

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

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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.

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Risk factors for the development of chronic obstructive pulmonary disease (COPD) include exposure to cigarette smoke¹ and family history.² 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.^{3,4} The mutation may affect α -1-antitrypsin gene regulation during the acute phase response.⁵ 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

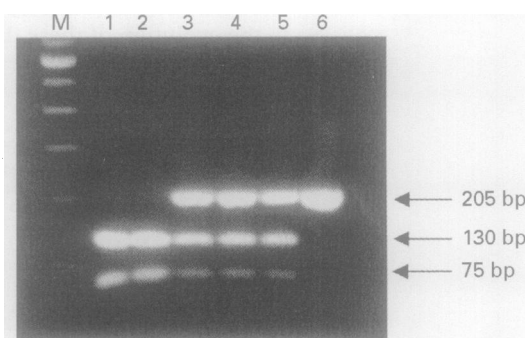


Figure 1 Restriction enzyme analysis of the α -1-antitrypsin 3' mutation. Lanes 1 and 2: homozygous wild type. Lanes 3-5: heterozygous. Lane 6: homozygous mutant. M=100 bp DNA molecular weight marker.

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/forced vital capacity (FVC) ratio <70%. Non-obstructed controls were defined by an FEV₁ >85% predicted and an FEV₁/FVC >75%. Samples of purified DNA^{6,7} or microwaved whole blood⁸ were used as templates for genotyping by the polymerase chain reaction (PCR) with the following primers: 5' CTACCAGGAATGGCC TTGTCC 3' and 5' CTCTCAGGTCTGGT-GTCATCC 3'. The mutation was detected by digesting the PCR product with *TaqI* restriction enzyme. The wild type allele produced 130 bp and 75 bp fragments, whereas the mutant allele remained uncut (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_{Lmax}) and

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Table 1 Population characteristics and pulmonary function values in obstructed versus non-obstructed groups

Phenotype	Obstructed (n=185) (Mean (SD))	Non-obstructed (n=69) (Mean (SD))
Age	64 (8)	58 (12)
Male/female ratio	4.1/1	1.8/1
Smoking (pack years)	60 (34)	43 (27)
FEV ₁ % predicted	60 (13)	99 (11)
FEV ₁ /FVC %	58 (8)	80 (3)
P _{Lmax} % predicted	80 (39)	99 (32)
Upstream resistance (R _{US})	3.1 (2.2)	1.3 (0.9)

Table 2 Frequency of wild type (1) and mutant (2) alleles of the 3' mutation of the α -1-antitrypsin gene in obstructed and non-obstructed groups

Genotype	Obstructed	Non-obstructed
1,1	166 (90%)	62 (90%)
1,2	18 (10%)	7 (10%)
2,2	1 (1%)	0

Table 3 Mean lung function measurements in the COPD patients associated with 3' mutation genotypes (1=wild type allele, 2=mutant allele)

Measurement	Genotype	No	Mean (SD)	p value
FEV ₁ % predicted	1,1	166	60 (13)	0.38
	1,2/2,2	19	57 (9)	
FEV ₁ /FVC %	1,1	166	58 (9)	0.58
	1,2/2,2	19	57 (8)	
P _L MAX % predicted	1,1	110	77 (28)	0.30
	1,2/2,2	13	105 (86)	
R _{US} (cmH ₂ O/l/s)	1,1	106	2.9 (1.7)	0.09
	1,2/2,2	12	5.1 (4.4)	

inflammatory airway narrowing (R_{US}) 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.^{3,4} 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,^{3,4} 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.

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