	NA	No information on the visual function available.	No information on the retinal phenotype available.	BBS type 3	–
<i>BBS1</i> ^{2a}	NA	AR	1–2	Severe visual loss, may reach LP by 5 th –6 th decade of life. Severe constriction of VFs up to 5°–10° in the 4 th decade.	Nystagmus, possible macular atrophy, cataract (PSC and cortical).	BBS type 1	–
<i>BBS2</i> ^{2a}	74	AR	1–2	Severe, relative early visual loss: HM or LP before the age 60. VFs are severely constricted.	Macular atrophy, bull's eye maculopathy, PSC, ERM.	BBS type 2	–
<i>BBS9</i> ^{2a}	NA	AR	NA	No further information available.	No information on the retinal phenotype available.	BBS type 9	–
<i>BEST1</i> ^{2a}	50	AD, AR	1–2 (5)	Night blindness may be absent. Loss of VA is a prominent symptom.	Yellow fundus flecks in the mid-periphery, pigmentation in far periphery, CME, ERM. Macula relatively spared unless serous macular detachments.	–	BYMD, AVMD, ARB, ADVRC
<i>C2orf71</i> ^{1a}	54	AR	1–2	Night blindness may be absent. Ring scotomas in 4 th –5 th decade of life. Photophobia may occur.	Foveal atrophy. Early onset associated with severe chorioretinal atrophy.	Hearing loss, ataxia and cerebellar atrophy	–
<i>C8orf37</i> ^{1a}	64	AR	1–2	Severe visual loss to HM/LP in the 4 th decade. The VF is constricted to 5°. Sometimes photophobia.	High myopia, cataract. Marked geographic macular atrophy.	BBS type 21	CRD
<i>CA4</i> ^{2b}	17 ^c	AD	2–3	VA levels of 20/200 (age 11) and LP (58 years).	Pigment clumping at the level of the RPE has been described (in 1 patient).	–	–
<i>CDHR1</i> ^{2a}	65	AR	2	VA loss to HM by the 4 th or 5 th decade of life. Severe color vision defects, VF constriction to 5–10°, sometimes with mid-peripheral residue. Photophobia described in 3 rd decade.	In early stage: sparse bone spicule pigment migration. Dense pigment migration and (patchy) atrophy also in macula in later stages.	–	CRD
<i>CERKL</i> ^{1a}	26	AR	2–3	VA generally severely affected and may decrease to LP around the 5 th decade. Photophobia.	Early macular involvement, sometimes with hyperpigmentation. Pericentral localization of bone spicules. Normal appearance of optic disc.	–	–
<i>CLN3</i> ^{1a}	NA	AR	1–5	VA may be reduced to HM by the 5 th decade. Severe constriction of VFs up to 5°–10° in the 6 th decade.	Sparse bone spicule pigmentation, macular atrophy, CME.	JNCL	CRD
<i>CLRN1</i> ^{3a}	61	AR	NA	Classic RP phenotype.	Typical RP features.	USH type 3	–
<i>CNGA1</i> ^{1a}	49	AR	1	A gradual decrease in VA may occur from the 4 th decade onwards. Concentric constriction of the VF during the 3 rd decade of life.	Sometimes macular atrophy, pericentral RP (described once).	–	–
<i>CNGB1</i> ^{1a}	45	AR	1–2	Macular involvement with VA loss to LP. VF loss from a mean age of 33 years (13–40). Sometimes photophobia.	Macular atrophy, pericentral RP (described once).	–	–
<i>CRB1</i> ^{1a}	12	AR	1–5	50% of patients have a VA < 20/200 at age 35 years.	Nystagmus (± 40%), hyperopia, CME (50%), PPRPE, Coats-like vasculopathy, optic disc drusen, retinal vascular sheathing, asteroid hyalosis, thickened retina, bull's eye maculopathy and yellow round deposits in the posterior pole. Occasional dense pigmentation.	Nanophthalmos	LCA, PPRCA
<i>CWC27</i> ^{2a}	NA	AR	1	VF is severely constricted early in the disease course.	No information on the retinal phenotype available.	Brachydactyly, craniofacial abnormalities, short stature, neurologic defects	LCA
<i>DHDDS</i> ^{1a}	59	AR	2–3	VA is generally mildly affected, although in some eyes VA decreases to LP levels.	Occasional CME. Parafoveal atrophy of the RPE and pericentral localization of pigmentation.	–	–
<i>EYS</i> ^{1a}	25	AR	2–3	VA loss from the 4 th decade to levels of 20/200 to NLP in the 7 th decade.	Variable levels of bone spicule pigmentation and macular atrophy. PSC.	–	–
<i>FAM161A</i> ^{1a}	28	AR	2–3	Legally blind in 6 th –7 th decade. VF constriction to 10°.	Limited number of bone spicules. Macular atrophy. PSC.	Hearing problems, hyposmia	–
<i>FSCN2</i> ^{2a}	30	AD	1	VA and VF relatively spared until the 4 th decade, then VA loss to levels of HM.	Early vessel attenuation. Occasional macular atrophy.	–	MD
<i>GNA11</i> ^{3a}	Unclear if FSCN2 is involved in RP, because the c72delG mutation does not segregate in Chinese families	AR	2	Variable VA: 20/20 (80 years) to 20/80 (32 years).	Round pigment clumps and typical bone spicules. ERM.	–	CSNB

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Table 2 (continued)

Gene	RP type	IP	Decade of onset	Visual function	Ophthalmic features	Syndromic associations	Other IRD phenotypes
<i>GUC1B</i> ^{2b}	48	AD	NA	Variable visual function: 20/20 (62 years)–20/100 (47 years).	Highly variable retinal expression in (Japanese) patients: normal fundi, sector RP with macular involvement, only macular atrophy or diffuse RP.	–	MD
<i>HGSNAT</i> ^{2b}	73	AR	1–2 5–6	Severe VA loss to CF at age 60 years. VA is more preserved in case of late disease onset.	CME, ERM, limited number of bone spicules, pericentral RP.	MPS type IIIC	–
<i>HK1</i> ^{1b}	79	AD	1–4	Highly variable VA loss. VA loss to CF in 3 rd decade reported. Photophobia.	Bull's eye maculopathy, pericentral RP.	HMSN, nonspherocytic hemolytic anemia	–
<i>IDH3A</i> ^{2b}	NA	AR	1–2	VA loss dependent on the presence of macular pseudocoloboma.	Macular pseudocoloboma, CME.	–	–
<i>IDH3B</i> ^{2b}	46	AR	NA	Classic RP phenotype.	Typical RP features, PSC.	–	–
<i>IFT140</i> ^{1a}	NA	AR	1–4	Vision loss from 3 rd –5 th decade, VA may eventually reduce to LP.	Macular atrophy, CME, ERM, early cataract or white dots. Dense pigmentation in 7 th decade reported.	SRTD type 9	LCA
<i>IFT172</i> ^{2a}	71	AR	1–2	Night blindness is the initial symptom. Further symptoms have not been specified.	Variable macular involvement; macular atrophy, CME, ERM.	SRTD type 10, BBS type 20	–
<i>IMPDH1</i> ^{1a}	10	AD, AR	1–3	AD disease: variable degrees of VA loss. Legal blindness before the age of 40 has been described.	AD disease: CME, significant vitreous disturbances, PSC.	–	LCA
<i>IMPG2</i> ^{1b}	56	AR	1–2	AR disease: no information on the visual function available. Central vision generally affected.	AR disease: macular involvement.	–	VMD
<i>KIZ</i> ^{2b}	69	AR	2	Classic RP phenotype.	Macular atrophy and bull's eye maculopathy. Sheathing of peripheral vessels.	Obesity, hearing problems	–
<i>KLHL7</i> ^{2b}	42	AD	3	VA remains (near) normal up to the 5 th or 6 th decade. VF loss usually is the initial symptom.	Fundus appearance can be normal up to the 4 th decade. Later: CME and parafoveal atrophy.	CISS	–
<i>LRA1</i> ^{1a}	NA	AR	1	Severe, early VA loss to 20/100–20/200 and VF constriction to 30°–60° before age 10. Photophobia.	High hyperopia, nystagmus, poorly reactive pupils. Sparse or absent bone spicules (age 9 years). RPA. Reduced FAF signal.	–	LCA
<i>MAK</i> ^{1b}	62	AR	2–5	May show initial preservation of nasal VF.	Macula generally not involved, but sometimes CME (in 1 patient) or macular atrophy.	–	–
<i>MERTK</i> ^{1a}	38	AR	1–2	VA loss to ≤20/200 in the 2 nd decade. Variable VF loss: normal VF (3 rd decade)–5° (2 nd decade). Legal blindness: ± 40 years.	Nystagmus, bull's eye maculopathy, macular atrophy. Pallor of the optic disc may be absent.	–	LCA
<i>MVK</i> ^{2b}	NA	AR	3	Dyschromatopsia.	Arterial tortuosity, PSC, ERM, thickening of the nerve fiber layer on OCT, CME (described once).	MKD (MEVA or HIDS)	–
<i>NEK2</i> ^{2a}	67	AR	NA	No information on the visual function available.	No information on the retinal phenotype available.	–	–
<i>NR2E3</i> ^{1a}	37	AD, AR	1–3	AD disease: VF loss from the 2 nd –3 rd decade.	AD disease: nummular and spicular pigmentation. Early-onset cataract. FAF: 2 or 3 hyperfluorescent rings may be visible. Pericentral RP.	ESCS	–
<i>NRL</i> ^{1a}	27	AD, AR	1	AR disease: early VA loss.	AR disease: clumped pigment deposits	–	–
				AD disease: VA loss from the 4 th decade: 20/20–20/200. VF diameters: 50–60° in the 3 rd decade and decrease up to 10° in the 8 th decade.	AD disease: nystagmus, minimal or absent hyperpigmentation in 2 nd decade. Round pigment clumps. Chorioretinal atrophy, macular atrophy, bull's eye maculopathy, PSC. Peripheral retinal telangiectasis (that may cause serous retinal detachment)	–	–
				AR disease: visual function is more severely affected compared to AD disease.	AR disease: peripheral pigment clumps. Retinal features are similar to NR2E3-associated enhanced S-cone syndrome.	–	–
<i>ORD1</i> ^{2a}	23	XL	1	Early loss of central vision. Only temporal and inferior VF residues.	Grayish spots at the level of the RPE. Granularity of macular RPE.	JS, OFDS type 1, SGBS type 2	–
<i>PANK2</i> ^{2a}	NA	AR	5	VA reduction to HM in the 6 th decade.	No information on the retinal phenotype available.	HARP syndrome, NBIA1 (HSS)	–
<i>PDE6A</i> ¹	43	AR	1	Marked peripheral VF loss.	CME, PSC and dense pigmentation.	–	–
<i>PDE6B</i> ^{1a}	40	AR	1	Loss of peripheral VF is a prominent symptom that occurs during the 2 nd –3 rd decade.	CME, PSC, dense pigmentation at high age (80 years). Pericentral RP (described once).	–	CSNB
<i>PDE6G</i> ^{2a}	57	AR	1	Marked constriction of the VF up to 5–10°.	Normal vessels and optic discs in young patients. CME in all patients (1 family).	–	–
<i>POMGNT1</i> ^{1a}	76	AR	1–2 (3–4)	Variable VA loss, may decrease to LP. VF constriction to 5° in the 6 th –7 th decade.	Macular involvement, CME.	MEB	–
<i>PRCD</i> ^{1a}	36	AR	1–3	Relative early visual loss.	Various macular involvement: bull's eye maculopathy, macular atrophy, CME, ERM, PSC. Fairly normal-colored optic disc.	–	–

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Table 2 (continued)

Gene	RP type	IP	Decade of onset	Visual function	Ophthalmic features	Syndromic associations	Other IRD phenotypes
<i>PROM1</i> ^{1a}	41	AR	1	Visual loss during the 1 st decade.	Large inter- and intrafamilial variability: isolated (bull's eye) maculopathy, pericentral RP, severe RCD. Nystagmus.	Polydactyly	CRD, AD MD
<i>PRPF3</i> ^{1a}	18	AD	1 (4)	Classic RP phenotype.	Classic RP phenotype.	–	–
<i>PRPF4</i> ^{2a}	70	AD	2–3	Variable visual loss, may reach HM. VF constriction to 5–10° in the 6 th decade.	Variable degree of macular atrophy.	–	–
<i>PRPF6</i> ^{3b}	60	AD	2–4	VA initially spared, but may decrease to LP. Constriction of VFs to 30–40° (4 th decade) and ± 10° (6 th decade).	Macular atrophy in later stages. Optic nerve heads may initially be normal. PSC.	–	–
<i>PRPF8</i> ^{1a}	13	AD	1–2	VA may remain normal up to the 3 rd –4 th decade, with progression to 20/200 in the 7 th decade. VF constriction to ± 10° in 4 th decade.	Dense intraretinal pigment migration (in 1 patient).	–	–
<i>PRPF31</i> ^{1a}	11	AD	1–2	Variable presentation. Incomplete penetrance suggested in asymptomatic patients. Mean annual VF loss: 6.9%. Legal blindness: 4 th decade.	Macular atrophy. CME, PSC. May present with para-arteriolar absence of pigmentation. Pericentral RP (described once). No abnormalities observed in patients that lack penetrance.	–	–
<i>PRPH2</i> ^{1a} (RDS)	7	AD, DG	2–6	VA usually spared, but dependent on the degree of macular involvement.	Variable macular involvement, CME, RPA, pericentral RP (described once).	–	MD, PD, CRD, LCA
<i>RBP3</i> ^{2a}	66 ^d	AR	1	<i>Early-onset disease</i> : early visual loss. Strabismus.	<i>Early-onset disease</i> : (high) myopia, PSC.	–	–
			4–6	<i>Late-onset disease</i> : blurred vision is an early symptom; night blindness may be absent.	<i>Late-onset disease</i> : PSC, (high) myopia. ERG: cone-rod pattern may occur.	–	–
<i>RDH12</i> ^{1a}	53	AD	AD: 2–5	<i>AD disease</i> : classic RP phenotype.	<i>AD disease</i> : typical RP features.	–	LCA
		AR	AR: 1–3	<i>AR disease</i> : VA at presentation: 20/40–20/200, may reach HM-LP. VF constriction to < 5° in the 2 nd –3 rd decade. Central scotoma may occur.	<i>AR disease</i> : nystagmus, macular atrophy, dense pigmentation with para-arteriolar sparing, may reach into the macular region. Preservation of peripapillary RPE, CME, PSC.	–	–
<i>REEP6</i> ^{2a}	77	AR	1–2	Photophobia. Gradual VA loss, although a decline to 20/400 at the age of 32 has been described.	CME, PSC, vascular sheathing.	Anosmia	–
<i>RGR</i> ^{1b}	44	AR	NA	VA loss to ≤ 20/200. Severe VF constriction.	Macular atrophy in patients with severely affected VA.	–	–
			Unclear if <i>RGR</i> is involved in RP, or due to parallel occurrence of <i>CDHR1</i> mutation			–	–
<i>RHO</i> ^{1a}	4	AD, AR	1–2	Highly variable clinical course: mean annual VA decline: 1.6%, annual VF loss: 2.6%. Legal blindness: 6 th –8 th decade.	Sector RP, and to a lesser extent pericentral RP. CME.	–	CSNB
			(4)			–	–
<i>RLBP1</i> ^{1a}	NA	AR	2	Variable VF loss from the 3 rd decade, to < 5° residues.	Minimal or absent bone spicules, RPA.	–	BRD, FA, NFRCD
<i>ROM1</i> ^{1a}	NA	DG	NA	No information on the visual function available.	No information on the retinal phenotype available.	–	–
<i>RP1</i> ^{1a}	1	AD, AR	AD: 2–3	<i>AD disease</i> : moderate decrease in VA in 4 th –5 th decade.	<i>AD disease</i> : PSC. RP sine pigmento (described once).	–	–
					<i>AR disease</i> : macular atrophy, CME, myopia.	–	–
<i>RP1L1</i> ^{3a}	NA	AR	AR: 1	<i>AR disease</i> : relative early loss of VA to CF or HM in the 5 th decade. VF constriction to 10° in the 3 rd decade.	Typical RP features.	Hearing loss, ataxia, cerebellar atrophy	OMD
<i>RP2</i> ^{1a}	2	XL	4–5	Moderate decrease in VA to ± 20/80. VF constriction to 5° in the 8 th decade.		–	–
			1	Early loss of central vision. Central scotoma in 50% of patients. Severe VF constriction in 2 nd decade. Large intrafamilial differences.	Myopia. Bull's eye maculopathy, macular atrophy, sometimes choroideremia-like degeneration. A tapetal-like reflex (reported once).	–	–
<i>RP9</i> ^{3b}	9	AD	1–2	<i>Female carriers</i> : can be affected as well. Presentation highly variable. Highly variable presentation. Incomplete penetrance suggested in asymptomatic patients. Relative early VF constriction: < 20° in 3 rd decade.	PSC, CME, macular atrophy.	–	–
		NP			Early stage: regional (or 'patchy') loss of rod and cone function.	–	–
<i>RPE65</i> ^{1a}	20	AD (NP)	AD:	<i>Autosomal dominant disease</i> : incomplete penetrance suggested. Early loss of central vision.	<i>AD disease</i> : (sparse) nummular and spicular pigmentation. Extensive chorioretinal atrophy, macular atrophy, PSC.	–	LCA
		AR	AR: 1	<i>Autosomal recessive disease</i> : severely, relative early visual loss: CF or HM in the 1 st decade. Photophobia is generally absent.	Nystagmus, macular atrophy. Bone spicule pigmentation is often sparse. Lack of FAF.	–	–
<i>RPGR</i> ^{1a}	3	XL	1–2	Early loss of central vision. Annual VF loss: 4.7–9%. Mean age legally blind: 45 years.	Variable macular involvement: from no abnormalities to atrophic lesions. Coats-like vasculopathy (1 patient). OCT: ellipsoid zone width constriction ± 175 µm/year; ONL thinning ± 2.50 µm/year.	Hearing loss, respiratory infections	CRD, CD, MD
				<i>Females carriers</i> : can be affected as well. Presentation highly variable. Relative early VA loss to levels of 20/200-CF in 3 rd decade.	<i>Female carriers</i> : tapetal-like reflex possible. Nystagmus, macular atrophy, pigmentary changes may be sparse or absent.	–	LCA, CRD

(continued on next page)

Table 2 (continued)

Gene	RP type	IP	Decade of onset	Visual function	Ophthalmic features	Syndromic associations	Other IRD phenotypes
<i>SAG1^a</i>	47	AD	2	<i>AD disease:</i> VF constriction to 10°.	<i>AD disease:</i> typical RP features, OCT: hyperreflective foci.	–	Oguchi disease
		AR		<i>AR disease:</i> VA loss may precede NB.	<i>AR disease:</i> macular atrophy, CME. Golden-yellow fundus reflex with Mizuo-Nakamura phenomenon.	–	
<i>SAMD11^{3b}</i>	NA	AR	3–4	VA loss from 6 th decade, may eventually reach HM. VF constriction to < 10°. Occasional photophobia.	Foveal atrophy, ERM, PSC. Occasional: CME, corneal guttata.	–	–
<i>SEMA4A^{2a}</i>	35	AD	NA	No information on the visual function available.	No information on the retinal phenotype available.	–	CRD
<i>SLC7A14^{2a}</i>	68	AR	1–2	Visual loss, may reach HM in the 4 th decade.	Extensive chorioretinal atrophy, including macular atrophy.	–	–
<i>SNRNP 200^{1a}</i>	33	AD	1–4	Variable progression. Generally slow VA loss to HM in the 8 th decade.	Macular atrophy, CME. May present with heavy pigment clumping.	–	–
		NP		VF constriction to 10°.	PSC (patients > 45 years).	–	–
<i>SPATA7^{1a}</i>	NA	AR	1	Considerable VA loss in case of macular involvement. Severe VF constriction.	Nystagmus, maculopathy, PSC.	LCA with fertility- or auditory dysfunction	LCA
<i>TOPORS^{1a}</i>	31	AD	2–5	VA is maintained in most patients. Constriction of VF to 10°.	ERG: rod-cone pattern possible in early disease.	–	–
<i>TTC8^{3a}</i>	51	AR	1–2	NB and photophobia are early symptoms. Early VA loss to 20/200.	Pericentral RPE atrophy in young patients, which progresses to a diffuse pigmentary retinopathy with choroidal sclerosis.	–	–
<i>TULP1^{1a}</i>	14	AR	1	Rapid progression. VA: 20/200 at age 20, may decrease to HM or even LP. VF loss to 10°.	May include macular atrophy, sparse bone spicule pigmentation.	BBS type 8	–
		AR		VA relatively intact to 3 rd to 4 th decade, then annual VA decline: 2.6%.	Nystagmus, hyperopia, PSC, macular atrophy; yellow perifoveal annular ring. Pericentral RP (described once).	–	LCA
<i>USH2A^{1a}</i>	39	AR	3	Annual loss V4e VF area: 7.0%.	CME can be observed.	USH type 2A	–
		AR		Legal blindness (based on VA): 6 th –7 th decade.	FAF: distinctive pattern of diffuse and homogeneous peripheral hypoauteofluorescence. Pericentral RP.	–	–
<i>ZNF408^{2a}</i>	72	AR	2–4	VA generally remains ≥ 20/40 in the 5 th decade VF constriction to 10° at age 50 years. Photophobia is common.	High myopia. Vitreous condensations, PSC, ERM, CME (in 1 patient).	–	FEVR
<i>ZNF513^{1a}</i>	58	AR	1	Visual loss to 20/200-LP.	Macula: atrophy, sometimes with hyperpigmentation.	–	–
Candidate genes							
<i>ADGRA3^{3b}</i>	NA	AR	NA	No information on the visual function available.	No information on the retinal phenotype available.	–	–
<i>(GPR125)</i>							
<i>ARL3^{3a}</i>	NA	AD	3	Photopsias.	CME, PSC.	–	–
<i>CRX^{3a}</i>	NA	AD	6–7	VA may decrease to CF in the 8 th .	Early macular involvement, pericentral pigmentation.	–	LCA, CRD
<i>DHX38^{3b}</i>	NA	AR	1	VA severely affected by macular colobomas. Early loss of LP.	Macular colobomas.	–	–
<i>EMC1^{3b}</i>	NA	AR	NA	No information on the visual function available.	No information on the retinal phenotype available.	Cerebellar atrophy, psychomotor retardation	–
		AR	NA	No information on the visual function available.	No information on the retinal phenotype available.	–	–
<i>KIAA1549^{3b}</i>	NA	AR	2	VA loss from the 3 rd decade.	PSC has been reported.	MODY/late-onset diabetes, neurological abnormalities	–
<i>NEUROD1^{3a}</i>	NA	AR				–	–
Loci							
<i>RP6³</i>	6	XL	1–2	Classic RP phenotype.	<i>Female carriers:</i> tapetal-like reflex.	CGD, McLeod phenotype, mental retardation	–
<i>RP17³</i>	17 ^c	AD	NA	VA in 3 rd decade can range from 20/20 to 20/200. Variable VF constriction: from pericentral scotoma to 10° residue.	Atrophic patches, pigment dispersion, granular aspect of the RPE.	–	–
<i>RP22³</i>	22	AR	1	Rapidly progressive decline in VA, leading to severe visual impairment at the age of 40.	Absence of pigmentation has been described.	Obesity, hexadactyly mental retardation, hypogonadism	–
<i>RP24³</i>	24	XL	1	Peripheral VF loss in 4 th decade.	Typical RP features.	–	–
				<i>Female carriers:</i> asymptomatic, although perimetry reveals sensitivity losses.			
<i>RP29³</i>	29	AR	2–3	Onset VA loss: 3 rd decade. VA may decrease to NLP in 5 th decade.	Anterior and posterior polar cataracts, vitreous cells, obliteration of peripheral blood vessels.	–	–
<i>RP32³</i>	32	AR	1	Severely, relatively early visual loss: HM in 3 rd decade to LP or worse in 4 th , 5 th decade.	Generalized grayish carpet-like retinal degeneration. Bull's eye maculopathy, macular atrophy.	–	–
<i>RP34³</i>	34	XL	2	Nycalopia is the initial symptom, despite a cone-rod pattern on ERG.	Typical RP features. ERG: cone-rod pattern.	–	–
<i>RP63³</i>	63	AD	2–5	Early impaired color vision. Blurred vision is an early symptom. Yet, VA generally is normal or near normal.	Macular atrophy in some patients.	–	–

(continued on next page)

Table 2 (continued)

Gene	RP type	IP	Decade of onset	Visual function	Ophthalmic features	Syndromic associations	Other IRD phenotypes
Withdrawn RP subtypes							
RP5	Second <i>RHO</i> (RP4) locus						
RP8	Initially described in an Irish family with RP and sensorineural hearing loss that was not linked to the known RP loci. Later the genetic defect in this family was mapped to 9q, and finally the causative gene, the mitochondrial <i>MT-TS2</i> gene, was identified. Same subtype as the former RP21 subtype. Remapped to the RP3 locus (current <i>RPGR</i> gene).						
RP15							
RP16							
RP21							
RP52	Appeared to be the same subtype as the former RP8 subtype.						

For references or the extended version of this table, see [Supplementary Table 2](#).

A gene is considered a candidate for causality if it has been described in association with non-syndromic RP in only one patient or family. However, this does not include a single family with non-syndromic RP caused by a gene known to be associated with syndromic RP. The caveat should be entered that some clinical characteristics are based on limited numbers of patients. The number of times a gene has been described in association with non-syndromic RP: ¹ = more than 5 families described, ² = 3–5 families described, ³ = 1 or 2 families described, ^a = animal model that displays a retinal phenotype have been described, ^b = no animal models have been described.

^aPossible second locus, ^dSecond RP 66 gene, – none.

Abbreviations: AD: autosomal dominant, ADVIRC: autosomal dominant vitreoretinopathy, ARB: autosomal recessive bestrophinopathy, AVMD: adult onset vitelliform macular dystrophy, AR: autosomal recessive, BBS: Bardet-Biedl syndrome, BRD: Bothnia retinal dystrophy, BVMD: Best vitelliform macular dystrophy, CACD: central areolar choroidal dystrophy, CD: cone dystrophy, CGD: Chronic granulomatous disease, CISS: Cold-induced sweating syndrome, CF: counting fingers, CRD: cone-rod dystrophy, CSNB: congenital stationary night blindness, DG: digenic, ERM: epiretinal membrane, ESCS: enhanced S-cone syndrome, FA: fundus albipunctatus, FAF: fundus autofluorescence, HARP: hypoprebetalipoproteinemia, acanthocytosis, RP and pallidal degeneration, HIDS: hyper-immunoglobulin D and periodic fever syndrome, HM: hand movements, HMSN: hereditary motor and sensory neuropathy, HSS: Hallervorden-Spatz syndrome, IP: inheritance pattern, IRD: inherited retinal dystrophy, JNCL: juvenile neuronal ceroid-lipofuscinoses, JS: Joubert syndrome, LCA: Leber congenital amaurosis, LP: light perception, MD: macular dystrophy, MEB: muscle-eye-brain disease, MEVA: mevalonic aciduria, MODY: maturity-onset diabetes of the young, MPS: mucopolysaccharidosis, MR: moderately reduced, MRCS: microcornea, rod-cone dystrophy, cataract, posterior staphyloma, MVK: mevalonate kinase deficiency, NA: not available, NB: night blindness, NBIA1: neurodegeneration with brain iron accumulation 1, NFRCD: Newfoundland rod-cone dystrophy, NLP: no light perception, NP: non-penetrance, NR: nonrecordable, OCT: optical coherence tomography, OFDS: orofaciocigital syndrome, OMD: occult macular dystrophy, PD: pattern dystrophy, PPRPE: preserved para-arteriolar retinal pigment epithelium, PSC: posterior subcapsular cataracts, RPA: retinitis punctata albescent, RPE: retinal pigment epithelium, SGBS: Simpson-Golabi-Beckwith syndrome, SIFD: sideroblastic anemia, B-cell immunodeficiency, recurrent fevers and developmental delay, SR: severely reduced, SRTD: Short-rib thoracic dysplasia, STGD: Stargardt disease, USH: Usher syndrome, VA: visual acuity, VF: visual field, VMD: vitelliform macular dystrophy.

Table 3
Common clinical characteristics of the genetic subtypes of non-syndromic RP.

Clinical feature	Associated genes
Age of onset < 5 years	<i>BBS1</i> , <i>C2orf71</i> , <i>C8orf37</i> , <i>CRB1</i> , <i>CNGA1</i> , <i>DHX38</i> , <i>FSCN2</i> , <i>IDH3A</i> , <i>IFT140</i> , <i>LRAT</i> , <i>MERTK</i> , <i>NR2E3</i> , <i>NRL</i> , <i>OFD1</i> , <i>PDE6G</i> , <i>PRPF3</i> , <i>PRPF31</i> , <i>RBP3</i> , <i>RDH12</i> , <i>RP2</i> , <i>RP32</i> locus, <i>RPE65</i> , <i>RPGR</i> , <i>RPGRIP1</i> , <i>SNRNP200</i> , <i>SPATA7</i> , <i>TTC8</i> , <i>TULP1</i>
Age of onset < 10 years	<i>ABCA4</i> , <i>AGBL5</i> , <i>BBS2</i> , <i>BEST1</i> , <i>CLN3</i> , <i>CNGB1</i> , <i>CWC27</i> , <i>HGSNAT</i> , <i>IFT172</i> , <i>IMPDH1</i> , <i>IMGP2</i> , <i>PDE6A</i> , <i>PDE6B</i> , <i>POMGNT1</i> , <i>PRCD</i> , <i>PROM1</i> , <i>PRPF8</i> , <i>REEP6</i> , <i>RHO</i> , <i>RLBP1</i> , <i>RP9</i> , <i>SLC7A14</i> , <i>ZNF513</i> , <i>RP6</i> locus, <i>RP22</i> locus, <i>RP24</i> locus
Age of onset > 50 years	<i>CRX</i> , <i>RBP3</i> , <i>HGSNAT</i>
Early macular atrophy	<i>C2orf71</i> , <i>C8orf37</i> , <i>CDHR1</i> , <i>CERKL</i> , <i>CRX</i> , <i>DHX38</i> , <i>FSCN2</i> , <i>GUCA1B</i> , <i>HK1</i> , <i>IDH3A</i> , <i>IFT140</i> , <i>IMGP2</i> , <i>MERTK</i> , <i>PROM1</i> , <i>PRPF6</i> , <i>RDH12</i> , <i>RP2</i> , <i>RPGR</i> , <i>RPGRIP1</i> , <i>SAG</i> , <i>SPATA7</i> , <i>TTC8</i> , <i>ZNF513</i>
Bull's eye maculopathy	<i>BBS2</i> , <i>CDHR1</i> , <i>CRB1</i> , <i>IMGP2</i> , <i>HK1</i> , <i>MERTK</i> , <i>NRL</i> , <i>PRCD</i> , <i>PROM1</i> , <i>RP2</i> , <i>RP32</i> locus
Dense pigment migration	<i>BEST1</i> , <i>CDHR1</i> , <i>CRB1</i> , <i>EYS</i> , <i>IFTA140</i> , <i>PDE6A</i> , <i>PDE6B</i> , <i>PRPF8</i> , <i>RDH12</i> , <i>SNRNP200</i>
Absence/scarcity of retinal hyperpigmentation	<i>CDHR1</i> , <i>CLN3</i> , <i>FAM161A</i> , <i>HGSNAT</i> , <i>LRAT</i> , <i>NRL</i> , <i>OFD1</i> , <i>RLBP1</i> , <i>RP1</i> , <i>RPE65</i> , <i>RPGRIP1</i> , <i>TTC8</i> , <i>USH2A</i>
Pericentral pigmentary retinopathy	<i>CERKL</i> , <i>CNGA1</i> ^a , <i>CNGB1</i> ^a , <i>CRX</i> ^a , <i>DHDDS</i> ^a , <i>HGSNAT</i> , <i>HK1</i> , <i>NR2E3</i> , <i>PDE6B</i> , <i>PRPF31</i> ^a , <i>PROM1</i> ^a , <i>PRPF2</i> , <i>RHO</i> , <i>TOPORS</i> , <i>TULP1</i> ^a , <i>USH2A</i>

For references, see [Supplementary Table 2](#).

^a Phenotype described once.

4.1. Nomenclature

To understand the relatively confusing nomenclature used for RP subtypes, one must consider its origins. In the early days of genetic research on RP, subtypes were numbered according to the order in which the RP-linked loci were discovered; thus, the RP1 locus at chromosome 1 was the first RP locus discovered. Unfortunately, the order in which various RP-associated genes were identified differs from this locus-based numbering system. For example, the rhodopsin (*RHO*) gene was the first RP-linked gene identified; however, the RP subtype caused by mutations in the *RHO* gene is actually called RP4, as the *RHO* locus was the fourth RP locus identified. Over the years, the list of RP subtypes has undergone numerous changes; for example, the RP1 locus was re-defined from chromosome 1 to chromosome 4, and subtypes RP5, RP8, RP15, RP16, RP21, and RP52 have been withdrawn. The RP subtypes are listed in [Table 2](#) and are organized according to the underlying gene (or locus if the causative gene has not been identified), rather than the traditional classification for RP subtypes, as a classification system based on the underlying gene is more informative, less subject to change, and provides a direct link to the underlying mechanism as well as possible therapeutic options.

4.2. Age of onset

In most RP cases, the disease manifests in adolescence; however, the age of onset for RP varies widely. [Table 3](#) summarizes the genes associated with early-onset and late-onset RP. Early forms of RP and LCA have many causative genes in common; these common genes—with the exceptions of the *CWC27*, *IMPDH1*, and *CRX* genes—are all associated with an onset of RP before the age of five years. *HGSNAT*-linked RP can manifest either early or later in life, ranging from well under the age of 10 years to after the fifth decade; this wide range in onset is likely due to a large genetic-modifying effect. In addition to *HGSNAT*, two other RP genes—*CRX* and *RBP3*—have also been associated with late-onset RP. In patients who develop symptoms at a later age, one must always consider the possibility of a pseudoretinitis (see [Table 1](#)).

4.3. Refractive errors

Both myopia and hyperopia—particularly high myopia (odds ratio 10.1) and high hyperopia (odds ratio 9.7)—are more prevalent in RP patients compared to the general population ([Hendriks et al., 2017](#)). Hyperopia is typical among RP patients with mutations in the *CRB1* ([Talib et al., 2017](#)), *LRAT* ([den Hollander et al., 2007](#)), or the *NR2E3* ([Bandah et al., 2009](#)) gene. Interestingly, hyperopia is frequently associated with LCA, particularly among patients with a mutation in the *GUCY2D*, *RPGRIP1*, *CRX*, or *CEP290* gene ([Hanein et al., 2006](#)). Myopia is associated with Usher syndrome and the following five genetic

subtypes of RP: *RP1*, *RBP3*, and *ZNF408* in autosomal recessive RP, and *RPGR* and *RP2* in X-linked RP ([Arno et al., 2015](#); [Avila-Fernandez et al., 2015](#); [Chassine et al., 2015](#); [Habibi et al., 2017](#); [Hendriks et al., 2017](#); [Krantz et al., 2010](#)).

4.4. Pigmentary abnormalities

4.4.1. Peripheral retinal pigmentation

In addition to the typical bone spicule pigmentation that originates in the mid-periphery of the retina and has an apparent predilection for the perivascular area, other shapes and/or localizations have also been reported. Round clumps of pigment are common in patients carrying mutations in the *ARHGEF18* ([Arno et al., 2017](#)), *GNAT1* ([Carrigan et al., 2016](#)), *NR2E3* ([Bandah et al., 2009](#)), or *NRL* ([Bessant et al., 2003](#)) gene. In *BEST1*-associated RP, these pigments are typically located in the outermost periphery of the retina ([Davidson et al., 2009](#)). Para-arteriolar absence of pigmentation is a feature of RP in patients with mutations in the *CRB1* ([Talib et al., 2017](#); [van den Born et al., 1994](#)), *PRPF31* ([Fig. S2](#)) or *RDH12* ([Mackay et al., 2011](#)) gene.

4.4.2. Absence of retinal hyperpigmentation

An absence or scarcity of typical RP-related hyperpigmentation—known as RP sine pigmento—has been described in several RP subtypes (see [Table 3](#)), although this finding may also be related to the fact that pigmentation is sometimes absent in the early stages of RP ([Pearlman et al., 1976](#)). The absence of pigmentation in RP patients over 20 years of age has been reported in patients with mutations in the *RLBP1* ([Bocquet et al., 2013](#); [Hipp et al., 2015](#)), *RP1* ([Ma et al., 2013](#)), *RPGRIP1* ([Booij et al., 2005](#); [Huang et al., 2017a](#)), and *USH2A* ([Chen et al., 2014](#)) genes; it is important to note, however, that only the patient with *RP1*-associated RP was over 30 years of age. The reason for this lack of retinal hyperpigmentation is unclear, although myopic degeneration may be a factor in some RP patients ([Bandah-Rozenfeld et al., 2010b](#)). Nevertheless, an absence of pigmentation should not be used to exclude a diagnosis of RP, particularly in young patients, although other disorders ([Table 1](#)) should also be considered. Minimal pigmentary changes have also been associated with mutations in the *BBS* genes; however, with the exception of *TTC8* (*BBS8*), this only concerns syndromic cases ([Deveault et al., 2011](#); [Priya et al., 2016](#)).

4.4.3. Pigmentary abnormalities in the macula

In certain RP subtypes, central RPE alterations and atrophy occur relatively early in the disease course (i.e., earlier than one would expect based on the degree of visual field constriction). These subtypes are associated with a more rapid decline in visual acuity ([Flynn et al., 2001](#)) and can be difficult to distinguish from a cone-rod dystrophy. The genes associated with early macular atrophy are listed in [Table 3](#). In patients with the *DHX38* ([Ajmal et al., 2014](#)) or *IDH3A* ([Pierache](#)

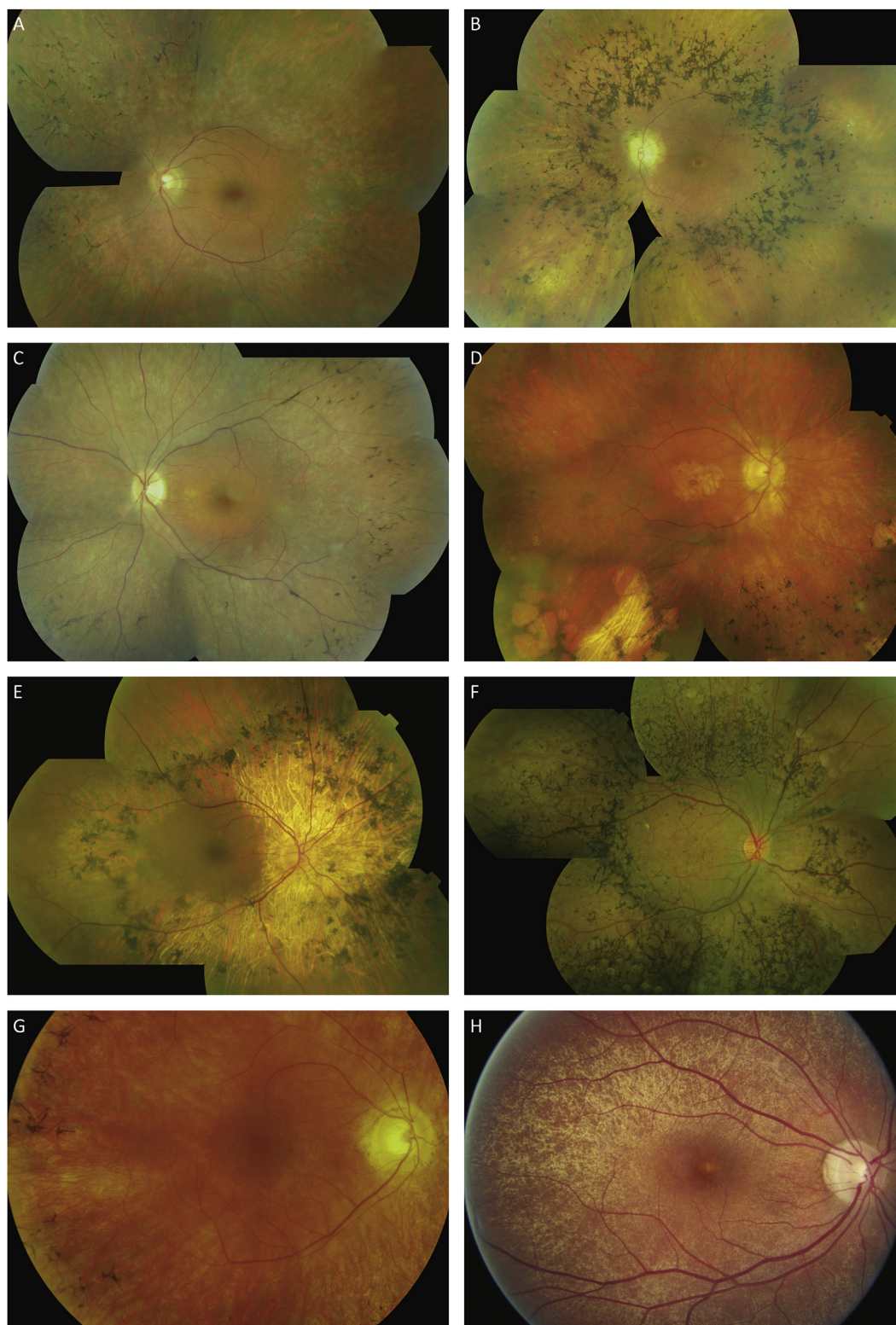


Fig. 6. Fundus photographs of patients with various non-syndromic RP subtypes. (A) Composite fundus photograph of a 47-year-old male patient with *USH2A*-associated RP, showing bone spicule pigmentation in the mid-periphery, and attenuated vessels. (B) Composite fundus photograph of a 59-year-old female patient with *IMPG2*-associated RP, showing marked bone spicule pigmentation in the mid-periphery, waxy pallor of the optic disc, attenuated vessels, and macular atrophy. (C) Composite fundus photograph of a 27-year-old female patient with *PDE6B*-associated RP, showing bone spicule pigmentation in the mid-periphery, vessel attenuation, and CME. (D) Composite fundus photograph of a 46-year-old male patient with *CDHR1*-associated RP, showing vessel attenuation, bone spicule like pigmentation, and patchy atrophy in the periphery and macula. (E) Composite fundus photograph of a 67-year-old male patient with *CNGB1*-associated RP, showing attenuated vessels, RPE atrophy, and mid-peripheral pigment clumping. (F) Composite fundus photograph of a 21-year-old male RP patient carrying a mutation in the *CRB1* gene, showing dense pigment migration with para-arteriolar absence of pigmentation. (G) Fundus photograph of a 42-year-old female patient with *CA4*-associated RP, showing the classical triad of bone spicule pigmentation in the mid-periphery, attenuated vessels, and waxy pallor of the optic disc. (H) Fundus photograph of a 46-year-old female *RPGR* carrier, showing a tapetal-like fundus reflex.

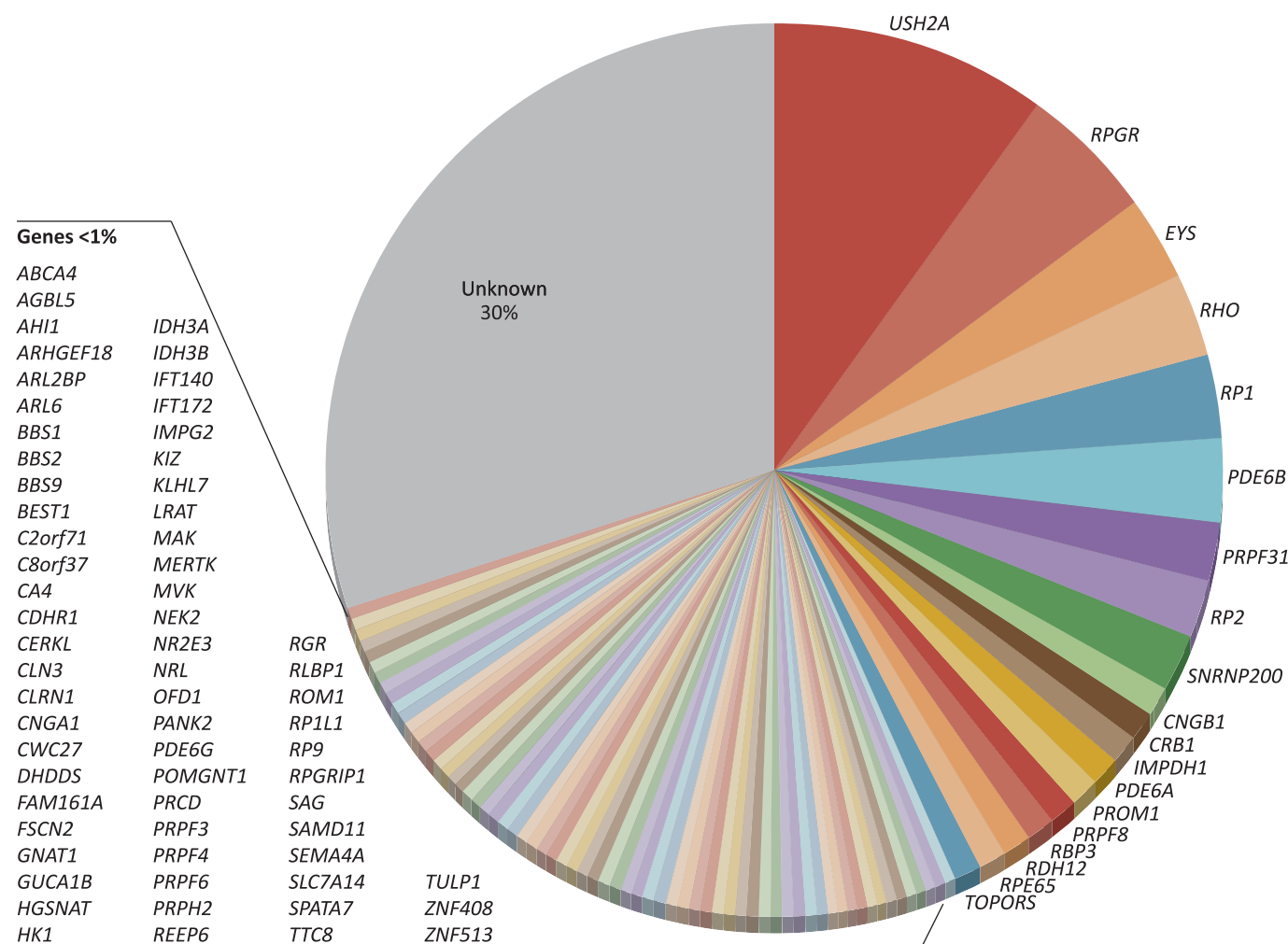


Fig. 7. Estimated relative contribution of genes to non-syndromic retinitis pigmentosa. The estimates are based on personal experience and a search of the literature. It is important to realize that the frequency may vary depending on the geographic region.

et al., 2017) subtype, the macular atrophy is often referred to as macular pseudocoloboma, which is a rather unfortunate term, as a pseudocoloboma should not be confused with a “true” coloboma, which results from a closure defect in the embryonic fissure during development and is often accompanied by other closure defects. In contrast to a loss of pigmentation due to RPE atrophy, deposits of macular pigments have been described in early-onset RP subtypes due to mutations in either the *ABCA4* or *RDH12* (Cremers et al., 1998; Schuster et al., 2007) gene. In these subtypes, the pigment deposits extend from the periphery/mid-periphery to the macular region; in other subtypes, the macula usually remains free of pigment clumping.

4.5. Cystoid macular edema

CME is a common finding among RP patients and is prevalent in all age groups (Hajali et al., 2008) (Table 2). The reported prevalence among patients with an autosomal dominant form of RP is relatively high (Sandberg et al., 2008a; Testa et al., 2014), although this finding has not been widely confirmed by other groups (Hajali et al., 2008; Liew et al., 2015; Makiyama et al., 2014). One report also suggested an association between CME and female patients (Testa et al., 2014). The relatively high prevalence of CME among RP patients suggests that it may not be subtype-specific. A combination of CME and cells in the vitreous body has been reported in children with variants in the *CRB1* or *RP1* gene, as well as in young adults with mutations in the *PRPF31* or *USH2A* gene (Hettinga et al., 2016; Murro et al., 2017). This

combination of clinical findings can lead to an incorrect diagnosis of intermediate uveitis, particularly in children with RP in which retinal abnormalities are subtle or even absent (Verhagen et al., 2016; Yoshida et al., 2013). The therapeutic options for CME are discussed in section 6.3.

4.6. Vascular abnormalities

Coats-like exudative retinopathy, which is characterized by retinal telangiectasia, lipid deposits, and exudative retinal detachment, has been reported in 7–15% of patients with *CRB1*-associated RP (Aleman et al., 2011; Henderson et al., 2011; Mathijssen et al., 2017; Talib et al., 2017) and in one patient with a mutation in exon ORF15 in the *RPGR* gene (Demirci et al., 2006). Unlike Coats' disease, which is usually unilateral, the Coats-like phenotype in RP patients is frequently bilateral (Khan et al., 1988). However, not all affected siblings present with the Coats-like phenotype, which suggests the presence of non-genetic factors (den Hollander et al., 2001). Finally, vascular sheathing has been reported in some patients with mutations in the *CRB1* gene (van den Born et al., 1994), *IMPG2* (van Huet et al., 2014), or *REEP6* gene (Fig. S2).

4.7. Localized forms of RP

4.7.1. Sector RP

Although RP is considered a generalized photoreceptor dystrophy,

in some patients the retinal abnormalities are limited to a specific region of the retina. In 1937, Bietti was the first to describe a form of RP in which the pigmentary alterations were limited to the inferonasal quadrant of both eyes (Bietti, 1937). This so-called sector RP is an atypical form of RP characterized by symmetrical areas of regional pigmentary alterations, usually restricted to the inferior quadrants of the retina (Van Woerkom and Ferrucci, 2005). Visual field defects often correspond to the boundaries of these retinal pigmentary alterations, although the abnormalities visible on fluorescein angiography and ERG can extend beyond the affected areas seen with ophthalmoscopy (Abraham, 1975; Abraham et al., 1976). Sector RP usually progresses slowly, but can evolve to a panretinal RP phenotype (Hellner and Rickers, 1973; Ramon et al., 2014). Sector RP has been described primarily in patients with an autosomal dominant form of RP caused by pathogenic mutations in the *RHO* gene (Heckenlively et al., 1991; Ramon et al., 2014; Sullivan et al., 1993). Other groups have reported sector RP in *GUCA1B*-associated autosomal dominant (Sato et al., 2005) and *RPGR*-associated X-linked forms of RP (Chang et al., 2016; Heckenlively, 1988). Nevertheless, why the atrophic pigmentary abnormalities are initially limited to a specific region—despite the fact that the underlying molecular defects are most likely expressed ubiquitously throughout the retina—remains unclear. Localized differences in the retina's exposure to light have been suggested as a possible explanation in RP patients with mutations in the *RHO* gene (Ramon et al., 2014).

4.7.2. Pericentral pigmentary retinopathy

Several RP genes have been associated with pigmentary alterations and annular chorioretinal atrophy that extends temporal from the optic disc along or adjacent to the vascular arcade and tends to spare the far periphery (Table 3) (Chakarova et al., 2007; Comander et al., 2017; Matsui et al., 2015; Sullivan et al., 2014). The clinical findings reported in this pericentral pigmentary retinopathy (PPR) vary among patients, including both slow progression and stationary forms of the disease (de Crecchio et al., 2006; Matsui et al., 2015; Sandberg et al., 2005). PPR can be considered part of the RP spectrum, particularly in patients with progressive disease, a history of night blindness, an annular scotoma, and reduced rod activity measured on ERG. This clinical picture corresponds with reports that family members of PPR patients can present with a more typical RP phenotype (Matsui et al., 2015). PPR can resemble pigmented paravenous retinochoroidal atrophy (PPRCA) and postinflammatory changes in retinal pigmentation.

4.8. Retinitis punctata albescens

Some RP patients can present with white punctate deposits that are distributed diffusely throughout the retina and often decrease in number before the onset of atrophy. Although this clinical phenomenon has been described as a distinct form of retinal dystrophy called retinitis punctata albescens, it can also be considered a descriptive subtype of non-syndromic RP. Retinitis punctata albescens can be caused by mutations in the *LRAT* (Littink et al., 2012), *PRPH2* (Kajiwara et al., 1993), *RHO* (Souied et al., 1996), or *RLBP1* (Morimura et al., 1999) genes. Mutations in the *RLBP1* gene have also been associated with Bothnia retinal dystrophy (Burstedt et al., 1999) and Newfoundland rod-cone dystrophy (Eichers et al., 2002), two specific RP subtypes characterized by the same white punctate deposits present in retinitis punctata albescens (Burstedt et al., 2001). These white deposits have been attributed to the accumulation of all-*trans*-retinyl esters in the RPE (Saari et al., 2001); however, given that retinitis punctata albescens patients with *LRAT* mutations produce little to no retinyl esters, the precise composition of these deposits remains unclear (Dessalces et al., 2013).

4.9. Miscellaneous

Optic disc drusen are a common finding in RP patients, particularly

patients with mutations in the *CRB1* gene, in which the prevalence approaches 1 in 3 patients (Mathijssen et al., 2017; Talib et al., 2017).

A tapetal-like fundus reflex is a yellow-golden sheen similar to the Mizuo-Nakamura phenomenon observed in Oguchi disease, although this sheen typically does not disappear after dark adaption. This reflex is best visualized using red-free or near-infrared reflectance (Acton et al., 2013). Originally, this finding was believed to be pathognomonic for female carriers of *RPGR*-associated RP; however, it has also been reported in female carriers of X-linked *RP2* (Flaxel et al., 1999).

Besides the well-recognized hyperautofluorescent ring, other FAF characteristics have been reported in certain genetic subtypes. For example, mutations in the *RPE65* or *LRAT* gene, which are both involved in the visual cycle, can lead to a reduced or even absent signal on FAF imaging (Dev Borman et al., 2012; Lorenz et al., 2004). The presence of 2 or 3 hyperautofluorescent rings has been associated with mutations in the *NR2E3* gene (Coppieters et al., 2007; Escher et al., 2012).

5. Genes and proteins involved in RP

To date, 84 genes (Fig. 7) and 7 candidate genes have been linked to non-syndromic RP. Each of these genes encodes a protein that plays a role in vital processes within the neuroretina and/or RPE (e.g., the phototransduction cascade and the visual cycle) or an underlying structure (e.g., the connecting cilium). Therefore, a mutation in a gene within a specific pathway can cause the whole pathway to become impaired or even disrupted entirely. In principle, a certain degree of clinical overlap is to be expected among RP subtypes that are caused by mutations in genes associated with a common pathway. In practice, however, genetic variants that modify a pathway's activity can increase the clinical and/or genetic heterogeneity of diseases that involve a common pathway. Identifying the pathways affected in non-syndromic RP is therefore important for understanding the underlying pathogenesis. In this chapter, we provide an overview of the principal pathways that are affected in RP, and we discuss the location and function of the genes/proteins involved in RP (Fig. 8, Table S3). Specifically, we focus on the phototransduction cascade (with 10 RP genes involved), the visual cycle (7 RP genes), ciliary structure and transport (35 RP genes), and the interphotoreceptor matrix (1 RP gene); the remaining 38 RP genes and their function are listed in Table S3.

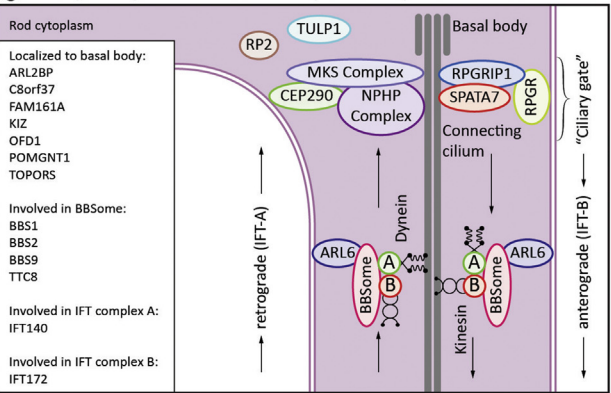
5.1. The phototransduction cascade

The phototransduction pathway is a cascade of successive reactions triggered by excitation of the opsin molecule by a photon, resulting in an electrical signal that is transmitted via the optic nerve to the visual cortex, leading to the perception of an image (see panel 3 in Fig. 8). This cascade is largely similar between rods and cones, with slight differences due to their different functions in dim light versus bright light.

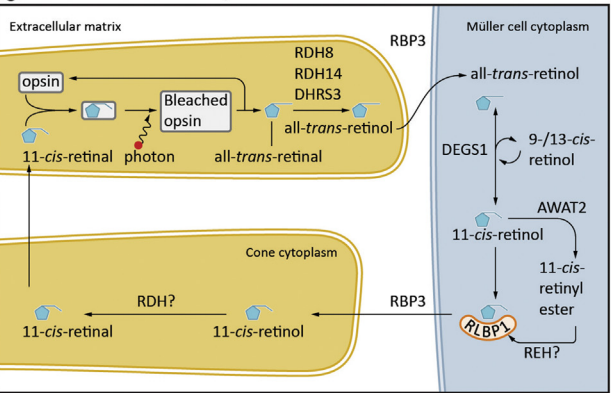
In rod cells, rhodopsin (encoded by the *RHO* gene) consists of the apoprotein opsin and the chromophore 11-*cis*-retinal. Upon capturing a photon, 11-*cis*-retinal converts to the all-*trans*-retinal isomer, which changes the structure of rhodopsin into that of the photoactive metarhodopsin II (Wald, 1968). Metarhodopsin II activates the G protein transducin (encoded by the *GNAT1* gene), which then activates the cyclic guanosine monophosphate (cGMP) phosphodiesterase (with subunits encoded by the *PDE6A*, *PDE6B*, and *PDE6G* genes), which hydrolyzes cGMP to form 5'-GMP (Stryer, 1986). This process decreases the concentration of cGMP in the photoreceptor's cytoplasm, which closes cGMP-gated cation channels (with subunits encoded by the *CNGA1* and *CNGB1* genes) in the plasma membrane. This in turn hyperpolarizes the plasma membrane due to a large decrease in intracellular calcium concentration; this hyperpolarization of the plasma membrane leads to decreased glutamate release at the photoreceptor's synapse.

After phototransduction, the system returns to the pre-photoactivation

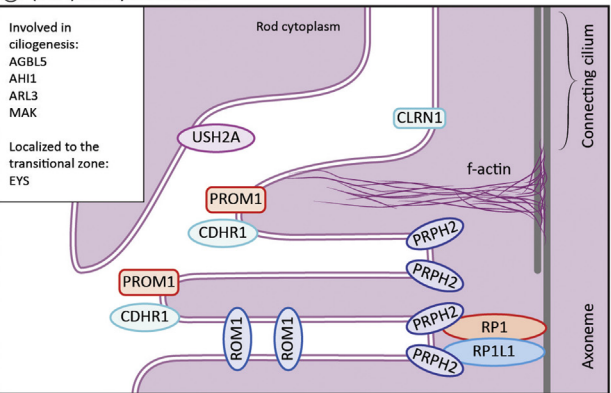
① Ciliary transport in rod and cone photoreceptors



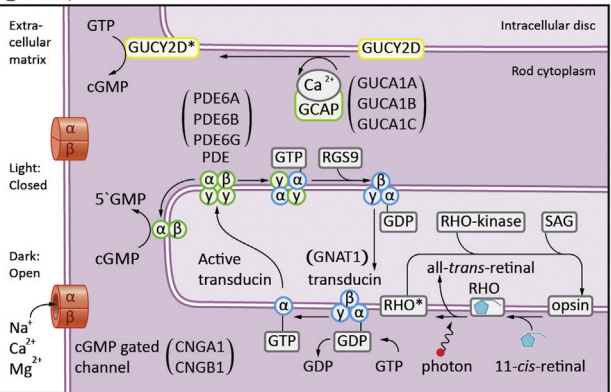
⑤ Non-canonical visual cycle



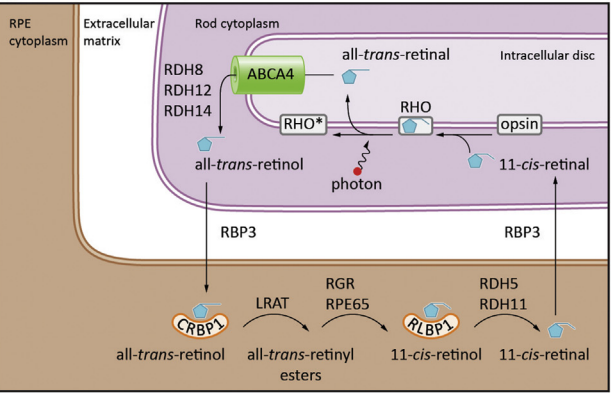
② (Peri)ciliary structure



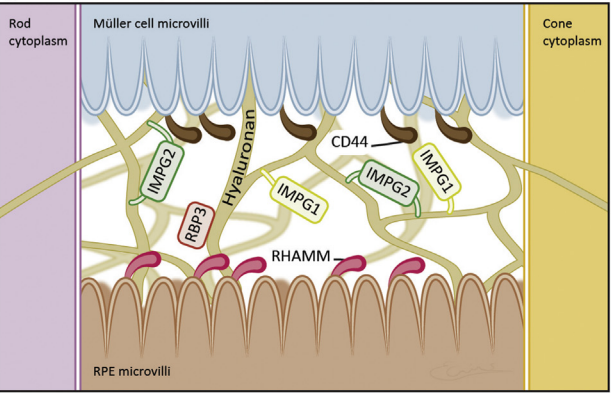
③ The phototransduction cascade



④ Canonical visual cycle



⑥ Interphotoreceptor matrix (not to scale)



(caption on next page)

(caption on next page)

Fig. 8. Schematic representation of a human rod photoreceptor (purple), cone photoreceptor (orange), Müller cell (blue), RPE cells (brown), and the interphotoreceptor matrix (beige). The six separate panels provide detailed information regarding the genes involved in four key processes (panels 1, 3, 4, and 5) and two structures (panels 2 and 6). Note that genes are not shown in italics. These processes are described in detail in sections 5.1–5.5.; Abbreviations: cGMP: cyclic guanosine monophosphate; GCAP: guanylate cyclase-activating protein; GDP: guanosine diphosphate; GTP: guanosine triphosphate; PDE: phosphodiesterase; RHAMM: receptor for hyaluronic acid-mediated mobility; RHO*: activated rhodopsin; RPE: retinal pigment epithelium.

state via the following steps: i) phosphorylation of metarhodopsin II by rhodopsin kinase and the subsequent binding of arrestin (encoded by the *SAG* gene), which deactivates transducin (Gurevich et al., 2008; Palczewski, 1994); ii) dissociation of all-*trans*-retinal from the visual pigment and conversion to 11-*cis*-retinal via the visual (retinoid) cycle (see below); iii) inactivation of transducin by GTPase-accelerating proteins (in particular, RGS9), thereby inactivating the phosphodiesterase (Krispel et al., 2006; Pugh, 2006); and iv) the return of intracellular cGMP to normal levels by guanylate cyclase (encoded by the *GUCY2D* gene) which is activated by guanylate cyclase-activating protein (encoded by the *GUCA1A* *GUCA1B*, and *GUCA1C* genes) (Haeseleer et al., 1999; Koch and Stryer, 1988). After all-*trans*-retinal has dissociated from opsin, 11-*cis*-retinal binds to opsin to produce rhodopsin, which then dissociates from arrestin. Rhodopsin is then de-phosphorylated by protein phosphatase 2A. Thus, in the dark, rhodopsin is predominantly in the non-phosphorylated state.

The majority of molecules in the rod phototransduction cascade have a homolog that performs a similar function in cone cells. There are two principal differences between rods and cones with respect to phototransduction. First, cone cells express three different opsins, each of which is specific—albeit less sensitive—to a given wavelength. Second, opsins in cone cells have faster kinetics than rod opsins and are nearly unsaturable. Although the functional consequence of this difference in kinetics is not completely clear, most research suggests that the faster kinetics in cones translates to a shorter recovery phase. This may be due to the more rapid phosphorylation of activated cone pigments, a faster dissociation rate of all-*trans*-retinal, and/or faster inactivation kinetics of transducin (Tachibanaki et al., 2001, 2005). Hydrolysis of transducin-bound GTP is the rate-limiting reaction in rod cells; however, compared to rods, cones contain ten-fold higher concentrations of the GTPase-accelerating protein complex.

5.2. The visual cycle

The vitamin A derivative 11-*cis*-retinal is an essential component in the phototransduction cascade. Dietary vitamin A (all-*trans*-retinol) is absorbed from the blood, enters the RPE, and is converted to 11-*cis*-retinal. The visual cycle is a complex process that focuses on regenerating 11-*cis*-retinal from all-*trans*-retinal produced in the phototransduction cascade (see panel 4 in Fig. 8) and occurs simultaneously with phototransduction.

Upon photoactivation, all-*trans*-retinal is released from the activated visual pigment into the lumen of the outer segment discs, where it reacts with phosphatidylethanolamine to form *N*-retinylidene-phosphatidylethanolamine (Liu et al., 2000). Via the flippase activity of the ABC (ATP-binding cassette) transporter ABCR (encoded by the *ABCA4* gene), all-*trans*-retinal is released into the cytoplasm of the photoreceptor, where it is reduced to all-*trans*-retinol by the enzyme all-*trans*-retinal dehydrogenase (encoded by the *RDH8*, *RDH12*, and *RDH14* genes) (Haeseleer et al., 1998; Rattner et al., 2000). All-*trans*-retinol is then transported into the subretinal space, where it binds to interphotoreceptor retinoid-binding protein (IRBP, encoded by the *RBP3* gene) and is transported to the RPE (Gonzalez-Fernandez, 2002). In the cytoplasm of the RPE cell, all-*trans*-retinol binds to cellular retinol-binding protein (encoded by the *CRBP1* gene) and is re-isomerized via a cascade involving lecithin-retinol acyltransferase (LRAT), RPE65 (also known as retinoid isomerohydrolase), retinal G protein-coupled receptor (RGR), and 11-*cis*-retinol dehydrogenase (encoded by the *RDH5* and *RDH11* genes) (Deigner et al., 1989; Moiseyev et al., 2005; Saari and Bredberg, 1989; Saari et al., 2001; Trehan et al., 1990).

The resulting 11-*cis*-retinal is then transported into the interphotoreceptor matrix by cellular retinaldehyde-binding protein (CRALBP, encoded by the *RLBP1* gene) and is subsequently transported back into the photoreceptor's cytoplasm by IRBP. Once back in the photoreceptor, 11-*cis*-retinal binds to opsin to form a new rhodopsin molecule. This pathway, known as the canonical visual cycle, catalyzes the re-isomerization of retinal in rod cells.

Recent studies have shown that in addition to the above-mentioned visual cycle, cones also have a second, non-canonical visual cycle that operates in cone outer segments and Müller cells (see panel 5 in Fig. 8); this cycle regenerates 11-*cis*-retinal at a 20-fold faster rate (Mata et al., 2002; Tang et al., 2013), although all of the proteins in this cycle have not yet been identified. This cycle is initiated when cone-specific opsin is photobleached and releases all-*trans*-retinal into the cell's cytosol, where it is then reduced to all-*trans*-retinol by retinol dehydrogenases (encoded by the *RDH8* and *RDH14* genes) and the cone-specific enzyme retSDR1 (encoded by the *DHRS3* gene) (Sahu and Maeda, 2016). All-*trans*-retinol then binds to IRBP and is transported into Müller cells, where dihydroceramide desaturase-1 (DES1, encoded by the *DEGS1* gene) catalyzes the direct isomerization of all-*trans*-retinol to produce 11-*cis*-retinol, as well as 9-*cis*-retinol and 13-*cis*-retinol (Kaylor et al., 2013; Tang et al., 2013). Because the isomerization reaction catalyzed by DES1 is reversible (Kaylor et al., 2013), the newly formed 11-*cis*-retinol is susceptible to re-isomerization. The cell uses two mechanisms to reduce this susceptibility to re-isomerization. First, 11-*cis*-retinol can be esterified by multifunctional *O*-acyltransferase (MFAT, encoded by the *AWAT2* gene) to form 11-*cis*-retinyl-ester, and secondly, newly formed 11-*cis*-retinol can be captured by CRALBP (Kaylor et al., 2014). A currently undefined 11-*cis*-retinol-ester hydrolase (labeled “REH?” in Fig. 8) hydrolyzes 11-*cis*-retinyl-ester to form 11-*cis*-retinol; this occurs only when CRALBP is available to bind 11-*cis*-retinol and prevent re-isomerization by DES1 (Stecher et al., 1999). When bound to CRALBP, 11-*cis*-retinol is released into the interphotoreceptor matrix, where it binds IRBP and is taken up by the cone outer segment (Saari et al., 2009). There, an unknown RDH (labeled “RDH?” in Fig. 8) oxidizes 11-*cis*-retinol to form 11-*cis*-retinal, which then binds to opsin, forming a new pigment molecule. This final oxidation reaction can occur in cone outer segments, but not in rod outer segments (Tang et al., 2013); thus, the non-canonical visual cycle is specific to cone cells.

5.3. Ciliary transport

Cilia are slender, longitudinal, microtubule-based projections that extend from the surface of most mammalian cells and vary in both shape and size depending on the cell type (Satir and Christensen, 2008). Cilia can be divided in two main categories: motile cilia and non-motile (primary) cilia. Motile cilia are used in specific organs and processes that require the movement of ciliary fluid; examples include the establishment of left-right asymmetry of viscera in the developing embryo, the clearance of mucus from the airways, and sperm motility. In contrast, primary cilia are present on the vast majority of non-motile eukaryotic cells and serve as sensory “antennae” in most sensory organs (Berbari et al., 2009; Singla and Reiter, 2006). Given the nearly ubiquitous presence of cilia throughout the body, mutations in genes encoding ciliary proteins can lead to so-called ciliopathies, which often involve a syndromic phenotype with multiple affected organs and cellular processes (Hildebrandt et al., 2011; Reiter and Leroux, 2017).

Photoreceptor cells contain a highly specialized sensory cilium that consists of the connecting cilium and associated basal body, as well as

an apical outer segment, a highly specialized structure in which phototransduction takes place (Roepman and Wolfrum, 2007). Because the outer segment lacks biosynthetic machinery, all of its components are synthesized and partially pre-assembled in the inner segment and then transported to the outer segment via the connecting cilium, a process facilitated by intraflagellar transport (IFT). IFT is also used to assemble and maintain the cilia (Bhogaraju et al., 2013a; Hao et al., 2011; Kozminski et al., 1993; Kubo et al., 2016; Ye et al., 2013). To date, mutations in more than 30 ciliary protein-encoding genes have been linked to non-syndromic retinal diseases (Table S3) (Daiger et al., 2017; Estrada-Cuzcano et al., 2012b). The functions of these ciliary proteins in the connecting cilium have been identified, and most of these proteins are involved in either IFT function/regulation or ciliary structure.

IFT is a bidirectional transport system that uses microtubule-based motor molecules to transport cargo both from the cilia's base to the tip (i.e., anterograde transport, which is driven by kinesin motor proteins) and from the tip to the base (i.e., retrograde transport, which is driven by dynein motor proteins) (Rosenbaum and Witman, 2002; Scholey, 2003; Wren et al., 2013). This transport system is capable of moving thousands of molecules per second in each photoreceptor cell, including the anterograde transport of RHO and the light-dependent transport of arrestin and transducin (Besharse et al., 1977; Sokolov et al., 2002; Strissel et al., 2006; Young, 1968).

Many genes associated with non-syndromic RP encode proteins that are involved in various aspects of ciliary transport (Table S3). For example, ARL3 and RP2 mediate the localization of motor units at the ciliary tip (Schwarz et al., 2017). In addition, IFT is mediated by the so-called IFT proteins (e.g., IFT140 and IFT172) that form two complexes (complex A and complex B), which bind and transport ciliary cargo (Bhogaraju et al., 2013b; Taschner et al., 2012). Moreover, the BBSome complex (in which BBS stands for Bardet-Biedl syndrome) serves as an adaptor between cargo and the IFT complex (Mourao et al., 2016; Nachury et al., 2007). The BBSome complex consists of eight protein subunits (BBS1, -2, -4, -5, -7, -8 (TTC8), -9, and -18) (Mourao et al., 2016). Mutations in BBSome subunits generally give rise to Bardet-Biedl syndrome (Mockel et al., 2011); however, four of the genes that encode BBSome subunits (BBS1, BBS2, BBS9, and TTC8), as well as the gene that encodes ARL6 (a protein that recruits the BBSome complex to the membrane), are associated with non-syndromic RP (Abu-Safieh et al., 2012; Estrada-Cuzcano et al., 2012a; Goyal et al., 2015; Jin et al., 2010; Mourao et al., 2014; Murphy et al., 2015; Pretorius et al., 2011; Riazuddin et al., 2010; Shevach et al., 2015).

The entry and exit of cargo on the ciliary IFT machinery is regulated by the “ciliary gate”, a specialized ciliary structure located at the base of the primary cilium; this structure forms a general barrier against periciliary particle diffusion and therefore regulates transport to and from the structurally isolated outer segment (Christensen et al., 2007; Emmer et al., 2010; Goncalves and Pelletier, 2017; Leroux, 2007; Nachury et al., 2010; Rosenbaum and Witman, 2002). The gate's function is mediated by transition fibers and the transition zone. Transition fibers (also known as distal appendages) anchor the cilium to the plasma membrane, and the transition zone is a modular structure containing Y-shaped linkers that are believed to act as a “molecular sieve” in order to restrict and select the entry and exit of ciliary cargo. The photoreceptor-connecting cilium is both structurally and functionally analogous to a prototypical transition zone. However, the elongated shape of this cilium is likely required to achieve the high trafficking rate for transporting biosynthetic material, as approximately 10% of the outer segment is renewed each day through shedding and replacement of materials at the tip (Young, 1967). In addition, a ciliary pore complex, which is homologous to the nuclear pore complex, functions as an active molecule gate at the base of the cilium (Takao and Verhey, 2016). Two interacting protein modules—namely, the Meckel/Joubert syndrome (MKS/JBTS) and nephronophthisis (NPHP) associated modules—assemble the transition zone and control its gating function (Chih et al., 2011; Garcia-Gonzalo et al., 2011; Sang et al.,

2011). These modules consist of several ciliopathy-associated proteins and interact with nearby transition zone components (e.g., the BBSome complex) and a complex that contains the protein encoded by the *RPGR* gene, which accounts for 70–90% of X-linked RP cases and 10–20% of all RP cases (Goncalves and Pelletier, 2017; Megaw et al., 2015). The RPGR protein is anchored to the connecting cilium by RPGR interacting protein 1 (RPGRIP1), the localization of which requires another ciliary protein, spermatogenesis-associated protein 7 (SPATA7). Defects in the RPGR-RPGRIP1-SPATA7 complex lead to the aberrant localization of specific opsins; therefore, this complex is believed to play a role in the transport of specific opsins (Eblimit et al., 2015). For a thorough overview of the interactions between RPGR and other ciliary proteins such as centrosomal protein 290 (CEP290), phosphodiesterase 6D (PDE6D), nephrocystin 1 (NPHP1), nephrocystin 4 (NPHP4), and Whirlin (WHRN), the reader is referred to a recent review by Megaw and colleagues (Megaw et al., 2015).

5.4. Outer segment structure

The cilium of the photoreceptor cell consists of the connecting cilium and the outer segment, the latter of which contains a highly specialized compartment consisting of stacks of intracellular discs (in rod cells) or lamellae (in cone cells) (Cohen, 1961; Sjostrand, 1953). Goldberg et al. reviewed the morphogenesis and architecture of intracellular discs in the outer segment (Goldberg et al., 2016). Some subtypes of non-syndromic RP are associated with proteins that are involved in the development and/or orientation of outer segment discs (Table S3 and Fig. 8), and their genes are discussed below.

Outer segment discs develop from the connecting cilium as evaginations in the plasma membrane that are subsequently internalized to form a stack of intracellular discs (Ding et al., 2015). F-actin microfilaments located at basal axonemal microtubules are required for the initiation of new disc evagination (Goldberg et al., 2016). The RP-associated gene *FSCN2* encodes retinal fascin homolog 2 (FSCN2), which crosslinks and bundles F-actin filaments (Saishin et al., 2000; Tubb et al., 2000). Peripherin-2 (PRPH2) plays a role in the formation of the outer segment disc rim, and loss of PRPH2 leads to the absence of outer segment discs (Cohen, 1983; Goldberg et al., 2016). PRPH2 has also been suggested to play a role in disc stability and disc shedding (Edrington et al., 2007; Goldberg et al., 2016). Recently, Salinas et al. reported that the photoreceptor cilium can release large numbers of ectosomes (Salinas et al., 2017), similar to the process recently described in primary cilia, in which ciliary G protein-coupled receptors are dispatched in extracellular signaling-competent vesicles via actin-mediated ectocytosis (Nager et al., 2017). PRPH2 maintains this process at the appropriate level, enabling retained ectosomes to morph into outer segment discs (Salinas et al., 2017). The formation of PRPH2 is regulated by the rod outer segment membrane protein-1 (ROM1) protein, thereby regulating the process of disc internalization (Loewen and Molday, 2000). The initiation of outer segment disc formation requires the membrane-bound protein prominin-1 (PROM1), which is localized to the nascent disc edge (Goldberg et al., 2016). PROM1 also appears to link outer segment disc rims, thereby helping to stabilize the stack (Fetter and Corless, 1987). Cadherin-related family member 1 (also known as protocadherin-21 and encoded by the *CDHR1* gene) has also been implicated in disc rim formation and has been suggested to function cooperatively with PROM1, as it also resides at the nascent disc edge (Yang et al., 2008). The photoreceptor-specific cytosolic protein RP1 is associated with the ciliary axoneme and is required for outer segment disc morphogenesis (Liu et al., 2004). Thus, RP1 plays a role in outer segment disc orientation and has been suggested to serve as the link between outer segment discs and the axoneme (Liu et al., 2003). Finally, RP1 has a synergistic interaction with RP1L1, a protein that has a similar localization pattern and is also required for outer segment morphogenesis (Yamashita et al., 2009).

5.5. The interphotoreceptor matrix

The interphotoreceptor matrix fills the subretinal space, which extends from the external limiting membrane (i.e., the basal ends of the Müller cells) to the apical surface of the RPE; the inner and outer segments of photoreceptor cells are also embedded in this space (Hollyfield, 1999). For many years, the interphotoreceptor matrix was believed to simply provide support to the retinal tissue, with no other significant functions. However, we now know that the interphotoreceptor matrix plays an important role in many key processes, including: i) retinal (retinoid) metabolism; ii) retinal adhesion to the RPE (Hageman et al., 1995; Lazarus and Hageman, 1992; Marmor et al., 1994; Yao et al., 1994); iii) intercellular communication in terms of outer segment shedding and phagocytosis by the RPE; iv) matrix turnover; v) photoreceptor alignment; vi) growth factor presentation (Hageman and Johnson, 1991); and vii) regulation of the transport of oxygen and nutrients to photoreceptor cells (Ishikawa et al., 2015; Rhodes and Simons, 2007). In addition, this extracellular matrix may also play a key role in the clinical presentation of progressive retinal degeneration (Al-Ubaidi et al., 2013).

The interphotoreceptor matrix is composed of proteins and carbohydrates that are secreted by photoreceptors and RPE cells (Kanan et al., 2009). The principal components of this matrix are proteoglycans, hyaluronic acid, collagen and elastin fibers, and other proteins such as fibronectin, fibrillin, laminins, and fibulins. Hyaluronic acid polymers form extremely large (100–10,000 kDa) polysaccharides that interconnect to produce a three-dimensional mesh network (Hollyfield, 1999). This network is connected to Müller cells via CD44 and to the RPE via proteins containing RHAMM (receptor for hyaluronic acid-mediated motility)-type binding motifs. In addition, other extracellular matrix components such as SPACR, SPACRCAN, pigment epithelium-derived factor (PEDF), and IRBP also contain RHAMM-binding motifs and are also linked to the hyaluronic acid network (Hollyfield, 1999; Inatani and Tanihara, 2002).

Three genes (*IMP2*, *RBP3*, and *EYS*) associated with non-syndromic RP encode proteins that bind to the hyaluronic acid network (Abd El-Aziz et al., 2008; Bandah-Rozenfeld et al., 2010a; Collin et al., 2008; den Hollander et al., 2009; Littink et al., 2010; Valverde et al., 1998; van Huet et al., 2014). SPACRCAN (encoded by the *IMP2* gene) is a proteoglycan that binds both hyaluronic acid and chondroitin sulfate and plays several functional roles, including organizing the interphotoreceptor matrix and regulating the growth and maintenance of the photoreceptor outer segment (Acharya et al., 2000; Foletta et al., 2001). IRBP (encoded by the *RBP3* gene) is the primary soluble protein in the interphotoreceptor matrix and—as discussed above—plays a role in the visual cycle (see section 4.2).

In humans, the *EYS* gene encodes the human ortholog of the *Drosophila* eyes shut protein and is one of the largest genes expressed in the retina. The resulting protein contains several sites for the attachment of glycosaminoglycans side chains; in *Drosophila*, this protein is an extracellular protein (Husain et al., 2006; Zelhof et al., 2006). The high degree of homology between the human and *Drosophila* orthologs suggests that the human protein also functions in the extracellular matrix. In humans, however, this protein, which has four isoforms (Alfano et al., 2016), can localize to subcellular compartments in the cytoplasm and to the axoneme of the connecting cilium; moreover, deleting *EYS* expression in zebrafish causes mislocalization of outer segment proteins, suggesting a functional role in ciliary transport (Lu et al., 2017). In addition, posttranslational modifications may allow the protein to target to specific locations (Alfano et al., 2016). Finally, the RP1 protein also contains hyaluronic acid-binding motifs and may interact with the hyaluronic acid scaffold if it associates with the photoreceptor's plasma membrane (Hollyfield, 1999).

6. Management of RP

Retinitis pigmentosa can profoundly impact the physical and emotional lives of patients and their families. Therefore, providing adequate support to patients and their relatives is an essential component in managing RP. In this chapter, we discuss ophthalmic and genetic counseling, we describe the current options for genetic testing, we emphasize the importance of regular visits to the clinic, and we discuss both current and future therapeutic options.

6.1. Ophthalmic and genetic counseling

A multidisciplinary approach that combines ophthalmic and genetic counseling services can optimize both the diagnostic process and the long-term management of RP (Branham and Yashar, 2013). In recent years, the field has witnessed significant advances in the methods used to identify genes. For example, some centers have switched from using targeted panel sequencing tests for diagnostics and now perform exome sequencing using a vision-related gene filter (Haer-Wigman et al., 2017). In exome sequencing, all coding regions (i.e., exons) within the entire human genome are sequenced. The addition of a gene filter containing all known IRD genes can limit the risk of incidental findings in genes that are not necessarily related to the disease. The advantage of exome sequencing is that if the causative gene is not identified in any of the known RP genes, the search can be readily expanded to include other genes, thereby potentially identifying novel RP-related genes. On the other hand, exome sequencing is not usually the first choice for obvious cases of X-linked forms of RP. Although mutations in the *RPGR* gene account for 70–75% of all patients with an X-linked form of RP, this gene is not suitable for exome sequencing (Huang et al., 2015), particularly due to the highly repetitive, purine-rich ORF15 region. Therefore, this region is better suited to direct sequencing. Currently, exome sequencing provides a molecular diagnosis in 60–80% of RP patients (Abu-Safieh et al., 2013; Haer-Wigman et al., 2017); the remaining patients likely have a variant that cannot be detected using exome sequencing, which can include structural rearrangements, mutations in non-coding and/or GC-rich regions, and mutations in genes that have not yet been associated with retinal dystrophy (Carss et al., 2017; Nishiguchi et al., 2013). The introduction of whole-genome sequencing in routine diagnostics will likely further increase our ability to obtain molecular diagnoses, although determining the functional role of many of these putative causative variants will remain a challenge.

Genetic testing often raises a wide range of questions, and patients are usually referred for genetic counseling, where questions regarding the reliability of the test results and the implications to the patient and his/her relatives can be addressed. Performing presymptomatic and/or predictive testing at too early an age may increase the likelihood of an unfavorable impact on quality of life; therefore, the ideal age for undergoing genetic testing is currently under debate (Godino et al., 2016). To help ensure their future autonomy, children rarely undergo presymptomatic testing; however, the availability of new treatment options, which ideally are applied in the earliest possible stage of the disease, may warrant testing at a younger age.

Genotyping usually improves the outcome of ophthalmic counseling; however, the number of well described phenotypes for a given genetic subtype is usually limited, and the phenotypes can vary widely within a subtype and even between family members who share identical mutations. Nevertheless, the information discussed in Chapter 4 can provide the clinician with an overview of the clinical aspects associated with the various genetic subtypes. For example, central visual function often deteriorates rapidly in RP patients with a mutation in the *CERKL* gene, whereas visual acuity is generally preserved much longer in RP patients with a mutation in the *TOPORS* gene. Therefore,

understanding the underlying genetic profile and other modifiers that can influence the phenotype will help provide a more reliable clinical prognosis. In anticipation of such an in-depth genetic analysis, thorough follow-up examinations that include visual field analysis, SD-OCT, and FAF will serve to monitor the clinical progression of the retinal dystrophy, as well as to predict the decline in visual function. In addition, other ocular pathologies such as cataract and CME may also be identified at an early stage and treated accordingly.

6.2. Visual rehabilitation

In recent years, visual rehabilitation for RP patients with low visual acuity has evolved into a multidisciplinary approach that focuses on the patient's functional abilities and needs (Herse, 2005), thereby providing high value to patients with RP. Vision rehabilitation centers provide support and training, including orientation and mobility training combined with low-vision aids such as flashlights, night-vision goggles, and/or reverse telescopes in order to optimize residual visual function. In advanced disease, the patient's independence and functional quality of life can be improved using text-to-speech software to allow the patient to interpret text, and a guide dog can further increase the patient's mobility and independence. However, the social impact of the gradual deterioration of the visual field should not be underestimated.

6.3. Treatment of associated ocular abnormalities

The visual gain realized following cataract surgery in RP patients depends largely on the amount of residual macular function. The likelihood of visual recovery is highest in RP patients who have an intact—or only slightly disrupted—foveal ellipsoid zone (Nakamura et al., 2015; Yoshida et al., 2015a).

Some reports indicate that RP patients may have an increased risk of developing complications during and following cataract surgery; these complications can include zonular insufficiency (in 19% of cases) (Dikopf et al., 2013), posterior capsular opacification (44–95% of cases) (Bayyoud et al., 2013; De Rojas et al., 2017; Yoshida et al., 2015a), and anterior capsule contraction (10–38% of cases) (Hayashi et al., 1998; Jackson et al., 2001; Yoshida et al., 2015a). Although the scientific evidence is absent, some surgeons report a more severe post-operative inflammation in RP patients. In general, pre-operative treatment with steroids may be useful in patients with RP to prevent this inflammation as well as CME. There is currently no indication that surgery accelerates the progression of RP (De Rojas et al., 2017). On the other hand, the subjective visual gain following cataract surgery in RP patients is often considerable. Therefore, cataract extraction should be seriously considered in visually significant cataracts, even in the presence of advanced RP.

To date, no large randomized controlled clinical trial has been performed to evaluate the effect of treating CME in RP patients. The treatment of choice for CME is carbonic anhydrase inhibitors (Strong et al., 2017). A meta-analysis conducted by Huang et al. showed a mean reduction in central retinal thickness of 46% (Huang et al., 2017b). However, often there is no correlation between anatomical and functional improvement (Huang et al., 2017b). Prescribed dosages for oral acetazolamide vary between 125 and 500 mg daily, and topical carbonic anhydrase inhibitors like 1–2% dorzolamide or brinzolamide are typically administered three times a day. Since the optimal therapeutic dose for the individual is still unknown, a trial and error approach is advised. Recurrence of CME can occur after cessation of carbonic anhydrase inhibitor treatment (Huang et al., 2017b), and efficacy may diminish during prolonged treatment (Huckfeldt and Comander, 2017). Retreatment with carbonic anhydrase inhibitors after a period of discontinued use, may again have a favorable effect (Thobani and Fishman, 2011). Refractory CME can be treated with intravitreal steroids (Huckfeldt and Comander, 2017). The use of intravitreal anti-VEGF (vascular endothelial growth factor) in RP patients remains unclear, as

studies do not agree with respect to the beneficial effects; moreover, VEGF levels are markedly lower in the aqueous humor of RP patients (Strong et al., 2017). It is important to note that the amount of CME can fluctuate over time—particularly in children—even without intervention; this should be taken into account during treatment (Huckfeldt and Comander, 2017).

Although epiretinal membranes are prevalent among RP patients, few reports address the effects of membrane peeling in RP patients. Ikeda et al. reported morphological improvement following epiretinal membrane peeling in 9 out of 11 eyes, although only three of these eyes—two of which underwent concomitant cataract extraction surgery—had long-term improvement in visual acuity (Ikeda et al., 2015). This relatively limited rate of success, together with the potential toxicity associated with direct intraocular illumination, suggests that epiretinal membrane peeling should be used with caution in patients with RP.

6.4. Treatment options for RP

Significant advances in our knowledge regarding the genetic causes of RP have been paralleled by significant progress in the development of novel strategies for treating this disease (Scholl et al., 2016). These strategies can be subdivided into two general categories: i) approaches that are gene-specific or even mutation-specific, and ii) approaches that exert a therapeutic effect independent of the underlying genetic defect. Below, we discuss the main features of the various therapeutic approaches, including their potential advantages and limitations with respect to treating patients with RP.

6.4.1. Gene-specific and mutation-specific approaches

The majority of genes mutated in RP encode proteins that are expressed either in photoreceptor cells or in the RPE. Therefore, to be effective, gene-specific and/or mutation-specific approaches require the presence of the cells that will be targeted; as a result, these approaches are most successful in the early stages of the disease, before cell degeneration. With gene augmentation therapy-based approaches, a construct driving the expression of a wild-type copy of the cDNA corresponding to the mutated gene is introduced into the target cells, with the goal of restoring wild-type expression in these cells. In the case of RP and allied diseases, virus-based vectors such as adeno-associated viruses (AAVs) are often used to deliver the genetic cargo to target cells in the retina; the virus is usually administered via intravitreal or sub-retinal injection. In 2008, the first studies to test the safety and efficacy of using *RPE65* gene augmentation therapy in patients with LCA or early-onset RP due to bi-allelic *RPE65* mutations were reported (Bainbridge et al., 2008; Hauswirth et al., 2008; Maguire et al., 2008). The promising results obtained from these studies provided an enormous boost to the field and led to phase I/II clinical trials designed to test gene therapy-based approaches for treating several other genetic subtypes of retinal disease, including choroideremia (MacLaren et al., 2014), *MERTK*-associated RP (Ghazi et al., 2016), and—more recently—*CNGA3*-associated achromatopsia, *PDE6A*-associated RP, *RPGR*-associated X-linked RP, retinoschisis, and Stargardt disease (see www.clinicaltrials.gov). The recent phase 3 study in patients with a *RPE65*-mediated inherited retinal dystrophy who were treated with voretigene neparvovec, confirmed treatment safety and efficacy; patients showed improved light sensitivity, visual fields and navigational ability under dim light conditions (Russell et al., 2017). Subsequently, this led to the first US FDA approved gene therapy for retinal disease. Despite these initial advances, however, important challenges must be overcome before gene augmentation therapy can be widely implemented. For example, it is unclear whether one-time administration of a therapeutic vector can provide long-term, long-lasting clinical benefits. The cargo capacity of the most commonly used viral vectors is also relatively limited and is therefore not suitable for delivering the large cDNAs corresponding to several of the genes that are mutated in

many patients with RP (for example, the *EYS* and *USH2A* genes). Other challenges include controlled expression levels, dominant-negative mechanisms, the relative small number of patients for the genetic subtypes as well as the financial costs of the highly individualized forms of treatment.

Other emerging therapeutic strategies involve antisense oligonucleotides (AONs), which are small, versatile RNA molecules that can modify pre-mRNA splicing by specifically binding to a target region in the pre-mRNA, thereby suppressing aberrant splicing events caused by certain mutations (Collin and Garanto, 2017), and genome editing, for example using the CRISPR/Cas9 system. This latter technique introduces a highly precise double-strand break in the genomic DNA at the site of the mutation, and can be used to repair a primary genetic defect directly within the patient's genome (Yanik et al., 2017).

Another class of highly versatile therapeutic compounds that can act in a gene-specific and/or mutation-specific manner are the small-molecule compounds. In early-onset retinal degeneration in patients with a mutation in the *LRAT* or *RPE65* gene, the visual cycle—in which all-*trans*-retinal is converted back into 11-*cis*-retinal via several enzymatic reactions—is disrupted. Oral treatment with 9-*cis*-retinoid, an analog of 11-*cis*-retinal, was well tolerated and moderately effective in early-phase clinical trials in patients with a mutation in the aforementioned genes; moreover, treatment efficacy was correlated with residual retinal integrity (Scholl et al., 2015).

Although beyond the scope of this review, it is important to note that diet-based treatment can prevent or reduce disease progression in the following three syndromic forms of RP: adult Refsum disease, Bassen-Kornzweig syndrome, and α -tocopherol transfer protein deficiency (also known as familial isolated vitamin E deficiency).

6.4.2. Mutation-independent approaches

In recent years, several dietary changes and dietary supplements (e.g., vitamin A) have been recommended for the treatment of RP (Brito-Garcia et al., 2017). However, a Cochrane systematic review conducted by Rayapudi et al. (2013) found no clear evidence that vitamin A and/or the fish oil docosahexaenoic acid has beneficial effects in RP patients in general.

Cell replacement therapy is the administration of ocular-derived retinal progenitor cells (RPCs) or non-ocular-derived stem cells such as embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) into the vitreous body or subretinal space. Each of these cell types has specific advantages and disadvantages (Tang et al., 2017). For example, RPCs are relatively easy to process, and the recipient does not require immunosuppression therapy; however, obtaining sufficient donor cells is problematic. In contrast, stem cells require a more extensive manufacturing process. The key difference between ESCs and iPSCs is that iPSCs can be derived from the patient, thereby allowing the autologous transplantation of iPSC-derived RPE or photoreceptor cells, thus avoiding immunosuppressive treatment; moreover, the underlying genetic defect can even be corrected prior to transplantation using genome editing (Li et al., 2016). However, such highly individualized treatments are associated with extremely high costs. Therefore, options for using human leukocyte antigen (HLA)-matched iPSCs from a databank are receiving increasing attention (Chakradhar, 2016; de Rham and Villard, 2014). Various transplantation approaches are currently used, including transplantation of stem cell-derived RPE cells and/or photoreceptor cells (Seiler and Aramant, 2012). Phase I/II trials using RPCs are currently being performed in RP patients in order to assess the *in vivo* safety, long-term survival, and function of the graft (see www.clinicaltrials.gov). Although clinical applications are still in their infancy, stem/progenitor cell-based therapeutic approaches represent a promising future for patients with advanced RP.

Another emerging approach is the use of electronic retinal implants for end-stage RP patients with little or no light perception. Two retinal implants are currently available on the market. The Argus II epiretinal

implant (produced by Second Sight Medical Products Inc. in Sylmar, CA) has received both European CE certification and US FDA approval, and the Alpha AMS subretinal implant (produced by Retina Implant AG in Reutlingen, Germany) has received CE certification (Mills et al., 2017). Both of these implants function by stimulating the inner retinal layers and therefore require an intact inner retinal architecture. An epiretinal implant is connected to a miniature camera mounted on eyeglasses; the implant then stimulates the residual retinal ganglion cells directly. In contrast, a subretinal implant consists of a light-sensitive micro-photodiode array that stimulates the bipolar cell layer. Retinal implants can restore basic visual function, improve performance in vision-related tests, and increase the daily mobility of patients with RP (da Cruz et al., 2016; Stingl et al., 2017; Zrenner et al., 2011). For example, improvement in visual acuity from light perception without projection to 20/546 was recently reported in a patient who received an Alpha AMS implant (Stingl et al., 2017). Despite these promising results, visual rehabilitation for patients with these prostheses is complex, and several challenges must still be overcome, including adverse effects, device longevity, and resolution (Cheng et al., 2017; Zrenner, 2013).

Yet another relatively new approach that can provide therapeutic benefits in patients who have lost photoreceptor and/or RPE cells is optogenetics, which uses gene therapy to express light-activated ion channels in the residual retinal neurons, thereby restoring photosensitivity (Busskamp et al., 2012). Despite promising results in both cell-based models and animal models, the true potential of this approach needs to be tested fully in a clinical setting.

Finally, several neuroprotective factors have been shown to slow photoreceptor loss in numerous animal models, including brain-derived neurotrophic factor (BDNF) (Okoye et al., 2003), basic fibroblast growth factor (bFGF) (Faktorovich et al., 1990), ciliary neurotrophic factor (CNTF) (Liang et al., 2001), glial cell-derived neurotrophic factor (GDNF) (Dalkara et al., 2011), nerve growth factor (NGF) (Lenzi et al., 2005), and rod-derived cone viability factor (rdCVF) (Byrne et al., 2015). However, there is currently no evidence that these compounds are beneficial in treating RP (Birch et al., 2016). Transcorneal electrical stimulation (TES), a novel therapeutic approach for retina disease and optic neuropathy, also seems to exert its effect through the release of neurotrophic factors after corneal electrostimulation. Proof of principle of TES has been established in animal models (Morimoto et al., 2007) and treatment appears to be safe in patients (Schatz et al., 2011, 2017; Wagner et al., 2017), although larger studies are needed to provide treatment efficacy over a prolonged time.

7. Conclusions

In this review, we provided an overview of the clinical characteristics of RP in general, as well as the specific features of genetically defined RP subtypes. This information can help the clinician identify the clinical RP entity and better predict the disease course, ultimately providing the patient with the best possible information regarding prognosis. In addition, we discussed the main pathways affected in RP, as well as the location and function of the proteins involved, thereby revealing high genetic and clinical similarity between RP and other IRDs, including LCA and cone-rod dystrophies. Together, these disorders are currently considered to represent a continuum of retinal dystrophies with significant clinical and genetic overlap.

Our rapidly increasing knowledge of affected biological pathways has shifted attention to the individual genetic subtypes of RP. This is paralleled by various treatment strategies exploring the applications of gene and cell-based therapies, retinal implants or transplantation. The nature of the genetic defect, the resulting molecular pathogenesis and the extent of the degeneration will determine which therapeutic modality will be the most appropriate in the individual RP patient.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.preteyeres.2018.03.005>.

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