EDITORIAL

ADVANCES IN THE UNDERSTANDING OF RETINITIS PIGMENTOSA

Ophthalmologists must all be aware of the rapid and exciting developments which are occurring in molecular genetics and we can feel justifiably proud that in our field the very considerable endeavours in genetic studies are now bearing fruit of great interest and importance. In this edition of 'Eye' are published a number of papers and posters presented at the 1991 Oxford Ophthalmological Congress and in particular, the outstanding Robert Doyne memorial lecture by Professor Thaddeus Dryja on the subject of rhodopsin and autosomal dominant retinitis pigmentosa.

Retinitis pigmentosa is a condition sufficiently prevalent for it to be in the regular experience of most ophthalmologists and it is fascinating to learn that the obviously widely differing modes of inheritance encompassing autosomal dominant, autosomal recessive and X linked patterns and also the wide variations of clinical severity are now being understood in terms of many possible genetic loci where mutations can occur. Professor Dryja describes first the reverse genetics or linkage approach which relies upon locating a disease gene on a chromosome map by finding a marker which is co-inherited with the disease within affected families and is therefore close to the affected gene. This approach has led to the identification of novel proteins such as dystrophin and cystic fibrosis trans membrane regulator which are absent or defective in Duchenne muscular dystrophy and cystic fibrosis respectively, and has led to the identification of the anti-oncogene which is defective in retinoblastoma. Professor Dryja was able to build on the discovery by P. Humphries of an Irish family in whom a DNA marker was identified on the long arm of chromosome 3 which was known to be the site of the rhodopsin gene. Professor Dryja then used the candidate gene approach in which he was able to screen affected individuals from his large pool of clinical cases with autosomal dominant retinitis pigmentosa and was able to demonstrate a point mutation in the rhodopsin gene in five unrelated patients and subsequently in 10% of patients with autosomal dominant retinitis pigmentosa. Over 30 distinct rhodopsin mutations have since been discovered accounting for 25–30% of cases, although demonstration of polymorphism within the gene suggests that many apparently unrelated families with the same rare mutation probably have a common ancestor. The next step in the detective story has been to consider the biochemical abnormalities which are associated with the mutations. The mutations found in the DNA sequence of the rhodopsin gene are almost all point mutations and these appear to cause mutent forms of rhodopsin which in some way is toxic to photo-receptors. Rhodopsin is synthesised in the rod photo-receptors and normally undergoes a continuous process of production within the rods and catabolism after ingestion by the neighbouring pigment epithelial calls which consume the tips of the rod outer segments. Professor Dryja suggests that the mutant rhodopsin molocules are unable to maintain their normal shape and cannot be transported to the outer segment of the rod and might well accumulate within the rod and build up a toxic level of rhodopsin. The possibility is raised that the degeneration of cones found in retinitis pigmentosa may be due to the preponderance of damaged rods providing a hostile environment to the less abundant cones and raises the possibility that if cone function be protected from the over accumulation of mutant rhodopsin, then perhaps vision might be maintained.

The clinical variability of the severity of retinitis pigmentosa may be explained in terms of the different mutations of the rhodopsin gene and it may be that the identification of the affected gene in an individual may be helpful with regard to prognostic advice. Not all autosomal dominant retinitis pigmentosa is caused by mutations in the rhodopsin gene and this leads to a wider field of bichemical abnormalities to be considered, it nevertheless underlines the reality that molecular genetic studies are now getting close to realising the possibility of suggesting rational therapy. Mutations in other genes, for example the peripherin-RDS gene, have been recently demonstrated in affected families and undoubtedly other genes will be shown to be involved in the future. There should be little doubt that the understanding of the mechanisms of retinal degeneration which is now occurring as a result of these studies will eventually lead to rational prevention and treatment. We are privileged to live in exciting times.

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