LETTERS TO THE EDITOR

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TIMP-3 promoter gene polymorphisms in BFL

Bird fanciers’ lung (BFL) is a form of hypersensitivity pneumonitis induced by inhalation of antigens from birds.1 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.1

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 promoter alleles in Dutch patients with BFL (−1296C and −915G 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 0.513 (95% CI 0.277 to 0.950; p = 0.0312); table 1). Hill described a similar association in Mexico.1 He found a reduction 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, −12.6%; −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–father–child trios from Utah with northern and/or western European ancestry: http://www.ncbi.nlm.nih.gov/SNP/snp_viewTable.cgi?pop = 1409; http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs = 9619311). BFL in Mexicans has a similarly poor prognosis and a decreased carriership of the rare TIMP-3 promoter alleles were proposed.1-3 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.2-4 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.1

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.

The authors thank Hattie Alpar, Jan Brooss and Helga Dissel for their technical support.

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doi: 10.1136/thx.2005.046581

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 AF508.1 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 azospermia 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 polypsis. 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

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Table 1 Timp-3 promoter allele frequencies in Mexican and Dutch controls and BFL patients

Mexican2 Dutch

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References


Data are given as absolute numbers with percentages in parentheses.
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 CT 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 litres (100% predicted), and forced expiratory flow 25–75% 61% of predicted. Arterial oxygen tension was normal. Both sputum and bronchoalveolar lavage cultures were positive for mucinous Aspergillus fumigatus but no mycobacteria or fungi were found. Serological examination for Mycobacterium tuberculosis 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 coding sequence of the CFTR gene 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. 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 penetrant CF patients with suspected or confirmed CF. Whether IVS8-5T homozygosity may present as non-classic CF with sinusopulmonary disease and male infertility.

This observation shows that individuals homozygous for the IVS8-5T allele as the sole mutation of the whole CFTR coding sequence 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.

\[ \text{References} \]


\[ \text{doi: 10.1136/thx.2005.048207} \]