

## MEDICAL GENETICS: ADVANCES IN BRIEF

### Expression of Xist during mouse development suggests a role in the initiation of X chromosome inactivation

Kay GF, Penny GD, Patel D, Ashworth A, Brockdorff N, Rastan S. *Cell* 1993; 72:171-82.

This paper reports a possible causative role for the Xist gene in inactivation of one of the two X chromosomes in female mammals. This gene has been previously shown to map to the X inactivating centre (Xic) region and found to be expressed exclusively from the inactive chromosome. Kay *et al* have investigated the expression of Xist in developing mouse embryo and shown that it precedes the first detection of X inactivation suggesting that it may be involved in initiating this process. The expression of Xist is imprinted in the very early stages of development such that only the paternal Xist is expressed. This may explain the non-random inactivation of the paternal X chromosome in the trophoblast and primitive endoderm at this stage. Furthermore, the Xist imprint is lost shortly before gastrulation and the onset of random X inactivation in the embryonic lineage. Alleles at the X chromosome controlling element (Xce), which have previously been shown to influence which X is inactivated, also affect imprinted Xist expression. In female embryonic stem (ES) cells in vitro, Xist expression also coincides with the onset of differentiation and X inactivation, mirroring the situation in vivo. These interesting findings suggest a causative role for Xist in X inactivation. Investigation of factors regulating Xist expression should provide valuable insights into the mechanism of X inactivation.

N S THAKKER

### Direct diagnosis of myotonic dystrophy with a disease-specific DNA marker

Shelbourne P, Davies J, Buxton J, *et al*. *N Engl J Med* 1993;328:471-5.

### Reverse mutation in myotonic dystrophy

Brunner HG, Jansen G, Nillesen W, *et al*. *N Engl J Med* 1993;328:476-9.

Since the identification of a specific expanded unstable CTG repeat in patients with myotonic dystrophy (DM), mutation analysis has increasingly replaced linkage analysis combined with EMG and slit lamp studies for presymptomatic diagnosis of DM. The size of the expanded insert often increases between one generation and the next, especially during oogenesis, largely explaining the maternal transmission of congenital DM. In the first paper DNA extracted from 112 unrelated patients with DM and their families was analysed after Southern blotting and amplification by polymerase chain reaction. Probe p5B1.4 allowed direct identification of the DM mutation in 108 of the 112 patients. In three families for whom the clinical and genetic data obtained by linkage were ambiguous, p5B1.4 identified presymptomatic subjects. In one family

the size of the unstable fragment decreased on transmission to offspring, who remained asymptomatic. In the second paper two further families are described in whom the at risk haplotype for close flanking markers was transmitted without the expansion and without symptoms or signs occurring. This confirms that the CTG repeat can decrease in size between generations. So far this has only been shown for spermatogenesis and not for oogenesis. A few families with DM have an as yet unidentified mutation in the same gene and traditional methods of diagnosis remain useful.

ANDREW NORMAN

### Mutations in the Cu/Zn superoxide dismutase gene are associated with familial amyotrophic lateral sclerosis

Rosen DR, Siddique T, Patterson D, *et al*. *Nature* 1993;362:59-62.

Little is known about the aetiology of motor neurone disease (MND), one of the most distressing of all illnesses, and there is no effective treatment. This paper illustrates the value of studying rare familial examples of usually sporadic diseases, and offers an important conceptual breakthrough in understanding what causes MND. Previous studies had shown linkage of the disease to chromosome 21q in some, but not all, families: in particular the cytosolic Cu/Zn superoxide dismutase (SOD1) gene showed no recombination in six families likely to be 21q linked. Rosen *et al* decided to look for mutations in SOD1 using single strand conformational polymorphism (SSCP) analysis and DNA sequencing. This 'candidate gene' approach was a brave move, because the upper confidence limit for the recombination fraction was still over 10%! Amazingly, the authors detected 11 different missense mutations in 13 of approximately 150 families screened by this method, none of which was found in normal controls (an additional five SSCP variants were not sequenced). SOD1 is a well studied enzyme that catalyses the conversion of toxic superoxide radicals to hydrogen peroxide and oxygen. As well as the implications for understanding the pathogenesis of MND, this discovery suggests immediate therapeutic approaches to combating the illness - a gratifying and relatively unusual state of affairs for the identification of a new disease gene.

ANDREW WILKIE

### Intellectual development at age of 12 years of children with congenital hypothyroidism diagnosed by neonatal screening

Glorieux J, Dussault J, Van Vliet G. *J Pediatr* 1993;121:581-4.

Neonatal screening for congenital hypothyroidism (CH) has been carried out in most developed countries since the mid-1970s. This report from Quebec documents the developmental outcome of 27 12 year old children diagnosed with CH neonatally. For the purposes of the study 12 of the

children were classified as severe and 15 as moderate CH on the basis of their T<sub>4</sub> level (<26 nmol/l = severe) and area of knee epiphyses (<0.05 cm<sup>2</sup> = severe) at the time of diagnosis. The patients in these two subgroups did not differ in age at time of treatment, therapeutic follow up, or socioeconomic level. The Wechsler Intelligence Scale for Children was used for psychological assessment and where possible a sib of a similar age was used as a control (16/27). The results showed that children with moderate CH had good intellectual development with verbal, non-verbal, and global IQ scores on a par with their unaffected sibs. Children with severe CH, however, had significantly lower non-verbal (mean = 93) and global (mean = 88) IQs than their unaffected sibs and the children with moderate CH. These data are consistent with several previous reports of significant loss of IQ points in younger children with severe CH. Although these results must be considered encouraging for the children with the less severe form of the disease, strategies for improving the treatment of patients with severe CH must be sought. These include starting treatment at an earlier age or using higher initial doses of T<sub>4</sub> or both.

DAVID FITZPATRICK

### Congenital bilateral perisylvian syndrome: study of 31 patients

Kuzniecky R, Andermann F, Guerrini R, and the CBPS Multicenter Collaborative Study *Lancet* 1993;341:608-12.

Bilateral thickening of the cortex, with a pattern suggestive of polymicrogyria, affecting the opercular and perisylvian regions of the brain is reported in this paper. Although somewhat unclear from the methods, it appears that all 31 patients recruited had a congenital neurological disorder characterised by pseudobulbar palsy, cognitive defects, and diplegia of facial and masticatory muscles. Remarkably all 31 shared the distinctive radiological findings on MRI scanning. Clinical descriptions of approximately 200 patients with a broadly similar condition were first documented 40 years ago by Worster-Drought. The earlier report of Foix, Chavany, and Marie in 1926 emphasised a comparable clinical picture as an acquired phenomenon, now thought to be the result of bilateral cerebral infarctions affecting the opercular and perisylvian regions. At first glance this may appear an eccentric choice for review in a journal appealing largely to clinical geneticists. The aspect which this report glosses over is the familial observation of this syndrome in this report (one sib pair and possibly an uncle also affected) and a number of others hidden in genetic and neurological publications. This valuable paper is a milestone in the emergence of a specific syndrome, probably of heterogeneous aetiology, but with a definitive and hitherto unsung genetic component. A specific genetic study is required, but already the counselling implications are considerable.

W REARDON