MEDICAL GENETICS: ADVANCES IN BRIEF

Mitochondrial ribosomal RNA mutation associated with both antibiotic-induced and non-syndromic deafness

Prezant TR, Agopian JV, Bohlman MC, *et al.* *Nature Genet* 1993;4:289-94.

Mutations of mitochondrial (mt) DNA have recently been identified in patients with sensorineural deafness and diabetes mellitus. Last year, the description in this Journal of a six generation pedigree (including 55 affected subjects) with exclusively maternally transmitted deafness further strengthened the link between hearing loss and mt disease (*J Med Genet* 1992;29:86-90). The present paper describes the sequencing of the mtDNA in two subjects from this pedigree, together with the investigation of three Chinese families segregating for maternally inherited, aminoglycoside induced deafness. Many sequence alterations were identified, most of which could be explained as natural polymorphisms or previous sequencing errors. However, one point mutation was found in all four families, a 1555 A to G substitution in the 12S rRNA gene. Functional evidence strongly suggests that this mutation is causally related to the deafness. It lies in that part of the ribosome to which aminoglycosides bind when altering translational fidelity in prokaryotes (mitochondria are thought to be evolutionary relics of symbiotic bacteria), and two point mutations of the adjacent base pair have been observed in the small rRNAs of aminoglycoside resistant yeast mt and *Tetrahymena*. This work, if replicated, will provide a whole new dimension to pharmacogenetics: if mt DNA mutations are found in sporadic aminoglycoside induced deafness, the service implications will be enormous.

ANDREW WILKIE

Functional interaction of the retinoblastoma protein with mammalian D-type cyclins

Ewen ME, Sluss HK, Sherr CJ, Matsushime H, Kato J-Y, Livingstone DM. *Cell* 1993;73:487-97.

Physical interaction of the retinoblastoma protein with human D cyclins

Dowdy SF, Hinds PW, Louie K, Reed SI, Arnold A, Weinberg RA. *Cell* 1993;73:499-511

The retinoblastoma tumour suppressor protein (pRb) is a negative regulator of cell proliferation. Its activity is modulated by phosphorylation. Hypophosphorylated pRb is found in resting cells and in early stages of cell cycle and inhibits cell cycle progression. Removal of pRb induced block and progression through cell cycle is associated with pRB hyperphosphorylation. It is suggested that pRb can regulate cell cycle by binding growth promoting proteins such as E2F transcription factor which can only associate with pRb in its hypophosphorylated form. Binding of E2F prevents it from acting as a positive transcription element for genes involved in cell cycle progression. These two papers report physical and functional interaction of the pRb with a subtype (D) of a group of cellular proteins (cyclins) involved in cell cycle control. D type cyclins form complexes with pRb by binding to the same sites as DNA tumour virus oncoproteins. Some cyclins (for example, D2) appear to act by inducing hyperphosphorylation of pRb on binding, thus preventing its interaction with E2F. In contrast, other cyclins such as D1 are unable to phos-

phorylate pRb. Furthermore, the activity of D1 may be regulated by pRb in much the same way as E2F suggesting that D1 may have a similar role. These findings provide insight into the link between positive and negative regulators of cell cycle and are fascinating in view of the recent demonstration of cyclin D1 overexpression in a variety of epithelial and lymphoid tumours as a consequence of gene amplification events and translocations respectively. It may be that overproduction of the D1 proteins outstrips the ability of pRb to bind them, thus allowing cells to overcome pRb regulation of cell cycle.

N S THAKKER

Charcot-Marie-Tooth disease type 1A: association with a spontaneous mutation in the PMP22 gene

Roa BB, Garcia CA, Suter U, *et al.* *N Engl J Med* 1993;329:96-101.

Charcot-Marie-Tooth disease (CMT) is the most common inherited peripheral neuropathy. CMT type 1A is associated with a 1.5 Mb DNA duplication at 17p11.2-12 in most patients. The *PMP22* gene encodes a myelin protein and is mapped within the duplication. The myelin deficient *trembler* and *trembler^o* mouse models of CMT type 1 contain point mutations in murine *Pmp22*. This paper describes 32 unrelated patients with CMT type 1 characterised by neuropathological features, including hypertrophic neuropathy with 'onion bulb' formation and slowed motor nerve conduction, who did not have the 1.5 Mb tandem duplication of 17p11.2-12. A combination of PCR, heteroduplex analysis, and direct sequencing identified a C to G transversion leading to substitution of cysteine for serine in the 79th codon (S79C) of *PMP22* in one family. This substitution occurs in a putative transmembrane domain. A different *PMP22* point mutation has recently been described by Valentijn *et al* in *Nature Genetics*. The low frequency of *PMP22* mutations observed in patients without the duplication is probably the result of locus heterogeneity.

ANDREW NORMAN

Twin studies in medical research: can they tell us whether diseases are genetically determined?

Phillips DIW. *Lancet* 1993;341:1008-9. *Lancet* 1993;341:1418-19 (letters). *Lancet* 1993;342:52.

Twin studies revolve around the thesis that a higher disease concordance between monozygous than matched dizygous twins reflects a genetic contribution to the disease aetiology. Phillips challenges this doctrine, emphasising the importance of prenatal differences in environment and the effects of same on the interpretation of twin studies. In particular monozygotic twins have poorer fetal growth, higher perinatal mortality, and greater incidence of congenital malformation (not a universal finding) than do their dizygotic counterparts. Consequently Phillips contends that twin studies may be misleading in conditions where prenatal environment (as reflected in birth weight, for instance) is thought to contribute to disease aetiology. Such conditions would include hypertension and diabetes. Other authors disagree. The nub of the argument appears to be that Phillips believes that the adverse prenatal environment of monozygous twins relative to their dizygous counterparts will increase monozygotic concordance, thus overestimating gen-

etic contribution to a disease. In contrast, MacDonald and Duffy independently argue that differences in birth weight between monozygous twins lead to discordance, thereby reducing estimates of genetic contribution to disease aetiology. Phillips's counterargument is that birth weight variability between monozygous twins merely adds further to the difficulties in separating genetic from environmental influences, thereby underlining the inherently doubtful value of such studies as determinants of genetic contribution to disease. This interesting correspondence is hindered by the difficulties which epidemiologists have in clearly communicating the principles of the argument to the clinical audience. Nevertheless, I suspect that many clinical geneticists, particularly of the younger generation, have been so preoccupied by advances in molecular genetics of single gene disorders that insufficient deliberation has been given to longer established strategies such as twin and sib pair studies and their interpretation. This spirited exchange of views will prompt the motivated to a deeper excavation of such time honoured strategies.

WILLIE REARDON

Mice with null mutation of the TGF α gene have abnormal skin architecture, wavy hair and curly whiskers and often develop corneal inflammation

Mann GB, Fowler KJ, Gabriel A, Nice EC, Williams L, Dunn AR. *Cell* 1993;73:249-61.

TGF deficiency results in hair follicle and eye abnormalities in targeted and Waved-1 mice

Luetteke NC, Qiu TH, Peiffer RL, Oliver P, Smithies O, Lee DC. *Cell* 1993;73:263-78.

Transforming growth factor α (TGF α) is a member of the epidermal growth factor family and is expressed in a variety of normal tissues both in the adult and in the embryo. Functional roles for TGF α are implicated in wound healing, cell migration, angiogenesis, and cell differentiation. It is also expressed by neoplastic cells which also often coexpress EGF or the TGF α receptor suggesting the creation of autocrine loop which allows independent growth. These two papers report the changes in mice homologous for null mutations of the TGF α gene. The mouse gene was disrupted by homologous recombination in embryonic stem cells. The mice showed surprisingly few changes and were viable and fertile suggesting that recruitment of related molecules, that is, other members of the EGF family, may compensate for the lack of TGF α . The most pronounced and interesting changes were waviness of the coat and whiskers with derangement of the hair follicles. In addition, developmental abnormalities of the eye, open eyelids at birth, and corneal inflammation were observed in both the homozygous and, to a lesser extent, heterozygous mice. Waved-1 mice have been previously shown to have similar changes and both Northern analysis of TGF α expression in Wa-1 mice and crosses between the TGF disrupted mice and Wa-1 mice confirmed that Wa-1 and TGF α are allelic. These studies are interesting not only because they demonstrate the physiological roles of TGF α but also because they suggest that disruption of genes of such growth factors may be important in inherited conditions in which ectodermal dysgenesis is observed.

N S THAKKER