

MEDICAL GENETICS: ADVANCES IN BRIEF

Genetic determinants of airways' colonisation with *Pseudomonas aeruginosa* in cystic fibrosis

Kubesch P, Dork T, Wulbrand U, *et al.*
Lancet 1993; 341:189-93.

Some 10 to 15% of patients with cystic fibrosis retain adequate pancreatic function to be termed 'pancreatic sufficient'. This study of 267 affected patients has shown that the missense and splice site mutations, previously identified as 'low risk' with regard to pancreatic function, are also associated with a highly significant delay in colonisation of the bronchial tree by *Pseudomonas aeruginosa*. Although by no means the sole factor in determining onset of *Pseudomonas* colonisation, the genotype of the mutation has now been identified as a key determinant of basic risk of colonisation. In contrast, compound heterozygotes for $\Delta 508$ and mutation in the nucleotide binding fold encoding exons had universal pancreatic dysfunction and an increased risk of early onset *Pseudomonas* colonisation. The key feature of this study is the identification of relative high and low risk genotypes for *Pseudomonas* colonisation, a watershed in the downward spiral of respiratory compromise. An impressive body of clinical work over a 10 year period, meticulous attention to detail, and painstaking laboratory procedures in both bacteriological and genetic aspects form the backdrop to this study. The authors do not, however, share their vision as to possible benefits in clinical practice of their observations.

WILLIE REARDON

Identification of a second pseudo-autosomal region near the Xq and Yq telomeres

Freije D, Helms C, Watson MS,
Donis-Keller H. *Science* 1992;258:1784-7.

We have grown accustomed to the idea of a single pseudoautosomal region on the distal short arms of the human sex chromosomes with shared sequence homology, an obligatory chiasma at meiosis, and demonstrable levels of recombination. Knowing that cytogenetic interaction between distal Xq and Yq is sometimes seen at meiosis, and having already generated a YAC contig near the factor VIII gene which showed sequence homology between Xq and Yq, this team were able to identify two new polymorphic microsatellite markers, one within and the other just outside the region of homology. Thirty-two informative CEPH families were then used to show recombination between these new markers in four out of 195 meioses. A second pseudoautosomal region is therefore indicated, as reported by these authors at the American Society of Genetics Meeting in November 1992. These findings raise many interesting questions. Can an occasional chiasma account for the 2% recombination between physically close markers. Could the new region play a role in the meiotic arrest associated with interaction between the sex vesicle and some cytogenetic rearrangements? Does this region at the tip

of the X and distal to the Y heterochromatin contain genes and would imbalance of these produce a distinct phenotype?

JOHN C K BARBER

Mosaicism for a specific somatic mitochondrial DNA mutation in adult human brain

Soong NW, Hinton DR, Cortopassi G,
Arnheim N. *Nature Genet* 1992;2:318-23.

Mitochondrial DNA deletions in human brain: regional variability and increase with advanced age

Corral-Debrinski M, Horton T, Lott MT,
Shoffner JM, Beal MF, Wallace DC.
Nature Genet 1992;2:324-9.

The cause of ageing must be one of the oldest scientific puzzles. Generally, big slow organisms age less rapidly than little fast ones, but why? A possible connection with basal metabolic rate was reinforced by the finding that mitochondrial function declines with age in liver and muscle. Furthermore, mosaic deletion of segments of mitochondrial (mt) DNA (notably a specific 4977 nucleotide (nt) deletion, arising from a repeated sequence motif) has been shown in certain neuromuscular conditions, notably progressive external ophthalmoplegia and Kearns-Sayre syndrome. Using a sensitive polymerase chain reaction method to look for low levels of the 4977 nt deletion, two groups have now examined the brains of normal subjects dying at various ages. Both report that the deleted mtDNA is readily detectable and the amount increases progressively with age. The proportion of deleted mtDNA varies in different parts of the brain, being highest (possibly up to 12%) in the subcortical nuclei (substantia nigra, putamen, and globus pallidus) and lowest in the cerebellum. Is this the answer to ageing? As pointed out in an editorial by A Harding, patients with recognised mtDNA diseases do not show features of premature ageing; instead, the observations might simply reflect the tendency for all tissues to accumulate mutations, both nuclear and mitochondrial, with time. So perhaps those awaiting the invention of an elixir of life will just have to grow a little older.

ANDREW WILKIE

Prevention of the first occurrence of neural-tube defects by periconceptual vitamin supplementation

Czeizel A, Dudás I. *N Engl J Med*
1992;327:1832-5.

The risk of recurrent neural tube defect (NTD) is reduced in women who take folic acid during the periconceptual period. The extent to which supplementation can reduce first occurrence of such defects is not known. In this Hungarian study women planning a pregnancy (mostly their first) were randomised to receive either a single multivitamin tablet containing 0.8 mg folic acid or a tablet containing trace elements and

a low dose of vitamin C daily for at least one month before conception, continuing until the second missed period or later. Pregnancy was confirmed in 4753 women. The outcome was known in 2104 women in the multivitamin supplemented group and 2052 women in the non-vitamin supplemented group. Congenital malformations were significantly more prevalent in the latter group (22.9 per 1000 *v* 13.3 per 1000, $p=0.02$). NTD occurred in six of the pregnancies, none of which had received multivitamin plus folic acid tablets ($p=0.029$). However, the prevalence of cleft lip with and without cleft palate was the same in both groups. Periconceptual vitamin use decreases the incidence of first occurrence of NTD. It is likely that folic acid is the important ingredient. The recent publication from an expert advisory group of the UK Departments of Health, *Folic acid and the prevention of neural tube defects*, recommended 0.4 mg folic acid daily as a periconceptual medicinal or food supplement. Clearly, further investigation is needed to determine the optimum dose and means of administration of folic acid for this purpose.

ANDREW NORMAN

A mammalian cell cycle checkpoint utilizing p53 and GADD45 is defective in ataxia-telangiectasia

Kastan MB, Zhan Q, El-Deiry WS, *et al.*
Cell 1992;71:587-97.

Previous studies indicate that the tumour suppressor gene p53 plays a critical part in G1 arrest that follows exposure to DNA damaging agents. Such cell cycle delays are thought to be important in allowing DNA repair before DNA replication and chromosomal segregation. Cells with abnormal p53 genes and cells from ataxia-telangiectasia (AT) patients both fail to arrest in G1 after DNA damage. This paper reports a role for p53 in signal transduction pathway that controls the cell cycle arrest after DNA damage and shows that this pathway is defective in AT cells. AT cells failed to show an increase in p53 protein levels suggesting that the normal AT gene products may be involved in p53 induction after DNA damage. Cells with abnormal p53, like AT cells, were also shown to be deficient in induction of the growth arrest and DNA damage inducible (GADD) gene, GADD45. Furthermore p53 binding by the wild type but not the mutant form to a conserved sequence in GADD45 gene was shown. This suggests that p53 may be involved in the induction of GADD45 and other GADD genes which regulate the G1 arrest. These observations indicate a shared physiological pathway between AT gene products and p53 and are interesting in view of the high incidence of lymphoid malignancies in both AT patients and p53 deficient mice. It is likely that cells with abnormalities of this pathway will have a greater chance of developing heritable DNA abnormalities after DNA damage.

N S THAKKER