# LETTERS TO THE EDITOR

## Cystic fibrosis and deafness

During our preliminary molecular survey of the cystic fibrosis (CF) ΔF508 mutation in 18 patients selected by positive sweat tests, we found one patient with agenesis of the cochlea (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 ΔF508/ non-ΔF508 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 ΔF508 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*[1] showed that 46% of their patients in a more homogeneous racial region of Brazil were homozygous for the ΔF508 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 could 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.[2] 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 Genética Médica, Instituto Fernandes Figueira, FIOCRUZ, Av Rui Barbosa, 716 – Flamengo, 22.250-020 – Rio de Janeiro, Brazil.*

WIN DEGRAVE
ANTONIO DE MIRANDA
PHILLIP SUFFYS
*Departamento de Bioquímica e Biologia Molecular, FIOCRUZ, Rio de Janeiro, Brazil.*

1 Raskin S, Phillips JA III, Kaplan G, *et al.* DNA data suggest the incidence of CF in Brazil may be tenfold more than observed. *Am J Hum Genet (Suppl)* 1992;**51**:A342.
2 Kupchik GS, Vasquez-Levin M, Chaparro C, *et al.* Cystic fibrosis (CF), congenital bilateral absence of the vas deferens (CBAVD) and genotype–phenotype correlation. *Am J Hum Genet (Suppl)* 1992;**51**:A384.

## 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: couple[1] and two step[2] screening. Miedzybrodzka *et al*[3] 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 only when each partner has a detectable CF allele and a 1 in 4 risk of affected outcome. All others (only one partner tested, both tested but only one with a CF allele) are given a composite residual risk of a CF child. With 85% of CF alleles detectable, this is 1 in 8000.

Contrary to our initial expectations, the take up rate of couple screening has been almost as high as two step screening (67%[4] versus 71%[2]). Its cardinal virtues are simplicity and economy. The main problem in two step screening has been the time that must be dedicated to the skilled counselling of CF carriers, one in every 26 participants even at an 85% detection rate.[2] If this form of CF screening is to become part of routine NHS antenatal care (the obvious 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 EH4 2XU, UK.*

1 Wald NJ. Couple screening for cystic fibrosis. *Lancet* 1991;**338**:1318–19.
2 Mennie ME, Gilfillan A, Compton M, *et al.* Prenatal screening for cystic fibrosis. *Lancet* 1992;**340**:214–16.
3 Miedzybrodzka Z, Haites N, Dean J. A new approach to prenatal cystic fibrosis carrier screening. *J Med Genet* 1993;**30**:86.
4 Livingstone J, Axton RA, Mennie M, Gilfillan A, Brock DJH. A preliminary trial of couple screening for cystic fibrosis: designing an appropriate information leaflet. *Clin Genet* (in press).

**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 informed.[1,2] Unless careful research can show that those screened and their families do not benefit from information provided by good counselling of carriers, we believe that disclosure of results 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 information 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.[3]

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[4]). Once 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.

Although couple screening avoids the need for counselling of detected carriers, proper counselling and explanation is still required to allow couples to give informed consent to carrier testing. Failure to obtain truly informed consent to a screening test is unethical and exposes a health authority to risk of litigation.[5] Carrier testing must be explained by staff who fully understand its advantages, limitations, and drawbacks.

ZOFIA MIEDZYBRODZKA
NEVA HAITES
JOHN DEAN
*Departments of Medicine and Therapeutics and Obstetrics and Gynaecology, University of Aberdeen, Foresterhill, Aberdeen AB9 2ZD, UK.*

1 Miedzybrodzka Z, Dean J, Haites N. Screening for cystic fibrosis. *Lancet* 1991;**338**:1524–5.
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4 Miedzybrodzka Z, Haites N, Hall M, *et al.* Two approaches to antenatal carrier screening for cystic fibrosis. *Br J Obstet Gynaecol* 1993;**100**:292.
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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 (S1255X/G542X, W1316X/R553X, G542X/G542X, R553X/R553X, and R1162X/R1162X) have been reported.[1–6] These patients were mildly affected, suggesting that the nonsense mutation alone may lead to mild expression of the disease, particularly mild lung symptoms.[1–6] 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 (3) the partial substitution of the missing function by alternative pathways occurring only in pulmonary epithelium.[4] 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 in contrast to many monogenic diseases, such as haemophilia, in which the presence of nonsense mutations is frequently associated with a more severe clinical picture when compared to that associated with missense mutations.[7] In these cases, nonsense mutations cause severe illness because premature termination of translation creates 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 sputum cultures, then *Pseudomonas aeruginosa* and *Klebsiella*. After 15 days of IV treatment with cephalosporins and aminosides, followed by aerosol colimycin, his pulmonary state improved. Abundant stools were passed. Under treatment with pancreatic enzymes, the clinical course improved but nutritional indices remain low. Lung function as expressed by blood gas values was abnormal (pO2 59 mm Hg and pCO2 33 mm Hg in the absence of pulmonary infection) and oral antibiotics were necessary after discharge.

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

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