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 agenesia of the cochlea (Mondini’s syndrome), several bouts of dehydra-
tion, 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 com-
binations of CF mutations may be found in a
rather different distribution compared to Eu-
ropean countries. Recently, Raskin et al.
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 agenesia
of the cochlea and delta F508 mutation, who resulted from a
similar mechanism to, for example, congenital
agenesia of the vas deferens in infertile males,
in whom CF mutations have recently been
reported.1 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.

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1 Raskin S, Phillips JA III, Kaplan G, et al. DNA data suggest that
ΔF508 of CF in Brazil may be tenfold more than observed. Am J Hum Genet (Suppl) 1992;51:A342.
2 Kapchik GS, Vasquez-Levin M, Chaparro C, et al. Cystic fibrosis (CF), congenital bilateral

Approaches to prenatal cystic fibrosis carrier
screening

Two general approaches to the detection of
cystic fibrosis (CF) heterozygotes in the ante-
natal clinic have been proposed: couple1 and
two step2 screening. Miedzybrodzka et al3
suggested 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 the results of testing of both a CF allele
and a 1 in 4 risk of affected outcome.
All others (only one partner tested, both
terminated, both with a CF allele) are given
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
almost as high as expected (67% versus
71%). 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
care, and as proposed by the ethical goal of pilot trials), there will need to be a trained coun-
seller in every maternity hospital. A similar
problem confronts disclosure couple screening.
In contrast non-disclosure couple screening
with 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.

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

Professor Brock favours non-disclosure cou-
ple screening over two step screening on econ-
omic 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
carriers, giving information for future preg-
nancies with different partners and allowing
relatives to be counselled before the birth. Our
search can show that those screened and their
family do not benefit from information pro-
vided by good counselling of carriers, we believe that knowledge of hereditary disease is an ethical
necessity. We accept that counselling of
 carriers requires resources, but, especially as the
population becomes more aware of genetic
risks, it also questions the benefits of those
to high risk. Disclosure couple screening
would allow carrier information to be of
benefit, but the anxiety associated with a
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 screen-
ing).6 Our full results of our psychological
and economic evaluation are available and we
will be able to comment further on the suita-
dility of different approaches to
Screening.

North East Genet Clinics wish to advise counselors of
detected carriers, proper
counselling and explanation is still required
to allow couples to give informed consent
to carrier testing. To obtain true
to the involved consent to a screening test is not
exclusively and has a health authority to risk
of litigation. Carrier testing must be explained
by staff who fully understands its advantages,
limitations, and drawbacks.

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1 Miedzybrodzka Z, Dean J, Haytes N. Screening carriers of cystic fibrosis. Lancet 1992;i:621-2.
2 Miedzybrodzka Z, Haytes N, Dean J. A new approach to prenatal cystic fibrosis carrier
4 Miedzybrodzka Z, Haytes N, Hall M, et al. Two approaches to antenatal screening for

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

Several homozygous nonsense mutations in the CFTR gene (S125X, G542X, W1316X, R553X, G542X, G542X, R553X, and R1126X) have been described.7 These
were mildly affected, suggesting
that the nonsense mutation alone may
lead to mild expression of the disease,
particularly mild lung disease.8,9 Some
hypotheses have been proposed to explain
the minor pulmonary involvement in
contrast 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 the partial
substitution of the missing function by alter-
native pathways occurring only in pul-
monary epithelium.2 None of these explana-
tions has yet to be 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 mono-
ogenic diseases, such as haemophilia, in which
the presence of nonsense mutations is fre-
quently associated with a relatively mild
picture when compared to that associated with
missense mutations.7 In these cases, nonsense mutations cause severe illness because of premature truncation of the
molecular programmes.

We present the clinical and molecular
findings in a child homzygous for G542X with
severe pancreatic and pulmonary disease.

This Turkish boy was born at term (birth
weight 3200 g) and presented with meco-
nium ileus, successfully treated with enemas.
Cystic fibrosis (CF) was confirmed by twopositive sweat tests at 3 months and conven-
tional treatment for CF was started. Because
of an episode of pulmonary infection, he was
admitted to hospital at 5 months; Haem-
ophilus influenzae first isolated from spu-
tum cultures, then Pseudomonas aeruginosa
and Kibibacter. After 15 days of IV treatment
with cefepim and aminosides, followed by
aerosol colicynic, his pulmonary state improved.
A bronchial biopsy revealed a meconium
plug. Under treatment with pancreatic enzymes,
the clinical course improved but nutritional
indices remain low. Lung function as expressed by single
breath nitric oxide (pO2 59 mm Hg and pCO2 33 mm Hg
in the absence of pulmonary infection) and oral anti-
biotics were necessary after discharge.

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