Beckwith-Wiedemann syndrome in a child with chromosome 18q deletion

C M Brewer, W W K Lam, C Hayward, E Grace, E R Maher, D R FitzPatrick

Abstract
Molecular genetic investigation of a female infant with Beckwith-Wiedemann syndrome (BWS) showed loss of IGF2 imprinting but no evidence of uniparental disomy. In addition, a deletion of chromosome 18q22.1 was identified in this infant without clinical features of 18q- syndrome (microcephaly, short stature, hypotonia). The association of a chromosome 18 deletion and BWS may be coincidental or may indicate the location of a trans activating regulator element for maintenance of IGF2 imprinting.

Keywords: chromosome deletion; chromosome 18q22.1; Beckwith-Wiedemann syndrome; imprinting

Deletion of the distal portion of chromosome 18q is a well recognised cytogenetic syndrome with well over 100 published cases. There is a phenotype common to many of the cases, characterised by microcephaly, midface hypoplasia, proximal thumbs, tapering fingers, hypotonia, short stature, and intellectual impairment. However, features are variable and clinical features do not always correlate with the size or location of the deleted portion. Atypical phenotypes have been reported with karyotypes apparently identical to those with the typical phenotype.

Beckwith-Wiedemann syndrome (BWS) is a fetal overgrowth syndrome characterised by pre- and postnatal overgrowth, macroglossia, anterior abdominal wall defects, and ear lobe creases in the majority of cases and hypoglycaemia, hemihypertrophy, and an increased frequency of embryonal tumours in many. The diagnosis is made clinically and guidelines put forward by Elliott and Maher require the presence of three major (abdominal wall defect, macroglossia, or overgrowth) or two major and three minor features. Chromosomes are usually normal in BWS although cytogenetic rearrangements involving chromosome 11p15 occur in 2–3% of cases. BWS usually occurs sporadically although around 15% of cases are familial.

Linkage studies in the familial cases together with cytogenetic evidence have located the gene(s) responsible for BWS at chromosome 11p15. Three genes (insulin-like growth factor 2 (IGF-2), H19, and p57KIP2) have been implicated in the pathogenesis of BWS. All three genes map to 11p15.5 and are imprinted. IGF2 is a fetal growth promoter expressed from the paternal allele. H19 and p57KIP2 are suggested to have growth suppressor functions and are expressed from the maternal allele. Paternal uniparental disomy for chromosome 11 occurs in approximately 20% of cases of sporadic BWS. Biallelic IGF2 expression can be shown in the majority of non-disomic BWS cases. Recently, mutations in p57KIP2 have been described in BWS.

Case report
The female infant was born to healthy parents who already had two normal sons and had suf-
Beckwith-Wiedemann syndrome in a child with chromosome 18q deletion

Figure 2 (A) Patient's chromosomes 18 with deletion at 18q22.1. (B) Chromosomes 18 from patient's father showing gap in band q22.

Early progress was slow, in part because of upper airways obstruction by her large tongue, and she required tube feeds until the age of 3 months and supplemental oxygen until 8 months. Transient hyperbilirubinaemia occurred during the first six weeks and phototherapy was given on two occasions. An abdominal ultrasound scan was normal and showed no signs of visceromegaly or renal malformation.

A diagnosis of BWS was likely on the basis of clinical findings, and although at birth her weight was not above the 90th centile, she has displayed postnatal overgrowth, thereby satisfying the diagnostic criteria.

Chromosome analysis produced the unexpected finding of a chromosome deletion, 46,XX,del(18)(q22.1) (fig 2A). Parental chromosomes were normal apart from an apparent fragile site at 18q22.1 in 2/60 and 1/140 cells in two separate lymphocyte cultures from her father (fig 2B).

MOLECULAR GENETIC ANALYSIS

BWS

Investigation for uniparental disomy was carried out using microsatellite markers at the TH locus as described previously, but this was uninformative. To investigate further for UPD, the H19 methylation index was estimated as described by Reik et al and Catchpoole et al and was within normal limits, thus making UPD unlikely. We proceeded to look at IGF2 expression using the Apal polymorphism as previously described. This showed clear evidence of IGF2 expression from both maternal and paternal alleles (fig 3).

---

Figure 3 Analysis of IGF2 expression using exon 9 polymorphism. Lanes 1-3 are from a normal control. (1) Genomic DNA tract showing heterozygosity for Apal polymorphism. (2) Normal monoallelic expression pattern of IGF2 using reverse transcriptase (RT) PCR. (3) Negative RT control to show absence of DNA contamination. Lanes 4, 5, and 6 are from BWS patient. (4) Genomic DNA tract showing heterozygosity for the Apal polymorphism. (5) Clear biallelic expression pattern. (6) Negative RT control showing absence of DNA contamination.
164

abnormalities in BWS although a chromosome 16 rearrangement has been described previously. The location of the chromosome 18 breakpoint may reflect the observation of a previously undescribed fragile site in the father of our case, analogous to the association of a (CGG)n repeat at a rare autosomal folate sensitive fragile site (11p) in the parent of a child with Jacobson syndrome. A site-specific effect, such as the deletion of a downstream transcriptional repressor element, may explain why other deletions involving this chromosome region do not result in BWS. Investigations to identify the deletion breakpoint are currently in progress.


9 Beckwith JB. Extreme cytomegaly of the adrenal fetal cortex, omphalocele, hyperplasia of the kidneys and pancreas and Leydig cell hyperplasia - another syndrome? Presented at the Annual Meeting of Western Society for Pediatric Research, Los Angeles, California, 21 November 1963.


