MEDICAL GENETICS: ADVANCES IN BRIEF

Partial isodisomy for maternal chromosome 7 and short stature in an individual with a mutation at the COLIA2 locus

Spotila LD, Soreda L, Prockop DJ. *Am J Hum Genet* 1992; 51:1396-405.

This article describes a third case of maternal isodisomy for the long arm of chromosome 7. The way that the case was identified is intriguing. His mother was included in a study of collagen in women with post-menopausal osteoporosis. A mutation was identified in the $\alpha 2$ chain of type I collagen causing a serine for glycine substitution at position 661. Relatives were screened for the mutation as part of the study and her 30 year old son was found to be homozygous for the mutation. He had features of osteogenesis imperfecta but was disproportionately short and his birth weight at term had been 4.5 lbs. On further investigation maternal isodisomy was confirmed. The previous cases of maternal isodisomy for chromosome 7 both had cystic fibrosis but were investigated further because they also had short stature out of keeping with the diagnosis.

JUDITH GOODSHIP

Complete characterization of a large marker chromosome by reverse and forward chromosome painting

Blennow E, Telenius H, Larsson C, *et al.* *Hum Genet* 1992;90:371-4.

The introduction of alaphoid centromere probes has allowed additional marker chromosomes to be typed on the basis of the origin of their centromeres, but these authors show how unwise it is to assume that the origin of the centromere indicates the origin of a whole marker chromosome. In the subject of this report, the marker chromosome was separated from the rest of the chromosomes by flow sorting and a library of probes specific to the separated marker created by the degenerate oligonucleotide primed PCR (DOP-PCR) technique. This library was then hybridised to the patient's metaphases and painted the whole of the marker chromosome, the pericentromeric area of chromosome 7, the distal long arm of chromosome 5, and the distal short arm of the X. Libraries for chromosomes 5, 7, and X were then used to discover which part of the marker was derived from each of the three constituent chromosomes, and a cosmid used to determine the orientation of the pericentromeric region. The technique requires that the marker be large and distinct enough to sort from the normal chromosomes but this case beautifully illustrates the potential of the reverse painting technique for characterising regions of unknown origin.

JOHN C K BARBER

ERCC6, a member of a subfamily of putative helicases, is involved in Cockayne's syndrome and preferential repair of active genes

Troelstra C, van Gool A, de Wit J, Vermeulen W, Bootsma D, Hoeijmakers JHJ. *Cell* 1992;71:939-53.

Cockayne's syndrome is characterised by UV hypersensitivity, growth retardation, and progressive neurological degeneration. The primary defect in CS is thought to be the loss of preferential repair of active genes. This paper reports the characterisation of a gene, ERCC6, that is involved in the preferential repair of the transcribed strand of DNA. ERCC6 corrects both the UV sensitivity and the inability to resume RNA synthesis after UV exposure of CS cells from complementation group B (the most common form of the disease). It also corrects the defect in UV sensitive excision repair deficient rodent cell lines. Mutations of both alleles of the ERCC6 gene resulting in truncated protein were identified in primary cultures of fibroblasts and cell lines derived from a CS-B patient. The ERCC6 gene codes for a protein of 1493 amino acids and has seven consecutive motifs that are conserved in genes encoding for RNA and DNA helicases. This helicase segment also bears significant homology with similar domains in yeast and *Drosophila* genes involved in DNA repair, transcriptional regulation, and chromosomal stability. These data provide further evidence that DNA helicases are involved in the processing of damaged DNA. It is intriguing that a primary defect of DNA repair is associated with mental retardation and neurological abnormalities; further investigation of the function of the ERCC6 protein should yield very interesting information.

N S THAKKER

Association between polymorphism of the glycogen synthase gene and non-insulin-dependent diabetes mellitus

Groop LC, Kankuri M, Schalin-Jantti C, *et al.* *N Engl J Med* 1993;328:10-14.

There is strong evidence that non-insulin dependent diabetes mellitus (NIDDM) is a genetic disorder. Concordance in monozygotic twins nears 90%, and the lifetime risk for offspring of one parent with NIDDM is about 40%. The storage of glucose as glycogen in skeletal muscle is frequently impaired in patients with NIDDM and their relatives, suggesting the gene for glycogen synthase, a key enzyme in this pathway, as a candidate gene. The cDNA for glycogen synthase identifies two polymorphic alleles A₁ and A₂ with XbaI. The gene is on chromosome 19. The A₁A₂ or A₂A₂ genotype was found in 30% of 107 patients with NIDDM, but in only 8% of 164 non-diabetic subjects without a family history of NIDDM ($p < 0.001$). The diabetic patients with the A₂ allele had a stronger family history of NIDDM ($p = 0.019$), a higher prevalence of hypertension ($p = 0.008$),

and a more severe defect in insulin stimulated glucose storage ($p = 0.001$) than the diabetic patients with the A₁ allele. However, the concentration of the enzyme in biopsy specimens of skeletal muscle from the patients with the A₂ allele was normal, and the mutation responsible for the XbaI polymorphism is intronic and well downstream of the stop codon, suggesting that these results are an example of allelic association and that mutations in the glycogen synthase gene are unlikely to be a direct cause of NIDDM.

ANDREW NORMAN

Abnormal expression of dystrophin-associated proteins in Fukuyama-type congenital muscular dystrophy

Matsumura K, Nonaka I, Campbell KP. *Lancet* 1993;341:521-2.

The exciting identification of dystrophin as the abnormal gene product in Duchenne muscular dystrophy has now given way to studies of the complex cellular interactions of this protein in both the normal and pathological states. Several sarcolemmal glycoproteins have been observed to participate in these interactions, collectively known as dystrophin associated proteins, part of whose function is to provide a link to laminin in the extracellular matrix. Disruption of this link is thought to underlie sarcolemmal instability and consequent muscle necrosis. In this elegant report, the authors show, by immunohistochemical methods, that dystrophin expression is normal in Fukuyama-type congenital muscular dystrophy (FCMD) but that the expression of dystrophin related protein, notably 43 DAG, is greatly reduced. These authors have already identified a similar deficiency of 50 DAG in severe childhood autosomal recessive muscular dystrophy (SCARMD). It is intriguing to observe abnormalities of related sarcolemmal proteins as the underlying basis in diseases which are phenotypically so similar (DMD and SCARMD) and so distinct (DMD and FCMD). In practical terms, the observed deficiency appears to be pathognomonic and will be of value diagnostically. Moreover, clinical practice and counselling will be aided by further studies of this nature aimed at defining the relationship between FCMD and the other forms of congenital muscular dystrophy, classification of which is currently based on clinical criteria for want of better.

W REARDON

Rearrangement of the PAX3 paired box gene in the paediatric solid tumour alveolar rhabdomyosarcoma
Barr FG, Galili N, Holick J, Biegel JA, Rovera G, Emanuel BS. *Nature Genet* 1993;3:113-17.

The human PAX3 gene maps to chromosome band 2q35 and belongs to the paired box family of DNA binding proteins, originally isolated by homology with *Drosophila*