Cystic fibrosis and deafness

During our preliminary molecular survey of the cystic fibrosis (CF) AF508 mutation in 18 patients selected by positive sweat tests, we found one patient with agenesis of the cochlea (Mondini’s syndrome), several bouts of dehydratation, and absence of pulmonary digestive complications. This 12 year old girl was born to unrelated, non-Caucasian parents and a heterozygous AF508/non-AF508 genotype was found in her lymphocytes. In our study only 33.5% of patients were found to be homozygous for the classical CF mutation, 11.8% were heterozygous, and the remaining majority of patients were not carriers of the AF508 mutation. As expected in our mixed non-Caucasian population, several other combinations of CF mutations may be found in a rather different distribution compared to European countries. Recently, Raskin et al. showed that 46% of their patients in a more homogenous racial region of Brazil were homozygous for the AF508 mutation. As a consequence, minor and uncommon clinical presentations of CF would be expected to occur in our population. Our patient with sensorineural deafness as a result of agenesis of the cochlea has not been ruled out and a similar mechanism to, for example, congenital agenesis of the vas deferens in infertile males, in whom CF mutations have recently been reported. It is possible in our population that CF patients may be found more frequently in different clinics seeking medical attention for other reasons than those expected in classical CF patients.

JUAN C LLERENA Jr
Centro de Genetica Medica, Instituto Fernandes Figueira, FIOCRUZ, Av Rui Barbosa, 716 – Flamengo, 22.250-020 – Rio de Janeiro, Brazil.

WIN DEGRAVE
ANTONIO DE MIRANDA
PHILIP SUFFYS
Departamento de Bioquimica e Biologia Molecular, FIOCRUZ, Rio de Janeiro, Brazil.

1 Raskin S, Phillips JA III, Kaplan G, et al. DNA data suggest that the CF gene in Brazil may be tenfold more than observed. Am J Hum Genet (Suppl) 1992;S1:A342.

Approaches to prenatal cystic fibrosis carrier screening

Two general approaches to the detection of cystic fibrosis (CF) heterozygotes in the antenatal clinic have been proposed: couple1 and two step2 screening. Miedzybrodzka et al3 suggest a variant, termed disclosure couple screening. It differs from the original concept of couple screening in that results of testing are fully disclosed to all participants. In our trial of couple screening,4 we report back in detail our experience with couple screening and a1 in 4 risk of affected outcome. All others (only one partner tested, both tested but with a CF allele) are reported as a composite residual risk of a CF child. With 85% of CF alleles detectable, this is 1 in 800.

Contrary to our initial expectations, the take up rate of couple screening has been as high as 94%. In one patient (67.5% versus 71%), its cardinal virtues are simplicity and economy. The main problem in two step screening has been the time that must be devoted to the skillful counselling of CF carriers, one in every 26 participants even at an 85% detection rate.5 If this form of CF screening is to become part of routine antenatal care (as it is the skilful goal of pilot trials), there will need to be a trained counsellor in every maternity hospital. A similar problem confronts disclosure couple screening. In contrast non-disclosure couple screening can be effectively operated by existing midwife staff and the rare 1 in 4 risk couples referred to a consultant obstetrician. In support of this statement is the fact that our two step screening trial has now been discontinued at the obstetrician’s request and replaced by non-disclosure couple screening.

DAVID BROCK
Human Genetics Unit, University of Edinburgh, Western General Hospital, Edinburgh EH12 9 EX, UK.

This letter was shown to Dr Miedzybrodzka et al, who reply as follows.

Professor Brock favours non-disclosure couple screening over two step screening on economic grounds, as two step screening requires satisfactory counselling of carriers and causes maternal anxiety until a partner’s result is available. Nevertheless, we believe that carrier information may be of benefit to those screened, giving information for future pregnancies with different partners and allowing relatives to be screened. We have been careful to search and to show that those screened and their families do not benefit from information provided by good counselling of carriers, we believe that carrier information is an ethical necessity. We accept that counselling of carriers requires resources, but, especially as the population becomes more aware of genetic risks, it allows targeting of genetic risks to those at high risk. Disclosure couple screening would allow carrier information to be of benefit, but the anxiety associated with two step screening might be decreased as partners’ results would be immediately available.

The Edinburgh finding of no difference in uptake of the two forms of screening mirrors the results of our own randomised trial of couple v two step screening (91% uptake of two step screening v 89% for couple screening).6 On the full results of our psychological and economic evaluation are available we will be able to comment further on the suitability of different approaches to screening.

N HAITES, J Mennie, K Coull
Western General Hospital, Edinburgh EH13 9YW.


Severe cystic fibrosis in a child homozygous for the G542 nonsense mutation in the CFTR gene

Several homozygous nonsense mutations in the CFTR gene (S125X, G542X, W1316X, R553X, G542X, G542X, R553X, R553X) have been identified. These patients were mildly affected, suggesting that the nonsense mutation alone may lead to mild expression of the disease, particularly mild lung symptoms.1,2 Some hypotheses have been proposed to explain the minor pulmonary involvement in comparison to the severe pancreatic dysfunction in these patients: (1) the possible presence of tissue specific RNA splicing minimising the effect of the nonsense mutation, (2) residual function of the truncated protein in certain tissues such as lung epithelium, the partial substitution of the missing function by alternative pathways occurring only in pulmonary epithelium.3 None of these explanations has yet been substantiated. These papers suggested that the lack of CFTR protein in airway cells may be less damaging than the presence of a structurally abnormal protein. This is contrasted to many monogenic diseases, such as haemophilia, in which the presence of nonsense mutations is frequently associated with a normal phenotype picture when compared to that associated with missense mutations.4 In these cases, nonsense mutations cause severe illness because the translated truncated proteins create truncated proteins, which are usually non-functional or unstable.

We present the clinical and molecular findings in a child homozygous for G542X with severe pancreatic and pulmonary disease. This Turkish boy was born at term (birth weight 3200 g) and presented with meconium ileus, successfully treated with enemas. Cystic fibrosis (CF) was confirmed by two positive sweat tests at 3 months and conventional treatment for CF was started. Because of an early episode of pulmonary infection, he was admitted to hospital at 5 months; Haemophilus influenzae was first isolated from spu- tum cultures, then Pseudomonas aeruginosa and Klebsiella. After 15 days of IV treatment with cephalosporins and aminosides, followed by aerosol colyminc, his pulmonary state improved. About 1 month after discharge, he was readmitted. Under treatment with pancreatic enzymes, the clinical course improved but nutritional indices remain low. Lung function as expressed by vital capacity (60% predicted, pO2 59 mm Hg and pCO2 33 mm Hg in the absence of pulmonary infection) and oral anti- biotics were necessary after discharge.

A homozygous G542X mutation was found by DGG and identified by exon 11
amplification using a modified primer on the 5' side of codon 542 and subsequent digestion with the restriction enzyme Ncol. The mutation (G→T at position 1756) was characterized by direct sequencing using the Sequenase USB kit by standard methods. G542 is a nonsense mutation in which a glycine at codon 542 is replaced with a stop codon G542X in the cystic fibrosis transmembrane conductance regulator gene. This boy has a severe lung involvement, meconium ileus, and pancreatic insufficiency, as indicated by the high degree of steatorrhea. The G542 nonsense mutation was associated with a severe clinical phenotype in the neonatal period.

This case shows that, in contrast to earlier reports, the G542 nonsense mutation alone, which truncates the gene product to 37% of its length, may lead to severe cystic fibrosis. The explanation for these conflicting results may be resolved by RNA studies. Nevertheless, a severe phenotype in the neonatal period may change with age to a moderate phenotype and vice versa. Environmental, epigenetic, and therapeutic factors can influence the clinical course and it is difficult to predict the severity of the disease. This case illustrates again that the presence of any specific CFTR mutation offers little in the way of a prognostic indicator in the individual patient.

Cutis laxa and the Costello syndrome

We reported a series of children with cutis laxa in this Journal in 1987. Prompted by a recent article by Kaloustian et al on the Costello syndrome, and concerns that our case 5 had some atypical features of cutis laxa, we have taken the opportunity to review this child and found she has now developed nasal laxa. The most striking feature clearly has the Costello syndrome. This syndrome was originally described by Costello in the Australian Paediatric Journal in 1977. The author described two unrelated children with growth and developmental delay together with lax skin and the onset of nasal papillomata in the first decade of life. Two further cases of the syndrome have been reported subsequently. Since it remains a rare but very characteristic syndrome we would like to update our original case report.

The proband was originally seen when she was 2½ years of age. At that time the coarse facial features and loose skin had suggested a diagnosis of cutis laxa (fig 1). A subsequent skin biopsy showed that the elastic fibres were normal on histological examination, but there was a relative deficiency of well formed collagen fibres. Her development has continued to be considerably delayed. She walked at 5 years and has received special education. Feeding has remained a problem, although no anatomical or physiological abnormality has been specifically identified. She was treated with growth hormone from 4 years of age and at 10 years her height is 118.5 cm (<3rd centile). She has always been relatively macrocephalic (head circumference has been on the 25th centile) and her anterior fontanelle was late in closing. Her facial features have been relatively coarse with a flat nasal bridge, hypertelorism, downward slanting palpebral fissures, a short neck, and a barrel shaped chest. She has a moderate lumbosacral scoliosis with limitation of movement at the knees and elbows. There is pes planus with a tendency to walk with the feet in an everted position.

At 6 years of age she developed nasal warts which have tended to recur in spite of aggressive treatment using cryosurgery. She has no warts elsewhere and she has had no adverse reaction to other viral infections. Her routine immunological parameters are normal. Although she is of West Indian origin, her skin is considerably darker than the other members of her family especially over the dorsum of her hands. Hyperpigmentation has also been reported in previous cases of Caucasian origin. One of the striking features which distinguishes this syndrome from other causes of cutis laxa is the deep palmar creases and thickened dermal ridges which have an unusual ‘velvety’ feel (fig 2). All cases of Costello syndrome have been isolated cases. In this family the parents have had a further unaffected son since the original report. The inheritance pattern therefore remains unclear.