correspondence

No CFTR: are CF symptoms milder?

Sir — Cystic fibrosis (CF) is a recessive disease caused by mutations in a single gene[1] that codes for the cystic fibrosis transmembrane conductance regulator (CFTR), a small conductance, cAMP-activated Cl⁻ channel[2,3]. Many mutations that cause CF, including the most common mutation (ΔF508), lead to abnormal processing of CFTR[4], and most symptoms of CF are linked to decreased plasma membrane Cl⁻ conductance[5]. How do different alleles affect phenotype, and what can this tell us about CFTR function?

In an early attempt to relate specific alleles with phenotype, two African-American CF patients who were homozygous for CFTR stop mutations were reported to have milder pulmonary symptoms than ΔF508 homozygotes[6], suggesting that absence of CFTR protein may be less deleterious than altered CFTR protein[6]. Shortly after that report, processing of ΔF508 CFTR (and several other missense mutations) was found to be grossly abnormal in cultured cells expressing recombinant ΔF508 CFTR[4]. It was concluded that misprocessing of CFTR is the basis of most CF[4], and that protein harbouring a missense mutation might retain partial activity while trapped at incorrect cellular locations, causing a more general dysfunction than complete absence of protein[4]. Two more CF patients were found to be homozygous for stop mutations, and were interpreted as having a milder form of CF[7,8]. One of the earlier homozygous stop codon patients ing defect[10]. In short, the surprising notion that ΔF508 mutations are worse than the complete absence of CFTR protein has caught on[4,6–10].

However, the disruptive effects proposed for ΔF508 should give rise to a dominant rather than recessive pattern of inheritance[4,6]. Because CF is a recessive disease, the conclusion that missense mutations are worse than nonsense mutations bears close scrutiny.

A large study of CF subjects has established that ΔF508 homozygotes are almost always pancreatic insufficient and have greatly variable lung function, which is, on average, poorer

Table 1 Selected features of CF patients with missense and nonsense mutations

Mutation	n	Age(yr)	Sweat Cl⁻(mM)	ᵃFEV$_1$	Ref.
R553X/W1316X	1	21	116	82	6
G542X/S1255X	1	11	114	66	6
G542X/G552X	1	12.5	positive	120	7
R553X/R553X	1	13.5	160	mod. affected	8
W1282X/W1282X	16	9.3±7.5	113	64±27	12
G542X/W1282X	1	16	–	63	12
ΔF508/ΔF508	149	17±10	106	76–62ᵇ	11

n= 11>age 6
ᵃ% of predicted value
ᵇapproximate values for linear regression at ages 10 and 20 respectively

than it is for pancreatic sufficient patients[11]. The positive correlation between function of pancreas and lungs holds for ΔF508 heterozygotes and CF subjects homozygous for non-ΔF508 mutation[11]. The variation in lung function for ΔF508 homozygotes is very large. For example, one measure of lung function, forced expiratory volume in 1 s (FEV$_1$), ranged from ~12–120% of that expected in the 10–15 age group[11]. This large variance in patients homozygous for one allele establishes the importance of factors other than CF genotype in the pathophysiology of CF lung disease. The four subjects homozygous for stop codons were 11, 12.5, 13.5 and 21 years old (see Table) and have all been pancreatic insufficient since infancy. At least two are colonized with *Pseudomonas aeruginosa*, and all have clear signs of pulmonary dysfunction. FEV$_1$ scores were and 66, 82, and 120% of expected values, and "moderately affected". These values lie within the distribution of pulmonary dysfunction for ΔF508 homozygotes[11]. Recently, a sample of 18 individuals homozygous for CFTR stop mutations was discovered among CF patients of Ashkenazi Jewish origin. These patients have severe pulmonary disease[12]. Taken together, there is no basis for claiming a significant difference in clinical phenotype between patients with nonsense mutations and ΔF508 homozygotes. Importantly, all patients with nonsense mutations and all but 2 ΔF508 subjects from ref. 11 (not included in the table) are pancreatic insufficient.

In conclusion, present evidence suggests that many CFTR mutations have a common phenotype which seems traceable to reduced cAMP-activated Cl⁻ conductance. Whether loss of Cl⁻ conductance occurs because the mutant CFTR channels are absent, reduced in amount and open probability[14], or completely nonconducting appears to have less consequence for clinical status than other genetic and environmental factors. A smaller set of CFTR mutations is associated with pancreatic sufficiency, milder pulmonary disease, and improved sweat gland function[11,13]. The Cl⁻ impermeability hypothesis of CF predicts that these should be associated with residual CFTR Cl⁻ channel function, and preliminary evidence supports that prediction[15]. This conclusion is consistent with the recessive nature of CF. It also means that gene or protein replacement therapies for CF should be effective on their own, without requiring concomitant silencing of the ΔF508 gene.

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