

MEDICAL GENETICS: ADVANCES IN BRIEF

X-linked borderline mental retardation with prominent behavioural disturbance: phenotype, genetic localization, and evidence for disturbed monoamine metabolism

Brunner HG, Nelen MR, Van Zandvoort P, *et al.* *Am J Hum Genet* 1993;52:1032-9.

The behavioural disturbance referred to in the above title takes the form of aggressive episodes in mildly mentally retarded men who are normally shy and withdrawn. Actions carried out during the periods of aggression included grievous bodily harm, rape, and arson. The episodes followed triggering events but were out of proportion to those events. Each episode lasted one to three days during which the subject slept little. Metabolic studies in three affected males, presumably not during an aggressive episode, showed increased urinary levels of monoamine oxidase substances (normetanephrine, tyramine, 3 methoxytyramine) and decreased levels of monoamine oxidase products (vanilacetic acid, 5 hydroxyindole acetic acid). Platelet monoamine oxidase B activity was normal implying an abnormality in platelet monoamine oxidase A. In support of this in a linkage study no recombinations were found between affected status and a CA repeat within the MAOA gene with a two point lod score of 2.635. An aspect not discussed in the paper but of obvious practical importance is whether identification of the metabolic defect opens the prospect for treatment to prevent such outbursts. If further studies show that the metabolic abnormality in this large Dutch family is present in even a small proportion of male offenders and if therapeutic intervention would alter the behaviour, the ethical and legal implications are far reaching.

JUDITH GOODSHIP

Molecular genetic heterogeneity of myophosphorylase deficiency (McArdle's disease)

Seichi T, Shanske S, DiMauro S. *N Engl J Med* 1993;329:241-5.

Myophosphorylase deficiency (McArdle's disease) is one of the most common causes of exercise intolerance, muscle cramps, and recurrent myoglobinuria. The myophosphorylase gene has been sequenced and assigned to 11q13. The authors extracted RNA from muscle biopsy specimens from four patients with McArdle's disease and amplified and sequenced the myophosphorylase gene cDNA. Three point mutations were identified. Primers were designed for PCR amplification of the regions of genomic DNA containing these three mutations. A further 40 patients were then screened for these mutations by restriction analysis and the results confirmed by sequencing the PCR fragments. Eighteen patients were homozygous for a stop codon mutation in exon 1, six were compound heterozygotes for the known mutations, and 11 were presumed compound heterozygotes for a known and an unknown mutation; only five patients had none of the three mutations. Five members of a family with pseudodominant transmission had various combinations of the three mutations. The authors state that their results suggest that the diagnosis of McArdle's disease can

be made from study of DNA extracted from peripheral blood without the need for muscle biopsy in about 90% of patients. However, this implies that the diagnosis will be accepted in the presence of appropriate symptoms and only one allele with a known mutation. In practice, 60% of patients should be diagnosed using the three known mutations, and muscle biopsy would still be necessary in the remaining 40%, until further mutations have been described.

ANDREW NORMAN

Mitochondrial gene mutation in islet-cell-antibody-positive patients who were initially non-insulin-dependent diabetics

Oka Y, Katagiri H, Yazaki Y, Murase T, Kobayashi T. *Lancet* 1993;342:527-8.

Point mutation at position 3243 of the mitochondrial genome involving the tRNA leucine gene, common in patients with MELAS, has now been documented as a heteroplasmic finding in several pedigrees presenting with diabetes mellitus with or without deafness. Noteworthy among the families so described has been the interindividual variability in the profile of the diabetes. This has ranged from clinical presentation in the teenage years to the sixth decade and therapeutic requirements ranging from dietary control to insulin requirement against a clinical background of non-insulin dependency to insulin dependency. The apparent message is that the beta islet cells in these patients are undergoing a progressive exhaustion, presumably as a function of the mutation and the proportion of mutated mitochondria in the pancreatic beta islet cells. Oka *et al* now report three patients, aged 21, 50, and 54, with the 3243 mutation. All three were islet cell antibody positive, a state more commonly seen in insulin dependent diabetes, and progressed to insulin dependency in a short time. This observation suggests that the mitochondrial mutation may underlie the positive antibody status, at least in these patients, and that the autoimmune response may be consequent on the mtDNA 3243 mutation. This remarkable observation is almost submerged in a paper which adheres rigidly to traditional diabetological terms. Surely glucose intolerance is no more than a final common pathway for a multitude of genetic mutations. As the molecular and cellular processes emerge, traditional terms need to be seen as having occupied a position of transient value in the leap from ignorance to understanding. Recognition of the limited value of traditional concepts is vital if the true worth of future molecular observations in diabetology is to be highlighted appropriately.

W REARDON

Isolation of a Miller-Dieker lissencephaly gene containing G protein β -subunit-like repeats

Reiner O, Carrozzo R, Shen Y, *et al.* *Nature* 1993;364:717-21.

Miller-Dieker syndrome (MDS) comprises the association of lissencephaly (absent or

reduced brain gyri) with facial dysmorphism. Work from Ledbetter's laboratory previously showed that MDS and isolated lissencephaly were associated with deletions of chromosome band 17p13.3 in 90% and 15% of cases respectively. This suggested that a gene involved in neuronal migration mapped to this region, and that the MDS phenotype might represent a 'contiguous gene syndrome' (CGS) resulting from the deletion of additional neighbouring genes. This paper, from the same laboratory, describes the isolation of a candidate MDS gene, termed *LIS-1*. The primary evidence for its identification is that *LIS-1* cDNA spans between two large non-overlapping deletions present in different MDS patients that extend outside the gene in opposite directions. Northern blot and DNA sequence analysis of *LIS-1* show that it is expressed in brain and contains tandem repeats homologous to members of the β -transducin family, involved in signal transduction. Nevertheless, the evidence would be more convincing if the authors had shown an intragenic mutation in one of their patients: the involvement of a closely adjacent or intronic gene is not excluded. At face value, the results suggest that all the features of MDS are explained by haploinsufficiency of *LIS-1* alone, indicating that it is not a CGS, but results from the pleiotropic effects of a single gene; but then why do other patients with similar deletions have isolated lissencephaly alone?

ANDREW WILKIE

Amyotrophic lateral sclerosis and structural defects in Cu, Zn superoxide dismutase

Deng H-X, Hentati A, Tainer JA, *et al.* *Science* 1993;261:1047-51.

Amyotrophic lateral sclerosis (ALS) or motor neurone disease is a progressive and usually fatal degeneration of CNS motor neurones with onset in middle age. Members of this team have already shown that one of the autosomal dominant familial forms of ALS is caused by defects in the superoxide dismutase (SOD1) gene which codes for an enzyme responsible for the processing of free radicals and which was mapped long ago to chromosome 21. Now these authors have identified 12 point mutations distributed over four of the SOD1 gene's five exons by using a single strand conformational polymorphism approach. SOD is a dimeric enzyme and a model of its structure derived from crystallographic studies allows the authors to predict that each mutation disrupts conserved sequences essential for the three dimensional structure of both dimer subunits or the interface between them. Interactions between wild type and mutant subunits may explain the dominance of familial ALS and the reduction of red cell enzyme activity to less than 50% in the 15 heterozygotes tested. The authors propose that free radical generating toxins or protective enzymes may contribute to the 90% of ALS cases which are sporadic, inherited forms of ALS which are not linked to chromosome 21, and neurodegenerative diseases other than ALS.

JOHN C K BARBER