X linked progressive cone dystrophy

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

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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_1/a_T 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 COD_1, which assigns the progressive cone dystrophy gene (COD_1) in this family to Xp21–p11·1. Differential diagnosis with congenital cone dystrophies is discussed.

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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.[1-6]

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[4] and abnormal dark adaptation curves. So far, evidence has been provided for a progressive cone dystrophy locus in Xp11[6,7] and in Xq28.[8]

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 (COD_1) in this family to Xp21–p11.1.

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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 30° 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 a_1-, and a_2-waves for a white stimulus of 1 joule in the dark. The ratio of the cone a_1-wave to the sum of the cone a_1- and rod a_2-wave (a_1/a_T).

(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.

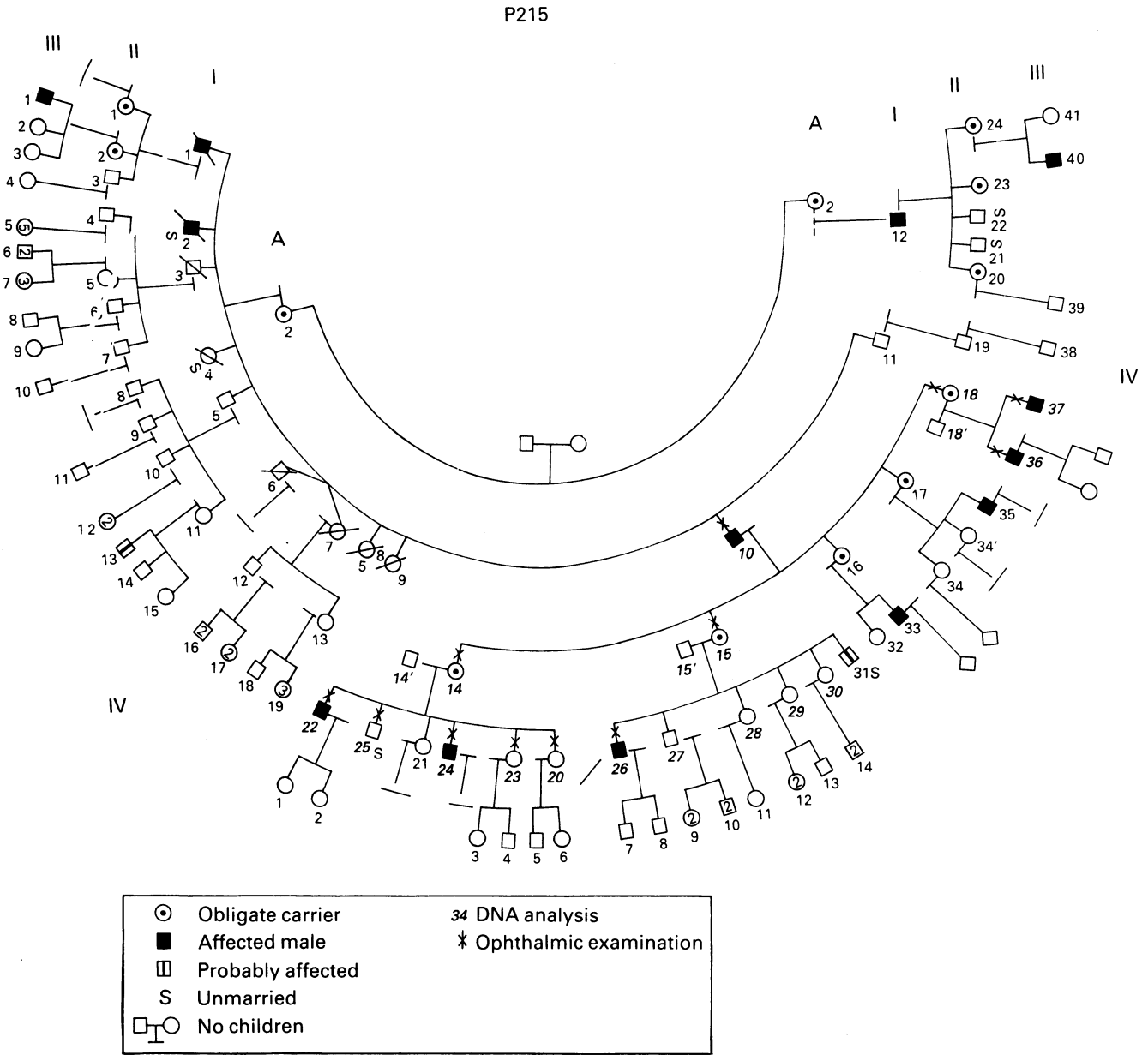

Figure 1 Pedigree of a family with X linked progressive cone dystrophy (P215).

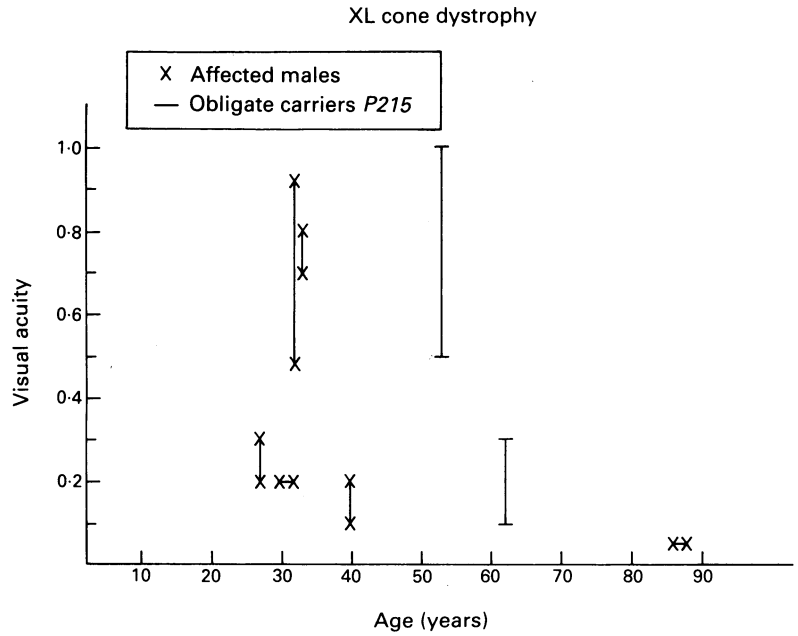

Figure 2 Visual acuity in the affected males and female carriers. A solid line connects visual acuity for each eye.

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 asb 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]

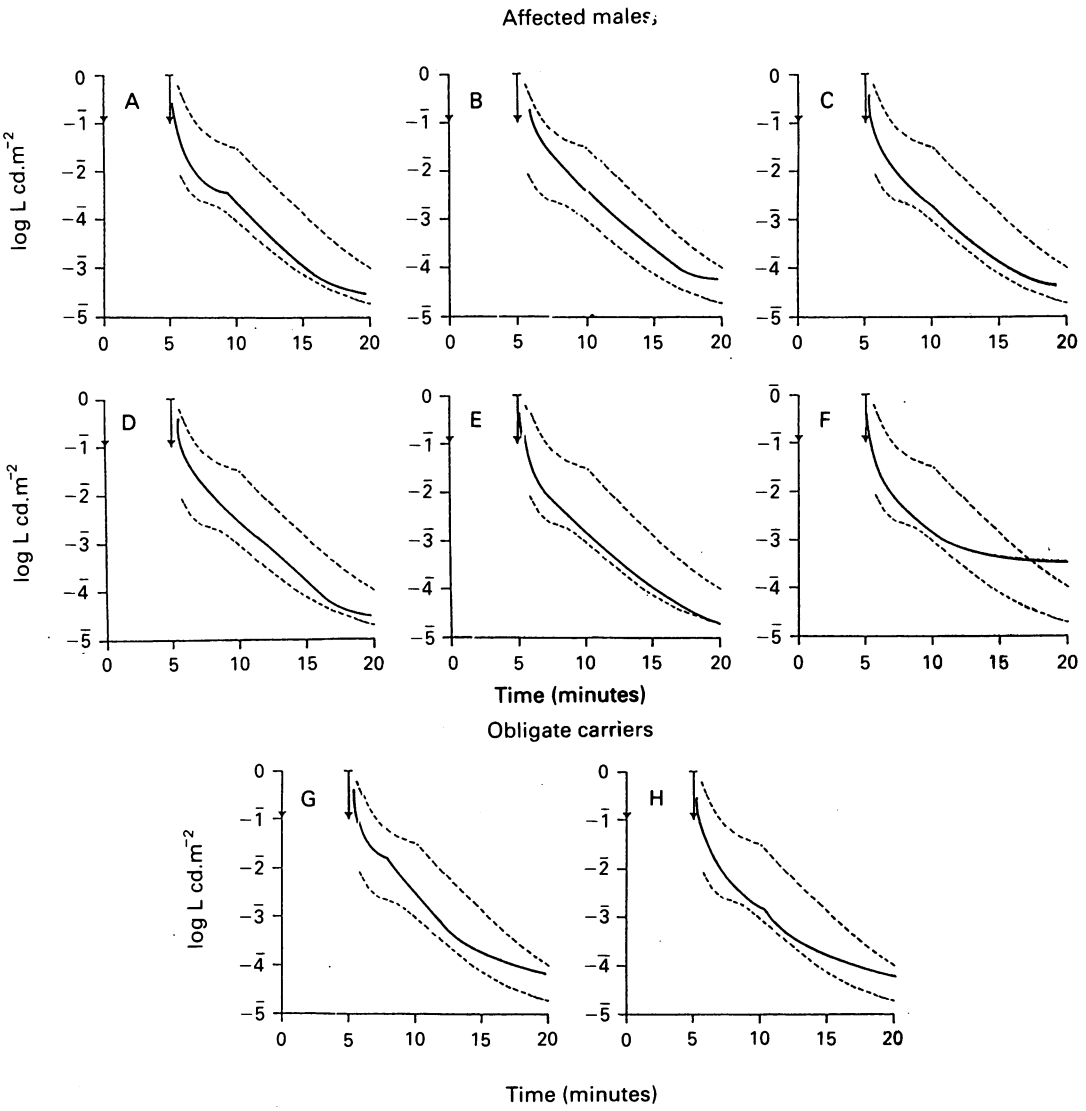

Figure 3 Range of dark adaptation obtained for normal people in our department Dark adaptation for: affected males (A-F) (III-22, III-24, III-26, III-36, III-37, I-10) and female carriers (G-H) (II-14, II-18) showing monophasic curve in most patients with a rapid breakdown of the curve and elevated final threshold in subject I-10.

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

		Photopic ERG b-wave				*Scotopic ERG b-wave*				*Scotopic ERG a-wave*				
		White		*Red*	*Blue*	*White (1 J)*		*White (40 J)*		*White (1 J)*	*White (40 J)*	*Ratio*	*Ratio bphot/*	
Case	*Age*	*AV*	*PT*	*AV*	*AV*	*AV*	*PT*	*AV*	*OP*	*AV*	*AV*	a_1/a_T	*bscot*	*EOG*
Affected males:														
I-10	86	60	44	–	40	80	54	180	–	–	200	–	0·33	NP
		60	44	–	100	140	58	220	–	–	220	–	0·27	NP
III-26	40	80	42	–	100	190	48	220	–	10	130	–	0·36	135
		130	40	–	180	230	52	360	–	30	260	–	0·27	133
III-22	32	160	38	–	320	360	50	520	–	60	380	0·32	0·30	156
		140	42	–	380	380	54	480	–	140	400	0·35	0·29	136
III-24	29	100	40	–	280	300	48	540	+	80	420	0·10	0·18	185
		120	42	–	300	340	48	560	+	80	460	0·20	0·21	185
III-36	32	130	40	–	300	320	52	600	+	50	480	0·40	0·22	153
		150	40	–	280	360	52	600	+	80	490	0·43	0·25	156
III-37	27	180		–	280	300	48	520		60	450	0·32	0·31	NP
Obligate carriers:														
II-14	62	140	46	20	280	340	46	460	+	100	360	0·34	0·31	171
		180	44	30	340	400	48	550	+	110	400	0·33	0·32	170
II-18	53	170	36	40	330	480	48	780	+	120	580	0·54	0·22	170
		160	36	30	380	500	52	810	+	100	600	0·48	0·20	182
II-15	60	160	34	60	440	520	40	800	+	200	560	0·45	0·20	NP
		160	36	50	460	600	40	820	+	220	600	0·52	0·39	NP
Possible carriers:														
III-20	35	240	36	180	380	500	38	720	+	180	600	0·55	0·33	200
		260	34	160	460	520	40	760	+	160	600	0·56	0·34	190
III-23	30	340	36	160	500	440	42	720	+	100	600	0·66	0·47	NP
		320	36	180	560	600	44	880	+	220	640	0·63	0·36	NP
Normal people:														
X		223	35	112	330	432	40·2	570	+	127	485	0·68	0·45	198
SD		42	1·5	14	35	70	1·4	65		32	80	0·08	0·06	24·7

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

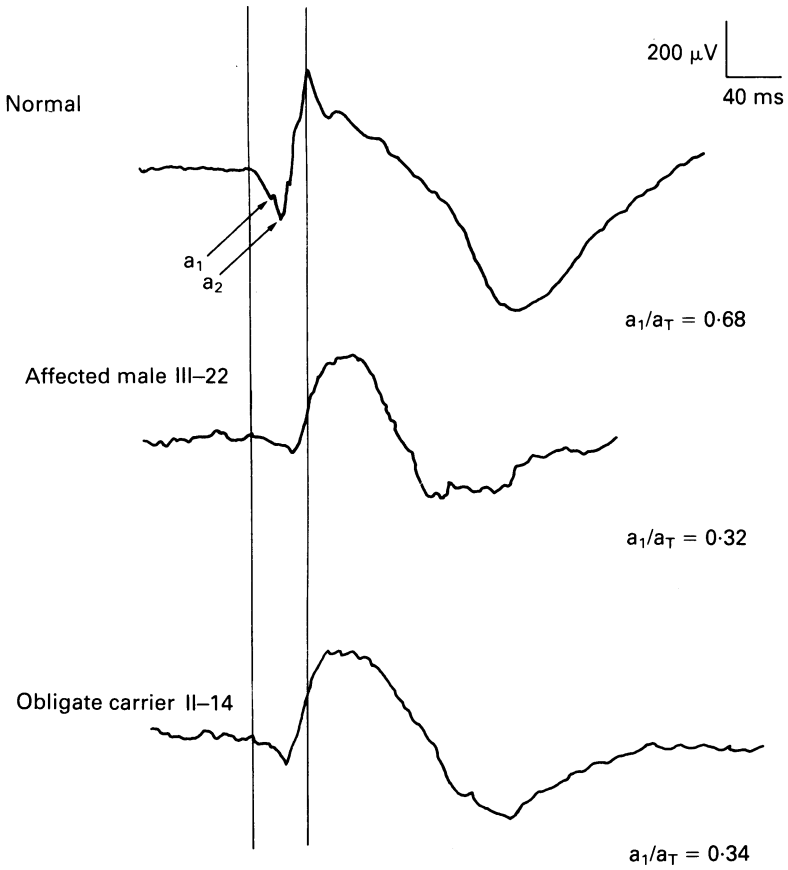

Figure 4 Scotopic electroretinogram with white stimulus of 1 joule. The ratio a_1/a_T of the cone a_1-wave to the sum of the cone a_1 and rod a_2-wave. Note the reduced a_1-wave in affected male and one of the affected carriers. $a_T=a_1+a_2$.

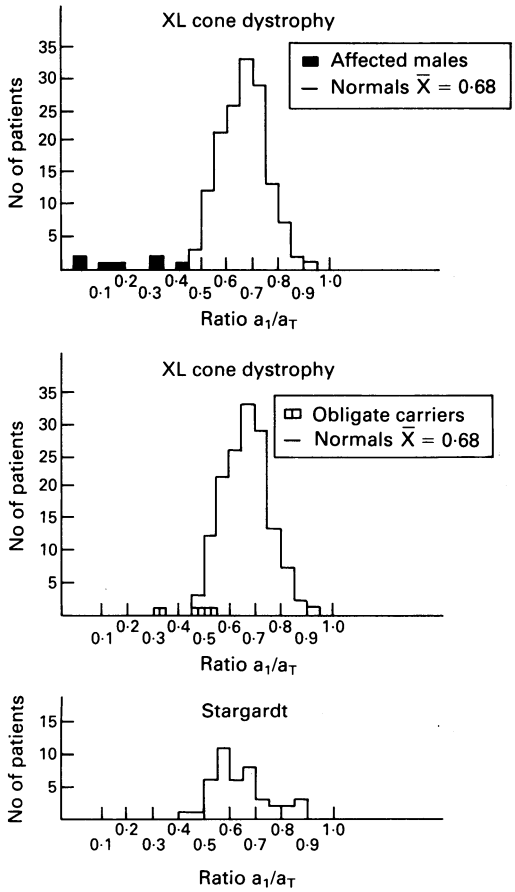

Figure 5 Distribution of a_1/a_T ratio for white stimulus of 1 joule in the dark adapted state for affected males and carriers with XL cone dystrophy and for patients with Stagardt disease (after Dr A De Rouck).

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_1/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

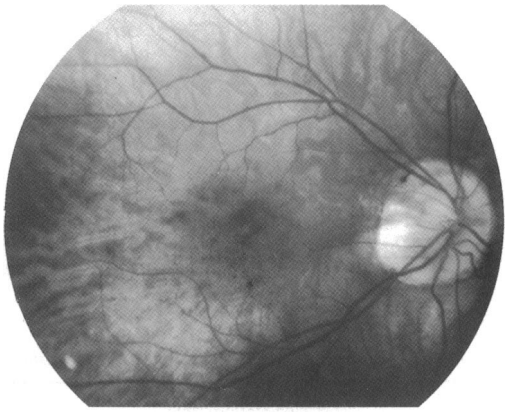

Figure 6A Fundus of affected male III-36 (age 32 years). The picture illustrates myopic degeneration with prominent choroidal pattern and a granular aspect of the macula with absence of the foveal light reflexes.

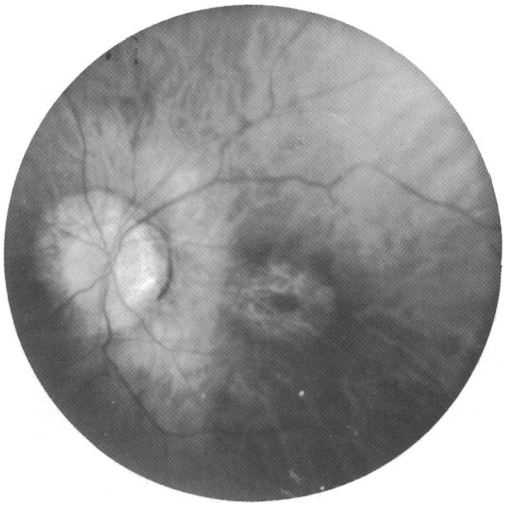

Figure 6B Fundus of affected male III-26 (age 40 years). Note the well demarcated atrophy of the macula.

disease is also plotted. The ratio in our patients is found to be less than the mean −2 SD (χ=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_1/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 COD_1 and Xp loci

					Θ					
Locus	*Probe*	*PCR*	Θ_{max}	Z_{max}	*0·00*	*0·01*	*0·05*	*0·10*	*0·20*	*0·30*
DXS269	P20		0·00	1·51	1·51	1·48	1·39	1·28	1·02	0·73
DXS84	754		0·00	2·10	2·10	2·07	1·95	1·78	1·43	1·02
MAOB		$(CA)_n$	0·00	2·10	2·10	2·07	1·95	1·78	1·43	1·02
DXS426		$(CA)_n$	0·00	2·10	2·10	2·07	1·95	1·78	1·43	1·02

Table 3 Clinical, electrophysiological examination and DNA analysis

	XL cone dystrophy COD_1	*XL cone dystrophy (Reichel)*[8]	*XL blue cone monochromatism*
Nystagmus	−	−	+
Visual acuity	20/25 ↓ Finger counting	20/30 ↓ 20/200	20/60 ↓ 20/200
Refraction	High myopia		Myopia Achromatopsia
Colour vision	Normal ↓ Achromatopsia	Protanopia ↓ Achromatopsia	
Fundus	No foveal reflex ↓ Macular atrophy	No foveal reflex ↓ Macular atrophy	No foveal reflex ↓ Macular atrophy
Dark adaptation	Monophasic	Monophasic	Monophasic
ERG			
Cone response	Reduced	Reduced	Reduced
Rod response	Normal ↓ Reduced	Normal	Normal
Gene locus	X p11	X q28 red pigment gene	X q28 red+green pigment genes

RESULTS OF DNA ANALYSIS

Two point linkage results between COD_1 and several proximal Xp loci are presented in Table 2. Close linkage without recombination was found between COD_1 and DXS269 (Z_{max}=1·51), and between COD_1 and the loci DXS84, MAOB, and DSX426 (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[3 4] 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_1/a_T ratio for the white light of 1 joule. Therefore, based on a small number of female carriers in our family, the a_1/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.[5] Patients with progressive cone dystrophy may present with a tapetal-like sheen,[3 4] 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 (COD_1) and proximal Xp markers. This localisation is in agreement with previous DNA analyses in the disease[6 7] and clearly separates the COD_1 gene localisation from the gene localisation of X linked congenital cone dysfunctions, including blue cone monochromatism and the progressive cone dystrophy reported by Reichel[8] 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*[17] and has also been reported by Nathans *et al*.[18] DNA studies revealed alterations in the red and green visual pigment gene cluster.[17]

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.[8] 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 differentation 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).

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