MEDICAL GENETICS: ADVANCES IN BRIEF

Comments on important genetic topics from papers in other journals

Haemophilia A diagnosis by analysis of a hypervariable dinucleotide repeat within the factor VIII gene

Lallnoz MRA, McVey JH, Pattinson JK, Tuddenham EGP. *Lancet* 1991;338:207-11.

Haemophilia A, the most common of the inherited bleeding disorders, is a genetically heterogeneous condition consequent on mutations in the factor VIII gene on Xq. In excess of 150 molecular defects of this gene are known. Carrier detection is unreliable when based on factor VIII coagulant and antigen levels alone. Prenatal diagnosis and carrier state determination by direct DNA analysis have depended hitherto on gene tracking using linked polymorphisms. Extragenic linked polymorphisms are hampered by the propensity to recombination and intragenic linked polymorphisms are limited in clinical application by their paucity and lack of informativeness owing to linkage disequilibrium. This report characterises a dinucleotide repeat sequence within intron 13 of the factor VIII gene which may be easily detected using PCR amplification. Advantages related to dinucleotide repeat sequence detection of increased informativeness, rapid availability of results, and prerequisite of only minute quantities of DNA from an affected family member will now apply to haemophilia A. Clearly this will have widespread implications for family members whose carrier status has been unresolved by previously available methods.

W REARDON

Disease and evolution

Howard JC. *Nature* 1991;352:565-7.

The extraordinary polymorphism of the major histocompatibility complex (MHC) is well known, but how and why is this diversity maintained? In 1949, JBS Haldane speculated that this might reflect a continuous 'arms race' between parasites, developing new mechanisms of attack, and the organism, developing new defences. JC Howard discusses two papers (in the same issue of *Nature*) that strengthen this interpretation. In contrast to autoimmune diseases, it has proved surprisingly difficult to show specific associations between human leucocyte antigens (HLAs) and susceptibility to infectious diseases. Hill *et al* now show that in life threatening malaria in The Gambia, the class I antigen, Bw53, and class II haplotype, DRB1*1302-DQB1*0501, are significantly underrepresented in cases compared with controls. Since these HLA alleles are also particularly common in West Africa, their combined protective effect (15%) exceeds even the sickle gene (12%), supporting Haldane's ideas. Potts *et al*, studying mating preferences in mice, encountered a different, but equally remarkable result: mice selectively

avoid partners having the same MHC haplotypes as themselves. The resulting offspring have artificially high MHC heterozygosities, presumably (the argument goes) maximising their disease resistance. How is this selection achieved? Different HLA haplotypes may confer different odours to the urine, which the mice can distinguish, introducing a new twist to the complexities of animal and, just possibly, human behaviour.

ANDREW WILKIE

X linked recessive nephrolithiasis with renal failure

Frymoyer PA, Scheinman SJ, Dunham PB, Jones DB, Heuber BS, Schroeder EI. *N Engl J Med* 1991;325:681-6.

Renal tract stones are a common problem in medicine. Hereditary nephrolithiasis occurs as a consequence of a number of conditions. Frymoyer *et al* describe a new X linked recessive condition of nephrolithiasis with renal failure. A total of 162 family members from six generations of a single kindred were studied. There were nine affected males related through the maternal line. They had 11 sons, all unaffected. No daughter of an affected male showed any important urinary abnormality, but five of these women had an affected son. Nephrolithiasis, nephrocalcinosis, renal tubular dysfunction, and renal insufficiency developed in these males who became symptomatic by the age of 10. Renal biopsies showed tubular atrophy, interstitial fibrosis, and glomerulosclerosis, and these findings preceded abnormalities of calcium, phosphate, potassium, and uric acid excretion. The pathological abnormalities distinguish this condition from Bartter syndrome (which is characterised by hyperplasia of the juxtaglomerular apparatus), and the absence of deafness and glomerular basement membrane splitting distinguish it from Alport syndrome. The affected male in the first generation moved from Ireland to the USA in the mid 19th century. This kindred manifests a previously undescribed X linked recessive syndrome of nephrolithiasis with renal failure. Linkage studies are awaited with interest.

ANDREW NORMAN

Becker's model and prenatal diagnosis in proximal spinal muscular atrophy (SMA): a note of caution

Muller B, Clerget-Darpoux F. *Am J Hum Genet* 1991;49:238-40.

Occasionally interesting short reports or letters are at risk of being overlooked when they appear in a journal full of important and substantive papers. This could easily prove to be the fate of the above letter. SMA, a neurological disorder of variable severity, but

frequently lethal in childhood, is thought to segregate with autosomal recessive inheritance and was mapped to 5q12-q14 in 1990. However, two phenomena require further explanation: the increased incidence of SMA in second degree relatives of affected children and the apparent variation of phenotypes within families. The authors hypothesise that Becker's allelic model may apply and that as well as a normal allele *a* (frequency 90%) and rare disease allele *a*⁺, two activator alleles *a'* and *a''* with a combined frequency of 10% might coexist, and that genotypes *a*+*a*⁺, *a*+*a'*, and *a*+*a''* result in affected subjects. This would imply a 50% risk to offspring of couples with the genotype *a*+*a* × *a'*(*a''*)/*a'*(*a''*) and 1.5% risk to the offspring of an unaffected sib of an affected subject, both unexpectedly high for an autosomal recessive model. In addition, a parent who is homozygous for the activators has the potential for causing errors in prenatal diagnosis and linkage studies as both chromosomes have the same 'disease causing potential'. The next few years will hopefully clarify whether this theory is irrelevant or an erudite thought experiment with an important message.

T R P COLE

Mutations of chromosome 5q21 genes in FAP and colorectal cancer patients

Nishisho I, Nakamura Y, Miyoshi Y, *et al*. *Science* 1991;253:665-9.

Familial adenomatous polyposis (FAP) is a dominantly inherited predisposition to colorectal cancer (CRC) which has already been mapped to chromosome 5. Using a PCR based approach to screen a large number of tumours this multinational team has now identified five distinct point mutations within three exons of the putative APC (adenomatous polyposis coli) gene in kindreds with either FAP or Gardner's syndrome and a further four mutations in the same gene in sporadic tumours. Surprisingly, in further sporadic cases, a total of six mutations has been found in a second contiguous gene termed MCC (for Mutated in Colorectal Cancer) which shows some sequence homology with the APC locus. All these 15 mutations create stop codons or destroy splice site recognition elements. In eight of the 10 mutations in sporadic tumours, both wild type and mutant gene products are present, indicating that mutations are not limited to cases with allelic deletions for the same region. The authors estimate that as many as 15% of colorectal cancers may contain MCC mutations; an estimate for the APC gene should follow when the gene is better characterised. These observations are a major step towards the day when mutation screening may obviate the need for repeated colonoscopies and help to reassure patients in families at risk for inherited colorectal cancer.

J C K BARBER