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Linkage Relationships between X-linked Retinitis Pigmentosa and Nine Short-Arm Markers: Exclusion of the Disease Locus from Xp21 and Localization to between DXS7 and DXS14

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SUMMARY

Linkage data between X-linked retinitis pigmentosa (XLRP) and nine X-chromosomal markers are reported. To test the assignment of XLRP to the Xp21 region (as considered at Human Gene Mapping 8), an analysis of XLRP and six markers flanking this region was undertaken. The XLRP locus was found to be excluded from the chromosome distal to ornithine transcarbamylase (OTC) ($P = 6.5 \times 10^{-5}$). Further data were accumulated with three more probes proximal to DXS7 (L1.28), the closest linked probe. Multipoint analysis of these data suggests a posterior probablility of .94 that XLRP is proximal to DXS7 (L1.28), which has been mapped to the region Xp11.3.

INTRODUCTION

In X-linked retinitis pigmentosa (XLRP) there is a progressive retinal degeneration of unknown cause, with onset in males in the first decade of life, progressing to severe visual handicap by the fourth decade (Boughman et al. 1980; Jay

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1982; Heckenlively 1983). A gene responsible for this condition has been reported to be linked to a restriction-fragment-length polymorphism (RFLP), identified by DNA probe DXS7 (L1.28), located on the short arm of the X chromosome, in band Xp11.3 (Bhattacharya et al. 1984, 1985; Friedrich et al. 1985; Mukai et al. 1985; Nussbaum et al. 1985; Clayton et al. 1986). However, there is uncertainty as to whether the disease locus is proximal or distal to DXS7. The evidence of Nussbaum et al. (1985) supports a distal location, on the basis of two trebly informative meioses (OTC, XLRP, and DXS7), and that of Friedrich et al. (1985) suggests a proximal one, on the basis of linkage data between DXS7, XLRP, and a centromeric heteromorphism, including three trebly informative meioses. This problem has been accentuated by the discovery of a male with a deletion in band Xp21 who had retinitis pigmentosa, together with Duchenne muscular dystrophy, chronic granulomatous disease, and McLeod syndrome (Francke et al. 1985). The X-chromosome committee of Human Gene Mapping 8 considered this observation to be sufficient to make it possible that the locus for XLRP lies in Xp21. The upper confidence limit on the distance between DXS7 and XLRP, on the basis of two-point linkage analysis, is 17 centimorgans (cM), a result that argues against but does not exclude the possibility that the disease locus lies within this deletion and is therefore distal to DXS7 (Clayton et al. 1986). To date, there have been no published data that preclude this assignment.

To test this hypothesis, the linkage relationships between XLRP and six polymorphic markers known to be distal to DXS7 have been examined, with particular emphasis on the DNA probes lying within or near the Xp21 deletion. A simultaneous multipoint analysis of all seven loci has been undertaken to establish the probabilities of all possible gene locations.

Multipoint linkage analysis was also applied to data from a further three RFLPs located proximal to DXS7, from three RFLPs lying immediately distal to DXS7, and from DXS7 itself.

METHODS

The criteria used in the diagnosis of both XLRP and the carrier state have been described elsewhere (Wright et al. 1983). The genetic status of males who were normal on examination but under the age of 13 years was not inferred. Females were taken to be heterozygous on the basis of either the pedigree (obligate heterozygotes) or clinical tests (presumptive heterozygotes), in which case both an abnormal fundal appearance and confirmatory result on electrodiagnostic or psychophysical testing were required. The tests consisted of visual field testing by Goldman perimetry, dark adaptometry, electroretinography, and a rod-flicker sensitivity test (Bird 1975; Berson et al. 1979; Arden et al. 1983). All other at-risk females were taken to be XLRP status unknown. Pedigree details were obtained from family members and, wherever possible, were checked at the centralized Registers for Births, Marriages and Deaths.

Whole blood anticoagulated with ethylenediaminetetraacetate was used for DNA extraction by means of the method of Kunkel et al. (1982). DNA was digested with restriction endonuclease (3–5 units μg^{-1} DNA), electrophoresed

TABLE 1

LOCI AND PROBES USED

Locus	Probe	Location	Enzyme	Frequency[a]	Reference
XG	...[b]	p22.3-pter	...	0.7	Mann et al. 1962
DXS85 ...	782	p22.2-p22.3	*Eco*RI	0.6	Hofker et al. 1985
DXS41 ...	99.6	p22.1-p22.2	*Pst*I	0.7	Aldridge et al. 1984
DXS84 ...	754	p21.1-p21.2	*Pst*I	0.6	Hofker et al. 1985
OTC	pHOC	p21	*Msp*I	0.6	Nussbaum et al. 1986
DXS7	L1.28	p11.3	*Taq*I	0.7	Wieacker et al. 1984
DXS14 ...	58.1	p11-cen	*Msp*I	0.7	Bruns et al. 1984
DXS1	p8	q11-q13	*Taq*I	0.8	Bruns et al. 1984
DXYS1 ..	pDP34	q13-q21.1	*Taq*I	0.6	Page et al. 1982

[a] Correct to 1 decimal place.
[b] Serological testing with anti-Xg[a].

through 0.8% agarose, denatured, neutralized, and transferred to nitrocellulose (Schleicher and Schuell) or nylon (Genescreen Plus; Amersham) filters by means of the method of Southern (1975). Filters were baked under vacuum for 2 h at 80 C. Prehybridization was carried out for 3 h at 68 C in 4 × Denhardt's, 4 × SSC, 0.1%–1.0% sodium dodecyl sulfate (SDS), 1.0% sodium pyrophosphate, 10% dextran sulfate, and 100 μg salmon-sperm DNA ml^{-1}. The probes were labeled to specific activities of $1–2 \times 10^8$ dpm μg^{-1} DNA by means of nick-translation (Rigby et al. 1977) or to 1×10^9 dpm μg^{-1} DNA by means of oligolabeling (Feinberg and Vogelstein 1983) with use of ^{32}P-dTTP (800 Ci $mmol^{-1}$; Amersham International). Filters along with the denatured probe were hybridized for 16–20 h at 68 C in the above mixture at a concentration of 5–10 ng ml^{-1}, together with $5–10 \times 10^4$ cpm ^{32}P-labeled phage lambda marker/filter. After hybridization, filters were washed twice in 2 × SSC containing 0.1%–1.0% SDS and then for two or more 20-min periods in 0.1–1.0 × SSC/SDS at 68 C. Filters were autoradiographed using Kodak X-AR film and an intensifier screen for 3–7 days at −70 C.

Xg blood grouping was performed as described elsewhere (Mann et al. 1962). The probes used in the present study are described in table 1.

Serial two-point and simultaneous multipoint linkage analyses of the data were undertaken. For these analyses the order of the marker loci—although not the interlocus distances—was taken to be fixed. The XLRP locus was allowed to take each of the seven or eight possible orders with respect to this backbone. For each such order, the point of maximum likelihood (produced by varying each interlocus distance) was calculated.

For orders with significant maximum likelihoods, an array of likelihoods was calculated, with each interlocus distance arbitrarily taking on the values 2, 8, 16, 24, and 32 cM, thereby resulting in an array of $5^7 = 78,125$ likelihoods for an eight-point analysis. From these arrays, joint likelihoods—and hence posterior probabilities of the orders—were calculated, as described elsewhere (Clayton 1986). The relationship between recombination fraction (θ) and genetic distance was assumed to obey Kosambi's (1944) mapping function. All calcula-

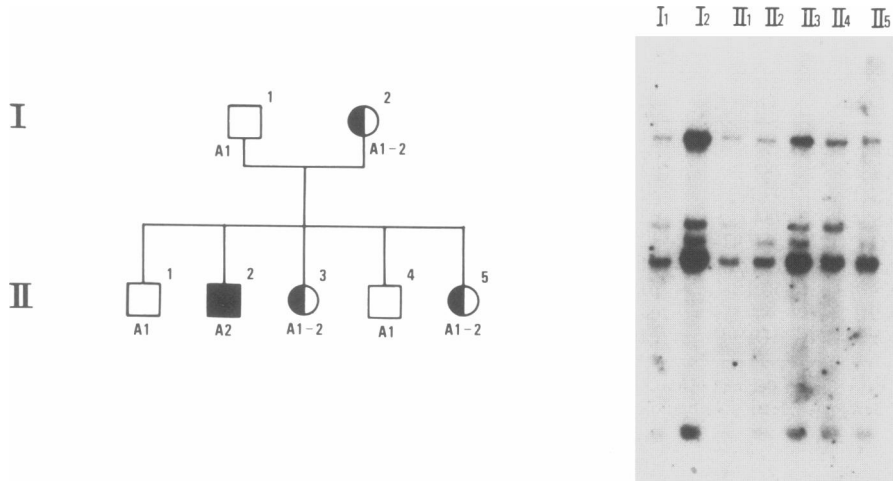

FIG. 1.—A family (m21) segregating for XLRP and the OTC/*Msp*I polymorphism (6.6 kb, 6.2 kb). Individual I.2 is heterozygous for both XLRP and OTC. No definite recombinants are seen, although linkage phase can only be inferred. □ = Normal male; ○ = obligate carrier; ■ = affected male; and ◐ = female with retinal changes and electrophysiological abnormalities.

tions, including that of lod scores, were performed by means of the MOLL/SITU program package (Clayton 1986).

RESULTS

In the present study there were 20 kindreds, in three of which subdivision was necessary to reduce the amount of computation. There are six large kindreds that each have > 10 XLRP-status-known offspring of obligate heterozygous mothers. Figures 1 and 2 show two kindreds with the results for DXS84 (754) and OTC. In figure 1, there is no evidence of recombination between OTC and XLRP, although the linkage phase is only inferred. In figure 2, two of four individuals are recombinant between XLRP and both OTC and DXS84.

The two-point linkage data are summarized in table 2 in the form of lod scores between each marker and the XLRP locus. There is no evidence of linkage betwen XLRP and the most distal locus, XG or DXS85 (782). The next most proximal loci, DXS41 (99.6) and DXS84 (754), show positive lod scores, with the maximum-likelihood estimate of θ_{max} being 0.26 and 0.32, respectively. The θ_{max} between OTC and XLRP is 0.16 with a lod score of 2.80, and that between DXS7 (L1.28) and the disease is 0.06 with a lod score of 9.35. The current estimates of the distances DXS84-DXS7 and OTC-DXS7 are 20 cM and 15 cM, respectively (Goodfellow et al. 1985), as compiled at Human Gene Mapping 8. The more centromeric loci, DXS14 and DXYS1, show increasing rates of recombination with XLRP. However, DXS1 (p8) has a θ of 0.07, but the sample size is small. Thus the maximum-likelihood estimates of θ_{max} values, as based on two-point analysis, are arguably consistent with a location for

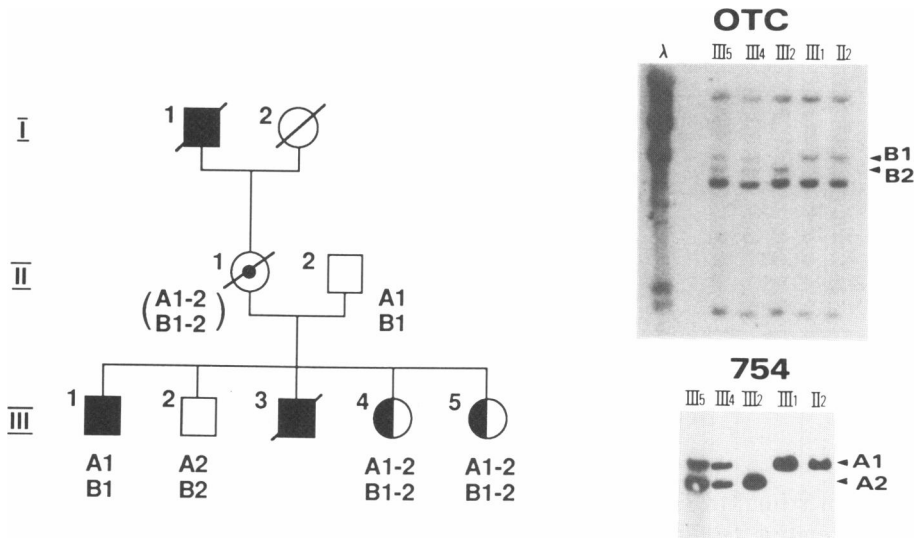

FIG. 2.—A family (m11) segregating for XLRP, the OTC/*Msp*I polymorphism, and the DXS84/*Pst*I polymorphism. No recombination is demonstrated between OTC and DXS84. However, there are two recombinants and two nonrecombinants between each probe and XLRP. Linkage-phase assumptions in II.1 merely change which individuals are classified as recombinant. Symbols are as defined in the legend to fig. 1.

XLRP either proximal or distal to DXS7. In this situation, multipoint analysis provides a more effective and quantitative means of answering the question.

To quantify the hypothesis of Francke et al. (1985) that XLRP lies in the Xp21 region, simultaneous seven-point analysis was undertaken using XLRP and the loci from XG to DXS7 (L1.28). These loci were used in order to flank the postulated position of the disease locus. Table 3 summarizes the results of this analysis. The order with the highest maximum-likelihood value is that with

TABLE 2

LOD-SCORE TABLES FOR θ_{max} VALUES BETWEEN XLRP AND EACH MARKER LOCUS

LOCUS	θ							Lod_{max}[a]	θ_{max}
	0.05	0.10	0.15	0.20	0.25	0.30	0.40		
XG	−3.15	−1.59	−0.80	−0.34	−0.06	0.10	0.17	0.18	0.38
DXS85 (782)	−7.99	−4.18	−2.26	−1.12	−0.42	0.01	0.28	0.28	0.40
DXS41 (99.6)	−2.56	−0.27	0.73	1.19	1.33	1.26	0.74	1.33	0.26
DXS84 (754)	−7.61	−3.00	−0.80	0.39	1.02	1.26	0.99	1.28	0.32
OTC	1.49	2.53	2.79	2.73	2.47	2.09	1.09	2.80	0.16
DXS7 (L1.28)	9.34	9.07	8.38	7.46	6.39	5.19	2.56	9.35	0.06
DXS14 (58.1)	0.37	1.84	2.39	2.54	2.44	2.17	1.24	2.54	0.20
DXS1 (p8)	2.02	2.02	1.87	1.65	1.39	1.08	0.41	2.05	0.07
DXYS1 (pDP34) ...	−15.30	−8.67	−5.24	−3.12	−1.73	−0.81	0.08	0.16	0.44

NOTE.—Lod_{max} = maximum lod score.

TABLE 3

RESULTS OF SIMULTANEOUS MULTIPOINT ANALYSIS OF DATA RELATING XLRP AND SIX MARKER LOCI

XLRP Position	Likelihood Ratio	Posterior Probability
pter-XLRP-Xg	7.48×10^{-11}	NC
Xg-XLRP-DXS85	6.20×10^{-11}	NC
DXS85-XLRP-DXS41	3.03×10^{-6}	NC
DXS41-XLRP-DXS84	1.63×10^{-8}	NC
DXS84-XLRP-OTC	3.78×10^{-4}	6.5×10^{-5}
OTC-XLRP-DXS7	0.205	.151
DXS7-XLRP-Xcen	1.00	.849

NOTE.—For all seven possible orders, the maximum-likelihood ratio is presented relative to the order with the greatest maximum likelihood. Also shown are the posterior probabilities of the three orders with the greatest maximum likelihoods, all on seven-point analysis. NC = not calculated.

XLRP proximal to DXS7 (L1.28), and the likelihoods of the other orders are shown relative to this. The second most likely location for XLRP is between OTC and DXS7, for which the likelihood ratio is 0.205. The order DXS84-XLRP-OTC has a likelihood ratio of 3.78×10^{-4}, whereas the orders with XLRP distal to DXS84 have such small maximum likelihoods that they can be confidently excluded. These have not been used in further analysis. The posterior probabilities (table 3) indicate that XLRP is also very unlikely to lie between OTC and DXS84. This analysis therefore indicates that XLRP can be confidently excluded ($P = 6.5 \times 10^{-5}$) from all regions distal to OTC. These data also produce a posterior probability of .85 that XLRP lies proximal to DXS7, but this result is superceded by further analysis.

An eight-point analysis was undertaken to better define the position of XLRP with respect to the more proximal probes. In this analysis data from the loci between DXS41 (99.6) and DXYS1 (pDP34) were used. The result is shown in table 4. XLRP is shown to lie between DXS7 (L1.28) and DXS14 (58.1) with a high (.94) probability. Most of the remainder of the probability (.058) is taken up by the possibility that XLRP lies between DXS7 and OTC. This eight-point

TABLE 4

SIMULTANEOUS EIGHT-POINT ANALYSIS WITH USE OF PROBES FLANKING THE LOCUS DXS7 (L1.28)

XLRP Position	Likelihood Ratio	Posterior Probability
pter-XLRP-DXS41	7.6×10^{-9}	NC
DXS41-XLRP-DXS84	1.6×10^{-10}	NC
DXS84-XLRP-OTC	7.2×10^{-5}	NC
OTC-XLRP-DXS7	7.4×10^{-2}	.058
DXS7-XLRP-DXS14	1.0	.942
DXS14-XLRP-DXS1	4.2×10^{-6}	NC
DXS1-XLRP-DXYS1	2.7×10^{-6}	NC
DXYS1-XLRP-qter	7.7×10^{-12}	NC

NOTE.—See table 3 note for details of analysis.

analysis also produced mean estimates of the genetic distances between XLRP and each of the four nearest probes. The distance to OTC was 24 cM, to DXS7 (L1.28) 9cM, to DXS14 (58.1) 19 cM, and to DXS1 (p8) 26 cM.

DISCUSSION

Data summarizing the genetic relationship between XLRP and nine polymorphic markers on the short arm of the X chromosome have been presented. The results support the assignment of the XLRP locus to the proximal region of the short arm. On the basis of two-point analysis, markers from the distal region of the short arm showed no evidence of linkage, but the more proximal markers showed increasing evidence of linkage in accordance with their proximity to DXS7. However, this analysis was insufficient to allow firm conclusions to be drawn about the position of the XLRP locus relative to the marker loci. The situation was improved considerably by the use of multipoint analysis.

It has been postulated that the locus for XLRP could be in the Xp21 region, which was partly deleted in the patient with a pigmentary retinopathy, as reported by Francke et al. (1985). This postulate has been questioned on clinical grounds (Clayton et al. 1986), and it has now been shown to be impossible to reconcile it with the linkage data. Probe DXS84 (754) lies within the deletion, and probes DXS41 (99.6) and OTC flank it (Francke et al. 1985). If the postulate were true, there should be close linkage between at least one of these probes and XLRP. However, all three probes independently display significant rates of recombination with XLRP (0.26, 0.32, and 0.16; table 3). Simultaneous multipoint analysis of six loci (XG to DXS7 [L1.28]) shows that the two possible locations for XLRP within the Xp21 deletion (i.e., with XLRP immediately proximal or distal to DXS84) are highly unlikely (table 3). The order with XLRP lying between DXS41 and DXS84 has a likelihood ratio of 10^{-8}. The order with XLRP between DXS84 and OTC has a likelihood ratio of 3.78×10^{-4} and a posterior probability of only 6.5×10^{-5}. Therefore it can be said with a high degree of certainty that, in the families studied, the XLRP locus lies outside the Xp21 region.

These results beg the question of what the difference is between the XLRP in these families and the retinal dystrophy in the patient reported by Francke et al. (1985). The simplest explanation is that distinct loci result in the clinical differences setting this patient apart from the families studied here (Clayton et al. 1986). A less likely alternative is that the pigmentary changes in the Francke et al. patient were secondary to chronic granulomatous disease, a disease in which Martyn et al. (1972) noted focal or extensive pigmentary retinal lesions in a series of six patients, only one of whom had evidence of septic embolus formation; however, in none of these six cases was visual loss the initial symptom, as it was in the Francke et al. patient. It is also possible that the disease in the Francke et al. patient was autosomal recessive rather than X-linked recessive. These difficulties illustrate the potential problems of using single patients with complex phenotypes as a basis for assigning the location of disease loci.

It is a matter of some importance to establish the position of the XLRP locus

with respect to DXS7. The need for high accuracy in prenatal diagnosis requires that, where possible, markers bridging the disease locus should be used. The data of Nussbaum et al. (1985), which suggest a location distal to DXS7, are derived from two meioses informative for OTC, XLRP, and DXS7, each showing recombination between XLRP and DXS7 but not with OTC. On the other hand, the study by Friedrich et al. (1985) supports the notion of proximal location. Neither of these conclusions was quantified, and both depended on the interpretation of single meiotic events. The simultaneous eight-point analysis of the data presented here, a method that used probes on either side of DXS7, indicated that XLRP probably ($P = .94$) lies proximal to locus DXS7 but distal to locus DXS14.

Almost inevitably, some kindreds in the present study display apparently aberrant patterns of recombination in their X-chromosomal short arms. This phenomenon produced, for example, the smaller observed θ_{max} between XLRP and DXS1 than between XLRP and DXS14 (table 2). However, such aberrations have been observed both between marker and disease and between marker and marker. Most probably, it represents simple statistical fluctuation. The overall results with respect to DXS7 (L1.28) are compatible with the existence of a single XLRP locus within this sample of families (Clayton et al. 1986). However, the possibility of genetic heterogeneity, either of the XLRP locus or of interlocus recombination rates, has not yet been excluded by means of multipoint data. Multipoint analysis should prove a potent means of detecting such phenomena.

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