with a known association, in their case between chromosome band 9p21 and a number of cancers including melanoma. Using markers derived from their previous physical mapping of the region, deletions centred on a single cosmid were found in over 50 of 100 melanoma cell lines. The sequences from this cosmid were then used to screen the GenBank database and were found to share homology with p16, a previously identified inhibitor of a cyclin dependent protein kinase (cdk-4), thought to play a major role in the control of cell division. Furthermore, homozygous deletions as implied by the lack of PCR amplification of sequences from this region, was found not only in melanoma cell lines but also in multiple cell lines from leukaemias or tumours of nine other types including breast, lung, and ovary. Compound heterozygotes for deletions and a variety of point mutations within the first two exons of this new multiple tumour suppressor gene (MTS1) have been identified. The mutability and range of tumours affected by this gene promises to exceed that of p53, suggesting significant potential for new therapeutic or gene replacement approaches to cancer treatment and prevention.

JOHN C K BARBER

Analysis of limb reduction defects in babies exposed to chorionic villus sampling

Firth HV, Boyd PA, Chamberlain PF, MacKenzie IZ, Morriss-Kay GM, Huson SM. *Lancet* 1994;343:1069-71.

Several reports have documented the occurrence of oromandibular-limb hypogenesis conditions and limb reduction defects in babies after exposure to chorionic villus sampling (CVS) in utero. Seventy-five cases, 70 of which had already been independently reported, of limb defects following CVS are now analysed. The defects are classified according to anatomical degree, ranging from 1 to 5 on a scale of reducing severity. A clear relationship emerges between gestational age at CVS and degree of severity, more severe disruptions correlating positively with earlier CVS. This is true both of uncomplicated limb reduction defects and of limb abnormalities

associated with oromandibular abnormality. The body of data presented here strengthens the likely aetiological relationship between CVS and limb reduction defects, although a clear biological basis to this relationship has yet to emerge. The current view is that the dynamics of blood flow are disrupted in the developing limb $\pm$ mandible. Experimental evidence from rats supports a causative link between limb defects and disrupted blood flow, consequent on haemorrhage and tissue necrosis. This paper emphasises the relationship between CVS and limb reduction disruptions, explores the temporal effect of CVS on the severity of outcome, and investigates possible underlying biological mechanisms which may be relevant to the pathogenesis.

W REARDON

Progression of aortic dilatation and the benefit of long-term β -adrenergic blockade in Marfan's syndrome

Shores J, Berger KR, Murphy EA, Pyeritz RE. *N Engl J Med* 1994;330:1335-41.

Over 20 years ago, medical geneticists from Johns Hopkins suggested that β -adrenergic blockade might reduce the risk of aortic dissection in patients with Marfan's syndrome. In the absence of conclusive human data to support this idea, some medical scepticism has remained although the majority of patients with Marfan's syndrome and aortic root dilatation are managed with β -adrenergic blockade. This report is of a 10 year open label, randomised trial of propranolol in 70 adolescent and adult patients with classic Marfan's syndrome. The treatment group received individualised high doses of propranolol to ensure a negative inotropic effect. When compared with the control group, the treated group had a significantly slower rate of dilatation of the aortic root, and an improved survival with fewer treated patients reaching a clinical end point (death, congestive heart failure, or aortic regurgitation, aortic dissection, or cardiovascular surgery). Hints of underlying heterogeneity, with a likely underlying molecular basis were observed in both the treatment and control groups and the authors point out that there is a need for circumspect interpretation of the

results. Overall, the definitive results of this carefully conducted and controlled prospective study have finally placed medical treatment for Marfan's syndrome on a firm basis. While the study shows a benefit from propranolol for patients with Marfan's syndrome and mild to moderate dilatation of the aortic root, the authors point out that the results provide a basis for considering instituting β -adrenergic blockade at an early age. They also point out that the newer, longer acting β -selective agents have potential advantages over the non-selective effects of propranolol.

DAVID RAVINE

Localization of the achondroplasia gene to the distal 2.5 Mb of human chromosome 4p

Francomano CA, Ortiz de Luna RI, Hefferon TW, et al. *Hum Molec Genet* 1994;3:787-92.

Achondroplasia is often used as a paradigm of autosomal dominant inheritance and the short limbed dwarfism and facial dysmorphism to which it gives rise are well known. Collaborative research has already linked achondroplasia to the distal tip of the short arm of chromosome 4 (4p16.3). In this paper part of the same collaborative team used 10 PCR amplified polymorphic markers to localise this condition further to a 2.5 Megabase interval between DS43 and the telomere. These markers provide the means to offer reproductive choice to achondroplastic families and especially to achondroplastic mothers at risk of having homozygous achondroplastic offspring who normally die before the age of 1. The achondroplasia gene appears to be dosage insensitive in that neither deletions (which lead to Wolf-Hirschhorn syndrome) nor duplications of this region give rise to a phenotype with obvious similarities to achondroplasia. The authors speculate that achondroplastic mutations may act by a dominant negative effect. No evidence for genetic heterogeneity has been found among the 18 families tested and this localisation should enhance the prospect that the achondroplasia gene will finally be isolated.

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