LETTERS TO
THE EDITOR

Beckwith-Wiedemann syndrome

We note with interest the reports by Moutout et al. and Viljoen and Ramesar[2] providing further evidence for paternal 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 cyto-genetic 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 in humans has been related to the Igf2 gene.[4] We would like to draw attention to an alternative to this ‘gene dosage’ model recently reported by Fidler et al.[4] and known after the maternal Igf2 gene. The 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 paramacentric 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, exophalmas, 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 a gene at the 11p15.5 inversion breakpoint was disrupted and that BWS was caused by lack of the genetically 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.[7] 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.

We wish to comment and 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 necessarily true in BWS. 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.

A M NORMAN
A P READ
D DONNAI
Department of Medical Genetics
St Mary’s Hospital, Hatfield Road,
Manchester M13 0JH.


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] The most common mutation in populations of north European origin, ΔF508, accounts for about 70% of cystic fibrosis chromosomes analysed throughout the world.[3-5] 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 rare mutations account for about 2 to 4% of the non-ΔF508 CF chromosomes. While screening for CF mutations in a population of Celtaic origin (Brittany, western France)[6] we have found a quite frequent mutatation located in exon 7. This frameshift mutation, 1078 del T, initially described by M Clastres (personal communication), is the most common mutation at ΔF508 sites, 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 is present in the French population,[6] it is possible to check for this mutation by PCR and SSCP, which can be done in a few days. In the first family, both parents were CF mutation carriers, and the child is a non-carrier. In the second family, both parents were CF mutation carriers, and the child is a non-carrier.

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, supraorbital arch 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. Supraorbital arch stenosis and other features of the syndrome may follow an autosomal dominant inheritance pattern with variable penetrance and expression.[7]

In several patients with the Williams phenotype chromosome 18 abnormality has been found, but no consistent abnormality has emerged. Chromosomes 4, 6, 8, 9, 12, 15, 17, and 19 have been implicated in different patients. One has described a Williams syndrome and an unbalanced 13;18 trans- location, 45,XX,-13,-18,+der(18)(13:18)(q13q23), was described by Colley et al.[8] 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.