Figure 2 Multipoint across the VMD2 critical region run through family E. Multipoints were performed using LINKMAP as part of the FASTLINK package.^{8,9}

Is p57^{KIP2} mutation a common mechanism for Beckwith-Wiedemann syndrome or somatic overgrowth?

A genetic locus within the chromosome 11p15.5 region has been implicated in the Beckwith-Wiedemann syndrome.^{1,2} H19 and insulin-like growth factor II (IGF2) play important roles in regulating embryonic growth and are strong candidate genes for the BWS.^{3,4} Both genes are imprinted and located approximately 90 kb apart within the chromosome 11p15.5 region,^{5,6} which frequently undergoes paternal uniparental isodisomy in BWS patients.^{7,8} Loss of imprinting of IGF2/H19 has been found in Wilms tumour and rhabdomyosarcoma, which form part of the BWS.⁹⁻¹¹ Similar constitutional epigenetic changes have been implicated in the pathogenesis of BWS and detected in some children with non-syndromic overgrowth.^{12,13}

p57^{KIP2} is another imprinted gene which is located within the chromosome 11p15.5 region and is located within 400 kb centromeric to IGF2.¹⁴⁻¹⁶ Recently, two cases of p57^{KIP2} mutation were reported in nine cases of Beckwith-Wiedemann syndrome (BWS).¹⁷ Furthermore, a recent report showed that various phenotypic features of the BWS were present in mice homozygous for a p57^{KIP2} deletion, such as omphalocele, renal medullary dysplasia, and adrenal cortical hyperplasia.¹⁸

p57^{KIP2} therefore represents another strong candidate 11p15.5 gene for the BWS, so we have investigated whether p57^{KIP2} mutations are common in BWS and whether mutations can be involved in other overgrowth disorders which are sometimes associated with Wilms tumour. This analysis included 40 cases of BWS (including five familial cases), three cases of hemihyperplasia (one case with Wilms tumour), and 11 cases with extensive somatic overgrowth (one case with Wilms tumour).

Mutations and deletions of p57^{KIP2} in these children were analysed by SSCP using peripheral blood DNA. Six pairs of PCR primers yielding products of 250-259 bp were designed to encompass all four exons of the p57^{KIP2} gene. Four different electrophoresis conditions were examined for each PCR product (200-259 bp in length) to maximise the sensitivity of the technique, that is, electrophoresis was done either at ambient temperature or 4°C, and the gels included either 0% or 10% glycerol. These conditions have been reported to detect 89-100% of mutations with PCR products 170-230 bp in length.¹⁹ Using these conditions we did not detect any mutations, deletions, or polymorphisms except the published PAPA repeat polymorphism²⁰ in the region described above. Mutations in p57^{KIP2} therefore represent a relatively rare event in the BWS and children with idiopathic overgrowth disorders.

We have previously shown that imprinting of p57^{KIP2} occurs independently of the IGF-2/H19 domain and that p57^{KIP2} cannot function as an imprinted tumour suppressor gene in Wilms tumour, which is the most frequent tumour in the BWS.²⁰ In a small subset of BWS cases, maternal disruption of p57^{KIP2} may contribute to the observed phenotype. However, we conclude that p57^{KIP2} mutation is not a major cause of BWS or other idiopathic overgrowth disorders.

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