Simple tests for rhodopsin involvement in retinitis pigmentosa

Retinitis pigmentosa (RP) is an inherited retinal degeneration affecting approximately 1 in 5000 people. The genetic basis of RP is complex, with X linked, autosomal dominant, and autosomal recessive inheritance, and multiple loci for each. This makes it difficult for diagnostic laboratories to provide useful information to RP patients and their families, especially in dominant RP, which maps to at least eight loci. However, our work on dominant RP over the last five years indicates that there are three simple tests which can be performed to identify the genetic defect. These tests include FISH analysis, linkage analysis, and mutation analysis, each of which can provide useful information.

Published estimates for the frequency of rhodopsin mutations as a proportion of dominant RP range from 20 to 31%, but our own recent analyses in large families suggest a figure as high as 50% (Inglehearn et al., manuscript in preparation). Rhodopsin is therefore a good candidate gene for patients with a dominant family history, and it has also been implicated in several cases of recessive RP. The markers which have been used in the past to exclude rhodopsin are RPE65 in RP gene carriers (D3S47), the FLRF marker first linked to ADRP at 3q21, and a microsatellite in intron 1 of the gene itself. However, C17 is not expressed in any of these 18 RP cases from rhodopsin while the intragenic microsatellite has a heterozygosity of only 33%. We have therefore placed the rhodopsin gene on the microsatellite map of Gapyay et al by linkage analysis, and this RFLP maps in Haplotype analysis (data not shown) to the rhodopsin gene in a 5 cM gap between markers D3S1589 (heterozygosity 0.68) and D3S1292 (heterozygosity 0.85). By pooling data in linked families we obtained maximum lod scores of 8.5 at 0.0 = 0.07 from marker D3S1589 and 21-75 at 0.0 = 0.02 for marker D3S1292. These are therefore highly informative microsatellite markers with which to test for rhodopsin linkage in dominant RP. Screening for mutations in the rhodopsin gene is also complex, since over 60 have now been reported. The Pro-23-His mutation is the most common, found in 30% of families. However, this has not been reported in any other populations and is now thought to represent a founder effect. Two other mutations have been reported in different populations, which are not present in the remaining 70% of families. These are probably mutation hotspots for rhodopsin mutations leading to ADRP and may be worth screening in dominant and sporadic cases of RP. This can be done by a simple assay involving PCR amplification followed by restriction digestion, using Mpl for codon 347 (destroys a site) and Ddel for codon 58 (creates a site). Our own data on screening for these mutations showed five patients with the codon 347 Pro-Leu substitution and two with the codon 58 Thr-Arg substitution. These were identified in a sample of 120 RP patients who attended the Moorfields Eye Hospital genetics clinic and gave a family history indicating dominant RP. It is worth noting that both codon 58 pedigrees have a rare recessive RP phenotype. Sectoral RP cases should therefore be made a priority in testing for the codon 58 mutations.

In summary ADRP families can quickly be assessed for linkage to rhodopsin, using markers D3S1589 and D3S1292, which span the locus. In addition around 6% of dominant RP cases can be characterised by simple PCR restriction digestion tests at codon 58 and 347 of the rhodopsin gene.

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With the rapid increase in mapping and cloning of genes for many human diseases, more accurate prenatal diagnosis becomes technically possible. Newer methods, such as in- terphase FISH for prenatal diagnosis of chromosomal aneuploidies, are now becoming cornerstones of the clinical scene. Faced with the prospect of being superseded almost immediately, the production of a textbook covering such an expanding field is a daunting task.

Undaunted, Bouë et al have written a comprehensive textbook which covers a wide range of topics. They include sections on basic cytogenetics and molecular genetics, as well as extensive descriptions of procedures involved in prenatal samples and in sample analysis. The book does not set out to cover all the areas of fetal medicine, and issues such as ultrasound based diagnosis, immunisation, or exchange transfusion, are specifically excluded. However, the use of prenatal diagnosis in the management of maternal viral infection is covered, with detailed discussion of the relative merits of specific screening or diagnostic tests. The authors have made a great resource of practical experience in prenatal diagnosis in France has been brought together, and that the authors have a deep understanding of the problems and pitfalls in fetal medicine.

The book is aimed at obstetricians, general practitioners, and paediatricians, to help them address the questions asked by their patients. There is an appropriate emphasis on detection of chromosomal aneuploidies, but the short section on maternal serum screening does not discuss the improved detection brought about by triple marker screening. A large chapter on prenatal diagnosis of single gene disorders covers both biochemical and DNA based diagnosis of a wide range of conditions. For some diseases, there are discussions of the clinical genetic issues for families at different degrees of risk. There is a considerable amount of detail on the specific DNA markers used in different monogenic conditions. All the markers mentioned are RFLPs analysed by Southern blot, which in many cases have now been superseded by PCR based microsatellites, of which there is no mention. The amount of technical detail may be somewhat overwhelming for the general reader, especially as such detail must inevitably become outdated. There is only a brief reference to PCR in the section on molecular methods, which is unfortunate, as PCR is not the mainstay of DNA technology in molecular diagnostic laboratories.

The editor has wisely included a chapter on ethical issues in prenatal diagnosis, and focuses on the ethical implications of "screening" for genetic disease in selected populations, citing the statements of the French National Consultative Committee on Ethics. Bouë et al. rightly emphasize that prenatal diagnosis needs a multidisciplinary approach, and involves obstetricians, clinical an- malologists, laboratory geneticists, and ultrasonographic experts.

This textbook also draws together information from different disciplines, and has successfully covered a large area of the management of pregnancies at increased risk of disease. Even though the editor accepts that the volume will rapidly be superseded, the core of this textbook will remain valuable for a considerable time to come.


There is much evidence that persistent sleep disturbance is very common and that it can have serious psychological or even physical effects, and yet this topic is often marginalized or ignored in professional teaching and training courses. Sleep disturbance specific to children generally receives even less attention. However, this book would provide a clinician...