Medical genetics: advances in brief

Evidence for genetic basis of multiple sclerosis

Sadovnick AD, Ebers GC, Dyment DA, Risch NJ, and the Canadian Collaborative Study Group. *Lancet* 1996;347:1728-30.

The aetiology of multiple sclerosis is ill understood. Although familial clustering of cases has been well recognised in the past, the possibility that this clustering is environmentally mediated has remained. The risk of identical twins both being affected is 300 times that of the general population, and yet this event is rare. The authors of this study examined half sibs of multiple sclerosis patients for the presence of the disease, as this provided a group of related people who may well have had differing environments (they are about equally likely to have been raised apart as together). A total of 16 000 multiple sclerosis patients was identified from 14 regional neurology clinics. Standard interview procedures were used to obtain pedigree information about both maternal and paternal half sibs, and information about whether there was a common environment with the half sib. Information about the occurrence of other medical conditions in the half sibs was sought as controls. The half sibs readily separated into those who had lived together, those who had visited occasionally, and those who had not been in contact in childhood.

A total of 939 of the original cohort had 1395 full sibs and 1839 half sibs (1033 maternal and 806 paternal) for whom information on age and health was available; 39 of the full sibs and 18 of the half sibs were affected with multiple sclerosis. The risk of 3.46% for sibs of index cases to be affected with multiple sclerosis compared well with previous studies. A similar age adjusted risk for half sibs from this study was significantly lower at 1.32%, consistent with a polygenic mode of inheritance. The risks for half sibs raised together or apart was similar, increasing the evidence for a genetic cause for familial aggregation of cases. There was no evidence for a maternal effect.

Although this study elegantly illustrates the importance of genetic factors in the aetiology of multiple sclerosis it leaves unanswered questions about the inheritance of this con-

dition and does not reveal the environmental factors which must also play a role in its aetiology.

ANGELA BARNICOAT

Human homolog of *patched*, a candidate gene for the basal cell nevus syndrome

Johnson RL, Rothman AL, Xie J, et al. *Science* 1996;272:1668-71.

Gorlin or basal cell naevus syndrome (BCNS) is a rare but well known condition leading to rib and craniofacial abnormalities as well as a predisposition to a variety of tumours, especially one of the commonest human cancers, basal cell carcinoma of the skin. This team began their work by cloning the *Drosophila patched* gene which is involved in the spatial patterning of the early fruit fly embryo. They went on to clone the mouse homologue and then used mouse *patched* cDNA probes to pull out the human homologue which was found to map to 9q22.3, a region already associated with BCNS. Single strand conformational polymorphism analysis was then used to identify an insertion cosegregating with the disease in three affected members of a BCNS family. A constitutional deletion was also found in a patient with both developmental defects and tumours, but not in the unaffected parents or in 84 control chromosomes. In addition, a C to T transition was identified in a tumour from one of 12 patients with sporadic basal cell carcinoma. *Patched* codes for a 1447 amino acid protein with 12 transmembrane and two extracellular domains. In other organisms, *patched* represses transcription of signalling proteins induced by another important development gene, *hedgehog*, which has its own homologues in multiple organisms. The body of knowledge concerning its function in lower organisms promises rapid progress in elucidating its role and importance in human development, disease, and cancer. The publication of this article also coincides with the identification and mapping of 66 other human cDNA clones with homology to known mutant *Drosophila* genes (Banfi et al. *Nat Genet* 1996;13:167-74). Further advances from this

bottom-up approach to candidate gene identification can therefore be expected.

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X-linked Alport syndrome: an SSCP-based mutation survey over all 51 exons of the COL4A5 gene

Renier A, Bruttini M, Galli L, et al. *Am J Hum Genet* 1996;58:1192-204.

X linked Alport's syndrome (hereditary nephritis with deafness and characteristic ophthalmological signs) is caused by mutations in the COL4A5 gene which codes for the $\alpha 5$ chain of type IV collagen. The gene was cloned in 1990 but, in common with other disorders caused by a faulty collagen gene, mutation detection is difficult because collagen genes are large (COL4A5 has 51 exons). On average, about 15% of patients with X linked Alport's syndrome (AS) have been found to have large deletions which are detectable by Southern blotting. Around 25% have smaller mutations, and most groups researching in this area have achieved a mutation detection rate of up to 40% in total using a variety of mutation detection strategies. In this paper the authors report the first large scale study using systematic analysis of all 51 exons of COL4A5 in 201 Italian patients with AS. Overall they detected nine major rearrangements and 48 small mutations, the latter comprising 10 glycine substitutions in the triple helical domain of the protein, nine frameshift mutations, four in frame deletions, one start codon, one nonsense and five splice site mutations. These mutations were either unique, or found in just two apparently unrelated kindreds. Overall the mutation detection rate in patients with certain or probable X linked AS was 45%, just 5% higher than the international average. So where are the remaining 55% of the mutations? (Linkage studies suggest that all X linked families map to the same locus.) Either there is a significant number of mutations in the non-coding segments of COL4A5, or there is another gene very close by which is also involved.

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