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# Causes and consequences of inherited cone disorders

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ABSTRACT

Hereditary cone disorders (CDs) are characterized by defects of the cone photoreceptors or retinal pigment epithelium underlying the macula, and include achromatopsia (ACHM), cone dystrophy (COD), cone-rod dystrophy (CRD), color vision impairment, Stargardt disease (STGD) and other maculopathies. Forty-two genes have been implicated in non-syndromic inherited CDs. Mutations in the 5 genes implicated in ACHM explain ~93% of the cases. On the contrary, only 21% of CRDs (17 genes) and 25% of CODs (8 genes) have been elucidated. The fact that the large majority of COD and CRD-associated genes are yet to be discovered hints towards the existence of unknown cone-specific or cone-sensitive processes. The ACHM-associated genes encode proteins that fulfill crucial roles in the cone phototransduction cascade, which is the most frequently compromised (10 genes) process in CDs. Another 7 CD-associated proteins are required for transport processes towards or through the connecting cilium. The remaining CD-associated proteins are involved in cell membrane morphogenesis and maintenance, synaptic transduction, and the retinoid cycle. Further novel genes are likely to be identified in the near future by combining large-scale DNA sequencing and transcriptomics technologies. For 31 of 42 CD-associated genes, mammalian models are available, 14 of which have successfully been used for gene augmentation studies. However, gene augmentation for CDs should ideally be developed in large mammalian models with cone-rich areas, which are currently available for only 11 CD genes. Future research will aim to elucidate the remaining causative genes, identify the molecular mechanisms of CD, and develop novel therapies aimed at preventing vision loss in individuals with CD in the future.


**Contents**



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## 1. Introduction

Cone disorders (CDs) are a group of inherited diseases of the cone, or cone and rod photoreceptors, or retinal pigment epithelium (RPE), that are associated with various forms of stationary or progressive visual impairment. Linkage analysis, homozygosity mapping, and more recently whole exome sequencing (WES), facilitated the identification of genes mutated in patients with CDs such as achromatopsia (ACHM), cone dystrophy (COD), cone-rod dystrophy (CRD), and other cone-related disorders. CDs can follow all modes of Mendelian inheritance, i.e. autosomal recessive (AR), autosomal dominant (AD) and X-linked (XL), and can present as non-syndromic and syndromic forms. Thus far, reviews were focused on stationary cone disorders (Michaelides et al., 2004b) as well as the genetic spectrum of cone disorders (Berger et al., 2010). Here, we provide an overview of the expanded genetic repertoire of inherited cone disorders and novel genotype–phenotype correlations. Despite the high clinical and genetic heterogeneity of CDs the genetic defects underlying 21–93% of certain subsets of the cases have been identified. The proteins encoded by CD-associated genes are involved in a variety of processes, including the cone phototransduction cascade, visual cycles, photoreceptor development, ciliary transport, disk membrane morphogenesis and synaptic transport. Studies in mammalian models show that gene replacement therapies, due to the accessibility and immune-privileged nature of the eye, provide an opportunity to correct the visual impairment. In this review we present a comprehensive overview of the genes and associated disease mechanisms of non-syndromic CDs, touch upon the genetic causes of syndromic CDs, and evaluate therapeutic strategies aiming to prevent vision loss in CD in the future.

## 2. Phenotypic and genetic characteristics of cone disorders

Hereditary CDs constitute a large clinically heterogeneous group of diseases in which the cone photoreceptors or RPE are primarily affected. Cone photoreceptor cells account for only 5% of the total number of photoreceptors, the other 95% consisting of rods. In humans, the retina contains 3–6 million cone photoreceptors concentrated in the fovea enabling detailed vision, spatial resolution, reading, facial recognition and color vision. These important cone functions explain why CDs have such a disabling impact on the daily living tasks of those affected, further compounded by the early onset of disease and severe visual outcome of many of these disorders.

We analyzed all publicly available literature on CDs and, to estimate the contribution of specific genes, only included studies with clearly defined patient cohorts (Supplementary Tables 1–5). Using this approach, we estimated that AR/isolated (I) CDs are found in 76.7% of cases, AD inheritance in 21.6% of cases and X-linked inheritance in the remaining 1.4% (Fig. 1). In this chapter we

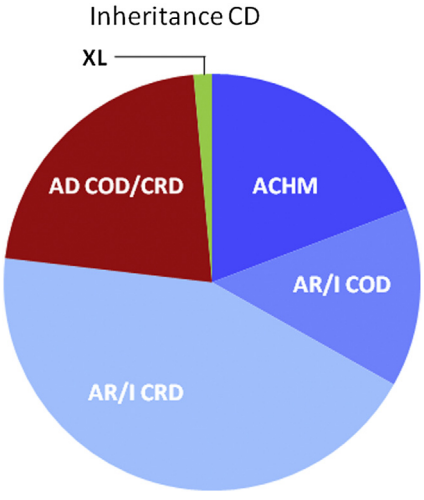


**Fig. 1.** Frequency of clinical subtypes and inheritance patterns of genetically heterogeneous cone disorders. Estimate of the frequencies of clinical subtypes and modes of inheritance of the genetically heterogeneous forms of CD, i.e. achromatopsia (ACHM), which invariably is inherited in an AR manner, cone dystrophy (COD), and cone-rod dystrophy (CRD). The majority of the AR COD and AR CRD cases are isolated (I) cases in which a recessive mode of inheritance is most likely. In most studies in which AD forms of COD and CRD were analyzed, no clear distinction was made between these disease entities, and therefore they are grouped together.

provide an overview of the clinical and genetic characteristics of different forms of non-syndromic and syndromic CDs.

### 2.1. Clinical methods

Ophthalmic examination and diagnostic testing is essential to differentiate cone-rod from rod-cone (i.e. RP) disorders. Although a number of tests are helpful in the diagnostic process, color vision testing of all three color axes such as Hardy Rand and Rittler tests, full-field ERG, and Goldmann perimetry, have been proven to be the most useful (Thiadens et al., 2013). With SD-OCT the morphology of the cone photoreceptor cells can be visualized. A single-section scan to obtain a longitudinal section across the center of the macula, and a volume scan should be performed to ensure capturing the center of the fovea. Retinal thickness measurements in the fovea including the outer nuclear layer, inner and outer segments of the cone cells, and RPE. For future gene therapy purposes, SD-OCT can be considered as a useful diagnostic tool for visualizing the severity of cone photoreceptor loss.

In Table 1, we summarized the ophthalmic symptoms and characteristics for ACHM, oligocone trichromacy (OT), blue cone monochromatism (BCM), COD, CRD and Stargardt disease (STGD). Further details of these and other CDs can be found below.

### 2.2. Clinical and genetic characteristics of non-syndromic cone disorders

#### 2.2.1. Achromatopsia

Patients with ACHM (Fig. 2A and B, Table 1) present shortly after birth with significantly reduced visual acuity, severe photophobia, a congenital pendular nystagmus, and color vision defects in the protan, deutan and tritan color axes. High refractive errors are common in these patients. The macula can have a variable appearance ranging from no abnormalities to atrophic lesions. Full-field electroretinography (ERG) demonstrates absent or residual cone responses with normal rod responses (Kohl et al., 2000; Thiadens et al., 2009b). The first signs of pathology on SD-OCT are loss of inner- and outer cone segments with disruption of the ciliary layer, which may be followed by the appearance of an optical empty cavity with cell loss in the cone photoreceptor layer, at least in some studies. The end stage is generally characterized by a complete loss of photoreceptors and atrophy of the RPE in the fovea (Genead et al., 2011; Sundaram et al., 2014). For future gene therapy purposes, SD-OCT can be considered as a useful diagnostic tool for visualizing the severity of cone photoreceptor loss.

The estimated prevalence of ACHM is 1:40,000 individuals and it is exclusively inherited in an AR manner. The genetic etiology of ACHM has been almost completely unraveled. Mutations in the five genes associated with ACHM (Fig. 3A) explain 93% of cases in the Caucasian population. All causal genes encode essential proteins in the cone phototransduction cascade (see paragraph 3) (Kohl et al., 2000; Thiadens et al., 2009b). Importantly, the limited number of genes involved in ACHM renders this disease a suitable candidate for future gene-based therapies. Nevertheless these therapies can only succeed if viable cone photoreceptor cells are still present in the retina (Carvalho et al., 2011; Komáromy et al., 2010; Michalakis et al., 2010; Pang et al., 2010).

#### 2.2.2. Cone dystrophy

Patients with cone dystrophy (COD, Fig. 2C and D, Table 1) have normal cone function initially, but present with loss of visual acuity and color vision disturbances in the first or second decades of life. Complaints of photophobia or hemeralopia may also exist. In X-linked (XL) COD cases with a mutation in the ORF15 region of *RPGR*, hemeralopia has been reported as a first symptom preceding visual loss in more than a quarter of the patients (Thiadens et al., 2012a). These *RPGR*-associated COD patients typically have high myopic refractive errors of more than 6 diopters (Thiadens et al., 2012a). Because the cone function is initially normal in COD, nystagmus is usually not observed. Macular abnormalities may be present ranging from no abnormalities to a bull's eye maculopathy or RPE atrophy. The optic nerve may have variable degrees of temporal pallor. Goldmann perimetry shows a reduced central sensitivity or (relative) scotoma with intact peripheral visual fields (Michaelides et al., 2006). Color vision is generally affected in all three axes. Reduced cone responses with preserved rod responses on ERG are an important clinical hallmark for the diagnosis of COD, although the vast majority of patients with COD develop rod involvement over time complicating the diagnosis. The mean onset of disease is at adolescence but the course of the disease may vary. Visual acuity generally worsens to legal blindness before 50 years of age (Thiadens et al., 2012a).

COD has an estimated prevalence of 1:30,000–40,000 (Michaelides et al., 2004b). Although all Mendelian inheritance patterns have been reported the AR form is by far the most common. The genetic causes of the autosomal dominant (AD) and XL forms have been solved to a large extent, but 75% of AR forms remain to be elucidated (see Fig. 3B). This is remarkable and hints towards the existence of completely unknown and uncharacterized cone-specific or cone-sensitive processes. Some of the genes associated with AR forms have a characteristic phenotypic appearance, like COD patients with mutations in the *KCNV2* gene. Mutations in this gene show supra-normal rod responses on ERG. Besides these remarkable ERG findings, most young patients also have a relatively late onset in loss of visual acuity (Zelinger et al., 2013). The rod responses on ERG do not appear to coincide with a gain of rod visual acuity, on the contrary, studies showed loss of acuity for rod as well as cone cells in patients carrying *KCNV2* mutations (Robson et al., 2010; Stockman et al., 2014; Zelinger et al., 2013). The clinical course of *ABCA4*-associated COD has also been studied in detail. This gene encodes a transmembrane protein located in rod and cone outer segments. AR-COD patients with mutations in this gene show an earlier onset, a rapid decline of visual acuity, and a significantly worse visual outcome than patients without *ABCA4* mutations (Thiadens et al., 2012a).

#### 2.2.3. Cone-rod dystrophy

Cone-rod dystrophy (CRD, Fig. 2E and F, Table 1) can be distinguished from COD by early rod involvement or concomitant loss of both cones and rods on ERG. Symptoms resemble those of COD, with complaints of loss of visual acuity and central vision, sometimes photophobia, and color vision disturbances. However, patients may also experience nyctalopia due to rod degeneration. With an onset in childhood and a rapid decline of the visual function to legal blindness before the age of 40, the course of CRD seems more severe than for COD (Thiadens et al., 2012a). The macular appearance resembles that of COD, but patients may also develop retinal vascular attenuation and peripheral pigment deposits. Visual fields show a (relative) central scotoma with variable degrees of peripheral involvement. CRD is usually non-syndromic but it can manifest as part of a syndrome (see 2.3).

As in COD the prevalence of CRD is 1:30,000–40,000 and can be inherited in an AR, AD or XL manner (Hamel, 2007). Currently, 17 genes and some additional loci are known to be involved in AR CRD explaining approximately 22% of the cases (Fig. 3C). As COD and CRD cases often are difficult to distinguish clinically, we have combined genetic data from the autosomal dominant forms of COD and CRD. In AD COD/CRD 21% of the cases were solved (Fig. 3D) and in XL COD/CRD 74% (Fig. 3E).

**Table 1**
Clinical characteristics to differentiate the major inherited cone disorders.

| | ACHM | OT | BCM | COD | CRD | STGD |
|---|---|---|---|---|---|---|
| Vision | 0.05−0.20 | 0.05−0.40 | ~0.10 | 0.05−0.40 | 0.05−0.40 | 0.1−0.5 |
| Nystagmus | + | ± | + | − | − | − |
| Color vision | Disturbed in protan/deutan/tritan color axes | Not disturbed | Disturbed in protan and deutan color axes | Disturbed in protan/deutan/tritan color axes | Disturbed in protan/deutan/tritan color axes | Disturbed in protan/deutan color axes |
| Photophobia | + | ± | + | ± | ± | ± |
| Hemeralopia | − | − | − | ± | ± | − |
| Nyctalopia | − | − | − | − | ± | − |
| Hypermetropia >+2D | +; ~30% | ? | − | − | − | − |
| Myopia <−2D | +; ~25% | ? | + | +; ~20% even more than >−6D | +; ~20% even more than >−6D | − |
| Retinal appearance | Normal to bull's eye/atrophic macular lesions | Normal to bull's eye/atrophic macular lesions | Normal to macular atrophy and RPE atrophy | Normal to bull's eye/atrophic macular lesions, temporal pallor of optic disc | Normal to bull's eye/atrophic lesions, peripheral RPE atrophy, vascular attenuation | Bull's eye, mostly surrounded by flecks. In rare cases flecks spread up to the arcades |
| SD-OCT | Normal- absence of central cone PRL | Thinner central retina, no absence of cone PRL | Absence of central cone PRL | Normal-absence of central cone PRL | Normal-absence of central cone PRL, central retinal thinning | Thinning or absence of central cone PRL |
| FAF | Normal to absent FAF in the macula | ND | Normal to absent FAF in the macula | Normal to absent FAF in the macula | Normal to absent FAF in the macula | 70% dark choroid |
| Goldmann perimetry | Reduced central sensitivity to (relative) central scotoma | Reduced central sensitivity | Reduced central sensitivity to (relative) central scotoma | Reduced central sensitivity to (relative) central scotoma | Reduced central sensitivity to (relative) central scotoma, with variable peripheral involvement | Reduced central sensitivity |
| mfERG | Reduced/non detectable macular responses | Reduced/non detectable macular responses | Reduced/non detectable macular responses | Reduced/non detectable macular responses | Reduced/non detectable macular responses | Reduced |
| ffERG | Reduced/absent cone responses. Normal rod responses | Normal to slightly reduced cone responses. Normal rod responses | Reduced/absent cone responses with a preservation of the blue cones | Reduced/absent cone responses. Initial normal rod responses | Cone responses are absent or more severely reduced than rod responses | Reduced cone responses |

+, Present; −, absent; ACHM, achromatopsia; AD, autosomal dominant; AR, autosomal recessive; BCM, blue cone monochromatism; COD, cone dystrophy; CRD, cone-rod dystrophy; D, Diopters; FAF, fundus autofluorescense; ffERG, full-field electroretinogram; mfERG, multifocal electroretinogram; NA, not analyzed; ND, not described; OT, oligocone trichromacy; PRL, photoreceptor layer; SD-OCT, spectral domain-optical coherence tomography; STGD, Stargardt disease; XL, X-linked.

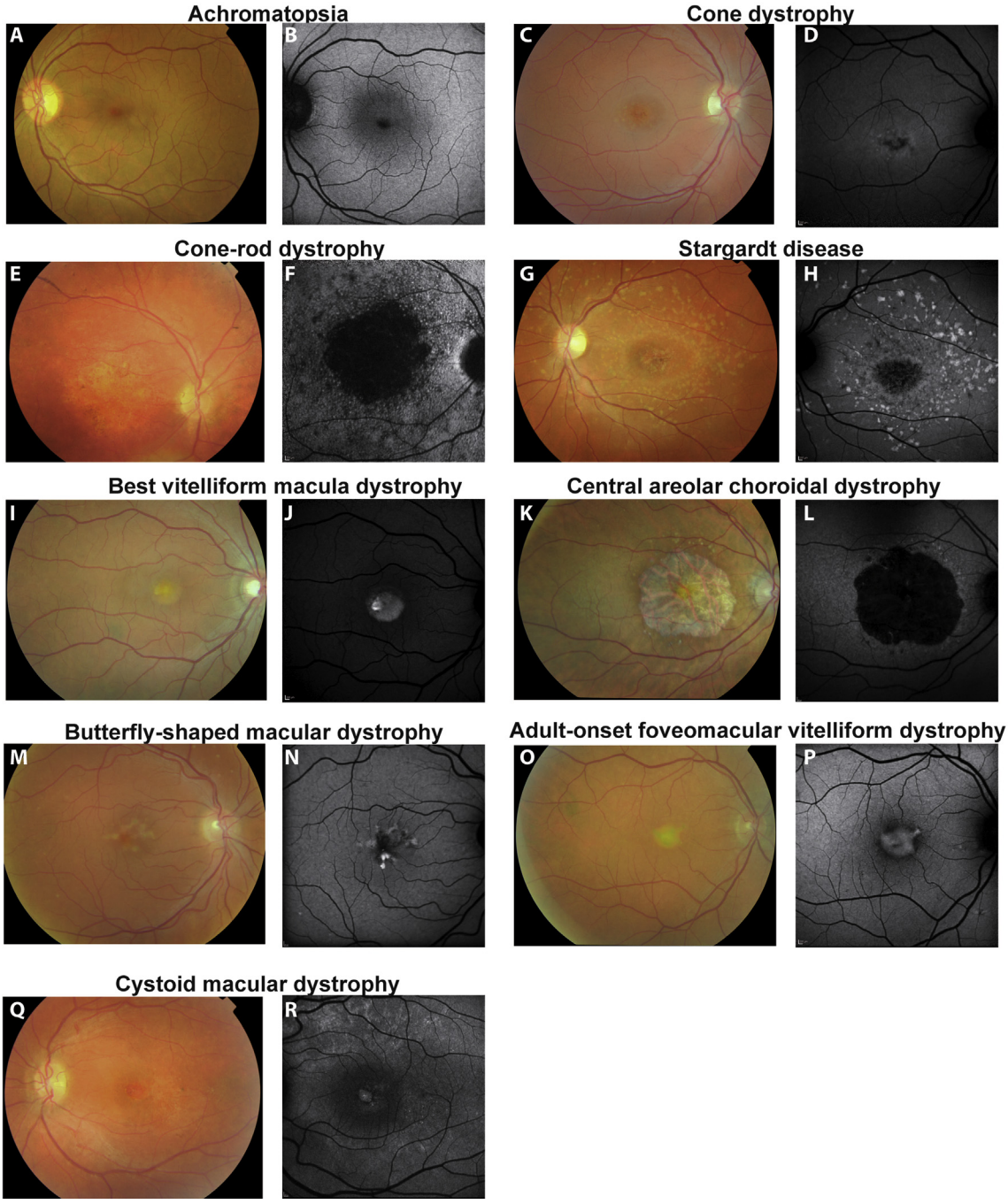


**Fig. 2.** Fundus and autofluorescence images of cone disorders and other maculopathies. Fundus and autofluorescence images of patients with a cone disorder (CD), in order of description in the article from left to right and up and down (A–R). A/B) Achromatopsia. A) The central macula shows mottling of the RPE, which corresponds with B) the small region of absent fundus autofluorescence (FAF) in the center due to the RPE alterations. C/D) Cone dystrophy. C) The optic disc shows temporal pallor of the optic disc; the macula presents with a bull's eye maculopathy with mottling of the RPE (color photograph). D) The fovea shows a small central region with absent FAF caused by RPE atrophy, surrounded by discrete hyperfluorescent lesions (FAF image). E/F) Cone-rod dystrophy. E) The central macula shows an area of diffuse RPE degeneration (color photograph). F) The lesion corresponds to absence of FAF in the center, surrounded by a discrete lesion of higher FAF intensity (FAF image). G/H) Stargardt disease. G) The posterior pole shows multiple yellow fish-tailed flecks, some pigment clumping, and bull's eye maculopathy with RPE atrophy (color photograph). H) The central macula shows decreased FAF, whereas the flecks exhibit increased FAF on a background of irregular FAF (FAF image). I/J) Best vitelliform macula dystrophy. I) The macula has an egg-yolk appearance corresponding to the vitelliform stage of Best (color photograph). J) The FAF of the lesion is intensely increased (FAF image). K/L) Central areolar choroidal dystrophy. K) In the macula a sharply demarcated lesion with RPE atrophy is visible, surrounded by a few small round white lesions (color photograph). L) The atrophic area causes a decreased FAF bordered by a small band of increased FAF (FAF image). M/N) Butterfly-shaped macular dystrophy. M) The macula shows an irregular yellow pigmented lesion with some RPE degeneration (color photograph). N) The central area has decreased FAF while the yellow pigment show increased FAF resembling a 'pattern' (FAF image). O/P) Adult-onset foveomacular vitelliform dystrophy. O) The macula reveals an oval yellow subfoveal lesion with central pigment (color photograph). P) The lesion shows an intensely increased FAF; the border of the lesion shows a band of decreased FAF (FAF image). Q/R) Cystoid macular dystrophy. Q) The macula shows focal thickening of the retina in the center (color photograph). R) The pooling of fluid in the macula gives a classical flower-petal pattern of FAF (FAF image).

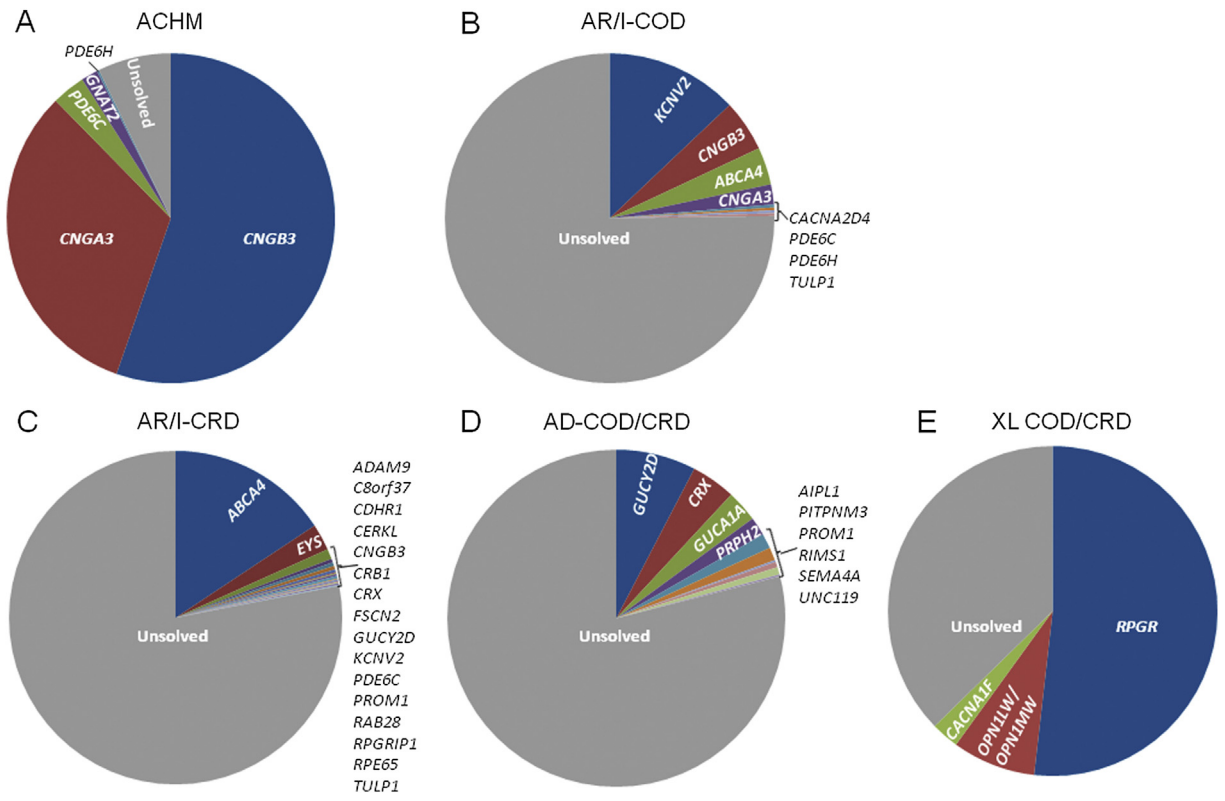


**Fig. 3.** Frequency and genetic causes of cone disorders. Estimates of the current frequency and genetic causes in cone disorders (CD). We only assessed studies in which cohort sizes were clearly indicated. A) ACHM. Mutations in five genes explain 93% of the cases, with the largest contribution by *CNGB3*, followed by *CNGA3*. For the included studies see Supplemental Table 1. B) Autosomal recessive and isolated COD. Eight genes each are mutated in a small proportion of the cases and together form the basis of disease in 25% of the cases. For the included studies see supplemental Table 2; DNA samples in the study of Littink et al. (2010) have been scanned using homozygosity mapping (no Sanger sequencing) and therefore have been excluded from numerical analysis, C) Autosomal recessive and isolated CRD. Seventeen genes are implicated in AR/I CRD, together responsible for 23% of the cases, of which only *ABCA4* is mutated in a significant proportion. For the included studies see supplemental Table 3. D) Autosomal dominant COD and CRD. Ten genes are mutated in these conditions, mutations in which explain not more than 20% of the cases. For the included studies see Supplemental Table 4, and E) X-linked COD and CRD. For the included studies see Supplemental Table 5.

Mutations in the *ABCA4* gene are not only implicated in Stargardt disease, but also the most prevalent cause of AR CRD. However its involvement varies widely between studies. In the Caucasian population this percentage varies between 26 and 65% (Maugeri et al., 2000; Thiadens et al., 2012a); in a recent Chinese study only 1/47 cases carried *ABCA4* variants. This also suggests a much lower prevalence of Stargardt disease (STGD1) in this population as previously suggested (Baum et al., 2003; Huang et al., 2013). In CRD patients with two pathogenic *ABCA4* variants, the observed visual prognosis is significantly worse than in patients with mutations in other genes, with a mean age of legal blindness more than 20 years earlier (Thiadens et al., 2012a).

One study suggested that *CNGB3* (3/47) and *PDE6C* (2/47) are involved in CRD (Huang et al., 2013), while previous studies only identified *CNGB3* and *PDE6C* mutations in COD. Reasons for this discrepancy could include different genetic backgrounds, or incomplete phenotyping.

### 2.2.4. Color vision impairment

Normal human color vision is mediated by three types of cone photoreceptors that are maximally sensitive to light at 565 nm (the red cones, long [L] wavelength sensitive), at 535 nm (the green cones, middle [M] wavelength sensitive), and at 440 nm (the blue cones, short [S] wavelength sensitive). The rods are maximally sensitive to light at 500 nm, mediate vision in dim light, and contribute little to color sense. Humans thereby generally have trichromatic color perception. The most frequent form of color vision impairment is dichromacy, which is observed in ~6% of males and 0.4% of females. Dichromats have lost one class of pigment, either the L, M or S pigments, and are named protanopes, deuteranopes, and tritanopes, respectively, the latter of which are very rare. The more frequent protanopes and deuteranopes carry deletions of the red (*OPN1LW*) or green (*OPN1MW*) pigment genes, nonsense mutations in these genes, or missense mutations that influence their spectral tuning (Gardner et al., 2010, 2012).

Persons with X-linked blue cone monochromatism (XL-BCM) have a similar clinical presentation as those with ACHM with photophobia, nystagmus, severe color vision disturbances, and a low visual acuity of ~0.10 in early childhood (Table 1) (Gardner et al., 2009). To distinguish BCM from ACHM it is necessary to use color vision tests that specifically select for the blue color axis such as Berson plates (Berson et al., 1983). Color ERGs may also distinguish between responses from different cone types and may detect signals from intact blue cones on a background of absent signals from red and green cones (Scholl and Kremers, 2003). XL-BCM is very rare with a prevalence of 1:100,000 individuals (Michaelides et al., 2004b). The red and green cone opsins are absent which in almost 40% of BCM can be explained by deletions in the locus control region, the region regulating transcription of the red and green opsin genes (Nathans et al., 1989; Gardner et al., 2009). Other BCM patients carry a p.Cys203Arg variant in a single green or red–green hybrid gene that remained after non-homologous recombination (Nathans et al., 1989). Together with a cystein at

amino acid position 126, this cystein forms a conserved disulfide bond that is important for protein stability.

Bornholm eye disease is an XL disease that has been reported in a large Danish family originating from the Danish island of Bornholm, characterized by a low visual acuity, a reduced photopic ERG, moderate to high myopia, and deuteranopia. Linkage analysis mapped the defect to a chromosomal region encompassing the red and green opsin gene array, suggesting overlap with congenital color blindness (deuteranopia). Recently, families with Bornholm eye disease, that display dichromacy and myopia, were shown to carry sequence variants in the first *OPN1LW* gene copy, which presumably lowers the amount of functional protein (McClements et al., 2013; Michaelides et al., 2005b; Ueyama et al., 2012).

Oligocone trichromacy (OT) is a rare condition first described in 1973 by van Lith (van Lith, 1973). It is characterized by reduced visual acuity, mild photophobia, nearly normal color vision, a normal fundus appearance, and reduced cone responses with normal rod responses on multifocal ERG (Table 1). It has been proposed that these patients have a reduced number of central cones or a reduced number in total number of cones (oligocone). The disease has an AR inheritance, and genetically there is considerable overlap with ACHM, as mutations in *CNGA3*, *CNGB3* and *GNAT2* have been associated with this form of CD (Michaelides et al., 2004a; Vincent et al., 2011).

### 2.2.5. Maculopathies

Autosomal recessive Stargardt disease (STGD1, Fig. 2G and H, Table 1) is the most prevalent inherited AR juvenile retinal dystrophy, with an estimated frequency of ~1:10,000 (Blacharski, 1988). Fundus flavimaculatus is a largely overlapping phenotype with a later onset, slower progression, and more widespread distribution of flecks (Franceschetti, 1963; Noble and Carr, 1979; Stargardt, 1909). Hereafter, fundus flavimaculatus will not be mentioned separately. STGD1 can arise in the first decade, but can also have an onset much later in life (up to 70 years of age). The outcome is generally poor central vision developing only a few years after the age of onset, but the prognosis may be better due to foveal sparing in some cases (Rotenstreich et al., 2003; Westeneng-van Haaften et al., 2012; Yatsenko et al., 2001). STGD1 patients show a dark choroid in ~80% of the cases upon fluorescein angiography due to the lipofuscin accumulation, which prevents the background fluorescence of the choroid (Armstrong et al., 1998; Fishman et al., 1999).

A combination of a mild and a severe, or two moderately severe mutations in *ABCA4* gives rise to STGD1 (Allikmets et al., 1997; Maugeri et al., 1999), whereas the combination of two severe mutations in *ABCA4* are known to cause panretinal, severe CRD which, at the end stage, may be difficult to discriminate from typical retinitis pigmentosa (RP) (Cremers et al., 1998). The estimated carrier frequency of *ABCA4* variants in the normal population can be as high as 1:20 (Maugeri et al., 1999). As described in more detail in paragraph 3.2, a deficiency of ABCA4 results in accumulation of lipofuscin in the RPE which can be seen in and around the macula as yellowish white flecks. In animals as well as in patients, it was shown that a defective ABCA4 protein causes accumulation of N-retinylidene-PE in the RPE, which forms a potential toxic component inducing photoreceptor death (Mata et al., 2000; Weng et al., 1999).

In persons with CRD and *ABCA4* mutations there appears to be an intrinsic and severe defect in photoreceptors, which directly leads to photoreceptor loss and lipid accumulations in the RPE are mostly absent.

### 2.2.6. Other maculopathies

Mutations in *PRPH2* have been associated with AD central areolar choroidal dystrophy (CACD, Fig. 2K and L), "pseudo-Stargardt pattern dystrophy" (Boon et al., 2007), pattern dystrophies like butterfly-shaped pigment dystrophy (BSMD, Fig. 2M and N) and adult-onset foveomacular vitelliform dystrophy (Fig. 2O and P), as well as AD retinitis pigmentosa (Boon et al., 2008). The *PRPH2* protein product RDS/peripherin is a photoreceptor-specific glycoprotein crucial in photoreceptor outer segment discs development and maintenance (Fig. 4, left lower panel) (Arikawa et al., 1992; Connell et al., 1991; Travis et al., 1991). It has been hypothesized that abnormal RDS/peripherin protein results in an altered cone outer segment structure and potentially an altered rod outer segment structure (Boon et al., 2009a). This may interfere with the photoreceptor outer segment-RPE interaction leading to accumulation of lipofuscin and byproducts in the RPE cells resulting in apoptotic cell death of RPE and photoreceptor cells. Pattern dystrophies due to *PRPH2* mutations are presumed to arise by disruption of the photoreceptor disc membranes (Wickham et al., 2009; Zhang et al., 2002a).

Best vitelliform macular dystrophy (BVMD, Fig. 2I and J), a member of the group of "bestrophinopathies", is caused by AD inherited mutations in the *BEST1* (or *VMD2*) gene, which encodes the bestrophin-1 protein, a calcium-activated chloride channel located at the baso-lateral membrane of RPE cells, that also influences voltage-gated calcium channels within the RPE. Furthermore, BEST1 localized mostly to the ER close to the baso-lateral plasma membrane and is involved in the storage-dependent Ca-influx into RPE cells (Gomez et al., 2013). The age at onset of central vision loss is highly variable ranging from the first to the sixth decade (Clemett, 1991; Wabbels et al., 2006). The disease-course of BVMD begins with the asymptomatic carrier ("pre-vitelliform") stage, progressing to variable clumping of vitelliform material in the vitelliruptive or "scrambled-egg" stage, culminating in variable degrees of chorioretinal atrophy and subretinal scarring in the cicatricial stage. Patients with AR bestrophinopathy have more extensive retinal abnormalities and carry a *BEST1* mutation on both alleles (Burgess et al., 2008). Hypothetically, causes of RPE dysfunction in BVMD are related to abnormal ionic transport leading to the accumulation of subretinal fluid and vitelliform material originating from photoreceptor outer segment-waste products and lipofuscin loaded pigmented cells (Boon et al., 2009b). The overload of the RPE eventually leads to photoreceptor and RPE dysfunction.

*PRPH2* variants have also been associated with BVMD and like *BEST1* mutations, are also associated with a high phenotypic heterogeneity and limited genotype–phenotype correlation (Boon et al., 2008, 2009b).

Genes with a minor contribution to AD macular dystrophies are *C1QTNF5*, *EFEMP1*, *FSCN2*, *GUCA1B*, *HMCN1*, *IMPG1*, *RP1L1* and *TIMP3*. Three of these present a rare but particular phenotype; *EFEMP1* mutations are a cause of AD Doyne honeycomb retinal degeneration (Malattia Leventinese) (Stone et al., 1999) which presents with drusen deposits at the level of Bruch's membrane in the macula around the edge of the optic nerve head (Gregory et al., 1996). Occult macular degeneration is caused by heterozygous mutations in *RP1L1* and is involved in central cone dysfunction and vision loss with a normal appearing retina (Akahori et al., 2010). Sorsby's fundus dystrophy develops due to mutations in *TIMP3* and is recognized by loss of central vision from subretinal neovascularization, as well as atrophy of the choriocapillaris, RPE and retina (Weber et al., 1994).

For seven other AD macular conditions, the underlying genetic causes are not yet known. Autosomal dominant macular dystrophy with cystoid macular edema (dominant cystoid macular dystrophy, DCMD; a.k.a. cystoid macular dystrophy, CYMD, Fig. 2Q and R) causes visual acuity loss in the second decade of life with or without strabismus (Deutman et al., 1976). As the disease progresses, the

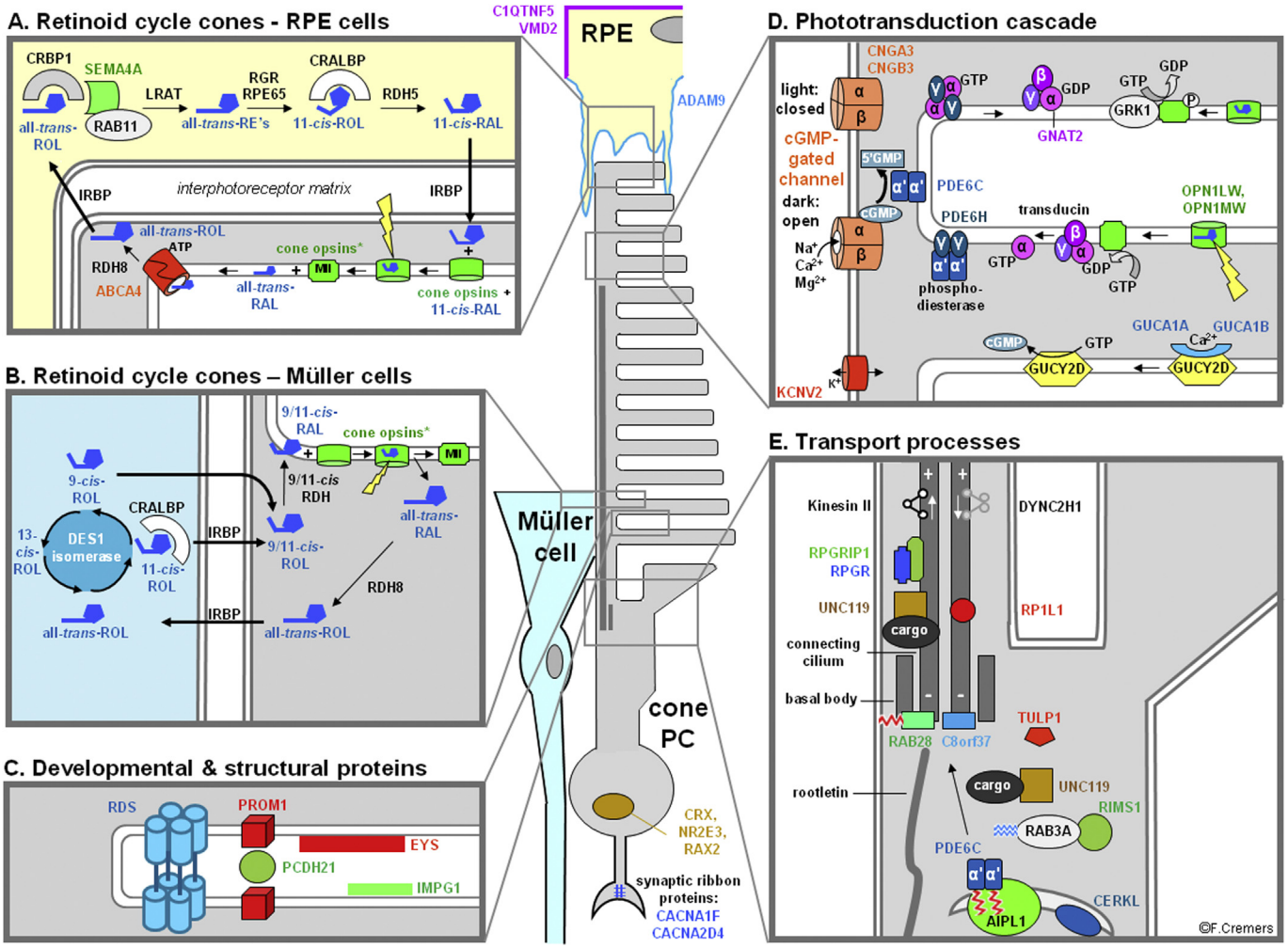


**Fig. 4.** Schematic representation of the roles of the non-syndromic cone disorder-associated proteins in the human retina. Schematic representation of five major functionalities of human cone photoreceptor cells (PC), Müller cells and the RPE. The locations and functions of proteins involved in non-syndromic CDs are depicted in different colors. Proteins which are relevant for the different cellular processes and not mutated in CDs are given in black lettering. Some CD-associated proteins are not shown in this figure either because of their wide-spread localization in the retina (EFEMP1, FSCN2, HMCN1), or because they localize to structures not shown (TIMP3). Left upper panel) The retinoid cycle taking place in cone photoreceptor cells and the RPE. Upon photoactivation (indicated by a lightning symbol), 11-*cis*-retinal is converted into all-*trans*-retinal and dissociates from activated cone opsins, OPN1LW and OPN1MW (activated opsins indicated by an asterix). All-*trans*-retinal is then recycled to 11-*cis*-retinal via several enzymatic steps in the RPE. Transport of all-*trans*-retinal is mediated by ABCA4. Left middle panel) Retinoid cycle in cones and Müller cells. Upon photoactivation, isomerization of 11-*cis* to all-*trans*-retinal in a cone opsin takes place. After dissociation, all-*trans*-retinal is reduced to all-*trans*-retinol by RDH8 and then released from the cone outer segment into the interphotoreceptor matrix where it is bound by IRBP and taken up by the Müller cells. All-*trans*-retinol is isomerized by dihydroceramide desaturase-1 (DES1) to 11-*cis*-retinol, 9-*cis*-retinol and 13-*cis*-retinol, of which 11-*cis*-retinol is subsequently bound to cellular retinal-binding protein (CRALBP). The interphotoreceptor retinoid-binding protein (IRBP) transports 11-*cis*-retinol to the cone outer segments. 9-*cis*-retinol diffuses directly to the interphotoreceptor matrix and into cone outer segments, and together with 11-*cis*-retinol is oxized by an unknown retinol dehydrogenase to 9/11-*cis*-retinal which subsequently is combined with apo-opsin to form a new chromophore. Left lower panel) Developmental and structural proteins. Three transcription factors mutated in non-syndromic CDs are CRX, NR2E3 and RAX2. Other proteins important in the morphogenesis and structure of the cone photoreceptor cell are EYS, IMPG1, PRPH2, PROM1, and PCDH21. Right upper panel) The phototransduction cascade in cone photoreceptor cells. Upon activation, amplification of the signal is mediated by the α-subunit of transducin and the α′- and γ-subunits of cone phosphodiesterase, encoded by *PDE6C* and *PDE6H*. This results in closure of the cGMP-gated channel composed of CNGA3 and CNGB3, a hyperpolarization of the cell and a reduction in glutamate release at the synaptic region. The *KCNV2* gene encodes a voltage-gated potassium channel subunit together with other channel components and regulated the potassium current in the cell and affects its excitability potential. PDE6 and transducin subunits are marked as alpha (α), alpha' (α′), beta (β), and gamma (γ). Right lower panel) CD-associated proteins involved in transport processes in the cone photoreceptor cell. AIPL1 is a chaperone of the putative farnesylated protein PDE6C. Farnesylated proteins are marked with a red zig-zag icon. C8orf37, RAB28, RIMS1, and TULP1, based on immunolocalisation studies act predominantly in transport processes toward and at the base of the connecting cilium, whereas RPGR and RPGRIP1 act throughout the connecting cilium. UNC119 is responsible for ciliary delivery of myristoylated proteins as well as the dissociation of transducin in separate subunits in mice. ATP, adenosine-triphosphate; GTP, guanosine-5′-triphosphate; GDP, guanosine diphosphate; GMP, guanosine monophosphate; cGMP, cyclic GMP; IRBP, interphotoreceptor retinol binding protein, the product of *RBP3*; MII, metarhodopsin II; P, phosphorylation; RAL, retinal; RE, retinyl esters; REH, retinyl ester hydrolase; ROL, retinol.

macula will develop a central zone of "beaten bronze" atrophy. The DCMD locus was positioned to an approximately 20-cM region between markers D7S493 and D7S526 on chromosome 7p15-p21 (Kremer et al., 1994), but the gene has remained elusive.

North Carolina macular dystrophy (NCMD) is an AD macular dystrophy with an early childhood onset and a stable course (Lefler et al., 1971; Schworm et al., 1998; Small et al., 1991). The highly variable phenotype contains yellow drusen-like lesions with retinal pigmentary changes of variable severity (Small, 1989; Small et al., 1991). The corresponding locus, MCDR1, was identified on chromosome 6q16 (Small et al., 1992; Yang et al., 2008), but the gene and its presumed function are currently unknown. Benign concentric annular macular dystrophy (BCAMD) is described in a Dutch family and may be caused by a mutation in *IMPG1* (van Lith-

Verhoeven et al., 2004). An early-onset AD macular dystrophy (MCDR3) resembling NCMD has been mapped to chromosome 5 (Michaelides et al., 2003; Rosenberg et al., 2010). The defect in a Greek family with macular dystrophy has been positioned on chromosome 19q (MCDR5) (Yang et al., 2006).

### 2.3. Clinical and genetic characteristics of syndromic cone disorders

In a minority of cases, cone-rod disorders are not limited to a degeneration of the retina, but show systemic involvement as well. Ocular signs and symptoms may precede or follow the onset of systemic features and it is therefore recommended to incorporate a comprehensive ophthalmologic examination into the regular clinical work-up of patients with additional non-ocular features.

CD can be part of a syndrome or complex disease like Danon disease, Alström syndrome, or Jalili syndrome. Danon is a rare genetic condition caused by mutations in the X-linked lysosome-associated membrane protein gene (*LAMP2*), and consists of the triad muscle weakness, cardiomyopathy, and mental impairment. The mortality rate in males is high; the most frequent cause of death is a heart arrhythmia. Female carriers can show a milder phenotype, often restricted to cardiomyopathy (Maron et al., 2009). Ophthalmic involvement has been reported in several cases, varying from macular abnormalities to CRD (Prall et al., 2006; Thiadens et al., 2012b). In one family, with a missense mutation in *LAMP2*, affected males presented with all features of CRD. The onset in this family was relatively late (middle-age) and visual acuity declined to legal blindness within two decades thereafter (Thiadens et al., 2012b).

Another example is the very rare AR Alström syndrome. It is characterized by CRD, hearing loss, obesity, diabetes, short stature, cardiomyopathy, and a progressively failure of lungs, liver and kidney. The disease manifests in early childhood and leads to a reduced life expectancy. Age of onset, severity of symptoms and prognosis may vary depending on genetic background. Alström syndrome is caused by mutations in the *ALMS1* gene, which codes for a ciliary protein present in basal bodies, centrosomes and cytosol of the cells. Patients with Alström disease present with a low visual acuity, nystagmus and photophobia on occasion, atrophic lesions of the retina, and an abnormal cone-rod ERG. Phenotypically this ciliopathy shows similarities to Bardet-Biedl syndrome (Marshall et al., 2011).

Jalili syndrome (cone dystrophy with amelogenesis imperfecta) is caused by autosomal recessive mutations in *CNNM4*, encoding a metal transporter protein. Patients present with a demineralization of both primary and secondary dentition with or without COD. A large Arab family with Jalili syndrome showed low visual acuity since early childhood, photophobia and nystagmus in some cases, absent color vision, and a bull's eye maculopathy or atrophic macular degeneration. Cone responses were more reduced than rod responses (Jalili, 2010), consistent with a retinal diagnosis of CORD.

A novel syndrome of North Carolina-like macular dystrophy with progressive sensorineural hearing loss (MCDR4) was linked to chromosome 14q (Francis et al., 2003).

### 2.4. Differential diagnosis

CDs form a genetically complex disease spectrum with a large phenotypic variability. Different mutations can result in similar phenotypes, whereas many genetic factors may contribute to the phenotypic variability of one causative mutation. Traditionally, Leber congenital amaurosis (LCA) has been considered as the congenital form of retinal dystrophy and it is typically associated with a very low vision at birth accompanied by roving nystagmus, amaurotic pupils, and a high hypermetropic refractive error. Visual acuity ranges from 0.10 Snellen visual acuity to no light perception. Eye poking (oculodigital reflex) can be observed in young children. Most often no fundus abnormalities are present, but in later stages round subretinal pigment clumps or bone-spicule-like pigment changes can develop. ERG responses are undetectable for both rods and cones before the age of one year. With an inconclusive ERG result, it is sometimes necessary to repeat the ERG after the age of 1 year to obtain the correct diagnosis. The prevalence of LCA varies from 1:30,000 to 1: 81,000 (Koenekoop, 2004; Stone, 2007). In most cases the inheritance modus is AR, but cases of AD inheritance have been described. Systemic disorders that are associated with LCA or a LCA-like ocular phenotype are Alström syndrome (Alström et al., 1959), Batten disease (Steinfeld et al., 2006; Vesa et al., 1995), Joubert syndrome (Lambert et al., 1989), peroxisomal diseases (Ek et al., 1986) and Senior Løken syndrome (Ellis et al., 1984).

## 3. Cone disorder mechanisms

### 3.1. Phototransduction cascade

The processes involved in the conversion of light into an electric neural signal are called phototransduction. The phototransduction cascade takes place in the outer segments of the rod and cone (Fig. 4, upper right panel) photoreceptors. Defects in various components of the phototransduction cascade can lead to CD: the red and green opsins, the cone transducin $\alpha$ subunit, the cone phosphodiesterase $\alpha'$ and $\gamma$ subunits, the cone-specific cGMP-gated $\alpha$ and $\beta$ subunits, the retinal guanylyl cyclase-1, and the voltage-gated potassium channel subunit.

Deletions of, or mutations in, the red and green opsin genes may cause color blindness (see 2.2.4.). A gene conversion event in which exon 3 of the red opsin gene, carrying the p.Trp177Arg variant, was transferred into the red opsin gene, was shown to underlie X-linked COD (Gardner et al., 2010). Mutations in the *GNAT2*-encoded $\alpha$-subunit of cone transducin leads to ACHM (Kohl et al., 2002; Sundin et al., 2000; Wissinger et al., 2001). The identified mutations are null alleles, which are predicted to prevent either the formation of the trimeric transducin protein complex or its interaction with cone opsin and phosphodiesterase-$\gamma$ (Aligianis et al., 2002; Kohl et al., 2002). Gene defects in *PDE6C* and *PDE6H*, encoding the $\alpha'$ and $\gamma$ subunits of the cone cGMP phosphodiesterase, are a cause of ACHM and COD (Kohl et al., 2012; Thiadens et al., 2009a). Mutations in the *PDE6C* gene are null alleles leading to absence of the $\alpha'$ subunit, or missense mutations causing a loss or reduction of the catalytic activity resulting in reduced hydrolysis of cGMP (Chang et al., 2009; Grau et al., 2011). The absence of transducin or phosphodiesterase activity can be considered functionally analogous since in both cases the phototransduction cascade is interrupted and the photoreceptor remains in the dark state (Chang et al., 2009).

Mutations in the *CNGA3* and *CNGB3* genes encoding the $\alpha$- and $\beta$-subunits of the cone cGMP-gated channel can cause ACHM and COD (Kohl et al., 2000, 1998; Sundin et al., 2000; Wissinger et al., 2001). A defect or lack of the cGMP-gated channel impairs the resting state dark current and the establishment of a proper cone photoreceptor membrane potential (Chang et al., 2009), causing apoptosis by perpetual influx of calcium ions (Biel et al., 1999; Thiadens et al., 2012a). The majority of *CNGB3* mutations are truncating, resulting in the absence or altered protein levels of the $\beta$-subunit (Pang et al., 2010). Amino acid substitutions in the highly conserved CNGA3 protein have an even more severe phenotypic impact. The reason may lie in the fact that CNGA3 can form a functional channel in the absence of CNGB3, while CNGB3 cannot establish the ion currents without the presence of CNGA3 (Johnson et al., 2004; Matveev et al., 2010). *CNGA3* missense mutations can

**Table 2**
Non-syndromic cone disorder genes, their associated human phenotypes, animal models, and gene therapy studies.

| Gene | Associated phenotypes | Expression site | Mouse model | Reference mouse model | Other animal model | Reference animal model | Potential function | Gene therapy model | Reference gene therapy |
|---|---|---|---|---|---|---|---|---|---|
| *ABCA4* | AR-COD, AR-CRD, AR-RP, AR-STGD1 | Cones and rods | KO | (Golczak et al., 2008; Weng et al., 1999) | – | – | All-*trans*-retinal flippase | Mouse | (Allocca et al., 2008; Han et al., 2012; Kong et al., 2008) |
| *ADAM9* | AR-CRD | RPE | KO | (Weskamp et al., 2002) | Dog | (Goldstein et al., 2010; Kropatsch et al., 2010) | Outer segment-RPE junction protein | – | – |
| *AIPL1* | AD-CRD, AR-LCA | Cones and rods | KO | (Dyer et al., 2004; Liu et al., 2004; Ramamurthy et al., 2004) | – | – | PDE chaperone | Mouse | (Ku et al., 2011; Sun et al., 2010; Tan et al., 2009) |
| *BEST1* | AD-MD, AR-Bestrinopathy | RPE | KI, KO | (Marmorstein et al., 2006; Zhang et al., 2010) | Dog | (Zangerl et al., 2010) | Calcium channel | Dog | (Guziewicz et al., 2013) |
| *C1QTNF5* | AD-MD | RPE, lens and ciliary epithelium | Trapped, KI, KI, reporter[b] | (Chavali et al., 2011; Shu et al., 2011; Zambrowicz et al., 2003) | – | – | Unknown | – | – |
| *C8orf37* | AR-CRD, AR-RP | Cones and rods | – | – | – | – | Transport across the CC | – | – |
| *CACNA1F* | XL-CRD, XL-CSNB | ONL and INL | KO, spontaneous | (Chang et al., 2006; Mansergh et al., 2005; Specht et al., 2009) | Rat | (Zheng et al., 2012) | Calcium channel | – | – |
| *CACNA2D4* | AR-COD | Ubiquitously | Spontaneous | (Ruether et al., 2000) | – | – | Calcium channel | – | – |
| *CDHR1* | AR-CRD, AR-RP | Ubiquitously | KI, KO | (Boland et al., 2009; Rattner et al., 2001) | – | – | Involved in the assembly of OS discs | – | – |
| *CERKL* | AR-CRD, AR-RP | Cones and rods | KD, KD | (Garanto et al., 2012; Graf et al., 2008) | – | – | Sphingolipid metabolism | – | – |
| *CNGA3* | AR-ACHM, AR-COD | Cones | KO, spontaneous | (Biel et al., 1999; Hawes et al., 2006) | Sheep | (Reicher et al., 2010) | Subunit of cGMP-regulated cation channel | Mouse | (Michalakis et al., 2012; Pang et al., 2012) |
| *CNGB3* | AR-ACHM, AR-COD, AR-CRD | Cones | KO | (Ding et al., 2009) | Dog | (Sidjanin et al., 2002; Yeh et al., 2013) | Subunit of cGMP-regulated cation channel | Mouse, dog | (Carvalho et al., 2011; Komáromy et al., 2010) |
| *CRX* | AD-CRD, AR- AD- *de novo* LCA, AD-RP | Cones and rods | KO, chemically induced | (Furukawa et al., 1999; Won et al., 2011) | Cat | (Menotti-Raymond et al., 2010) | Transcription factor | Mouse | (Homma et al., 2013) |
| *EFEMP1* | AD-MD | RPE | KI, KO[b], KI, KO | (Fu et al., 2007; Marmorstein et al., 2007; McLaughlin et al., 2007) | – | – | Unknown | – | – |
| *EFEMP1* | AD-MD | RPE | KI, KO[b], KI, KO | (Fu et al., 2007; Marmorstein et al., 2007; McLaughlin et al., 2007) | – | – | Unknown | – | – |
| *ELOVL4* | AD-MD | Endoplasmatic reticulum | KO, KO, reporter, KI, KI, targeted | (Barabas et al., 2013; Cameron et al., 2007; Li et al., 2007; McMahon et al., 2007; Raz-Prag et al., 2006; Vasireddy et al., 2006) | Pig | (Sommer et al., 2011) | Catalyzing very-long-chain fatty acid synthesis | – | – |
| *EYS* | AR-CRD, AR-RP | Cones and rods | No mouse ortholog | – | – | – | Photoreceptor morphogenesis and maintenance | – | – |
| *FSCN2* | AD-MD, AD-RP | Cones and rods | Spontaneous, KO, KO | (Johnson et al., 2008; Yokokura et al., 2005) | – | – | Actin structure assembly of CC plasma membrane; photoreceptor disc formation | – | – |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| *GNAT2* | AR-ACHM | Cones | Spontaneous, spontaneous | (Chang et al., 2006; Jobling et al., 2013) | – | – | Subunit of cone transducin | Mouse | (Alexander et al., 2007) |
| *GUCA1A* | AD-COD, AD-CRD | Cones and rods | KI, KO, KO | (Buch et al., 2011; Mendez et al., 2001; Mendez and Chen, 2002) | – | – | $Ca^{2+}$-activated interactor of GUCY2D | Mouse | (Jiang et al., 2011) |
| *GUCA1B* | AD-MD, AD-RP | Cones and rods | KO, KO | (Makino et al., 2008; Mendez et al., 2001) | – | – | $Ca^{2+}$-activated interactor of GUCY2D | – | – |
| *GUCY2D* | AD-CRD, AR-CRD, AR-LCA | Cones and rods | Reporter, reporter, KO | (Hu et al., 2007; Leinders-Zufall et al., 2007; Walz et al., 2007) | Pig, zebrafish | (Kostic et al., 2013; Stiebel-Kalish et al., 2012) | Generation cGMP | Mouse | (Boye et al., 2013) |
| *HMCN1* | AD-MD | RPE | – | – | – | – | Unknown | – | – |
| *IMPG1* | AD-MD | Interphotoreceptor space | – | – | Rhesus macaque | (Singh et al., 2007) | Unknown | | |
| *KCNV2* | AR-CDSRR | Cones and rods | – | – | – | – | Ion channel subunit | – | – |
| *NR2E3* | AR-ESC, AR-RP | Neural retina | KO, spontaneous | (Akhmedov et al., 2000; Chang et al., 2002) | – | – | Transcription factor | – | – |
| *OPN1LW* | XL-COD | Cones | – | – | – | – | Red-light sensitive opsin | – | – |
| *OPN1MW* | XL-COD | Cones | KI | (Smallwood et al., 2003) | – | – | Green light sensitive opsin | – | – |
| *PDE6C* | AR-ACHM, AR-COD | Cones | Spontaneous | (Chang et al., 2005) | – | – | Phosphodiesterase subunit α′ | – | – |
| *PDE6H* | AR-ACHM, AR-COD | Cones | – | – | – | – | Phosphodiesterase subunit γ | – | – |
| *PITPNM3* | AD-CRD | Retina (rat) | – | – | – | – | Membrane turnover of photoreceptor cells (transport) | – | – |
| *PROM1* | AD-STGD, AR-CRD | Ubiquitously | Reporter, KI, KO, reporter | (Nishide et al., 2009; Shmelkov et al., 2008; Zacchigna et al., 2009; Zhu et al., 2009) | – | – | Photoreceptor membrane morphogenesis | – | – |
| *PRPH2* | AD-CRD, AD-MD, AD-RP, | Cones and rods | KI, spontaneous[b], chemically induced | (McNally et al., 2002; Nystuen et al., 2008) | – | – | Membrane morphogenesis | Mouse | (Barber et al., 2013; Sarra et al., 2001) |
| *RAB28* | AR-CRD | Ubiquitous | – | – | – | – | Transport towards the CC | – | – |
| *RAX2* | [a]CRD | ONL and INL | – | – | – | – | Transcription factor | – | – |
| *RIMS1* | AD-CRD | Presynaptic ribbons in retina and brain | KO, KI[b], KO, floxed | (Kaeser et al., 2008; Schoch et al., 2002) | – | – | Neurotransmitter release and synaptic plasticity | – | – |
| *RP1L1* | AD-MD | Cones and rods | KO | (Yamashita et al., 2009) | – | – | Stabilization of microtubules | – | – |
| *RPGR* | XL-CRD, XL-RP | Cones and rods | Reporter, targeted, spontaneous | (Hong et al., 2000; Huang et al., 2012; Thompson et al., 2012) | Dog, dog | (Zhang et al., 2002b) | Transport across the CC | Dog | (Beltran et al., 2012) |
| *RPGRIP1* | AR-CRD, AR-LCA | Cones and rods | KO, chemically induced[b] | (Zhao et al., 2003) | Dog | (Kuznetsova et al., 2012) | Transport across the CC, intracellular trafficking | Mouse, dog | (Lhériteau et al., 2013; Pawlyk et al., 2010) |
| *SEMA4A* | AD-CRD, AD-RP | Ubiquitous | KO, trapped | (Kumanogoh et al., 2005; Rice et al., 2004) | – | – | Interactor of CRBP1 and endosomal sorting | – | – |
| *TIMP3* | AD-Sorsby fundus dystrophy | RPE | Reporter[b], KO, KO[b], KO, KO, KI | (Janssen et al., 2008; Kawamoto et al., 2006; Leco et al., 2001; Weber et al., 2002) | – | – | Extracellular matrix remodeling | – | – |
| *TULP1* | AR-COD, AR-CRD, AR-RP | Cones and rods | KO | (Ikeda et al., 2000) | – | – | Transport towards the CC | – | – |
| *UNC119* | AD-CRD | Neural retina | KO | (Ishiba et al., 2007) | – | – | Transport across the CC | – | – |

ACHM, achromatopsia; AD, autosomal dominant; AR, autosomal recessive; CD, cone dystrophy; *CDHR1*, encodes protocadherin 21; CDRSS, cone dystrophy with supranormal rod response; CRD, cone-rod dystrophy; CC, connecting cilium; CSNB, congenital stationary night blindness; ESC, enhanced S-cone syndrome; KD, knockdown; KI, knock-in; KO, knockout; LCA, Leber congenital amaurosis; MD, macula dystrophy; *RAX2*, retina and anterior neural fold homeobox 2, encodes QRX; RP, retinitis pigmentosa; RPE, retinal pigment epithelium; OS, outer segment; XL, X-linked. aa, amino acids; bp, basepair; ERG, electroretinogram; ORF, open reading frame.

[a] Mode of inheritance is unknown.

[b] Mouse Genome Informatics direct data submission.

lead to an interfering conformational change of the active channel due to an altered secondary structure (Matveev et al., 2010). The impaired channel will cause cellular mistrafficking (Liu and Varnum, 2005; Reuter et al., 2008) and altered targeting to the plasma membrane due to impaired surface expression (Ding et al., 2010; Koeppen et al., 2008).

Remarkably, unlike COD and CRD, autosomal dominant inheritance has not been observed for ACHM, despite the fact that many cone-specific proteins act in multimeric complexes in which dominant-negative disease mechanisms would be plausible.

The *KCNV2* gene encodes a voltage-gated potassium channel subunit in cone and rod photoreceptors and mutations cause COD with supranormal rod responses on ERG. The subunit encoded by *KCNV2* is unable to form a functional potassium channel but needs heteromerization with other channel components, thereby altering the potassium current in the cell and affecting its excitability potential (Czirjak et al., 2007; Ottschytsch et al., 2002). It is unclear how mutations in this gene cause repolarization disturbances in rods (Wissinger et al., 2008; Wu et al., 2006).

Specific heterozygous *GUCY2D* missense mutations are a cause of AD CRD, whereas homozygous or compound heterozygous inactivating mutations in this gene can cause AR-LCA. *GUCY2D* encodes the membrane-bound retinal guanylyl cyclase-1 protein (RetGC-1), which is expressed in both types of photoreceptors but predominantly in the cone outer segment (Gregory-Evans et al., 2000; Kelsell et al., 1998; Kitiratschky et al., 2008; Payne et al., 2001). In mammalian photoreceptor cells RetGC-1 and RetGC-2 together synthesize cyclic 3′, 5′-guanosine monophosphate (cGMP) from guanosine triphosphate. RetGC-1 restores the $Ca^{2+}$-sensitive cGMP levels after light activation of the phototransduction cascade, together with its associated activator proteins GUCA1A and GUCA1B (Hunt et al., 2010). Cyclase activity is regulated by $Ca^{2+}$, which binds to the GC-associated proteins, GCAP1 and GCAP2 encoded by *GUCA1A* and *GUCA1B*, respectively. The majority of dominant missense mutations causing AD COD and AD CRD are found in the $Ca^{2+}$-binding EF hands of the proteins. Similar to the dominant *GUCY2D* mutations, these mutations generally alter the cyclase sensitivity to inhibit the $Ca^{2+}$ levels after a light flash.

### 3.2. Retinoid cycles

To maintain the phototransduction cascade, recycling of the chromophore all-*trans*-retinal to 11-*cis*-retinal is required. This process is referred to as the retinoid or visual cycle. The rod and cone visual cycles take place in their respective outer segments, and the RPE cells (Fig. 4, left upper panel). Moreover, part of the visual cycle of the cones takes place in the cone OS and the Müller cells (Fig. 4, left middle panel). Although several genes encoding proteins of the retinoid cycles have been found to be defective in inherited retinal dystrophies, only the *ABCA4* and *SEMA4A* genes are implicated in CDs (Table 2).

Upon photo-excitation all-*trans*-retinal dissociates from opsin and is subsequently transferred to the cytoplasmic space by ABCA4. In rods, ABCA4 is located at the rim of the outer segments discs and essential in the transport of all-*trans*-retinal from the inner to the outer leaflet of the disks through an ABCA4-mediated flippase of N-retinylidene-phosphatidylethanolamine (PE), the Schiff base conjugate of retinal and PE. In the cytoplasm, all-*trans*-retinal separates from PE and is converted to all-*trans*-retinol (Molday et al., 2000; Sun et al., 1999; Sun and Nathans, 1997; Weng et al., 1999). In cones, N-retinylidene-PE is translocated from the exocytoplasmic leaflet (lumen/extracellular) to the cytoplasmic leaflet, and upon dissociation from PE, all-*trans*-retinal is reduced to all-*trans*-retinol by retinol dehydrogenase 8 (RDH8) (Fig. 4, left upper panel) (Maeda et al., 2007; Miyazono et al., 2008).

A defective ABCA4 protein leads to the accumulation of A2E in RPE cells which basically consists of all-*trans*-retinal conjugated to N-retinylethanolamine (N-retinylidene-N-retinylethanolamine; N-retinylidene-PE) and another all-*trans*-retinal molecule cells (Quazi et al., 2012; Radu et al., 2004), which is toxic to these cells in higher concentrations (Sparrow et al., 2003).

In cone and rod photoreceptors, all-*trans*-retinal is converted to all-*trans*-retinol (i.e. vitamin A), and absorbed by the RPE cell. In these cells, vitamin A is converted to all-*cis*-retinal and recycled to be introduced back into the phototransduction cascade (Travis et al., 2007). Under light conditions cones have a higher demand for vitamin A compared to rods, which can be provided through an alternate visual cycle between the cone photoreceptor cells and the Müller cells. In the fovea, Müller cells exist in a 1:1 ratio to cones. In cone-dominated retinas (from ground squirrel and chicken) it was found that all-*trans*-retinol was isomerized to 11-*cis*-retinol directly, without the intermediate molecule all-*trans*-retinyl (Mata et al., 2002). Recently, Kaylor and colleagues showed that all-*trans*-retinol is isomerized by dihydroceramide desaturase-1 to 11-*cis*-retinol, 9-*cis*-retinol and 13-*cis*-retinol, of which 11-*cis*-retinol is subsequently bound to cellular retinal-binding protein (CRALBP). The interphotoreceptor retinoid-binding protein (IRBP) transports 11-*cis*-retinol to the cone OS. 9-*cis*-retinol diffuses directly to the interphotoreceptor matrix and into cone OS, and together with 11-*cis*-retinol is oxized by an unknown retinol dehydrogenase to 9/11-*cis*-retinal which subsequently is combined with apo-opsin to form a new chromophore (Kaylor et al., 2013). Although more knowledge on the cone visual cycle has been gained, compared to the rod cycle challenges remain regarding the differences between the cycles. More studies could possibly address these challenges, potentially revealing novel candidate genes for CD.

Semaphorin 4A (SEMA4A) plays a role in endosomal sorting in the RPE (Fig. 4, left upper panel). As a response to oxidative stress, SEMA4A acts as a switch converting endosomal sorting in the lysosome to exosomal release, thereby preventing light-induced photoreceptor apoptosis. In the absence of oxidative stress, SEMA4A sorts retinoid-binding proteins with retinoids, a RAB11-facilitated process by which 11-*cis*-retinal is regenerated and transported back to photoreceptors (Toyofuku et al., 2012).

### 3.3. Photoreceptor development and structure

During development, photoreceptor specification is initiated by transcription factors OTX2 and RB by influencing the multipotent retinal neuroepithelial cells to exit the cell cycle. It is hypothesized that CRX is the competence factor in photoreceptor precursor cells after mitosis (Oh et al., 2007). Cells that only express CRX have the fate to become cone precursors, while NRL-expressing cells will develop into rod photoreceptor cells with subsequent expression of NR2E3 (Oh et al., 2007). The transcription factor RAX2 (QRX) is thought to synergistically increase the transactivating function of CRX and NRL and also to interact with CRX (Wang et al., 2004). Other, as yet unknown transcription factors are necessary to complete the development to mature photoreceptors.

Dominant gain-of-function mutations in *CRX* were found to be a cause of AD CRD (Freund et al., 1997), by impairing CRX-mediated transcriptional regulation of photoreceptor genes (Chen et al., 2002). Recessive loss-of-function, and dominant mutations in *NR2E3* cause enhanced S-cone syndrome, AR RP and rod related syndromes (Escher et al., 2009; Haider et al., 2000; Schorderet and Escher, 2009; Yzer et al., 2013). The molecular mechanism underlying phenotypes due to *NR2E3* mutations involves the absence of the NR2E3 repressor function on cone-specific gene promoters, either by the absence of NR2E3 protein because of nonsense mutations or aberrant splicing, absence of DNA binding because of

mutations in the DNA-binding domain, or impaired co-repressor binding because of mutations in the ligand-binding domain (Roduit et al., 2009).

The rod photoreceptor outer segments represent a unique and complex example of specialized sensory cilia by their dense stacks of rhodopsin-laden discs. Disc renewal takes place at the proximal side and it has been estimated that 10% of the rod photoreceptor discs at the distal tips of the OS in humans are removed every day by undergoing phagocytosis by the overlying RPE cells (Young, 1967). The process of disc morphogenesis is critical for the viability of the photoreceptor cells as shown by several vertebrate models, where blockage of disc morphogenesis resulted in cell death and retinal degeneration (Eckmiller, 1987; Steinberg et al., 1980). A relevant difference between cone and rod photoreceptors is the continuity of the disc membranes in cones and the presence of separate discs in rods.

The transmembrane protein peripherin/RDS forms homotetramers, or heterotetramers with ROM1. Some heterozygous variants in the gene encoding RDS, *PRPH2*, are associated with AD cone disorders (Kitiratschky et al., 2011; Nakazawa et al., 1996a, 1996b; Renner et al., 2009). Other heterozygous variants in *PRPH2*, in combination with heterozygous variants in *ROM1*, are associated with digenic RP (Dryja et al., 1997; Kajiwara et al., 1994; Poloschek et al., 2010). These molecules are proposed to play a critical role in disk membrane morphogenesis and to keep the rod discs in a flattened configuration by connecting to similar molecules on the other side of the disc through disulphide bridges (Fig. 4, left lower panel). Possibly, RDS has a similar function in cones to flatten the invaginations.

PROM1 interacts with protocadherin 21 (PCDH21) and actin filaments, which are also crucial for disk membrane morphogenesis. For ADAM9 it has been suggested that it may be involved in adhesion at the junction of the outer segments (OS) and the RPE. Alternatively, the transmembrane ADAM9 protein may be involved in the remodeling of the extracellular matrix between the RPE and the OS or in the shedding of factors essential for the maintenance of the extracellular matrix (Parry et al., 2009). *FSCN2* and *ELOVL4,* two genes involved in AD macular degeneration (Ambasudhan et al., 2004; Wada et al., 2003), are expressed in different parts of the photoreceptor cells and are also thought to have a role in maintaining the structure and/or physiological function of photoreceptor cells.

### 3.4. Transport processes

The narrow 'channel' or 'conveyer belt' connecting the inner segment with the outer segment of the photoreceptor cells is called the connecting cilium (CC; see Fig. 4, right lower panel). In the process of vision, transport of proteins from the inner segments critically occurs through docking at the basal body (or adjacent membrane) and subsequent transport via the CC towards the outer segment (Insinna and Besharse, 2008). Intraflagellar transport (IFT) complexes tightly regulate the anterograde flow of proteins necessary for the assembly, maintenance and renewal of outer segment discs (Li et al., 2012) as well as the retrograde transport of proteins.

Several proteins involved in CD have been identified at the CC. These proteins include AIPL1, C8orf37, RAB28, RPGR, RPGRIP1, TULP1, and UNC119. Mutations in *RPGR* causing COD are localized in ORF15, a highly repetitive region coding for a glutamic acid and glycine-rich C-terminal domain, while mutations causing RP are found throughout the protein. It has been hypothesized that the phenotype is determined by the type of opsin which is mislocalized, depending on the type of mutation (Hong et al., 2000; Zhao et al., 2003). Alternatively, the genetic background may determine the disease outcome to be cone-dominated or rod-dominated (Brunner et al., 2010).

The transition zone protein RPGR has a wide expression, but mutations predominantly affect photoreceptor function, with few cases of hearing loss, sino-respiratory infections and sperm dysfunction (Iannaccone et al., 2004; Koenekoop et al., 2003; van Dorp et al., 1992; Zito et al., 2003). RPGR binds to RAB8a (Anand and Khanna, 2012), and via crystal modeling it was proposed that RPGR has an interplay with PDEδ and Arl2/3 to regulate ciliary targeting of farnesylated cargo (Wätzlich et al., 2013). RPGRIP1 is linked to cilium integrity with RPGR via Nek4 serine/threonine kinase (Coene et al., 2011) and localizes exclusively to the photoreceptor CC. Absence of RPGRIP1 in mice resulted in a strongly decreased formation of photoreceptor outer segments and a rapid degeneration of these neurons, leading to vision loss (Won et al., 2009).

AIPL1 functions as a chaperone of rod PDE6 and interacts with its α-, β-, and γ-subunits (Kolandaivelu et al., 2009) and is thereby indirectly also involved in the phototransduction cascade. The cone PDE6 α′ but not the γ subunit carries a carboxy-terminal prenylation motif (as do the rod α and β PDE6 subunits), and it has been hypothesized that AIPL1 also acts as a chaperone for cone PDE6 (Kirschman et al., 2010). It recently has been shown that AIPL1 is essential for cone PDE6 stability (Kolandaivelu et al., 2013). AIPL1 is necessary for proper assembly of the rod PDE6-complex (Kolandaivelu et al., 2009) and also functions as a chaperone of other farnesylated proteins. The absence of AIPL1 results in disorganized rod and cone outer segments, although presence of viable rod cells may prevent a rapid degeneration (Kirschman et al., 2010). Interestingly, null mutations in RAB28 were recently found to be associated with AR CRD (Roosing et al., 2013). RAB28 belongs to a superfamily (>60 members in humans) of small GTPases that fulfill a myriad of intracellular transport functions. Strikingly, RAB28 is uniquely farnesylated at its carboxy terminus, whereas almost all other RABs contain two geranylgeranyl groups for membrane attachment and very few RABs can be farnesylated or geranylgeranylated. The expression of RAB28, as is the case for most RABs, is not restricted to the retina. It is not known why mutations in RAB28 only result in a retinal phenotype.

UNC119, also known as Retina Gene 4 protein (RG4), has been shown to be crucial for transducin transport in the absence of light (Zhang et al., 2011). In one mouse model UNC119 can dissociate transducin subunits from each other and the membrane, and subsequently inhibits rhodopsin-dependent activation of transducin (Gopalakrishna et al., 2011). Furthermore, UNC119 has the capacity of binding myristoylated proteins, e.g. NPHP3, which is regulated by the small GTPase ARL3 (Wright et al., 2011).

Mutations in the gene coding for RIMS1 are a cause of AD CRD, which is characterized by a progressive loss of photoreceptors along with retinal degeneration (Michaelides et al., 2005a). RIMS1 was found to be essential to short- and long-term synaptic plasticity by affecting the readily releasable pool of vesicles (Castillo et al., 2002; Schoch et al., 2002) and RIMS1 proteins were found to be required for normal $Ca^{2+}$-triggering of exocytosis (Schoch et al., 2006).

### 3.5. Synaptic transduction

A subset of genes associated with CD encode proteins that are localized in the synaptic region, i.e. CACNA1F, CACNA2D4, RIMS1, and UNC119. The transmission of L-glutamate at the photoreceptor synapses to the horizontal and bipolar cells is a calcium-dependent event. Transmitter release is increased with depolarization, as voltage-dependent calcium channels in a depolarized state have an increased capability of channel opening (Thoreson and Witkovsky,

1999). CACNA1F and CACNA2D4 are involved in a continuous calcium-dependent transmitter release and when disturbed cause CD. The reduction of functional calcium-channel densities in synaptic terminals may lead to inefficient photoreceptor-signal transmission and may account for the electronegative ERG (Wycisk et al., 2006). The RIMS1 protein plays a role in basic synaptic vesicle release as well as long- and short-term pre-synaptic plasticity (Castillo et al., 2002; Coppola et al., 2001; Schoch et al., 2002). The RIMS1 p.Arg655His missense mutation identified in CRD abolishes the hyperpolarization of current activation, likely resulting in impaired synaptic transmission of ribbon synapses of the visual system (Miki et al., 2007).

UNC119 may also have an important function in photoreceptor neurotransmission as it also is localized at the ribbon synapses formed between photoreceptors and the horizontal and bipolar cells of the retina (Kobayashi et al., 2000).

### 3.6. Miscellaneous

Several other CD-associated proteins cannot be assigned to one of the five major functionalities of the cone photoreceptor, RPE cells, and Müller cells, and are listed below.

Sphingolipids consist of a sphingoid base linked to a variety of polar groups and fatty acid chains (Hannun and Obeid, 2008). CERKL is an endoplasmic reticulum and golgi apparatus membrane associated protein, which seems to be involved in the sphingolipid metabolism due to the shared homology with CERK (Tuson et al., 2009). However its exact role is currently unknown. Knockdown mice showed reduced levels of several sphingolipids, such as glucosylceramide or sphingomyelin. Enzymes in the synthesis/degradation pathway of these sphingolipids are associated with sphingolipidoses, which among other features also can show retinal degeneration (Garanto et al., 2013). Furthermore, ceramides are involved in oxidative stress and apoptosis, and it has been shown that CERKL protects from induced oxidative stress *in vitro* (Tuson et al., 2009). CERKL has been shown to localize in mouse cone photoreceptors and ganglion cells (Garanto et al., 2011, 2012; Vekslin and Ben-Yosef, 2010), and *in vitro* assays suggest that CERKL interacts with GUCA1A and GUCA1B (Nevet et al., 2012). Morpholino oligonucleotide injected zebrafish showed abnormal eye development with lamination defects, photoreceptor outer segment developmental abnormalities, reduced eye size and increased apoptosis of retinal cells, suggesting that CERKL is relevant for survival and protection of retinal tissue (Riera et al., 2013).

In humans, *PITPNM3* is shown to be expressed in the brain, spleen and ovary, although the analysis of expressed sequence tags predicted a wider expression pattern (Kohn et al., 2007; Lev et al., 1999). The zebrafish homologue of *PITPNM3* is predominantly expressed in the inner segments of cone photoreceptor cells (Elagin et al., 2000). In the rat expression however is seen throughout the retina in all cell layers including the inner segment and outer plexiform layers containing photoreceptor terminals with predominant expression in Müller cells (Tian and Lev, 2002). Members of the PITP-family play a role in multiple processes such as phospholipase C-mediated inositol signaling, ATP-dependent $Ca^{2+}$-activated secretion, lipid metabolism, trafficking from Golgi-membranes and exocytosis (Lev, 2004). The importance of a PIT domain was observed in rdgB mutant flies with light-dependent retinal degeneration rescued by transfer of the PIT-domain (Milligan et al., 1997). The signaling pathway for mammalian PITPNM3 is not completely understood (Kohn et al., 2007).

Extracellular matrix components or plasma membrane components proteins encoded by *BEST1*, *C1QTNF5*, *EFEMP1*, *HMCN1* and *TIMP3*, are expressed in the RPE. A heterozygous p.Ser163Arg variant in *C1QTNF5*, encoding the short-chain collagen CTRP5, causes late-onset macular degeneration. It was proposed that mutant CTRP5, which is secreted by the RPE, is unable to fulfill its adhesive property between the RPE and Bruch's membrane (Hayward et al., 2003). Although the functions of fibulin-3 (*EFEMP1*) and fibulin-6 (*HMCN1*) are unknown, interaction of fibulin-3 with TIMP3, an inhibitor of matrix metalloproteinases, has been demonstrated. *TIMP3* mutations are a cause of Sorsby maculopathy, a drusen associated dystrophy (Klenotic et al., 2004). It has been hypothesized that misfolding and accumulation of mutant fibulin-3 underlies drusen formation although the protein itself is not a major component of the drusen (Marmorstein et al., 2002).

Another component of the rod and cone photoreceptor extracellular matrix is IMPG1 (a.k.a. SPACR). Although its exact function is unknown, IMPG1 could be important in RPE-photoreceptor attachment (Acharya et al., 1998). Alternatively, mutations in *IMPG1* lead to impaired metabolism of the photoreceptors and/or RPE resulting in an accumulation of vitelliform deposits in the retina (Manes et al., 2013).

RP1L1 was shown to closely interact with RP1 via its two DCX domains, which functions in the assembly and stabilization of axonemal microtubules (Yamashita et al., 2009). Whereas autosomal recessive and dominant mutations in *RP1* lead to rod photoreceptor dysfunction, autosomal recessive variants in *RP1L1* lead to late-onset RP; heterozygous variants are associated with AD occult macular dystrophy (Akahori et al., 2010; Park et al., 2010; Sisk et al., 2010).

## 4. Mammalian models for cone disorders

### 4.1. Mouse models for cone disorders

To learn more about the etiology, progression, underlying disease mechanisms, and to explore treatment of CDs, rodent animal models have been used. Rodent models have significantly improved our knowledge of retinal diseases as the disease process can be followed entirely, and invasive studies can be done. The life span and development of these animals permit a degenerative process to be followed in a matter of weeks to months also enabling thereby the effects of treatment to be monitored. The largest disadvantage of the mouse as a model for CD is the lack of the cone-dominated region or macula in mice, as well as the fact that humans have genes encoding three different types of cones (long, middle and short wavelength), whereas the mouse only contains cones sensitive for middle and short wavelengths (Bridges, 1959). Therefore, retinal phenotypes may differ significantly between mice and humans. In some cases, mice indeed do not mimic the human phenotype, as is the case for the *Adam9* (Weskamp et al., 2002), *Cerkl* (Garanto et al., 2012), *Gcap1* and *Gcap2* (Howes et al., 2002; Makino et al., 2008) mutant mice, or have not been described in detail for genes like *CDHR1*, *GUCY2D* and *RIMS1*. Secondly, the eye of the mouse differs in size and anatomy from humans hindering the development of gene delivery approaches that are suitable in human. Finally, the relatively short life span of a mouse can limit the relevance of the model. The ability to genetically modify mice has increased in the past decades. Besides genetic modification, a number of spontaneous and chemically- induced models have been identified. In Table 1, 42 genes are listed that are associated with non-syndromic CDs. Naturally occurring or generated mouse models are available for 31/42 (74%) CD-associated genes, including 33 knockouts, 14 knock-ins, two knockdowns, eight reporter models, three chemically induced, two targeted, two trapped, one floxed and 10 spontaneous mouse models (Table 2). For 10 of the CD associated genes, no mouse model is available. This is also true for the *EYS* gene, which represents the only CD-associated gene that is absent in the mouse (Abd El-Aziz et al., 2008; Collin et al., 2008). To

**Table 3**
Non-syndromic cone disorder genes, their human open reading frame sizes, the mouse model names, synonyms, and the retinal phenotype description.

| Gene | aa | ORF (bp) | Model name[b] | Synonym[b] | Retinal phenotype description[b, c] |
|---|---|---|---|---|---|
| *ABCA4* | 2273 | 6,819[a] | tm1Ght, tm1Kpal | Abcr$^{-}$, Abca4$^{-}$ | Delayed rod dark adaptation. Model for juvenile macular degeneration |
| *ADAM9* | 819 | 2457 | tm1Bbl | mdc9$^{-}$ | No retinal phenotype |
| *AIPL1* | 384 | 1152 | tm1Mad, tm1Tili, tm1Visu | Aipl1$^{-}$, Aipl1$^{h}$ | Complete retinal degeneration and lack of ERG responses. Hypomorphic mutants display less severe retinal degeneration and impaired ERG responses |
| *BEST1* | 605 | 1815 | tm1.1Amar, tm1Lmar | Best1$^{W93C}$, Vmd2$^{-}$ | Altered eye electrophysiology |
| *C1QTNF5* | 243 | 3914 | Gt(OST522586)Lex, tm1.1Geno, tm1.1Itl, tm1.1(KOMP)Vlcg, rd6, rdx | C1qtnf5$^{Ser163Arg}$, C1qtnf5$^{S163R}$, C1qtnf5$^{tm1.1Igl}$, CTRP5$^{S163R}$, Mfrp$^{174delG}$ | Increased retina vasculature leakage, retinal degeneration, and features of late-onset macular degeneration Mice homozygous for the same knock-in generated by a different group are normal |
| *C8orf37* | 208 | 624 | – | – | – |
| *CACNA1F* | 1977 | 5,931[a] | tm1.1Sdie, tm1Ntbh, nob2 | Cav1.4$^{nob2}$, nob2, Cacna1f$^{deltaEx14-17}$, Cacna1f$^{G305x}$ | Impaired eye electrophysiology, abnormal retinal neuronal layer, bipolar cell, and horizontal cell morphology, and impaired retinal synapse morphology |
| *CACNA2D4* | 1137 | 3411 | lob | – | Severe loss of retinal signaling associated with abnormal photoreceptor ribbon synapses and cone-rod dysfunction |
| *CDHR1* | 859 | 2577 | tm1(cre)Kbal, tm1Nat | Pcdh21/Cre, prCAD$^{-}$ | Progressive degeneration of retinal photoreceptor cells and a slight reduction in light responses |
| *CERKL* | 558 | 1674 | tm1.1Geno | – | No photoreceptor phenotype, retinal apoptosis and decreased amplitudes and increased implicit time of oscillatory potentials |
| *CNGA3* | 676 | 2028 | tm1Biel, cpfl5 | CNG3$^{-}$ | Progressive loss of cone photoreceptor cells |
| *CNGB3* | 809 | 2427 | tm1Dgen | – | Cone degeneration and decreased photopic response |
| *CRX* | 299 | 897 | tm1Clc, tvrm65 | Crx– | A lack of photoreceptor outer segments and rod and cone activity, reduced expression of several photoreceptor- and pineal-specific genes, and altered circadian behavior |
| *EFEMP1* | 494 | 1482 | tm1Eap, tm1Lex, tm1Lmar, tm2Lmar | Efemp1$^{R345W}$, Efemp1$^{ki}$ | Knock-out mice display a normal phenotype. Homozygous R345W mice develop deposits below the retinal pigment epithelium |
| *ELOVL4* | 315 | 945 | tm1Kzh, tm1Rayy, tm1Sie, tm1Wked, tm2Kzh | Elovl4$^{del}$, E_mut$^{-}$, Elovl4$^{270x}$ | Knock-out mice die before or around birth. Mice heterozygous for a null allele breed poorly and display mild retinal abnormalities |
| *EYS* | 3144 | 9,432[a] | – | – | – |
| *FSCN2* | 517 | 1551 | ahl8, tm1Sykk, tm2Sykk | Fscn2$^{R109H}$, Fscn2$^{p}$ neo(−), Fscn2$^{g}$ neo$^{-}$ | Retinal generation with structural abnormalities of the outer segment and depressed rod and cone ERGs that worsen with age |
| *GNAT2* | 354 | 1062 | cpfl3, c.518A > G | – | Progressive degeneration of photoreceptors and normal ERG responses |
| *GUCA1A* | 202 | 606 | tm1.1Hunt, tm1Itl, tm1Jnc | COD3, GCAP$^{-}$, GCAP1$^{-}$GCAP2$^{-}$, GCAPs$^{-}$ | Photoreceptor degeneration and loss of cone and rod function |
| *GUCA1B* | 201 | 603 | tm1Amd, tm1Jnc | GCAP$^{-}$, GCAP1$^{-}$GCAP2$^{-}$, GCAPs$^{-}$ | Abnormal rod electrophysiology |
| *GUCY2D* | 1103 | 3309 | tm1Mom, tm1Sdm | GCD-ITL, Gucy2d$^{-}$ | Not analyzed for retinal phenotype |
| *HMCN1* | 5636 | 16,908[a] | – | – | – |
| *IMPG1* | 798 | 2394 | – | – | – |
| *KCNV2* | 545 | 1635 | – | – | – |
| *NR2E3* | 410 | 1230 | tm1Dgen, rd7 | – | Rosettes and a reduced number of nuclei in the retinal outer nuclear layer |
| *OPN1LW* | 364 | 1092 | – | – | – |
| *OPN1MW* | 364 | 1092 | tm1(OPN1LW)Nat | Opn1mw$^{R}$, R | A knock-in allele encoding a derivative of the human red cone pigment results in hemizygous male and homozygous female mice with a ~45-nm red shift in retinal sensitivity |
| *PDE6C* | 858 | 2574 | cpfl1 | – | Abnormal cone photoreceptor function |
| *PDE6H* | 84 | 252 | – | – | – |
| *PITPNM3* | 974 | 2922 | – | – | – |
| *PROM1* | 865 | 2595 | tm1.1(DTA)Toko, tm1Pec, tm1(cre/ERT2)Gilb, tm1Rafi | Prom1$^{lacZ,DTA,}$ Prom$^{1C-L}$ | Abnormal retina morphology, vasculature, and electrophysiology |
| *PRPH2* | 346 | 1038 | tm1Nmc, rd2, Nmf193 | Prph2$^{delta307}$, rds-307, Prph2$^{Rds}$, Rd-2, rds, rds-, Rds, Rds$^{Rd2}$ | Slow retinal degeneration with thinning and loss of the outer nuclear layer, loss of photoreceptor outer segments, and increased numbers of Müller cells |
| *RAB28* | 221 | 663 | | | – |
| *RAX2/QRX* | 184 | 552 | | | – |
| *RIMS1* | 1692 | 5,076[a] | tm1Sud, tm3.1Sud, tm2Sud, tm3Sud | RIM1alpha$^{-}$, RIM1alphabeta$^{-}$, RIM1 S413A-KI, fRIM1, RIM1alphabeta$^{floxed}$ | No retinal phenotype |
| *RP1L1* | 2401 | 7,203[a] | tm1Jnz | | Knock-out mice exhibit retinal photoreceptor abnormalities, including scattered outer segment disorganization, reduced ERG amplitudes, and progressive retinal rod cell degeneration |

(*continued on next page*)

**Table 3** (*continued*)

| Gene | aa | ORF (bp) | Model name[b] | Synonym[b] | Retinal phenotype description[b, c] |
|---|---|---|---|---|---|
| *RPGR* | 1152 | 3456 | tm1Tili, tm1Wbrg, rd9 | RPGR$^{-}$, Rpgrdelta$^{exon4}$ | Ectopic location of cone opsins, reduced levels of rhodopsin in rod cells, and partial degeneration of both cone and rod photoreceptors by 2–6 months of age |
| *RPGRIP1* | 1286 | 3858 | tm1Tili, nmf247 | RPGRIP$^{-}$ | Photoreceptor cell dysmorphology. By 3 months of age mutant animals show near complete loss of photoreceptor cells |
| *SEMA4A* | 761 | 2283 | tm1Kik, Gt(OST393408)Lex | Sema4a$^{Gt22Lex}$ | Severe retinal degeneration with reduced retinal vessels, depigmentation and dysfunction of both rod and cone photoreceptors |
| *TIMP3* | 212 | 636 | tm1.1(KOMP)Vlcg, tm1Hest, tm1(KOMP)Vlcg, tm1Osya, tm1Rkho, tm1Web | timp-3$^{-}$, Timp-3-null, Timp3$^{S156C}$ | Knock-out mice die prematurely with lethargy, ruffled hair, and a hunched posture, displaying impaired bronchiole branching, reduced alveologenesis and abnormal mammary gland involution. S156C knock-ins provide a mouse model for Sorsby fundus dystrophy |
| *TULP1* | 542 | 1626 | tm1Pjn | Tulp1$^{-}$ | Retinal degeneration |
| *UNC119* | 240 | 720 | tm1Gina | | Retinal degeneration characterized by thinning of the outer nuclear layer of the retinal that is visible at 6 months and progresses rapidly after 17 months to end-stage by 26 months |

[a] ORF sizes are larger than 4.7 kb and therefore not suitable targets for adeno-associated virus-therapy.
[b] Data collected from MGI Jackson lab.
[c] Phenotype among different models can vary.

date mouse model studies have contributed to our understanding of disease, in addition gene therapy has been successfully applied in 10 of these models (Table 1).

Compared to rod phototransduction studies in mice, studies in cones have been limited to ERG studies, mainly due to the low percentage of cones (3%) and fragility of the cone outer segments. To further study the mechanism, function and etiology of cones, mouse models were designed to increase the number of cones in the mouse retina (Fu, 1995). The Nrl knockout forces the cell fate of rod photoreceptor cells into cone-like photoreceptors (Daniele et al., 2005; Mears et al., 2001; Nikonov et al., 2005). In a second model, EGFP was expressed in mouse cones to increase detection and identification of cones (Fei and Hughes, 2001), and in the third model, rod phototransduction was blocked by a knockout of the rod transducin α-subunit (*Gnat1*$^{-/-}$) (Calvert et al., 2000).

### 4.2. Other animal models of cone disorders

Compared to small animal models like mouse or rat, larger animal models have a few advantages. Anatomically, the retinas of dogs and cats are more similar to those of humans, as they have a cone-rich area, which is similar to the macula. Chicken have a cone-rich retina in which cones outnumber the rods at 6:1, while in humans the cone-rod ratio is 1:20. Chicken cones have a higher density in the rod-free region analogous to the human fovea (Bruhn and Cepko, 1996; Thanos and Mey, 2001). Chicken also have retinal glia (Müller) cells, a fully sequenced genome and relatively low maintenance costs. The size of the eyes makes the chick especially suitable for experimental manipulation (Cebulla et al., 2012). Next to the cone-rich retina of chickens, pigs are also equipped with a cone-dominated retina. Although no naturally occurring cone disease related defects have been discovered in pigs, Mussolino et al. (2011) showed that the porcine retina is suitable for developing novel AAV-mediated therapies using AAV2/5 or AAV2/8 to transduce both RPE and photoreceptor cells without safety issues (Mussolino et al., 2011).

*Xenopus laevis* is an ideal animal model to study the role of the interphotoreceptor matrix in RPE-photoreceptor interactions (Garlipp and Gonzalez-Fernandez, 2013), due to the fact that 30% of its photoreceptors are cones, and because they have relatively large photoreceptors, which is helpful in cellular, transgenic and imaging studies (Moritz et al., 1999). The *Xenopus* genome is available (Hellsten et al., 2010; James-Zorn et al., 2013) and strategies using morpholino oligonucleotide antisense knock-down offer a powerful reverse genetics approach (Gonzalez-Fernandez et al., 2011).

Currently there are only few large animal models which are suitable for investigating inherited CDs. Canine models with gene mutations in *ADAM9, BEST1, CNGB3*, *RPGR* and *RPGRIP1*, are currently used to develop therapy models. In three dog models the retinal degeneration was successfully treated (Beltran et al., 2012; Komáromy et al., 2010; Lhériteau et al., 2013) (Table 2). A great potential in the discovery of novel canine models for CDs resides in the several hundred dog breeds affected by progressive retinal atrophy with a currently unidentified gene defect (RWJ Collin (Nijmegen), K. Stieger (Giessen) and H. Lohi, (Helsinki), personal communications).

Other large animal models for CD are sheep, which carry a spontaneous nonsense mutation in *CNGA3* to investigate ACHM (Reicher et al., 2010), and a feline model with a single nucleotide deletion in *CRX* (Menotti-Raymond et al., 2010).

## 5. Therapeutics for cone disorders

Currently, to (partially) restore gene function in CDs, several strategies are being applied with the use of animal models. A specific vector is always necessary to deliver the target gene into the cell, as naked DNA is not able to enter the cell efficiently.

The success of retinal gene augmentation is dependent on the vector and delivery method. Vector choice depends on the size of the cDNA of the relevant gene, the type of targeted cells, stability of expression and immunogenicity. Although the eye is a complex organ, the advantages of the eye are its immune privileged nature, its small size, accessibility, and functional assessment.

Adeno-associated viruses (AAVs) have been successfully used as vectors for gene therapy. AAVs enable the incorporation of a healthy copy of the gene that is defective in the patient. An advantage of this technology is its low toxicity due to the absence of the original viral coding sequences as shown in its application in muscle, brain, liver, lung, RPE and the neural retina (Travis et al., 2007). A restriction of this technology is its limited cargo size, only enabling the transport of cDNAs of genes up to 4.7 kb, and therefore potentially are able to accommodate 36 of the 42 CD-associated genes (see Table 3). Putative immune responses to the viral capsid may also limit recurrent treatments.

In *Cnga3*$^{-/-}$ mice, AAV5-mediated gene replacement therapy restored cone function and thereby visual processing. The non-functional cones were capable of producing photoreceptor responses and transferring the generated signals to the bipolar cells. Treated mice showed normalized levels of cGMP in the cones as well as a delayed cone cell death, and the inflammatory response typically seen in retinal degeneration was reduced (Michalakis et al., 2005, 2010). Treatment was successful when the subretinal injections were performed in 1- and/or 3-month-old knockout mice, and the therapeutic effect was still present after 8 months. Improved cone function using the AAV5 vector was confirmed in another *Cnga3* study (Pang et al., 2012).

A similar strategy was used to treat a deficiency of *CNGB3*-associated ACHM. In two canine models it was shown that long-term restoration of cone function and diurnal vision could be achieved by subretinal delivery of AAV5 vectors expressing human *CNGB3* under the control of a 2.1 kb human red cone opsin promoter (Komáromy et al., 2010). The same authors were also able to circumvent the unexplained reduction in therapeutic effect after 54 weeks in dogs by administration of ciliary neurotrophic factor (CNTF). Administration of this neuroprotective and axogenic factor for retinal ganglion cells however led to immature photoreceptors with shorter outer segments and reduced gene expression. This effect was reversible with photoreceptors returning to expected developmental maturity and function thereafter. This approach to photoreceptor replacement enabled successful gene therapy in dogs up to 42 months (Komáromy et al., 2013). As the treatment with CNTF in the dog model showed measurable phenotypic improvements, the first clinical trials in humans with *CNGB3* mutations using intraocular implants releasing CNTF are currently ongoing (http://clinicaltrials.gov/ct2/show/NCT01648452?term=achromatopsia&rank=1).

Long-term improvement of retinal function was also found in a study using AAV8 mediated therapy. In both M- and S-cones, the β-subunit of the CNG-channel could be detected after subretinal AAV8 vector injection. In addition, increased levels of the α-subunit of the CNG-channel were found, reduced cone death, improved density and a positive effect of the outer segment structure of the cone and subcellular compartmentalization of the cone opsins (Carvalho et al., 2011).

The current status of treatment of *CNGA3* and *-B3*-associated channelopathies in animal models have shown solid and encouraging results and hold great promises for future treatment of patients with similar defects (Schön et al., 2013). A human Phase 1 trial for patients with *CNGA3* mutations is being developed (B. Wissinger, personal communication). The human situation however may be more complex and limitations may occur due to the age-dependent results for *CNGB3*, which argues to treat only younger patients. Possibly, the same or a similar treatment with CNTF could create treatment opportunities for older patients too.

In *GNAT2* knockout mice, AAV-mediated therapy has also proven to be successful (Alexander et al., 2007). However, for those genes in which AAV-mediated therapy is not feasible due to their size, other strategies need to be developed. The *ABCA4* open reading frame (ORF) measures 6.8 kb and therefore an alternative approach using the nanoparticle (a.k.a. non-virus) mediated therapy has been applied. Compacted DNA nanoparticles were constructed with the human *ABCA4* cDNA and the IRBP or mouse opsin promotor. Nanoparticles have a high transfection efficiency in post-mitotic cells, are biodegradable, and cause minimal toxicity even after repeated doses to the eye, lung and brain (Han et al., 2012, and refs therein). This non-viral approach has been performed subretinally on *Abca4*$^{-/-}$ mice. *ABCA4* transgene expression was identified up to 8 months after injection resulting in significant structural and functional rescue of Stargardt disease, with improved dark adaptation recovery and reduced lipofuscin granules in the RPE (Han et al., 2012). These results suggest that nanoparticle-mediated gene delivery has the potential to target many diseases caused by mutations in large genes. Alternatively, lentiviral vectors can be used (Kumar et al., 2001) which can accommodate cDNAs up to ~10 kb. This strategy is currently also used for the development of *ABCA4* gene therapy. Equine infectious anemia virus (EIAV)-derived lentiviral vectors expressing either the human *ABCA4* gene or the *LacZ* reporter gene under the control of the constitutive (CMV) or photoreceptor-specific (Rho) promoters were subretinally injected in *Abca4*$^{-/-}$ mice. High transduction efficiency of rod and cone photoreceptors and a significant reduction of accumulation of A2E were observed in these mice suggesting the potential of lentiviral gene therapy in treating *ABCA4*-associated maculopathies (Kong et al., 2008). Similar results in rabbit and macaque were shown in the study by Binley et al. (2013). In this study "StarGen" was used, a lentivirus vector containing a normal copy of the human *ABCA4* gene, which is currently in a Phase I/IIa stage with individuals affected with STGD1 (Binley et al., 2013) (http://clinicaltrials.gov/ct2/show/NCT01367444?term=abca4&rank=6).

One of the challenges for gene therapy is the limited time window to achieve a successful treatment outcome. Some CDs exhibit a fast progression of disease and therefore the window of opportunity of treatment is smaller compared to slow or non-progressive phenotypes. Hence, treatment opportunities may expand beyond our initial expectations now that SD-OCT and adaptive optics may determine the viability of the cone cell bodies, which have shown the capability of being reactivated in mice (Busskamp et al., 2010). In persons with very early onset CD, gene augmentation therapy however should ideally start as early as possible.

## 6. Future perspectives

### 6.1. Identification of CD-associated genes

WES, combined with homozygosity mapping or linkage analysis, has proven successful in the discovery of novel retinal disease genes (Estrada-Cuzcano et al., 2012; Roosing et al., 2013; Zeitz et al., 2013). In a recent Saudi Arabian study of predominantly AR inherited retinal dystrophies, ~80% of DNA samples analyzed using homozygosity mapping and/or WES were solved by the identification of mutations in either known or novel genes (Abu-Safieh et al., 2013). In six of 86 families with causal variants, mutations in different new genes were found. This suggests that most of the undiscovered CD genes (Fig. 3) are mutated in very low percentages of affected individuals.

In the next few years, WES and whole genome sequencing (WGS) will facilitate the identification of novel gene defects in individuals for which WES could not identify the pathologic defect. WGS can robustly identify heterozygous deletions, duplications, inversions, and intronic variants (Nishiguchi et al., 2013). However, proving causality of rare variants in candidate CD genes will be challenging, as in most cases only few family members are available for segregation analysis. This may be partially solved by testing large patient cohorts through collaborative efforts. In addition, the causality of novel variants can be tested through cellular and animal model studies.

### 6.2. Molecular diagnostics

Up to a few years ago it was not possible to, stabilize or improve impaired vision in persons with CD. With the emerging options for treatment of CD, early molecular diagnostics has become highly relevant. In addition, early molecular diagnosis may be important

in cases in which genetic defects are associated with extra-ocular features, some of which may develop later in life and be amenable to pre-symptomatic management, e.g. in nephronophthisis, in which the kidney is involved.

For some CD's (e.g. *ABCA4* in STGD1, *CNGB3* and *CNGA3* in ACHM, and *KCNV2* in CD with supranormal rod response), Sanger sequencing of one or a few genes will identify the causal variants in a significant proportion of cases. For the remaining phenotypes, novel high-throughput sequencing approaches may need to be used, in which either all CD-associated genes are analyzed or all human genes are analyzed in a single experiment by WES. WES may reveal the causal variants in elusive genes in 7.4–79% of cases, depending on the clinical subtype (Fig. 3). However causal variants may be missed due to the difficulty sequencing exons with a high GC content. To identify the non-exonic (deep-intronic) variants and structural variations, WGS and transcriptome analysis can be used.

### 6.3. Transcriptomics

Introns are riddled with rare variants that theoretically can have an impact on RNA splicing if they are situated in an intronic splice enhancer or inhibitor site, or if they increase the splicing potential of a cryptic splice site, leading to the transcription of an aberrant mRNA product. The latter was recently shown for *ABCA4*, as a few deep intronic variants led to aberrant splicing in persons with STGD1 (Braun et al., 2013). Farkas et al. (2013) identified 79,915 novel alternative splice events and more than one hundred novel genes expressed in human retinal tissue, which will aid the difficult task of discriminating benign from causal variants. 15–36% of the novel splicing events resulted in mRNAs with an open reading frame (Farkas et al., 2013). This demonstrates that the retinal transcriptome is more complicated than previously thought, and the knowledge of naturally occurring splice events may aid the interpretation of RNA analysis of known retinal disease genes in patients. Importantly, only approximately 35% of the genes involved in retinal dystrophies are expressed at high enough levels in lymphoblastoid cells to scrutinize the transcriptome from an individual's blood sample (K. Neveling, unpublished data).

Alternatively, photoreceptor precursor cells can be differentiated from patient's keratinocytes through generation of induced pluripotent stem cells (iPSC) (Tucker et al., 2013). iPSCs can be generated from adult somatic cells by expressing a set of transcription factors, and subsequently can be differentiated into retinal cells (Mekala et al., 2013, and refs therein). RNA analysis of such cells is likely to more closely mimic the situation in the diseased tissue, enabling the detection of splice defects that might not be detectable in lymphoblastoid cells. The generation of a homogeneous population of fully differentiated cells remains a challenge, in particular regarding the neural retina.

### 6.4. Alternative cone rescue strategies

A great promise in treating early onset degenerative diseases, like CD, are cell replacement therapies using retinal progenitor cells derived from embryonic stem cells (ESCs) or iPSCs. These cells could be very valuable in cell-based therapies. Proof of concept using mouse retinal progenitor cells harvested in a specific developmental time window (postnatal day 4–8) was obtained recently (Gonzalez-Cordero et al., 2013). It is critical to transplant a sufficient number of cells that can populate a significant fraction of the diseased retina. The transplanted cells differentiated into adult photoreceptor cells, were positioned at the correct location, and formed connections with bipolar cells (Gonzalez-Cordero et al., 2013; MacLaren et al., 2006; Pearson et al., 2010; West et al., 2008), demonstrating the potential of this approach to rescue retinal function in future clinical trials.

## 7. Conclusions

The early aim of CD research has been the identification of the genetic bases of CD. Advances in this field compounded by technologies such as WES and WGS technologies have created a new era for molecular diagnostics in CD. In the next few years, the remaining genetic causes of CD will most likely be elucidated representing an enormous achievement. The prevalence of novel genetic defects however will be very low, and in particular regarding rare missense variants, functional modeling of their effects in animal models or cellular systems will be crucial to understand their mode of action. The ultimate aim remains the development of therapies that rescue cone photoreceptors. For the 31/42 CD-associated genes in which mammalian models are available, 14 have successfully been used for gene augmentation studies and a few human trials are underway. Nevertheless, large naturally occurring animal models, In particular canine models with progressive retinal atrophy, need to be identified for CDs as they can more closely mimic the human diseases and are a more relevant model with respect to the development of gene therapy. The rescue of cone photoreceptors not only is important to treat cone dysfunctions, but also will be crucial to maintain vision in rod-dominated diseases.

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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.2014.05.001.

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