MEDICAL GENETICS: ADVANCES IN BRIEF

Prevalence and spectrum of germline mutations of the p53 gene among patients with sarcoma

Toguchida J, Yamaguchi T, Dayton SH, *et al.* *N Engl J Med* 1992;326:1301-8

Germline mutations of the p53 tumor-suppressor gene in children and young adults with second malignant neoplasms

Malkin D, Jolly KW, Barbier N, *et al.* *N Engl J Med* 1992;326:1309-15.

These two papers appeared together with an editorial. Recent studies have identified germline mutations of the p53 tumour suppressor gene in families with the Li-Fraumeni syndrome, an autosomal dominant disease characterised by high risk of sarcomas, breast cancer, and other tumours. Acquired mutations in this gene have also been found in sporadic colon, breast, and lung cancers. The first paper aimed to discover what proportion of sporadic sarcomata was associated with new germline mutations of p53. The entire coding sequence and splice junctions of p53 were analysed for mutations. Samples were screened from 196 patients and 200 controls. Eight germline mutations were found, four causing amino acid substitutions and four causing premature stop codons. New germline mutations of p53 are rare among patients with sporadic sarcoma. The second paper investigated the possibility that p53 germline mutations are associated with second primary cancers in children and young adults who do not belong to Li-Fraumeni families. Samples from 59 such patients were analysed. Three mutations were found which were identical to one found previously, a fourth was the first germline mutation to be discovered at exon 9. These findings identify a subgroup of young patients with cancer who have germline p53 mutations, and whose high risk relatives could be identified. However, it is not yet clear whether screening for tumours in those subjects will affect survival.

ANDREW NORMAN

Mutations in the DNA ligase I gene of an individual with immunodeficiencies and cellular hypersensitivity to DNA-damaging agents

Barnes DE, Tomkinson AE, Lehmann AR, Webster DB, Lindahl T. *Cell* 1992;69:495-503.

A fibroblast strain derived from a patient with a syndrome of immunodeficiency, stunted growth, and sun sensitivity, resembling but not identical to Bloom's syndrome, has been previously shown to be sensitive to a wide range of DNA damaging agents and to have a reduced rate of joining of strand breaks. This paper describes the identification of two missense mutations in different alleles of the DNA ligase I gene in these cells. One of these mutations was shown to be maternally inherited. The DNA ligase activity in the fibroblast cell line was also shown to be greatly reduced confirming de-

fective enzyme function. In contrast, cells derived from subjects with Bloom's syndrome, which appear to have defective DNA ligation, did not have DNA ligase I mutations. The demonstration of mutations in the DNA ligase I gene and the resultant biochemical defect confirm the role of the enzyme in DNA replication and suggest a role in excision repair of DNA. The immunodeficiencies may result from inadequate ligation during immunoglobulin and T cell receptor gene rearrangements. These findings suggest that investigation of the enzymes involved in DNA replication, repair, and recombination may prove fruitful in the search for defects in other syndromes featuring both hypersensitivity to DNA damaging agents and immunodeficiency.

N S THAKKER

Linkage of type 2 diabetes to the glucokinase gene

Hattersley AT, Turner RC, Permutt MA, *et al.* *Lancet* 1992;339:1308-9.

Absence of a clear pattern of inheritance along with difficulty in ascertaining large pedigrees owing to disease morbidity have bedevilled efforts to pinpoint genetic factors in the aetiology of type II diabetes. These factors have been less problematical in the relatively uncommon specific subgroup of type II diabetes, maturity onset diabetes of the young (MODY), which is inherited as an autosomal dominant condition. This paper presents evidence of linkage between the glucokinase gene and MODY in a large pedigree (max lod=4.6, $\theta=0$) and absence of linkage between a second MODY family and glucokinase, thereby confirming genetic heterogeneity for this condition. The title of this paper is misleading: after all, MODY is thought to account for only a small proportion of type II diabetes so why the need for a sensational headline? That heterogeneity should be found is hardly surprising given the diversity of factors known to influence glucose metabolism. Indeed heterogeneity between the two pedigrees in the study might almost have been expected given the significantly different family profiles observed in regard of mean age at diagnosis, mean fasting plasma glucose on treatment, and treatment requirements.

W REARDON

The gene for the peripheral myelin protein PMP-22 is a candidate for Charcot-Marie-Tooth disease type 1A

Patel PI, Roa BB, Welcher AA, *et al.* *Nature Genet* 1992;1:159-65.

The peripheral myelin gene PMP-22/GAS-3 is duplicated in Charcot-Marie-Tooth disease type 1A
Valentijn LJ, Bolhuis PA, Zorn I, *et al.* *Nature Genet* 1992;1:166-70.

These paper, and two others in the same issue (by Timmerman *et al* and Matsunami *et*

al), all reach the same conclusion - that the peripheral myelin protein gene PMP-22 lies within a segment of human 17p11.2 that is duplicated in type 1A Charcot-Marie-Tooth disease (CMT1A; hereditary motor and sensory neuropathy with reduced nerve conduction velocity, and mapping to chromosome 17). Although the duplication process was recognised only last year, progress has since been rapid. Normally the duplication is submicroscopic and encompasses about 1.5 Mb of DNA, but subjects with cytogenetically visible dup(17p) also appear to have CMT, suggesting that gene duplication per se may cause the disease. The question is: duplication of which critical gene(s)? A 1.5 Mb segment could contain up to 30 genes, but these papers testify to the rapid focusing of interest on PMP-22. The previously characterised mouse gene maps to chromosome 11, which is syntenic with human 17; the pattern of expression is appropriate (high levels in peripheral nerves, low in brain and other tissues), and point mutations of the gene cause hypomyelination (*trembler* mutant). The new work thus provides circumstantial evidence of a causative role for PMP-22 duplication in CMT1A. The hunt is on for the possible rare point mutations or duplications of PMP-22 alone that would clinch its relationship with CMT.

ANDREW WILKIE

Familial case with sequence variant in the testis-determining region associated with two sex phenotypes

Vilain E, McElreavey K, Jaubert F, Raymond J-P, Richaud F, Fellous M. *Am J Hum Genet* 1992;50:1008-11.

This paper describes an intriguing family in which there are three 46,XY females in two generations. All three women had presented with primary amenorrhoea. There is good evidence for the role of the SRY gene in testis determination with at least two documented 46,XY females who have a de novo mutation within the open reading frame of this gene. In this family a single base substitution causing a valine to leucine amino acid change in the conserved domain of the SRY open reading frame was detected in the 46,XY female. The same mutation was also present in the phenotypically normal father of two of these women. This paper shows yet again that there is still much to be learned about the control of sexual differentiation.

JUDITH GOODSHIP

Fumarase deficiency: two siblings with enlarged cerebral ventricles and polyhydramnios in utero

Remes AM, Rantala H, Hiltunen JK, Leisti J, Ruokonen A. *Pediatrics* 1992;89:730-4.

This case report is of two male sibs with a very rare tricarboxylic acid cycle defect, fumarase deficiency. The index case pre-