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LETTERS TO THE EDITOR

Severe cystic fibrosis phenotype in a ΔF508/3272-26A→G compound heterozygote

In the May 1995 issue of the Journal, Kanavakis *et al*[1] described three cystic fibrosis (CF) compound heterozygotes for the mutation 3272-26A→G. The patients had a mild clinical phenotype as indicated by advanced age of diagnosis, absence of pancreatic insufficiency, and absence of or mild obstructive lung disease.[1]

However, we found during the investigation of 100 French adult CF patients, one compound heterozygous ΔF508/3272-26A→G male patient with a severe type of CF. This mutation 3276-26A→G in intron 17a was detected by denaturing gradient gel electrophoresis and was identified by direct sequencing.[2] In this CF patient, pneumothorax appeared in the neonatal period and bronchitis and sinusitis were frequent from the age of 10 months. CF was diagnosed only at the age of 8 years by a positive sweat test associated with pulmonary function abnormalities. There was no evidence of pancreatic insufficiency or other gastrointestinal symptoms, but the patient developed severe nasal polyposis. At the age of 16 years, typical prominent CF problems included chronic airways infection with *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Forced vital capacity was 32% of theoretical values and forced expiratory volume in one second was 28% of theoretical values. He was admitted to hospital at the age of 21 years because of pulmonary decompensation and died a few months later.

This case shows that, in contrast to earlier reports, the 3276-26A→G mutation, which creates an alternative cryptic acceptor splice site that competes with the normal acceptor splice site during RNA processing and probably reduces splicing from the correct site, may lead to severe cystic fibrosis.[1 3] The explanation for these conflicting results may be resolved by RNA studies. Environmental, genetic, and medical factors can influence the clinical course and it is very difficult to predict the severity of the damage in the different tissues. This case illustrates again that the presence of any specific CFTR mutation offers little in the way of a prognostic indicator in the individual patient.[4 5]

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2 Bienvenu T, Cazeneuve C, Kaplan JC, Beldjord C. Mutation heterogeneity of cystic fibrosis in France: screening by denaturing gradient gel electrophoresis using psoralen-modified oligonucleotide. *Hum Mutat* 1995;6:23–9.
3 Fanen P, Ghanem N, Vidaud M, *et al.* Molecular characterization of cystic fibrosis: 16 novel mutations identified by analysis of the whole cystic fibrosis conductance transmembrane regulator (CFTR) coding regions and splice junctions. *Genomics* 1992;13:770–6.
4 Bienvenu T, Beldjord C, Fonknechten N, *et al.* Severe cystic fibrosis in a child homozygous for the G542 nonsense mutation in the CFTR gene. *J Med Genet* 1993;30:621–4.
5 Estivill X, Ortigosa L, Perez-Frias J, *et al.* Clinical characteristics of 16 cystic fibrosis patients with the missense mutation R334W, a pancreatic insufficiency mutation with variable age of onset and interfamilial clinical differences. *Hum Genet* 1995;95:331–6.

MURCS in a male

I read with interest the article in the Journal reporting on a man with Klippel-Feil deformity, unilateral renal agenesis, and azoospermia.[1] The authors suggest that Wolffian duct hypoplasia was responsible for the azoospermia and therefore would be analogous to the Müllerian duct hypoplasia found in female patients with MURCS. We saw a similar patient affected with Klippel-Feil anomaly and azoospermia in whom bilateral agenesis of the vas deferens was diagnosed. The patient was sent for further investigations, in particular to determine the condition of the kidneys. However he did not return for follow up. This observation led us to wonder whether Wolffian anomalies in males is the phenotype corresponding to the Müllerian anomalies in females.[2] No such relationship was found in the analysis of the phenotypes of males with associations and syndromes in which Müllerian duct anomalies are frequent and of females in families in which anomalies of the Wolffian ducts are found. The only relationship between the Müllerian and Wolffian defects seems to be a developmental one: in the case of early insult, anomalies are found both in males and females. One example is the association of renal agenesis with Müllerian or Wolffian defects. An early insult in the region of the 7th to 14th somite, in which the cervical spine develops, may cause faulty development of the spine as well as the genitourinary structures because of the intimate spacial relationship to the pronephros and the pronephrotic ducts. This might explain the relatively high frequency of renal abnormalities in the Klippel-Feil anomaly and the presence in females of Mullerian duct anomalies (MURCS association). Since, as expected, renal anomalies are also frequent in males with the Klippel-Feil anomaly, Wolffian defects should be searched for in those males, as suggested by Wellesley and Slaney.[1]

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BOOK REVIEWS

If you wish to order or require further information regarding the titles reviewed here, please write to or telephone the BMJ Bookshop, PO Box 295, London WC1H 9JR. Tel 071 383 6244. Fax 071 383 6662. Books are supplied post free in the UK and for BFPO addresses. Overseas customers should add 15% for postage and packing. Payment can be made by cheque in sterling drawn on a UK bank or by credit card (Mastercard, Visa, or American Express) stating card number, expiry date, and full name. (The price and availability are occasionally subject to revision by the Publishers.)

Genetic Engineering. Principles and Methods. Volume 16. Editor J K Setlow. (Pp 280; £75.00.) New York: Plenum. 1994

This book belongs to a series that has been published annually since 1979. It provides sophisticated reviews, with an emphasis on methodology, of relatively narrow but diverse topics covering the whole spectrum of organisms, prokaryote and eukaryote, plant and animal. Even the most eclectic "genetic engineer" is only likely to find a minority of the articles of relevance, while only those readers of the Journal with a particular interest in the molecular nitty gritty are likely to want even to open this book. Having said that, I did find two chapters of direct relevance to my own work, and a number of others that might potentially be of interest.

The present volume comprises 15 chapters. Five are exclusively on plants, and might be deemed irrelevant to this readership, but the article "Plant genetic engineering and future agriculture" (S Riazuddin) is of importance to all of us. The author is based in Pakistan, and it was particularly refreshing to read an exploration of this subject in relation to the world's burgeoning population problem from the perspective of a developing country. As with gene therapy applied to humans, the technical and ethical hurdles are formidable and, although much is promised, the impact on agricultural production as yet appears to have been small.

Space does not permit all the other 10 articles to be mentioned individually, but I have picked out six which will be of particular interest to those in the human genetics community and help to convey a flavour of the subject matter of the volume. "Transfer of YACs to mammalian cells and transgenic mice" (C Huxley) provides a timely overview of this subject. The advantage of yeast artificial chromosomes (YACs) in transgenesis is that the problem of dissecting all the *cis*-acting control elements required for normal in vivo expression of the gene of interest can be neatly bypassed by introducing a large genomic DNA segment that contains all the necessary flanking sequences. Furthermore, the readiness of yeast to undergo homologous recombination facilitates genetic manipulation of the transgene, for example, the introduction of selectable markers or particular mutations. There are useful tables summarising the confusing diversity of YAC vectors available and published transgenic

experiments using YACs. In general, with the exception of the immunoglobulin genes, these experiments have fulfilled expectations in conveying developmentally regulated, position independent expression of the inserted gene.

"The P1 vector system for the preparation and screening of genomic libraries" (N Shepherd and D Smoller) reviews the use of this relatively new phage system for large insert (up to 80 kb) cloning. There is a balanced appraisal of its advantages and disadvantages relative to other systems, for example, YACs and bacterial artificial chromosomes. The main advantages of the P1 system are the ability to prepare large amounts of the fragment of interest, and its stability against rearrangement. However, it does seem rather fiddly to use and unless it appears in a kit form, will probably remain the province of the specialist cloner.

"Internal initiation of mRNA translation in eukaryotes" (A Kaminski *et al*) is, at 42 pages, the longest chapter in the book and provides a very detailed overview of a piece of fundamental biology. Whereas internal mRNA initiation is a common feature of prokaryotes, permitting the translation of polycistronic messages, until recently it was only well known among eukaryotic systems in the poliovirus. Recently such internal initiation has been shown for two cellular mRNAs, those for immunoglobulin heavy chain binding protein (BiP) and the *antennapedia* gene in *Drosophilia*. In the case of BiP this mechanism was initially suspected because its translation persisted after poliovirus infection, which results in repression of the cap dependent mode of translation initiation. *Antennapedia* was scrutinised because it has a very long 5′ untranslated region, comprising several exons and containing numerous apparently silent AUG codons. Given these precedents, other examples will doubtless soon be discovered. The significance of internal initiation is that it allows efficient use of particular mRNA species under conditions in which the majority of mRNAs would be down regulated.

"The unmasking of maternal mRNA during oocyte maturation and fertilization" (J L Grainger) addresses a problem of great biological interest, again involving mRNA. In this case it appears that the modification (by phosphorylation) of proteins binding to specific elements in the 3′ untranslated regions is critical for the activation of translation at fertilisation. This illustrates another mechanism for the control of gene expression, which again may turn out to be of wider relevance.

Two other articles of possible interest are "Genetic recombination analysis using sperm typing" (K Schmitt and N Arnheim) and "Recognizing exons in genomic sequences using Grail II" (Y Xu *et al*). However, the former is too short, and the latter too impenetrable, to be of great value.

In summary, although this book contains some useful articles I would not recommend personal purchase. It would, however, be worth making sure that the series is stocked by at least one library within a university faculty.

ANDREW WILKIE

Genetics of Mental Disorders. Part I. Theoretical Aspects. Balliere's Clinical Psychiatry International Practice and Research. Volume 1/Number 1, February 1995. Editors J Mendlewicz, G N Papadimitrou. (Pp 172; £30.00.) London: Baillière Tindall. 1995.

The preface states that the aim of this slim volume (172 pages) is to focus on the theoretical aspects of genetic research into mental disorders for the benefit of researchers and clinicians interested in the link between genetic factors and mental disorders. A second volume which will focus on more clinical topics by the same editors is to be published in 1996.

The editors have assembled an international panel of authors representing backgrounds in clinical psychiatry, molecular biology, and biostatistics. There are 12 chapters which have been grouped into three sections: "Strategies in clinical research", "Applications of molecular biology in mental disorders", and "Genetics and neurobiology".

In general the book meets its aim of providing reviews of several important areas of clinical, molecular biological, and statistical methodology relevant to psychiatric genetics. Several of the chapters are well written and cover interesting material. However, the book shares problems common to many multiauthor volumes. First, the chapters are of very varied style and quality. Second, there is often repetition of the same material in different chapters. For example, twin studies are discussed in sections in each of the first three chapters. Third, some contributions focus more on the author's own work rather than addressing the stated aim of the book. An example is chapter 11 on the genetics of sleep which, although interesting in its own right, seems out of place in this volume.

Further, despite the stated aim of focusing on theoretical issues, several chapters, such as those on twin and adoption studies (chapters 2 and 3), are mainly a review of data from specific studies.

Despite the fact that non-parametric methods of analysis have assumed increasing important in the analysis of complex disorders, very little space is devoted to such approaches. Further, and rather disconcertingly, one of the few statements about sib pair methods is false: "The main limitation of the sib pair method is that it has to be assumed that phenocopies do not exist" (p13).

In summary, although this volume presents a useful review of several theoretical issues in psychiatric genetics, the chapters are of variable quality and insufficient emphasis is given to non-parametric and newer methods of analysis. Nonetheless, the book may be a useful addition to library collections that do not already include a recent multiauthor book on the same topic.

NICK CRADDOCK

NOTICES

3rd International Symposium on Genetics, Health and Disease

The 3rd International Symposium on Genetics, Health and Disease will be held on 1–4 December 1995 in Amritsar. For further details contact: Professor Dr Jai Rup Singh, Centre for Genetic Disorders, Guru Nanak Dev University, Amritsar 143005, India. Fax: +91-183-258863/258820.

European School of Medical Genetics—9th course

The European School of Medical Genetics—9th course will be held in Sestri Levante, Genoa, Italy on 24–31 March 1996. Directors: Professor V A McKusick (Baltimore), Professor G Romeo (Genoa). *Topics*: Introduction to human molecular genetics, linkage analysis, cytogenetics, population genetics, molecular genetics, multifactorial diseases, clinical genetics, cancer genetics. *Registration fee*: 495 000 Italian Lire. *Applications*: Send your CV, a brief description of your research interests, a letter of presentation (if you wish to present a clinical case during an evening session and to apply for a travel fellowship in case there are some available, please state it clearly in your covering letter), and a certificate of your knowledge of English before 15 December to Dr Caterina Cogorno, Laboratory of Molecular Genetics, Istituto G Gaslini, 16148 Genova, Italy. Tel: +39/10/5636370-400, Fax: +39/10/3779797.