Autosomal dominant retinitis pigmentosa (ADRP): a rhodopsin mutation in a Scottish family

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The term retinitis pigmentosa describes a range of hereditary degenerative disorders of the retina, which are both clinically and genetically heterogeneous. Autosomal dominant retinitis pigmentosa (ADRP) accounts for 22% of the retinitis pigmentosa population.¹ Linkage of an ADRP locus to the marker D3S47 on the long arm of chromosome 3 (3q) has been established.² Rhodopsin, the major integral membrane protein of the rod outer cells and also located on 3q,³ was an obvious candidate gene. An intensive search for muta-

tions in the rhodopsin gene of RP patients has shown several different mutations.⁴⁻⁶

We searched for mutations in the rhodopsin gene of a Scottish family defined as having the diffuse type⁷ of ADRP (referred to as ADRP3 in reference 8 and T family in reference 9). Using direct sequencing, affected members of the family were shown to be heterozygous for the point mutation (TAC to TGC) in codon 178 of the rhodopsin gene (fig 1). This mutation, previously described,^{5,6} results in the substitution of a tyrosine residue by a cysteine

Figure 1 Nucleotide sequence encompassing the base substitution at codon 178 (TAC-TGC) in exon 3 of the rhodopsin gene. The affected subject (A) is heterozygous for the mutation and the unaffected (B) has the normal sequence. The amino acids coded by this sequence are denoted alongside the sequence.

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Figure 2 Alignment of the gel, showing *RsaI* digested exon 3 PCR products, with the pedigree. Tracks are numbered 1 to 19 as shown and correspond with the above numbered subjects in the pedigree. Unaffected subjects have fragments of 166, 105, and 76 bp and affected subjects, heterozygous for the mutation, have a fragment of 271 bp in addition to these. Lane 20 is size standard kb ladder.

residue in the first codon of exon 3. The mutation also destroys an *RsaI* site and thus RP patients may be screened quickly for the presence of the mutation by simple restriction analysis. The segregation of the mutation with the disease in this family is shown in fig 2.

Codon 178 occurs in an intradiscal loop of rhodopsin which is implicated in determining normal rhodopsin tertiary structure.¹⁰ It is likely that a mutation alters this structure, which in turn causes changes related to the pathogenesis of the disease.

The family also shows significantly decreased levels of certain polyunsaturated acids in the plasma of affected subjects compared to unaffected relatives.⁹ It is possible that a gene involved in the synthesis or transport of these fatty acids is linked to the rhodopsin gene.

Although the exact mechanism is unknown, knowledge of the actual mutation presents an opportunity for accurate counselling of affected persons.

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