A156E11 probes in the PWS/AS region showed the PWS/AS region to be present twice in the marker (data not shown).

The parents of the index patient are illiterate, went to school for children with learning difficulties, and have a simple job in a sheltered environment. They have had no seizures.

In out of 32 lymphocytes analysed in the mother, the same marker was present. The karyotype of the father was normal. The marker was not found in 100 lymphocytes from the maternal grandparents. Sibs of the mother were not available for further study and we have no information on their mental status.

Numerous cases of small familial inv dup(15) supernumerary markers have been reported.12-13 Apparently, most of these markers have no adverse phenotypic effects. Many of these familial cases have been ascertained accidentally by prenatal screening. To our knowledge, however, only three familial cases of inv dup(15) where mental retardation was a feature have been reported.12-13 All retarded probands in these three families inherited the marker from their mother. One of these mothers was mentally retarded herself, but she was a proven mosaic. Another two families, ascertained through mentally retarded probands, have been reported. However, in these cases it was not likely that the mental retardation be attributed to the inv dup(15), since other carriers of the familial marker were not retarded.14 In both families the inv dup(15) was small and unlikely to contain the PWS/AS region. Finally, one report concerned a prenatal diagnosis of an inv dup(15) in a carrier mother, who was described as “mentally slow”. No information on the development of the child was presented.15

In the present report another family is described, in which an inherited inv dup(15) is associated with mental retardation. To our knowledge this is the second familial case where the presence of additional copies of the PWS/AS region was shown by molecular techniques,14 and the first familial inv dup(15) in which two extra copies of this region were identified. This case confirms that an inv dup(15) may be inherited, even when two copies of the PWS/AS region are present in the marker. The phenotype caused by such a large marker, however, does not always have to be severe, but may be milder owing to a mosaic state, as illustrated by the mother of our index case. The use of FISH probes for the PWS/AS region appears to be of importance in counselling parents, who may be mosaics for an inv dup(15) supernumerary marker, with respect to the expected phenotype of their non-mosaic offspring.

We sincerely thank Dr F A Beemer for his advice and critical remarks with regard to this manuscript.


Simple tests for rhodopsin involvement in retinitis pigmentosa

Retinitis pigmentosa (RP) is an inherited retinal degeneration affecting approximately 1 in 5000 people.1 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 provide useful information to patients and their families. We have developed an additional test, which can be used as a starting point for DNA analysis, each of which have a reasonable chance of providing useful information.

Published estimates for the frequency of rhodopsin mutations as a proportion of dominant RP range from 20 to 31%, and our own recent analyses in large families suggest a figure as high as 50% (Ingelhearn et al., manuscript in preparation). Rhodopsin is therefore a good candidate gene for patients with a dominant family history, and it has been implicated in several cases of recessive RP.1 The markers which have been used in the past to exclude rhodopsin mutations in dominant RP are C17 (D3S47), the RFLP marker first linked to ADRP at 3q21, and a microsatellite in intron 1 of the gene itself. However, C17 is now restricted to some 18 C*M from rhodopsin while the intragenic microsatellite has a heterozygosity of only 33%. We have therefore placed the rhodopsin gene on the microsatellite map of Guyap et al2 by linking analysis of haplotypic RH linkage. While the Haplotype analysis (data not shown) locates 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 8.55 at 0 = 0.07 from marker D3S1589 and 21.75 at 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.1 The Pro-23-His mutation is the most commonly found mutation in the rhodopsin gene. This mutation has been reported in approximately 50% of cases of RP in the UK, German, and Japanese populations, and three other base substitutions have been found at the same site. Similarly, Thr-58-Arg substitution is found in 80% of cases of RP in the UK, German, and Japanese populations. These are therefore 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 Mpi for codon 347 (deletes a site) and DdeI 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 retina clinic and gave a family history indicating dominant RP. It is worth noting that both codon 58 pedigrees have a rare sectoral 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 and RP cases can be characterised by simple PCR/ restriction digestion tests at codon 58 and 347 of the rhodopsin gene.

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Undaunted, Boué 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 a wealth of clinical and laboratory experience involved both in prenatal sampling and in sample analysis. The book does not set out to cover all the areas of fetal medicine, and includes such as ultrasound based diagnosis, cytogenetics, and 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 cases. The book covers diagnostic tests, and describes the text that 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 be 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. Boué also rightly emphasizes that prenatal diagnosis needs a multidisciplinary approach, and involves obstetricians, clinical and laboratory geneticists, and ultrasonographic expertise.

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.

**BOOK REVIEWS**


With the rapid increase in mapping and cloning of genes for many human diseases, more and more prenatal diagnosis becomes technically possible. Newer methods, such as interphase FISH for prenatal diagnosis of chromosomal aneuploidies, are now beginning to come on 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.


There is much evidence that persistent sleep disturbances are 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
Simple tests for rhodopsin involvement in retinitis pigmentosa.

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