

Molecular genetics as a 'probe' in ophthalmology

Under the seemingly endless assault of molecular techniques, an ever increasing number of genes for inherited defects in vision are being identified and disease specific mutations characterised. In this issue, Fullwood *et al* present the clinical features and the results of linkage analysis of a family with X linked exudative vitreoretinopathy (X linked FEVR). Clinically, this condition is characterised by retinal traction, peripheral vitreous opacities, subretinal and intraretinal exudates, and retinal detachment and has been described in families with both X linked and autosomal dominant inheritance.¹

Although polymorphisms at 20 loci on the X chromosome were studied, owing to the small number of individuals available in one family and the limited amount of information that can be obtained from some of the polymorphisms, it has not been possible for Fullwood *et al* to pinpoint the location of the gene precisely. Their results fail to prove linkage at any of the loci studied but do however point to two regions, Xp11 and Xq21.3, which require further analysis in this and other similar families.

This highlights one of the essential features of the many successful studies which have produced candidate genes for rare inherited diseases. In order to ensure that linkage studies will produce useful information, it is necessary to have access to as many large multigenerational families as possible for DNA analysis. It is therefore important for clinicians to consider storing the DNA of known affecteds, their spouses, and sibs - affected or unaffected - so that, in collaboration with others, the molecular pathology of other rare diseases may be further elucidated.

Using such an approach, an international collaboration of workers has recently published linkage information for the autosomal dominant form of familial exudative vitreoretinopathy (adFEVR).² Studying a large German family and a smaller Dutch family these workers made use of highly informative polymorphisms to show that the gene for this condition maps on chromosome 11q and it now remains for them to extend this work to identify possible candidate genes.

Two groups recently published their results on the isolation and characterisation of the gene at Xp11.2-p11.3 for Norrie disease. This is another rare X linked disorder characterised by congenital blindness, retinal dysplasia with pseudoglioma, and often mental retardation and progressive sensorineural deafness.^{3,4} This familial condition is one of the differential diagnoses which may be considered for X linked FEVR. It has been suggested by Fullwood that these two conditions may be allelic but as yet there is little hard evidence to support such a hypothesis. However, in both conditions defective vascularisation occurs during the development of the eye and it is possible that this occurs at different times during development in these two conditions producing differences in the type and severity of congenital malformation. It is thus possible that different types of mutations within the one gene could produce these two phenotypes by a differential timescale of expression.

Mutations including deletions and point mutations have now been identified within the coding regions of the candidate gene for Norrie disease.⁵ The gene codes for a cDNA of 1.9 kb which produces an apparently previously unknown protein with no significant homology to known proteins, therefore suggesting a gene of 'new' function.

Other conditions for which genes have recently been identified include retinitis pigmentosa (RP) and choroideraemia.

Mutations in two genes, the rod photoreceptor, rhodopsin on chromosome 3q,^{6,7} and another transmembrane photoreceptor gene, peripherin on chromosome 6p,⁸ have been shown to segregate with some forms of autosomal dominant RP. Linkage studies have also demonstrated that other genes, one on the pericentromeric region of chromosome 8q21-q22⁹ and another, at an as yet unknown locus, can cause the autosomal dominant forms of RP.¹⁰ Mutations in the rhodopsin gene have also been found in a large family with dominant congenital complete nyctalopia.¹¹

Recently, mutations in the gene, ROM1, on chromosome 11q, have been found to cosegregate with the RP phenotype in a small family. Linkage studies also implicate this locus or others nearby in Usher syndrome type I and Best vitelliform macular dystrophy.¹² ROM1 and peripherin are two of a family of retinal proteins found in the rod photoreceptors; they are structurally similar and non-covalently associated *in vivo*.

In only one case to date has a gene been implicated in an autosomal recessive form of RP and in this individual, the result of a consanguinous marriage, it was a null mutation in a rhodopsin gene which was the cause.¹³ In contrast, another null mutation predicted to produce only a very small fragment of the peripherin protein, segregates with a dominant form of retinitis punctata albescens.¹⁴

The gene for choroideraemia (hCHM), an X linked progressive degeneration of the choroid and the retina was identified two years ago¹⁵ and now mutations including deletions, point mutations, and aberrant splicing at the exon/intron junction have been found to be associated with the abnormal phenotype.¹⁶ An autosomal homologue of this gene, human choroideraemia-like (hCHML) gene, colocalises with the Usher syndrome type II locus on the distal part of chromosome 1q.¹⁷ As there are clinical similarities between these two conditions, hCHML must now be considered a candidate gene for Usher syndrome type II.

As can be seen from this brief review, different genes have now been shown to produce clinically similar phenotypes (for example, RP) and different mutations in the same gene can produce apparently different clinical phenotypes (for example, peripherin mutations).

Studies such as those described above and as presented by Fullwood *et al* in this journal will continue to produce information on the genes coding for novel proteins involved in the development and function of the eye. The logical extensions of such work will then provide us with an understanding of the molecular mechanisms causing these diseases and eventually improve our knowledge of the stages of normal neurodevelopment.

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