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 carrier-ship of the rare TIMP-3 alleles in Dutch patients with BFL compared to the homozygous for the respective alleles. We were therefore able to deduce two haplotypes (YA and CG). The TIMP-3 CG haplotype frequency in BFL patients was significantly lower than in controls (p = 0.0434; OR 0.51 (95% CI 0.27 to 0.95); p = 0.0312; table 1).

Hill described a similar association in Mexican patients with pigeon breeder’s lung. We found a reduced carrier-ship of the rarer TIMP-3 alleles in Dutch patients with BFL compared to the homozygous for the respective alleles, 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. Only two previously published genetic association studies to date have focused on the TIMP-3 promoter polymorphisms and BFL. However, the mechanism by which the TIMP-3 variant 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, nor 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 polyps.

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 congestion, and an 85% reduction in FEV1 on exercise.

Table 1 TIMP-3 −1296T>C and −915A>G allele frequencies in Mexican and Dutch controls and BFL patients

<table>
<thead>
<tr>
<th>Allele</th>
<th>Mexican (n = 335)</th>
<th>Dutch (n = 335)</th>
<th>Mexican (n = 232)</th>
<th>Dutch (n = 232)</th>
</tr>
</thead>
<tbody>
<tr>
<td>−1296T</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T</td>
<td>90 (64.4)</td>
<td>120 (69.1)</td>
<td>77 (70.7)</td>
<td>90 (73.1)</td>
</tr>
<tr>
<td>G</td>
<td>44 (35.6)</td>
<td>40 (30.9)</td>
<td>15 (12.3)</td>
<td>20 (16.9)</td>
</tr>
<tr>
<td>−915G</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T</td>
<td>90 (64.4)</td>
<td>80 (61.5)</td>
<td>70 (60.1)</td>
<td>90 (73.1)</td>
</tr>
<tr>
<td>G</td>
<td>44 (35.6)</td>
<td>41 (38.5)</td>
<td>25 (19.9)</td>
<td>30 (26.9)</td>
</tr>
</tbody>
</table>

Controls (n = 232) and BFL patients (n = 41). 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 of 0.73, total lung capacity 7 litres (100% predicted), and forced expiratory flow 25–75% of predicted. Arterial oxygen tension was normal. Both sputum and bronchoalveolar lavage cultures were positive for mucinous Aspergillus fumigatus and protein. Heterozygous IVS8-5T polymorphism is considered equivalent to a “mild” CFTR mutation. Whether IVS8-5T homozygosity may be sufficient by itself to cause disease has not hitherto been established. Non-classic CF was reported in a 48 year old woman homozygous for IVS8-5T, but the M470V polymorphism and TG12 repeat mutation known to modulate the disease penetrance of IVS8-5T were also present. This observation shows that individuals homozygous for the IVS8-5T allele as the sole variation of the whole CFTR coding sequence may present as non-classic CF with sinusopulmonary disease and male infertility.

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. 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 effective usage of the intron 8 splice acceptor site compared with the two other existing alleles (7T and 9T) and results in frequent skipping of exon 9. Patients homozygous for the IVS8-5T allele have lower than normal levels of full length CFTR messenger RNA and protein. Heterozygous IVS8-5T polymorphism may be responsible for congenital bilateral absence of the vas deferens or recurrent pancreatitis. It may modulate the variable expression of “mild” CFTR mutations such as when present in cis of the R117H mutation, thus causing a CF phenotype.

Compound heterozygotes with IVS8-5T and AF508 may present with classic or late onset CF. Whether IVS8-5T homozygosity may be sufficient by itself to cause disease has not hitherto been established. Non-classic CF was reported in a 48 year old woman homozygous for IVS8-5T, but the M470V polymorphism and TG12 repeat mutation known to modulate the disease penetrance of IVS8-5T were also present. This observation shows that individuals homozygous for the IVS8-5T allele as the sole variation 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.

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In the paper entitled “Relationship between reduced 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.

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