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 dehydratation, 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. 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 (Mondini’s syndrome) may result 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 possible in our population that CF patients may be found more frequently in diagnostic clinics seeking medical attention for other reasons than those expected in classical CF patients.

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Ronald O., et al. have reported a higher frequency of the ΔF508 mutation in non-Caucasian populations, a finding which is consistent with the higher frequency of the ΔF508 mutation in the overall white population. The fact that our patient was born in Brazil indicates that the ΔF508 mutation is not limited to any specific geographic region.

Cystic fibrosis is a genetic disorder characterized by the malfunction of the CFTR gene, which is responsible for the production of chloride ions in the body. The ΔF508 mutation, which is the most common mutation in CF, results in a premature stop codon, leading to the production of a truncated and non-functional protein. This truncated protein is processed and secreted by the cell, leading to the accumulation of chloride ions in various tissues, including the lungs, pancreas, and sinuses. The high chloride concentration in these tissues leads to the formation of thick, tenacious mucus, which can cause respiratory, digestive, and reproductive system complications.

The ΔF508 mutation is present in the majority of patients with CF, but it is not the only mutation that can cause the disease. Other mutations, such as those that result in a loss of function of the CFTR protein, can also cause CF. These mutations are often referred to as “null” mutations, as they do not result in the production of a functional protein.

Screening for the ΔF508 mutation is an important aspect of CF management, as it allows for early detection and management of the disease. Screening can be done through a variety of methods, including genetic testing, which is the most accurate method for detecting the ΔF508 mutation. However, genetic testing can be expensive and may not be available in all areas.

Recently, there has been increasing interest in the use of non-invasive methods for screening for CF. These methods may be less invasive and may allow for earlier detection of the disease. However, the effectiveness of these methods has yet to be fully established.

In conclusion, the ΔF508 mutation is the most common mutation in CF, and its presence is an important factor in the diagnosis and management of the disease. Further research is needed to better understand the impact of different mutations on disease severity and to develop more effective methods for screening and managing CF.

References:
3. The Edinburgh finding of no difference in uptake of the two forms of screening mirrors the results of our own randomised trial of one vs two step screening (91% uptake of two step screening vs 89% for couple screening). Our full paper on the psychological and economic evaluation is available and we will be able to comment further on the suitability of different approaches to screening.
4. Although two step screening addresses the need for counselling of detected carriers, proper counselling and explanation is still required to allow couples to give informed consent to carrier testing. Until we obtain truly informed consent to a screening test is unethical and exposes a health authority to risk of litigation. Carrier testing must be explained to staff who fulfill all its advantages, limitations, and drawbacks.

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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. 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, and (3) the partial substitution of the missing function by alternative pathways occurring only in pulmonary epithelium. 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 less severe picture when compared to that associated with missense mutations. In these cases, nonsense mutations cause severe illness because premature termination of the 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 aminoglycosides, followed by aerosol colomycin, his pulmonary state improved. Abdominal pain and anorexia continued. Under treatment with pancreatic enzymes, the clinical course improved but nutritional indices remained low. Lung function as expressed by forced expiratory volume in one second (FEV1) (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