
MEDICAL GENETICS: ADVANCES IN BRIEF

Genetic susceptibility in familial multiple sclerosis not linked to the myelin basic protein gene

 Rose T, Gerken S, Lynch S, *et al. Lancet* 1993;341:1179–81.

This column has previously alluded to the many problems which beset researchers attempting to identify loci for aetiologically complex diseases such as multiple sclerosis (*J Med Genet* 1993;30:174). Those comments were made in relation to the presentation of evidence suggesting linkage between myelin basic protein (MBP) and multiple sclerosis in several Finnish families. A certain ironic inevitability surrounds the appearance of the report of Rose *et al* who sought to confirm the linkage between familial MS and MBP and found no corroborative evidence in a cohort of families from the USA. As with the earlier report, analysis of results in the absence of a clear model of inheritance necessitated the trial of several different putative models and varying degrees of penetrance. The predominantly negative lod scores, ranging from -3 to $+1$ depending on the variables used, once again emphasise the limitations of current approaches to multifactorial disease aetiology. In direct contrast to the Finnish data, MBP alleles show no significant cosegregation with MS in multiplex families. Perhaps the area which most needs to be resolved in comparing these two reports are the diagnostic criteria. While preparedness to accept heterogeneity as likely, indeed probable, is unavoidable in conditions such as MS, comparison of family studies is only helpful if the family cohorts are comparable. Rose and colleagues overlook this important aspect and, consequently, it is difficult to evaluate the potential relationship of the Finnish and USA data.

W REARDON

Genetic mapping of a locus predisposing to human colorectal cancer

 Peltomaki P, Aaltonen LA, Sistonen P, *et al. Science* 1993;260:810–12.

Clues to the pathogenesis of familial colorectal cancer

 Aaltonen LA, Peltomaki P, Leach FS, *et al. Science* 1993;260:812–16.

Microsatellite instability in cancer of the proximal colon

 Thibodeau SN, Bren G, Schaid D. *Science* 1993;260:816–19.

This trio of papers reports the intriguing finding of a locus on chromosome 2 which cosegregates in large kindreds with hereditary non-polyposis colorectal cancer (HNPCC) and is associated with changes in microsatellite repeat sizes at multiple sites throughout the genome. PCR screening with 345 microsatellite markers was required to establish close linkage between a polymorphism at D2S123 and this form of cancer. No loss of heterozygosity for this marker was found when tumour and normal tissue were compared suggesting that this locus is not linked to a tumour suppressor gene. However, unexpected increases and decreases in the number of dinucleotide (CA) $_n$ repeats in tumour tissue were found at D2S123 and other unrelated loci in a proportion of both familial and sporadic cases. This instability was also particularly associated with cancer of the proximal or right side of the colon. HNPCC is thought to account for between 4 to 13% of all colorectal cancers; D2S123 linked families and high or low risk subjects within them can now be screened for. Elucidation of the mechanism by which this putative gene gives rise to genomic instability and the role of this instability in the neoplastic process will be of great interest.

JOHN C K BARBER

Increased expression of neurofilament subunit NF-L produces morphological alteration that resembles the pathology of human motor neurone disease

 Xu Z, Cork LC, Griffin JW, Cleveland DW. *Cell* 1993;73:23–33.

Progressive neuronopathy in transgenic mice expressing the neurofilament heavy gene: a mouse model of amyotrophic lateral sclerosis

 Coté F, Collard JF, Julien JP. *Cell* 1993;73:34–46.

Structural abnormalities of intermediate filaments such as keratin have been shown recently to be associated with certain pathoses, for example in epidermolysis bullosa simplex and epidermolytic hyperkeratosis. The papers by Xu *et al* and Coté *et al* now show that the overexpression of certain subunits of the intermediate filament, neurofilament (NF), can lead to degenerative changes similar to those seen in the commonest human motor neurone disease, amyotrophic lateral sclerosis. The two groups have produced transgenic mice that overexpress different subunits of NF. These mice showed excessive accumulation of the appropriate NF subunits in the motor neurones of the anterior spinal horn accompanied by axonal degeneration, proximal axonal swelling, and severe skeletal muscle atrophy. Similar changes were also noted in some other neurones. Additionally, the mice developed clinically manifest neurological abnormalities the severity of which correlated directly with the level of overexpression of the NF-L. Although these findings suggest that the accumulation of NFs in motor neurones is an important step in the pathogenesis of motor neurone disease, it is not clear what mechanism is responsible for the accumulation of the NF. It is possible that defective axonal transport of NFs, possibly associated with structurally altered filaments, may be responsible.

N S THAKKER