LETTERS TO THE EDITOR

Beckwith-Wiedemann syndrome

We note with interest the reports by Moutou *et al*¹ and Viljoen and Ramesar² providing further evidence for maternal transmission of Beckwith-Wiedemann syndrome (BWS) and supporting a mechanism involving genomic imprinting.

The location of the insulin-like growth factor-2 gene (Igf2) at 11p15.5, the region implicated by both linkage analysis and cytogenetic studies as the site of BWS, led to the suggestion that overproduction of Igf2 may be responsible for overgrowth seen in BWS.³ This was supported by the finding that only the paternal Igf2 allele is transcribed in most tissues in the mouse, and that some cases of BWS are the result of paternal uniparental disomy. We would like to draw attention to an alternative to this 'gene dosage' model recently reported by Fidler *et al*⁴ and known as the 'trans-sensing' hypothesis. Their proposal is that in the normal developing fetus the maternal Igf2 allele exerts a suppressive influence on the expression of the paternal allele by synaptic pairing. Disruption of the maternal allele or extra copies of the paternal allele lead to failure of pairing and deregulated expression of the paternal Igf2.

We recently reported a family with BWS and a paracentric inversion of 11p with a breakpoint at 11p15.5.⁵ The family came to our notice when a baby was born at 29 weeks' gestation with features of BWS including birth weight greater than the 97th centile, exomphalos, macroglossia, and bilateral horizontal double ear creases. Her karyotype was 46,XX,inv(11)(p11.2p15.5). Her mother had the same karyotype, but no convincing evidence of BWS. She has since delivered a further baby, again with this karyotype, who also has BWS. The maternal grandmother had normal chromosomes.

We proposed that a gene at the 11p15.5 inversion breakpoint was disrupted and that BWS was caused by lack of a maternally imprinted gene, the inversion having been inherited either from the maternal grandfather (who was unavailable for study), or having arisen *de novo* during spermatogenesis. Our findings would also be consistent with the hypothesis of lack of regulation of the paternal Igf2 gene by disruption of a maternal Igf2 suppressor gene at 11p15.5⁶ and would be difficult to explain with a model requiring increased copies of paternal alleles, as suggested by Little *et al*.³ Furthermore, the two babies in our report had different fathers.

We also proposed that when sporadic cases of BWS are the result of uniparental disomy, other maternal material on 11p is lost predisposing to malignancy, especially Wilms' tumour, and that the surviving baby may be at lower risk of this complication compared to sporadic cases of BWS. However, the hypothesis of Fidler *et al*⁴ suggests otherwise, as the deregulated paternal Igf2 allele may predispose to neoplasia.

It will be interesting to see whether Wilms' tumour incidence in BWS differs between cases involving unbalanced paternal translocations, paternal 11p isodisomy, and

balanced maternal 11p translocation. This requires further study.

Trans-sensing operates in *Drosophila*, where homologous chromosomes are closely associated in interphase nuclei. This is not normally the case in man. Thus to make trans-sensing a plausible mechanism for BWS it would be necessary to show that probes from the candidate region give only a single spot in fluorescent *in situ* hybridisation with interphase cells.

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A mutation in exon 7 of the CFTR gene is common in the western part of France

Cystic fibrosis is the most common severe genetic disease found in Caucasians.¹ The gene causing it, called cystic fibrosis transmembrane conductance regulator (CFTR), was cloned three years ago.^{2,4} The most common mutation in populations of north European origin, $\Delta F508$, accounts for about 70% of chromosomes analysed throughout the world.⁵ During the past three years more than 100 non- $\Delta F508$ mutations have been found in the CFTR gene, many of them being very rare. In general, in various countries, the most common of these rare mutations accounts for about 2 to 4% of the non- $\Delta F508$ CF chromosomes. While screening for CF mutations in a population of Celtic origins (Brittany, western France)⁶ we have found a quite frequent mutation located in exon 7. This frameshift mutation, 1078 del T, initially described by M Claustres (personal communication), is the most common mutation after $\Delta F508$ and accounts for 27.3% of our non- $\Delta F508$ chromosomes or 4.93% of our CF chromosomes (18 of 363 chromosomes). The deletion can be detected either by denaturing gradient gel electrophoresis (DGGE), single stranded conformation polymorphism (SSCP), or allele specific oligonucleotide (ASO) hybridisation. As this mutation was, in each case, found on a C haplotype (XV2c allele 2, KM19 allele 1) it is more than likely that the 1078 del T arose in a common ancestor in these 18 families originating from a similar genetic background. A founder effect may explain the occurrence of this mutation in 4.93% of our CF chromosomes. It remains to be shown if this fre-

quency is particular to our population or whether it is also observed in other Celtic areas.

An additional point which is worth stressing is that in our population screening for three mutations, that is $\Delta F508$ (81.16%), 1078 del C (4.93%), and G551D (4.10%) (which account for more than 90% of our CF gene pool) greatly improves genetic counselling and carrier detection of cystic fibrosis.

However, we would like to draw attention to the fact that the ethnic origin of CF patients is important to take into account in genetic counselling for CF. Identification of almost all the non- $\Delta F508$ mutations is a crucial step in improving genetic diagnosis of CF or in planning a screening test for our population of CF carriers.

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Williams syndrome and chromosome 18

Williams syndrome in its classic form is characterised by a typical facies with malar flattening and a full lower face, supravalvular aortic stenosis and peripheral pulmonary artery stenosis, mild to moderate mental retardation with a friendly, outgoing personality, and growth deficiency. Various other symptoms may be observed. The aetiology of the syndrome is unknown. In the great majority of cases Williams syndrome is a sporadic event. Supravalvular aortic stenosis and other features of the syndrome may follow an autosomal dominant inheritance pattern with variable penetrance and expression.^{1,2}

In several patients with the Williams phenotype chromosome abnormalities have been found, but no consistent abnormality has emerged. Chromosomes 4, 6, 8, 9, 12, 15, 17, and 19 have been implicated in different patients.^{3,4} Recently a patient with Williams syndrome and an unbalanced 13;18 translocation, 45,XX,-13,-18,+der(18),t(13;18)(q13;q23), was described by Colley *et al*.⁵ The chromosome translocation had resulted in loss of material from the proximal long arm of chromosome 13 and from the distal long arm of chromosome 18.

We report here a female patient with Williams syndrome who showed typical dysmorphic features, a characteristic personality, and bilateral renal artery stenosis. This patient has an apparently balanced reciprocal translocation involving chromosomes 1 and 18: 46,XX,t(1;18)(q12;q23). Thus the breakpoint of chromosome 18 in band q23 is in the same band as in the patient reported by Colley *et al.*⁵ The father of the present patient carries the same balanced translocation and is apparently healthy. Studies of this chromosome region at DNA level are currently being performed.

We conclude that there are now two patients with Williams syndrome showing a chromosomal rearrangement involving 18q23. On one hand a gene defect at a locus at 18q23 might lead to a phenocopy of Williams syndrome. Alternatively, patients with the Williams syndrome not showing any chromosomal abnormality might have a submicroscopic deletion or a mutation located at 18q23, or an anomaly of genomic imprinting might be involved.

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BOOK REVIEWS

All titles reviewed here are available from the BMJ Bookshop, PO Box 295, London WC1H 9TE. Prices include postage in the UK and for members of the British Forces Overseas, but overseas customers should add 15% to the value of the order 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.

Analysis of Human Genetic Linkage. Jurg Ott. (Pp 302; \$34.00.) Baltimore: Johns Hopkins University Press. 1991.

It is curious, when the Human Genome Project engages the energies of so very many scientists, that there is only this one book on

human linkage analysis. Perhaps Ott is so pre-eminent in this field that nobody else would presume to compete. The field Ott addresses is, however, quite narrow. He is strictly concerned with human linkage analysis program packages such as LIPED or LINKAGE. He does not discuss the interplay of genetic and physical (especially FISH) methods, or of human and mouse genetics, which underpins the construction of the human gene map. He does not even give much space to the various forms of extended sib-pair analysis or to exclusion mapping or to mosaicism. His aim is to help people produce valid lod scores for mendelian characters.

Guidance in this area is extremely welcome. It is relatively easy to master setting up the input files for LIPED or MLINK: after a few crashes and some hair tearing, most of us can get the computer to churn out lod scores. The real problem is to know what the scores mean. What is a valid penetrance to use on a sample of families showing apparently dominant schizophrenia? How does one set up the liability classes for fragile X or adenomatous polyposis? What is a reasonable threshold lod score to aim for if a collection of disease families is tested for 50 random markers? If you read, learn, and inwardly digest Ott's book you will be able to think through such problems (though I still don't agree with him about multiple markers). He offers a wealth of useful formulae and references, and draws on his unrivalled experience to discuss innumerable practical issues encountered in reducing a genetic problem to a lod score.

Compared to the first edition, this revised version puts much more stress on multilocus mapping and on the problem of locus heterogeneity. There is much useful discussion of locus ordering and of the meaning of multilocus lod scores. It is a pity that no reference is made to some fundamental arguments about the validity of multilocus mapping. When the man who set this whole industry in motion has written a paper titled 'Multipoint mapping and the Emperor's Clothes' (Morton NE. *Ann Hum Genet* 1988;52:309-18), a little discussion would have been in order. Believable multilocus maps usually depend not just on lod scores but on results with chromosomal breakpoints, in situ hybridisation, and pulsed field mapping. If there is a weakness in the book, it is that Ott concentrates on statistical approaches, even when molecular methods can give a surer answer. But of course that is what the book is about: likelihoods, not biochemistry.

It is not always easy reading. Ott's motto might well be "Listen carefully, I shall say this only once". He doesn't waste words, and many sections require close reading. Problems, some quite difficult but with solutions provided, help. The mathematics of human linkage analysis can be formidable. Ott gives plenty of mathematical formulae, but always concentrates on what they mean. Probably very few of us have much idea how the Elston-Stewart algorithm works, or why it is so clever. This doesn't matter - you can drive a car safely without knowing anything about tappets, just as long as you know your Highway Code. Ott provides a Highway Code for linkage projects. It is a unique and indispensable book, and everybody who generates or uses lod scores needs a copy. But they must remember that this is only one facet of human gene mapping.

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Practical Genetics. R N Jones, G K Rickards. (Pp 228; £13.50.) Milton Keynes: Open University Press. 1991.

Practical work is an essential component of any genetics course and thus it is surprising to find few books devoted to this area. The authors aim to help rectify this deficiency with *Practical Genetics* which is aimed at school/college/university undergraduate courses in genetics. It is based on the authors' teaching experience and includes chromosome analysis in mitosis and meiosis, *Drosophila* breeding experiments, complementation of yeast strains, meiotic analysis in *Sordaria* and *Aspergillus* fungi, and population genetics studies on white clover. Each set of experiments is easy to follow and well illustrated and there is a particularly useful emphasis on the interpretation of results and observations. The authors claim that each experiment is known to work well repeatedly and to be within the means of a modestly equipped teaching laboratory.

In contrast, practical work in human genetics has marked limitations and the authors emphasise the hazards of handling blood samples, the need to avoid both family studies which might reveal non-paternity, and chromosome analysis on students. Overall the experiments were well chosen to illustrate classic genetic principles but the lack of emphasis on molecular genetics was surprising given the central role of this field for genetics and other biological sciences. This might in part be explained by the desire to contain costs for 'wet' practicals and this might be circumvented in a future edition by the inclusion of analysis of data sets (linkage analysis using DNA polymorphisms, population genetic studies of DNA polymorphisms, DNA sequence analysis, etc).

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Principles of Genetics. 8th edition. E J Gardner, M J Simmons, D P Snustad. (Pp 649; £21.50.) New York: John Wiley. 1991.

This is a new edition of a well respected textbook which was written for undergraduate courses in genetics. Each chapter has been revised and expanded with new information on gene structure and function (especially in relation to development) and new chapters on transposable elements and methodologies of genetic engineering. The text is clear and accurate and the multicolour illustrations are excellent aids to understanding. Key points and principles are highlighted in the text and each chapter is followed by a summary and sets of problems.

Some aspects of human genetics are included but, surprisingly, other areas with general implications for genetics such as unstable mutations, imprinting, tumour suppressor genes, microsatellite repeats, and mitochondrial heteroplasmy are not. The sections on gene therapy and diagnosis of genetic disease by linkage with RFLPs and mutational analysis could also be expanded to help emphasise the authors' goal of indicating the general population relevance of genetics.

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