**TimP-3 promoter gene polymorphisms in BFL**

Bird fanciers' lung (BFL) is a form of hypersensitivity pneumonitis induced by inhalation of antigens from birds. Only a small percentage of bird fanciers will develop BFL, so it is likely that these patients have a certain genetic predisposition to the disease. Matrix metalloproteinases (MMP) are zinc enzymes responsible for the degradation of the extracellular matrix. The proteolytic activities of MMP are counter-regulated by tissue inhibitors of MMP (TIMP). Hill found a decreased carriership of the rare TimP-3 (-1296C and -915G) promoter alleles in Mexican patients with pigeon-induced BFL, suggesting a protective effect of these alleles against the development of this disease. Only two previously published genetic association studies to date have focused on the susceptibility to BFL and both were performed in Mexican pigeon breeders. We have undertaken a study to validate the association between BFL susceptibility in Mexicans and TimP-3 promoter polymorphisms in a group of Dutch white patients with BFL.

Forty-one patients with BFL (35 keeping pigeons, 10 keeping budgerigars, 3 keeping parrots and 1 keeping canaries; 19 women and 22 men) and 335 controls were genotyped using sequence specific primers and polymerase chain reaction. The diagnosis of BFL was established in concordance with the criteria used in the Mexican study. The control group comprised healthy employees from our hospital. We did not include a group of bird fanciers without BFL since Hill did not find differences in TimP-3 allele distributions between Mexican controls with or without exposure to birds.

The Dutch population was in Hardy-Weinberg equilibrium. In contrast to the previous TimP-3 study in Mexicans, we found 100% linkage between the -1296C and -915A alleles and between the -1296C and -915G alleles in subjects homozygous for the respective alleles. We were therefore able to deduce two haplotypes (Y'A and C‘G). The TimP-3 C‘G haplotype frequency in BFL patients was significantly lower than in controls (p = 0.0434; OR 0.51 (95% CI 0.277 to 0.950; p = 0.0312); table 1).

Hill described a similar association in Mexican patients with pigeon-induced BFL, finding a reduced frequency of the rarer TimP-3 alleles in Dutch patients with BFL (-1296C and -915G, -11%), comparable to the reduction found in Mexican BFL patients (-1296C, -11.6%; -915G, -10.8%; table 1). However, there were differences between the findings of the two studies. The TimP-3 -1296C and -915G allele frequencies in Dutch controls were significantly lower than in the Mexican controls (-1296C, p = 0.0008; -915G, p = 0.0183; table 1). A search on the National Center for Biotechnology Information website showed similar TimP-3 -1296C frequencies in Dutch and American controls (30 mother-child trios from Utah with northern and/or western European ancestry; http://www.ncbi.nih.gov/SNP/snp_viewTable.cgi?pop = 1409; http://www.ncbi.nih.gov/SNP/snp_ref.cgi?rs = 9619311). BFL in Mexicans has a similarly poor prognosis to idiopathic pulmonary fibrosis, which contrasts with the more benign clinical course in Europeans. Although most patients in our study had severe symptoms at presentation with profound pulmonary function abnormalities, symptoms and pulmonary function improved in the majority of cases during follow-up. Furthermore, we included an approximately equal number of male and female patients and bird fanciers who kept birds other than pigeons, while all the Mexican patients were female and kept pigeons only. Despite these genotypical and phenotypical differences, the rarer TimP-3 promoter alleles were protective in both ethnic populations which makes an underlying functional cause of the C‘G haplotype likely.

In conclusion, we found a decreased carriership of the TimP-3 C‘G haplotype in Dutch patients with BFL, indicating a protective effect against the development of this disease. Studying the influence of polymorphisms on disease susceptibility in multiple ethnically and geographically distinct disease and control populations is important. Our study is the first to confirm an association between polymorphisms and susceptibility to BFL, which adds importance to the mechanism by which the TimP-3 variants may cause such a protective effect has yet to be determined.

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**References**


**Late CF caused by homozygous IVS8-5T CFTR polymorphism**

The distribution of cystic fibrosis (CF) transmembrane conductance regulator (CFTR) genotypes is not well characterised in patients with CF diagnosed after childhood, the majority of whom are compound heterozygotes for AF508. We describe such a patient with a rare genotype more commonly associated with inherited infertility in males.

A 54 year old man who had never smoked was referred with bilateral bronchiectasis and chronic sinusitis. He had no known allergy, no history of pancreatitis, and no family history of CF or consanguinity. Obstructive infertility with azoospermia had been established by spermography. The patient reported recurrent lower respiratory tract infections since childhood and pneumonia at the age of 45. He had undergone sinus surgery for nasal polyposis.

CF was suspected. A first sweat test was positive with a chloride concentration of 65 mmol/l (normal <40 mmol/l). The patient had chronic cough productive of purulent sputum, mild dyspnoea, chronic nasal
obstruction with nasal polyps and anosmia. His weight was 70 kg and his height 1.75 m. He had no digestive symptoms. Lung and heart auscultation was normal. A chest CF scan showed diffuse bronchiectasis predominating in the right upper and left lower lobes (fig 1). Lung function was near normal with forced expiratory volume in 1 second (FEV1) of 3.1 l (89% predicted), FEV1/forced vital capacity 0.73, total lung capacity 7 l (100% predicted), and forced expiratory flow25–75% 61% of predicted. Arterial oxygen tension was normal. Both sputum and bronchoalveolar lavage cultures were positive for mucinous Pseudomonas aeruginosa but no mycobacteria or fungi were found. Serological examination for Aspergillus fumigatus was negative. Exocrine pancreatic sufficiency was confirmed by normal elastase levels in the stools. A second sweat test was normal (25 mmol/l).

A screening test for the 22 most frequent mutations of the CFTR gene encountered in France was negative. However, mutations of the CFTR gene were confirmed by the presence of homozygosity for the 5T allele in the polythymidine tract of intron 8 (IVS8-5T) with 11 TG repeats. The M470V polymorphism was absent. Sequencing of the full CFTR coding sequence including all 27 exons and the flanking splice sites showed no other mutation.

This patient had clinical features typical of CF involving several organs (bilateral bronchiectasis, chronic sinus disease, male infertility) together with two pathogenic CFTR gene mutations, so a diagnosis of non-classic CF can be made.7 The sweat test was positive on only one of two occasions, suggesting partial dysfunction of the CFTR protein.

The IVS8-5T allele is associated with poorly penetrance of IVS8-5T were also present. This observation shows that individuals homozygous for the IVS8-5T allele as the sole cause of disease. The IVS8-5T allele may present as non-classic CF with sinusopulmonary disease and male infertility. However, given the high prevalence of the IVS8-5T allele (5–10% in the general population), the expected frequency of individuals homozygous for IVS8-5T may be higher than the prevalence of CF, suggesting that other factors may contribute to the disease. The IVS8-5T allele should be included in the systematic screening for CFTR mutations in patients with suspected or confirmed CF.

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In the paper entitled “Relationship between predicted forced expiratory volume in one second and the risk of lung cancer: a systematic review and meta-analysis” by S Wasswa-Kintu et al which appeared on pages 570–575 of the July 2005 issue of Thorax, the correct figure for the worldwide mortality from lung cancer in 2000 (mentioned in the second line of the first paragraph) is 0.85 million, not 328 million as stated in the article.