Sex dependent transmission of Beckwith-Wiedemann syndrome associated with a reciprocal translocation t(9;11)(p11.2;p15.5)

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Abstract

Beckwith-Wiedemann syndrome (BWS), a disorder associated with neonatal hypoglycaemia, increased growth potential, and predisposition to Wilms's tumour (WT) and other malignancies, has been mapped to 11p15. The association with 11p15 duplications of paternal origin, of balanced translocations and inversions with breakpoints within 11p15.4-p15.5 of maternal origin, and the demonstration of uniparental paternal 11p15 isodisomy in some sporadic cases point towards the involvement of genomic imprinting. In agreement with this, we show the paternal origin of a de novo 9;11 translocation in a phenotypically normal mother, whose carrier daughter developed BWS. This supports the fact that BWS associated with balanced chromosome mutations is transmitted in the same sex dependent pattern as non-cytogenetic forms of familial BWS.

Beckwith-Wiedemann syndrome (BWS) is a generalised overgrowth disorder characterised by large size at birth, neonatal hyperinsulinaemia and hypoglycaemia, macroglossia, umbilical abnormalities, visceromegaly, hemihypertrophy, and a highly increased risk of Wilms's tumour, adrenocortical carcinoma, and other malignancies. Although sporadic in many cases, the segregation in familial cases suggests autosomal dominant inheritance, with incomplete penetrance or variable expressivity. In many families only female carriers have affected offspring. This apparent sex dependent transmission has recently been explained by the demonstration of uniparental paternal disomy in association with sporadic cases of BWS, suggesting that genomic imprinting is involved.

The cytogenetic abnormalities which have been found in association with BWS include two cases with interstitial deletion of the proximal part of 11p, several cases with duplication of the distal part of 11p, either as de novo rearrangements or as a result of familial

Figure 1  Facial appearance of the proband at the age of 6½ years.
translocations/inversions,9–16 and apparently balanced chromosomal rearrangements associated with BWS (five reciprocal translocations, one inversion).16–17

The involvement of genomic imprinting in BWS is also supported by the parental origin of the different types of associated chromosomal rearrangements. All cases analysed with duplications of 11p with a known parental origin have been paternally derived,9–16 and all the balanced rearrangements have been of maternal origin.16–17 Furthermore, all the mothers who carried the same balanced translocations/inversions as their affected offspring have been phenotypically normal. In the context of genomic imprinting this could be explained if these maternal rearrangements were of paternal origin.

We show here the paternal origin of a de novo reciprocal translocation, t(9;11)(p11;p15.5), associated with BWS in a subsequent generation.

Materials and methods

CASE REPORT

The proband was the first child of a 29 year old healthy woman who had had a spontaneous abortion in the 10th gestational week. Paternal age was 31 years. She was delivered by caesarian at 30 weeks because of pre-eclampsia. Birth weight was 1233 g and length 40 cm. Apgar scores were 2/1, 5/5, 7/10, and 9/20. Neonatally she developed hypoglycaemia, which was treated adequately, and respiratory distress syndrome. At the age of 2 months she was readmitted to hospital with failure to thrive and sucking difficulties and macroglossia was observed. One month later an umbilical hernia was diagnosed.

At the age of 51 years her height was 126 cm (+3 SD) and her weight 23 kg (+1 SD). Slight facial dysmorphism included reduced bitemporal diameter, frontal bossing, high vaulted palate with paresis of the soft palate, and macroglossia. There were bilateral ear creases/grooves and ear pits on the right side (fig 1). A 5 cm umbilical hernia was observed. Her right leg was approximately 1 cm longer than the left, and she had a lumbar scoliosis convex to the left. There was bilateral hypertrophy of the femoral muscles (fig 2). Mentally she was only slightly retarded. There was no evidence of visceromegaly. She is now followed up every six months by abdominal ultrasound and urinary 17-ketosteroids.

Clinical examination of the mother and father shows no signs of BWS.

CYTOGENETICS

Routine Q banding, C banding, and high resolution RBA banding of the proband, both parents, and the maternal grandparents was performed essentially as described previously.18 For staining of the heterochromatic region on chromosome 9, the methyl green/DAPI method19 was applied.

PCR ANALYSIS OF FLOW SORTED TRANSLOCATION CHROMOSOMES

Flow analysis and sorting of the derivative translocation chromosomes and of the normal chromosome 11 from a lymphoblastoid cell line established from the mother was performed on a FACStar Plus (Beckton Dickinson) essentially as described previously.20 Each PCR analysis involving a specific primer set and chromosome fraction was performed a minimum of four times on 200 sorted template chromosomes. After analysis of genomic DNA from the family, primer sets of two informative chromosome 11 loci were chosen for PCR analysis of flow sorted chromosomes: D11S35 located at 11q22 (ACAATTGGATTACTTAC-TACTAGC and TGATTTGTATCGATTAAAC) and D11S436 located at 11p11.22-p12 (CTCAAATCGAGGGGAC and CACACCTGCAATTTGCAA). The PCR conditions (94°C, one minute; 55°C, one minute; 72°C, one minute) for 30 cycles run on

Figure 2  Front view showing bilateral femoral hypertrophy.

Figure 3  High resolution RBA banding of chromosomes 9 and 11. Arrows indicate the breakpoints on the two derivative translocation chromosomes.

Figure 4  C banding of (a) normal chromosome 9, (b) derivative 9, and (c) derivative 11.

Figure 5  Methyl green/DAPI staining of chromosome 9 and derivative 9 in the proband (open arrow), the parents, and the maternal grandparents. Large arrows indicate the segregation of the large heterochromatic block from the maternal grandfather.
Figure 6  Flow karyotype of the maternal translocation carrier. The sorted fractions are boxed.

Figure 7  Illustration of paternal origin of t(9;11) by PCR analysis of sorted chromosomes. The lanes below the pedigrees show the PCR pattern of genomic DNA. Arrowheads indicate the paternal alleles.

Discussion
A likely candidate locus for BWS is insulin growth factor 2 (IGF2). In previous reports only the paternal allele of IGF2 was transcribed in most tissues in the mouse, and duplication of the chromosomal segment containing the paternal IGF2 allele resulted in abnormal large mice, and maternal transmission of a defective IGF2 locus resulted in small mice. Along with this it has been suggested that an increased dosage of paternally derived IGF2 alleles, by duplication or by paternal disomy, may be involved in BWS.

However, a preferential loss of heterozygosity of maternal 11p15 alleles in BWS associated tumours also supports the involvement of a maternally imprinted recessive tumour suppressor locus. Two clusters of breakpoints associated with the balanced translocation and inversion chromosomes associated with BWS have been identified, one at 11p15.5 near IGF2 as found in the present translocation, and one at p15.4. This led to the suggestion that there may be an additional, proximal locus in the 11p15.4 region involved in BWS, which may be maternally imprinted and which may regulate (suppress) a growth promoting locus in the region. The observation of loss of heterozy-
Sex transmission of Beckwith-Wiedemann syndrome

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18 Donlon TA, Magenis RE. Methyl green is a substitute for distamycin A in the formation of distamycin A/DAPI C-band. Hum Genet 1986;73:144-5.

[References omitted for brevity]