

## PERSPECTIVE

## The cone dysfunction syndromes

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The cone dystrophies comprise a heterogeneous group of disorders characterised by visual loss, abnormalities of colour vision, central scotomata, and a variable degree of nystagmus and photophobia. They may be stationary or progressive. The stationary cone dystrophies are better described as cone dysfunction syndromes since a dystrophy often describes a progressive process. These different syndromes encompass a wide range of clinical and psychophysical findings. The aim is to review current knowledge relating to the cone dysfunction syndromes, with discussion of the various phenotypes, the currently mapped genes, and genotype-phenotype relations. The cone dysfunction syndromes that will be discussed are complete and incomplete achromatopsia, oligocone trichromacy, cone monochromatism, blue cone monochromatism, and Bornholm eye disease. Disorders with a progressive cone dystrophy phenotype will not be discussed.

Affected individuals usually present in infancy with pendular nystagmus, poor visual acuity, and photophobia. A hypermetropic refractive error is common and it is often found that the nystagmus wanes with time.<sup>5</sup> Fundal examination is usually normal; however, infrequently, central or mid-peripheral retinal pigment epithelial abnormalities are present. Electroretinography (ERG) reveals absent cone responses and normal rod responses.<sup>6</sup> Affected individuals usually achieve a visual acuity of 6/60, have absent colour vision, and have normal rod function but absent cone function on psychophysical testing.<sup>7</sup>

Achromatopsia is recessively inherited and genetically heterogeneous. To date, three achromatopsia genes have been identified, *CNGA3*, *CNGB3*, and *GNAT2*; all three genes will be described in detail in the discussion that follows. The first molecular genetic report of achromatopsia was a cytogenetic analysis of a 20 year old woman with achromatopsia and multiple developmental abnormalities.<sup>8</sup> Maternal isodisomy of chromosome 14 was demonstrated (both copies of chromosome 14 were of maternal origin). However, there has been no subsequent confirmation of a locus on chromosome 14. In 1997 a genome-wide search for linkage was performed in a consanguineous Jewish kindred, establishing linkage to a 14 cM region on 2q11.<sup>9</sup> This disease interval was further refined to a 3 cM region in 1998 in a study of eight families of different ethnic and racial origins, and *CNGA3* was identified as a candidate gene within this interval.<sup>10</sup> *CNGA3* encodes the  $\alpha$ -subunit of the cGMP gated (CNG) cation channel in human cone photoreceptors, the final critical effector in the phototransduction cascade. In the dark, cGMP levels are high in cone photoreceptors, therefore enabling cGMP to bind to the  $\alpha$  and  $\beta$ -subunits of CNG channels, resulting in them adopting an open conformation and permitting an influx of cations, with consequent cone depolarisation. However, in light conditions, activated photopigment initiates a cascade culminating in increased cGMP phosphodiesterase activity, thereby lowering the concentration of cGMP in the photoreceptor which results in closure of CNG cation channels and consequent cone hyperpolarisation.<sup>11</sup>

The cone dystrophies are characterised by bilateral visual loss, colour vision abnormalities, central scotomata, variable degrees of nystagmus and photophobia, together with electrophysiological or psychophysical evidence of abnormal cone function. There is considerable clinical and genetic heterogeneity; cone dystrophies showing autosomal dominant, autosomal recessive, and X linked recessive inheritance have all been reported. These disorders may be stationary or progressive. The stationary subtypes are congenital with normal rod function, whereas in progressive cone dystrophies, onset is usually in childhood or early adult life and patients often develop rod photoreceptor dysfunction in later life. The stationary disorders are better described as cone dysfunction syndromes. In this review we will describe the various phenotypes and disease causing genes that have been recently identified in this group of disorders (table 1). We will not consider the various forms of colour vision deficiency; the molecular genetic basis of these disorders has now been well characterised and several reviews have been published on the subject.<sup>1–2</sup>

**COMPLETE ACHROMATOPSIA**

Complete achromatopsia, typical achromatopsia or rod monochromatism, is a stationary disorder in which there is an absence of functioning cone photoreceptors in the retina.<sup>3–5</sup> It is uncommon with an incidence of about 1 in 30 000.<sup>3–4</sup>

Missense mutations in highly conserved residues of *CNGA3* were initially described in five families with complete achromatopsia from Germany, Norway, and the United States.<sup>12</sup> Since then more recent studies have revealed more than 50 disease causing mutations in *CNGA3*.<sup>13–14</sup> Mutations have been identified throughout the *CNGA3* protein, including the five transmembrane domains, the pore region,

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**Table 1** Summary of the cone dysfunction syndromes

Cone dysfunction syndrome	Alternative names	Mode of inheritance	Visual acuity	Refractive error	Nystagmus	Colour vision	Fundi	Mutated gene(s) or chromosome locus
Complete achromatopsia	Rod monochromatism Typical achromatopsia	Autosomal recessive	6/36–6/60	Often hypermetropia	Present	Absent	Usually normal	<i>CNGA3</i> <i>CNGB3</i> <i>GNAT2</i> Chromosome 14 <i>CNGA3</i>
Incomplete achromatopsia Oligocone trichromacy	Atypical achromatopsia Oligocone syndrome	Autosomal recessive Autosomal recessive	6/24–6/60 6/12–6/24	Often hypermetropia Equal incidence of myopia and hypermetropia	Present Usually absent	Residual Normal	Usually normal Normal	<i>CNGA3</i>
Cone monochromatism	–	Uncertain	6/6	–	Absent	Absent or markedly reduced	Normal	–
Blue cone monochromatism	X linked atypical achromatopsia X linked incomplete achromatopsia	X linked	6/24–6/60	Often myopia	Present	Residual tritan discrimination	Usually normal	(i) Deletion of the LCR  (ii) Single inactivated L/M hybrid gene* Xq28
Bornholm eye disease	–	X linked	6/9–6/18	Moderate to high myopia with astigmatism	Absent	Deuteranopia	Myopic	–

LCR = locus control region; deletion in this region abolishes transcription of all L and M genes in the opsin pigment gene array and therefore inactivates both L and M cones.

\*In the second class of mutations the LCR is preserved but changes within the L and M gene array lead to loss of functional pigment production. The most common genotype in this class consists of a single inactivated L/M hybrid gene. The most frequent inactivating mutation described results in a cysteine to arginine substitution, (Cys203Arg), a mutation known to disrupt the folding of cone opsin molecules.

and cGMP binding site. However, four mutations in particular (Arg277Cys, Arg283Trp, Arg436Trp and Phe547Leu) are found most commonly, accounting for approximately 40% of all mutant *CNGA3* alleles.<sup>13</sup> Moreover, subsequent analysis of the homologous *CNGB3* knockout mouse model showed complete absence of physiologically measurable cone function, a decrease in the number of cones in the retina, and morphological abnormalities of the remaining cones.<sup>15</sup>

The second gene identified in patients with achromatopsia was aided by a population with an unusually high incidence of the disease; 5% to 10% of the Pingelapese people of the Eastern Caroline Islands in Micronesia in the western Pacific have achromatopsia.<sup>16</sup> This is most probably related to the sharp reduction of the island's population to approximately 20 individuals following a typhoon in 1775, with the island being subsequently repopulated during two centuries of isolation. In 1999 linkage analysis excluded 2q but demonstrated linkage to 8q21–q22.<sup>17</sup> Sundin *et al* narrowed the region to 1.4 cM and identified a missense mutation, Ser435Phe, in the Pingelapese achromats, at a highly conserved site in *CNGB3*, the gene coding for the  $\beta$ -subunit of cone photoreceptor CNG cation channels.<sup>18</sup> They also identified two independent frameshift deletions in a different population, Pro273fs and Thr383fs, thereby establishing that achromatopsia is the null phenotype of *CNGB3*. A similar study by Kohl *et al* identified six mutations in *CNGB3*; three were novel—Arg203stop, Glu366stop, and a putative splice site defect.<sup>19</sup> Rojas *et al* have since identified Asp149fs in a consanguineous Chilean family.<sup>20</sup> The most frequent mutation of *CNGB3* identified to date is the 1 base pair frameshift deletion, 1148delC (Thr383fs), which accounts for up to 84% of *CNGB3* mutant disease chromosomes.<sup>19–21</sup>

Currently there is far greater allelic heterogeneity of *CNGA3* mutants (over 50 mutations described) when compared to *CNGB3* (~7). It is known that *CNGA3* subunits can form functional homomeric channels when expressed alone, whereas *CNGB3* subunits alone do not appear to form functional channels.<sup>22</sup> In our opinion it is therefore plausible that some *CNGB3* null mutations are not detected since sufficient channel function is possible solely with normal *CNGA3* subunits, leading to a relatively normal phenotype.

These studies of *CNGA3* and *CNGB3* have demonstrated that both the  $\alpha$  and  $\beta$ -subunits of the CNG cation channel are essential for phototransduction in all three classes of cones. The majority of *CNGA3* mutations identified to date are missense mutations, indicating that there is little tolerance for substitutions with respect to functional and structural integrity of the channel polypeptide. This notion is supported by the high degree of evolutionary conservation among CNG channel  $\alpha$ -subunits. In contrast, the majority of *CNGB3* alterations are nonsense mutations. It is currently proposed that approximately 25% of achromatopsia results from mutations of *CNGA3*<sup>13</sup> and 40–50% from mutations of *CNGB3*.<sup>19–21</sup> Therefore, while mutations in the cone channel subunit genes, *CNGA3* and *CNGB3*, account for the majority of achromats, there is a significant proportion of patients for whom neither *CNGA3* nor *CNGB3* mutations can be found (~30%). The phenotype associated with mutations in these two channel protein genes appears to be in keeping with previous clinical descriptions of achromatopsia.<sup>12–14 18–20</sup>

It is of interest that missense mutations in *CNGA3* have also been reported in two individuals with cone-rod dystrophy and in a single individual with a progressive cone dystrophy phenotype.<sup>13</sup> Possible reasons for a progressive phenotype in these individuals may include the particular combination of missense mutations present in these three subjects; some amino acid substitutions may be more deleterious to channel function than others. Other potential

phenotypic influences include the presence of other modifier genes or environmental effects.

Cone degeneration (cd) is an autosomal recessive canine disease that occurs naturally in the Alaskan Malamute and German shorthaired pointer breeds and is phenotypically similar to human achromatopsia.<sup>23</sup> Canine *CNGB3* mutations have recently been identified in both of these breeds, thereby establishing these cd affected dogs as the only naturally occurring large animal model of human achromatopsia, and therefore providing a valuable system for exploring disease mechanisms and evaluating potential genetic therapeutic intervention in human achromatopsia.<sup>23</sup>

*GNAT2*, located at 1p13, is the third gene to be implicated in achromatopsia.<sup>24, 25</sup> *GNAT2* codes for the  $\alpha$ -subunit of cone specific transducin. In cone cells, light activated photopigment interacts with transducin, a three subunit guanine nucleotide binding protein, stimulating the exchange of bound GDP for GTP. The cone  $\alpha$ -transducin subunit, which is bound to GTP, is then released from its  $\beta$  and  $\gamma$ -subunits and activates cGMP phosphodiesterase by removing the inhibitory  $\gamma$ -subunits from the active site of this enzyme. cGMP phosphodiesterase lowers the concentration of cGMP in the photoreceptor which results in closure of cGMP gated cation channels.<sup>11</sup> All the *GNAT2* mutations identified to date result in premature translation termination and in protein truncation at the carboxy terminus.<sup>24, 25</sup> However, mutations in this gene are thought to be responsible for less than 2% of patients affected with this disorder,<sup>24</sup> suggesting the presence of further genetic heterogeneity in achromatopsia.

We have recently undertaken a detailed description of the phenotype associated with *GNAT2* inactivation in a large consanguineous Pakistani family.<sup>26</sup> The phenotype is characterised by mild photophobia, nystagmus, abnormal colour vision, and poor visual acuity (6/36 to counting fingers). On detailed colour vision testing, residual colour discrimination was detected in three individuals. ERGs revealed absent cone responses, with normal rod specific ERGs. We were able to record S cone ERG responses in all patients. In two older subjects, a worsening of visual acuity with age has been documented, although we have no definite evidence of progressive deterioration in retinal function. The residual S cone function detected in this *GNAT2* associated phenotype is intriguing. The evidence that *GNAT2* is expressed in all three cone types comes from the immunohistochemical demonstration that an antibody raised against cone  $\alpha$ -transducin peptides cross reacts with all three classes of cone photoreceptor in the human retina.<sup>27</sup> This does not however definitively rule out the possibility that S cones may express an alternative form of  $\alpha$ -transducin, since identical epitopes may be present on both forms. It may also be significant that Southern blot analysis of human genomic DNA indicated that there may be more than one cone  $\alpha$ -transducin gene.<sup>27</sup> Therefore, it remains a possibility that *GNAT2* is not expressed in S cones, and that the residual S cone function detected in our family arises from the use of another distinct form of  $\alpha$ -transducin. The residual tritan colour discrimination detected may be accounted for by a comparison between quantum catches in the remaining functional S cones and rod photoreceptors, in the manner proposed to underlie colour discrimination detected in blue cone monochromatism.<sup>28</sup>

The three genes described to date associated with achromatopsia, *CNGA3*, *CNGB3* and *GNAT2*, encode proteins in the cone phototransduction cascade. It is therefore reasonable to propose that further cone specific intermediates involved in phototransduction represent good candidates. These include the genes encoding the cone specific  $\beta$  and  $\gamma$ -transducin subunits and cone phosphodiesterase. It is of note that immunological studies of the canine cd affected retina have demonstrated a specific absence or delocalisation of

$\beta$  and  $\gamma$  cone specific transducin subunits from the outer segments of pre-degenerate cone photoreceptors. However, genes for both subunit proteins have been excluded as canine cd genes.<sup>29, 30</sup>

### INCOMPLETE ACHROMATOPSIA

Previously, before the underlying pathogenesis of blue cone monochromatism (BCM) had been identified, BCM was known as X linked incomplete or atypical achromatopsia. However, the term incomplete/atypical achromatopsia is best reserved for the description of individuals with autosomal recessive disease where the phenotype is a variant of complete achromatopsia. Individuals with incomplete achromatopsia (atypical achromatopsia) retain residual colour vision and have mildly better visual acuity (6/24–6/60) than those with complete achromatopsia.<sup>5, 31</sup> In all other respects, the phenotype of these two conditions is indistinguishable. Three subtypes of incomplete achromatopsia have been demonstrated via colour matching experiments<sup>31</sup>:

- colour matches are governed by rods and M cones (incomplete achromatopsia with protan luminosity)<sup>32</sup>;
- colour matches are governed by L and M cones;
- colour matches mediated by rods, L cones, and S cones (incomplete achromatopsia with deutan luminosity).<sup>33, 34</sup>

As in the complete form, mutations in *CNGA3*, the gene encoding the  $\alpha$ -subunit of the cGMP gated cation channel in cones, have been identified in individuals with incomplete achromatopsia.<sup>13</sup> The psychophysical data provided in this study<sup>13</sup> are inadequate to be able to classify these individuals into the three colour matching subtypes described above.<sup>31–34</sup> The 19 mutations identified were all missense mutations, located throughout the channel polypeptide including the transmembrane domains, ion pore, and cGMP binding region. However, only three of these missense mutations, Arg427Cys, Arg563His, and Thr565Met, were found exclusively in patients with incomplete achromatopsia.<sup>13</sup> Therefore in the majority of cases of incomplete achromatopsia, factors other than the specific causative mutation, such as modifier genes, or environmental influences, may dictate the phenotype. The missense variants identified in incomplete achromatopsia must be compatible with residual channel function since the phenotype is milder than in complete achromatopsia.

Mutations in *CNGB3* or *GNAT2* have not been reported in association with incomplete achromatopsia, despite mutant *CNGB3* alleles being identified twice as commonly as *CNGA3* variants as the cause of complete achromatopsia. However all *GNAT2* mutations to date, and the vast majority of *CNGB3* mutants, result in premature termination of translation, and thereby truncated and most probably non-functional phototransduction proteins. Therefore an incomplete achromatopsia phenotype is unlikely to be compatible with these genotypes which are predicted to encode mutant products lacking any residual function.

### OLIGOCONE TRICHROMACY

Oligocone trichromacy is a rare cone dysfunction syndrome, which is characterised by reduced visual acuity, mild photophobia, normal fundi, reduced amplitude of the cone electroretinogram but with colour vision within normal limits. The disorder was first described by Van Lith in 1973.<sup>35</sup> Since then Keunen *et al* have described a further four patients,<sup>36</sup> while Neuhann *et al*, and, more recently, Ehlich *et al* have each reported a single case.<sup>37, 38</sup> The two cases reported by Van Lith and Ehlich both had pendular nystagmus.

It has been proposed that these patients might have a reduced number of normal functioning cones (oligocone

syndrome) with preservation of the three cone types in the normal proportions, thereby permitting trichromacy.<sup>35</sup> Keunen *et al* tested this hypothesis by screening foveal cone photopigment density.<sup>36</sup> A reduced density difference of the foveal cone photopigment with a normal time constant of photopigment regeneration was found in all patients. Colour matching and increment threshold spectral sensitivity were normal. This provided evidence for the hypothesis of a reduced number of foveal cones (decreased density differences) with otherwise normal functioning residual cones.

We have recently detailed the phenotype of six patients with oligocone trichromacy.<sup>36a</sup> All six affected patients had a history of reduced visual acuity from infancy (6/12 to 6/24). They complained of very mild photophobia, but were not aware of any colour vision deficiency. They had no nystagmus and fundi were normal. On examination, all patients were found to have good colour vision. The various colour vision tests either revealed completely normal colour vision or slightly elevated discrimination thresholds. Anomaloscopy revealed matching ranges within normal limits, indicating the presence of long and middle wave cones of normal spectral sensitivity at the macula, while the absence of pseudoprotanomaly suggests that photopigment is present at normal optical densities in individual cone photoreceptors. The slightly elevated discrimination thresholds that were detected are compatible with a reduction in cone numbers. The cone ERG findings in our patients were poorly concordant, but could broadly be divided into two classes. In the first group (five individuals) cone responses were absent or markedly reduced. In the second group (one individual), cone b-waves were more markedly reduced than a-waves, implying a predominantly inner retinal abnormality in the cone system. These electrophysiological data suggest that there may be more than one disease mechanism and therefore more than one disease causing gene.

Oligocone trichromacy is likely to be inherited as an autosomal recessive trait. The molecular genetic basis of the disorder is unknown. Genes involved in retinal photoreceptor differentiation, when cone numbers are being determined, may represent good candidate genes.

### CONE MONOCHROMATISM

Monochromatic vision is diagnosed by a patient's ability to match any two colours merely by adjusting their radiance, when all other cues are absent. In rod monochromatism there is an absence of functioning cone photoreceptors with visual perception depending almost exclusively on rods. The rod monochromat therefore has markedly reduced visual acuity and total colour blindness.

Cone monochromatism is another rare form of congenital colour blindness, in which visual acuity is normal.<sup>39-40</sup> The incidence of cone monochromatism is estimated at one in 100 million.<sup>41</sup> Unlike rod monochromatism, cone monochromatism has never been noted in more than one family member.<sup>39</sup> The colour vision defect may be incomplete for certain colours and may vary both with the size of the field viewed and the level of luminance.<sup>39-40-42</sup> A normal ERG is present in this disorder thereby supporting the notion of abnormal processing central to the retinal photoreceptors and bipolar cells.<sup>43-44</sup> This notion was first proposed following the demonstration of red and green sensitive pigments at the fovea in cone monochromats<sup>40</sup> and the ability of such patients to use ocular chromatic aberration as a cue for altering accommodation.<sup>45</sup> In addition, Gibson has been able to demonstrate the presence of three mechanism sensitivity curves for the cone monochromat that are similar to those found in normal individuals, representing evidence of colour mediating mechanisms in the cone monochromat, and

thereby providing further evidence for a post-receptoral defect in this disorder.<sup>46</sup>

### BLUE CONE MONOCHROMATISM

Blue cone monochromatism (BCM), previously also known as X linked incomplete achromatopsia, affects fewer than 1 in 100 000 individuals, and is characterised by absence of L and M cone function.<sup>47</sup> Thus, the blue cone monochromat possesses rod vision and a normal short wavelength sensitive cone mechanism.

As in rod monochromacy, BCM typically presents in infancy with reduced visual acuity, pendular nystagmus, photophobia and normal fundi.<sup>48</sup> The nystagmus often wanes with time. Visual acuity is of the order of 6/24 to 6/60. Eccentric fixation may be present and myopia is a common finding.<sup>48</sup> BCM is distinguished from rod monochromatism (RM) via psychophysical and electrophysiological testing. The photopic ERG is profoundly reduced in both, although the S cone ERG is well preserved in BCM.<sup>49</sup> Classification can also be aided by family history, because BCM is inherited as an X linked recessive trait, whereas both subtypes of rod monochromacy show autosomal recessive inheritance.

Rod monochromats cannot make colour judgments, but rather will use brightness cues to differentiate between colours. This contrasts with blue cone monochromats who do have access to colour discrimination, though this does depend upon the luminance of the task: at mesopic levels, they have rudimentary dichromatic colour discrimination based upon a comparison of the quantum catches obtained by the rods and the S cones (blue cones).<sup>28-50</sup> Colour discrimination is reported to deteriorate with increasing luminance.<sup>51</sup> Therefore blue cone monochromats may be distinguished from rod monochromats by means of colour vision testing: blue cone monochromats are reported to display fewer errors along the vertical axis in the Farnsworth 100 Hue test (fewer tritan errors), and they may also display protan-like ordering patterns on the Farnsworth D-15.<sup>52</sup> In addition, the Berson plates have been claimed to provide a good separation of blue cone monochromats from rod monochromats.<sup>53-54</sup> Therefore, in order to clinically distinguish RM and BCM one needs to use colour vision tests that probe the tritan axis of colour as well as the deutan and protan, since the presence of residual tritan discrimination suggests BCM.<sup>52-54</sup>

In order to derive colour vision, the normal human visual system compares the rate of quantum catches in three classes of cone; the short (S) wavelength sensitive, middle (M) wavelength sensitive, and long (L) wavelength sensitive cones are maximally sensitive to light at 430 nm, 535 nm, and 565 nm, respectively. Whereas the L (red) and M (green) pigment genes are located on the X chromosome, the S cone (blue) pigment is encoded by a gene located on chromosome 7.<sup>55-56</sup> The wild type arrangement of the L and M opsin genes consists of a head to tail tandem array of two or more repeat units of 39 kb on chromosome Xq28 that are 98% identical at the DNA level.<sup>55-56</sup> The highly homologous L and M opsin genes are as a consequence predisposed to unequal intergenic and intragenic recombination. Transcriptional regulation of the L and M visual pigment genes is controlled by an upstream locus control region (LCR).<sup>57</sup> Mutations in the L and M pigment gene array that result in the lack of functional L and M pigments, and thus inactivate the corresponding cones, have been identified in the majority of BCM cases studied.<sup>57-58</sup>

Mutation analyses introduced by Nathans and collaborators have proved highly efficient at establishing the molecular basis for BCM.<sup>57-58</sup> The mutations in the L and M pigment gene array causing BCM fall into two classes. In the first class, a normal L and M pigment gene array is inactivated by

a deletion in the LCR, located upstream of the L pigment gene. A deletion in this region abolishes transcription of all genes in the pigment gene array and therefore inactivates both L and M cones.<sup>59</sup> In the second class of mutations the LCR is preserved but changes within the L and M pigment gene array lead to loss of functional pigment production. The most common genotype in this class consists of a single inactivated L/M hybrid gene. The first step in this second mechanism is unequal crossing over reducing the number of genes in the array to one, followed in the second step by a mutation that inactivates the remaining gene. The most frequent inactivating mutation that has been described is a thymine to cytosine transition at nucleotide 648, which results in a cysteine to arginine substitution at codon 203 (Cys203Arg), a mutation known to disrupt the folding of cone opsin molecules.<sup>60</sup> Reyniers *et al* have also described a family where BCM is the result of Cys203Arg mutations in both L and M pigment genes in the array.<sup>61</sup> A third molecular genetic mechanism has been described in a single family of BCM where exon 4 of an isolated red pigment gene had been deleted.<sup>62</sup>

BCM is generally accepted to be a stationary disorder, although Fleischman and O'Donnell reported one BCM family with macular atrophy and noted a slight deterioration of visual acuity and colour vision during a 12 year follow up period, as well as foveal pigmentary changes.<sup>63</sup> There are two further reports of individuals with BCM displaying a progressive retinal degeneration.<sup>57 64</sup> In two of the families that we have studied there has also been progression in the severity of the condition<sup>64a</sup> in that visual acuity and residual colour vision have been seen to deteriorate.

Combined results of previous studies<sup>57 58 64 65</sup> provide evidence for the general conclusion, first put forward by Nathans *et al*, that there are different mutational pathways to BCM. The data suggest that 40% of blue cone monochromat genotypes are a result of a one step mutational pathway that leads to deletion of the LCR. The remaining 60% of blue cone monochromat genotypes comprise a heterogeneous group of multistep pathways. The evidence thus far shows that many of these multistep pathways produce visual pigment genes that carry the inactivating Cys203Arg mutation, which eliminates a highly conserved disulphide bond.<sup>66</sup> This cysteine residue is located in the second extracellular loop of the opsin and, together with a conserved cysteine residue at position 126 in the first extracellular loop, forms a disulphide bond necessary for stabilisation of the tertiary structure of the protein.<sup>60</sup>

These studies have failed to detect the genetic alteration that would explain the BCM phenotype in all assessed individuals.<sup>58 65</sup> Indeed, Nathans *et al*<sup>58</sup> found that in nine out of 35 individuals with BCM (25%), the structure of the opsin array did not reveal the genetic mechanism for the disorder. This failure to identify disease causing variants in the opsin array may suggest that there is genetic heterogeneity yet to be identified in BCM.

## BORNHOLM EYE DISEASE

Myopia can be inherited as an autosomal recessive, autosomal dominant, or as an X linked trait and, in the latter case, it is well known as a component of congenital stationary night blindness<sup>67</sup> and retinitis pigmentosa.<sup>68</sup> X linked myopia has been reported in a large five generation Danish family that had its origins on the Danish island of Bornholm. The syndrome has therefore been named Bornholm eye disease (BED).<sup>69 70</sup> In that family, the syndrome manifests as moderate to high myopia combined with astigmatism and impaired visual acuity. Additional signs are moderate optic nerve head hypoplasia, thinning of the retinal pigment epithelium in the posterior pole with visible choroidal

vasculature, and abnormal photopic ERG flicker function as the most constant finding.<sup>69</sup> Affected members in this family are all deuteranopes, with a stationary natural history. This disorder is therefore best characterised as an X linked cone dysfunction syndrome with myopia and deuteranopia.

Linkage analysis performed in the original BED family has mapped the locus to Xq28, in the same chromosomal region therefore as the L/M opsin gene array.<sup>70</sup> It remains to be seen whether molecular genetic analysis of the opsin array will reveal mutations that account for both the cone dysfunction and the colour vision phenotype. However, it may also be possible that rearrangements within the opsin gene array will be found to account for the colour vision findings, while the cone dysfunction component of the disorder may be ascribed to mutation within an adjacent but separate locus. The cone dystrophy that has been mapped to Xq27 (COD2) however, displays a different phenotype which is progressive.<sup>71</sup> Nevertheless, it is becoming increasingly common in retinal molecular genetics to find that disparate phenotypes can be caused either by different mutations in the same gene, or even the same mutation in the same gene. In the latter situation it is currently believed that other genetic factors—namely, the “genetic context” within which the primary disease causing mutation is expressed, and/or environmental factors may determine the final phenotype.

## MANAGEMENT

There is currently no specific treatment for any of the cone dysfunction syndromes. Nevertheless, it is important that the correct diagnosis is made in order to provide accurate information on prognosis and to offer informed genetic counselling. Prenatal diagnosis is possible when the mutation(s) causing disease in the family is known.

Although there is no specific treatment available for this group of disorders, the provision of appropriate spectacle correction, low vision aids, and educational support is very important. Photophobia is often a prominent symptom in the cone dysfunction syndromes and therefore tinted spectacles or contact lenses may be beneficial to patients, in terms of both improved comfort and vision. In achromatopsia spectacle or contact lens tint aims to prevent rod saturation while maintaining residual cone function. In complete achromatopsia a deep red tint is most effective, allowing wavelengths of low luminous efficiency for rod photoreceptors to be transmitted to the retina, while those of a higher luminous efficiency (short wavelength light) are absorbed by the filter.<sup>54 72</sup> Incomplete achromats are thought to benefit more from reddish brown lenses rather than deep red lenses, which on account of their narrow spectral transmission, would eliminate their residual colour discrimination.<sup>54</sup> In contrast, magenta tints which prevent rod saturation while allowing transmission of blue light are indicated in BCM.<sup>54</sup>

## CONCLUSIONS

The cone dysfunction syndromes comprise a group of disorders that are both clinically and genetically heterogeneous. Their phenotypes are now well characterised both clinically and psychophysically and many causative genes have been identified. Perhaps not surprisingly these genes mainly encode proteins involved in the cone phototransduction pathway. Other genes remain to be identified before the complete molecular pathology of this interesting group of disorders can be established.

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## REFERENCES

- 1 Mollon JD. '...aus dreierley Arten von Membranen oder Molekülen': George Palmer's legacy. In: Cavonius CR, ed. *Colour vision deficiencies XIII*. Amsterdam: Kluwer Academic Publishers, 1997:3-20.
- 2 Neitz M, Neitz J. Molecular genetics of color vision and color vision defects. *Arch Ophthalmol* 2000;**118**:691-700.
- 3 Sharpe LT, Nordby K. Total colour-blindness: an introduction. In: Hess RF, Sharpe LT, Nordby K, eds. *Night vision: basic, clinical and applied aspects*. Cambridge: Cambridge University Press, 1990:253-89.
- 4 Sharpe LT, Stockman A, Jagle H, et al. Opsin genes, cone photopigments and colourblindness. In: Gegenfurtner K, Sharpe LT, eds. *Color vision: from genes to perception*. Cambridge: Cambridge University Press, 1999:3-52.
- 5 Simunovic MP, Moore AT. The cone dystrophies. *Eye* 1998;**12**:553-65.
- 6 Andreasson S, Tornqvist K. Electroretinograms in patients with achromatopsia. *Acta Ophthalmol (Copenh)* 1991;**69**:711-16.
- 7 Hess RF, Nordby K. Spatial and temporal limits of vision in the achromat. *J Physiol* 1986;**371**:365-85.
- 8 Pentao L, Lewis RA, Ledbetter DH, et al. Maternal uniparental isodisomy of chromosome 14: association with autosomal recessive rod monochromacy. *Am J Hum Genet* 1992;**50**:690-9.
- 9 Arbour NC, Zlotogora J, Knowlton RG, et al. Homozygosity mapping of achromatopsia to chromosome 2 using DNA pooling. *Hum Mol Genet* 1997;**6**:689-94.
- 10 Wissinger B, Jagle H, Kohl S, et al. Human rod monochromacy: linkage analysis and mapping of a cone photoreceptor expressed candidate gene on chromosome 2q11. *Genomics* 1998;**51**:325-31.
- 11 Stryer L. Visual excitation and recovery. *J Biol Chem* 1991;**266**:10711-14.
- 12 Kohl S, Marx T, Giddings I, et al. Total colour-blindness is caused by mutations in the gene encoding the alpha-subunit of the cone photoreceptor cGMP-gated cation channel. *Nat Genet* 1998;**19**:257-9.
- 13 Wissinger B, Gamber D, Jagle H, et al. CNGA3 mutations in hereditary cone photoreceptor disorders. *Am J Hum Genet* 2001;**69**:722-37.
- 14 Eksandh L, Kohl S, Wissinger B. Clinical features of achromatopsia in Swedish patients with defined genotypes. *Ophthalmic Genet* 2002;**23**:109-20.
- 15 Biel M, Seeliger M, Pfeifer A, et al. Selective loss of cone function in mice lacking the cyclic nucleotide-gated channel CNG3. *Proc Natl Acad Sci USA* 1999;**96**:7553-7.
- 16 Brody JA, Hussels I, Brink E, et al. Hereditary blindness among Pingelapese people of Eastern Caroline Islands. *Lancet* 1970;**1**:1253-7.
- 17 Winick JD, Blundell ML, Galke BL, et al. Homozygosity mapping of the achromatopsia locus in the Pingelapese. *Am J Hum Genet* 1999;**64**:1679-85.
- 18 Sundin OH, Yang J-M, Li Y, et al. Genetic basis of total colour-blindness among the Pingelapese islanders. *Nat Genet* 2000;**25**:289-93.
- 19 Kohl S, Baumann B, Broghammer M, 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**:2107-16.
- 20 Rojas CV, Maria LS, Santos JL, et al. A frameshift insertion in the cone cyclic nucleotide gated cation channel causes complete achromatopsia in a consanguineous family from a rural isolate. *Eur J Hum Genet* 2002;**10**:638-42.
- 21 Kohl S, Jagle H, Zrenner E, et al. The genetics of achromatopsia. *Invest Ophthalmol Vis Sci* 2001;**42**:S324 (Abstract 1745).
- 22 Finn JT, Krautwurst D, Schroeder JE, et al. Functional co-assembly among subunits of cyclic-nucleotide-activated, nonselective cation channels, and across species from nematode to human. *Biophys J* 1998;**74**:1333-45.
- 23 Sidjanin DJ, Lowe JK, McElwee JL, et al. Canine CNGB3 mutations establish cone degeneration as orthologous to the human achromatopsia locus ACHM3. *Hum Mol Genet* 2002;**11**:1823-33.
- 24 Kohl S, Baumann B, Rosenberg T, et al. Mutations in the cone photoreceptor G-protein alpha-subunit gene GNAT2 in patients with achromatopsia. *Am J Hum Genet* 2002;**71**:422-5.
- 25 Aligianis IA, Forsheo T, Johnson S, et al. Mapping of a novel locus for achromatopsia (ACHM4) to 1p and identification of a germline mutation in the alpha subunit of cone transducin (GNAT2). *J Med Genet* 2002;**39**:656-60.
- 26 Michaelides M, Aligianis IA, Holder GE, et al. Cone dystrophy phenotype associated with a frameshift mutation (M280fsX291) in the alpha-subunit of cone specific transducin (GNAT2). *Br J Ophthalmol* 2003;**87**:1317-20.
- 27 Lerea CL, Bunt-Milam AH, Hurley JB. Alpha transducin is present in blue-, green-, and red-sensitive cone photoreceptors in the human retina. *Neuron* 1989;**3**:367-76.
- 28 Reitner A, Sharpe LT, Zrenner E. Is colour vision possible with only rods and blue-sensitive cones? *Nature* 1991;**352**:798-800.
- 29 Akhmedov NB, Piriev NI, Pearce-Kelling S, et al. Canine cone transducin-gamma gene and cone degeneration in the cd dog. *Invest Ophthalmol Vis Sci* 1998;**39**:1775-81.
- 30 Akhmedov NB, Piriev NI, Ray K, et al. Structure and analysis of the transducin beta3-subunit gene, a candidate for inherited cone degeneration (cd) in the dog. *Gene* 1997;**194**:47-56.
- 31 Pokorny J, Smith VC, Pinckers AJ, et al. Classification of complete and incomplete autosomal recessive achromatopsia. *Graefes Arch Clin Exp Ophthalmol* 1982;**219**:121-30.
- 32 Smith VC, Pokorny J, Newell FW. Autosomal recessive incomplete achromatopsia with protan luminosity function. *Ophthalmologica* 1978;**177**:197-207.
- 33 Smith VC, Pokorny J, Newell FW. Autosomal recessive incomplete achromatopsia with deutan luminosity. *Am J Ophthalmol* 1979;**87**:393-402.
- 34 van Norren D, de Vries-de Mol EC. A case of incomplete achromatopsia of the deutan type. *Doc Ophthalmol* 1981;**51**:365-72.
- 35 van Lith GHM. General cone dysfunction without achromatopsia. In: Pearlman JT, ed. *10th ISCERG Symposium, Doc Ophthalmol Proc Ser* 1973;**2**:175-80.
- 36 Keunen JEE, De Brabandere SRS, Liem ATA. Foveal densitometry and color matching in oligocone trichromacy. In: Drum B, ed. *12th IRGCV Symposium—Colour vision deficiencies XII*. Amsterdam: Kluwer Academic Publishers, 1995:203-10.
- 36a Michaelides M, Holder GE, Bradshaw K, et al. Oligocone trichromacy—a rare and unusual cone dysfunction syndrome. *Br J Ophthalmol* 2004;(in press).
- 37 Neuhann T, Krastel H, Jaeger W. Differential diagnosis of typical and atypical congenital achromatopsia. Analysis of a progressive foveal dystrophy and a nonprogressive oligo-cone trichromacy (general cone dysfunction without achromatopsia), both of which at first had been diagnosed as achromatopsia. *Albrecht Von Graefes Arch Klin Exp Ophthalmol* 1978;**209**:19-28.
- 38 Ehlich P, Sadowski B, Zrenner E. Oligocone trichromasy, a rare form of incomplete achromatopsia. *Ophthalmologica* 1997;**94**:801-6.
- 39 Weale RA. Cone monochromatism. *J Physiol* 1953;**121**:548-69.
- 40 Weale RA. Photosensitive reactions in foveae of normal and cone-monochromatic observers. *Opt Acta* 1959;**6**:158-174.
- 41 Pitt FHG. Monochromatism. *Nature* 1944;**154**:466-8.
- 42 Crone RA. Combined forms of congenital colour defects: a pedigree with atypical total colour blindness. *Br J Ophthalmol* 1956;**40**:462-72.
- 43 Ikeda H, Ripps H. The electroretinogram of a cone-monochromat. *Arch Ophthalmol* 1966;**75**:513-17.
- 44 Krill AE, Schneiderman A. Retinal function studies, including the electroretinogram, in an atypical monochromat. *Clinical Electroretinography, Supplement to Vision Research*. New York: Oxford Press, 1966:351-61.
- 45 Fincham E. Defects of the colour-sense mechanism as indicated by the accommodation reflex. *J Physiol* 1953;**121**:570-80.
- 46 Gibson IM. Visual mechanisms in a cone-monochromat. *J Physiol* 1962;**161**:P10-11.
- 47 Pokorny J, Smith VC, Verriest G. Congenital color defects. In: Pokorny J, Smith VC, Verriest G, Pinckers AJ, eds. *Congenital and acquired color vision defects*. New York: Grune & Stratton, 1979:183.
- 48 Weleber RG, Eisner A. Cone degeneration ('bull's eye dystrophies') and colour vision defects. In: Newsome DA, ed. *Retinal dystrophies and degenerations*. New York: Raven Press, 1988:233-56.
- 49 Gouras P, MacKay CJ. Electroretinographic responses of the short-wavelength-sensitive cones. *Invest Ophthalmol Vis Sci* 1990;**31**:1203-9.
- 50 Alpern M, Lee GB, Maaseidvaag F, et al. Colour vision in blue cone monochromacy. *J Physiol* 1971;**212**:211-33.
- 51 Young RS, Price J. Wavelength discrimination deteriorates with illumination in blue cone monochromats. *Invest Ophthalmol Vis Sci* 1985;**26**:1543-9.
- 52 Weis AH, Biersdorf WR. Blue cone monochromatism. *J Pediatr Ophthalmol Strabismus* 1989;**26**:218-23.
- 53 Berson EL, Sandberg MA, Rosner B, et al. Color plates to help identify patients with blue cone monochromatism. *Am J Ophthalmol* 1983;**95**:741-7.
- 54 Haegerstrom-Portnoy G, Schneck ME, Verdon WA, et al. Clinical vision characteristics of the congenital achromatopsias. II. Color vision. *Optom Vis Sci* 1996;**73**:457-65.
- 55 Nathans J, Thomas D, Hogness DS. Molecular genetics of human colour vision: the genes encoding blue, green, and red pigments. *Science* 1986;**232**:193-202.
- 56 Nathans J, Piantanida TP, Eddy RL, et al. Molecular genetics of inherited variation in human color vision. *Science* 1986;**232**:203-10.
- 57 Nathans J, Davenport CM, Maumenee IH, et al. Molecular genetics of human blue cone monochromacy. *Science* 1989;**245**:831-8.
- 58 Nathans J, Maumenee IH, Zrenner E, et al. Genetic heterogeneity among blue-cone monochromats. *Am J Hum Genet* 1993;**53**:987-1000.
- 59 Wang Y, Macke JP, Merbs SL, et al. A locus control region adjacent to the human red and green visual pigment genes. *Neuron* 1992;**9**:429-40.
- 60 Kazmi MA, Sakmar TP, Ostrer H. Mutation of a conserved cysteine in the X-linked cone opsins causes color vision deficiencies by disrupting protein folding and stability. *Invest Ophthalmol Vis Sci* 1997;**38**:1074-81.
- 61 Reyniers E, Van Thienen MN, Meire F, et al. Gene conversion between red and defective green opsin gene in blue cone monochromacy. *Genomics* 1995;**29**:323-8.
- 62 Ladejaer-Mikkelsen AS, Rosenberg T, Jorgensen AL. A new mechanism in blue cone monochromatism. *Hum Genet* 1996;**98**:403-8.
- 63 Fleischman JA, O'Donnell FE. Congenital X-linked incomplete achromatopsia. Evidence for slow progression, carrier fundus findings, and possible genetic linkage with glucose-6-phosphate dehydrogenase locus. *Arch Ophthalmol* 1981;**99**:468-72.
- 64 Ayyagari R, Kakuk LE, Coats EL, et al. Bilateral macular atrophy in blue cone monochromacy (BCM) with loss of the locus control region (LCR) and part of the red pigment gene. *Mol Vis* 1999;**5**:13-18.
- 64a Michaelides M, Johnson S, Simunovic M, et al. Blue cone monochromatism: a phenotype and genotype assessment with evidence of progressive loss of cone function in older individuals. *Eye* 2004;(in press).
- 65 Ayyagari R, Kakuk LE, Bingham EL, et al. Spectrum of color gene deletions and phenotype in patients with blue cone monochromacy. *Hum Genet* 2000;**107**:75-82.
- 66 Karnik SS, Khorana HG. Assembly of functional rhodopsin requires a disulfide bond between cysteine residues 110 and 187. *J Biol Chem* 1990;**265**:17520-4.
- 67 Musarella MA, Weleber RG, Murphy WH, et al. Assignment of the gene for complete X-linked congenital stationary night blindness (CSNB1) to Xp11.3. *Genomics* 1989;**5**:727-37.
- 68 Kaplan J, Pelet A, Martin C, et al. Phenotype-genotype correlations in X linked retinitis pigmentosa. *J Med Genet* 1992;**29**:615-23.

- 69 **Haim M**, Fledelius HC, Skarsholm D. X-linked myopia in a Danish family. *Acta Ophthalmol (Copenh)* 1988;**66**:450–6.
- 70 **Schwartz M**, Haim M, Skarsholm D. X-linked myopia: Bornholm Eye Disease. Linkage to DNA markers on the distal part of Xq. *Clin Genet* 1990;**38**:281–6.
- 71 **Bergen AA**, Pinckers AJ. Localization of a novel X-linked progressive cone dystrophy gene to Xq27: evidence for genetic heterogeneity. *Am J Hum Genet* 1997;**60**:1468–73.
- 72 **Terry RL**. The use of tinted contact lenses in a case of congenital rod monochromatism. *Clin Exp Optom* 1988;**71**:188–90.

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