Lack of evidence for genetic heterogeneity in Best vitelliform macular dystrophy

We have previously presented data suggesting that the VMD2 disease locus in the pericentromeric region of chromosome 11 may be excluded in a small German kindred (family E) segregating Best's disease. We ran a multipoint linkage analysis, using markers D11S905, D11S1355, D11S903, D11S986, and D11S1357 that excluded in excess of 10 cM on either side of these markers. Given the estimate that the critical region was between D11S903 and PYGM, and approximated 3.7 cM in distance, we suggested that the data provided evidence for genetic heterogeneity in this disorder. However, it has been suggested that, as the markers used all map to the centromeric side of the VMD2 disease locus, and that estimates of the extent of the VMD2 critical region differ, some doubt would still exist as to whether or not there is substantive evidence for genetic heterogeneity. We used markers known to be on both sides of the disease locus to run a multipoint analysis in the family. Accurate distances between these markers were determined by the construction of a detailed map of the region (fig. 1). Multipoint linkage analysis using markers D11S903, D11S1357-D11S4191-D11S883-PYGM-D11S1889-11q excluded a region between D11S903 and PYGM. However, haplotype analysis showed that exclusions on the 11q distal side of the disease locus were based on two unaffected subjects who shared the same haplotype as all the affected members of the family. Clinical reassessment resulted in the redetermination of the frequency of these as affected. It was not possible to see the other patient for re-examination; her status was therefore deemed uncertain as non-penetrance has previously been noted in VMD2. Reanalysis of marker data under these circumstances gives a maximum lod score (Zmax) of 2.709 at 0=0.00 with the marker PYGM. Multipoint analysis using the same markers as listed above now gives maximum lod scores just under 3 at zero recombination with D11S1883 and PYGM (fig 2). This would suggest linkage of the disease locus to the VMD2 region, thus overturning previous evidence of locus heterogeneity in Best's disease based on family E.

Data from the CEPH version 8.0 database is available through ftp://ftp.ceph.fr/pub/CEPH/
Is p57KIP2 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. H19 and insulin-like growth factor II (IGF2) play important roles in regulating embryonic growth and are strong candidate genes for the BWS. Both genes are imprinted and located approximately 90 kb apart within the chromosome 11p15.5 region, which frequently undergoes paternal uniparental isodisomy in BWS patients. Loss of imprinting of IGF2/H19 has been found in Wilms tumour and rhabdomyosarcoma, which form part of the BWS. Several constitutional epigenetic changes have been implicated in the pathogenesis of BWS and detected in some children with non-syndromic overgrowth. p57KIP2 is another imprinted gene which is located within the chromosome 11p15.5 region and is located within 400 kb centromeric to IGF2. Recently, two cases of p57KIP2 mutation were reported in nine cases of Beckwith-Wiedemann syndrome (BWS). Furthermore, a recent report showed that various phenotypic features of the BWS were present in mice homozygous for a p57KIP2 deletion, such as omphalocele, renal medullary dysplasia, and adrenal cortical hyperplasia. p57KIP2 therefore represents another strong candidate 11p15.5 gene for the BWS, so we have investigated whether p57KIP2 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 p57KIP2 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 p57KIP2 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. Using these conditions we did not detect any mutations, deletions, or polymorphisms except the published PAPA repeat polymorphism in the region described above. Mutations in p57KIP2 therefore represent a relatively rare event in the BWS and children with idiopathic overgrowth disorders.

We have previously shown that imprinting of p57KIP2 occurs independently of the IGF2/H19 domain and that p57KIP2 cannot function as an imprinted tumour suppressor gene in Wilms tumour, which is the most frequent tumour in the BWS. In a small subset of BWS cases, maternal disruption of p57KIP2 may contribute to the observed phenotype. However, we conclude that p57KIP2 mutation is not a major cause of BWS or other idiopathic overgrowth disorders.

Figure 2 Multipoint across the VMD2 critical region run through family E. Multipoints were performed using LINKMAP as part of the FASTLINK package.

BOOK REVIEWS

If you wish to order or require further information regarding the titles reviewed here, please write to or telephone the BMJ Bookshop, PO Box 295, London WC1 H 9JZ. Tel: 0171 383 6244. Fax 0171 383 6660. Books are supplied post free in the UK and for BFPO addresses. Overseas customers should add 15% for postage and packing.

Payment can be made by cheque in sterling drawn on a UK bank or by credit card.
Lack of evidence for genetic heterogeneity in Best vitelliform macular dystrophy.

F Mansergh, T Meitinger, G Rodolph, P Humphries and G J Farrar

doi: 10.1136/jmg.35.1.85

Updated information and services can be found at:
http://jmg.bmj.com/content/35/1/85.citation

These include:

**Email alerting service**
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/