Medical genetics: advances in brief

The mutational spectrum in Treacher Collins syndrome reveals a predominance of mutations that create a premature-termination codon. Edwards SJ, Gladwin AJ, Dixon MJ. *Am J Hum Genet* 1997;60:515-24. (*J Med Genet* 1997;34:700)

Treacher Collins syndrome (TCS) is an autosomal dominant disorder of craniofacial development which affects about 1 in 50 000 live births. It causes symmetrical abnormalities of: (1) the ears, including abnormalities of the external ears, malformation of the middle ear ossicles, and conductive hearing loss; (2) lateral downward sloping of the palpebral fissures, often with colobomata of the lower eyelid; (3) hypoplasia of the mandible and zygomatic complex; (4) cleft palate. Complete non-penetrance is rare, but gene expression is very variable, which can make genetic counselling difficult, particularly as about 60% of cases appear to represent new mutations. The TCS locus was mapped to 5q31-34 in 1991, and positionally cloned in 1996. More recently the 3' and 5' ends have been identified, and the complete genomic organisation of the gene elucidated. Ten mutations were reported initially, and in this paper a further 25 are described, representing an overall mutation detection rate of 60%. The latest 25 mutations are spread across the gene, and all but one of the 35 mutations described so far result in the introduction of a premature termination codon into the predicted protein treacle. Seven different families have a common 5 bp deletion in exon 24, and two families have a recurrent splicing mutation in intron 3, but the remaining 26 families have family specific mutations. Eight of the 35 mutations described are sporadic and each of these is unique. The authors suggest that the mutational spectrum supports the hypothesis that TCS results from haploinsufficiency. They also postulate that other acrofacial dysostoses (such as Nager and Miller syndromes) and hemifacial microsomia/Goldenhar syndrome could result from mutations within the same gene, given that a number of the craniosynostoses have been shown to be allelic. (In the first

arch mouse mutant *far*, the same mutation may result in either bilateral or unilateral features, depending on the genetic background on which the mutation is placed.)

FRANCES FLINTER

Unstable insertion in the 5' flanking region of the cystatin B gene is the most common mutation in progressive myoclonus epilepsy type 1, EPM1. Lafrenière RG, Rochefort DL, Chrétien N, et al. *Nat Genet* 1997;15:3:298-302.

Unstable minisatellite expansion causing recessively inherited myoclonus epilepsy, EPM1. Virtaneva K, D'Amato E, Miao J, et al. *Nat Genet* 1997;15:4:393-6.

These papers describe the identification of a minisatellite repeat sequence expansion which causes myoclonus epilepsy type 1 (EPM1), an autosomal recessive disorder. The expanded sequence is present in most patients studied in both Finnish and Mediterranean populations. It maps to a GC rich polymorphic tandem repeat sequence at the 5' end of the cystatin 2B gene on chromosome 21q22.3 and results in decreased cystatin B expression although the causative mechanism is unclear. Expansion lengths in affected subjects range from 0.5-1.5 kb but no obvious correlation between expansion size and disease severity was found. Unlike trinucleotide repeat expansions there was no evidence of intergenerational instability and there appears to be no anticipation or threshold effect. However, different sized alleles with the same flanking haplotype were detected on different affected chromosomes suggesting some instability over the course of many generations. Minisatellite repeat alleles have previously been shown to influence transcription of the insulin and H-ras genes but in these cases large repeat expansions are not involved. A minisatellite expansion causing the common fragile site FRA16B has been recently reported and this is more analogous to the EPM1 mutation. However,

the EPM1 site is the first documented example of a large minisatellite expansion associated with a recognised disease phenotype.

DAVID O ROBINSON

Gene locus for autosomal recessive distal myopathy with rimmed vacuoles maps to chromosome 9. Ikeuchi T, et al. *Ann Neurol* 1997;41:432-7.

Various types of hereditary inclusion body myopathies map to chromosome 9p1-q1. Argov Z, et al. *Ann Neurol* 1997;41:548-50.

It may come as a surprise to many that the most common primary muscle disease in patients over the age of 50 is inclusion body myositis, a sporadically occurring chronic polymyositis pathologically characterised by the presence of vacuoles and filamentous inclusion within muscle fibres. Interestingly, the abnormal muscle fibres contain accumulations of proteins which are strikingly similar to those found in the Alzheimer's disease brain. A group of hereditary myopathies have virtually identical pathological findings, the hereditary inclusion body myopathies (h-IBMs). Gene localisation to chromosome 9p was reported in 1996 for autosomal recessive h-IBM in Iranian-Jewish families, and the papers above report the same gene location for further autosomal recessive families with very similar clinical and pathological features, but different ethnic origins. All of the families showing linkage to chromosome 9 have had disease which spares the quadriceps muscles, and another family with autosomal recessive h-IBM with quadriceps involvement has not shown linkage to this locus. In view of these findings and the striking similarity in pathology between sporadic inclusion body myositis and h-IBM, the characteristic vacuolation and protein accumulation may be a "final common pathway" for processes with a variety of different genetic and perhaps environmental triggers. Might these cellular processes have similarities to those involved in Alzheimer's disease?

EVAN REID