

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 X₂autosomal 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