MEDICAL GENETICS: ADVANCES IN BRIEF

Maternal but not paternal transmission of 15q11-13-linked nondeletion Angelman syndrome leads to phenotypic expression

Wagstaff J, Knoll JHM, Glatt KA, Shugart YY, Sommer A, Lalande M. *Nature Genet* 1992;1:291-4.

The involvement of chromosome 15q11-13 mutations in two clinically distinct syndromes, those of Angelman (AS) and Prader-Willi (PWS), has provided several new insights in human genetics over the past few years, and represents perhaps the best example of imprinting effects in human disease. Most cases of PWS result from de novo paternal deletion or maternal uniparental disomy; about 60% of AS is caused by de novo maternal deletion, with a small contribution from paternal uniparental disomy. In the remaining ~40% of AS, however, neither of these mechanisms seems to occur: the identification of this group is particularly important because the recurrence risk may be higher, approaching 50%. Wagstaff *et al* now describe a very instructive family in which three clinically normal sisters have between them borne four offspring with AS, together with three healthy children. A fourth sister has had two healthy children. The authors show that the four affected children all share a 15q11-13 haplotype inherited from the maternal grandfather; the unaffected children have either inherited a grandmaternal haplotype, or (in a child of the fourth sister) the opposite haplotype from the maternal grandfather. As well as serving as a beautiful example of imprinting (the mutation must be transmitted through the female to be manifest), the family provides further evidence that non-deletion AS may be linked to 15q11-13 and that the locus is distinct from that for PWS.

ANDREW WILKIE

A cDNA encoding a pRB-binding protein with properties of the transcription factor E2F

Helin K, Lees JA, Vidal M, Dyson N, Harlow E, Fattay A. *Cell* 1992;70:337-50.

Expression cloning of a cDNA encoding a retinoblastoma binding protein with E2F-like properties

Kaelin WG Jr, Krek W, Sellers WR, *et al*. *Cell* 1992;70:351-64.

Recent evidence suggests that the retinoblastoma protein (pRB) plays an important role in the negative regulation of cell proliferation. However, details of how pRB exerts its functions have not been completely elucidated. A specific domain ('pocket') in pRB is a major target for both transforming viral oncoproteins and naturally occurring mutations, indicating functional significance for this region. Several cellular proteins have been identified that interact with the pRB pocket. Of these, the transcription factor E2F is most directly implicated in growth control. Both the papers report the cloning and characterisation of a cDNA encoding

a polypeptide (RBP3/RBAP-1) with properties of E2F. RBP3/RBAP-1 copurified with E2F and bound to pRB both in vivo and in vitro. The pRB binding was completed by viral oncoproteins known to bind to the pRB pocket. The expression of RBP3/RBAP-1 was shown to be cell cycle regulated. Like E2F, RBP3/RBAP-1 showed binding to adenovirus E4 protein and contains a transactivating domain. These findings suggest that RBP3/RBAP-1 is either E2F or a member of a family of E2F-like proteins. The availability of a cDNA encoding E2F or E2F-like protein should enable further investigation of the mechanisms involved in cell cycle regulation by pRB and E2F.

N S THAKKER

Antenatal maternal serum screening for Down's syndrome: results of a demonstration project

Wald NJ, Kennard A, Densem JW, *et al*. *BMJ* 1992;305:391-4.

The authors set out to assess how maternal serum screening for Down's syndrome worked in practice in hospital and community antenatal clinics; 12 603 women of all ages with singleton pregnancies were offered screening using the markers α fetoprotein, unconjugated oestriol, and human chorionic gonadotrophin, and combining results with maternal age to give an estimate of the risk of the fetus having Down's syndrome at term. Women with a risk estimate of 1 in 250 or greater were classified as screen positive and offered amniocentesis. Uptake of screening was 74%, with a detection rate for Down's syndrome of 48% (12/25), and false positive rate 4.1%, consistent with results expected from previous observational studies. Some cases may have been missed because ultrasound confirmation of gestational age was only routinely performed in screen positive cases, and the composite risk is dependent on accurate estimation of this variable. They suggest that if ultrasound confirmation is to be used it should be performed for all those who accept screening. Approximately a quarter of those who accepted serum screening initially declined amniocentesis when found to be screen positive and I think the reasons for this would be worthy of further study. Antenatal maternal serum screening should now become available throughout Britain.

ANDREW NORMAN

Six-year results of a randomised prospective trial of human growth hormone and oxandrolone in Turner syndrome

Rosenfeld RG, Frane J, Attie KM, *et al*. *J Pediatr* 1992;121:49-55.

Short stature is a serious and almost universal feature of Turner's syndrome. This paper reports the outcome of a multicentre study of the treatment of short stature in 70 girls with partial or complete monosomy X. To be

admitted to the study the girls had to have a karyotypic diagnosis with the ages at entry ranging from 4.7 to 12.4 years. All were at least 1 SD below the mean height for normal girls of equivalent chronological age, had annual growth velocities of <6 cm/year, and had serum growth hormone levels of >7 μ g/l. The subjects were randomly assigned to have (1) no treatment, (2) oxandrolone alone (0.125 mg/kg/day), (3) human growth hormone (hGH) alone (0.125 mg/kg three times per week), or (4) a combination of oxandrolone and hGH. However, after one to two years in the study the no treatment group was abandoned and the groups were changed to hGH alone (at the same weekly dose as above but in daily divided doses) or hGH and oxandrolone (now 0.0625 mg/kg/day). Subjects were reviewed every three months and the treatment was stopped when the skeletal age was >14 years. The results showed over a six year period there were significantly greater than baseline annual growth rates in both the group receiving hGH alone and those on combination therapy. This resulted in a 12.2 cm (hGH) and 18.3 cm (hGH + ox) increment over expected growth in these groups. In the 30 subjects whose therapy has now been terminated the mean final height is 151.9 cm (8.1 cm greater than the mean projected adult height). This study has not attempted to define either an optimal age for starting therapy or an ideal dose for the medications. It has, however, shown that therapy with hGH with or without oxandrolone can lead to sustained and significant increase in vertical growth rates and increase the final height of Turner women to within the normal adult range.

DAVID FITZPATRICK

Nucleoside triphosphates are required to open the CFTR chloride channel

Anderson MP, *et al*. *Cell* 1991;67:775-84.

The majority of the mutations causing CF occur within the two nucleotide binding domains (NBD1 and NBD2). Although some of these NBD mutants are normally processed, they fail to generate the Cl⁻ channel activity suggesting an important role for the NBDs in the normal functioning of cystic fibrosis transmembrane conductance regulator (CFTR) Cl⁻ channel activity. This paper describes the effect of ATP on Cl⁻ channel activity in cell free membrane patches derived from two different cell types expressing normal or mutant CFTR. Hydrolysis of ATP was directly required to open PKA phosphorylated Cl⁻ channels. The effect was not the result of reversible phosphorylation of the channel or the R domain. Furthermore, ATP reversibly opened Cl⁻ channel in cells expressing mutant NBD2 suggesting that hydrolysis of ATP by NBD1 was sufficient to open CFTR. These findings explain why CF associated mutations in the NBDs block Cl⁻ channel activity and are interesting because of the disproportionately greater incidence of the mutations in the NBD1.

N S THAKKER