Mapping the Lowe Oculocerebrorenal Syndrome to Xq24-q26 by Use of Restriction Fragment Length Polymorphisms

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Abstract

A molecular linkage analysis of four large families with the Lowe oculocerebrorenal syndrome (LS) provided a subregional localization of LS to the distal long arm of the X chromosome at Xq24-q26. Probes from two loci that identify restriction fragment length polymorphisms (RFLPs) and map to Xq24-q26 showed no recombination with LS. A maximum likelihood recombination distance ($\hat{\theta}$) = 0.00 was obtained for DXS10 with the logarithm of the odds (lod) of 6.450. For DXS42, $\hat{\theta}$ = 0.00 with a lod of 5.087. Assignment of the gene or genes for LS to Xq24-q26 has the potential of improving carrier detection and providing prenatal diagnosis in families at risk for the disease.

Introduction

The Lowe oculocerebrorenal syndrome (LS)[1] is an X-linked hereditary disorder characterized by congenital cataract, mental retardation, and defective renal tubular reabsorption of bicarbonate, phosphate, and amino acids (1, 2). At least 150 cases of LS have been reported in the literature and males account for all but a few cases (3–6). Female carriers have normal neurological and renal function but may demonstrate micropunctate cortical lens opacities (7). The basic biochemical defects underlying LS are unknown. Genetic counseling for LS is limited by an inability to perform prenatal diagnosis and by uncertainty about both the sensitivity and specificity of carrier detection by ophthalmologic examination (7). Therefore, accurate linkage information for LS has the potential of improving carrier detection and providing prenatal diagnosis in families at risk for the disease. Previous linkage studies suggested that LS was not closely linked to either the Xg blood group (Xp22.3-pter) (8, 9) or to glucose-6-phosphate dehydrogenase (Xq28) (9). In the present study, we have used restriction fragment length polymorphisms (RFLPs) (10, 11) on the X chromosome in order to identify marker loci that show tight linkage with LS. Segregation analysis was performed with LS and eight X chromosomal loci. Two of the eight loci, DXS10 and DXS42, were found to be tightly linked to LS and support a provisional map assignment of LS to the distal long arm of the X chromosome at Xq24-q26.

Methods

Four multigenerational families with inheritance of LS, each with more than one affected male, were ascertained through the Cullen Eye Institute (Baylor College of Medicine) and by regional and national referral. Each subject, or the responsible adult on behalf of minors, signed a Consent for Participation approved by the Institutional Review Boards for Human Research at Baylor College of Medicine, the Methodist Hospital, and the Texas Children's Hospital, Houston.

Diagnostic criteria for LS in affected males include presence of congenital cataract with or without infantile glaucoma, mental retardation, and characteristic renal tubular dysfunction inherited in an X-linked manner in each family. Females were classified as carriers of LS based on one or both of the following criteria: (*a*) genetic evidence by their position in the pedigree as obligatory heterozygotes, or (*b*) ophthalmologic evidence of characteristic lenticular opacities. These opacities are typically punctate to irregular in outline, off-white in color, and distributed in radial clusters or wedges in the peripheral rather than the central cortex of the lens. Because carrier detection may not be complete, females who met neither of these criteria were considered to be of unknown carrier status and were therefore excluded from the analysis. Overall, the genotypes of 48 individuals could be determined at the LS locus. These individuals, consisting of 24 females identified as carriers and 24 males, were used for linkage analysis.

Heparinized venous blood from all available family members was used both as a source of DNA and to establish permanent lymphoblastoid lines in culture (12).

DNA isolation, gel analysis, and filter hybridization. High molecular weight genomic DNA was prepared by published procedures (13). For RFLP analysis, 5–10 μg of DNA was digested with an excess of the restriction enzymes Taq I, Bgl II, or Bam HI under the recommended buffer and temperature conditions for 8 h to overnight. Electrophoresis was carried out in 0.6–0.8% agarose gels in Tris acetate buffer (0.4 M Tris, 20 mM EDTA, 100 mM Na acetate, pH = 8). DNA from the gel was transferred to a Zetabind membrane (AMF Cuno, Meriden, CT) in 10 × standard saline citrate (SSC, 0.15 M NaCl, 0.015 M Na citrate) using the method of Southern (14). After transfer, filters were rinsed in 2 × SSC and baked for 2 h at 80°C. Prehybridization and hybridization were carried out at 42°C in 50% formamide by published procedures (15) using probe labeled to a specific activity of 10^9 counts per microgram

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1. *Abbreviations used in this paper:* HPRT, hypoxanthine phosphoribosyl transferase; lod, logarithm of the odds of linkage; LS, Lowe oculocerebrorenal syndrome; RFLP, restriction fragment length polymorphism.

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by synthesis with random oligonucleotide primers (16, 17). After hybridization the filters were washed twice for 10 min each in 2 × SSC, 0.1% sodium dodecyl sulfate at room temperature and twice for 30 min each in 2 × SSC, 0.1% sodium dodecyl sulfate at 65°C. Autoradiography was carried out at −80°C for 16–48 h using Kodak X-Omat AR film (Eastman Kodak Co., Rochester, NY) and an intensifying screen.

Linkage analysis. Linkage analysis was conducted using the computer program package LINKAGE (18). Confidence limits were calculated as described (19). To provide parameters for the LINKAGE programs MLINK and LINKMAP, the frequency of LS was estimated to be 10^{-3} and the RFLP allele frequencies used were the previously published values (13, 15, 20–24). Varying the disease frequency had no effect on the results of the linkage analysis. Calculation of genetic distances for the multilocus analysis with LINKMAP was performed by converting published recombination frequencies to genetic distances with Haldane's mapping function which assumes no interference.

Results

DNA from a total of 48 individuals derived from four families was digested with restriction enzymes, separated by electrophoresis, and blotted onto Zetabind filters. The filter was hybridized with a specific DNA probe identifying the RFLP for each of the eight X-chromosomal loci tested.[2] For each locus tested, segregation of the RFLP alleles with LS was assessed and a maximum likelihood estimate of the recombination frequency was determined. At least three generations were available for each of the four families, allowing assignment of the phase of linkage in many cases by determination of the RFLP genotype of the fathers of obligate carriers.

Tight linkage was found between LS and two RFLP loci, DXS10 (Xq26) and DXS42 (Xq24-q26). Fig. 1 shows the segregation of the RFLP alleles at DXS10 with LS in family XL-49. Individuals II-1, II-2, and II-4 are obligate carriers and are heterozygous for the DXS10 RFLP alleles 7.0 kilobase pairs (kb)/5.0 kb. They inherited the 7.0-kb allele from their mother and the 5.0-kb allele from their father, I-2. The phase of linkage can be identified in this family and shows the LS mutation to be in coupling phase with the 7.0-kb allele in generation II. The carrier daughters of II-2 inherited the 7.0-kb allele from their mother. The carrier daughter of II-4 also inherited the 7.0-kb maternal allele. The unaffected son of II-4 inherited the 5.0-kb allele and the affected son the 7.0-kb allele. The carrier daughters of II-1 inherited the same maternal allele, but the father was not available. Individual IV-1 inherited the 7.0-kb allele and is affected. Thus, no obligatory recombinants were observed between LS and DXS10 in the five phase-known and three phase-unknown meiotic events in this family.

The RFLP alleles for DXS10 were segregating in three of the four families with no obligatory recombinants observed in a total of 22 meiotic events (19 phase-known, 3 phase-unknown). If the gene or genes for LS are assumed to be identical in these three families, the maximum likelihood estimate of the recombination distance ($\hat{\theta}$) between DXS10 and LS is calculated to be 0.00 with the logarithm of the odds (lod) of 6.450 (90% confidence interval $\theta \leq 0.09$).

Tight linkage was also observed between LS and DXS42 (Xq24-q26) in three families informative for this RFLP. Combining data from these three families also gave $\hat{\theta} = 0.00$ with

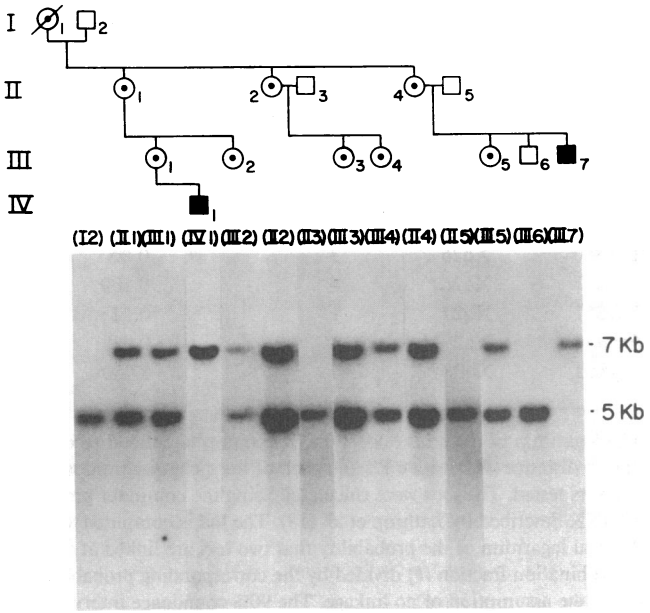

Figure 1. The segregation of RFLP alleles at DXS10 with LS in family XL-49. The pattern of 7.0-kb and/or 5.0-kb alleles in Taq I digested DNA is shown directly under the symbol for the corresponding member of the pedigree. The solid square is an affected male; the circle with the dotted center is a carrier female; the empty square is an unaffected male. Probe 36B-2 is a 2.0-kb Hind III fragment cloned into the Hind III site of pUC9. p36B-2 detects the same polymorphic Taq I site as the previously described probe 6A-1. Approximate allele frequencies are 0.33 and 0.67 (15).

the associated lod of 5.087 (90% confidence interval $\theta \leq 0.13$). Varying mutation rates and RFLP frequencies had no significant effect on these results. There was no evidence for linkage disequilibrium between LS and DXS10 or DXS42.

Table I lists the maximum likelihood estimate of the recombination distance and the lod at $\hat{\theta}$ between LS and each of the eight markers tested. Obligatory recombinants were observed between LS and all X-chromosomal loci flanking DXS10 and DXS42 with the exception of Factor IX (Xq27) which had no obligatory recombinants with LS in the one family informative at that locus. The lower lod and broader 90% confidence interval of $\theta \leq 0.20$ provides less support for close linkage than the higher lods for DXS10 and DXS42.

The presence of many well-mapped marker loci on the X chromosome enabled us to obtain linkage data for use in a multilocus analysis of LS. Lathrop et al. (18) have proposed using maximum likelihood methods to assess the relative odds of various locations of a new marker of unknown map position with respect to a previously established linkage map. We used the computer program LINKMAP to perform a multilocus analysis of LS with the closely linked marker DXS42 and flanking loci DXS17 and hypoxanthine phosphoribosyl transferase (HPRT). The locations of DXS17 and HPRT are well known from somatic cell hybrid mapping (25, 26), and for DXS17 from in situ hybridization (27). The position of DXS42 is less well known. The initial map position was given as Xq24-qter (13). In their linkage analysis of X-chromosomal markers, Drayna and White (28) placed DXS42 distal to HPRT but this order was only 1.8 times as likely as the next most likely order. However, the physical mapping of DXS42 with somatic cell hybrids in our laboratory supports placement of DXS42 proximal to HPRT and therefore

2. The official locus designation and chromosomal map location of the eight RFLP loci tested were as follows: DXS3 [Xq21.3-q22] (13); DXS17 [Xq21.3-q22] (20); DXS42 [Xq24-q26] (13); DXS10 [Xq26] (15); HPRT [Xq26] (21); DXS51 [Xq27] (20); Factor IX [Xq27] (22, 23); and DXS52 [Xq28] (24).

Table I. Linkage Analysis of Eight X-chromosomal Loci with the Lowe Oculocerebrorenal Syndrome

Locus number	Chromosome location	Number of informative families	$\hat{\theta}$	lod
DXS3	Xq21.3-q22	4	0.325	0.492
DXS17	Xq21.3-q22	3	0.325	0.386
DXS42	Xq24-q26	3	0.000	5.087
DXS10	Xq26	3	0.000	6.450
HPRT	Xq26	4	0.100	3.160
DXS51	Xq27	1	0.125	0.757
Factor IX	Xq27	1	0.000	3.116
DXS52	Xq28	4	0.450	0.010

The logarithm of the odds (lod) at the maximum likelihood recombination distance ($\hat{\theta}$) between LS and each of the eight X-chromosome markers tested. The lods were calculated using the computer program MLINK described by Lathrop et al. (18). The lod is computed as the decimal logarithm of the probability that two loci are linked at a given recombination fraction (θ) divided by the corresponding probability under the assumption of no linkage. The 90% confidence interval is calculated as the range of θ values for which the lod is within one unit of the maximum (19). This yields a 90% confidence interval of $\theta \leq 0.09$ for LS and DXS10 and $\theta \leq 0.13$ for LS and DXS42. Calculations were performed assuming mutation rates for LS of 0, 10^{-6}, and 10^{-5}.

within Xq24-q26 (29). Fig. 2 is a graph of the likelihood of the genetic map location of LS with respect to the three fixed markers DXS17, DXS42, and HPRT. Results from the LINKMAP analysis suggest that the most likely order is DXS17-(LS, DXS42)-HPRT and are consistent with the lods calculated between LS and each marker separately. In Fig. 2, the probability for placing LS in the most likely order vs. a location unlinked to all three markers is 9.31×10^8 to 1. The probability of LS being in the next most likely order, DXS17-DXS42-HPRT-LS, is 9.64×10^5 to 1. The relative probability of the most likely order compared with the next most likely order is therefore 9.31×10^8 to 9.64×10^5, or 966:1.

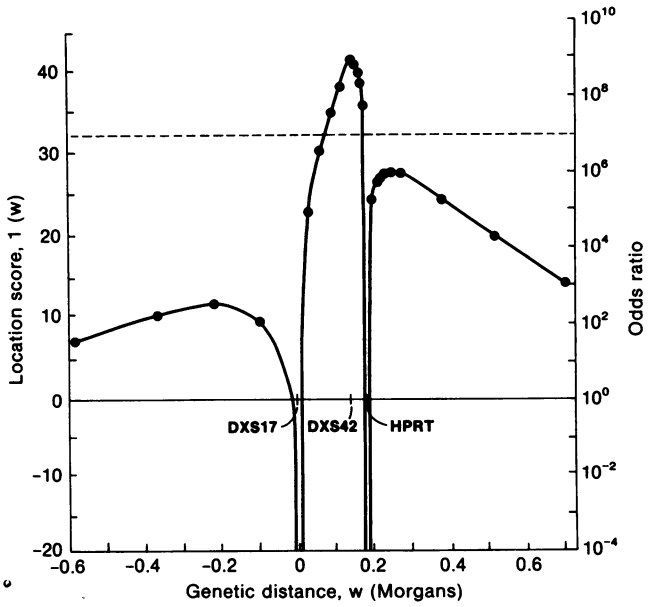

Figure 2. Likelihood of the map location of LS with respect to X-chromosomal markers DXS17, DXS42, and HPRT. The horizontal axis is the genetic distance w from DXS17. The right vertical axis is the odds ratio for the location of LS at each distance w vs. the location of LS at an infinite distance from the three fixed markers. The left vertical axis is the location score, $1(w)$, defined as twice the natural logarithm of the odds ratio. The dotted line indicates the lower limits for the location of LS with odds < 100:1 relative to the overall maximum. The relative probability of the most likely order of LS vs. the next most likely order with respect to the three test loci is calculated by comparing the odds for the location of LS at the relative maxima for each of the possible orders. The relative probability of the most likely order of LS, DXS17-(DXS42, LS)-HPRT, compared with the next most likely order, DXS17-DXS42-HPRT-LS, is 966:1.

Discussion

Our study of LS with eight X-chromosomal markers provides support for the first subregional localization of LS to Xq24-q26 by linkage analysis. This provisional map assignment is consistent with a recent report of a female with LS most likely due to a de novo X;3 translocation with the X-chromosome breakpoint at Xq25 (30). There was no evidence for the existence of widely spaced loci for LS, although the possibility that more than one gene is responsible for LS cannot be excluded on the basis of the present linkage data.

Identification of markers for LS will provide additional information for improving the sensitivity of carrier detection. In our study all 12 obligate carriers from the four families demonstrated characteristic lenticular opacities on slit lamp exam. Brown and Gardner (7) estimate that at least 82% of carriers of LS have lenticular opacities based on ophthalmologic examination of obligate genetic carriers combined with data from published reports. This is most likely an underestimate because the earlier reports did not state whether the ophthalmologic exam was performed with slit lamp magnification. However, most LS patients are sporadic cases with no prior family history of the disorder. In these situations the presence of characteristic lenticular opacities in the mother may be used to identify her as a carrier, but in the absence of opacities it cannot be determined if she is a carrier or if the affected son represents a new mutation. For isolated cases, RFLP linkage analysis of the affected son and his siblings, if any, could be used to provide a better estimate of the mother's risk of being a carrier and of the recurrence risk for the family.

Prenatal diagnosis has been unavailable for LS. Selective abortion of male fetuses in pregnancies at risk has been used to prevent the birth of males affected with LS but also leads to loss of all unaffected males. The availability of markers linked to the gene or genes for LS allows RFLP analysis of pregnancies at risk. The allele frequencies for DXS10 and DXS42 are 0.67/0.33 and 0.81/0.19, respectively. Approximately 61% ($1-[0.67^2 + 0.33^2][0.81^2 + 0.19^2]$) of the carriers for LS would be expected to be heterozygous at either DXS42 or DXS10 or both loci. Although the maximum likelihood estimate of the recombination distance between LS and each of the two linked RFLP markers is 0.00, the 90% confidence interval for the recombination distance could be used to provide a conservative estimate of the probability of an at risk male fetus being affected with LS. With RFLP analysis the risk of a male fetus being affected would be adjusted from 50% to $> \sim 90\%$ or $< \sim 10\%$ in informative families. The probability is calculated under the assumption that DXS10 and DXS42 are located on the same side of LS on the X chromosome. However, the adjustment of risk would change if DXS42 and DXS10 were determined to be

flanking LS. More accurate localization of LS, particularly with determination of close flanking markers, will provide more useful RFLP information for application to carrier detection and prenatal diagnosis.

In summary, our study of LS in four families has identified two genetic markers closely linked to LS and supports a map assignment of LS to Xq24-q26. The subregional mapping of LS will be valuable for genetic counseling for families at risk and could provide another approach to identifying the genetic defect by recombinant DNA techniques.

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