Am. J. Hum. Genet. 57:87–94, 1995

X-Linked Dominant Cone-Rod Degeneration: Linkage Mapping of a New Locus for Retinitis Pigmentosa (RP15) to Xp22.13-p22.11

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Summary

Retinitis pigmentosa is the name given to a heterogeneous group of hereditary retinal degenerations characterized by progressive visual field loss, pigmentary changes of the retina, abnormal electroretinograms, and, frequently, night blindness. In this study, we investigated a family with dominant cone-rod degeneration, a variant form of retinitis pigmentosa. We used microsatellite markers to test for linkage to the disease locus and excluded all mapped autosomal loci. However, a marker from the short arm of the X chromosome, DXS989, showed 0% recombination to the disease locus, with a maximum lod (log-odds) score of 3.3. On the basis of this marker, the odds favoring X-linked dominant versus autosomal dominant inheritance are $>10^5$:1. Haplotype analysis using an additional nine microsatellite markers places the disease locus in the Xp22.13-p22.11 region and excludes other X-linked disease loci causing retinal degeneration. The clinical expression of the retinal degeneration is consistent with X-linked dominant inheritance with milder, variable effects of Lyonization affecting expression in females. On the basis of these data we propose that this family has a novel form of dominant, X-linked cone-rod degeneration with the gene symbol "RP15."

Introduction

In 1855 Donders coined the phrase "retinitis pigmentosa" to describe a group of inherited disorders characterized by progressive degeneration of the retina (Heckenlively 1988). These disorders are marked by great clinical heterogeneity in terms of age at onset, rate of progression, severity, and specific clinical features. Manifestations of the disease include night blindness; progressive loss of peripheral vision, followed by difficulty with mid and central visual fields; and, in most patients, deposition of pigment in the retina, creating a bone spicule–like appearance. For many patients, progression of the disease culminates in legal blindness.

Constriction of the visual fields and changes in the appearance of the retina are preceded and accompanied by electroretinographic (ERG) changes characteristic of retinitis pigmentosa (Marmor et al. 1983). In general, the electrical response of the dark-adapted eye to low-intensity flash (scotopic ERG) measures rod function, whereas the response of the light-adapted eye to high-intensity flash (photopic ERG) measures cone function. For most forms of retinitis pigmentosa, both rods and cones are affected in the end stages of disease, often with nonrecordable ERGs. However, in the early and middle stages of disease, ERG patterns can be used to distinguish between two different clinical forms of retinal abnormality. In the most common form, the scotopic ERG is attenuated and abnormal whereas the photopic ERG is near normal (rod-cone degeneration). In the second, less common form, abnormalities in photopic ERG precede changes in scotopic response (cone-rod degeneration). In the latter case, retinal findings frequently include temporal disk atrophy, telangiectasia of disk vessels, and minimal pigmentary changes (Heckenlively et al. 1981*a*).

The clinical heterogeneity seen in retinitis pigmentosa can be explained, in part, by genetic heterogeneity. Pedigree studies demonstrate that the disease occurs in autosomal dominant, autosomal recessive, and X-linked recessive forms. This is true for both rod-cone and cone-rod forms of the disease. Gene mapping and molecular studies have demonstrated additional genetic heterogeneity within each of these categories. In 1984, the first retinitis pigmentosa locus (RP2) was mapped by linkage methods to the short arm of the X chromosome (Bhattacharya et al. 1984). Since then >50 genes causing retinal degeneration have been cloned and/or mapped (Daiger et al., in press). To date there are 15 distinct, mapped

Received January 10, 1995; accepted for publication April 19, 1995.

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0002-9297/95/5701-0011$02.00

loci for nonsyndromic retinitis pigmentosa including cone-rod dystrophies; there are 8 (CORD2, peripherin/RDS, rhodopsin, RP1, RP9, RP10, RP11, and RP13) for autosomal dominant disease, 5 (phosphodiesterase β, rhodopsin, rod cGMP-gated channel, RP12, and RP14) for autosomal recessive disease, and 3 (COD1, RP2, and RP3) for X-linked recessive disease. (For references, see the Genome Data Base [GDB] [Pearson et al. 1992]; reviewed in Daiger et al., in press.) There is also statistical evidence for a fourth recessive locus for retinitis pigmentosa on the X chromosome (RP6) and, on the basis of chromosomal deletions, for a locus for cone-rod dystrophy (CORD1) on 18q. In addition, there are a number of mapped retinopathies that are distinct from retinitis pigmentosa but that share features in common, such as congenital stationary night blindness (e.g., CSNB1 and CSNB2) and retinoschisis (RS). Beyond this already-complex situation, additional unmapped loci must also exist.

The family reported here, UTAD054, had earlier been believed to represent autosomal dominant cone-rod dystrophy, because of the presence of affected females (Heckenlively et al. 1981*b*). In UTAD054, we excluded the disease locus, from 13 mapped loci for autosomal retinitis pigmentosa, and we subsequently mapped the disease to Xp (McGuire et al. 1994). In this report we confirm X linkage and narrow the chromosomal localization to Xp22.13-p22.11, excluding COD1, RP2, RP3, and RS. Because of the dominant mode of inheritance, the exclusion of other X-linked retinopathies, and the unique clinical features of this family, we propose this as a new X-linked dominant locus, RP15.

Subjects, Material, and Methods

Subjects and Samples

Thirty-one members of a five-generation American family including seven affected females and five affected males were examined (fig. 1). Comprehensive ophthalmic examinations were performed, including slit-lamp and external examination, fundus photography, fluorescein angiography, and standardized ERG (Heckenlively et al. 1981*b;* Marmor et al. 1983). All clinical examinations were conducted by one ophthalmologist (J.R.H.), with repeat examinations spanning a period >15 years.

Participation in the genetic study was with the informed consent of adults or the consent of parents of minors. The study was approved by the Committee for the Protection of Human Subjects at the University of Texas—Houston. Two 10-cc vacutainers of venous blood were collected from each participating subject. Genomic DNA was prepared according to standard procedures using the PureGene DNA extraction kit (Gentra).

Detection of Microsatellite Polymorphisms

The forward primer for each microsatellite marker (Map Pairs; Research Genetics) was end-labeled with ^{32}P-γATP by incubating the primer at 37°C for 45 min followed by a 10-min incubation at 68°C to denature the kinase (New England BioLabs). The dinucleotide repeats were then amplified from 100 ng genomic DNA under standard conditions (Weber and May 1989). The amplified products were run on 6% denaturing polyacrylamide gels (Promega) for 2–4 h and were exposed overnight to x-ray film.

Data Analysis

Allele types in individuals were assigned according to the molecular weight of their dinucleotide repeats. Phenotypes were entered into the Cyrillic Pedigree Program, and haplotypes were determined by inspection. The likelihood ratio comparing X-linked dominant inheritance versus autosomal dominant inheritance was calculated using standard methods, and the probability that the family has X-linked dominant disease was calculated using Bayes's theorem. Linkage analysis was conducted using the MLINK program in the LINKAGE program package optimized for fast sequential computations on a Sun SPARCstation IPC (Lathrop and LaLouel 1988; Cottingham et al. 1993). A frequency of 0.1% for the disease allele, and a 98% penetrance in heterozygotes, were assumed for linkage testing. Unaffected, at-risk individuals who were <16 years of age were entered as disease type "unknown."

Results

Clinical Characteristics of Affected Family Members

Table 1 summarizes the ophthalmologic findings in family UTAD054. Males and females differ significantly in the findings and thus are reported separately.

Three young males in the family, when first tested (at age 7 mo to 11 years) had nonrecordable electroretinograms, central vision in the 20/50–27/70 range, and visual fields severely constricted to <10° with the IV-4 isopter. Final rod thresholds tended to be better than expected, given the visual field contraction. All five male patients showed diffuse retinal atrophy with round pigment cobblestone clumps and optic atrophy pallor with temporal loss. In addition, all affected males had myopia.

Six of the seven female patients were evaluated several times over a period of 14 years. When first examined, five of the six had electroretinograms ranging from nonrecordable to 80% of normal in the cone isolated ERG and ranging from nonrecordable to 45% of normal in the rod isolated ERG. Final rod thresholds were not >1.0 log unit elevated. Two affected females had moderately abnormal electroretinograms, which became

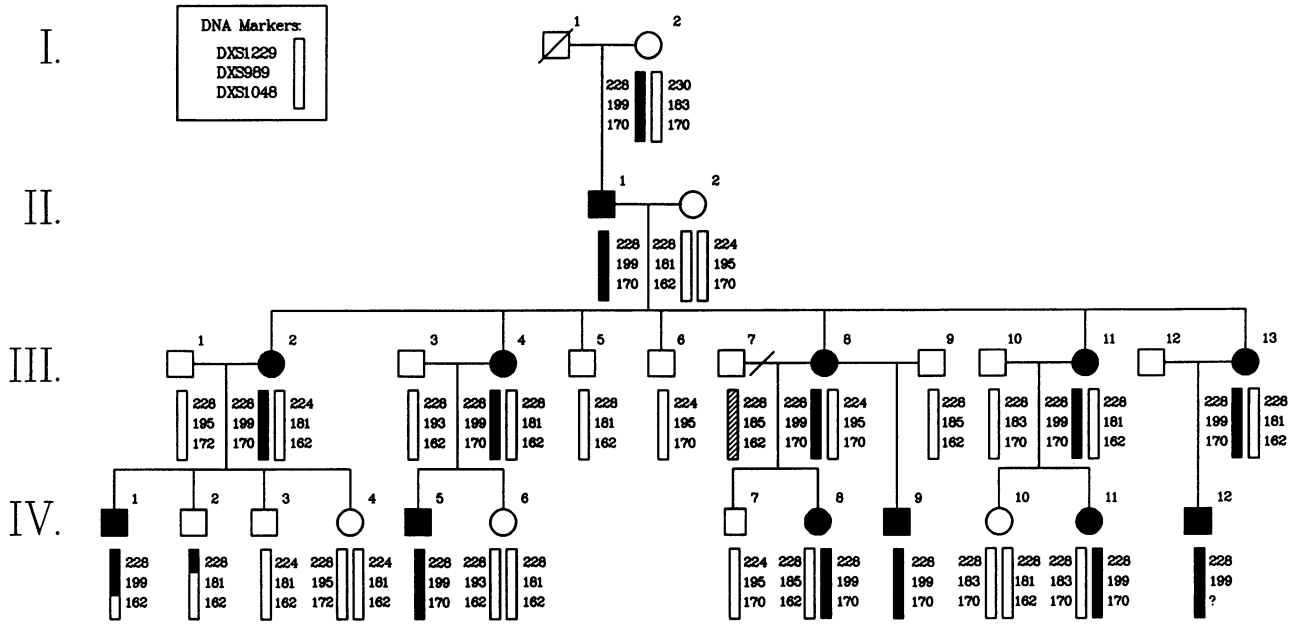

Figure 1 Pedigree of UTAD054, including disease status, microsatellite genotypes, and Xp haplotypes. Affected individuals, both males and females, are indicated by blackened symbols. The microsatellite genotypes and haplotypes for each individual tested, in the order DXS1229, DXS989, and DXS1048, are indicated below each symbol. The haplotype of the hatched chromosome was inferred from the daughter.

nonrecordable and barely recordable after 14 years. In these two individuals, diffuse retinal atrophy was present with fine-to-granular pigment in equatorial regions. Visual acuities were 20/25–20/50 and did not seem to worsen over 14 years.

Exclusion of Loci for Autosomal Dominant Retinal Degeneration

Originally the pedigree of UTAD054 suggested an autosomal dominant mode of inheritance (fig. 1 and Heckenlively et al. 1981*b*). For this reason, linkage testing was done by using microsatellite markers within or very near mapped autosomal loci causing retinitis pigmentosa (table 2). Table 2 shows that the disease locus was excluded from seven of the eight loci known to cause autosomal dominant retinitis pigmentosa. (The eighth locus, RP13, was mapped subsequent to this study.) Several autosomal recessive loci were also excluded.

Exclusion of known autosomal loci suggested that a previously unknown autosomal locus was involved. However, before undertaking a genomewide linkage search, we reconsidered the mode of inheritance of the disease locus. The absence of male-to-male transmission allowed the possibility of X-linked inheritance, under the assumption of a dominant mode of action with high or complete penetrance in females. Subsequent linkage testing substantiated this possibility.

Evidence for X Linkage

Serendipitously, the first X-chromosome marker tested, microsatellite locus DXS989 (Gyapay et al. 1994), was informative for linkage in the family and confirmed X-linked inheritance (table 3). One allele, with a fragment length of 199 bp, showed 100% concordance with the disease state; that is, all affected individuals but no at-risk, unaffected individuals carry this allele (fig. 1).

Two-point linkage analysis with DXS989 gives a maximum lod (log-odds) score (Z_{max}) of 3.3 at 0% recombination ($\hat{\theta}$). Although this lod score is strongly suggestive of X linkage, technically this computation is based on an a priori assumption of X-linked dominant inheritance. A more persuasive argument is that complete concordance of the 199 allele with the disease state is highly improbable unless the disease locus is X-linked dominant and is physically close to DXS989. Two alternative calculations confirm this observation. First, the relative likelihood (odds) of observing this segregation pattern if the disease is X-linked dominant versus autosomal dominant is $(^1/_2)^{18}/(^1/_2)^{36} = 2.6 \times 10^5$. Second, on the basis of these data and application of Bayes's theorem with both an a priori probability of 2% for X linkage and a $\hat{\theta}$ of 0%, the probability of X-linked dominant inheritance is 99.8%. Thus there is strong statistical evidence supporting X-linked dominant inheritance.

Regional Localization and Exclusion of Other X-Linked Retinopathies

An additional nine polymorphic microsatellite markers from Xp were tested for linkage to the dis-

Table 1

Summary of Ophthalmological Findings in Family UTAD054

	Reported Age at Onset	Age When First Seen	Visual Acuity[a]	ERG[b]	Visual Fields[c]	Retina Findings	Optic Nerve[d]
Males:							
II-1	Teens	55 years	OU 10/200	Nonrecordable	OU blind	Macular atrophy and pigment deposits	Pallor and TA
IV-1	7 years	7 years	OD 20/50 OS 20/60	Nonrecordable	OD 10° OS 8°	Diffuse atrophy, posterior pole preserved	Pallor and TA
IV-5	6 years	11 years	OD 20/40 OS 20/50	Nonrecordable	OD full OS I-4 10°	Cobblestone granular pigment	Pallor
IV-9	7 years	10 years	OD 20/50 OS 20/40	Nonrecordable	OD full OS I-4 9°	Diffuse atrophy with pigment deposits	Pallor and TA
IV-12	NA	7 mo	NA	Nonrecordable	NA	Dull macular reflex with vessel attenuation	Pallor
Females:							
III-2	28 years	33 years	OU 20/30	P 30% S 33%	OD full OS I-4 slight ↓	Nasal pigment, diffuse atrophy	TA
III-4	30 years	44 years	OD 20/25 OD 20/30	P 45% P 80%	Superior-temporal OS I-4 slight ↓	Tigroid, isolated pigment clumps	Pallor and TA
III-8	20+ years	35 years	OD 20/50 OS 20/40	P 40% S 40%	OD full OS I-4 slight ↓	Diffuse atrophy, bone spicule and paving-stone pigment	Slight TA
III-11	12 years	16 years	OU 20/30	Nonrecordable	OD 15° OS 6°	Diffuse atrophy, tigroid pigment deposits	TA
III-13	10 years	13 years	OD 20/25 OS 20/30	P 25% S 15%	OD I-4 11° OS I-4 8°	Diffuse atrophy, localized pigment	TA
IV-8	(No symptoms reported)	14 years	OU 20/40	P 33% S 40%	OD full OS I-4 40°	Fine anterior pigment	Slight pallor

NOTE.—NA = not applicable.

[a] OD = right eye; OS = left eye; and OU = both eyes.

[b] P = photopic ERG; and S = scotopic ERG; both are presented as % of mean normal value.

[c] Goldman visual fields (in degrees [°]) for using a 4-mm target size.

[d] TA = temporal pallor of optic nerve.

Table 2

Linkage Testing in Family UTAD054: Exclusion of Autosomal Loci Causing Retinal Degeneration (in Chromosomal Order)

Chromosomal Location[a]	Marker	Locus Excluded	Lod Score at θ = .0	.001	.01	.05	.1	.2	.3	.4
1p21-p13	D1S158	RP12	−21.20	−12.89	−10.14	−7.17	−4.90	−2.45	−1.15	−.40
3q21-q24	RHO-[CA]$_n$	RHO	−6.87	−5.78	−3.45	−1.58	−.81	−.17	.06	.10
4p16.3	E24-1	PDEB	−15.81	−11.08	−7.36	−3.98	−2.44	−1.03	−.36	−.06
6p	D6S291	RP14	−20.08	−14.22	−9.70	−6.00	−4.03	−2.01	−.95	−.33
6p21.1-cen	RDS-[CA]$_n$	RDS	−11.97	−8.36	−6.39	−5.00	−3.59	−1.77	−.81	−.27
7p	D7S460	RP9	−11.35	−9.70	−7.24	−4.20	−2.71	−1.27	−.54	−.16
7q	D7S480	RP10	−16.00	−13.73	−10.60	−6.12	−4.01	−2.02	−1.01	−.41
8q11-q21	D8S165	RP1	−6.65	−6.54	−5.89	−3.59	−2.11	−0.77	−.19	.03
8q34	D8S161	VMD1	−9.66	−3.31	−1.34	−.08	.33	.53	.42	.19
11q13	INT2-[CA]$_n$	VMD2, ROM1, etc.	−17.04	−11.93	−7.37	−3.69	−2.13	−.76	−.17	.05
11q13	D11S87	VMD2, ROM1, etc.	−4.60	−4.60	−3.84	−2.10	−1.30	−.57	−.22	−.05
19q13.3q-13.4	D19S254	CORD2, RP11	−11.80	−6.00	−3.41	−1.17	−.28	.34	.43	.28

Note.—Gene symbols and references are in GDB (Pearson et al. 1992).
[a] Of mapped disease gene.

ease locus in UTAD054 (table 3). The order of the markers was established by linkage testing (Gyapay et al. 1994) and physical mapping (Willard et al. 1994). The order and approximate genetic distances (in cM) are shown in figure 2. Several of the markers show additional evidence of linkage to the disease locus, with Z_{max}s >1.2; only DXS989, however, is maximal at $\hat{\theta}$ = 0%. These data place the disease locus close to DXS989.

Reconstruction of haplotypes for the Xp microsatellite markers confirms this localization. Figure 1 shows chromosomal haplotypes based on three highly informative, contiguous markers: DXS1229, DXS989, and DXS1048. Recombination events in affected individual IV-1 and unaffected individual IV-2 place the disease locus proximal to DXS1229 and distal to DXS1048. Physical mapping of these flanking markers assigns the disease locus to the cytogenetic interval Xp22.13-p22.11 (Willard et al. 1994).

At least six distinct loci causing retinal degeneration or related conditions have been assigned to the short arm of the X chromosome (table 4; see references in GenBank [Pearson et al. 1992]). In addition, specific mutations in the dystrophin locus (DMD; the cause of Duchenne and Becker muscular dystrophy) may also cause retinal abnormalities, while a third X-linked locus for recessive retinitis

Table 3

Two-Point Lod (Log-Odds) Scores for Xp Microsatellite Markers versus the Disease Locus in UTAD054

Marker[a]	Lod Score at θ = .00	.001	.01	.05	.10	.20	.30	.40	$\hat{\theta}$	Z_{max}
DXS987	−∞	−1.20	−.22	.39	.57	.62	.51	.30	.20	.62
DXS999	−∞	−.31	.66	1.22	1.33	1.23	.94	.53	.10	1.33
DXS1229	−∞	−.90	.08	.67	.83	.82	.65	.38	.10	.83
DXS989	3.29	3.29	3.24	3.05	2.79	2.23	1.60	.86	.00	3.29
DXS1048	−∞	−.62	.36	.93	1.07	1.01	.79	.45	.10	1.07
DXS1061	−∞	.08	1.04	1.58	1.66	1.48	1.12	.63	.10	1.66
DXS1214	−∞	−.01	.96	1.50	1.59	1.43	1.09	.61	.10	1.59
DXS1110	.54	.58	.88	1.14	1.22	1.12	.86	.49	.10	1.22
DXS993	−∞	−2.10	−1.11	−.44	−.19	.01	.07	.06	...	...
DXS1003	−∞	−2.26	−1.03	.02	.42	.64	.58	.36	.20	.64

Note.—Gene symbols and references are in GDB (Pearson et al. 1992).
[a] In chromosomal order, distal to proximal (Willard et al. 1994).

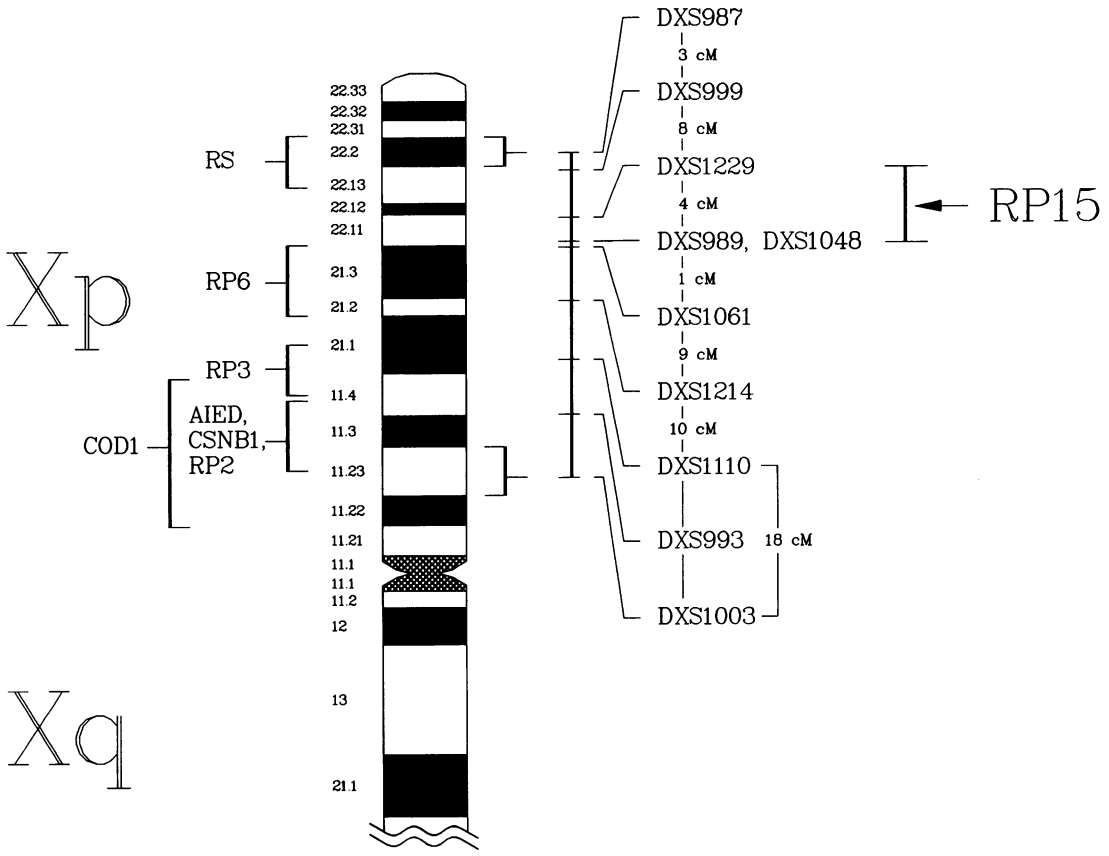

Figure 2 Summary ideogram of human chromosome Xp, showing microsatellite markers and mapped disease loci causing retinal degeneration and related conditions in UTAD054. The approximate cytogenetic location of disease loci is shown to the left of the ideogram (Willard et al. 1994). The order and approximate genetic distances (in cM) of the microsatellite loci used in this study are to the right (Gyapay et al. 1994). The approximate cytogenetic localization of RP15, Xp22.13-p22.11, is on the extreme right.

pigmentosa, RP6, has been tentatively mapped to Xp (Ott et al. 1990). Recent physical and linkage mapping (Willard et al. 1994), however, place each of these loci either distal to DXS1229 or proximal to DXS1048, outside the interval containing the disease locus in UTAD054 (table 3 and fig. 2). One possible exception is RP6, which is only poorly localized on Xp. But even this provisional locus is probably excluded by these data.

Table 4

Xp Genes Causing Retinal Degeneration and Related Conditions

Symbol	McKusick Number	Name	Location
AIED	300600	Åland Island eye disease	Xp11.4-q21
COD1	304020	Cone dystrophy 1	Xp21.1-p11.2
CSNB1	310500	Congenital stationary night blindness 1	Xp11.4-p11.2
CSNB2	310500	Congenital stationary night blindness 2	Xp11
DMD	310200	Oregon eye disease, possibly caused by dystrophin	Xp21.3-p21.2
NDP	310600	Norrie disease	Xp11.4-p11.3
RP2	312600	Retinitis pigmentosa 2	Xp11.4-p11.23
RP3	312610	Retinitis pigmentosa 3	Xp21.1
RP6	312612	Retinitis pigmentosa 6	Xp21.3-p21.2
RS	312700	Retinoschisis	Xp22.2-p22.1

NOTE.—Gene symbols and references are in GDB (Pearson et al. 1992).

Discussion

The Mode of Inheritance of Retinal Disease in UTAD054

Three lines of evidence establish X-linked dominant inheritance in UTAD054. First, exclusion of known autosomal dominant and recessive loci causing retinitis pigmentosa and related diseases is suggestive, although, taken alone, it is not convincing. Second, two-point linkage analysis, based on the assumption of X-linked dominant inheritance, gives a Z_{max} of 3.3 at $\hat{\theta} = 0\%$ to DXS989, which maps to Xp. Linkage testing is relevant to the placement of the disease locus within the X chromosome but does not explicitly compare the two hypotheses, X-linked inheritance versus autosomal dominant inheritance. Nonetheless, a Z_{max} of 3.3 does suggest X linkage. Third, a direct comparison of the two hypotheses shows that the odds favoring X-linked inheritance versus autosomal dominant inheritance are $>10^5$:1. In other words, the probability of X-linked dominant inheritance, given these data, is >99%. These calculations are not sensitive to initial assumptions, other than mode of inheritance.

The disease in this study is unique among X-linked retinopathies in that the gene is completely penetrant in females. In general, X-linked forms of retinitis pigmentosa are considered "recessive" because female carriers are either not affected or are mildly affected. In 1993, Freidrich et al. described a family with the RP2 form of X-linked retinitis pigmentosa in which the disease status in female carriers was highly variable (Freidrich et al. 1993). The variability of expression in these female carriers as well as in others with the RP2 or RP3 disease gene (Fishman et al. 1986; Peachey et al. 1988) may be the result of variable Lyonization. By contrast, in UTAD054, all female "carriers" are affected, and, on average, the degree of affectation (age adjusted) is greater than that observed in other X-linked retinopathies.

On clinical examination, affected males in this family appear to have early-onset pigmentary retinopathy that would be consistent with X-linked retinitis pigmentosa. The females, however, are very different, with almost no pigmentary changes until age 35–45 years. The female electroretinograms are present but attenuated during the first 2 decades of life, showing a deterioration, with poor responses by the 3d decade. Variability is seen between females and between the eyes of the same female patient, findings that are consistent with Lyonization.

Exclusion of Other X-Linked Retinopathies

Obligatory recombinations within the microsatellite haplotype segregating with the disease allele in this family exclude the two established loci for X-linked retinitis pigmentosa, RP2 and RP3, as well as loci for other Xp retinopathies, such as retinoschisis (RS), cone dystrophy (COD1), congenital stationary night blindness (CSNB1), and Åland Island eye disease (AIED) (fig. 2 and table 4). Although the chromosomal location for RP6 is not well defined, the map interval for this locus (if RP6 is, in fact, distinct from RP2 and RP3) does overlap with the disease locus in UTAD054. However, the two disease types are clinically distinct, and the map locations do not match closely. Thus we propose that this family has a heretofore unreported form of dominant, X-linked cone-rod degeneration, RP15.

Acknowledgments

We thank the members of the UTAD054 family for their enthusiastic cooperation and encouragement. This research was supported by grants from the RP Foundation Fighting Blindness and the George Gund Foundation (to S.P.D.), by National Research Service Award (NRSA) EY06467 (to L.S.S.), and by Institutional NRSA grant EY07024 (to R.E.M.)

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