

Cone rod dystrophies

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Abstract

Cone rod dystrophies (CRDs) (prevalence 1/40 000) are inherited retinal dystrophies that belong to the retinitis pigmentosa group, and more generally to pigmentary retinopathies. As such, they are characterized by retinal pigment deposits visible on fundus examination, predominantly localised in the macular region. In contrast with typical retinitis pigmentosa, also called the rod-cone dystrophies (RCDs) resulting from the primary loss in rod photoreceptors later followed by the secondary loss in cone photoreceptors, CRDs reflect the opposite sequence of events, that is primary cone involvement, or, sometimes, concomitant loss of both cones and rods. This explains that the symptoms of CRDs are predominantly decreased visual acuity, color vision defects, photoaversion and decreased sensitivity in the central visual field, later followed by progressive loss in peripheral vision and night blindness. Thus, the clinical course of CRDs is generally more severe and rapid than that of rod cone dystrophies, leading to earlier legal blindness (visual acuity less than 20/200) and disability. At end stage however, CRDs are not different from RCDs. The diagnosis of CRD is based on clinical history, fundus examination and electroretinogram, which typically shows a greater loss in amplitude of photopic responses over scotopic responses at first becoming then rapidly unrecordable. CRDs are most frequently non syndromic, but they may also be part of several syndromes, such as Bardet Biedl syndrome and SCA7 cerebellar ataxia. Non syndromic CRDs are genetically heterogenous with 10 cloned genes and 3 loci, and it remains unclear what percentage of patients are presently cloned genes accounting for. Nevertheless, the 4 major genes for CRDs among those currently known are ABCA4, that causes Stargardt disease and also 30 to 60 % of autosomal recessive CRDs, CRX and GUCY2D that are responsible for many reported cases of autosomal dominant CRDs, and RPGR, that causes about 2/3 of X-linked RPs and also an undetermined percentage of X-linked CRDs. Causal genes and presumably pathogenic mechanisms in CRDs are thus widely heterogenous. Nevertheless, it is likely that highly deleterious mutations in genes that otherwise cause RP or macular dystrophy may also lead to CRDs. Complications and treatments of this disorder are the same than for RPs.

Key-words

Cone-rod dystrophy, retinitis pigmentosa, retinal dystrophy, photoreceptor, retinal pigment epithelium

Disease name

Cone rod dystrophies (CRDs)

Diagnosis criteria / definition

CRDs are inherited retinal dystrophies that belong to the retinitis pigmentosa group, and more generally to pigmentary retinopathies.

Functional signs:

Decrease in visual acuity is the earliest symptom
Photophobia also occurs early,
Frequent dyschromatopsia
Night blindness occurs later

Visual field

- Central scotoma appears first, preventing fluent reading
- Patchy losses of peripheral vision follow;
- Total loss of vision occurs earlier than in rod cone retinitis pigmentosa.

Fundus

- Pigmentary deposits resembling bone spicules, frequently in macular area
- Attenuation of the retinal vessels
- Waxy pallor of the optic disc
- Various degrees of retinal atrophy

Electroretinogram

- Dramatic diminution of the amplitudes of a and b waves
- Predominant involvement of photopic (cones) over scotopic (rods) system

Differential diagnosis of non syndromic cone-rod dystrophies with other pigmentary retinopathies

CRDs are usually clearly differentiated from primary peripheral retinopathies and macular dystrophies. However, CRD may sometimes share features with several clinical entities.

Primary peripheral retinopathies

Typical RP (rod cone dystrophy). In typical rod cone dystrophies (RCD), the diagnosis is easy because the first symptom is night blindness. This symptom typically remains isolated for several years with normal visual acuity before vision loss in daylight becomes prominent. In the fundus, pigment deposits are located in the periphery.

RP with early macular involvement. In some cases, RCD has a typical slow progression but macular involvement occurs quite early with some loss in visual acuity. A disease history characterized by predominant night blindness and prominent rod involvement supports the diagnosis of RCD.

Early onset RP or late stage RP. In cases associated with early onset and severe RCD, the

decrease in visual acuity with macular involvement may also occur early. It is again important to determine which sign, either night blindness or loss in central vision, appeared first in the disease course. The diagnosis may be particularly difficult when patients are seen at late stage; at that time the electroretinogram is unrecordable.

Leber's congenital amaurosis (LCA). This disease is associated with a high degree of visual impairment, which is already present at birth, and appears either as a rod- or cone-predominant disease, or both. Nystagmus, poor light fixation and reactivity, visual acuity lower than 1/20 and flat electroretinogram are cardinal signs of the disease. Differential diagnosis with early onset CRD may be difficult because the two diseases share the same signs. The presence of a lapse time of several years before dramatic worsening of visual disability will allow to class the disease as a CRD rather than LCA.

Maculopathies.

Large, extended maculopathies may be difficult to differentiate from end stage CRD or RP.

Stargardt disease is a maculopathy in which peripheral retina usually remains free of lesions. The disease is easy to recognize with the presence of yellow flecks that may cover the entire fundus (fundus flavimaculatus), fluorescent macular lesions (bull's eye) and dark choroid on the fluorescein angiography. However, there are extended lesions in some late stage Stargardt cases, and in addition, a number of CRD are due to the "Stargardt gene", ABCA4. In these cases, the early stage of the disease may be alike Stargardt disease, but, in a decade, signs of peripheral involvement occur.

Cone dystrophies. Rods remain normal in these diseases. Signs are loss of visual acuity, photophobia, dyschromatopsia, and exclusive cone involvement at the electroretinogram. However, in some cone dystrophies, there may be some rod involvement, particularly in late stage. However rods remain at least partly spared at these stages, whereas 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 decreased. Other cone diseases like achromatopsia are easily diagnosed on the basis of the disease's lack of evolution and pure cone involvement.

Sorsby's disease

Frequency

Prevalence of RP is 1/40,000. Prevalence of CRD is estimated to be 1/10 of RP prevalence (Hamel *et al.*, 2000).

Clinical description

Non syndromic cone rod dystrophies

CRDs present first as a macular disease or as a diffuse retinopathy with predominance of the macular involvement. In contrast with the symptoms of the RCDs (typical retinitis pigmentosa) resulting from predominant rod involvement, i.e. night blindness and loss in peripheral vision, the clinical signs of CRDs reflect the predominant involvement of cones, which lead to decreased visual acuity and loss in the central visual field. This fits with the original description of the CRD entity in which cone loss precedes rod degeneration. However, in some cases, diffuse retinopathy affects simultaneously cones and rods, resulting in both night blindness and loss in visual acuity. These cases may also be considered as CRDs, although they overlap with other entities (see differential diagnosis). In general, CRDs appear as more severe than RCDs because the loss in autonomy of the patients occurs earlier. It is convenient to describe two stages in the disease course of CRD.

In the first stage, the main symptom is decreased visual acuity, which is usually discovered at school in the first decade and is not significantly improved with spectacles. Patients often have a noticeable deviated gaze to project images on parafoveal regions of their retina that are less damaged. Along with this symptom, there are intense photophobia and a variable degree of dyschromatopsia. By contrast, night blindness is not mentioned by patients or, when present, is never as prominent as the decrease in visual acuity. Visual field testing shows central scotomas, while periphery is spared. As a result, patients have no difficulties to move. Fundus examination shows pigment deposits and various degrees of retinal atrophy in the macular region. Retinal vessels are usually normal or moderately attenuated. The optic disc is often pale at early stages, particularly in the temporal side, which accounts for the macular fibre bundle. At this stage, the question is to differentiate CRDs from macular dystrophies such as Stargardt disease, cone dystrophies and other rarer macular conditions. Additional investigations help to decide. First, fluorescein angiography shows that the peripheral retina is also involved with heterogeneity in the fluorescence, but to a lesser extent than in the macula. Second, the electroretinogram shows a decrease in both cone and rod responses, but cone responses are more deeply affected than rod responses.

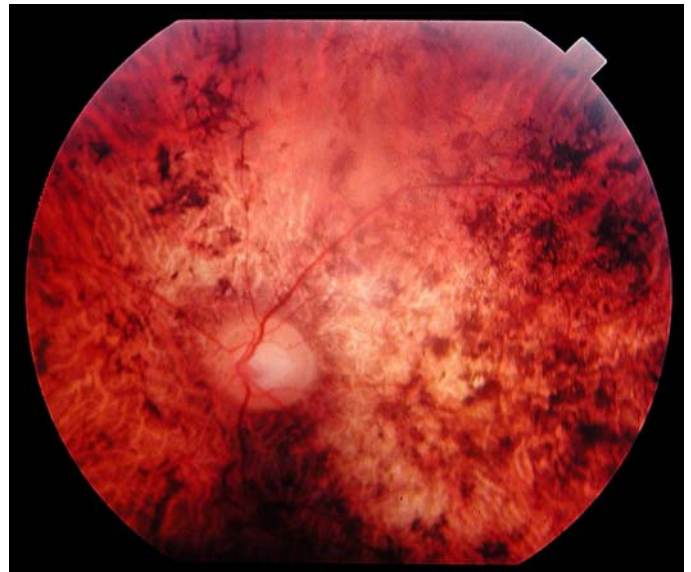


Figure 1: Fundus of a 45 year-old patient with cone rod dystrophy segregating with a loss-of-function mutation (E1087X) in ABCA4. Note the presence of various-shaped pigment deposits in the posterior pole with atrophy of the retina, while the retina appears less damaged in periphery (upper part of the photograph).

In the second stage, night blindness becomes more apparent and loss in the peripheral visual field progresses. Therefore, patients undergo difficulties to move autonomously. In addition, visual acuity has continued to decrease to a level where reading is no longer possible. There is often a nystagmus. At this stage, patients are legally blind (visual acuity < 1/20), even though large parts of the peripheral visual field remain.

Syndromic cone rod dystrophies

There are a few syndromes in which retinal degeneration features characteristically CRD rather than typical RP.

Bardet Biedl syndrome (BBS) is an autosomal recessive disease with a prevalence ranging from 1/13500 to 1/60000. It associates retinal dystrophy with postaxial polydactyly, obesity, hypogenitalism, slow mind and renal abnormalities that can lead to renal failure. The retinal dystrophy is classically described as a RCD but many variants have been reported with a prominent macular involvement indicating a CRD (Beales *et al.*, 1999). In fact, BBS patients have the diffuse type of CRD. In our experience, they always have a macular involvement, with decreased visual acuity, photophobia and foveomacular hyperfluorescence on retinal angiogram. The diagnosis of retinal dystrophy is often established in the first decade and legal blindness is reached before 20 years of age, but there are moderate forms of the disease. Diagnosis may be difficult when the clinical picture is incomplete. In this case, the presence of a CRD is an important sign. Seven BBS

genes encoding proteins involved in the cilium structure have been reported.

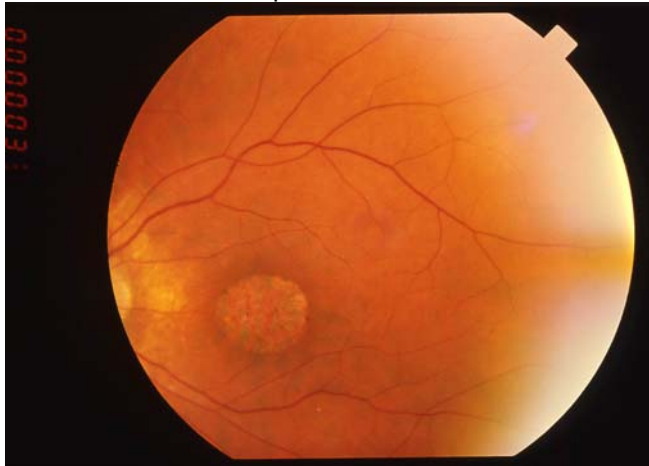


Figure 2: Fundus of a 31 year-old patient with Bardet Biedl syndrome. The peripheral retina does not show any large lesion but the macula is atrophic.

Type II cerebellar ataxia (SCA7) is an autosomal dominant spinocerebellar degeneration due to expansions of polyglutamine in the ataxin protein. The retinal disease often begins with granular macula progressively spreading out to the whole retina while the macula becomes atrophic (Aleman *et al.*, 2002). The disease often presents initially as an isolated retinal dystrophy; the characteristic macular involvement and the importance of visual impairment in a previously well seeing patient should lead to perform neurological investigations.

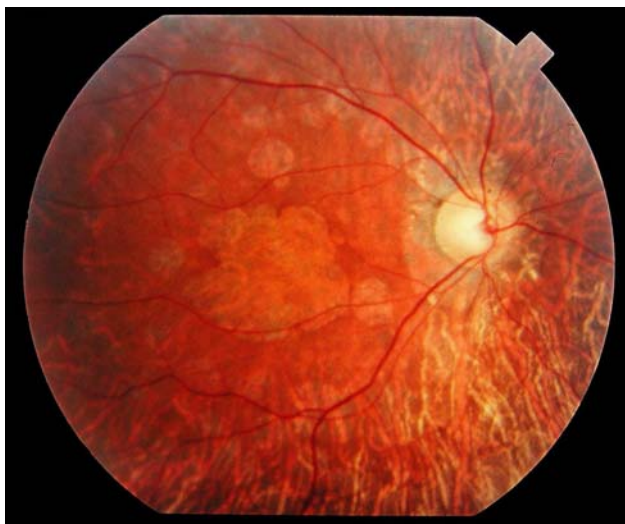


Figure 3: Fundus of a 34 year-old patient with cone rod dystrophy due to SCA7. Note that the macular area, and also the mid periphery, are atrophic.

Ectodermal diseases. CRD is sometimes encountered in:

Amelogenesis imperfecta. This refers to several conditions in which the tooth enamel is abnormal. In one form of autosomal recessive inheritance (OMIM # 217080), it is associated

with CRD and abnormally shaped teeth (Jalili *et al.*, 1988; Downey *et al.*, 2002; Michaelides *et al.*, 2004).

Hypotrichosis with juvenile macular dystrophy (Sprecher *et al.*, 2001). It is a rare form of autosomal recessive alopecia associated with macular dystrophy in which the retinal impairment is usually restricted to the macula but in a few occasions it has been reported to be a CRD (Samra *et al.*, 1988).

Dysmorphic syndromes. Occurrence of CRDs have been reported in spondylometaphyseal dysplasia (Walters *et al.*, 2004) and in cleft lip (Ausems *et al.*, 1996).

Metabolic dysfunctions. There are several metabolic diseases in which CRD has been reported. These are thiamine-responsive megaloblastic anemia (Meire *et al.*, 2000 ; Kipioti *et al.*, 2003), one case of mitochondrial mutation (T8993G, Porto *et al.*, 2001). In addition, infantile Refsum disease with augmented phytanic acid and pigmentary retinopathy is associated with a characteristic prominent macular involvement, and in Alport syndrome (deafness, progressive nephritis) the fundus shows whitish flecks looking like crystals around the macula rather than an authentic pigmentary retinopathy.

Management including treatment

Management is not different from typical RP. A particular emphasis should be put on filtering spectacles to minimize photophobia. Patients are often severely visually disabled or legally blind by the end of the second decade. Therefore, it is important that they undertake studies for an adapted professional occupation (teaching, computer based activities, physiotherapist).

Etiology

Non syndromic CRDs (syndromic CRDs have been reviewed in the above chapter) are, like typical RP, genetically heterogenous with the 3 mendelian type of inheritance being encountered. Today, there are 13 genes responsible for non syndromic CRD (10 cloned, 3 mapped). These genes can be classified in several categories.

The 1st category includes genes mostly responsible for CRD cases. The predominant one encodes the homeobox protein CRX, which controls the differentiation of photoreceptor rods and cones, but also the maintenance of their phenotype in adults. Most CRX mutations cause autosomal dominant CRD with a prevalence estimated at 5 to 10 % of dominant CRDs (Freund *et al.*, 1997; Swain *et al.*, 1997). The severity of the disease is highly variable with some mild cases and very severe cases. In fact, at this end of the spectrum, there have been a

few reports of dominant Leber congenital amaurosis (LCA), a condition, which is usually recessive, due to *CRX* mutations (Swaroop *et al.*, 1999; Perrault *et al.*, 2003), as well as a few RPs. Two other genes have been found only in CRDs. These are *RIM1*, reported in one family with autosomal dominant CRD (Johnston *et al.*, 2003) and *HRG4*, reported in one family with uncertain inheritance (Kobayashi *et al.*, 2000). Interestingly, both encoded proteins are involved in photoreceptor synaptic transmission.

The 2nd category includes genes mostly found in macular dystrophies. Today, it comprises essentially one gene, *ABCA4*, involved in the retinoid metabolism and causing Stargardt's disease. Mutations in *ABCA4* appear as a very frequent cause of autosomal recessive CRD since they are responsible for 30 to 60 % of recessive CRDs (Maugeri *et al.*, 2000; Papaioannou *et al.*, 2000; Briggs *et al.*, 2001; Ducroq *et al.*, 2002; Fishman *et al.*, 2003; Klevering *et al.*, 2004). In some cases, the disease begins as a Stargardt macular dystrophy, which soon extends to the periphery. In other cases, the disease starts as a diffuse retinopathy with predominance of macular involvement. It has been shown that mutations in *ABCA4*-linked CRDs are truncating mutations, often on both alleles, whereas amino acid change mutations are more frequently found in Stargardt disease. This suggests that more deleterious truncating mutations are associated with more severe conditions like CRD (Rozet *et al.*, 1999). Belonging to this 2nd category, mutations of *GUCA1A* have been described in one family with autosomal dominant CRD while all other *GUCA1A* mutations are responsible for cone dystrophies. *GUCA1A* encodes a protein activating the guanylate cyclase (Downes *et al.*, 2001), the guanylate cyclase itself being sometimes also involved in CRDs (see below).

The 3rd category includes two genes mostly found in RP cases. One codes for the outer segment protein peripherin/RDS and is usually involved in autosomal dominant RP. It is well known that there are inter- and intra-familial phenotypic variations with RDS mutations including cases of dominant macular dystrophy or dominant CRD (Nakazawa *et al.*, 1996). CRDs due to RDS are relatively moderate in comparison with autosomal recessive CRDs, the autonomy of patients being conserved in early adulthood. Another gene codes for RPGR involved in opsin trafficking, particularly that of cone opsins. *RPGR* is the major gene for X-linked RPs, but it also accounts for some X-linked CRD (Demirci *et al.*, 2002) and cone dystrophies. As for RPs, CRDs due to *RPGR* are severe and diagnosed early in life.

The 4th category includes genes found in LCA. Today, there have been together 3 reported CRD families with mutations in *RPGRIP1* (Hameed *et al.*, 2003) inherited as an autosomal recessive trait and *AIP1* (Sohocki *et al.*, 2000) inherited as an autosomal dominant trait, these genes being responsible usually for LCA. There have been also several reported CRD families with mutations in *GUCY2D* (Perrault *et al.*, 1998; Kelsell *et al.*, 1998), which is the major gene for LCA. In contrast to LCA patients, *GUCY2D*-related CRD patients have a dominant condition, the mutations being restricted to exon 13 encoding the dimerization domain of guanylate cyclase.

There remain also loci for which the gene has to be cloned. For autosomal dominant CRDs, *CORD1*, an undetermined localisation, has been found in a Danish family with CRD and mental retardation (Warburg *et al.*, 1991), and *CORD4* has been mapped in a Canadian family with CRD associated with neurofibromatosis (Klystra *et al.*, 1993). For autosomal recessive CRDs, there are *CORD8* mapped in a Pakistanese family (Khaliq *et al.*, 2000) and *CORD9* in a Brazilian family (Danciger *et al.*, 2001). For X-linked CRDs, *COD4* has been mapped in a Finnish family (Jalkanen *et al.*, 2003).

Taken together, it seems that most genes responsible for CRDs are involved in other types of retinal dystrophies, including RPs, macular dystrophies and cone dystrophies, thereby placing CRDs at the center of the vast panel of retinal dystrophies. One can therefore speculate that any retinal dystrophy gene may potentially be involved in CRD, and the challenge is to understand the underlying mechanisms. It seems clear that highly deleterious mutations of RP genes can cause very severe diseases, and hence CRDs, but it is not yet clear why some family members have macular dystrophy or RP, whereas other members with the same mutations have CRD.

Diagnostic methods

See [RP](#)

Genetic counseling

See [RP](#)

Antenatal diagnosis

See [RP](#)

Unresolved questions

See [RP](#)

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