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 cochleae (Mondini’s syndrome), several bouts of dehydration, 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 homogeneous 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 may have resulted from 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 also 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.

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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 al 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,3 we report back in detail the findings on a CF allele and a 1 in 4 risk of affected outcome. All others (only one partner tested, both tested with a CF allele and a 40% residual risk of a CF child. With 85% of CF alleles detectable, this is 1 in 800.

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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, and R112X/R112X) have been described. These patients were mildly affected, suggesting that the nonsense mutation alone may lead to mild expression of the disease, particularly mild lung symptoms. 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 and intestine, the partial substitution of the missing function by alternative pathways occurring only in pulmonary epithelium. None of these explanations have 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 in contrast to many monogenic diseases, such as haemophilia, in which the presence of nonsense mutations is frequently associated with a less than complete picture when compared to that associated with missense mutations. In these cases, nonsense mutations cause severe illness because the truncated protein creates a new epitope.

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 sputum cultures, then Pseudomonas aeruginosa and Klebsiella. After 15 days of IV treatment with cephalosporins and aminosides, followed by aerosol colicynicin, his pulmonary state improved. Abnormal high tone hearing was detected. Under treatment with pancreatic enzymes, the clinical course improved but nutritional indices remain low. Lung function as expressed by vital capacity was reduced (pO2 59 mm Hg and pCO2 33 mm Hg in the absence of pulmonary infection) and oral antibi-otics were necessary after discharge.

A homozygous G542X mutation was found by DGGE and identified by exon 11.