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Linkage of a medium sized Scottish autosomal dominant retinitis pigmentosa family to chromosome 7q

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Abstract

Retinitis pigmentosa is a group of hereditary retinopathies which is both clinically and genetically heterogeneous. Autosomal dominant (ADRP), autosomal recessive (ARRP), and X linked recessive (XLRP), as well as digenic forms of inheritance have been reported. ADRP has been linked to 3q, 6p, 7p, 7q, 8cen, 17p, 17q, and 19q. Three unrelated ADRP families have been reported to show linkage to 7q. We tested a Scottish ADRP family with microsatellite markers mapping within the 7q31-q35 region, and found three markers (D7S487, D7S514, D7S530) showing statistically significant evidence of linkage. A maximum two point lod score of 3.311 at 0% recombination was obtained for D7S514.

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Retinitis pigmentosa (RP) refers to a group of hereditary retinopathies. Clinical symptoms include impaired vision under reduced illumination and progressive loss of peripheral vision which eventually leads, in some cases, to complete blindness. The heterogeneity of this disorder, both clinically and genetically, has been well documented. The genes for at least two proteins have been implicated as being involved in the pathogenesis of autosomal dominant RP, rhodopsin[1] and peripherin/RDS.[2] Other as yet unidentified gene loci determined by linkage analysis include 7p,[3] 7q,[4] 8cen,[5] 17p,[6] 17q,[7] and 19q.[8] We have reported a number of rhodopsin mutations causing RP in the Scottish population, which included a Tyr178Cys mutation segregating in a Scottish ADRP family and a novel splice site mutation in intron 4.[9 10] We now report a medium sized ADRP family showing linkage to chromosome 7q (fig 1).

The affected members of the family, designated G6117, were diagnosed as having autosomal dominant retinitis pigmentosa on clinical findings and the diagnosis has been confirmed by ERG testing. Other members of the family have been examined and are unaffected. Onset of symptoms occurred at ages ranging from 12 to the early 20s with a severe deficit in vision noted in the fourth or fifth decade. Genomic DNA was extracted from blood samples using a method described elsewhere.[11] Samples were subjected to PCR amplification and the products were electro-

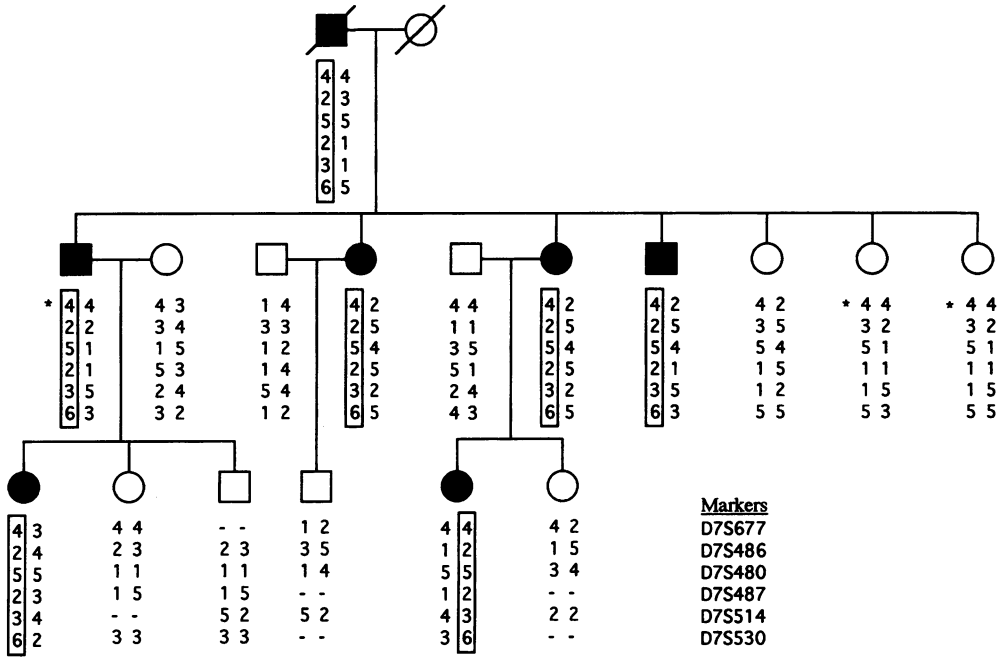

Figure 1 Pedigree of ADRP family G6117. Filled symbols denote affected family members. The numbers below each symbol represent genotypes corresponding to their respective markers. An asterisk indicates genotypes where phase is unknown. The boxed numbers indicate the haplotype most likely to be associated with the disease.

Table 1 Pairwise linkage between ADRP and six polymorphic microsatellite markers on 7q

DNA marker/ ADRP	θ *value*						
	0.00	*0.01*	*0.05*	*0.10*	*0.20*	*0.30*	*0.40*
D7S677	0.903	0.890	0.836	0.765	0.612	0.438	0.237
D7S486	2.709	2.666	2.486	2.252	1.740	1.161	0.515
D7S480	1.806	1.780	1.672	1.532	1.225	0.877	0.475
D7S487	**3.010**	2.960	2.761	2.506	1.940	1.307	0.595
D7S514	**3.311**	3.259	3.044	2.762	2.148	1.454	0.674
D7S530	**3.010**	2.960	2.761	2.506	1.940	1.307	0.595

phoresed on 5% denaturing polyacrylamide gels. (All PCR reactions were done under the following conditions: four minutes at 94°C (one cycle), one minute at 94°C, two minutes at 60°C, two minutes at 72°C (35 cycles), and one cycle of 72°C for 10 minutes. Primer information can be obtained from GDB(TM) Genome database online). Assignment of allele types were based on the difference in banding patterns produced by the polymorphic DNA markers (dinucleotide repeats). Linkage to rhodopsin, peripherin/RDS, and recoverin were excluded as recombinations were observed with intragenic markers. In addition, SSCP screening of rhodopsin and peripherin/RDS genes of affected subjects showed no variants. Microsatellite markers on 7p, 8cen, and 19q were also tested for linkage to the disease locus. Two point linkage analysis was conducted using the LINKAGE program package[12] and results showed exclusion by lod scores < -2 (data not shown).

A total of six polymorphic microsatellite markers located within the 7q31-q35 region were tested. No recombination event was detected, and pairwise analyses between individual markers and the disease locus showed positive lod scores (table 1). Only D7S514, D7S487, and D7S530 were found to be fully informative, showing statistically significant evidence of linkage with D7S514, giving a maximum lod score of 3.11 at 0% recombination.

The first report of an ADRP locus on 7q was made by Jordan *et al*[4] in a large Spanish family (FA-84) suffering from an early onset form of ADRP. The disease locus was found to be tightly linked to D7S480 (Z_{max}= 7.51). Two additional unrelated ADRP families were later found to show close linkage to markers on 7q; McGuire *et al*[13] obtained a maximum lod score for D7S514 (Z_{max}= 5.26) in a large American family (UTAD045) with late onset ADRP, while Millan *et al*[14] reported a lod score of 2.98 for D7S480 in a medium sized Spanish ADRP family. Our finding of a fourth unrelated RP10 family further emphasises the possibility of RP10 being an important causative gene for autosomal dominant retinitis pigmentosa. Efforts are now being channelled towards refining the localisation of the RP10 gene. Narrowing the candidate region will undoubtedly aid the search and hasten the characterisation of the RP10 gene.

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