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Clinical and Electroretinographic Findings of Female Carriers and Affected Males in a Progressive X-linked Cone-Rod Dystrophy (COD-1) Pedigree

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Objective: To study the clinical and electroretinographic findings of affected males and female carriers in a family with X-linked cone-rod dystrophy (COD-1).

Design: Observational case series.

Participants: Twenty-five members of a five-generation pedigree were examined.

Methods: A history of visual impairment including age at onset, loss of acuity, color vision abnormalities, photophobia, and nyctalopia was obtained. A complete ophthalmologic examination was performed, including kinetic perimetry with a Goldmann perimeter, FM 100-hue testing, and standardized Ganzfeld electroretinography following the ISCEV protocol.

Main Outcome Measures: Patients were classified as affected or unaffected on the basis of the clinical examination. All carrier females had affected sons.

Results: Nine affected males and seven female carriers were identified. Affected males noted decreased visual acuity and poor color vision within the first two decades of life. Early in the disease, macular retinal pigment epithelial (RPE) changes were found that progressed to an atrophic macular scar by the fifth decade. Evidence of progression from macular pigment mottling to an atrophic macular lesion over a 13-year period was identified in one patient. The photopic, single-flash, b-wave amplitude was low in all affected males and declined with age. The 30-Hz flicker b-wave implicit times were abnormally prolonged in all affected males. Female carriers were asymptomatic although three had slightly abnormal color vision and small paracentral field defects and subtle RPE defects were found in three carriers. Carriers demonstrated prolongation of the 30-Hz flicker b-wave implicit time and interocular asymmetry. Five of seven carriers and two affected males demonstrated reduced oscillatory potentials and an abnormal-appearing flattened photopic a-wave. Five men and two women demonstrated a characteristic tapetal-like retinal sheen.

Conclusions: Affected patients in this pedigree demonstrate early loss of visual acuity and poor cone function with late rod involvement. Female carriers may appear clinically normal or may be identified by subtle color vision defects, fundus abnormalities, prolongation of the 30-Hz flicker implicit time with interocular asymmetry, or an abnormal flattened photopic a-wave. Genetic linkage analysis of this family was recently reported and the disease-causing gene has been mapped to an approximately 1-Mb interval on chromosome Xp11.4. *Ophthalmology* 2000;107:1104-1110 © 2000 by the American Academy of Ophthalmology.

Children presenting with decreased visual acuity can present diagnostic challenges. Often the fundus appears normal and there may not be a family history of eye disease.

A thorough evaluation includes ruling out central nervous system and optic nerve causes of visual loss. Electrophysiologic testing may localize the abnormality to retinal photoreceptors. Hereditary abnormalities of cone function can be due to stationary or progressive disorders. The goals of correctly identifying the cause of the visual deficit, as well as providing accurate genetic counseling to parents, can be aided by studies of genotype-phenotype correlation. The growing body of molecular genetic data regarding ophthalmic diseases coupled with carefully detailed clinical evaluation can enhance our ability to achieve these goals.

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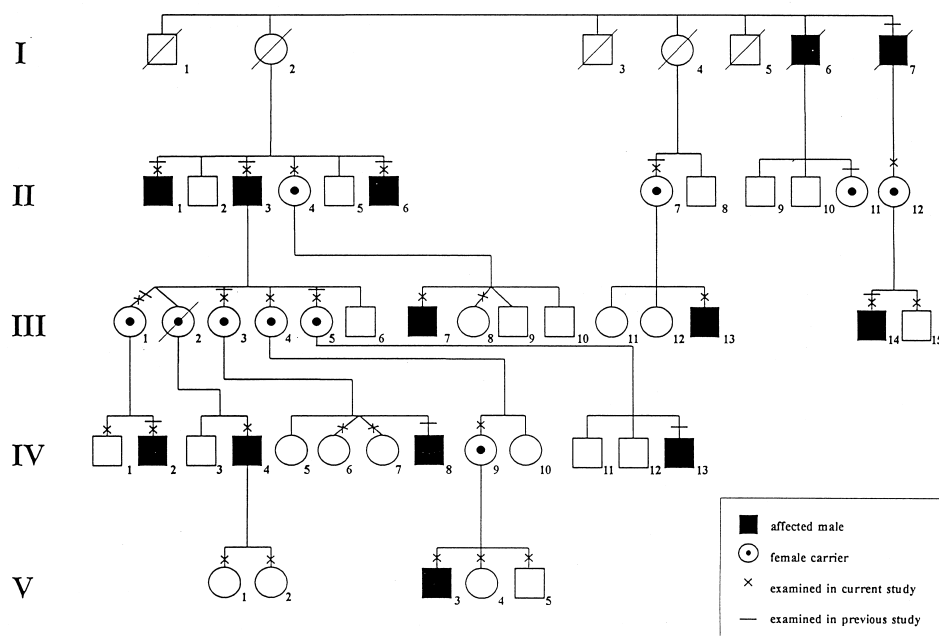


Figure 1. Pedigree of X-linked recessive cone-rod dystrophy family.

Progressive cone disorders can be classified as cone dystrophies or degenerations. Patients with cone dystrophies rarely demonstrate nystagmus but often present with decreased visual acuity, photophobia, and color vision abnormalities during the first two decades of life. Fundus findings may progress from patchy retinal pigment epithelial (RPE) defects to a “bull’s eye” maculopathy to central RPE atrophy. Many cone dystrophies demonstrate rod photoreceptor dysfunction later in the disease course. These patients may be classified as having cone-rod dystrophies.¹ Most cone dystrophies exhibit an autosomal dominant pattern of inheritance; however, autosomal recessive and X-linked recessive pedigrees have also been reported.^{1–16} Disease-causing genes have been identified in five forms of cone and cone-rod dystrophy.^{12–16}

In 1989, Jacobson and colleagues¹⁰ reported the clinical findings of a family with a progressive cone dystrophy with X-linked inheritance. Three affected males demonstrated a tapetal-like retinal sheen. Heckenlively and Weleber⁷ reported a family with a golden yellow-green tapetal-like sheen in the fundus of affected males and one carrier female with X-linked cone dystrophy. Because of the relatively small number of reported patients in the literature, the entire range of expression of male and carrier females is not fully known. Furthermore, limited electroretinographic data on these patients are available. Our goal was to re-examine the family first studied by Jacobson to characterize new cases, report on the range of the phenotypes in the expanded pedigree, perform standardized electroretinography, and document evidence of disease progression.

The COD-1 locus was first localized to a region between Xp11.3 and Xp21.1, an interval that encompassed the RP3 locus.⁶ Through ascertaining new members of this family, as well as two other extended families, we were able to

refine the previous genetic interval on chromosome Xp. The linkage data demonstrate that COD-1 is a distinct locus located within an approximately 1-Mb interval on Xp11.4.¹⁷

Methods

Twenty-five members of a five-generation pedigree were examined (Fig 1). A history of visual impairment including age at onset, loss of acuity, color vision abnormalities, photophobia, and nyctalopia was obtained. A complete ophthalmologic examination including refraction with Snellen visual acuity, perimetry, Farnsworth-Munsell (FM) 100-hue test, and ophthalmoscopy was performed. Standardized electroretinography was performed according to the ERG Standardization Committee of the International Society for Clinical Electrophysiology of Vision protocol¹⁸ on a UTAS E200 instrument (LKC Technologies, Gaithersburg, MD). Subjects consented to participate under protocols approved by the Institutional Review Board at the University of Iowa and the University of Pittsburgh.

Results

Affected Males

Affected male patients reported an onset of reduced visual acuity within the first two decades. Patients reported becoming aware of decreased visual acuity during grade school. All patients reported hemeralopia and noted that their best vision could be achieved at twilight. Problems with color vision were noted by the second decade. At this stage, the fundi appeared normal. The earliest findings were subtle defects in the macular RPE. The pigmentary changes could be identified on fundus fluorescein angiography as window defects (Fig 2). The optic nerve and the retinal vessels were normal. Snellen visual acuity during the first three decades was 20/25 to 20/50 (Table 1).

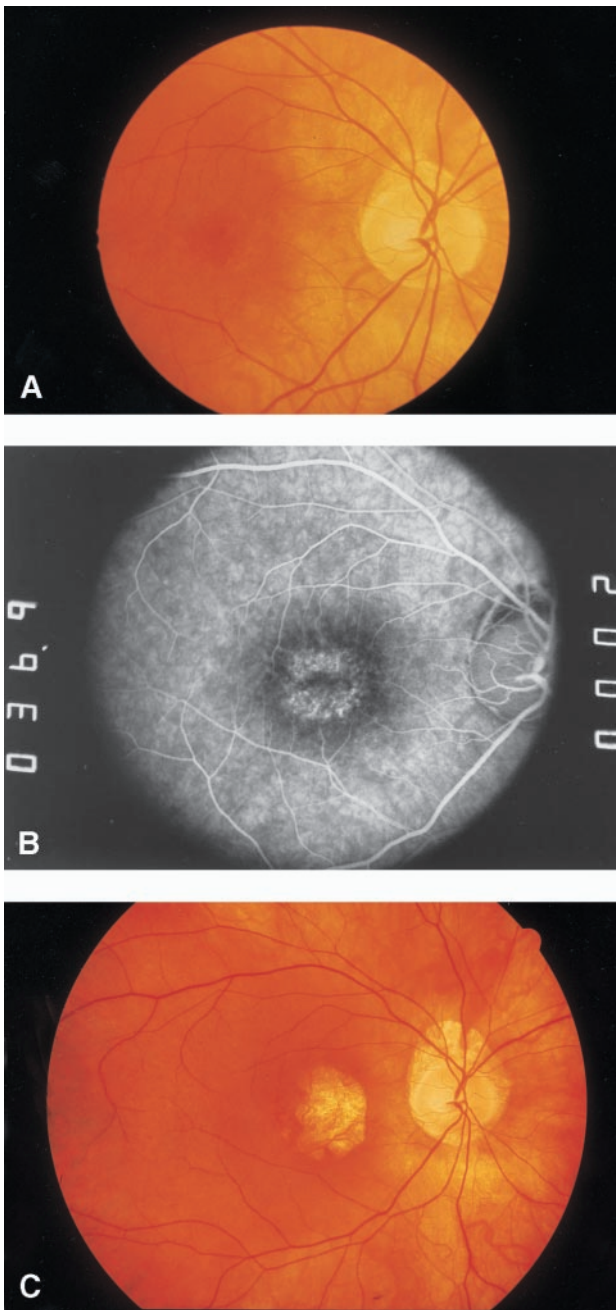


Figure 2. **A**, Patient III-7. Fundus photograph at age 29 of this affected man with subtle ring of retinal pigment epithelial (RPE) hypopigmentation. **B**, The early bull's eye lesion is more easily identified on fluorescein angiography. **C**, Thirteen years later, he has developed an atrophic macular lesion with more prominent peripapillary atrophy.

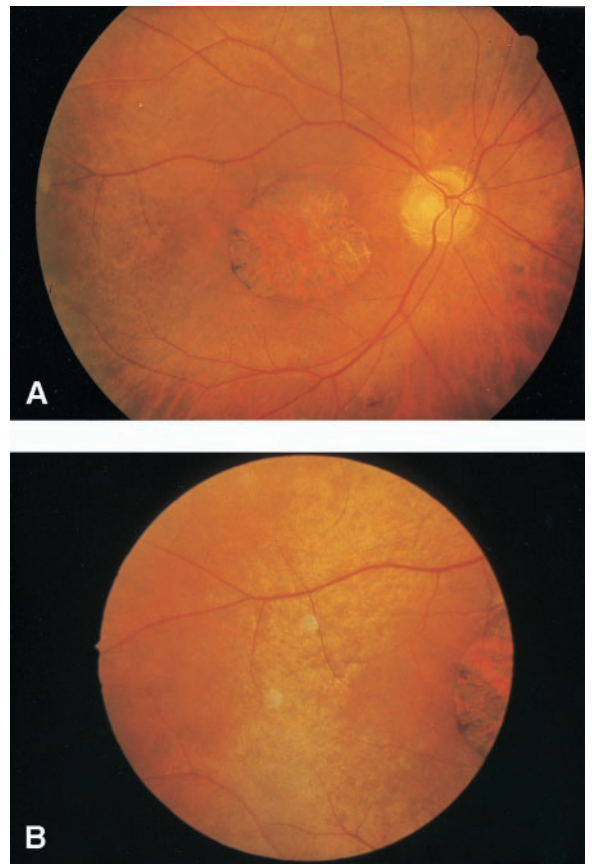


Figure 3. **A**, Patient II-6. Fundus photograph of 71-year-old patient demonstrated the atrophic macular lesions found in this pedigree after the fifth decade of life. Note the normal retinal vasculature and optic nerve. **B**, This patient demonstrated a tapetal-like sheen temporal to the atrophic lesion in the right eye.

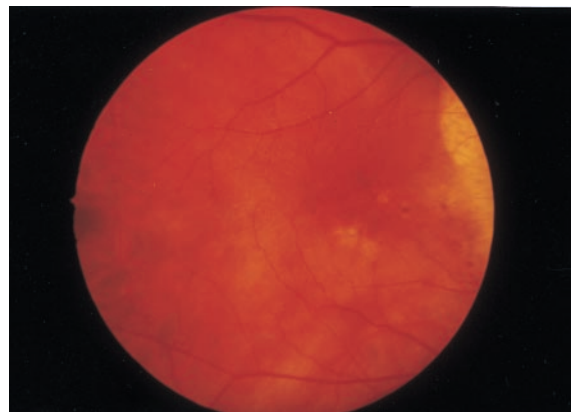


Figure 5. Subject II-4. Fundus photograph of right eye of a 75-year-old carrier with peripapillary atrophy and mild retinal pigment epithelium (RPE) defects. Note the tapetal-like reflex temporally.

Table 1. Affected Males

Patient	Age	Initial VA OD	Initial VA OS	Years of Follow-up	Final VA OD	Final VA OS
II-1	82	20/800	CF 7'	9	20/400	20/400
II-3	77	20/400	20/200	9	20/200	20/300
II-6	71	20/200	20/200	9	20/200	20/200
III-7	49				20/200	20/200
III-13	42	20/20	20/20	8	20/20	20/20
III-14	33	20/25	20/30	7	20/30	20/30
IV-2	16	20/50	20/40	9	20/50	20/50
IV-4	33				20/70	20/100
IV-13	28	20/25	20/50	9	20/50	20/50

Change in visual acuity of affected males during the follow-up period. Patients with one visual acuity measurement were examined only once.

CF = counting fingers; OD = right eye; OS = left eye; VA = visual acuity.

Patients reported that their visual acuity declined during the fourth through fifth decades of life and then stabilized. Best-corrected Snellen visual acuities confirmed these subjective impressions with 20/200 to 20/400 acuities in patients age 49 to 82 (Table 1). By the fifth decade, geographic atrophy of the

macular RPE was present (Fig 3). The progression from punctate RPE defects to macular geographic atrophy is well illustrated by patient III-7 (Fig 2). A tapetal-like retinal sheen was observed in five patients. No peripheral retinal bone spicule-type pigmentation was found in any patient. Two affected males maintained Snellen visual acuity of 20/30 or better at ages 33 and 42.

Kinetic visual field testing with a Goldmann perimeter revealed central and paracentral scotomas. The peripheral fields were full to the V4e and III4e test target in every subject, even in one patient in the ninth decade of life. All patients had higher error scores than age-matched normal subjects on Farnsworth-Munsell 100-hue testing.¹⁹ The errors were scattered with no specific axis.

Electroretinography demonstrated severe cone dysfunction early in life (Table 2). For example, patient IV-2 at age 16 had a photopic b-wave amplitude of 13 μ V (normal >74 μ V) with an implicit time of 37.5 msec (normal <32 msec). Rod-dominated responses were moderately reduced in all age groups. The 30-Hz flicker b-wave implicit time was abnormally prolonged in all affected males. Two affected males demonstrated an abnormally prolonged photopic a-wave (Fig 4). The photopic a-waves were too depressed in other affected males to evaluate the morphology. This abnormally prolonged a-wave was also found in female carriers (see following).

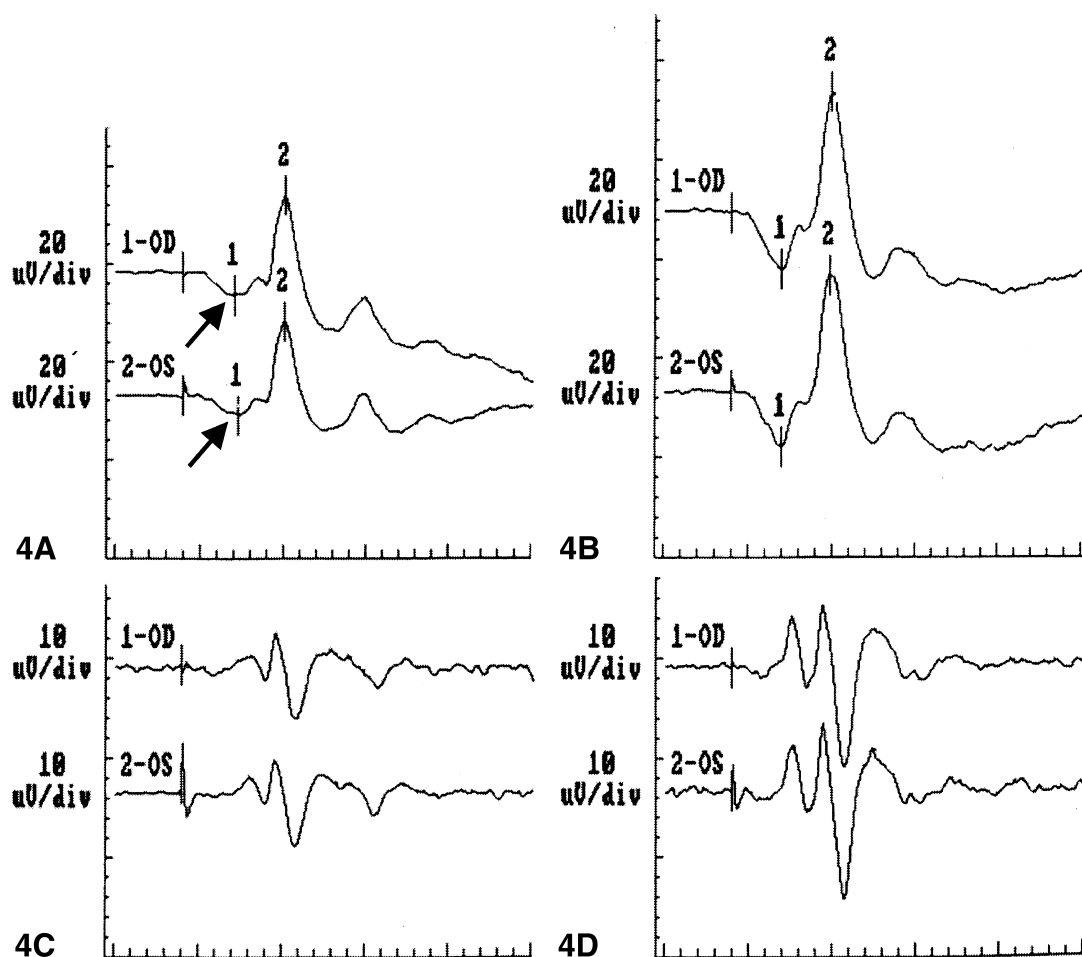


Figure 4. A, B, Electroretinography of patient IV-4. Photopic single-flash response. Note the flattened appearance to the a-wave. Oscillatory potential amplitudes were markedly reduced. C, D, Normal photopic a-wave with normal oscillatory potentials.

Table 2. Electroretinographic Values for Affected Males*

Patient	Age	Scotopic				Photopic							
		b-Wave 24 dB [†]				Single-Flash b-Wave				30-Hz b-Wave			
		Amplitude (μV)	Normal (μV)	Implicit Time (msec)	Normal (msec)	Amplitude (μV)	Normal (μV)	Implicit Time (msec)	Normal (msec)	Amplitude (μV)	Normal (μV)	Implicit Time (msec)	Normal (msec)
II-1	81	57/63	>28	103/108	<117	3/6	>22	39/40	<32	25/25	>10	42/45	<28
II-6	71	7/7	>45	101/113	<115	1/15	>30	37/44	<32	10/9	>15	33/37	<28
III-7	49	81/98	>82	113/116	<112	19/17	>47	34/35	<32	27/37	>28	35/36	<29
IV-2	16	58/39	>138	93/99	<106	13/15	>74	38/37	<32	16/8	>48	37/38	<30
IV-4	33	94/96	>109	94/96	<109	24/20	>60	31/31	<32	80/71	>60	29/29	<29

*Values displayed are the amplitudes and implicit times for both eyes (OD/OS). Normal values are age adjusted at the 95% confidence level. Note the prolonged photopic b-wave implicit times, reduced photopic b-wave amplitudes, and the mildly reduced scotopic b-wave amplitudes.

[†]The 24-dB response represents 24 dB of attenuation from the standard flash of 2.0 cds/m². The recording is made after 30 minutes of dark adaptation.

Female Carriers

All female carriers were asymptomatic. One woman described difficulty in distinguishing shades of brown, but this had not affected her activities of daily living. Visual acuity was 20/20 to 20/30 and remained stationary (Table 3). Farnsworth Munsell 100-hue testing revealed normal scores in four of seven carriers.¹⁹ The three carriers with abnormal scores showed nonspecific axes.

Table 3. Female Carriers

Subject	Age	Initial		Years of Follow-up	Final	
		Initial VA OD	Initial VA OS		Final VA OD	Final VA OS
II-4	75	20/30	20/30	8	20/30	20/25
II-7	74	20/20	20/200	8	20/30	20/200
II-11	58	20/20	20/20			
II-12	59	20/20	20/20	8	20/15	20/15
III-1	55	20/25	20/25	9	20/25	20/20
III-3	52	20/20	20/20	9	20/20	20/20
III-5	49	20/25	20/40	9	20/25	20/40
IV-9	30				20/15	20/15

Change in visual acuity of carrier females during the follow-up period. Patients with one visual acuity measurement were examined only once.

OD = right eye; OS = left eye; VA = visual acuity.

Kinetic perimetry was normal in four of seven carriers. Three carriers had visual field defects that included enlargement of the physiologic blindspot and small paracentral scotomas.

The maculae of the female carriers were significant for mild mottling of the retinal pigment epithelium, which was found in the oldest women. The most severely affected carrier, II-4, demonstrated pigment clumping with more prominent atrophy (Fig 5). She also had a tapetal-like sheen in the temporal macula. Three carriers had peripapillary atrophy that was not related to myopia.

Electroretinography varied from normal in four carriers to mild attenuation of cone responses in two carriers, to one 75-year-old carrier (II-4) with mildly attenuated rod responses and markedly delayed b-wave implicit times (Table 4). This carrier had normal cone b-wave amplitudes with markedly delayed implicit times (right eye, 38 msec; left eye, 36 msec; normal, <29 msec). Five carriers demonstrated an abnormally prolonged photopic a-wave (Fig 6).

Discussion

Early onset of photophobia, loss of visual acuity, impaired color vision, central field loss, and a tapetal-like retinal sheen characterize the cone-rod dystrophy in this pedigree. The earliest finding in affected males was the onset of reduced visual acuity by age 10 to 15. Photophobia and color vision difficulties were noted before age 20.

Table 4. Electroretinographic Values for Carrier Females*

Subject	Age	Photopic							
		Single-Flash b-Wave				30-Hz b-Wave			
		Amplitude (μV)	Normal (μV)	Implicit Time (msec)	Normal (msec)	Amplitude (μV)	Normal (μV)	Implicit Time (msec)	Normal (msec)
II-4	75	58/88	>27	38/36	<32	57/74	>12	38/36	<28
II-7	72	111/106	>29	33/33	<32	104/78	>14	31/32	<28
II-12	59	158/141	>39	30/30	<32	132/135	>22	26/26	<29
III-1	55	143/136	>43	31/32	<32	146/132	>24	29/29	<29
III-3	53	94/110	>44	32/31	<32	62/103	>26	27/28	<29
III-4	51	131/69	>46	31/32	<32	120/60	>27	27/27	<29
III-5	49	65/64	>47	34/34	<32	55/95	>28	32/33	<29

The photopic b-wave amplitudes and implicit times. Values shown are for both eyes. Normal values are age adjusted at the 95% confidence level. Note the presence of interocular asymmetry, most noticeable in the 30-Hz flicker b-wave amplitudes.

The peripheral fields remained intact into the ninth decade of life. No patients complained of nyctalopia. Standardized electroretinography demonstrated early reduction of cone-dominated responses, followed later by reduction of rod responses. An abnormally prolonged a-wave with reduction of oscillatory potential amplitudes was found in two affected males. The characteristic tapetal-like retinal sheen distinguishes this disease from other genetic types of cone dystrophy. In the late stages, geographic atrophy of the macular RPE developed, with visual acuity at the 20/200 to 20/400 level.

There was evidence of variable expressivity. One male maintained a visual acuity of 20/20 or better at age 42, whereas another family member demonstrated 20/100 visual acuity at age 33. Despite visual acuity of 20/20, abnormalities on the FM-100, macular RPE granularity, and poor photopic b-wave amplitudes were found in a mildly affected patient.

The carrier state is characterized by subtle RPE defects with mild color vision abnormalities. No single test was consistently abnormal in all carriers. Some female carriers may be identified by abnormal color vision testing, patchy RPE defects, prolongation of the photopic 30-Hz flicker implicit time, or interocular asymmetry. The older female carriers were more likely to demonstrate clinical abnormalities and complain of light sensitivity at night. Four obligate carriers, age 51 to 59, had essentially normal visual acuity, color vision, and electroretinography. It is important to note that a normal electroretinogram does not rule out the carrier state. This degree of phenotypic variability has also been observed in carriers of blue cone monochromatism²⁰ and X-linked retinitis pigmentosa.²¹

An abnormally prolonged a-wave was found in several affected males and female carriers. This interesting morphology demonstrated delayed b-waves and reduced oscillatory potential amplitudes. This finding may represent an abnormality in the cone on-bipolar cell pathway.²² This morphology may help identify female carriers when the b-wave amplitudes are within the normal range.

We were fortunate to examine seven affected males and six carrier females from Jacobson's original study and document the progression of the disease. Atrophic macular RPE changes evolved into macular geographic atrophy in patients in the fifth decade of life and older. A tapetal-like sheen in the temporal retina was found in older male patients and female carriers. It is likely that this family has the same genetic disease as the family described by Heckenlively and Weleber.⁷

There are at least two genetic types of X-linked progressive cone dystrophy. Bergen and Pinckers¹¹ studied a family in which the disease-causing gene maps to the long arm of chromosome X, whereas the disease in our family maps to the short arm of chromosome X. Previous work has demonstrated linkage at Xp21.1-p11.3 region in this family.^{6,17} The clinical characterization of additional patients in this study assisted in narrowing the genetic interval for COD-1 to approximately 1 Mb on Xp11.4.¹⁷

Carriers of X-linked cone dystrophy should be counseled that each male child has a 50% risk of being affected and each female child has a 50% risk of being a carrier. Affected

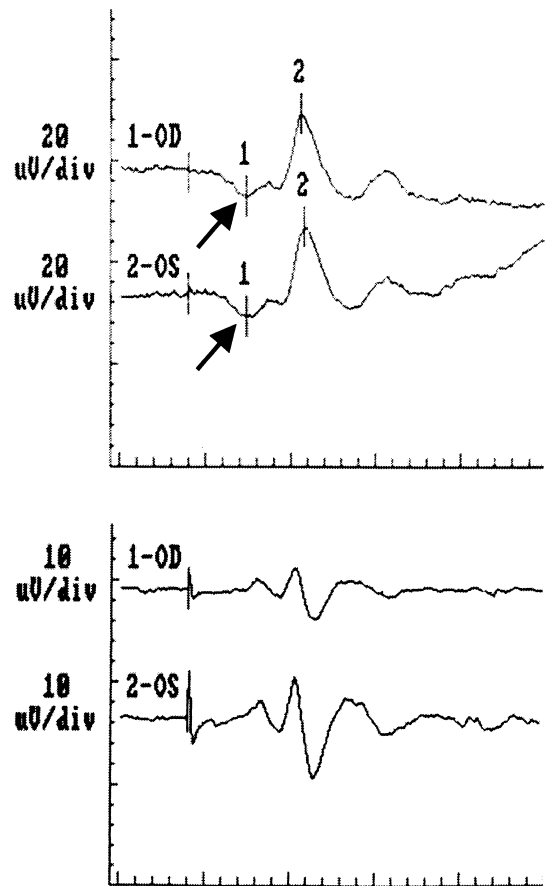


Figure 6. Electroretinography of 49-year-old female carrier, subject III-5. Note the delayed photopic b-wave with a flattened appearance of the a-wave. Oscillatory potential amplitudes are reduced.

male patients should be counseled that each female child will be a carrier and that no male children will be affected. Identifying carrier females during their childbearing years can be difficult. Furthermore, affected children who have mildly reduced visual acuity and color vision abnormalities may have minimal fundus findings. Identification of the gene responsible for XL cone dystrophy will greatly assist clinicians in diagnosis, and genetic counseling and may lead to treatments to prolong the viability of dying cone photoreceptors.

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