LETTER TO
THE EDITOR

Still no evidence for heterogeneity in Best's vitelliform macular dystrophy

In the November 1995 issue of the Journal, Mansergh et al. suggest that there is genetic heterogeneity in the autosomal dominant eye disorder Best’s vitelliform macular dystrophy (BMD) previously mapped to 11q13 (MIM 135700). They analysed markers from chromosome 11 in two families, BTMD1 of Irish origin and Fam E of German origin. The conclusion was that the gene previously mapped to 11q13 does not cause Best’s disease in the German Fam E family. However, all the markers included in the study, except for PYGM, lie on the centromeric side of the BMD gene. In table 1 of the paper, the two point lod scores for these markers are shown and Fam E was not analysed for PYGM. In the multipoint analyses, illustrated in fig 3, the data have been calculated assuming four different penetrance but they have failed to include a single marker on the telomic side of the gene. Not surprisingly then, Fam E showed lod scores below —2, the criterion used for exclusion of linkage. The authors thus arrive at the incorrect conclusion of excluding linkage to the BMD region, without including the BMD region in their analyses. In our opinion there is still no evidence of genetic heterogeneity in Best’s macular dystrophy and we are looking forward to seeing if the German Fam E shows linkage to the BMD region when more closely located flanking markers are analysed.

CAROLINE GRAFF CLAES WADELIUS
Department of Clinical Genetics, Upplands University Children’s Hospital, 5-751 85 Uppsala, Sweden.

BOOK REVIEWS

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This Methods in Molecular Biology volume is an attempt at bringing together “a coherent collection of protocols” for the construction, manipulation, and use of YACs. For the most part this is a successful attempt with protocols for: creating YAC libraries; analysing YACs; using YACs in mapping, construction of other libraries (cosmids, etc), and cDNA selection; engineering YACs, with specific modifications, fragmentation, and recombination to generate longer contiguous pieces; manipulating YACs such as moving them between strains; and finally reintroduction of the YAC inserts back into mammalian cells. However, this volume suffers from a lack of consistency. Some useful methods are missing and much improved versions of some of the protocols are available. This is the result of the inevitable advances made in the time it takes to go to press, some is because of lack of a coherent plan for the volume. In a collection of protocols where there is a large degree of overlap in media, solutions, and intervening steps of the methods, it would have been helpful if all the common components were gathered in one place or at least presented side by side. There are sporadic attempts at this in the collection, as in chapter 29 which many of the previous chapters refer to, but this is not consistent throughout. There are numerous versions of the same protocol, in this case, the YAC is slightly different. At least four different enzymes are used for digesting away the yeast cell wall throughout the collection where any one could do for most applications. One or two places there are steps such as “1 µg Highly purified YAC DNA” with no method or reference on how to get the DNA.

As a yeast geneticist who has been asked for help and advice from people dealing with YACs, I see several places for improvement. One is simply the language. A YAC containing yeast strain should not simply be called a YAC. The first time I was asked how to make high quality YAC DNA I assumed that the person wanted the YAC molecule isolated away from the yeast genomic DNA in quantities high enough for their particular use. This is much more difficult than just making good quality genomic DNA of the strain DNA containing the YAC, which is what was required in this instance. Another place for improvement is scale. There is little need for 1–4 mg of DNA obtained from 500 ml cultures. The amount needed for Southern analysis, YAC construction, and even “mini” library construction are orders of magnitude less. It’s much easier to work with 1–5 ml cultures. This reduction in scale also holds for preparing DNA in agarose plugs for pulsed field gel analysis. A third place for improvement is in the protocols themselves, at least the yeast specific ones. The lithium acetate transformation procedure for YACs is fine but very inefficient. Modifications exist that yield 107 to 108 transformants per µg of circular test plasmid (rather than the 10–106) and which are in fact easier than the protocols presented.

The editor has gathered protocols from experts in the field who have tried and tested their methods and generally give numerous hints at troubleshooting in the notes section at the end of each protocol. Many of the protocols can be used effectively as presented. However, in some cases these protocols would be difficult to master by the uninstructed. In particular, some of the techniques are not easy to get up and running in a non-yeast laboratory. I imagine a similar statement can be made about the transfection of mammalian cells chapters. Very few non–yeast laboratories will go to the trouble and expense of getting a micromanipulator for tetrad dissection. A more economical and easier method for meiotic manipulation of YACs is random spores in which spores are separated and plated onto media for screening for appropriate markers afterwards. This is particularly economical with time as AB1380 is a notoriously poor sporulator in many crosses making tetrad dissection difficult even for a person experienced in this. Screening for random spores would be useful. Similarly, the twin spot analysis of mitotic recombination events requires several difficult intermediary steps (protoplast fusion, selection, induction of recombination, etc). This method allows for the separation of two YACs in the same strain (a very common problem not directly addressed in this volume). However, a simpler method exists involving meiotic segregation (another protocol missing in this

Occasionally, the organisers of scientific meetings are lucky, and the date of the meeting coincides with the announcement of a huge step forwards in research in that field. The Vinerocate seminar on Autosomal Dominant Polycystic Kidney Disease took place in June 1984, just after Peter Harris and co-workers identified the PKD1 gene on chromosome 16, nine years after the gene was mapped. While the greatest excitement was focused on the news about the gene, in fact the other papers presented, each of which forms a chapter of the book, are in many cases also "state of the art" reviews. Early chapters consider the physiology of the kidney and the pathogenesis of renal cysts. Cysts are fluid filled structures, and below 200µm in diameter they communicate with the tubules from which they arise. Above 200µm, they are non-communicating structures, and continue to expand because of net fluid accumulation within their lumens. Cyst expansion leads to progressive renal failure, and if expansion could be halted, the renal function could be preserved. Recent studies have detected mitogenic activity in cyst formation by renal epithelial cells in vitro, and may have an important role in accelerating the proliferation of renal cyst epithelium in PKD.

The chapter on liver disease by Torres will be particularly interesting for nephrologists, as the frequency of cysts in ADPKD increases with age from 20% in the third to 75% in the seventh decade of life, and liver cysts cause significant clinical problems in some patients. A few even require liver transplantation.

Pirson's review of ADPKD associated intracranial aneurysms (ICA) will be of considerable relevance to any clinicians who have been considering the difficult issue of whom to screen for ICA and when to operate. About 4-10% of ADPKD patients have an asymptomatic ICA, but in only 14% of them is the aneurysm >6 mm, and about half of these patients have a positive family history.

Pirson concludes that it is reasonable, therefore, to restrict screening to young patients with a family history of ICA, and to operate only if the ICA is >7 mm diameter.

Screening by magnetic resonance angiography every five years is recommended, unless there are symptoms which warrant immediate investigation.

Granath's chapter on "Ethical Issues and Genetic Counselling" contains a check list of arguments for and against pre-symptomatic testing and figures for the gene penetrance using ultrasound scanning at 10 and 30 years. No distinction is made, however, between pre-symptomatic screening in adults and children, and it is suggested that CT scanning (or even MRI) may be offered to young patients with normal ultrasound scans. While clinicians will all agree that it is in the patients' best interests to detect treatable complications early (for example hypertension and urinary tract infections), this could be achieved by measuring the blood pressure and culturing the urine, without the need to look specifically for renal cysts. It seems that there are big differences between the United Kingdom and the USA in the extent to which pre-symptomatic screening is pursued in childhood.

Overall, this is a well written and clearly illustrated book which will be of considerable interest and practical use to both clinical geneticists and nephrologists, and both these groups will be keenly awaiting the next anticipated step forwards by the molecular biologist, that is, the development of mutation detection tests to provide definitive diagnostic/presymptomatic tests. It is very unfortunate, therefore, that it is likely to be some time before this becomes generally available, because the PKD gene lies largely within a genomic region which is duplicated elsewhere in the genome, making the search for mutations particularly difficult. It is likely that new methods of examination will be required if rapid progress is to be made towards solving these problems.


This book is one of a series aimed at bridging "the gap between pure research in the biomedical sciences and its practical application in clinical medicine". The series editors cite two objectives for books in the series: to promote (1) the understanding of the molecular basis of human physiology and disease, and (2) new techniques for diagnosis and treatment.

There is a brief introductory chapter by Duncan Shaw which outlines the techniques used by clinical and molecular geneticists in the rapid progress that has been made to identify genes responsible for many of the single gene disorders. The disorders are then dealt with in great depth in six of the remaining eight chapters. These chapters almost constitute a history book that catalogues the localisation, cloning, and identification of disease causing mutations for Duchenne/Becker muscular dystrophies, cystic fibrosis, Huntington's disease, fragile X, myotonic dystrophy, and neurofibromatosis type 1. They also address what is known about the function of the genes, ranging from seven pages for the CFTR protein to one sentence for the Huntington's disease protein. Diagnostic techniques for each of the disorders are discussed. It would have been useful to have a more uniform structure to the chapters; however, on the whole they are well referenced, with suggestions for additional reading.

Although I am not a graduate student of medicine, the reader at whom the book is aimed, I enjoyed, particularly, two of the chapters. The Genetic and Molecular Analysis of the Human Y Chromosome is an excellent, clearly written chapter by Jean Weissenbach. It encompasses sex reversal in mouse models and in humans, the mapping and identification of candidate genes for TDF, spermatogenesis, and Turner's syndrome.

The final chapter, The Genetics of Psychiatric Disorders, concentrates on the application of genetics to disorders that do not have simple, mendelian patterns of inheritance. Apart from describing the clinical syndromes of schizophrenia, manic depression, and the dementias, the approaches that will be used to unravel the genetic components of many common disorders, such as cancer and heart disease, are clearly and concisely explained. DNA marker studies are described (complete with a simple explanation of lod scores), as are association studies and family, twin, and adoption studies. Inevitably, this chapter is already out of date on the molecular genetic aspects of Alzheimer's disease, predating the identification of the presenilin genes. However, this is a minor detract from a chapter that addresses the next major challenge for geneticists, the identification of the genetic factors that contribute to multifactorial disorders.

Returning to the objectives of the series, perhaps the only one which receives scant mention is that of treatment for the genetically inherited disorders. The exception to this is the chapter on cystic fibrosis, which considers gene therapy as one possibility. There is much talk of collaboration throughout the book. Approaches to treatment for many of the genetically inherited disorders will require the collaboration of clinicians and scientists from a broad spectrum of disciplines, who will no doubt document their findings in another book.

JOANNE L WHITTAKER