X linked progressive cone dystrophy

Localisation of the gene locus to Xp21–p11.1 by linkage analysis

F M Meire, A A B Bergen, A De Rouck, M Leys, J W Dellemann

Department of Ophthalmology, Ghent, Belgium
F M Meire
A De Rouck
M Leys
The Netherlands Ophthalmic Research Institute, Department of Ophthalmogenetics, Amsterdam, The Netherlands
A A B Bergen
J W Dellemann
Acknowledged for publication 26 August 1993

Abstract
Six affected males, three female carriers, and two possible carriers were evaluated from a three generation pedigree with X linked progressive cone dystrophy. The affected males presented with progressive decrease of visual acuity, impairment of colour vision, and deterioration of electroretinogram, which ranged from absent response to red light in all young patients to abnormal cone–rod responses in the elderly ones. In most affected males dark adaptation curves were monophasic and the electro-oculogram values were reduced. While some obligate carriers showed functional anomalies, they all had reduced electroretinogram response to red light. The a/b-ratio for 1 joule white light was an appropriate indicator for carrier state. The family was studied with seven DNA markers from the proximal part of the short arm of the human X chromosome. So far, significant linkage has been found between three DNA markers and COD1, which assigns the progressive cone dystrophy gene (COD1) in this family to Xp21–p11.1. Differential diagnosis with congenital cone dystrophies is discussed.

(Br J Ophthalmol 1994; 78: 103–108)

The diagnosis of cone dystrophy is based on the clinical findings, funduscopy, and the results of colour vision testing, visual fields, dark adaptation, and electrophysiological examination. Determination of the inheritance pattern in the family is obligatory. Inheritance of progressive cone dystrophy is commonly autosomal dominant, although an X linked pattern of inheritance has been reported.¹

X linked cone dystrophy is characterised by the absence of nystagmus, progressive deterioration of visual acuity, myopic refraction, full peripheral visual fields with central scotomas, and colour vision impairment. The ophthalmoscopic appearance varies from a dark granular macula in the youngest affected to complete loss of retinal pigment epithelium (RPE) within the macula in the oldest ones.

The electroretinogram (ERG) reveals decreased cone mediated responses and normal rod mediated responses. However, in elderly affected males rod dysfunction is demonstrated by reductions of dark adapted ERG and abnormal dark adaptation curves. So far, evidence has been provided for a progressive cone dystrophy locus in Xp11¹¹ and in Xq28.²

We report ophthalmic data for six affected males, three obligate female carriers, and two possible carriers in a family presenting cone dystrophy with clearly X linked inheritance. Moreover, linkage analysis was performed which assigns the progressive cone dystrophy gene (COD1) in this family to Xp21–p11.1.

Materials and methods
The pedigree of a family with X linked progressive cone dystrophy is shown in Figure 1. The proband was referred to the department of ophthalmology for diagnosis. It appeared from family history that he suffered from an X linked disease. On subsequent examination the younger patients asked for genetic counselling. Therefore, ophthalmic examination in as many family members as possible was performed and blood was collected for DNA studies. A total of 11 patients were examined. We examined six affected males, three obligates, and two possible carriers.

OPHTHALMIC METHODS
Ophthalmic examination including refraction, determination of visual acuity, slit-lamp examination, and funduscopy were performed. Colour vision was examined with the Ishihara test, the Panel D-15 test, and the AOH-R-R. Affected males were examined either by kinetic perimetry or by static perimetry within the 30º field. The ERG was performed using Ganzfeld stimulation. Pupils were maximally dilated for all ERG recordings. Cone responses were obtained by white and red stimuli in a light adapted state. Rod responses were obtained by dim white and blue stimuli after 20 minutes of dark adaptation. Mixed cone–rod responses were obtained by bright flashes (1 and 40 joules) in a dark adapted state.

The following parameters were used:
(1) Cone responses: amplitudes of the b-wave for white and red stimuli.
(2) Rod responses: amplitudes of the b-wave for blue stimuli.
(3) Mixed responses: amplitudes of the a- and b-waves for white stimuli of 1 and 40 joules. Implicit time of the b-wave for 1 joule stimulus.
(4) Relation between a1- and a2-waves for a white stimulus of 1 joule in the dark. The ratio of the cone a1-wave to the sum of the cone a1 and rod a2-wave (a1/a2).
(5) Relation between the cone b-wave (white stimulus) and the mixed b-wave obtained with a stimulus of 40 joules in dark adapted state.
Pedigree of a family with X linked progressive cone dystrophy (P215).

DNA analysis

Obligate carrier
Affected male
 Probably affected
 Unmarried
 No children

Figure 1  Pedigree of a family with X linked progressive cone dystrophy (P215).

Figure 2  Visual acuity in the affected males and female carriers. A solid line connects visual acuity for each eye.

All results were compared with the normal values obtained in our clinic. Electro-oculography (EOG) was performed in seven patients. We used our standard technique as described previously.9 Dark adaptation was performed in all patients on the Goldmann-Weekers dark adaptometer after preadaptation to 2000 lux during 5 minutes.

DNA METHODS

Details concerning DNA probes and primers used are described elsewhere.10 Southern analyses were carried out as described.11 Polymer chain reaction (PCR) conditions and carcinoembryonic antigen (CEA) repeat polymorphism detection were essentially carried out according to Bergen et al.12 The variable part of the PCR cycle programs were: 30× (1 minute 94°C, 2 minutes 55°C, 2 minutes 72°C) for DXS426 and 25× (1 minute 94°C, 1 minute 55°C, 1 minute 72°C) for MAOB. LOD scores were calculated using the computer program LINKAGE, version 5·03.13
Figure 3  Range of dark adaptation obtained for normal people in our department. Dark adaptation for: affected males (A-F) (III-22, III-24, II-16, III-36, III-37, I-10) and female carriers (G-H) (II-14, II-18) showing monophasic curve in most patients with a rapid breakdown of the curve and elevated final threshold in subject I-10.

Table 1  Electroretinogram (ERG) and electro-oculogram (EOG) records in affected males/obligate and possible carriers

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>White</th>
<th>Red</th>
<th>Blue</th>
<th>White (1 J)</th>
<th>White (40 J)</th>
<th>White</th>
<th>Red</th>
<th>Blue</th>
<th>Scotopic ERG b-wave</th>
<th>Scotopic ERG a-wave</th>
<th>Scotopic ERG a-wave</th>
<th>Scotopic ERG a-wave</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>AV</td>
<td>PT</td>
<td>AV</td>
<td>AV</td>
<td>AV</td>
<td>AV</td>
<td>PT</td>
<td>AV</td>
<td>AV</td>
<td>AV</td>
<td>AV</td>
<td>AV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affected males:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I-10</td>
<td>86</td>
<td>60</td>
<td>44</td>
<td>-</td>
<td>40</td>
<td>80</td>
<td>54</td>
<td>180</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>200</td>
<td>-</td>
</tr>
<tr>
<td>III-26</td>
<td>40</td>
<td>80</td>
<td>42</td>
<td>-</td>
<td>100</td>
<td>190</td>
<td>48</td>
<td>220</td>
<td>-</td>
<td>10</td>
<td>130</td>
<td>30</td>
<td>-</td>
</tr>
<tr>
<td>III-42</td>
<td>40</td>
<td>130</td>
<td>40</td>
<td>-</td>
<td>180</td>
<td>230</td>
<td>52</td>
<td>360</td>
<td>-</td>
<td>60</td>
<td>260</td>
<td>-</td>
<td>27</td>
</tr>
<tr>
<td>III-42</td>
<td>32</td>
<td>160</td>
<td>38</td>
<td>-</td>
<td>320</td>
<td>360</td>
<td>50</td>
<td>520</td>
<td>-</td>
<td>60</td>
<td>380</td>
<td>0-32</td>
<td>0-30</td>
</tr>
<tr>
<td>III-24</td>
<td>29</td>
<td>140</td>
<td>42</td>
<td>-</td>
<td>380</td>
<td>380</td>
<td>54</td>
<td>480</td>
<td>-</td>
<td>140</td>
<td>400</td>
<td>0-35</td>
<td>0-29</td>
</tr>
<tr>
<td>III-36</td>
<td>32</td>
<td>120</td>
<td>42</td>
<td>-</td>
<td>300</td>
<td>340</td>
<td>48</td>
<td>560</td>
<td>-</td>
<td>80</td>
<td>420</td>
<td>0-19</td>
<td>0-18</td>
</tr>
<tr>
<td>III-36</td>
<td>32</td>
<td>130</td>
<td>40</td>
<td>-</td>
<td>300</td>
<td>320</td>
<td>52</td>
<td>600</td>
<td>+</td>
<td>60</td>
<td>450</td>
<td>0-43</td>
<td>0-25</td>
</tr>
<tr>
<td>III-37</td>
<td>27</td>
<td>150</td>
<td>40</td>
<td>-</td>
<td>280</td>
<td>360</td>
<td>52</td>
<td>600</td>
<td>+</td>
<td>60</td>
<td>450</td>
<td>0-32</td>
<td>0-31</td>
</tr>
<tr>
<td>III-37</td>
<td>27</td>
<td>180</td>
<td>40</td>
<td>-</td>
<td>280</td>
<td>300</td>
<td>48</td>
<td>520</td>
<td>-</td>
<td>60</td>
<td>450</td>
<td>0-32</td>
<td>0-31</td>
</tr>
</tbody>
</table>

Obligate carriers:

II-14  | 62  | 140   | 46  | 20   | 280         | 340          | 46    | 460 | +   | 100                 | 360                 | 0-34                | 0-31                |
| II-18  | 53  | 180   | 44  | 30   | 340         | 400          | 48    | 550 | +   | 110                 | 400                 | 0-33                | 0-32                |
| III-36 | 60  | 160   | 36  | 30   | 380         | 480          | 48    | 780 | +   | 120                 | 580                 | 0-34                | 0-22                |
| II-15  | 60  | 160   | 34  | 60   | 440         | 520          | 40    | 800 | +   | 200                 | 560                 | 0-45                | 0-20                |
| III-23 | 30  | 160   | 36  | 50   | 460         | 600          | 40    | 820 | +   | 220                 | 600                 | 0-52                | 0-39                |

Possible carriers:

III-20 | 35  | 240   | 36  | 180 | 380         | 500          | 38    | 720 | +   | 180                 | 600                 | 0-55                | 0-33                |
| III-20 | 35  | 260   | 34  | 160 | 460         | 520          | 40    | 760 | +   | 160                 | 600                 | 0-56                | 0-34                |
| III-36 | 30  | 340   | 36  | 160 | 500         | 440          | 42    | 720 | +   | 100                 | 600                 | 0-66                | 0-47                |
| III-23 | 30  | 320   | 36  | 180 | 560         | 600          | 44    | 880 | +   | 220                 | 640                 | 0-63                | 0-36                |

Normal people:

X      | 223  | 35   | 112  | 330 | 432        | 40-2         | 570   | +   | 127                 | 485                 | 0-68                | 0-45                |
| SD    | 42   | 1-5  | 14   | 35  | 70          | 1-4          | 65    |     | 32                  | 80                  | 0-08                | 0-06                |

NP= not performed; AV = wave amplitude (μV); OP = oscillatory potentials; PT = implicit time (ms).
Results

CHARACTERISTICS OF AFFECTED MALES

The age range of the patients was between 27 and 86 years. The visual acuity for the affected males deteriorated with advancing age (Fig 2). All affected males had myopic refractive error (S-5 up to S-15). None of the patients showed nystagmus. Colour vision tests demonstrated in the younger patients red-green defect with pseudoisochromatic plates; however, two of them passed the panel D-15 test. The Ishihara test for patient III-26 (40 years) and for the oldest patient (I-10) demonstrated complete achromatopsia. The visual fields in the patients showed a central scotoma. Dark adaptation was monophasic in five of six of the patients, with elevated final rod threshold in the oldest one (Fig 3). The results of ERG are shown in Table 1. Photopic ERG b-wave amplitudes were severely reduced in all affected males. An age-related deterioration was observed. The response to a red stimulus was absent in all patients. Scotopic ERGs for white stimulus of 1 joule for the patients are illustrated in Figure 4. Since the $a_1$-wave is predominantly the contribution of the cones, it was non-recordable (2/6) or severely reduced (4/6). The ratio $a_2/a_T$ for white stimulus of 1 joule in the dark adapted state is given in Figure 5. The distribution of the ratio for 147 normal people and for 43 patients with Stargardt
disease is also plotted. The ratio in our patients is found to be less than the mean $-2$ SD ($\chi=0.68$, SD=0.08). Oscillatory potentials were only obtained in two affected males. The most severely affected males had also subnormal rod mediated responses (attenuation of the scotopic b-wave amplitude for white 40 joule and reduced response for blue stimulus). The EOG was subnormal in three of four patients. Funduscopy revealed dark granular maculae in the young patients (Fig 6A) while in the oldest patients a well demarcated geographic atrophy of the RPE of the macula was observed (Fig 6B). None of the patients showed a tapetal-like sheen of the fundus.

**CHARACTERISTICS OF OBLIGATE CARRIERS**

One of the obligate female carriers (II-14) had high myopia with decreased visual acuity, being 0.1 in the right eye and 0.3 in the left eye. Funduscopy demonstrated myopic deterioration. Patient II-18 presented with anisometropia and relative amblyopia. Colour vision was not determined. Dark adaptation was monophasic in patient II-18 and biphasic in patient II-14 (Fig 3). All obligate carriers had reduced ERG response to a red light stimulus, a reduced photopic b-wave amplitude but normal scotopic b-response and prolonged implicit time (Table 1). The $a_i/a_T$ ratio (white light of 1 joule) was less than the mean value ($-2$ SD) or even more severely reduced (Figs 4 and 5). The EOG values were in lower range of the normal limit.

Examination, including visual acuity, colour vision, and dark adaptation, was normal in the two possible carriers. The ERG for both patients revealed a normal response for red stimulation.

### Table 2 X linked progressive cone dystrophy: two point linkage data between COD1 and Xp loci

<table>
<thead>
<tr>
<th>Locus</th>
<th>Probe</th>
<th>PCR</th>
<th>$\Theta_{max}$</th>
<th>$Z_{max}$</th>
<th>0.00</th>
<th>0.01</th>
<th>0.05</th>
<th>0.10</th>
<th>0.20</th>
<th>0.30</th>
</tr>
</thead>
<tbody>
<tr>
<td>DXS269</td>
<td>P20</td>
<td>0.00</td>
<td>1.51</td>
<td>1.48</td>
<td>1.39</td>
<td>1.28</td>
<td>1.02</td>
<td>0.73</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DXS84</td>
<td>754</td>
<td>0.00</td>
<td>2.10</td>
<td>2.07</td>
<td>1.95</td>
<td>1.78</td>
<td>1.43</td>
<td>1.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAOB</td>
<td>(CA)$_n$</td>
<td>0.00</td>
<td>2.10</td>
<td>2.07</td>
<td>1.95</td>
<td>1.78</td>
<td>1.43</td>
<td>1.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DIX426</td>
<td>(CA)$_n$</td>
<td>0.00</td>
<td>2.10</td>
<td>2.07</td>
<td>1.95</td>
<td>1.78</td>
<td>1.43</td>
<td>1.02</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 3 Clinical, electrophysiological examination and DNA analysis

<table>
<thead>
<tr>
<th>Gene locus</th>
<th>Cone response</th>
<th>Rod response</th>
<th>Colour vision</th>
<th>Refraction</th>
<th>Nystagmus</th>
<th>Visual acuity</th>
<th>Fundus</th>
<th>Dark adaptation</th>
<th>ERG</th>
<th>Xlinked cone dystrophy</th>
<th>Xcone dystrophy</th>
<th>X blue cone monochromatism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xp 11</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Normal</td>
<td>High myopia</td>
<td>20/25</td>
<td>20/30</td>
<td>Achromatopsia</td>
<td>Monophasic</td>
<td>Rod</td>
<td>Macular atrophy</td>
<td>Macular atrophy</td>
<td>Monophasic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No foveal reflex</td>
<td>Normal</td>
<td></td>
<td>Macular atrophy</td>
<td>Macular atrophy</td>
<td>Monophasic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No foveal reflex</td>
<td>Normal</td>
<td></td>
<td>Macular atrophy</td>
<td>Macular atrophy</td>
<td>Monophasic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No foveal reflex</td>
<td>Normal</td>
<td></td>
<td>Macular atrophy</td>
<td>Macular atrophy</td>
<td>Monophasic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No foveal reflex</td>
<td>Normal</td>
<td></td>
<td>Macular atrophy</td>
<td>Macular atrophy</td>
<td>Monophasic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No foveal reflex</td>
<td>Normal</td>
<td></td>
<td>Macular atrophy</td>
<td>Macular atrophy</td>
<td>Monophasic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No foveal reflex</td>
<td>Normal</td>
<td></td>
<td>Macular atrophy</td>
<td>Macular atrophy</td>
<td>Monophasic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No foveal reflex</td>
<td>Normal</td>
<td></td>
<td>Macular atrophy</td>
<td>Macular atrophy</td>
<td>Monophasic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No foveal reflex</td>
<td>Normal</td>
<td></td>
<td>Macular atrophy</td>
<td>Macular atrophy</td>
<td>Monophasic</td>
</tr>
</tbody>
</table>

**RESULTS OF DNA ANALYSIS**

Two point linkage results between COD1 and several proximal Xp loci are presented in Table 2. Close linkage without recombination was found between COD1 and DXS269 ($Z_{max}=1.51$), and between COD1 and the loci DXS84, MAOB, and DXS426 ($Z_{max}=2.10$). The latter loci were fully informative, and provide formal evidence for the assignment of a progressive cone dystrophy locus to the proximal Xp in this family.

DNA analysis in the possible carriers revealed that patient III-23 does not carry the gene. Unfortunately, because of recombinations, DNA analysis was not conclusive for patient III-20 (A A B Bergen et al submitted).

**Discussion**

The characteristics of the X linked progressive cone dystrophy disease previously reported$^{14}$ were observed in our family. The affected males presented with high myopia and progressive decrease of visual acuity. Impairment of colour vision was minimal in the young patients; the oldest patients demonstrated a complete achromatopsia. The dark adaptation curves for most patients were monophasic. Monophasic dark adaptation curves are also observed in achromates. Sloan obtained different dark adaptation curves in cone degeneration depending on the possibility of colour discrimination and the apparent presence of normal cones at the fixation point.$^{14}$ The ERG responses for our patients clearly demonstrated progressivity of cone dystrophy and finally deterioration of the rod responses. ERG responses in the elderly showed a cone-rod dysfunction. The subnormal EOG values in the patients also point to a diffuse involvement of the RPE. In this study all carriers showed reduced ERG recording elicited by red light and a reduction of the $a_i/a_T$ ratio for the white light of 1 joule. Therefore, based on a small number of female carriers in our family, the $a_i/a_T$ ratio seemed to be a valuable indicator of carrier state. Colour vision testing, especially with the Nagel anomaloscope and foveal densitometry, has been reported to allow detection of 87% of the obligate carriers. Patients with progressive cone dystrophy may present with a tapetal-like sheen,$^{14}$ however it was not observed in our patients. The retinal sheen is not a pathognomonic finding as it is also observed in Oguchi’s disease, and in female carriers of X linked retinitis pigmentosa.$^{15}$

The DNA study in our patients reveals a significant linkage between the cone dystrophy gene locus (COD1) and proximal Xp markers. This localisation is in agreement with previous DNA analyses in the disease$^{9}$ and clearly separates the COD1 gene localisation from the gene localisation of X linked congenital cone dysfunctions, including blue cone monochromatism and the progressive cone dystrophy reported by Reichel$^{6}$ which are localised to the distal part of the Xq arm. Patients with X linked blue cone monochromatism present with a congenital defect with nystagmus, photophobia, and visual acuity ranging from 20/60 to 20/200. Colour vision testing helps to distinguish the patients from those with rod monochromatism.$^{16}$
The condition has been considered stationary; nevertheless an age-related macular degeneration in patients with blue cone monochromatism has been personally observed during the follow up of the family described in 1965 by François et al and has also been reported by Nathans et al. DNA studies revealed alterations in the red and green visual pigment gene cluster.

Reichel et al reported on a family with progressive cone dystrophy with predominant loss of red (long wave) cone function in the affected males and female carriers. The visual acuity in the young patients was nearly normal but an age-related macular degeneration was observed. Colour vision showed a protan axis of confusion in the younger patients. The ERG showed reduced cone mediated responses. No evolution to cone rod dystrophy was observed. ERG recording allowed a differentiation between the disease and congenital protanopia. In both diseases a reduction of the oscillations to red light are noted, but in congenital protanopia normal amplitude in mixed cone rod responses to white light, and cone isolated responses to 30 Hz white flicker are found. DNA analysis with a red cone pigment gene probe disclosed a 6-5 kilobase deletion in the red cone pigment gene on the long arm of the X chromosome. Large DNA deletions in the green pigment gene were excluded.

The congenital cone dysfunctions also have a progressive course and the development of macular atrophy in the elderly affected males. Funduscopy does not allow the differentiation between the congenital diseases and the late onset X linked progressive cone dystrophy. Nevertheless, the results of clinical, electrophysiological examination and DNA analysis help to distinguish between the disease entities (Table 3).

The authors thank Dr Van Staey of the Department of Human Genetics of the University of Ghent for collecting blood for the DNA analysis and C Broux and A Uvils for the illustrations.

7 Bartley J, Geis C, Jacobson D. X-linked progressive cone dystrophy maps between DXS7 (L1-28) and DXS206 (X1j-1) and is linked to DXS84 (754). Cytogenet Cell Genet 1989; 51: 959.
X linked progressive cone dystrophy. Localisation of the gene locus to Xp21-p11.1 by linkage analysis.
F M Meire, A A Bergen, A De Rouck, M Leys and J W Delleman

doi: 10.1136/bjo.78.2.103

Updated information and services can be found at:
http://bjo.bmj.com/content/78/2/103

Email alerting service

These include:
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/