WEB WATCH

The gene trust

There is a lot of debate about the best way to find genes for complex diseases. But one thing seems certain — you need a very large patient population. Since August, DNA Sciences have been recruiting volunteers to donate blood samples for their screening programmes via the web — so far around 4,500 Americans have signed up.

DNA Sciences have dubbed this initiative the Gene Trust. Interested individuals are asked to fill in a questionnaire about their health and family history, and if their phenotype matches one that DNA Sciences is studying, the individual is invited to provide a blood sample for DNA analysis.

Ray White has recently been appointed as the Chief Scientific Officer at DNA Sciences, and an interview with Dr White — conducted by BioResearch Online — can be heard on the web.

All data collected by DNA Sciences are made anonymous, to protect the participants' identities, and the company has established the Kiva Genetics Foundation to study the wider ethical and societal issues raised by research into the genetics of complex disease.

Talking heads

Subscribers to the magazine Prospect can claim a copy of the human genome on CD with their October issue. The CD has been produced in collaboration with the Sanger Centre, Cambridge UK. The offering is accompanied on the web by the transcript of a conversation about the significance of the human genome project between such genetic luminaries as Jim Watson, Peter Goodfellow, Steve Jones, Steven Rose and Robert Plomin, the philosopher Nancy Cartwright and a British politician — Geoff Mulgan.

Mark Patterson

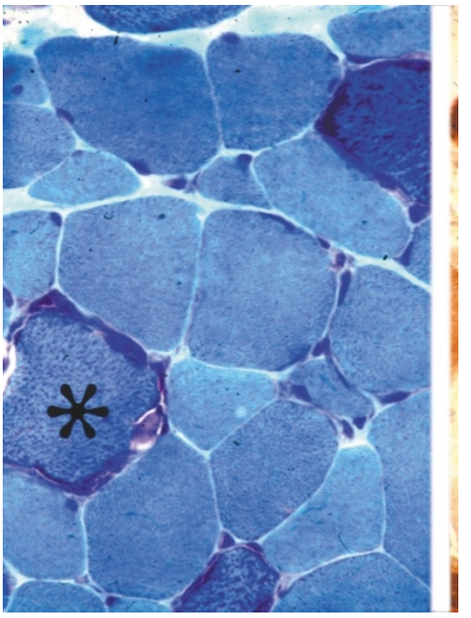
MITOCHONDRIAL GENETICS

A clever way to model defects…

Mutations in mitochondrial (mt) DNA underlie several sporadic human disorders but also accumulate throughout life and are associated with age-related illnesses and neurodegenerative disease. However, proving the pathological consequences of these mutations has been a challenge because it is not possible to introduce stable mtDNA mutations into mammalian cells. Inoue *et al.* have now side-stepped this technical difficulty to generate the first mouse model of a deletion in mtDNA.

The key to the authors' success was to isolate naturally occurring mtDNA mutations. This they did by fusing enucleated cells — prepared from mouse brain synaptosomes and carrying a mixed (heteroplasmic) population of mutated and wild-type mtDNA — with cells depleted of mtDNA, to make a cytoplasmic hybrid (cybrid) cell line. One cybrid clone was identified that carried a 4,696-base-pair mtDNA deletion, which removed six tRNA genes and seven structural genes. To generate mice with this deletion, the cybrid cells were enucleated, fused to pronuclear-stage embryos, and transplanted to female mice. Of 111 resulting newborn mice, 24 were heteroplasmic and, of these, five females — with varying loads of the deletion (5.7–13%) — transmitted the deletion to their offspring.

To investigate how closely the progeny of these mice modelled human mitochondrial disorders, the authors tested the mice for respiratory-chain function and for ragged red fibres (RRFs) in skeletal muscle, a feature caused by the accumulation of abnormal mitochondria. (The accompanying image shows muscle fibres from a person with a mtDNA deletion — the left asterix marks a RRF and the right one shows the loss of cytochrome *c* oxidase activity in the same fibre). Although the skeletal and cardiac muscles of mice with high loads of the deleted mtDNA were mosaic for respiratory-chain function, as is often seen in human mitochondrial disorders, typical skeletal RRFs, as well as other fea-



Courtesy of Ikuya Nonaka and Jun-Ichi Hayashi,

MITOCHONDRIAL GENETICS

… and a new way to rescue them

The mitochondrion has cut back its genome substantially since taking up residence in cells as a symbiont 1.5 billion years ago, but it retains its personal transcription, translation and protein-assembling systems, including its tRNA genes. Even so, the mitochondrion is not fully self-sufficient — to varying extents yeast, plants and protozoan cells can borrow nuclear-encoded tRNA molecules to ease the task of translating transcripts of their mitochondrial genes. New data indicate that nuclear-encoded tRNAs can even be used to salvage errors in mitochondrial transcripts.

In the yeast *Saccharomyces cerevisiae*, only one tRNA ($tRNA^{Lys}_{CUU}$) is carried into the mitochondrion, something it can do only if charged with an amino acid, and only if aided by cytosolic import factors. Among these factors is the precursor of the mitochondrial lysyl-tRNA synthetase (pre-MSK).

In the new work, researchers altered the aminoacylation identity of $tRNA^{Lys}_{CUU}$ so that it was charged with methionine rather than lysine. Both in live yeast cells and in isolated mitochondria, the engineered tRNA could enter the mitochondrion, where the radiolabelled methionine charged on the imported tRNA was incorporated normally into mitochondrial proteins. A second, modified $tRNA^{Lys}$ version with alanine identity was also successfully used *in vivo* to suppress an *amber* (UAG) stop codon (a nonsense mutation) in the mitochondrial *COX2* gene.

Defects in mitochondrial (mt) DNA, caused by base substitutions or rearrangements in genes that encode proteins or tRNAs, underlie a range of human pathologies (as discussed in the highlight above).

Could the technique used to modify mitochondrial mutations be adapted for use in humans, given that import of nuclear-encoded tRNAs into mammalian mitochondria has never been seen? It seems so, because isolated