

Secondary genetic factors in cystic fibrosis lung disease

Cystic fibrosis (CF) is the most common autosomal recessive genetic disorder amongst populations of northern European descent. Cloning of the cystic fibrosis transmembrane regulator (CFTR) gene in 1989¹ has allowed the assessment of clinical phenotype in patients with a specific genetic abnormality. Genotype/phenotype analysis showed a good correlation between the common CF mutation (deletion of phenylalanine at position 508 in the CFTR gene) and pancreatic insufficiency. This correlation does not hold for pulmonary disease which can vary markedly between patients with the same $\Delta F508$ CFTR mutation.² Many explanations have been advanced to account for this finding. Pulmonary disease is influenced by environmental factors such as the patient's age, pancreatic status, treatment regime, social class, smoking history, nutritional status, and colonisation with strains of *Pseudomonas aeruginosa* or *Burkholderia cepacia*.³⁻⁸ Moreover, those patients who receive care in a dedicated CF centre have better lung function when all the known environmental factors are taken into account.⁹

There is also evidence that the severity of pulmonary disease in CF is linked to other genetic factors outside the CFTR gene locus. Support for this comes from consortium and family studies^{2,10} and from the analysis of mice in whom the CFTR gene has been deleted.¹¹ Investigators have focused on genes involved in host defence and inflammation. Polymorphisms that result in high levels of anti-pseudomonas IgG,¹² high levels of tumour necrosis factor (TNF)- α ,¹³ low levels of glutathione S-transferase M1,¹³ and low levels of mannose binding protein^{14,15} have all been associated with more severe lung disease in patients with CF. The risk of colonisation with *P aeruginosa* is increased in CF patients with the class II DR7 allele,¹⁶ autoantibodies to bactericidal/permeability increasing protein,¹⁷ and with mild deficiency phenotypes of α_1 -antitrypsin.¹⁸ In our study these deficiency phenotypes were associated with better, rather than worse, lung function.¹⁹

It is on this background that Arkwright *et al* report their findings in this issue of *Thorax*.²⁰ They have chosen to assess polymorphisms in the transforming growth factor β (TGF- β) gene in 171 patients with the same CFTR mutation from three centres in Manchester, UK. The rationale for the study is that individuals who have polymorphisms in codon 10 and 25 express high levels of TGF- β and this has been associated with more severe lung fibrosis following lung transplantation and in animal models of radiation and drug induced pulmonary disease. The authors found an interesting association between a mutation in codon 10 and more rapid decline in lung function in patients with CF. The study took into account CF genotype and the patient's age but failed to correct for other factors such as nutritional status, smoking history, or the paediatric CF centre where the children received their care. These are important variables as they can introduce bias into the analysis. Ideally, studies should be designed to remove known confounding factors at the outset or should attempt to correct for these factors using statistical models and multivariate analysis.

The assessment of genetic polymorphisms using this type of observational study is of value in understanding disease mechanisms, but caution should be exercised in interpreting the results. They are subject to the bias that

resides in relatively small numbers of heterogeneous patients and only modest effects on lung function. Only when replicated by other groups and supported by in vivo data from the lungs of patients with CF do any of the reported associations have real meaning. The goal of establishing why some patients with CF have a more rapid decline in lung function is vital as it will allow the identification of a subset of patients who require more intensive medical care. Moreover, it will enable us to determine pathways that modify the effect of the CFTR mutation. Further studies of the proposed genetic factors are now required, ideally by a consortium, with sufficient numbers of patients to correct for confounding environmental and genetic variables.

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