Mutation in the 3' region of the α-1-antitrypsin gene and chronic obstructive pulmonary disease

A J Sandford, J J Spinelli, T D Weir, P D Paré

Abstract
A mutation in the 3' flanking region of the α-1-antitrypsin gene has been reported to be associated with chronic obstructive pulmonary disease (COPD). We have investigated the prevalence of this mutation in a group of 185 patients with airway obstruction and in 69 non-obstructed controls. The subjects were selected on the basis of their development of lung cancer and therefore had similar exposure to cigarette smoke, the major risk factor for COPD. In the majority of subjects, the level of airway inflammation and loss of elastic recoil was known, and therefore we were able to test whether the mutation was associated with one of these pathological mechanisms. The prevalence of heterozygotes for the mutation was 10% in both the obstructed group and controls. The mutation was not associated with increased airway inflammation or loss of elastic recoil. This result indicates that the 3' mutation is not a significant risk factor for COPD in this population, and suggests heterogeneity in the pathogenesis of the disease.

Keywords: COPD; α-1-antitrypsin; mutation

Risk factors for the development of chronic obstructive pulmonary disease (COPD) include exposure to cigarette smoke and family history. Two previous studies have shown an association between COPD and a G→A transition at position 1237 in the 3' region of the α-1-antitrypsin gene. The mutation may affect α-1-antitrypsin gene regulation during the acute phase response. We have investigated the prevalence of this mutation in a group of patients with COPD and a group of controls. We also determined whether the 3' mutation was associated with loss of elastic recoil or inflammatory airway narrowing, two pathophysiological processes underlying COPD. The subjects were selected from a population of white lung cancer patients who were all smokers.

Obstructed patients were those who had a forced expiratory volume in one second (FEV₁) <80% predicted and an FEV₁/FVC ratio <70%. Non-obstructed controls were defined by an FEV₁ >85% predicted and an FEV₁/FVC >75%. Samples of purified DNA or microwaved whole blood were used as templates for genotyping by the polymerase chain reaction (PCR) with the following primers: 5'CTACCGAGATGGCCTTGTCG 3' and 5'CCTCTAGAGTCTGTTGACCC 3'. The mutation was detected by digesting the PCR product with Taql restriction enzyme. The wild type allele produced 130 bp and 75 bp fragments, whereas the mutant allele remained uncleaved (fig 1).

The phenotypic characteristics of the study subjects are shown in table 1. Logistic regression was used to correct the results for differences between patients and controls for potentially confounding factors such as age, sex, and smoking history. In contrast to previous studies, no excess of heterozygotes was found in the obstructed group (table 2). The relative risk for airway obstruction associated with the mutant genotype was 1.31 (95% CI=0.48, 3.60) after correction for age, gender, and smoking history and was not significant (p=0.59). Among the COPD patients, measurements of lung elastic recoil (P<sub>EL</sub>max) and...
Table 3  Mean lung function measurements in the COPD patients associated with 3' mutation genotypes (1= wild type allele, 2 = mutant allele)

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Genotype</th>
<th>No</th>
<th>Mean (SD)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁ % predicted</td>
<td>1,1</td>
<td>166</td>
<td>60 (13)</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td>1,2/2,2</td>
<td>19</td>
<td>57 (9)</td>
<td>0.58</td>
</tr>
<tr>
<td>FEV₁/FVC %</td>
<td>1,1</td>
<td>166</td>
<td>58 (9)</td>
<td>0.58</td>
</tr>
<tr>
<td></td>
<td>1,2/2,2</td>
<td>19</td>
<td>57 (8)</td>
<td>0.30</td>
</tr>
<tr>
<td>P₃₁ max % predicted</td>
<td>1,1</td>
<td>110</td>
<td>77 (28)</td>
<td>0.30</td>
</tr>
<tr>
<td></td>
<td>1,2/2,2</td>
<td>13</td>
<td>105 (86)</td>
<td>0.09</td>
</tr>
<tr>
<td>R₁₀₀ (cmH₂O/l/s)</td>
<td>1,1</td>
<td>106</td>
<td>2.9 (1.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1,2/2,2</td>
<td>12</td>
<td>5.1 (4.4)</td>
<td></td>
</tr>
</tbody>
</table>

Inflammatory airway narrowing (R₁₀₀) were not significantly different between subjects with the mutation compared to the wild type (Table 3).

The prevalence of the 3' mutation in our population of lung cancer patients (10%) was twice that of previous reports of white populations. To determine whether the mutation was more common in the Vancouver population in general or just among lung cancer patients, we genotyped a random sample of the Vancouver population from a blood donor clinic. The prevalence of heterozygotes in this population was 13/104 (12.5%) which was not significantly different from our study group (p=0.45). Although it is possible that not all the blood donors were white, these results suggest that the 3' mutation is not associated with lung cancer.

The population used in this study had enough power to detect, at p<0.05, a genotype which imparted an odds ratio of 3.0 given a 10% prevalence of the 3' mutation in the obstructed population. The previous studies reported odds ratios for COPD associated with the 3' mutation of 3.2 and 4.8, which would have been detectable with our study design. The lack of association between the 3' mutation and COPD in this study may be the result of heterogeneity in the genetic basis of this disease.

This study was supported by a grant from the British Columbia Lung Association.

Mutation in the 3' region of the alpha-1-antitrypsin gene and chronic obstructive pulmonary disease.
A J Sandford, J J Spinelli, T D Weir and P D Paré

J Med Genet 1997 34: 874-875
doi: 10.1136/jmg.34.10.874

Updated information and services can be found at:
http://jmg.bmj.com/content/34/10/874

These include:

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/