

MEDICAL GENETICS: ADVANCES IN BRIEF

Association of facial haemangiomas with the Dandy-Walker and other posterior fossa malformations

Reese V, Frieden IJ, Paller AS, *et al.*
J Pediatr 1993; 122:379-84.

Approximately 10% of infants have haemangiomas and the vast majority of these are isolated, benign lesions that resolve without treatment. The authors of this paper present nine infants with large, unilateral facial haemangiomas and an abnormality of the posterior fossa central nervous system and review previously reported cases with similar findings. The most striking thing about the vascular lesions in these nine children was their aggressive nature, with seven of nine cases requiring active treatment. The intracranial lesions were also interesting with five of nine showing Dandy-Walker malformations and the remainder having ipsilateral cerebellar hypoplasia associated with their facial haemangioma. Significant ocular findings were present in five of the children (three of nine had choroidal haemangiomas and two cases had microphthalmos) and complex cardiac defects were present in two of nine. Eight of nine were female and all were isolated cases. The authors reviewed 19 previously reported cases with facial haemangiomas and posterior fossa abnormalities and these cases also had commonly associated ocular and cardiac defects with a marked excess of female cases. Although these cases are interesting, the frequency of haemangiomas in the population makes identification of a significant malformation association difficult without systematic study. There is also too little known about the developmental biology of either of these systems to make an informed guess about the embryopathogenesis of this proposed developmental field defect. However, the authors make the reasonable suggestion that cranial ultrasound and ophthalmological examination should be performed on children with large unilateral facial haemangiomas.

DAVID FITZPATRICK

Rubinstein-Taybi syndrome caused by submicroscopic deletions with 16p13.3

Breuning MH, Dauwerse HG, Fugazza G, *et al.* *Am J Hum Genet* 1993; 52:249-54.

February's issue of the *American Journal of Human Genetics* contains another report of a well recognised clinical syndrome being associated with submicroscopic chromosome deletions. The paper shows again the importance of careful clinical studies, in this case carried out by Raoul Hennekam and started in 1985, and the rapid progress that can be made when there is already a good molecular map of the region of interest, in this case 16p13, which has been extensively studied because of the linkage of the PKD1 locus to the short arm of chromosome 16. The investigation of 16p13 in Rubinstein-Taybi patients was prompted by reports of three affected patients who had chromosome translocations disrupting this band. Submicroscopic deletions were identified by a cosmid

mapping to 16p13.3 in six out of 24 patients. It may be that the proportion of cases with a microdeletion will prove to be higher as further cosmids are identified. Alternatively other cases may be because of mutations within a single gene mapping to this region or mutations at other chromosomal loci producing the same phenotype.

JUDITH GOODSHIP

Familial hyperglycemia due to mutations in glucokinase. Definition of a subtype of diabetes mellitus

Froguel P, Zouali H, Vionnet N, *et al.*
N Engl J Med 1993; 328:697-702.

Non-insulin dependent diabetes mellitus (NIDDM) is a genetically heterogeneous disorder. Maturity onset diabetes of the young (MODY), a form of NIDDM with an early age of onset and autosomal dominant inheritance, can result from mutations in glucokinase, a key enzyme of glucose metabolism in pancreatic β -cells and the liver. Thirty-two French families with MODY and 21 families with late onset NIDDM were studied to determine the frequency and clinical features of mutations of glucokinase. Fasting plasma glucose concentrations and oral glucose tolerance tests were used to determine metabolic status. There was substantial evidence of linkage between the glucokinase locus (GK, chromosome 7) and MODY, but not between this locus and late onset NIDDM. Individual exons of GK were amplified by PCR and analysed by SSCP and DNA sequencing. Sixteen mutations were identified in 18 of the 32 MODY families, but none was found in the other group. These included 10 mutations that resulted in amino acid substitution, three that resulted in synthesis of a truncated protein, and three that affected RNA processing. Subjects with GK mutations usually had mild hyperglycaemia that began during childhood, whereas in subjects with MODY and no GK mutation, hyperglycaemia usually appeared after puberty. Mutations in glucokinase are the primary cause of hyperglycaemia in a substantial fraction of French patients with maturity onset diabetes of the young and result in a relatively mild form of NIDDM that can be diagnosed in childhood.

ANDREW NORMAN

A novel meosin-, ezrin-, radixin-like gene is a candidate for the neurofibromatosis 2 tumour suppressor

Traffater JA, MacCollin MM, Rutter JL, *et al.* *Cell* 1993; 72:791-800.

Neurofibromatosis type 2 is an autosomal dominant condition that is characterised by the occurrence of bilateral vestibular schwannomas and other CNS tumours (usually multiple meningiomas). Previous linkage studies have mapped the NF2 locus to chromosome 22q12. Additionally, loss of alleles has frequently been observed at this locus in sporadic vestibular schwannomas

and meningiomas, and their counterparts in NF2. This paper reports the identification of a gene (merlin) from this region that shows overlapping deletions in two unrelated NF2 families. Two further smaller mutations associated with loss of the normal allele were found in meningiomas from two unrelated patients. This is consistent with the tumour suppressor model and adds further weight to merlin being the NF2 gene. Merlin codes for a 587 amino acid protein that surprisingly shows strong sequence homologies to a highly conserved group of proteins (meosin, ezrin, and radixin) which are thought to be involved in linking the cell surface to the cytoskeleton. This suggests that merlin may have a similar function and may represent a new class of tumour suppressor genes. It is unclear how such a protein may deregulate cell proliferation and characterisation of the function should prove extremely interesting.

N S THAKKER

Relaxation of imprinted genes in human cancer

Rainer S, Johnson LA, Dobry CJ, Ping AJ, Grundy PE, Feinberg AP. *Nature* 1993; 362:747-9.

Relaxation of insulin-like growth factor II gene imprinting implicated in Wilms' tumour

Ogawa O, Eccles MR, Szeto J, *et al.* *Nature* 1993; 362:749-51.

Chromosome band 11p15 currently seems to be one of the most interesting regions of the human genome to study. In the past couple of years, opposite patterns of imprinting in two of its genes have been shown: insulin-like growth factor II (IGF2) is transcribed only from the paternal chromosome, and H19 only from the maternal chromosome. In addition, abnormalities of this region have been observed both in Beckwith-Wiedemann syndrome (paternal duplication, paternal uniparental isodisomy, mendelian inheritance through the maternal line), and in Wilms's and other embryonal tumours (loss of heterozygosity). Can all these observations be tied together? These two papers show that, in contrast to the usual monoallelic expression of IGF2 and H19, biallelic expression of one or both genes occurs in some, but not all, Wilms's tumours (loss of heterozygosity having been excluded). Enhanced IGF2 expression through relaxation of imprinting would mimic the effect of paternal duplications and isodisomy; furthermore, loss of normal maternal IGF2 imprinting has been invoked to explain the maternal transmission of familial cases. Although this seems to tie these observations together rather neatly, a couple of caveats are in order. First, the relaxed imprinting was not universally observed, and might simply be a secondary effect; second, it is unlikely that altered IGF2 expression alone explains the complex Beckwith phenotype and tumour predisposition, and additional loci within 11p15 are likely to be involved.

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