

## MEDICAL GENETICS: ADVANCES IN BRIEF

### Homology of a candidate spermatogenic gene from the mouse Y chromosome to the ubiquitin-activating enzyme E1

Mitchell MJ, *et al. Nature* 1991;354:483-6.

The biology of sex determination is interesting both because of its fundamental nature and its clinical importance. Although the Y chromosome encoded testis determining factor (*TDF*) has now probably been identified (the *SRY* gene), this represents just a primary 'switch' in the complex developmental cascades leading to the male and female states. Evidence has been mounting for involvement of further genes on the Y chromosome, as well as other loci, in male sex differentiation. Mitchell *et al* and (independently, in the same issue of *Nature*) Kay *et al* have now identified a candidate for a Y encoded gene (*Spy*) implicated in mouse spermatogenesis. In the sex reversed (*Sxr*) mouse, *XXSxr* animals develop as males because a small portion of the Y chromosome, including *TDF*, has been translocated to the X chromosome. By positional cloning, exploiting *Sxr* mutants (*Sxr<sup>a</sup>* and *Sxr<sup>b</sup>*) that differ in both their Y chromosome content and capacity for spermatogenesis in *XSxrO* animals, both groups identified the same *Spy* candidate gene (variously termed *Sby* or *Als9Y-1*), which is specifically expressed in the testis. A close homologue on the X chromosome is widely expressed, undergoes X inactivation, and appears identical to the ubiquitin activating enzyme E1, which catalyses the first step in ubiquitin mediated protein degradation and is essential for nuclear DNA replication. The Y encoded form may provide a 'top-up' of this activity when the X chromosome is inactivated at the pachytene stage of male meiosis.

ANDREW WILKIE

### Effectiveness of routine ultrasonography in detecting fetal structural abnormalities in a low risk population

Chitty LS, Hunt GH, Moore J, Lobb MO. *BMJ* 1991;303:1165-9.

Congenital malformations occur in 2 to 3% of infants and account for a quarter of all perinatal deaths; 90% of malformations occur when the parents have no apparent risk factors. The authors performed a retrospective study of the ultrasonographic findings and outcome of all pregnancies in women scanned in 1988 to 1989 at a single district general hospital. There were 8733 births and 52 pregnancies were terminated after identification of a malformation; 95% of pregnancies had USS. A total of 130 fetuses (1.5%) had an abnormality at birth or after TOP; 125 had been scanned. In 93, abnormality was detected before 24 weeks (sensitivity 74.4%, 95%CI 66.7%-82.1%). Two false positive diagnoses occurred; in both, appar-

ently normal infants were produced at term (specificity 99.98%, CI 99.9%-99.99%). Of the 125 abnormalities, 87 were lethal or severely disabling; 72 of the 87 were detected by the routine screening programme (sensitivity 82.8%, CI 73.2%-90.0%). It is good to see this report of routine ultrasound, which is often uncritically regarded by women and their doctors as a risk free procedure. Geneticists are familiar with false positive diagnosis in high risk pregnancies, and this report will be helpful in increasing awareness of the same problem in low risk pregnancies among obstetricians, and in highlighting other dilemmas in counselling which may arise. I look forward to seeing similar larger prospective studies.

ANDREW NORMAN

### Early bacteriologic, immunologic and clinical courses of young infants with cystic fibrosis identified by neonatal screening

Abman SH, Ogle JW, Harbeck RJ, Butler-Simon N, Hammond KB, Accurso FJ. *J Pediatr* 1991;119:211-17.

From 1982 to 1987 a state wide initiative in Colorado used neonatal heel prick serum immunoreactive trypsinogen as the basis of a CF screening programme. Forty-two infants identified by this method have been the subject of a prospective, longitudinal study to determine the early course of CF. The median age at follow up for this report was 27 months. Each patient had regular physical examinations, chest x rays, throat cultures, and determinations of serum immunoglobulins and immune complex levels. At the time of study 19% of the patients had *P aeruginosa* cultured from a throat swab; 82% of these children had earlier isolates of *Staphylococcus aureus* or *Haemophilus influenzae* and all had previously received antibiotic therapy. Isolates of *P aeruginosa* were associated with a poorer clinical course determined by more frequent daily cough, lower chest x ray Brasfield score, and raised levels of circulating immune complexes. Another interesting result was that each patient had *P aeruginosa* that were genetically distinct (typed using probes to the 5' region of the exotoxin A gene) thus showing a lack of cross colonisation in this population. We can look forward to further valuable information coming from this cohort of CF patients.

DAVID FITZPATRICK

### Nucleoside triphosphates are required to open the CFTR chloride channel

Anderson MP, *et al. Cell* 1991;67:755-84.

The majority of the mutations causing CF occur within two nucleotide binding do-

mains (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 due to reversible phosphorylation of the channel or the R domain. Furthermore, ATP reversibly opened the 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

### Molecular analysis of X linked agammaglobulinemia with growth hormone deficiency

Conley ME, Burks AW, Herrod HG, Puck JM. *J Pediatr* 1991;119:392-7.

In this paper the authors used various laboratory techniques to investigate two families in which agammaglobulinaemia and isolated growth hormone deficiency were cosegregating as an X linked trait with the aim of finding out if this condition was allelic with X linked agammaglobulinaemia (XLA). Prometaphase chromosome analysis and dual beam flow cytometry were performed on affected subjects and failed to identify X chromosome deletions in either family. X inactivation studies were then done on somatic cell hybrids and showed random inactivation in the T cells of the obligate carriers with the markedly skewed inactivation in B cells typical of XLA heterozygotes. Linkage analysis using the available hybrids allowed isolation of the normal and mutant X chromosome. Twenty-eight probes spanning the long and short arms of the X chromosome were then used to map the defect to the interval between *DSX3* and *DSX94* by observing the recombination events in the mutant X in both families. This unconventional method of positional mapping thus suggested that the disease locus in these families lies in the same region of the long arm as XLA. The above data led the authors to postulate that agammaglobulinaemia and isolated growth hormone deficiency may be a contiguous gene defect involving the gene for XLA. An analysis using pulsed field gel electrophoresis looking for altered band sizes with *DSX3* and *DSX94* would have been desirable in this paper, but we can perhaps look forward to this in the future.

DAVID FITZPATRICK