Genetic refinement of the chromosome 5q lattice corneal dystrophy type I locus to within a 2 cM interval

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Abstract

Lattice corneal dystrophy type I (LCDI) is a relatively common corneal dystrophy which can cause severe visual impairment. Recent studies have suggested a genetic localisation for the disease to chromosome 5q. Independent genetic linkage analysis in a six generation LCDI pedigree confirmed linkage to the 5q region bounded by marker loci IL9 and D5S436 suggesting genetic homogeneity. A maximum two point lod score of 7.51 ($\theta=0.03$) was obtained with marker D5S393. Multipoint and haplotype data positioned the disease between loci D5S393 and D5S396 corresponding to a genetic distance of 2cM, thus refining linkage sufficiently to allow for physical mapping of this disorder.

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Lattice corneal dystrophy type I (LCDI) is a blinding and painful autosomal dominant disorder with complete penetrance.¹ The disease is characterised by the linear deposition of amyloid material in the corneal stroma. Clinically the condition presents in the first decade of life with recurrent corneal epithelial erosions. By the third decade there is extensive deposition of amyloid material in the central corneal stroma with secondary loss of corneal sensation and scarring, sufficient to require corneal transplantation to restore vision.¹ In contrast, lattice corneal dystrophy type II (LCDII) is a less severe phenotype with good visual acuity beyond the sixth decade and deposition of amyloid material in non-ocular tissues such as the skin and peripheral nerves.² A third type (LCDIII) is rare, with good preservation of acuity, no symptoms of recurrent corneal erosion, and no systemic amyloid deposits.³

Genetic defects associated with lattice corneal dystrophy on chromosome 16 and chromosome 9 have been identified.^{4,5} Avellino dystrophy has recently been mapped to chromosome 5q and has features similar to both granular and lattice corneal dystrophies.⁶ Additionally, in the same study two families with granular corneal dystrophy and two branches of one family with LCDI also showed linkage to the same locus. Both these conditions, which are more commonly seen independently, could result from mutations in the same gene. The clinical diversity in the various types of lattice dystrophy

and more specifically variation that has been seen within the LCDI group,⁷ however, suggests that genotypic heterogeneity may exist, similar to that seen in autosomal dominant retinitis pigmentosa.⁸ Also, it has been found that the amyloid deposits in Avellino dystrophy are not typical of those seen in LCDI^{9,10} and could be a secondary phenomenon. To determine whether heterogeneity exists within the LCDI phenotype, we undertook a genetic linkage study with a large family expressing "typical" type I lattice corneal dystrophy.

Patients and methods

From a six generation pedigree of English descent, 46 family members were studied including 24 affected subjects, 11 unaffected subjects, and 11 spouses (fig 1A). Subjects were assigned as affected if they had recurrent corneal erosions or characteristic corneal deposits as observed by slit lamp examination. Diagnosis was confirmed histologically in 16 cases after corneal transplantation. Six microsatellite markers¹¹⁻¹³ were used to genotype subjects as previously described.¹⁴ Two point lod scores were obtained using MLINK¹⁵ and multipoint analysis was undertaken using LINKMAP.¹⁵

Results

TWO POINT ANALYSIS

Two point lod scores for microsatellite markers mapping to the LCDI region and marker D5S412 localised 14 cM distal to D5S402 are presented in the table. A maximum two point lod score of 7.51 ($\theta=0.03$) with marker D5S396 confirmed tight linkage between LCDI and the 5q31 region.

MULTIPOINT LINKAGE ANALYSIS

A series of four three point analyses were performed with the linked markers to generate a multipoint map of the region and is presented as a single graph (fig 2). Two markers and disease were used in each analysis to calculate the likelihood of the disease gene being located between these two markers. The data suggest that the LCDI disease locus was most likely to be in the interval between D5S393 and D5S396 with a peak multipoint lod score of 10.02. A two lod confidence interval placed the disease locus between D5S393 and D5S396 within a 2 cM interval according to published data.⁹

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Figure 1 (A) Autosomal dominant lattice corneal dystrophy type I pedigree. Most likely haplotype linked to disease is indicated by bold type. (B) Physical localisation of the LCDI locus on chromosome 5q. X denotes critical recombination events in VI.2.

HAPLOTYPE ANALYSIS

A number of recombination events in the LCDI pedigree were identified. Haplotype analysis for unaffected subject VI.6 identified a crossover with marker D5S393, positioning the LCDI locus distal to D5S393 (fig 1A,B). Haplotype data for affected subject VI.2 identified two crossover events, one proximal to the D5S396 locus and one between D5S402 and D5S412 (fig 1A,B). However, no recombination was identified with D5S412 and the

disease. These data were interpreted as suggesting a second recombination event between D5S412 and the LCDI loci. The haplotype data therefore place the LCDI locus between D5S393 and D5S396.

Discussion

The confirmation of linkage of LCDI to the 5q region suggests that the differences in clinical presentation reported may not represent gen-

Figure 2 Multipoint analyses in the LCDI region. Each set of symbols represents a separate three point analysis. The genetic distance on the x axis is arbitrarily set at zero for marker IL9. The relative order of markers was obtained from published data.¹¹ D5S178 was not used in the analysis as it has not been positioned on any of the linkage maps published to date.

etic heterogeneity, but phenotypic variation owing to the effect of different mutations within the same gene. Further pedigrees need to be genotyped to confirm this hypothesis.

No corneal specific genes have been identified on chromosome 5q and none of the 14 known candidate amyloid genes maps to the region.⁷ Reports linking Avellino corneal dys-

trophy⁷ and granular dystrophy to chromosome 5q, however, do suggest that the region is important in corneal function.¹⁶ Further linkage refinement in pedigrees manifesting these phenotypes will be required to establish whether they map close to, or to the same 2 cM region that has been established in LCDI. This should determine whether these conditions map to a cluster of different genes or are allelic conditions.

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Two point lod scores between disease and 5q linked markers

Marker	Recombination fraction							Zmax	θ
	0-0	0-01	0-05	0-1	0-2	0-3	0-4		
IL9	—∞	3-46	4-95	5-06	4-27	2-98	1-46	5-09	0-08
D5S178	—∞	3-46	3-74	3-50	2-68	1-67	0-64	3-75	0-04
D5S393	—∞	7-35	7-41	6-89	5-43	3-69	1-77	7-51	0-03
D5S396	—∞	3-84	4-04	3-71	2-70	1-58	0-58	4-07	0-03
D5S402	—∞	4-92	5-71	5-52	4-43	2-98	1-37	5-71	0-06
D5S412	—∞	—5-60	—0-88	0-75	1-62	1-38	0-72	1-63	0-21