LETTERS TO THE EDITOR

Beckwith–Wiedemann syndrome

We note with interest the reports by Moutou *et al*[1] and Viljoen and Ramesar[2] 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 11p15.5[6] 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, ΔF508, accounts for about 70% of chromosomes analysed throughout the world.[5] During the past three years more than 100 non-ΔF508 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-ΔF508 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 ΔF508 and accounts for 27·3% of our non-ΔF508 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 frequency 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 ΔF508 (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-ΔF508 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.