Cone Disorders

S. Bournoutou

Abstract

Cone disorders (CDs) are a group of inherited diseases of the cone, or cone and rod photoreceptors,or retinal pigment epithelium,that are associated with various forms of stationary or progressive visual impairment.

They include achromatopsia (ACHM), cone dystrophy (COD),cone-rod dystrophy (CRD), color vision impairment, Stargardt disease (STGD) and other maculopathies.Non-syndromic inherited CDs are pathogenetically associated with forty-two genes.

Cone disorders present with a variety of clinical findings, including reduced visual acuity, photophobia and abnormal color vision.

The main diagnostic tools that can be used, except for the usual tests of visual acuity, colour vision and visual field testing are full-field electroretinogam(ffERG), fundus and near-infrared autofluorescence, optical coherence tomography(OCT) and spectral-domain optical coherence tomography(SD-OCT).

As far as cone disorders' treatment is concerned, gene therapy,molecular diagnosis and cell replacement therapies are useful tools,whereas there isn't currently any specific therapeutic plan preventing the evolution of cone and cone-rod dystrophies.The visual prognosis is generally poor, even though some treatment choices have been referred, including red filters and intravitreal injection of autologous bone marrow-derived mononuclear cells.

Key words: cone disorders, genetic mutations, syndromic cone disorders, photophobia, scotoma, electroretinogram, spectral-domain optical coherence tomography, gene therapy,molecular diagnostics.

General Hospital of Naousa, Imathia, Greece

Corresponding author: Sotiria K. Bournoutou
E-mail: sotiriabou@yahoo.gr

CAUSES-PATHOFYSIOLOGY

Hereditary cone disorders (CDs) constitute a large clinically heterogeneous group of diseases in which the cone photoreceptors or retinal pigment epithelium (RPE) are primarily affected and include achromatopsia (ACHM), cone dystrophy (COD),cone-rod dystrophy (CRD), color vision impairment, Stargardt disease (STGD) and other maculopathies. They can follow all modes of Mendelian inheritance, that means autosomal recessive(AR), autosomal dominant (AD) and X-linked (XL) and can present as non-syndromic and syndromic forms.

Forty-two genes have been implicated in non-syndromic inherited CDs. 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, photoreceptor development, ciliary transport, disk membrane morphogenesis and synaptic transport. In general, the phototransduction cascade (the processes involved in the conversion of light into an electric neural signal) (**FIGURE 1**), takes place in the outer segments of the rod and cone photoreceptors, the structure of which is depicted

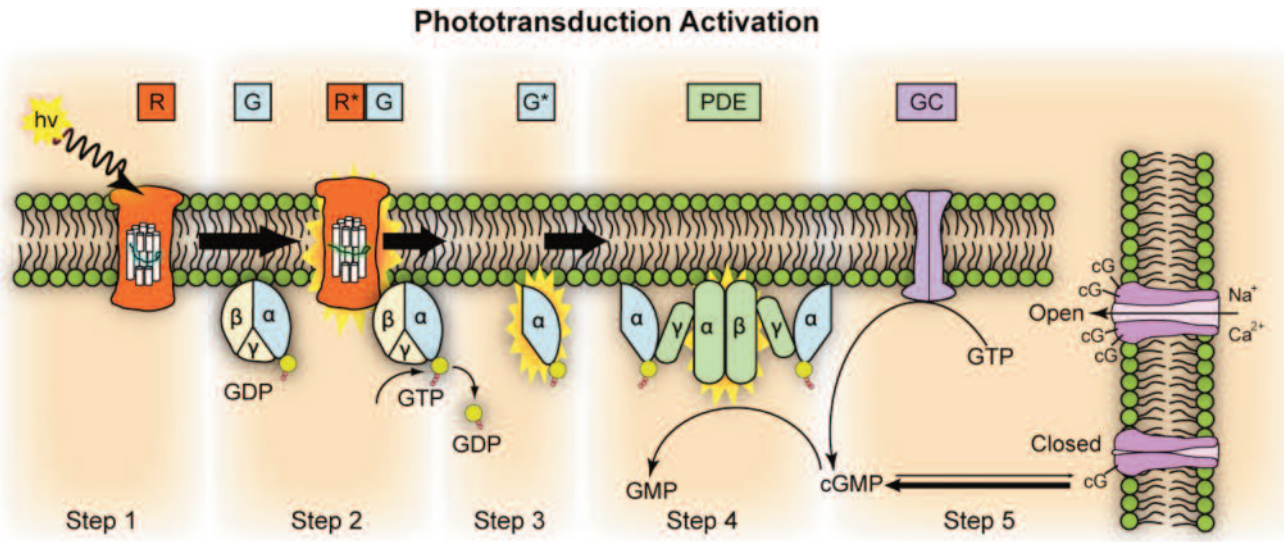

FIGURE 1: Representation of molecular steps in photoactivation. Depicted is an outer membrane disk in a rod. Step 1: Incident photon (hv) is absorbed and activates a rhodopsin by conformational change in the disk membrane to R. Step 2: Next, R* makes repeated contacts with transducin molecules, catalyzing its activation to G* by the release of bound GDP in exchange for cytoplasmic GTP, which expels its β and γ subunits. Step 3: G* binds inhibitory γ subunits of the phosphodiesterase (PDE) activating its α and β subunits. Step 4: Activated PDE hydrolyzes cGMP. Step 5: Guanylyl cyclase (GC) synthesizes cGMP, the second messenger in the phototransduction cascade. Reduced levels of cytosolic cGMP cause cyclic nucleotide gated channels to close preventing further influx of Na+ and Ca2+.*

below (**FIGURE 2**) and defects in various components of it can lead to CD,that means the red and green opsins, the cone transducin a subunit, the cone phosphodiesterase a′ and γ subunits, the cone-specific cGMP-gated a and β subunits, the retinal guanylyl cyclase-1 and the voltage-gated potassium channel subunit.

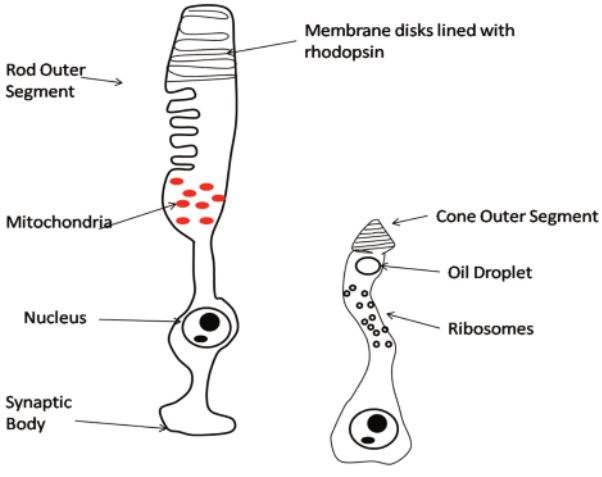

FIGURE 2: Structure of rod and cone photoreceptors.

It is estimated that AR/isolated CDs are found in 76.7% of cases, AD inheritance in 21.6% of cases and Xlinked inheritance in the remaining 1.4%.

Regarding **achromatopsia** (ACHM), it affects 1:40,000 individuals and is exclusively inherited in an AR manner. Its genetic etiology has been almost completely unraveled. Mutations in five genes (CNGB3, CNGA3, PDE6C, GNAT2, PDE6H, with the largest contribution by CNGB3, followed by CNGA3)are associated with ACHM and explain 93% of cases in the Caucasian population. All causal genes encode proteins essential in the cone phototransduction cascade.[1,2,3,4,5]

As far as **cone dystrophies** is concerned,they are an heterogeneous group of inherited disorders, resulting in dysfunction of the cone photoreceptors.[6] Apart from the cone, the cone-rod dystrophies belong also to the genetically and phenotypically very heterogeneous group of retinal degenerations.

According to the disease course, both kind of dystrophies can be divided into stationary and progressive disorders or by the genetic mode of inheritance into autosomal-recessive, autosomal-dominant and X-linked traits. To date, seven,mainly, genes for autosomal-recessive and nine for autosomal-dominant inherited forms of cone and cone-

rod dystrophy, as well as two underlying genes on the X chromosome, have been identified.[7]

As far as the **stationary cone dystrophies** is concerned, they have received more attention, so our knowledge of their molecular genetic, psychophysical and clinical characteristics is better developed. On the other hand, various methods of classification have been proposed for the progressive cone dystrophies, but none of them is completely satisfactory, primarily because the underlying disease mechanisms are poorly understood.[6]

A few years ago, however, a linkage was demonstrated between **autosomal dominant progressive cone dystrophy** (CORD5) and genetic markers on chromosome 17p12-p13 in a five-generation Swedish family.This survey was later continued by another group of scientists, as the gene causing the disease was not identified with the previous research. Thus, a mutation (p.Q626H) in the phosphatidylinositol transfer (PIT) membrane-associated protein (PITPNM3) (MIM 608921) was found in two Swedish families. PITPNM3, known as a human homologue of the Drosophila retinal degeneration B (rdgB), lacks the N-terminal PIT domain needed for transport of phospholipids, renewal of photoreceptors membrane and providing the electroretinogram (ERG) response to light. In that study, the mutation causing CORD5 is located in the C-terminal region interacting with a member of nonreceptor protein tyrosine kinases, PYK2. The finding on the first mutation in the human homologue of Drosophila rdgB indicates novel pathways and a potential important role of the PITPNM3 in mammalian phototransduction.[8,9]

Additionally,it was found that CORD5 is characterized by predominant cone dysfunction without signs of general involvement of the retinal pigment epithelium. The rod system also seems to be unaffected.In that way, CORD5 is different from other autosomal dominant CORDs where rod involvement is present to some degree in a late phase of the disease.[10]

Another gene associated with cone dystrophy is KCNV2, which encodes a voltage-gated potassium channel subunit in cone and rod photoreceptors and mutations cause the visual disorder 'COD with supranormal rod responses on ERG'.[11]

Regarding **cone rod dystrophies** (CRDs), their prevalence is 1/40,000 and they are inherited retinal dystrophies that belong to the group of pigmentary retinopathies. The four major causative genes associated with the pathogenesis of CRDs are ABCA4 (which causes Stargardt disease and also 30 to 60% of autosomal recessive CRDs), CRX and GUCY2D (which are responsible for many reported cases of autosomal dominant CRDs) and RPGR (which causes an undetermined percentage of X-linked CRDs).[12] 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.[13] GUCY2D mutations have been reported as a frequent cause for both autosomal dominant cone and cone-rod dystrophies [CORD6 (MIM 601777)]. Lately however, a novel recessive GUCY2D mutation in a family with autosomal recessive cone-rod dystrophy was identified, which is the first recessive GUCY2D mutation associated with an autosomal recessive form of CORD. More specifically, a sole homozygosity region on chromosome 17p13.3 was identified and GUCY2D, which encodes retina-specific guanylyl cyclase (retGC) and resides in this region, was selected as a strong candidate gene, due to its correlation with the dominant forms of cone and cone-rod dystrophies. Previously, recessive GUCY2D mutations have been associated with LCA (Leber's congenital amaurosis), which is the most severe form of inherited retinopathies and a common cause of childhood blindness. Therefore, that study linked for the first time a recessive GUCY2D mutation with a new phenotype, CORD. In this gene, CORD has been associated with only dominant mutations so far.[14,15] It is also possible that highly deleterious genetic mutations that otherwise cause Retinitis Pigmentosa or macular dystrophy may also lead to CRDs.[12]

Regarding the genetic mutations related to rod-cone dystrophies, many genes have been implicated in the pathophysiology of RCD, but several others remain to be identified.

Among the most known, is the RPE65 gene, where mutations on both alleles were found to be associated with early-onset severe rod–cone dystrophy. The RPE65 gene encodes a protein located in the retinal pigment epithelium called 'retinal pigment epithelium-specific protein 65kDa' which is involved in the conversion of all-trans retinol to 11-cis retinal during phototransduction and is then used in visual pigment regeneration in photoreceptor cells.[16]

A recent research also showed another mutation in a ciliary gene, which encodes the centrosomal protein kizuna (KIZ) and is associated with autosomal-recessive rod-cone dystrophy.[17]

A mutation in the tyrosine kinase receptor gene MERTK was also connected to severe rod-cone dystrophy.[18]

Regarding the **color vision impairment**, its most frequent form is dichromacy, which is observed in ~6% of males and 0.4% of females.

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. Therefore humans have generally trichromatic color perception. 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. In most cases, protanopes and deuteranopes carry deletions of the red (OPN1LW) or green (OPN1MW) pigment genes.[19,20]

Blue cone monochromatism (BCM) belongs also to the color vision disorders and especially XL-BCM is very rare with a prevalence of 1:100,000 individuals.[21] The red and green cone opsins are absent which can be explained by deletions in the locus control region, the region regulating transcription of the red and green opsin genes.[22]

Bornholm eye disease, belonged also to the category of diseases characterized by color vision impairment, is an XL disease where 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 presumedly lowers the amount of functional protein.[23,24,25]

A rare condition included also to diseases with color vision impairment is **oligocone trichromacy** (OT),where 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 cone disorder.[26,27]

Regarding the **maculopathies, Stargardt disease** (STGD1) is the most prevalent inherited AR juvenile retinal dystrophy, with an estimated frequency of ~1:10,000, whereas fundus flavimaculatus is a largely overlapping phenotype with a later onset, slower progression and more widespread distribution of flecks.

As already referred, STGD1is associated with ABCA4 gene. More specifically, a combination of a mild and a severe, or two moderately severe mutations in ABCA4 gives rise to STGD1,[28,29] 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).[30]

There are also some other noteworthy maculopathies, including AD central areolar choroidal dystrophy (CACD), associated with mutations in PRPH2, "pseudo- Stargardt pattern dystrophy",[31] pattern dystrophies like butterfly-shaped pigment dystrophy (BSMD) and adult-onset foveomacular vitelliform dystrophy, as well as AD retinitis pigmentosa.[32]

The PRPH2 protein product RDS/peripherin is a photoreceptor-specific glycoprotein crucial in photoreceptor outer segment discs development and maintenance.[33,34,35] Some heterozygous variants in the gene encoding RDS (PRPH2), are associated with AD cone disorders.[36] More specifically,it has been suggested that abnormal RDS/peripherin protein leads to an altered cone and potentially altered rod outer segment structure.[37] 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 assumed to arise by disruption of the photoreceptor disc membranes.[38,39]

Best vitelliform macular dystrophy, is a member of the group of "bestrophinopathies", 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 (endoplasmic reticulum) close to the baso lateral plasma membrane, is involved in the storage-dependent Ca-influx into RPE cells.[40] 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.[41] Eventually, the overload of the RPE 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.[32,41]

As far as **AD macular dystrophies** is concerned, genes with a minor contribution to them 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), which presents with drusen accumulated beneath the retinal pigment epithelium (RPE).[42] Heterozygous mutations in RP1L1 cause occult macular degeneration, which is involved in central cone dysfunction and vision loss with a normal appearing retina.[43]

FSCN2 along with ELOVL4,another gene also involved in AD macular degeneration,[44,45] are expressed in different parts of the photoreceptor cells and are thought to have a role in maintaining their structure as well as their physiological function.

Due to mutations in TIMP3, Sorsby's fundus dystrophy is developed, that is recognized by loss of central vision from subretinal neovascularization, as well as atrophy of the choriocapillaris, RPE and retina.[46]

For seven other AD macular conditions, the underlying

genetic causes are not yet known.

In **autosomal dominant macular dystrophy with cystoid macular edema** (dominant cystoid macular dystrophy, DCMD, also known as cystoid macular dystrophy, CYMD) locus was identified on chromosome 7p15-p21,[47] but the gene has remained elusive.

North Carolina macular dystrophy (NCMD) is an AD macular dystrophy, where the corresponding locus, MCDR1, was identified on chromosome 6q16, but the gene and its presumed function are currently unknown.[48,49]

Some other cases have also been reported, including **Benign concentric annular macular dystrophy** (BCAMD), described in a Dutch family and potentially caused by a mutation in IMPG1,[50] an early-onset AD macular dystrophy (MCDR3) resembling NCMD,which has been mapped to chromosome 5,[51,52] as well as a defect in a Greek family with macular dystrophy that has been positioned on chromosome 19q (MCDR5).[53]

Several proteins involved in CD have also been identified at the connecting cilium(CC), i.e the narrow 'channel' or 'conveyer belt' connecting the inner segment with the outer segment of the photoreceptor cells. 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.[54,55]

Furthermore, a subset of genes associated with CD encode proteins that are localized in the synaptic region, including 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.[56]

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.[57]

The RIMS1 protein plays a role in basic synaptic vesicle release as well as long- and short-term pre-synaptic plasticity.[58, 59, 60]

CLINICAL MANIFESTATIONS

Regarding syndromic cone disorders, there is a minority of cases where 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, as a result, it is 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 and the most frequent cause of death is heart arrhythmia. Female carriers can show a milder phenotype, often restricted to cardiomyopathy.[61] Ophthalmic involvement has been reported in several cases, varying from macular abnormalities to CRD.[62,63] 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.[63]

Another example is the very rare **AR Alström syndrome**, 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. The 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 low visual acuity, nystagmus and occasionally photophobia , atrophic lesions of the retina and an abnormal cone-rod electroretinogram (ERG). Phenotypically this ciliopathy shows similarities to Bardet-Biedl syndrome.[64]

Jalili syndrome, caused by autosomal recessive mutations in CNNM4 that encodes a metal transporter, is characterized by cone dystrophy associated with amelogenesis imperfecta. 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 also more reduced than rod responses,[65] a condition, consistent with a retinal diagnosis of CORD.

A novel syndrome of **North Carolina-like macular dystrophy**

was also referred, presenting with progressive sensorineural hearing loss (MCDR4) and linked to chromosome 14q.[66]

As far as **achromatopsia**(ACHM) is concerned, patients with ACHM 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 also common in these patients, while the macula can have a variable appearance ranging from no abnormalities to atrophic lesions.[25]

Regarding **cone dystrophies**, they present with highly variable clinical findings and often limited retinal changes, which may lead to misdiagnosis. The major clinical features though are photophobia, reduction and sometimes loss of visual acuity, central scotoma and abnormal colour vision.[6,67] Decrease in visual acuity and colour vision can be present in adolescence or early adult life.[15]

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.[68]

There is also a subgroup of patients with cone dystrophy, where the peripheral cone system is more affected than the central cone system. In that case, the clinical findings contain a mild temporal pallor of the optic disc in some patients, possible diminished visual acuity and abnormal color vision, a relative paracentral scotoma with rod sensiti-vity normal though.[69]

In many cases, the progressive nature of the clinical course reflects the peripheral vision loss, indicating rod degeneration. This may lead to severe nyctalopia so the condition is then called cone–rod dystrophy (CORD).[15]

Cone dystrophy appears to have a slightly more propitious clinical course than **cone-rod dystrophy**. However, both disorders progress to legal blindness in the majority of patients [that means visual acuity, in other words, vision of 20/200 (6/60) or less in the better eye with best correction possible]. Independent prognostic parameters for visual loss were mutations in the ABCA4 gene and early onset of disease.[13]

Furthermore, there is another clinical entity, called rod cone dystrophies (RCDs) or retinitis pigmentosa (RP), that reflect the opposite coherence of events compared to CRDs, as they result from the primary loss in rod photoreceptors, later followed by the secondary loss in cone photoreceptors.[12] **(FIGURE 3)**.

More specifically, CRD is characterized by primary cone involvement, or, sometimes, by concomitant loss of both cones and rods ,that explains the prevalent symptoms of CRDs: these are decreased visual acuity which is the earliest symptom, color vision defects(dyschromatopsia appears frequently), photophobia ,that also occurs early, photoaversion, that means dislike or avoidance of light and decreased sensitivity in the central visual field, later followed by progressive loss in peripheral vision and night blindness.

In general, the clinical course of cone-rod dystrophies is more rapid than that of RCDs, leading,as a result, to earlier legal blindness and disability.At the final stage, CRDs do not differ from RCDs though. Moreover, CRDs are more frequently non syndromic, but they may also be part of several syndromes, such as Bardet Biedl syndrome(a ciliopathic human genetic disorder characterized principally by retinitis pigmentosa ,obesity, polydactyly, hypogonadism and renal failure in some cases)and Spinocerebellar Ataxia Type 7 (SCA7)[12] **(FIGURE 4)**.

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. Furthermore eye poking (oculodigital reflex) can be observed in young children.

In most cases, no fundus abnormalities are present, but in later stages round subretinal pigment clumps or bone-spicule-like pigment changes can develop. The prevalence of LCA varies from 1:30,000 to 1: 81,000.[70,71] In most cases the inheritance modus is AR, but cases of AD inheritance have also been described.

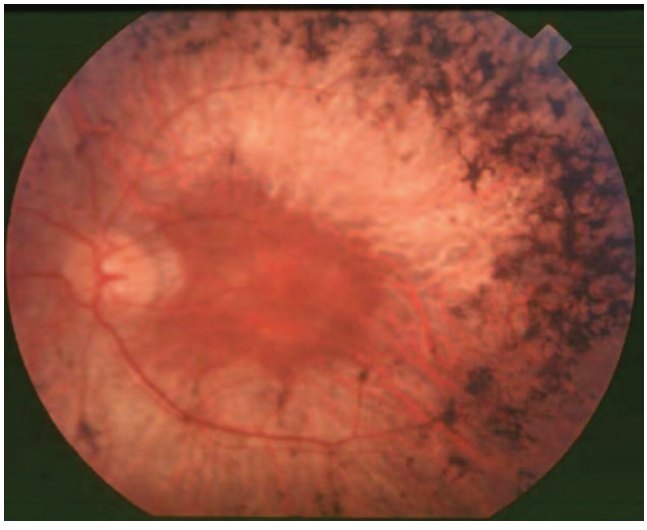

FIGURE 3: Fundus of a patient with retinitis pigmentosa(mid stage).Bone spicule-shaped pigment deposits are present in the mid periphery along with retinal at-

rophy, while the macula is preserved with a peripheral ring of depigmentation,though. Retinal vessels are attenuated.

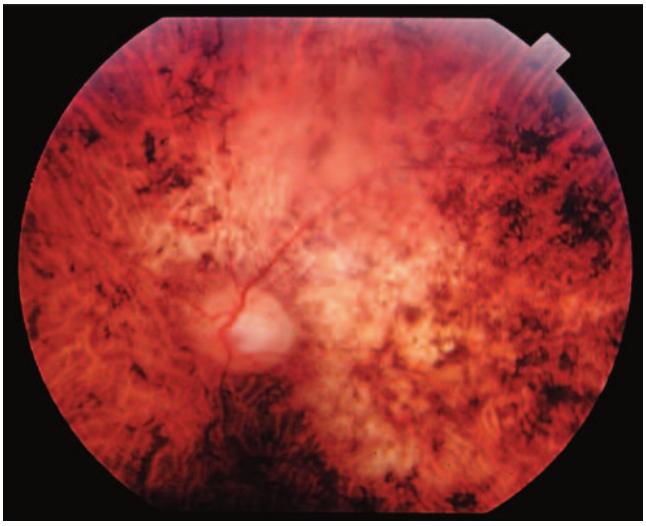

FIGURE 4: Fundus of a 34 year-old patient with cone rod dystrophy due to Spinocerebellar Ataxia Type 7 (SCA7). The macular area, as well as the mid periphery, are atrophic.

DIAGNOSIS

In general, ophthalmic examination and diagnostic testing is essential in order to differentiate cone-rod from rod-cone (like RP) disorders.

Regarding that in many cases there are no physical changes in the retina of someone suffering from certain types of cone disorders, such as in cone dystrophy, the ophthalmologist must rely on subtle symptoms and findings to know which tests to order.

The examinations that are normally done to arrive at a proper diagnosis are: 1) Visual Acuity Testing (visual acuity is another term for visual clarity). Most people are familiar with this test, in which they read letters from a chart while seated at a certain distance. A person with normal visual acuity is said to have 20/20 vision. A person with 20/40 vision can see at a distance of 20 feet what a person with "normal" vision can see at 40 feet.2) Color Testing,which measures a person's ability to see color. A series of images composed of many small circles is presented to the patient. Someone with normal color vision can recognize numbers within the images **(FIGURE 5)**. Other color vision tests may ask a patient to look at several small colored beads and place them in order. 3) Visual Field Testing .This test measures a person's field of vision. A light is brought in from the side on a screen and slowly moved to the center of vision. Patients press a button as soon as they see the light. For individuals with cone dystrophy, we do not expect the peripheral field of vision to be affected, although some may have a blind spot in the center of their vision. An example is depicted in the pictures below.In the left diagram, the black circle in the center represents the blind spot.[72]

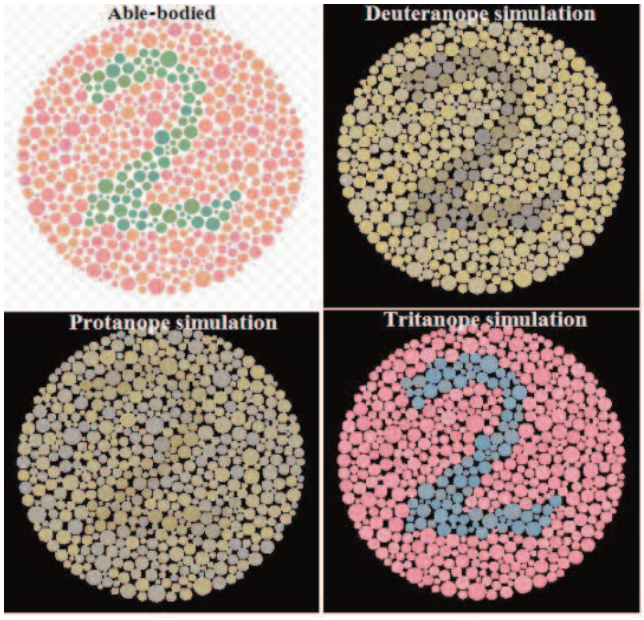

FIGURE 5: An example of color vision testing(Ishihara test image), as seen by subjects with normal color vision and by those with a variety of color deficiencies(Protanopia is a severe type of color vision deficiency caused by the complete absence of red retinal photoreceptors, deuteranopia is a color vision deficiency in which the green retinal photoreceptors are absent,tritanopia is a very rare color vision disturbance characterized by the presentation of only two cone pigments and a total absence of blue retinal receptors).

Among the diagnostic tests, 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.[73]

In the case of cone dystrophy, despite its difficulty due to unspecific subjective symptoms and absence of characteristic ophthalmoscopic findings, the diagnosis is determined by a full-field electroretinogram (ffERG), which gives reduced/absent cone responses with initial normal rod, while multifocal electroretinogram(mfERG) (a technique used to measure the function of localized portions of the retina) gives reduced/non detectable macular responses[68] **(FIGURE 6)**.

FIGURE 6: An Electroretinogram test(ERG).

Moreover, **fundus and near-infrared autofluorescence** (a non-invasive imaging technology that gives information for the distribution of melanin within the retinal pigment epithelial cell/choroid complex),as well as optical coherence tomography(OCT) are able to detect retinal structural abnormalities even when ophthalmoscopy's findings are normal.[12] More specifically, fundus autofluorescense (FAF) is normal to absent in the macula and Goldmann perimetry shows reduced central sensitivity to(relative) central scotoma in the case of cone dystrophy.[68]

Another diagnostic tool, with widespread adoption, is **high-resolution spectral-domain optical coherence tomography**(SD-OCT), which enables investigators to detect structural abnormalities in the retinal layers and to correlate them with functional status in many retinal diseases.It depicts four hyper-reflective bands in the outer retina, including external limiting membrane (ELM), the ellipsoid portion of the inner segments (ISe) (beneath the first band), a structure known as the outer segment(OS) contact cylinder, which is an ensheathment of the cone outer segments by an apical process of the retinal pigment epithelium(RPE) and the RPE.

In other words, 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. For future gene therapy purposes, SD-OCT can also be considered as a useful diagnostic tool for visualizing the severity of cone photoreceptor loss.[68]

The **major findings of SD-OCT**, regarding the morphologic changes in the outer retinal layers in cone dystrophy patients, can be divided into 4 categories: Category 0 is characterized by normal findings, that means no structural abnormalities. Category 1 showed irregular foveal loss of the ISe band and obscurity of the border between the ISe band and the external limiting membrane (ELM), due to the accumulation of reflective material between the 2 layers. Category 2 showed retinal thinning around the fovea and segmental (or irregular) foveal loss of the ISe band with an intact ELM and category 3 showed ISe band thickening around the fovea and irregular perifoveal loss of the ISe band. Moreover, in category 1 to 3, the OS contact cylinder layer was not discernible and the RPE layer was thickened. Therefore, it is suggested that the pathology of the retina in cone dystrophy occurs mainly between the photoreceptor outer segment and RPE layer.[74]

As far as the **late onset cone dystrophy** is concerned, its symptoms and signs may be unclear, therefore, establishing the proper diagnosis may be difficult in these cases. Patients may be misdiagnosed as having other diseases, especially when the macula's changes are absent or subtle. The electrophysiological testing is essential in these cases and ERG is the most useful clinical test in early and differential diagnosis of retinal dystrophies. More specifically, full-field electroretinogram (ffERG) reveals severe cone function impairment, with normal rod responses or slightly depressed in advanced stages in some cases.[75]

It is also argued that even corneal evaluation including topography is important in cone dystrophy, as a case of acute hydrops and perforation, leading to the diagnosis of keratoconus was described in a patient with cone dystrophy. The association between keratoconus and cone dystrophy is extremely rare, though.[76]

Regarding **cone-rod dystrophies**, that are characterized by retinal pigment deposits, mfERG gives reduced/non detectable macular responses and in ffERG cone responses are absent or more severely reduced than rod ones. FAF is normal to absent in the macula, Goldmann perimetry shows reduced central sensitivity to (relative) central scotoma, with variable peripheral involvement and SD-OCT is characterized by normal-absence of central cone photoreceptor layer (PRL) and central retinal thinning.[68]

In comparison with cone rod dystrophies, in **cone dystrophies**, rods remain normal and there is exclusive cone involvement in ERG. However, in some cone dystrophies, there may be some rod involvement, especially in late stage. In contrast to CRDs, rods remain partly spared at these late stages, while they are non recordable in late stage CRD. Another sign is the absence of macular lesions for many years, even though the visual acuity is diminished.[12]

As far as **achromatopsia** is concerned,full-field electroretinography (ffERG) demonstrates absent or residual cone responses with normal rod responses,[2,5] multifocal electroretinogram (mfERG) depicts reduced/non detectable macular responses, fundus autofluorescense (FAF) is normal

to absent in the macula, while Goldmann perimetry is characterized by reduced central sensitivity to (relative) central scotoma. On SD-OCT, the first signs of pathology, according to some studies, 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. The end stage is generally characterized by a complete loss of photoreceptors and atrophy of the RPE in the fovea.[77,78]

Regarding **oligocone trichromacy** (OT), the ffERG demonstrates normal to slightly reduced cone responses with normal rod, the mfERG gives reduced/non detectable macular responses, the Goldmann perimetry shows reduced central sensitivity, whereas the SD-OCT findings include thinner central retina with no absence of cone photoreceptor layer (PRL).

In the case of **blue cone monochromatism** (BCM), mfERG gives reduced/non detectable macular responses, the ffERG reduced/absent cone responses with a preservation of the blue cones, FAF is normal to absent in the macula, Goldmann perimetry shows reduced central sensitivity to (relative) central scotoma, while in SD-OCT, there is an absence of central cone PRL.

As far as **Stargardt disease** (STGD) is concerned, mfERG gives reduced responses and ffERG reduced cone responses, in FAF 70% dark choroid is dep icted, Goldmann perimetry shows reduced central sensitivity and SD-OCT demonstrates thinning or absence of central cone PRL.[68]

THERAPY

Currently, several strategies are being applied with the use of animal models,in order to (partially) restore gene function in CDs,so 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.

Adeno-associated viruses (AAVs) have been successfully used as vectors for **gene therapy**, as they 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.[79]

For those genes in which AAV-mediated therapy is not feasible due to their size, other strategies need to be developed. An alternative approach using the **nanoparticle, also known as 'non-virus' mediated therapy** has been applied. 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.[80] This kind of gene delivery has the potential to target many diseases caused by mutations in large genes.

Alternatively, **lentiviral vectors** can be used.[81] This strategy is currently used for the development of ABCA4 gene therapy.

In general, 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,so the window of treatment'sopportunity is smaller compared to slow or nonprogressive phenotypes. In persons with very early onset CD, gene augmentation therapy should ideally start as early as possible.

As far as cone dystrophy is concerned, it doesn't exist any specific therapeutic plan.

However, a case with small diameter soft toric lenses used in a 13-year-old girl who suffered from progressive cone dystrophy with associated nystagmus, achromatopsia and a high hyperopic-astigmatic prescription was described. The patient was fitted initially with partial correction contact lenses followed by lenses to the full correction some months later and the standard of vision finally achieved was favourable to that of spectacles.[82]

Moreover, a few years ago, a patient with this disease, empirically discovered that his vision improved when a red filter was placed in front of his eyes.[83]

Furthermore, taking into consideration that cone dystrophy belongs to the general group of retinal degenerations, it is believed that certain supplements, such as beta-carotenoids, lutein and zeaxanthin, as well as omega-3 fatty acids (docosahexaenoic acid and eicosapentaenoic acid) in conjunction with low glycemic index foods, can delay the progression of age related macular degeneration (AMD) and as a result provide similar benefits to cone dystrophy sufferers.[84,85]

Regarding cone-rod dystrophy, according to a prospective, nonrandomized study, intravitreal injection of **autologous bone marrow-derived mononuclear cells** in eyes with this kind of dystrophy, was associated with no detectable structural or functional toxicity over a period of 10 months. However, further studies are required in order to scrutinize the role, if any, of autologous bone marrow-derived mononuclear cell therapy in the management of retinal dystrophies.[86]

Despite all these references, there isn't currently any specific therapy that prevents the evolution of cone and cone rod dystrophies or restores the vision and the visual prognosis is poor. Generally, management intends to slow down the degenerative process, treat the complications and help patients to encounter the social and psychological impact of blindness.[12]

The future perspectives for cone disorders generally, include identification of CD-associated genes, molecular diagnostics and alternative cone rescue strategies.

Regarding the first one, **WES technology** (a combination of biological and mechanical process of converting organic waste into high quality, useable and marketable organic products, in the shortest possible time, clean and odorless), combined with homozygosity mapping or linkage analysis has proved to be successful in the discovery of novel retinal disease genes.[87, 88,89] In a recent Saudi Arabian study of predominantly AR inherited retinal dystrophies, almost 80% of DNA samples analyzed using homozygosity mapping and/or WES were solved by the identification of mutations in either known or novel genes.[90]

In the next few years, **WES and whole genome sequencing** (WGS) will also facilitate the identification of novel gene defects in individuals for which WES could not identify the pathologic defect.[91]

As far as molecular diagnostics is concerned, a few years ago it was not possible to stabilize or improve impaired vision in persons with CD,but 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, for example, in nephronophthisis, in which the kidney is involved.

For some CD's (ABCA4 in STGD1, CNGB3 and CNGA3 in ACHM, and KCNV2 in CD with supranormal rod response), Sanger sequencing (a method of DNA sequencing based on the selective incorporation of chain-terminating dideoxynucleotides by DNA polymerase during in vitro DNA replication)of one or a few genes, will identify the causal variants in a significant proportion of cases.

A great promise in treating early onset degenerative diseases, like CD, are also cell replacement therapies using retinal progenitor cells derived from embryonic stem cells (ESCs) or induced pluripotent stem cells iPSCs,that means stem cells that have the potential to differentiate into any of the three germ layers: endoderm (interior stomach lining, gastrointestinal tract, the lungs), mesoderm (muscle, bone, blood, urogenital), or ectoderm (epidermal tissues and nervous system). These cells could be very valuable in cell-based therapies. It is crucial 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 [92,93,94,95] demonstrating the possibility of this approach to rescue retinal function in future clinical trials.

To sum up, the early aim of CD research has been the identification of the genetic basis of CD. Advances in this field compounded by technologies such as WES and WGS, have created a new era for molecular diagnostics in CD. The ultimate goal remains the development of therapies that rescue cone photoreceptors,that is not only important to treat cone dysfunctions, but will also be crucial to maintain vision in rod-dominated diseases.

References

1. Kohl S, Baumann B, Rosenberg T, Kellner U, Lorenz B, Vadalà M, et al. Mutations in the Cone Photoreceptor G-Protein α-Subunit Gene GNAT2 in Patients with Achromatopsia. Am J Hum Genet 2002; 71(2):422–425.

2. Kohl S, Baumann B, Broghammer M, Jägle H, Sieving P, Kellner U, et al. Mutations in the CNGB3 gene encoding the beta-subunit of the cone photoreceptor cGMP-gated channel are responsible for achromatopsia (ACHM3) linked to chromosome 8q21. Hum Mol Genet 2000; 9(14):2107-2116.

3. Kohl S, Coppieters F, Meire F, Schaich S, Roosing S, Brennenstuhl C, et al. A nonsense mutation in PDE6H causes autosomal-recessive incomplete achromatopsia. Am J Hum Genet 2012; 91(3):527-532.

4. Kohl S, Marx T, Giddings I, Jägle H, Jacobson SG, Apfelstedt-Sylla E,et al. Total colourblindness is caused by mutations in the gene encoding the alpha-subunit of the cone photoreceptor cGMP-gated cation channel. Nat Genet 1998; 19(3):257-259.

5. Thiadens AA, Slingerland NW, Roosing S, van Schooneveld MJ, van Lith-Verhoeven JJ, van Moll-Ramirez N, et al. Genetic etiology and clinical consequences of complete and incomplete achromatopsia. Ophthalmology 2009; 116(10):1984-1949.

6. Simunovic MP, Moore AT. The cone dystrophies. Eye(Lond) 1998; 12:553-565.

7. Kohl S. Genetic causes of hereditary cone and cone-rod dystrophies. Ophthalmologe 2009; 106(2):109-115.

8. Balciuniene J1, Johansson K, Sandgren O, Wachtmeister L, Holmgren G, Forsman K. A gene for autosomal dominant progressive cone dystrophy (CORD5) maps to chromosome 17p12-p13. Genomics 1995; 30(2):281-286.

9. Köhn L1, Kadzhaev K, Burstedt MS, Haraldsson S, Hallberg B, Sandgren O, et al. Mutation in the PYK2-binding domain of PITPNM3 causes autosomal dominant cone dystrophy (CORD5) in two Swedish families. Eur J Hum Genet 2007; 15(6):664-671.

10. Reinis A, Golovleva I, Köhn L, Sandgren O. Ocular phenotype of CORD5, an autosomal dominant retinal dystrophy associated with PITPNM3 p.Q626H mutation. Acta Ophthalmol 2013; 91:259–266.

11. Czirják G, Tóth ZE, Enyedi P. Characterization of the heteromeric potassium channel formed by kv2.1 and the retinal subunit kv8.2 in Xenopus oocytes. J Neurophysiol 2007;

98(3):1213-1222. Epub 2007 Jul 25.

12. Hamel CP. Cone rod dystrophies. Orphanet J Rare Dis 2007; 2:7.

13. Thiadens AA, Phan TM, Zekveld-Vroon RC, Leroy BP, van den Born LI, Hoyng CB, et al. Clinical course, genetic etiology, and visual outcome in cone and cone-rod dystrophy. Ophthalmology 2012; 119(4):819-826.

14. Kitiratschky VB, Wilke R, Renner AB, Kellner U, Vadalà M, Birch DG, et al. Mutation analysis identifies GUCY2D as the major gene responsible for autosomal dominant progressive cone degeneration. Invest Ophthalmol Vis Sci 2008; 49(11):5015-5023.

15. Ugur Iseri SA, Durlu YK, Tolun A. A novel recessive GUCY2D mutation causing cone–rod dystrophy and not Leber's congenital amaurosis. Eur J Hum Genet 2010; 18(10):1121–1126.

16. Lorenz B, Gyürüs P, Preising M, Bremser D, Gu S, Andrassi M. Early-Onset Severe Rod–Cone Dystrophy in Young Children with RPE65 Mutations. Invest Ophthalmol Vis Sci 2000; 41(9):2735-2742.

17. El Shamieh S, Neuillé M, Terray A, Orhan E, Condroyer C, Démontant V. Whole-exome sequencing identifies KIZ as a ciliary gene associated with autosomal-recessive rod-cone dystrophy. Am J Hum Genet 2014; 94(4):625-633.

18. Charbel Issa P, Bolz HJ, Ebermann I, Domeier E, Holz FG, Scholl HP. Characterisation of severe rod-cone dystrophy in a consanguineous family with a splice site mutation in the MERTK gene. Br J Ophthalmol 2009; 93(7):920-925.

19. Gardner JC, Webb TR, Kanuga N, Robson AG, Holder GE, Stockman A, et al. X-linked cone dystrophy caused by mutation of the red and green cone opsins. Am J Hum Genet 2010; 87(1):26-39.

20. Gardner JC, Webb TR, Kanuga N, Robson AG, Holder GE, Stockman A,et al. A novel missense mutation in both OPN1LW and OPN1MW cone opsin genes causes X-linked cone dystrophy (XLCOD5). Adv Exp Med Biol 2012; 723:595-601.

21. Michaelides M, Hunt DM, Moore AT. The cone dysfunction syndromes. Br J Ophthalmol 2004; 88(2):291-297.

22. Ayyagari R, Kakuk LE, Bingham EL, Szczesny JJ, Kemp J, Toda Y,et al. Spectrum of color gene deletions and phenotype in patients with blue cone monochromacy. Hum Genet 2000; 107(1):75-82.

23. McClements M, Davies WI, Michaelides M, Young T, Neitz M, MacLaren RE,et al. Variations in opsin coding sequences cause x-linked cone dysfunction syndrome with myopia and dichromacy. Invest Ophthalmol Vis Sci 2013; 54(2):1361-1369.

24. Michaelides M, Johnson S, Bradshaw K, Holder GE, Simunovic MP, Mollon JD,et al. X-linked cone dysfunction syndrome with myopia and protanopia. Ophthalmology 2005; 112(8):1448-1454.

25. Ueyama H, Muraki-Oda S, Yamade S, Tanabe S, Yamashita T, Shichida Y,et al. Unique haplotype in exon 3 of cone opsin mRNA affects splicing of its precursor, leading to congenital color vision defect. Biochem Biophys Res Commun 2012; 424(1):152-157.

26. Michaelides M, Holder GE, Bradshaw K, Hunt DM, Mollon JD, Moore AT. Oligocone trichromacy: a rare and unusual cone dysfunction syndrome. Br J Ophthalmol 2004; 88(4):497-500.

27. Vincent A, Wright T, Billingsley G, Westall C, Héon E. Oligocone trichromacy is part of the spectrum of CNGA3-related cone system disorders. Ophthalmic Genet 2011; 32(2):107-113.

28.Allikmets R, Singh N, Sun H, Shroyer NF, Hutchinson A, Chidambaram A,et al. A photoreceptor cell-specific ATP-binding transporter gene (ABCR) is mutated in recessive Stargardt macular dystrophy. Nat Genet 1997; 15(3):236-246.

29. Maugeri A, van Driel MA, van de Pol DJ, Klevering BJ, van Haren FJ, Tijmes N. The 2588G-->C mutation in the ABCR gene is a mild frequent founder mutation in the Western European population and allows the classification of ABCR mutations in patients with Stargardt disease. Am J Hum Genet 1999; 64(4):1024-1035.

30. Cremers FP, van de Pol DJ, van Driel M, den Hollander AI, van Haren FJ, Knoers NV,et al. Autosomal recessive retinitis pigmentosa and cone-rod dystrophy caused by splice site mutations in the Stargardt's disease gene ABCR. Hum Mol Genet 1998; 7(3):355-362.

31. Boon CJ, van Schooneveld MJ, den Hollander AI, van Lith-Verhoeven JJ, Zonneveld-Vrieling MN, Theelen T,et al. Mutations in the peripherin/RDS gene are an important cause of multifocal pattern dystrophy simulating STGD1/fundus flavimaculatus. Br J Ophthalmol 2007; 91(11):1504-1511.

32. Boon CJ, den Hollander AI, Hoyng CB, Cremers FP, Klevering BJ, Keunen JE. The spectrum of retinal dystrophies caused by mutations in the peripherin/RDS gene. Prog Retin Eye Res 2008; 27(2):213-235.

33. Arikawa K, Molday LL, Molday RS, Williams DS. Localization of peripherin/rds in the disk membranes of cone and rod photoreceptors: relationship to disk membrane morphogenesis and retinal degeneration. J Cell Biol 1992; 116(3):659-667.

34. Connell G, Bascom R, Molday L, Reid D, McInnes RR, Molday RS. Photoreceptor peripherin is the normal product of the gene responsible for retinal degeneration in the rds mouse. Proc Natl Acad Sci U S A 1991; 88(3):723-726.

35. Travis GH, Sutcliffe JG, Bok D. The retinal degeneration slow (rds) gene product is a photoreceptor disc membrane-associated glycoprotein. Neuron 1991; 6(1):61-70.

36. Renner AB, Fiebig BS, Weber BH, Wissinger B, Andreasson S, Gal A,et al. Phenotypic variability and long-term follow-up of patients with known and novel PRPH2/RDS gene mutations. Am J Ophthalmol 2009; 147(3):518-530. Epub 2008 Nov 26.

37. Boon CJ, Klevering BJ, Cremers FP, Zonneveld-Vrieling MN, Theelen T, Den Hollander AI, et al. Central areolar choroidal dystrophy. Ophthalmology 2009; 116(4):771-782.

38. Wickham L, Chen FK, Lewis GP, Uppal GS, Neveu MM, Wright GA, et al. Clinicopathological case series of four patients with inherited macular disease. Invest Ophthalmol Vis Sci 2009; 50(8):3553-3561.

39. Zhang K, Garibaldi DC, Li Y, Green WR, Zack DJ. Butterfly-shaped pattern dystrophy: a genetic, clinical, and histopathological report. Arch Ophthalmol 2002; 120(4):485-490.

40. Gómez NM, Tamm ER, Strauβ O. Role of bestrophin-1 in store-operated calcium entry in retinal pigment epithelium. Pflugers Arch 2013; 465(4):481-495.

41. Boon CJ, Klevering BJ, Leroy BP, Hoyng CB, Keunen JE, den Hollander AI. The spectrum of ocular phenotypes caused by mutations in the BEST1 gene. Prog Retin Eye Res 2009; 28(3):187-205.

42. Stone EM, Lotery AJ, Munier FL, Héon E, Piguet B, Guymer RH,et al. A single EFEMP1 mutation associated with both Malattia Leventinese and Doyne honeycomb retinal dystrophy. Nat Genet 1999; 22(2):199-202.

43. Akahori M, Tsunoda K, Miyake Y, Fukuda Y, Ishiura H, Tsuji S, et al. Dominant mutations in RP1L1 are responsible for occult macular dystrophy. Am J Hum Genet 2010; 87(3):424-429.

44. Ambasudhan R, Wang X, Jablonski MM, Thompson DA, Lagali PS, Wong PW,et al. Atrophic macular degeneration mutations in ELOVL4 result in the intracellular misrouting of the protein. Genomics 2004; 83(4):615-625.

45. Wada Y, Abe T, Itabashi T, Sato H, Kawamura M, Tamai M. Autosomal dominant macular degeneration associated with 208delG mutation in the FSCN2 gene. Arch Ophthalmol 2003; 121(11):1613-1620.

46. Weber BH, Vogt G, Pruett RC, Stöhr H, Felbor U. Mutations in the tissue inhibitor of metalloproteinases-3 (TIMP3) in patients with Sorsby's fundus dystrophy. Nat Genet 1994; 8(4):352-356.

47. Kremer H, Pinckers A, van den Helm B, Deutman AF, Ropers HH, Mariman EC. Localization of the gene for dominant cystoid macular dystrophy on chromosome 7p. Hum Mol Genet 1994; 3(2):299-302.

48. Small KW, Weber JL, Roses A, Lennon F, Vance JM, Pericak-Vance MA. North Carolina macular dystrophy is assigned to chromosome 6. Genomics 1992; 13(3):681-685.

49. Yang Z, Tong Z, Chorich LJ, Pearson E, Yang X, Moore A,et al. Clinical characterization and genetic mapping of North Carolina macular dystrophy. Vision Res 2008; 48(3):470-477.

50. van Lith-Verhoeven JJ, Hoyng CB, van den Helm B, Deutman AF, Brink HM, Kemperman MH, et al. The benign concentric annular macular dystrophy locus maps to 6p12.3-q16. Invest Ophthalmol Vis Sci 2004; 45(1):30-35.

51. Michaelides M, Johnson S, Tekriwal AK, Holder GE, Bellmann C, Kinning E,et al. An early-onset autosomal dominant macular dystrophy (MCDR3) resembling North Carolina macular dystrophy maps to chromosome 5. Invest Ophthalmol Vis Sci 2003; 44(5):2178-2183.

52. Rosenberg T, Roos B, Johnsen T, Bech N, Scheetz TE, Larsen M,et al. Clinical and genetic characterization of a Danish family with North Carolina macular dystrophy. Mol Vis 2010; 16:2659-2668.

53. Yang Z, Kitsos G, Tong Z, Payne M, Gorezis S, Psilas K,et al. A novel locus on 19q13 associated with autosomal-dominant macular dystrophy in a large Greek family. J Med Genet 2006; 43(12):e57.

54. Hong DH, Pawlyk BS, Shang J, Sandberg MA, Berson EL, Li T. A retinitis pigmentosa GTPase regulator (RPGR)-deficient mouse model for X-linked retinitis pigmentosa (RP3). Proc Natl Acad Sci U S A 2000; 97(7):3649-3654.

55. Zhao Y, Hong DH, Pawlyk B, Yue G, Adamian M, Grynberg M,et al. The retinitis pigmentosa GTPase regulator (RPGR)- interacting protein: subserving RPGR function and participating in disk morphogenesis. Proc Natl Acad Sci U S A 2003; 100(7):3965-3970. Epub 2003 Mar 21.

56. Thoreson WB, Witkovsky P. Glutamate receptors and circuits in the vertebrate retina. Prog Retin Eye Res 1999; 18(6):765-810.

57. Wycisk KA, Zeitz C, Feil S, Wittmer M, Forster U, Neidhardt J, et al. Mutation in the auxiliary calcium-channel subunit CACNA2D4 causes autosomal recessive cone dystrophy. Am J Hum Genet 2006; 79(5):973-977. Epub 2006 Sep 27.

58. Castillo PE, Schoch S, Schmitz F, Südhof TC, Malenka RC. RIM1alpha is required for presynaptic long-term potentiation. Nature 2002; 415(6869):327-330.

59. Coppola T, Magnin-Luthi S, Perret-Menoud V, Gattesco S, Schiavo G, Regazzi R. Direct interaction of the Rab3 effector RIM with Ca2+ channels, SNAP-25, and synaptotagmin. J Biol Chem 2001; 276(35):32756-32762. Epub 2001 Jul 3.

60. Schoch S, Castillo PE, Jo T, Mukherjee K, Geppert M, Wang Y,et al. RIM1alpha forms a protein scaffold for regulating neurotransmitter release at the active zone. Nature 2002; 415(6869):321-326.

61. Maron BJ, Roberts WC, Arad M, Haas TS, Spirito P, Wright GB,et al. Clinical outcome and phenotypic expression in LAMP2 cardiomyopathy. JAMA 2009; 301(12):1253-1259.

62. Prall FR, Drack A, Taylor M, Ku L, Olson JL, Gregory D,et al. Ophthalmic manifestations of Danon disease. Ophthalmology 2006; 113(6):1010-1013.

63. Thiadens AA, Slingerland NW, Florijn RJ, Visser GH, Riemslag FC, Klaver CC. Cone-rod dystrophy can be a manifestation of Danon disease. Graefes Arch Clin Exp Ophthalmol 2012; 250(5):769-774.

64. Marshall JD, Maffei P, Collin GB, Naggert JK. Alström syndrome: genetics and clinical overview. Curr Genomics 2011; 12(3):225-235.

65. Jalili IK. Cone-rod dystrophy and amelogenesis imperfecta (Jalili syndrome): phenotypes and environs. Eye (Lond) 2010; 24(11):1659-1668.

66. Francis PJ, Johnson S, Edmunds B, Kelsell RE, Sheridan E, Garrett C,et al. Genetic linkage analysis of a novel syndrome comprising North Carolina-like macular dystrophy and progressive sensorineural hearing loss. Br J Ophthalmol 2003; 87(7):893-898.

67. Kellner U, Kellner S. Clinical findings and diagnostics of cone dystrophy. Ophthalmologe 2009; 106(2):199-108.

68. Roosing S, Thiadens AA, Hoyng CB, Klaver CC, den Hollander AI, Cremers FP. Causes and consequences of inherited cone disorders. Prog Retin Eye Res Epub 2014; 42C:1-26.

69. Kondo M, Miyake Y, Kondo N, Ueno S, Takakuwa H, Terasaki H. Peripheral cone dystrophy: a variant of cone dystrophy with predominant dysfunction in the peripheral cone system. Ophthalmology 2004; 111(4):732-739.

70. Koenekoop RK. An overview of Leber congenital amaurosis: a model to understand human retinal development. Surv Ophthalmol 2004; 49(4):379-398.

71. Stone EM. Leber congenital amaurosis - a model for efficient genetic testing of heterogeneous disorders: LXIV Edward Jackson Memorial Lecture. Am J Ophthalmol 2007; 144(6):791-811.

72. Amanda Openshaw, Kari Branham, John Heckenlively. Understanding Cone Dystrophy. University of Michigan,Kellogg Eye Center 2008: 7-8.

73. Thiadens AA, Hoyng CB, Polling JR, Bernaerts-Biskop R, van den Born LI, Klaver CC. Accuracy of four commonly used color vision tests in the identification of cone disorders. Ophthalmic Epidemiol 2013; 20(2):114-121.

74. Cho SC, Woo SJ, Park KH, Hwang JM. Morphologic characteristics of the outer retina in cone dystrophy on spectral-domain optical coherence tomography. Korean J Ophthalmol 2013; 27(1):19-27.

75. Langwińska-Wośko E, Szulborski K, Broniek-Kowalik K. Late onset cone dystrophy. Doc Ophthalmol 2010; 120(3):215-218.

76. Yeh S, Smith JA. Management of acute hydrops with perforation in a patient with keratoconus and cone dystrophy: case report and literature review. Cornea 2008; 27(9):1062-1065.

77. Genead MA, Fishman GA, Rha J, Dubis AM, Bonci DM, Dubra A,et al. Photoreceptor structure and function in patients with congenital achromatopsia. Invest Ophthalmol Vis Sci 2011; 52(10):7298-7308.

78. Sundaram V, Wilde C, Aboshiha J, Cowing J, Han C, Langlo CS, et al. Retinal structure and function in achromatopsia: implications for gene therapy. Ophthalmology 2014; 121(1):234-245.

79. Travis GH, Golczak M, Moise AR, Palczewski K. Diseases caused by defects in the visual cycle: retinoids as potential therapeutic agents. Annu Rev Pharmacol Toxicol 2007; 47:469-512.

80. Han Z, Conley SM, Makkia RS, Cooper MJ, Naash MI. DNA nanoparticle-mediated ABCA4 delivery rescues Stargardt dystrophy in mice. J Clin Invest 2012; 122(9):3221-3226. Epub 2012 Aug 13.

81. Kumar M, Keller B, Makalou N, Sutton RE. Systematic determination of the packaging limit of lentiviral vectors. Hum Gene Ther 2001; 12(15):1893-1905.

82. Stevenson G, Gardner L. Progressive cone dystrophy, nystagmus and contact lenses. Cont Lens Anterior Eye 2010; 33(5):228-230.

83. Young RS, Krefman RA, Fishman GA. Visual improvements with red-tinted glasses in a patient with cone dystrophy. Arch Ophthalmol 1982; 100(2):268-271.

84. Carpentier S, Knaus M, Suh M. Associations between lutein, zeaxanthin, and age-related macular degeneration: an overview. Crit Rev Food Sci Nutr 2009; 49(4):313-326.

85. Chiu CJ, Klein R, Milton RC, Gensler G, Taylor A. Does eating particular diets alter the risk of age-related macular degeneration in users of the Age-Related Eye Disease Study supplements? Br J Ophthalmol 2009; 93(9):1241-1246.

86. Siqueira RC, Messias A, Voltarelli JC, Scott IU, Jorge R. Intravitreal injection of autologous bone marrow-derived mononuclear cells for hereditary retinal dystrophy: a phase I trial. Retina 2011; 31(6):1207-1214.

87. Estrada-Cuzcano A, Neveling K, Kohl S, Banin E, Rotenstreich Y, Sharon D,et al. Mutations in C8orf37, encoding a ciliary protein, are associated with autosomal-recessive retinal dystrophies with early macular involvement. Am J Hum Genet 2012; 90(1):102-109. Epub 2011 Dec 15.

88. Roosing S, Rohrschneider K, Beryozkin A, Sharon D, Weisschuh N, Staller J,et al. Mutations in RAB28, encoding a farnesylated small GTPase, are associated with autosomal-recessive cone-rod dystrophy. Am J Hum Genet 2013; 93(1):110-117.

89. Zeitz C, Jacobson SG, Hamel CP, Bujakowska K, Neuillé M, Orhan E,et al. Whole-exome sequencing identifies LRIT3 mutations as a cause of autosomal-recessive complete congenital stationary night blindness. Am J Hum

Genet 2013; 92(1):67-75.

90. Abu-Safieh L, Alrashed M, Anazi S, Alkuraya H, Khan AO, Al-Owain M,et al. Autozygome-guided exome sequencing in retinal dystrophy patients reveals pathogenetic mutations and novel candidate disease genes. Genome Res 2013; 23(2):236-247.

91. Nishiguchi KM, Tearle RG, Liu YP, Oh EC, Miyake N, Benaglio P,et al. Whole genome sequencing in patients with retinitis pigmentosa reveals pathogenic DNA structural changes and NEK2 as a new disease gene. Proc Natl Acad Sci U S A 2013; 110(40):16139-16144.

92. Gonzalez-Cordero A, West EL, Pearson RA, Duran Y, Carvalho LS, Chu CJ,et al. Photoreceptor precursors derived from three-dimensional embryonic stem cell cultures integrate and mature within adult degenerate retina. Nat Biotechnol 2013; 31(8):741-747.

93. MacLaren RE, Pearson RA, MacNeil A, Douglas RH, Salt TE, Akimoto M,et al. Retinal repair by transplantation of photoreceptor precursors. Nature 2006; 444(7116):203-207.

94. Pearson RA, Barber AC, West EL, MacLaren RE, Duran Y, Bainbridge JW,et al. Targeted disruption of outer limiting membrane junctional proteins (Crb1 and ZO-1) increases integration of transplanted photoreceptor precursors into the adult wild-type and degenerating retina. Cell Transplant 2010; 19(4):487-503.

95. West EL, Pearson RA, Tschernutter M, Sowden JC, MacLaren RE, Ali RR. Pharmacological disruption of the outer limiting membrane leads to increased retinal integration of transplanted photoreceptor precursors. Exp Eye Res 2008; 86(4):601-611.