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 α2 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 alphoid 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, Hoeijimakers 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 A_1 and A_2 with *Xba*I. The gene is on chromosome 19. The A_1A_2 or A_2A_2 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 A_2 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 A_1 allele. However, the concentration of the enzyme in biopsy specimens of skeletal muscle from the patients with the A_2 allele was normal, and the mutation responsible for the *Xba*I 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*

genes. It entered the limelight last year when heterozygous PAX3 mutations were shown in a number of families with Waardenburg syndrome. These appeared to be null mutations, suggesting that two gene copies of PAX3 were required for normal development; Waardenburg syndrome thus represents a haploinsufficient effect. Barr *et al* now describe a completely different mechanism by which PAX3 can cause human disease. The consistent association of the rare tumour alveolar rhabdomyosarcoma with acquired t(2;13)(q35;q14) translocations led the authors to map various candidate genes relative to the breakpoints. Whereas a 3′ PAX3 probe mapped to the der(2), the 5′ probe mapped to the der(13), indicating that the PAX3 gene was split by the translocation: the breakpoint was localised to the penultimate intron in three independent cell lines. mRNA analysis of these lines showed a new 7·2 kb transcript, 3 kb larger than normal: this presumably represents a chimeric transcript with new functional properties (the chromosome 13 sequences have yet to be characterised). PAX3 therefore presents an unusual example of a gene that can be disrupted in two different ways to produce two unrelated human diseases.

ANDREW WILKIE

Experience with screening newborns for Duchenne muscular dystrophy in Wales
Bradley DM, Parsons EP, Clarke AJ. *BMJ* 1993; **306**:357–60.

This programme was set up to assess the acceptability of screening newborn boys for Duchenne muscular dystrophy (DMD). Screening was offered on the basis of informed consent in all maternity units throughout Wales using samples obtained through screening for phenylketonuria and congenital hypothyroidism. Creatine kinase activity was measured in blood samples obtained by heel prick, and if raised this was repeated with venous blood. Those parents whose boys had confirmed raised values were offered molecular genetic mutation analysis followed, if necessary, by muscle biopsy and dystrophin analysis. A total of 34 219 boys were screened out of a possible 38 357 (89%); 16 (1:2138) had raised creatine kinase which was confirmed in venous blood in nine (1:3802). The programme includes a prospective long term evaluation of family responses to early diagnosis and a comparison of their experiences and perceptions with those families who have undergone the later traditional clinical diagnosis. Eight families were very positive about the programme. Three chose not to complete the diagnostic process. The programme should permit a full evaluation of the issues involved and should serve as a model for other initiatives within the community for genetic disease. An accompanying editorial stresses the importance of the careful extensive community outreach organisation involved in the programme.

ANDREW NORMAN

Duplication in the hypoxanthine phosphoribosyl-transferase gene caused by Alu-Alu recombination in a patient with Lesch-Nyhan syndrome
Marcus S, Hellgren D, Lambert B, *et al.* *Hum Genet* 1993; **90**:477–82.

Ten to fifteen percent of the heterogeneous HPRT mutations that lead to Lesch-Nyhan syndrome are partial deletions. However, these authors present a second example of a partial duplication which in this case involves exons 8 and 9. HPRT activity in fibroblasts was undetectable. Furthermore, genomic PCR and sequence analysis showed homology over a 100 bp region of Alu sequences in introns flanking the duplication. An 18 bp junction fragment was included in this region and it is proposed that the duplication arose by unequal recombination between Alu sequences which constitute 25% of the HPRT DNA sequence. This mechanism is already believed to have generated mutations in the low density lipoprotein receptor, the α globin gene cluster, and the adenosine deaminase gene. In the first patient with a duplication, neither mental retardation nor self-mutilatory behaviour was recorded while in the subject of the present report no evidence of self-mutilation had been seen by the age of 22. It will be interesting to discover the extent to which a mitigated phenotype may be associated with duplications and whether this is related to evidence, currently limited to cell lines, that HPRT duplications are liable to somatic reversion.

JOHN C K BARBER

The gene involved in X-linked agammaglobulinaemia is a member of the *src* family of protein-tyrosine kinases
Vetrie D, Vorechovsky I, Sideras P, *et al.* *Nature* 1993; **361**:226–33.

This paper describes the identification of another important human disease gene, that for X linked (Bruton) agammaglobulinaemia (XLA). It also represents a tour de force for the positional cloning approach: most genes for the rarer X linked diseases have been identified from X;autosome translocations or candidate genes, but the XLA gene has been isolated using brute force linkage analysis, isolation of yeast artificial chromosomes (YACs), and mapping of candidate cDNAs. Perhaps the most innovative part of the strategy was the use of cDNA selection from a Burkitt lymphoma cDNA library against a candidate YAC clone. This resulted in 300 to 500 fold enrichment of transcripts within the region of the YAC: the correct cDNA was then pinpointed by screening a panel of DNAs from XLA patients and identifying genomic deletions and restriction site alterations. An impressive 25 independent clones of the equivalent cDNA were isolated: the full length sequence is included in the paper. Although the initiation codon cannot be unequivocally defined, the sequence places the gene product (termed *atk*) in a group related to the *src* family of intracellular tyrosine kinases, the first of this category to be implicated in a human disease. It seems likely that the *atk* product is involved in transducing a signal for pre-B cell maturation, and provides a starting point to identify the other effectors of this process.

ANDREW WILKIE

Investigation of inheritance of chronic inflammatory bowel disease by complex segregation analysis
Orholm M, Iselius L, Sørensen TIA, Munkholm P, Langholz E, Binder V. *BMJ* 1992; **307**:20–4.

Familial occurrence of chronic inflammatory bowel disease has been reported in several studies during the past 15 years. A study reported by this group in 1991 suggested the relative risk of ulcerative colitis and Crohn's disease among first degree relatives of patients with either disease was 10 times the population risk. They have used a cross sectional population based survey of the county of Copenhagen which has approximately 500 000 inhabitants (10% of the Danish population) to investigate the mode of inheritance. Of 504 patients with ulcerative colitis, 54 had 77 relatives with ulcerative colitis and of 133 patients with Crohn's disease, five had seven relatives with Crohn's disease. Analysis, using the computer program POINTER, suggested that a major dominant gene with penetrance 0.20–0.26 is present in 9 to 13% of adult patients with ulcerative colitis. For Crohn's disease the best fitting model included a major recessive gene with complete penetrance, for which 7% of patients are homozygous, but this model was not significantly different from a multifactorial model. The authors believe the recessive model for Crohn's disease is the more plausible of the two based on their data and that of other studies. However, it should not be forgotten that the histological findings in Crohn's disease have often been thought to be suggestive of an infectious cause, so a multifactorial model with genetic and infectious components cannot be dismissed.

ANDREW NORMAN