Autosomal dominant retinitis pigmentosa locus on chromosome 19q in a Japanese family

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Abstract

A large four generation Japanese family was studied, in which autosomal dominant retinitis pigmentosa (ADRP) of very variable expression was segregating. Positive lod scores with maxima between 1.557-5.118 at $\theta = 0.00$, strongly suggestive of linkage, were obtained for KLK, D19S180, D19S418, and D19S254 on chromosome 19q. Recently, an ADRP locus has been mapped to the same region in a British family, in which, again, several members subjectively had no clinical evidence of the disease although they had both an affected parent and an affected child.

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Retinitis pigmentosa (RP), a hereditary degenerative disorder of the retina, is a clinically and genetically heterogeneous condition. The mode of inheritance of RP can be autosomal dominant (AD), autosomal recessive, or X linked. Extensive allelic and non-allelic genetic heterogeneity of ADRP has become evident during the past few years.¹ In addition to mutations of the gene encoding rhodopsin on 3q and of that for peripherin on chromosome 6p, five other ADRP loci have been mapped on chromosomes 7p, 7q, 8cen, 17p,² and 19q.³ While rhodopsin and peripherin mutations account for about 25% and 3% respectively of all ADRP cases,¹ little is known about the relative frequency of mutations in the five other

regionally mapped but not yet identified ADRP genes as most of them have been found so far only in a single large kindred.

We performed linkage analysis on a large four generation Japanese family with ADRP (fig 1). Affected subjects first noticed night blindness in their teens and experienced slowly progressive visual disturbance and constriction of peripheral visual fields with relatively preserved central vision in later life. Ophthalmological and electrophysiological findings were typical of a rod-cone dystrophy. Of the thirteen affected subjects, two obligate carriers (II-2, aged 67, and II-11, aged 51) (fig 1) were subjectively asymptomatic. While the appearance of the fundus and fluorescein angiogram were nearly normal or only slightly abnormal in these patients, kinetic visual field testing and electroretinography (ERG) consistently disclosed constricted visual fields, especially in midperiphery, and considerably reduced amplitudes (37-50%) of rod isolated ERG responses. These findings suggest that while penetrance is complete the mutant allele of the ADRP gene has variable expression in the Japanese family.

A total of 31 members of the family were genotyped for polymorphic DNA markers from chromosomal regions known to harbour an ADRP locus. While linkage has been excluded on 3q, 6p, 7p, 7q, 8cen, and 17p, positive lod scores between 1.557-5.118 at recombination fraction (θ) 0.00, and therefore strongly suggestive of linkage, were obtained for KLK, D19S180, D19S418, and D19S254. Fig 2

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Figure 1 Pedigree of the Japanese family studied. A cross indicates subjectively asymptomatic carriers. A bar denotes subjects whose disease phenotype cannot be defined yet as they are too young.

Figure 2 Simplified linkage map of the human chromosome 19q with a summary of the linkage data obtained on the Japanese family with autosomal dominant retinitis pigmentosa.

summarises the maximum lod scores calculated and the likely order and position of the marker loci on the genetic map of chromosome 19q.^{4,5} The ADRP locus assigned previously to this region has been mapped in a British family.³ The highest two point maximum lod score (3.95) in that kindred was obtained for D19S180, as was the case in the Japanese family. Maximum lod scores of over 2.00 were

obtained in the Japanese family for D19S418 and D19S254, two marker loci originally not typed in the British family but assigned to the chromosomal interval^{4,5} in which the ADRP locus was located in the British pedigree by multipoint analysis.³ Remarkably, several asymptomatic carriers in the British family exhibited functional abnormalities both in electrophysiological and psychophysical testing (see results on family 4 in reference 6). It is interesting to note that disease expression is obviously very variable in both 19q linked ADRP families; an observation that should be taken into account in future mapping studies on ADRP families.

In conclusion, the present data provide strong and independent evidence that a gene for ADRP is on chromosome 19q. The analysis of additional genetic markers, already available and to be isolated from this particular region in the future, will help to narrow down the critical interval that is essential before physical mapping and cloning can be attempted.

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