

Cone dystrophies

Part 3: Progressive cone dystrophy

The cone dystrophies represent a heterogeneous collection of diseases characterised by cone-mediated electroretinogram (ERG) abnormalities and colour vision deficiency. Two principal forms of cone dystrophy are recognised: progressive cone dystrophy and stationary cone dystrophy.

Progressive cone dystrophy is typified by the deterioration of cone-mediated visual function. Clinical features include reduced visual acuity, colour vision deficiency, photophobia, nystagmus, visual field defects and abnormalities of the photopic ERG. Visual field defects include central scotomata^{1,2}, peripheral field loss¹, generalised depression of sensitivity² and ring scotomata³. Fundus examination usually shows a 'bull's-eye maculopathy' but in the later stages, there may be peripheral atrophy and pigmentation (Figure 1).

Other reported findings include white flecks at the level of the retinal pigment epithelium (RPE)^{1,4} and the so-called 'tapetal-like' sheen^{2,5}. Fluorescein angiography usually shows hyperfluorescence at the macula due to underlying RPE atrophy, and the so-called 'dark choroid' sign is commonly seen. Ophthalmoscopic abnormalities are usually confined to the macula in the early stages of the disease, however, at this stage there is normally psychophysical and electrophysiological evidence of widespread cone dysfunction⁶.

A distinction is sometimes drawn between progressive cone and cone-rod dystrophies. Patients with pure cone dystrophy have a normal rod function; in contrast, those with cone-rod dystrophy have a concomitant (and less severe) rod dysfunction. However, the distinction

between cone and cone-rod dystrophy is ambiguous and many patients described as having a pure cone dystrophy develop rod impairment as the disease progresses; in some cases, this deterioration may be profound¹.

Progressive cone and cone-rod dystrophies may be inherited as autosomal recessive, autosomal dominant or X-linked recessive traits, though most cases are sporadic. The most common inheritance pattern is autosomal dominant¹.

Classification of progressive cone dystrophies

Whilst the progressive cone dystrophies represent a wide array of conditions, various means of phenotypical classification have been proposed, which have involved psychophysics, electrophysiology and molecular/medical genetics. Perhaps the simplest means of classification is via inheritance pattern. There is, however, considerable genetic and phenotypic heterogeneity within each class of inheritance.

X-linked recessive

X-linked progressive cone dystrophy is uncommon, though there are detailed reports of several pedigrees^{2,5,6,8,24-27}. It is evident from the clinical descriptions of these families that there is rod dysfunction late in the disease. Therefore, these disorders might be better classified as

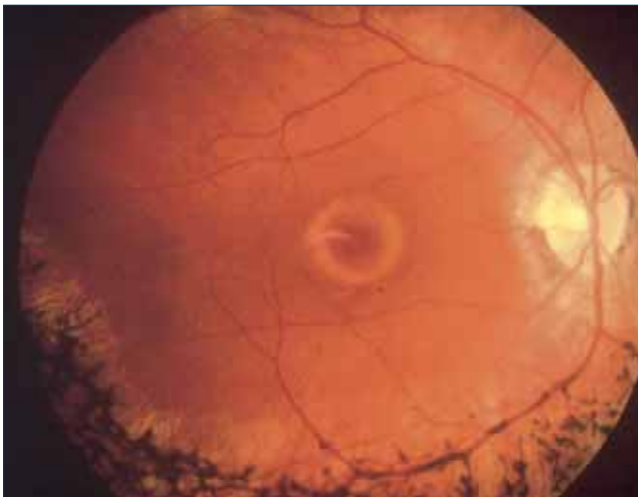
progressive cone-rod dystrophies.

Affected males are often myopic, and usually present with subnormal acuity and colour vision deficiency. A tapetal-like sheen, which diminishes with dark adaptation (the so-called 'Mizuo phenomenon'), has been reported in affected males from some families⁵. Most subjects with X-linked disease are reported to exhibit preferential involvement of the central cones early in the course of the disease; this later progresses to diffuse involvement. There are exceptions, however. For example, the family reported by Pinckers and Timmerman²⁸ showed early involvement of peripheral cones. Carrier females are usually asymptomatic but can sometimes be identified by subnormal electroretinographic responses²⁹ or subtle anomalies of colour vision. In the family studied by van Everdingen *et al*⁹, for example, 87% of obligate heterozygotes exhibited pseudoprotanomaly. The majority of carriers also showed reduced cone photopigment density on foveal densitometry.

X-linked progressive cone dystrophy has been mapped using genetic linkage studies to three loci: Xp11.4 (COD1)²⁴, Xq27 (COD2)³⁰ and to Xq28 (not assigned)⁸.

Although few families are available for comparison, there are clear differences in the phenotypes of families mapping to the three loci. Reichel *et al*⁸ have described a pedigree in which progressive cone dystrophy is accompanied by a protanopic colour vision deficiency: molecular analysis of the L-cone photopigment gene revealed a 6.5kb deletion. Histology has recently been performed on the eyes of one member of this pedigree³¹. The patient, a 71-year old male, had a visual acuity of 6/60 with evidence of macular degeneration at the time of his last ophthalmological examination. In the macular region, there was a severe loss of both rod and cone photoreceptors. In the peripheral retina, there appeared to be a relative preservation of the S-cones and rods. Kellner *et al*⁷ reported two patients with a similar phenotype, but with no family history of cone dystrophy. The patients, like those of Reichel *et al*, displayed a protan colour vision deficiency; screening of the photopigment array revealed that one patient possessed a single L/M-hybrid gene, whilst the other had a L/M-hybrid gene in combination with a normal M-cone photopigment gene.

Such genotypes usually result in congenital colour vision deficiency. It is unclear as to how such genotypes might



» **Figure 1**
Fundus changes associated with progressive cone dystrophy. There is a prominent loss of RPE in the classical 'bull's eye' pattern with peripheral 'bone-spicule' pigmentation

Syndrome	Inheritance	Ocular phenotype	Systemic phenotype	Reference
Bardet-Biedl syndrome	Autosomal dominant	CRD Myopia	Polydactyly, obesity, variable mental retardation, hypogonadism	Kwitek-Black <i>et al</i> (1993) ⁶⁰
Alström's syndrome	Autosomal recessive	Early onset CRD	Diabetes, obesity, deafness Other endocrine abnormalities	Michaud <i>et al</i> (1996) ⁶³
Pierre-Marie ataxia and CRD	Autosomal dominant	CRD	Ataxia	Bjork <i>et al</i> (1968) ⁶⁴
Amelogenesis imperfecta and CRD	Autosomal recessive	Early onset CRD	Defective tooth enamel	Jalili & Smith (1988) ⁶⁵
Obesity cardiomyopathy and retinal dystrophy	Autosomal recessive	Early onset CRD	Obesity, cardiomyopathy	Russell-Eggitt <i>et al</i> (1989) ⁶⁶
Liver disease and cone dystrophy	Autosomal recessive	Early onset CRD	Liver disease, endocrine dysfunction, hearing defects	Hansen <i>et al</i> (1976) ⁶⁷
Cone dystrophy with light fixation and ataxia	Autosomal recessive	Cone dystrophy	Seizures, facial abnormalities, abnormalities of the digits	Rauch <i>et al</i> (1999) ⁶⁸
Trichomegally and CRD	Autosomal recessive	Early onset CRD	Enlarged lashes Excessive body hair	Jalili (1989) ⁶⁹

Table 1

Syndromes with associated
cone or cone-rod dystrophy (CRD)

cause progressive cone dystrophy, and it is most likely that these patients were simply daltonians (i.e. they had congenital colour vision deficiency) and co-incidentally developed progressive cone dystrophy as a completely unrelated event. There is some evidence to suggest that substitution of cysteine for arginine at position 203 of the M- or L-cone opsin might give rise to visual impairment (i.e. beyond a simple red-green colour vision deficiency).

Meire *et al*²⁴ provided the first detailed report of the phenotype of an X-linked cone dystrophy which results from a mutation in the retinitis pigmentosa GTPase regulator (RPGR) gene at Xp11.4 (COD1)³². Affected patients were myopic, had impaired colour vision (leading to achromatopsia in older subjects) progressively impaired visual acuity, abnormal photopic ERGs and an abnormal electro-oculogram. Visual field testing revealed central scotomata, and the dark adaptation curve was monophasic, with no observable cone mediated phase. As noted above, carriers of this dystrophy are clinically normal, however, they have abnormal ERG responses to 30Hz flicker, minor colour vision abnormalities and small paracentral field defects²⁹. The exact function of RPGR is not precisely known, although it has been established that the protein localises to both rod and cone photoreceptor outer segments³³. The majority of mutations in the RPGR reported thus far are associated with retinitis pigmentosa.

The dystrophy linked to Xq27 (COD2)³⁴ appears to selectively affect the peripheral cones early in the course of the disease. The causative gene is yet to be established.

A recent study of a Finnish pedigree suggests that there may be a fourth distinct locus for X-linked recessive progressive cone dystrophy³³.

Autosomal dominant

Several genomic loci have been implicated in the aetiology of autosomal dominant progressive cone-rod dystrophy (PCRD). The disorder has been mapped to several loci; the CRX gene on chromosome 19q13.3³⁵⁻³⁷ the retinal guanylate cyclase gene on 17p12-p13³⁸⁻⁴⁰, the peripherin/RDS gene on chromosome 6p12⁴¹⁻⁴⁴, the guanylate cyclase activating protein 1 (GCAP1) gene on chromosome 6p21.1⁴⁵, the Rab3A-interacting molecule (RIM1) gene on chromosome 6q14⁴⁶ and to 8p11 (causative gene not yet identified)⁴⁷. In addition, the genetic defect in two sporadic cases of cone-rod dystrophy have been reported; the first was associated with a cytogenetically visible deletion of 18q211⁴⁸ and the second was associated with neurofibromatosis type 1, suggesting that there may be a further locus for PCRD on chromosome 17p⁴⁹.

The PCRD dystrophy linked to chromosome 19q results in a relatively severe phenotype. Loss of visual acuity occurs in the first decade and night blindness develops in the third decade, progressing to severe loss of visual function

by 50yr³⁷. Freund *et al*⁵⁰ have demonstrated that mutations in a novel photoreceptor-specific homeodomain transcription factor gene (CRX) give rise to an autosomal dominant form of PCRD linked to the COD2 locus on chromosome 19q13 in one large family, and in a second smaller family with a similar phenotype. CRX acts as a transcription factor, and is vital for photoreceptor development and maintenance.

Mutations to the Rab3A-interacting molecule (RIM1) gene on chromosome 6q causes a cone-rod dystrophy which shares some similarities with Stargardt's disease, including the so-called 'dark choroid sign' on fluorescein angiography⁵¹. In the retina, RIM1 is localised to the pre-synaptic ribbons of the photoreceptors⁴⁶.

Mutations of the peripherin/RDS gene on chromosome 6p have been reported in PCRD, as well as in a wide variety of dominantly inherited retinal dystrophies, including retinitis pigmentosa, pattern and macular dystrophies. Peripherin/RDS is a photoreceptor-specific glycoprotein which is present in both rod and cone outer segments and may be important in the stabilisation of outer segment structure.

* The chromosome 19q mutation in the original family described by Evans *et al* (1995) has yet to be identified (Simunovic & Moore, 1998)

Thus, mutations of the gene coding for peripherin/RDS would be expected to affect the function of both types of photoreceptor. Mutations associated with PCRD include Ser27Phe⁵², Tyr184Ser⁴², Asn244His⁴², Asn244Lys⁵³, Val200Glu⁴¹, Met67del⁴³ and Lys193del⁴³. The reported phenotypes associated with peripherin/RDS mutations are, with the exception of the family described by Fishman *et al*⁴⁴, of a relatively severe PCRD with early macular atrophy and later peripheral retinal atrophy. Whilst it is clear that a diverse range of retinal phenotypes result from mutations of the peripherin/RDS gene, the reason(s) why different mutations have such a variable effect on retinal function is poorly understood.

The PCRD associated with chromosome 17p12-p13 results in less severe visual loss with better preserved rod function. Recently, the genetic mutations for the 17p dystrophy were discovered. Kelsell *et al*⁵⁴ identified two dominant missense mutations in the retinal guanylate cyclase (RET-GC1) gene on 17p in four families with autosomal dominant cone-rod dystrophy. Homozygous mutations of this gene had already been identified as a cause of infantile rod-cone dystrophy (Leber's amaurosis) by Perrault *et al*⁵⁵.

It is improbable that simple haplo-insufficiency could account for CRD phenotype; rather it is likely that mutations behave in a dominant negative fashion, interfering with normal function of retinal guanylate cyclase. The function of the latter is itself modulated by GCAP1, a calcium sensitive activator of retinal guanylate cyclase. Like the peripherin/RDS gene, the gene for GCAP is on chromosome 6p.

Although RETGC and GCAP1 interact with one another, their mutations give rise to distinct phenotypes: mutations of RETGC give rise to a mixed photoreceptor dystrophy, whereas mutations in GCAP1 are associated with a pure cone dystrophy⁴⁵.

Went *et al*⁵⁶ have investigated a pedigree with a dominantly inherited progressive cone dystrophy characterised by the early onset of a tritan colour vision deficiency. Candidate analysis of the S-cone photopigment gene, however, failed to find evidence of abnormality.

Mutations of other genes responsible for progressive cone dystrophy remain to be discovered. These will be identified either by initial linkage studies in large families, followed by analysis of candidate genes mapping to the same loci, or by the study of genes which seem to be good candidates based upon careful investigation of the phenotype in smaller families.

Autosomal recessive

Most patients with progressive cone or cone-rod dystrophy have no affected relatives, and it is likely that many have autosomal recessive disease. In contrast to X-linked and autosomal dominant forms of the disorder, there is little documentation on the phenotype of individuals with progressive cone dystrophy in whom there is a family history compatible with recessive disease. It is likely, however, that autosomal recessive progressive cone dystrophy is genetically heterogeneous. Most of the syndromes, in which cone dystrophy is associated with other systemic abnormalities, display autosomal recessive inheritance (Table 1). In the majority, the retinal dystrophy is of early onset and has a

poor visual prognosis.

As yet, few of the causative genes have been identified. However, mutations of ABCA-4, which codes for a photoreceptor transmembrane transporter of vitamin A derivatives, have been implicated as a cause of autosomal recessive progressive cone dystrophy. This dystrophy is characterised by early involvement of the central retina, though there is some evidence of peripheral involvement in advanced disease⁵⁷. Candidate analysis suggests that mutations in the CNGA3 gene encoding the alpha-subunit of the cone photoreceptor cGMP-gated channel are also a cause of autosomal recessive progressive cone dystrophy, though such mutations are more commonly associated with rod monochromatism or incomplete achromatopsia⁵⁸. Whilst no other causative genes have been described, it should be noted that progressive cone dystrophy has been linked to chromosome 1q12-1q24⁵⁹, and the Bardet-Biedl syndrome has been mapped to chromosome 16q60 11q, 3q61 and 15q⁶².

Conclusion

Although most patients with progressive cone dystrophy undergo routine ophthalmological assessment, optometrists are closely involved in the management of symptoms, especially photophobia. The management of the cone dystrophies will be dealt with in the final article in this series.

References

For a full set of references, email nicky@optometry.co.uk.

MQs

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1. Progressive cone dystrophy may be associated with all of the following fundus abnormalities except which one?

- Peripapillary atrophy
- Peripheral pigmentation
- Bull's eye maculopathy
- Tapetal-like sheen

2. Which one of the following statements is true of the inheritance of progressive cone dystrophy?

- The mode of inheritance can always be established, and is most commonly autosomal dominant
- The most common mode of inheritance is X-linked recessive
- Whilst most cases are sporadic, the most common pattern of inheritance observed is autosomal dominant
- The most common mode of inheritance is autosomal recessive

3. Which one of the following forms of colour vision deficiency is not usually associated with progressive cone dystrophy?

- Protanomaly
- Classical tritan defects
- Tetartanopia
- Type II acquired

4. X-linked progressive cone dystrophy is generally characterised by which one of the following?

- Well preserved acuity
- Well preserved colour vision
- Preferential involvement of the central cones
- Preferential involvement of the peripheral cones

5. Which one of the following mutations is a cause of X-linked recessive cone dystrophy?

- Mutation of the rhodopsin gene
- Deletions in the L-cone opsin gene
- Deletions in the S-cone opsin gene
- Deletions in the cone transducin gene

6. Which one of the following statements is true of autosomal dominant progressive cone dystrophy?

- Carriers of autosomal dominant progressive cone dystrophy are phenotypically normal
- Autosomal dominant progressive cone dystrophy normally results from mutations in gene coding for cone opsins
- Autosomal dominant progressive cone dystrophy may be caused by mutations to genes coding for proteins expressed by both cones and rods
- Autosomal dominant cone dystrophy is the least common form of progressive cone dystrophy

Please note that this is a Q&A series.

Answers to Part 3 will be published with Part 4 on November 19.