A new family linked to the RP13 locus for autosomal dominant retinitis pigmentosa on distal 17p

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Abstract

A form of autosomal dominant retinitis pigmentosa (ADRP) mapping to chromosome 17p has been reported in a single large South African family. We now report a new family with severe early onset ADRP which maps to 17p. Linkage and haplotype analysis in this family places the ADRP locus in the 5 cM interval between markers AFMc024za5 and D17S1845, confirming the data obtained in the South African family. The discovery of a second 17p linked family may imply that this is one of the more common loci for dominant RP. In addition, the confirmation of an RP diagnosis at this locus is of interest since loci for a dominant cone dystrophy and Leber's congenital amaurosis (LCA1) have recently been linked to the same markers. While the cone dystrophy locus may be allelic with RP, our data and that of Goliath *et al* show that distinct genes are responsible for dominant RP and Leber's congenital amaurosis on chromosome 17p. (*J Med Genet* 1996;33:518-520)

Key words: retinitis pigmentosa; retina; 17p13.

Retinitis pigmentosa (RP) is the name given to a group of inherited retinal dystrophies char-

acterised by photoreceptor atrophy and pigment deposition in the retinal periphery. Patients experience narrowing of vision (tunnel vision) and night blindness, often progressing to complete blindness in later life. RP can be inherited in X linked, autosomal dominant, and autosomal recessive forms, and is also found in syndromes with other phenotypic defects.¹ Clinical heterogeneity is seen within each of these categories with respect to severity of disease and age of onset of symptoms^{2,3} and there is considerable genetic heterogeneity.

Approximately 25% of ADRP is caused by mutations in the rhodopsin gene,⁴⁻⁶ and another retinal gene, RDS/peripherin, causes the disease in about 5% of ADRP families.^{7,8} Six as yet uncharacterised ADRP genes have been localised to the pericentric region of chromosomes 8,⁹ 7p,¹⁰ 7q,¹¹ 19q,¹² 17p,¹³ and 17q.¹⁴ Each of these linkages was described in single large families. The reported ADRP locus on chromosome 17p was based on linkage of 17p microsatellites to the disease in a large South African family of British ancestry. This locus has now been given the name RP13 (MIM 600059).

We have carried out linkage studies on a panel of ADRP families from the Moorfields Eye Hospital genetic register. In one of these, family RP1729, originating in South Cumbria

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Figure 1 Haplotype analysis in pedigree RP1729. The five marker systems shown, from top to bottom, are: AFMc024za5, D17S1529, D17S831, D17S1845, and D17S796. The boxed haplotypes represent alleles associated with the disease chromosome. Critical recombination events can be seen in III-5, III-7, and III-9.

Table 1 Details of new microsatellites used in this study

Locus	Sequence
AFMc024za5	TGGATTCTGTAGTCCCAGG GGTTCAAAGACAACCTCCCC
D17S1529	TTGTTTCTATCCACGCAGGC GATGGCTGTGCTTGCTGGTA
D17S831	CGCCTTTCCTCATACTCCAG GCCAGACGGGACTTGAATTA
D17S1845	TGCCCCATGCTGACATA GACCTGACTAAANACTCCA

in the north of England, the disease was found to map to the 17p locus. The phenotype in this family is one of classical RP with relatively early onset and a severe prognosis in comparison with other forms of ADRP. Genealogical investigation has failed to show any link between this and the original 17p linked family, and their places of origin are geographically widely separated. Critical recombination events within this family allow us to place the RP13 locus within a 5 cM interval between the markers AFMc024za5 and D17S1845. This confirms the refinement data of Goliath *et al.*¹⁵ which localise RP13 to a 3 cM interval between the markers D17S1529 and D17S831.

Materials and methods

Affected members of pedigree RP1729 (fig 1) consistently report night blindness and visual field loss by 5 years of age, and are usually registered blind or partially sighted by 30. Central vision is preserved until much later in the disease process, though some patients report blurred vision. One patient (III.4 in fig 1) was seen at the age of 10 and found to have 5° visual fields with visual acuity of 6/18 in both eyes. She was then examined again at 25, with no significant evidence of progression in the interim period. Later complications in this form of RP include cystoid macular oedema and

cataract. Fundus examination in patients shows extensive bone spicule pigmentation in the mid-periphery, attenuated blood vessels, and disc pallor, all classical symptoms of retinitis pigmentosa. Thus ADRP in this family is severe in comparison to disease resulting from mutations at other autosomal dominant loci, with no evidence of incomplete penetrance.

Patient DNA was prepared from peripheral blood lymphocytes by standard protocols. Microsatellite markers were typed by PCR using one radioactively labelled primer. Four new unpublished Génethon markers, AFMc024za5, D17S1529, D17S831, and D17S1845, which have been localised to the region, were used to refine the locus. The primer sequences are shown in table 1. Amplification was carried out using 30 cycles of 94°C for 30 seconds, 55°C for 30 seconds (except for marker D17S1845 which annealed optimally at 60°C), and 72°C for 30 seconds. Products were separated on 6% acrylamide denaturing gels. Two point and multipoint lod scores were generated using the Linkage package version 5.1¹⁶ from data prepared by the LINKSYS data management package.¹⁷

Results

Five microsatellite markers were used to genotype 10 affected patients and eight unaffected sibs from family RP1729 (fig 1). The markers D17S849 and D17S796 from the second generation Génethon genome map¹⁸ were used to establish initial linkage to the 17p region. Four new unpublished Génethon markers, AFMc024za5, D17S1529, D17S831, and D17S1845, which have been localised to the region, were then used to refine the locus. The order and distance (in cM) between these markers is shown in fig 2.

The results of the two point linkage analysis between ADRP and each of the microsatellite markers are shown in table 2. The highest two point lod score obtained was 4.8 at a recombination fraction of zero with marker D17S831. The marker D17S1529 also showed no recombination with the disease. Multipoint analysis with markers AFMc024za5, D17S1529, and D17S831, using marker order and intermarker distances as shown on the current Génethon map of the region (unpublished data), gave a maximum lod score of 5.1 at D17S831.

Haplotype analysis for the markers in the region is shown with the pedigree in fig 1. Key recombination events were identified in subjects III.5 and III.9 which place the RP13 locus in a 5 cM region between markers AFMc024za5 and D17S1845. The crossover seen in III.5 is uninformative for D17S1529, so it remains possible that this crossover will prove to be proximal to D17S1529, further refining the locus. The RP13 region has recently been refined to a 3 cM interval between markers D17S1529 and D17S831.¹⁵ Our results therefore confirm the localisation and refinement data on the 17p ADRP locus in a new linked family.

Figure 2 Schematic diagram indicating the genetic distances (in cM) between chromosome 17p markers as described by Gyapay *et al.*¹⁸ and Génethon (unpublished data). The localisation of RP13 (this study) and LCA1¹⁹ are shown on the far right.

Table 2 Two point lod scores (Z) between ADRP and markers on chromosome 17p

DNA marker	Recombination fraction (0)					Zmax	θ max
	0.00	0.10	0.20	0.30	0.40		
tel							
D17S849	— ∞	1.6	1.3	0.9	0.5	1.6	0.086
AFMc024za5	— ∞	2.5	2.2	1.6	0.8	2.53	0.081
D17S1529	3.5	2.9	2.3	1.6	0.8	3.5	0
D17S831	4.8	4.0	3.1	2.2	1.1	4.8	0
D17S1845	— ∞	2.2	1.9	1.3	0.7	2.3	0.07
D17S796	— ∞	0.5	0.7	0.5	0.3	0.65	0.19
cen							

Discussion

We present data on an ADRP family RP1729, with a severe peripheral RP phenotype, which is the second family mapping to the 17p locus. Mutations in rhodopsin are thought to account for around a quarter of ADRP, making rhodopsin-RP the most frequent form of the disease. However, it has been impossible to determine the frequencies of the six as yet uncharacterised loci, although a review of current published reports may give some idea of the frequencies. A second 19q linked family has been reported,²⁰ and a further three have been identified (Al-Magthteh *et al*, manuscript in preparation). Two further 7q linked families have also been reported.^{21,22} These observations suggest that rhodopsin and the loci on 17p, 7q, and 19q are the more common ADRP loci, while those on 8q, 7p, 17q, and RDS/peripherin are rarer.

The confirmation of an ADRP phenotype at this locus is significant since Syrquin *et al*²³ have reported a locus for autosomal dominant cone degeneration linked to markers D17S513 and D17S796 in the same region. D17S796 is on the current Génethon map, but D17S513 is not placed on any of the available genome maps. Haplotype analysis in the RP13 linked family places this marker proximal to D17S1845 (data not shown). It is possible that the two disease phenotypes could be allelic, as is the case with ADRP and macular dystrophy mapping to chromosome 6p.²⁴ Mutations in the RDS/peripherin gene are responsible for both diseases despite wide variation in their phenotype.

Recently, a gene for Leber's congenital amaurosis (LCA), an autosomal recessive disease which causes congenital blindness, has also been mapped to 17p.¹⁹ Significant linkage was shown between LCA1 and markers D17S831, D17S796, D17S1353, and D17S786, with a peak lod score of 7.21 at a recombination fraction of zero at D17S1353. Haplotype analysis places the LCA gene between the markers D17S796 and D17S786, as shown in fig 2. The authors suggest that LCA1 may be allelic with RP13. However, our data and that of Goliath *et al*¹⁵ place the RP13 locus distal to D17S1845, proving that different genes are responsible for LCA1 and RP13.

By linkage analysis in RP1729 we have been able to confirm the earlier report of linkage to the RP13 locus, and localise RP13 to a 5 cM interval between markers AFMc024za5 and D17S1845. Given the general tendency for genetic maps to expand at the telomeres relative

to the physical map, this may correspond to a relatively small physical interval, so that a physical mapping and positional cloning approach could now be considered.

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