X-Linked Retinitis Pigmentosa: Functional Phenotype of an RP2 Genotype

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Rod- and cone-mediated function was studied with psychophysics and electroretinography in members of an X-linked retinitis pigmentosa pedigree with the RP2 genotype. An asymptomatic hemizygote with an early stage of the disease had cone dysfunction in the mid-periphery and an abnormal cone electroretinogram (ERG); rod function was normal. Hemizygotes with more advanced disease had cone and rod dysfunction in the mid-peripheral retina and cone dysfunction in the far periphery; cone and rod ERGs were abnormal. At very advanced stages, there was an absolute mid-peripheral scotoma and marked cone and rod dysfunction in the far peripheral and central retina. Cone and rod ERGs were severely abnormal or not detectable. Heterozygotes showed tapetal-like reflexes, patches of pigmentary retinopathy, and a range of functional findings from no detectable abnormalities to moderate levels of retinal dysfunction. There were regions of normal function adjacent to dysfunctional patches that had greater cone than rod sensitivity losses or comparable cone and rod losses. The results suggest that the phenotype of this RP2 genotype of X-linked retinitis pigmentosa, unlike other forms of retinitis pigmentosa, is first expressed as a cone photoreceptor system dysfunction, and as the disease progresses, both rod and cone systems are involved. Invest Ophthalmol Vis Sci 33:3481-3492, 1992

Molecular genetic studies have demonstrated that at least two different subregions of the short arm of the X chromosome are responsible for X-linked retinitis pigmentosa (XLRP). The two genotypes have been termed RP2, corresponding to the Xpl 1.2-3 region, and RP3, corresponding to the Xp21 region. Although there have been many studies of the phenotypes of XLRP hemizygotes and heterozygotes with unknown genotypes, the phenotypic expression of the retinal disease in XLRP patients known to have the RP2 or RP3 genotypes is not well understood. In one of two reports to date, an XLRP family with linkage to the RP3 locus showed diverse fundus abnormalities in the hemizygotes. The other study reported an association of the RP2 genotype with early onset of myopia and an association of the RP3 genotype with the visual symptom of late onset of night blindness.

We examined 70 members of a large XLRP family using molecular genetic techniques and ophthalmoscopy. In a subset of family members, we performed tests of visual function. Molecular genetic results indicated that this family has an RP2 genotype. The ophthalmoscopic examinations revealed tapetal-like reflexes in most of the heterozygotes and pigmentary retinopathy typical of RP in the hemizygotes. The visual function tests led to the definition of a functional phenotype for this family and provided insight into the nature and progress of this retinal degenerative disease. A brief report of some of this work has been published.

Materials and Methods

Seventy members of a family with XLRP were included in this study. All 70 members were examined with ophthalmoscopy, and their blood samples were collected for molecular genetic analysis. A subset of 10 family members, five hemizygotes and their mothers, had complete ocular examinations, Gold-
m mann kinetic perimetry, dark- and light-adapted static threshold perimetry, and full-field rod and cone electroretinography. Data from dark- and light-adapted static perimetry in 17 patients with autosomal dominant (AD) RP with rhodopsin mutations30,31 were analyzed and compared with those from the XLRF patients. Informed consent was obtained from the subjects after the nature of the procedures had been explained fully.

Molecular genetic analysis was achieved through genomic Southern blot analyses of leukocyte DNA from the family members using Xp markers known to be RP2 markers (TIMP, DXS426, DXS7) or RP3 markers (OTC, DXS84)32 and the ornithine amino transferase (OAT)-related sequences in the proximal short arm of the X chromosome.33,34 Linkage analysis was performed with the computer program LINKAGE.35

Goldmann kinetic perimetry was performed in one eye of hemizygotes and both eyes of heterozygotes using targets V (64 mm² area) and I (0.25 mm² area) at intensity 4e (318 cd/m²) on a 10 cd/m² white background. The visual field extent was quantified by a published method.25

Static threshold perimetry was performed in one eye of hemizygotes, both eyes of heterozygotes, and one eye of the ADRP patients with rhodopsin mutations using monochromatic stimuli (target area 64 mm²) in the dark- and light-adapted states. Dark-adapted perimetry was performed with 650 and 500 nm targets and light-adapted (10 cd/m²) perimetry was performed with a 600 nm target using a full field test strategy of 75 loci (12° grid) and a profile test along the horizontal meridian (2° spacing). Details of the technique, analysis methods, and normal results have been published.36-38 For the dark-adapted testing, the sensitivity difference between the 500 and 650 nm stimuli at each test location determines whether rods (≥28 dB), cones (≤12 dB), or both rods and cones (13-27 dB) are mediating detection of the stimulus. Sensitivity losses were calculated for rods (based on 500 nm test results, dark-adapted) and for cones (based on 600 nm test results, light-adapted) by comparison to normal mean values. At loci with no detectable function, maximum rod or cone sensitivity losses (ie, based on the mean normal sensitivities at that locus) were used in any further calculations. Dark- and light-adapted spectral sensitivity measurements and dark adaptometry were performed in some of the patients using procedures described previously.30,31

Full-field rod and cone electroretinograms (ERGs) were performed in one eye of hemizygotes and both eyes of heterozygotes using previously described methods.23,39 Two conventional suprathreshold stimuli were used to elicit rod and cone ERGs. The rod ERG was elicited with a dim blue flash in the dark-adapted state (−0.1 log scot-tr-s), and the cone ERG was elicited with white light (0.64 cd-sec/m²) flicker at 29 Hz on a white background light (6.9 cd/m²). In addition, intensity series were performed in the dark-adapted state with blue light flashes over a 3 log unit range, and in the light-adapted state with white light over a 2.8 log unit range flickering at 29 Hz on the white background.23,24,29 Waveforms were measured conventionally and the Naka-Rushton equation, \( V = \frac{V_{\text{max}} I^n}{I^n + K^n} \) was fit to the measured amplitudes from the rod intensity series.40 In the equation, \( V \) is rod b-wave amplitude; \( V_{\text{max}} \) is the amplitude at response saturation; \( I \) is the stimulus intensity; \( K \) is the intensity at half \( V_{\text{max}} \); and \( n \) is the exponent responsible for the slope of the function.23,24,39 To establish the relationship between rod and cone ERG amplitudes, rod \( V_{\text{max}} \) was plotted against the amplitude of the cone flicker response to our maximum luminance white flash for this stimulus condition (4.8 cd-sec/m²).

Results

Figure 1 is a pedigree that shows all of the subjects in this study. Female family members with tapetal-like reflexes, patches of pigmentary retinopathy, or both are shown as heterozygotes, as are obligate heterozygotes with or without funduscopic abnormalities. Those female and young male family members with normal-appearing fundi (even though they may have a 50/50 chance of being heterozygotes or hemizygotes, respectively) are shown as unaffected.

The results of the DNA linkage analysis suggested linkage of the disease in this family with Xp markers that are at DXS7 or proximal, including DXS426 and TIMP (maximum lod scores >2), whereas markers distal to DXS7, such as OTC and DXS84, did not show linkage (maximum lod scores <1). The OAT-related loci originally mapped at Xp11.2 and later proximal to TIMP showed cosegregation with the disease without recombination (Family M-441). Thus, the results were consistent with the genotype of the disease being RP2.9

Table 1 lists some clinical findings in the subset of 10 family members (denoted by underlined numbers in Figure 1) studied with complete eye examinations and retinal function tests. The hemizygotes are listed in the order of their age. The order of heterozygotes corresponds to that of their sons. The hemizygotes had varying degrees of myopia and astigmatism. There was no obvious relationship of age to degree of severity, as assessed by visual acuity or kinetic perimetry. Of interest, patient IV/14, the hemizygote with the largest visual field extent, had a tapetal-like reflex
across most of his fundus. This reflex had the unusual feature of appearing and disappearing with change in the direction of fundus illumination. The other hemizygotes showed attenuated retinal vessels and pigmentary abnormalities (bone spicule-like pigment, depigmentation, atrophy) mainly in the mid-peripheral and far peripheral retina. These findings are associated with typical RP of any genetic type. Central retinal pigmentary changes were less severe than those in the more peripheral retina. The heterozygotes had interocular asymmetries in fundus appearance and visual field extent. All five heterozygotes had a tapetal-like reflex and all but one showed patches of pigmentary retinopathy.

Figure 2 (upper) shows rod and cone ERG amplitude and timing results from the hemizygotes and heterozygotes. Rod ERG b-waves to a dim blue light in the dark-adapted state were reduced in amplitude and delayed in timing in all hemizygotes except patient IV/14. The rod ERG in patient IV/9 was not detectable. Cone flicker ERGs were measurable in all hemizygotes and had reduced amplitude and delayed timing. One heterozygote (patient III/6) showed normal rod and cone ERG parameters in both eyes. Two het-

Table 1. Clinical findings in XLRP hemizygotes and heterozygotes

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<th>Patient no.</th>
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* Expressed as a percent of normal mean. Two standard deviations below normal equals 90% for V-4e and 88% for I-4e.
† Tapetal-like reflex.
erozygotes (patients III/1 and III/2) had reduced rod b-wave amplitudes with or without timing abnormalities and had reduced and delayed cone ERGs in both eyes. In the remaining two heterozygotes (patients IV/17 and III/4), one eye had abnormal rod and cone ERGs, while the other eye showed normal rod parameters, but cone ERGs delayed in timing with normal or abnormal amplitude. The lines connecting the right and left eye data of the same heterozygote highlight interocular asymmetries.

The relationship between $V_{\text{max}}$ and $K$ from the rod ERG b-wave intensity-response functions is shown for hemizygotes and heterozygotes (Fig. 2, lower left). Only three of the hemizygotes had sufficient responses for calculation of Naka-Rushton parameters. Patient IV/14 had normal $V_{\text{max}}$, $K$, and $n$. In patients IV/2 and IV/4 $V_{\text{max}}$ was reduced. $K$ was normal in patient IV/4, but slightly abnormal in IV/2, and $n$ was normal in both patients (normal mean = 0.87; standard deviation = 0.12). Heterozygotes showed either normal or reduced rod ERG b-wave $V_{\text{max}}$. $K$ was normal in 9 of 10 eyes, and $n$ was normal in all eyes.

The relationship of rod and cone ERGs in the hemizyngotes and heterozygotes is quantified in Figure 2 (lower right). $V_{\text{max}}$ of the rod ERG b-wave intensity-response function is plotted against the maximum amplitude cone flicker ERG. These amplitude data are normalized to the mean amplitude of control subjects and expressed in log units. Based on this graph, it is evident that some hemizygotes show greater cone than rod ERG amplitude reduction, whereas others have results that fall close to the line expected when reduction is equal. The heterozygotes fall within the range of normal data, show relatively equal reduction of responses, or have greater cone than rod amplitude reduction.

Figure 3 shows gray scale maps of cone and rod sensitivity losses, determined from results of light- and dark-adapted static perimetry, in one eye of four hemizygotes. Patient IV/14, age 21 yr, has no rod sensitivity loss at any of the loci tested, but many extrafoveal loci show cone sensitivity loss (mean loss for abnormal loci = 5.2 dB; SD = 1.1 dB). Sensitivity at the foveal locus was normal. Patient IV/2, age 11 yr, has marked cone sensitivity losses in the superior and mid-peripheral fields with less pronounced cone dysfunction in the more peripheral field. Sensitivity at the foveal locus was normal. Patient IV/2, age 11 yr, has marked cone sensitivity losses in the superior and mid-peripheral fields with less pronounced cone dys- function in the more peripheral field. Sensitivity at the foveal locus was normal. Mean cone sensitivity loss is 15.7 dB (SD = 7.6 dB). There is considerable rod sensitivity loss in the mid-peripheral field, but sensitivities in the central and peripheral fields are within the normal limits. Mean rod sensitivity loss is 24.2 dB (SD = 17.1 dB). Patient IV/4, age 25 yr, shows a similar pattern of cone dysfunction to patient IV/2, but...
HEMIZYGOTES

CONE SENSITIVITY LOSS

ROD SENSITIVITY LOSS

Fig. 3. Dark- and light-adapted static threshold perimetry in one eye of four hemizygotes. Results of static perimetry are displayed as gray scales of rod and cone sensitivity losses. Gray scales have 16 levels of gray, ranging from 0–54 dB for rods and 0–30 dB for cones. Black indicates no detection of the stimulus. White indicates test result was within two standard deviations of the mean normal sensitivity for that locus. Physiologic blind spot is shown as a black square at 12° in the temporal field.

has a slightly greater extent of severe cone dysfunction in the mid-periphery (mean = 16.3 dB; SD = 8.1 dB). Rod dysfunction in patient IV/4 is greater than in patient IV/2. In the superior field, there is no measurable rod function, and no peripheral loci fall within the normal limits (mean = 29.7 dB; SD = 14.3 dB). Patient IV/9 has an extensive mid-peripheral scotoma with only a residual central island of impaired cone function and far peripheral islands of severely impaired rod and cone function. Mean cone sensitivity loss is 23 dB (SD = 5.6 dB) and mean rod sensitivity loss is 46 dB (SD = 8.6 dB).

The profile tests in Figure 4 provide greater detail of the rod- and cone-mediated function in the central 60° of the hemizygotes. The two-color (500 and 650 nm stimuli) dark-adapted profiles in patient IV/14 show there is rod mediation or mixed rod and cone mediation at the loci tested and that rod sensitivities to the 500 nm stimulus are within two standard deviations of the normal mean. The light-adapted (600 nm stimulus) profile indicates that cone sensitivity is normal at fixation, but at extrafoveal loci sensitivities are just below or at the normal limit. Patient IV/2 also shows rod or mixed mediation across the field. Rod sensitivity is within the normal limits only in the central 20°. At greater eccentricities, sensitivities are reduced by about 3 log units. Cone sensitivity is normal only at fixation, and there is decreasing sensitivity with increasing eccentricity from fixation. Patient V/2 retains rod sensitivity in the central 20–30°, but it is reduced by at least 1 log unit; rod function is even further reduced or unmeasurable at greater eccentricities. Cone sensitivity is substantial only in the central few degrees. In patient IV/9, there is no measurable rod sensitivity in the central 60°, and the residual cone-mediated function by dark- or light-adapted perimetry is severely reduced.

Figure 5 shows gray scale maps of cone and rod sensitivity losses in both eyes of two heterozygotes. These maps illustrate a number of points. First, the retinopathy is patchy, with regions of normal function adjacent to regions of dysfunction. Second, these heterozygotes show interocular asymmetry in visual field location and percentage of abnormal loci in each eye. Third, the percentage of loci with cone sensitivity loss is greater than the number with rod sensitivity loss. In the left eye of patient III/1, 75% of loci showed abnormally reduced cone sensitivity, while 58% of loci had abnormally reduced rod sensitivity. In the right eye, 56% of loci had abnormal cone sensitivity, while 27% had abnormal rod sensitivity. Patient IV/17's left eye showed 72% of loci with abnormal cone sensitivity versus 34% with abnormal rod sensitivity. The relationship in the right eye was 56% versus 27%.

The findings from dark- and light-adapted perimetry that there are retinal regions in hemizygotes and heterozygotes that exhibit normal or slightly reduced rod sensitivity and moderately impaired cone sensitivity are supported further in Figure 6, which shows measurements of dark-adapted (upper) and light-
adapted (lower) spectral sensitivity at select loci in the inferior field of one hemizygote and two heterozygotes. In patient IV/14, the hemizygote, the dark-adapted spectral sensitivity function corresponds to that of the rod system and is within the normal range of values for this locus. Light-adapted spectral sensitivity is reduced below the normal at all wavelengths greater than 480 nm. This finding of decreased sensitivity at longer wavelengths and normal short wavelength sensitivity was examined further in patient IV/14 with light-adapted (10 cd/m²) perimetry at 24 loci in the central 48° using 440 and 600 nm stimuli. In the right eye, 7 of 24 loci had abnormally reduced sensitivities (>2 SD below the mean normal at each locus) with the 440 nm stimulus, whereas 20 of the 24 loci were abnormal with the 600 nm stimulus. In the left eye, 4 of 24 loci were abnormally reduced in sensitivity with the 440 nm stimulus, whereas 17 of 24 loci were abnormal with the 600 nm stimulus.

Heterozygote III/4 also has normal dark-adapted (rod) sensitivity; light-adapted (cone) sensitivity is reduced at all wavelengths tested. Heterozygote IV/17
has a relatively small reduction of rod sensitivity, but pronounced cone sensitivity loss at this test locus. There was no detection of shorter wavelength stimuli. Dark adaptometry was performed in heterozygotes III/4 and IV/17 at the same loci that were tested for spectral sensitivity; the time course was normal.

Analyses of the relationship between rod and cone sensitivity losses determined from results of dark- and light-adapted perimetry are shown in Figure 7 for hemizygotes and heterozygotes. Data from patients with known genotypes of ADRP30,31 are presented for comparison. In Figure 7 (upper eight panels), double histogram gray scales show rod versus cone sensitivity losses for one eye of two hemizygotes (IV/14 and IV/12), both eyes of one heterozygote (IV/17), and one eye of four ADRP patients with different rhodopsin mu-

Fig. 5. Dark- and light-adapted static threshold perimetry in both eyes of two heterozygotes. The data are displayed in gray scale as in Figure 3.
Fig. 6. Spectral sensitivity measurements in the dark-adapted (upper panels) and light-adapted (lower panels) states in a hemizygote (patient IV/14) and two heterozygotes (patients III/4 and IV/17) compared to normal results (area between solid lines represents ±2 SD from the mean normal; n = 10, ages 20–45 yr). For patients IV/14 and III/4, the test locus was 20° in the inferior field. For patient IV/17, the test locus was 38° inferiorly.

Discussion

This study characterized the functional phenotypes of hemizygotc and heterozygotes in an XLRP family with a defined gene locus, RP2, on the short arm of the X chromosome. The phenotypes show intrafamilial consistency in the sense that patterns of rod and cone dysfunction in the more severely affected hemizygotes appear to reflect progression of patterns in more mildly affected members. Also, the dysfunction in patches of retinopathy of heterozygotes is like that in retinal regions of hemizygotes at various stages of the disease. The results suggest that the retinal degeneration in this XLRP RP2 family is expressed first as a cone photoreceptor system dysfunction and, as the disease progresses, the rod system also becomes involved. At many stages of the disease, cone and rod systems show comparable degrees of dysfunction, a pattern that is distinguishable from the pattern of greater rod than cone dysfunction found in many other forms of RP.

Based on the functional phenotypes of the five hemizygotes with different degrees of disease severity, we propose that in this family the following sequence of changes in visual function may occur as the retinal degeneration progresses. At an early stage, a hemizygote has cone dysfunction in the mid-peripheral retina and an abnormal cone ERG. Rod function measured by dark-adapted perimetry, dark-adapted spectral sensitivity, and rod ERGs is within normal limits.
At a further stage, there is an absolute scotoma for cone function in the superior field, the mid-periphery has both rod and cone dysfunction, and the peripheral retina begins to show cone dysfunction, but still has no rod dysfunction. Rod and cone ERGs both are reduced in amplitude. With increasing severity of expression, the mid-peripheral annular scotoma becomes complete and absolute and there is rod and cone dysfunction in the far periphery and central retina. Rod and cone ERGs are further reduced in amplitude. At an advanced stage, severely abnormal rod and cone function exists in islands of the far periphery, and only very reduced cone function is measurable centrally. A markedly diminished cone ERG is detectable. This functional pattern in the advanced stage is like that described previously in a study of two XLRP hemizygotes.15

Heterozygotes in this pedigree can show a tapetal-like reflex or patches of pigmentary retinopathy. There can be a range of findings on retinal function tests, from normal results to considerable rod and cone dysfunction. The perimetric results suggest there can be large regions of retinal dysfunction as well as more isolated loci of dysfunction. The patches and the loci show comparable rod and cone dysfunction or greater cone than rod abnormalities. The types of abnormalities in rod and cone ERG parameters that we found in the heterozygotes of this study are like those
found in earlier studies of XLRP heterozygotes of unknown genotype. Furthermore, we concur with previous observations that there can be equivalent reductions in cone and rod ERG amplitudes in XLRP heterozygotes. However, we also found that some heterozygotes in this family exhibit greater cone than rod ERG dysfunction.

When the results of the clinical, psychophysical, and electroretinographic tests are taken together, the phenotypic expression in this X-linked pedigree is not exactly like the phenotypes of other retinal degenerative diseases that have been studied with similar methods. The ERG results alone can lead to the impression that this family has a cone-rod dystrophy. Interestingly, "cone-rod" patterns of ERG results have been reported previously in XLRP patients with unknown genotype. The reduced rod b-wave V_max but normal or slightly abnormal K in our patients resemble the findings in some patients with cone-rod dystrophy and are unlike those usually described for RP. The relationship between rod and cone sensitivities determined psychophysically also could be found in cone-rod dystrophy, and we demonstrated that it differs from the result in ADRP patients with rhodopsin mutations, the only other RP genotypes that have been studied with the same techniques.

When the regional retinal variation of the disease is considered, however, the XLRP hemizygotes have patterns more like those found in typical RP than in cone-rod dystrophy. The hemizygotes show mid-peripheral funduscopic and functional abnormalities before peripheral and central changes. They do not manifest the early and severe central retinal degenerative and functional abnormalities and relative preservation of mid-peripheral function found in the cone-rod dystrophies. The finding of greater mid-spectral than S cone dysfunction in patient IV/14, the hemizygote with the mildest disease expression, differs from the finding in cone dystrophy and typical RP that S cone dysfunction precedes dysfunction in the other photoreceptor-mediated mechanisms. Also, although there are some similarities in the findings for patient IV/14 and young hemizygotes reported as having X-linked cone dystrophy with a tapetal-like sheen, our hemizygotes with more advanced disease were unlike the more advanced patients with this entity. An early onset of myopia recently has been reported to be associated with the RP2 locus in XLRP. The five hemizygotes in our study had various degrees of myopia, a finding consistent with previous reports of myopia in XLRP. However, the age of onset of the myopia in our patients is not known. Three other issues raised in earlier reports are worth noting. First, the suggestion that the tapetal-like reflex may be a funduscopic feature of XLRP heterozygotes exclusively in families with the RP3 locus is not supported by the findings in the present family. Second, the finding of "cone-rod" and "rod-cone" ERG patterns in the same XLRP family may not be evidence of "inconsistency" or clinical heterogeneity but may result from regional retinal variations of the disease at different stages of progression, such as was evident from results of rod and cone perimetry in the hemizygotes of the present study. Third, the observation based on clinical examinations alone that there can be intrafamilial variability of expression in XLRP is confirmed by the clinical results from the family in this study. However, more detailed testing of retinal function in this family led to the identification of a definite pattern of retinal dysfunction that showed intrafamilial consistency. Thus, understanding the relationship between phenotype and the newly identified genotypes in RP may require not only clinical examinations but also specialized tests aimed at defining the underlying pathophysiology.

Key words: cone photoreceptor, electroretinogram, retinitis pigmentosa, rod photoreceptor, X chromosome

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References


