Medical genetics: advances in brief

Complete restoration of a wild-type mtDNA genotype in regenerating muscle fibres in a patient with a tRNA point mutation and mitochondrial encephalomyopathy

Shoubridge EA, Johns T, Karpati G. *Hum Mol Genet* 1997;6:2239-42.

A variety of mutations in the 16.5 kb mitochondrial genome have now been reported in a range of multisystem disorders, many of which have major neurological or neuromuscular features. Typically, pathological mutations are heteroplasmic, that is both mutant and wild type mtDNA is present within the same cell. The clinical involvement of different tissues is thought to depend largely on whether the proportion of mutated to wild type mtDNA exceeds certain thresholds. In several mtDNA muscle diseases, wide variation between tissues has been observed. For example, in sporadic patients with large scale mtDNA deletions causing Kearns-Sayre syndrome (KSS) and other sporadic patients with tRNA point mutations, mutant mtDNA is characteristically rare or undetectable in unaffected tissues such as lymphocytes or fibroblasts, but abundant in affected skeletal muscle. Interestingly, in such patients, progenitor myogenic cells (satellite cells) which are responsible for muscle regeneration following damage or necrosis have been found to harbour very low or undetectable levels of mutant mtDNA. These authors describe a patient with KSS in whom they had previously found a point mutation in the mitochondrial tRNA^{eu(CUN)} gene. Increased muscle disease severity is associated with an increase in the proportion of fibres failing to stain for cytochrome c oxidase (COX), a respiratory chain component. In biopsies from two different sites in this patient, COX -ve muscle fibres contained around 95% mutant mtDNA while normal COX +ve fibres contained from 11-90% mutant mtDNA. Mutant mtDNA was undetectable in the satellite cells or blood. On rebiopsy at the same site three weeks later, regenerating fibres which could be distinguished by their morphological and immunohistochemical characteristics were all found to be COX +ve and had undetectable levels of mutant mtDNA. Very similar results have been reported recently in an unrelated patient with a different mutation in the tRNA^{eu(CUN)} gene following chemically induced localised muscle destruction (Clark KM *et al*, *Nat Genet* 1997;16:222-4). The authors discuss that the progressive nature of most mitochondrial neuromuscular disease appears to re-

flect an age related increase in the proportion of mutant mtDNA in skeletal muscle. To date the outcome of medical therapies for most mitochondrial disorders has been disappointing. Their results raise the interesting possibility that encouraging proliferation of satellite cells may ameliorate the muscle disease in patients with these types of mtDNA mutation. In the first instance they suggest trials of eccentric muscle contractions which are known to produce microscopic muscle damage repaired by satellite cells rather than the use of myotoxic agents.

LOUISE WILSON

An activating splice donor mutation in the thrombopoietin gene causes hereditary thrombocythaemia

Wiestner A, Schlemper R, van der Maas A, Skoda R. *Nat Genet* 1997;18:1:49-52.

Hereditary thrombocythaemia with AD transmission is a chronic myeloproliferative syndrome owing to sustained proliferation of megakaryocytes resulting in increased circulating platelets and thrombotic or haemorrhagic episodes. The knowledge that the thrombopoietin gene (THPO) encodes a lineage restricted growth factor which stimulates megakaryopoiesis and platelet production prompted Wiestner *et al* to analyse the THPO gene in a family with high penetrance and early age of onset of the condition. Affected subjects had raised THPO protein levels and a G>C transversion in the splice donor site of intron 3 of the gene. Mutations in GT splice donor sites cause either intron retention, exon skipping, or cryptic splice donor site activation. The authors did not have access to tissues expressing THPO, such as liver, kidney, or bone marrow, and were unable to detect ectopic THPO transcripts by RT-PCR in leucocytes. They therefore constructed a cosmid library from genomic DNA of the proband and identified clones containing the normal and mutated allele. Transfection into a hepatic cell line showed the mutant mRNA to exhibit exon 3 skipping and intron 3 retention, changing the signal peptide sequence but not the protein sequence. This resulted in overproduction of THPO protein, and in vitro translation analysis showed this to be because of increased translational efficiency. However, the authors speculate that such mutations may not commonly cause thrombocythaemia in isolated cases because somatic mutations in single liver cells are unlikely to overproduce THPO protein sufficiently. The authors have been resourceful in analysing the

expression profile of a mutant gene directly from an affected subject without access to expressing tissues, and have identified an interesting class of mutation causing overexpression of a gene.

DAVID O ROBINSON

Fragile X premutations are not a cause of early menopause

Kenneson A, Cramer DW, Warren ST. *Am J Hum Genet* 1998;61:1362-9.

Fragile X syndrome is caused by an expansion of the CGC repeat tract at the 5' untranslated region of the FMR1 gene. Normal alleles have 6-54 repeats, unstable premutation alleles 50-200 repeats (which are susceptible to expansion when passed on from a female carrier), and full mutation alleles have >230 repeats. The general population incidence of carriers of the premutation is 1 in 253 women. For the past decade it has been thought that there may be an increased incidence of ovarian dysfunction among carriers of the fragile X premutation. Ovarian response to exogenous stimulation was reported to be decreased in fragile X carriers, and DZ twinning was found to be increased (in one study in premutation carriers but not full mutation carriers); however another study found no significant difference in the twinning rate between fragile X carriers and haemophilia A carriers. There have also been reports of premature ovarian failure (menopause <40 years) cosegregating with a fragile X premutation in families. Several of these studies have been hampered by ascertainment problems, however. In this study 216 women with early menopause (<47 years), of whom 33 had premature menopause (<40 years), and 107 control women were screened for the fragile X mutation. No full mutation alleles were found and the only premutation allele occurred in a woman from the control group. These results are consistent with what would be expected purely on the basis of chance. The sample size was sufficient to rule out a >13-fold increased risk of early menopause and a >19-fold increased risk of premature menopause because of an FMR1 premutation. Before any final conclusions can be drawn it will be necessary to consider the results of other similar studies which are under way elsewhere, but meanwhile it is not clear whether or not the possibility of a premature or early menopause should be routinely mentioned to women who are premutation carriers.

FRANCES A FLINTER