Glutathione S-Transferase P1 and Lung Function in Patients With α1-Antitrypsin Deficiency and COPD*

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Background: The glutathione S-transferase P1 (GSTP1) gene is involved in detoxification of electrophilic substances of tobacco smoke. A polymorphism at nucleotide 315 of this gene alters its enzymatic activity.

Objective: We analyzed the association between the variability in the GSTP1 gene and impairment in lung function in smokers with and without α1-antitrypsin (AAT) deficiency and COPD.

Population and method: The study population consisted of 99 patients with smoking-related COPD and 69 patients with AAT deficiency; 198 healthy volunteers provided the frequency of the different polymorphisms in the general population. GSTP1 genotyping was performed by a real-time polymerase chain reaction amplification assay.

Results: The frequency (0.28) of the 105Val polymorphism was identical in COPD patients and the general population. However, the frequency was significantly increased (0.44) in patients with AAT deficiency (odds ratio [OR], 2.09; 95% confidence interval [CI], 1.17 to 3.72 compared to control subjects; and OR, 2.41; 95% CI, 1.27 to 4.59 compared to COPD). FEV1 percentage of predicted was significantly impaired in AAT-deficient carriers of 105Val. This effect was not observed in COPD patients.

Conclusions: These findings suggest that the frequency of the GSTP1 105Val polymorphism is increased in patients with AAT deficiency. Globally, GSTP1 genotypes, age, and tobacco smoking explained 41% of total FEV1 percentage of predicted variability in patients with AAT deficiency. The modulatory role of GSTP1 in lung disease has only been observed in smokers lacking AAT.

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Key words: α1-antitrypsin deficiency; COPD; genetics; glutathione S-transferase; smoking

Abbreviations: AAT = α1-antitrypsin; CI = confidence interval; GSTP1 = glutathione S-transferase P1; Ile = isoleucine; OR = odds ratio; PCR = polymerase chain reaction; PI = proteinase inhibitor; Val = valine

COPD is a major health problem with increasing prevalence and mortality. Although the major etiologic factor for the development of COPD is cigarette smoking, the fact that only 10 to 20% of chronic, heavy cigarette smokers acquire symptomatic COPD indicates that other factors influence its pathogenesis.1–3 At present, the most well-recognized genetic risk factor involved in the development of COPD is α1-antitrypsin (AAT) proteinase inhibitor (PI) deficiency. Patients with the homozygous form of PI ZZ have a very high risk for emphysema at an early age if they smoke and are prone to rapid deterioration of pulmonary function even without smoking.4 However, the phenotypic expression of the deficiency in the form of lung disease may vary greatly.5 In addition, the incidence of the PI Z variant is too low to adequately explain the genetic predisposition to COPD in the general population. Therefore, it has been suggested that other genetic factors may be involved in the pathogenesis of emphysema, although the current findings are still not conclusive.6–8

Human glutathione S-transferases are a functionally diverse family of soluble detoxification enzymes.
that use reduced glutathione in conjugation and a reduction reaction to eliminate many different toxic electrophiles and products of oxidative stress. The glutathione S-transferase P1 (GSTP1) subfamily of the glutathione S-transferases comprises a single gene, GSTP1, which is widely expressed in normal epithelial tissue including lung overexpressed in many tumors, and may be involved in acquired resistance to some anticancer drugs. The GSTP1 gene has also been found to be polymorphic at nucleotide 315 with an adenine to guanine substitution, producing an isoleucine (Ile) to valine (Val) substitution at codon 105. This residue lies in close proximity to the binding GSTP1 protein site for electrophilic substrates.

The influence of these polymorphisms in detoxification is controversial. In vitro complementary DNA expression studies suggest that the Ile105Val substitution reduces enzyme activity, and a study in human expression studies suggest that the Ile105Val substitution reduces enzyme activity, and a study in human resistance to some anticancer drugs. The GSTP1 gene has also been found to be polymorphic at nucleotide 315 with an adenine to guanine substitution, producing an isoleucine (Ile) to valine (Val) substitution at codon 105. This residue lies in close proximity to the binding GSTP1 protein site for electrophilic substrates. However, in other studies, it has been demonstrated that GSTP1 105Val is more active in detoxification reactions than GSTP1 105Ile. The influence of these polymorphisms on the risk of COPD development is also contradictory.

The aim of the present study was to evaluate the frequency of Ile105Val polymorphisms in the general population of our area, and compare it with that of a population of individuals with AAT deficiency and another population with smoking-related COPD. We also studied the role of GSTP1 genotypes on susceptibility to tobacco smoke in these two groups of patients.

**Materials and Methods**

**Subjects**

The study groups consisted of 99 Spanish white patients with smoking-related COPD and normal AAT serum concentrations recruited consecutively from the outpatient clinic of our institution (COPD group), and 69 unrelated patients with inherited AAT deficiency, demonstrated by AAT serum concentrations < 60 mg/dL recruited from the Spanish Registry of AAT (AAT group). These patients exhibit a wide range of lung function impairment, from near-normal lung function to severe COPD. The AAT deficiency, demonstrated by AAT serum concentrations < 60 mg/dL recruited from the Spanish Registry of AAT (AAT group). These patients exhibit a wide range of lung function impairment, from near-normal lung function to severe COPD. To avoid false estimates of allele frequencies due to accumulation in families, sibling pairs were not included in the study. All 69 AAT-deficient patients provided blood samples for phenotyping and genotyping. Spirometric data and complete smoking history were available in 65 patients with AAT deficiency, of whom 25 were never-smokers. Therefore, to analyze the susceptibility of the different GSTP1 genotypes to tobacco smoking, only the remaining 40 AAT-deficient subjects, either smokers or former smokers, were included in this latter analysis.

All patients with COPD had irreversible chronic airflow limitation. Diagnosis of COPD was made according to the Spanish Society of Pneumology and Thoracic Surgery criteria, in brief, proven fixed airflow obstruction with a FEV1/FVC ratio of < 70% of predicted and FEV1/FVC < 70%, and no significant response to the bronchodilator test.

The frequencies of the different polymorphisms of the GSTP1 gene in the general population of our area were obtained from 198 healthy Spanish, white, nonrelated volunteers who attended periodic medical checks up at our center, both smokers and non-smokers (115 men and 83 women) with a mean age of 44.1 years (range, 28 to 60 years) and free of pulmonary or hepatic disease. All participants with AAT serum concentrations below the normal range were excluded. The study was approved by the Ethics Committee of the Vall d’Hebron Hospital in Barcelona. All subjects gave informed consent for participation in the study.

**Genotyping for the GSTP1 Gene by Real-time Polymerase Chain Reaction**

Genomic DNA was extracted from 200 μL of ethylenediamine tetra-acetic acid blood using QAamp mini columns (Qiagen Ltd; Sussex, UK) according to the instructions of the manufacturer. Real-time polymerase chain reaction (PCR) amplification and genotyping was performed using the LightCycler system (Roche Biochemicals; Mannheim, Germany). Primers and probes corresponding to the GSTP1 gene were synthesized by TIB Molbiol (Berlin, Germany), according to the sequences previously described. The PCR conditions were as follows: 4 mM MgCl2, 4 pmol of each hybridization probe, 10 pmol of the two PCR primers, 2 μL of LightCycler Fast Start DNA Master Hybridization probe mix (Roche Diagnostics), and 2 μL of DNA sample in a total volume of 20 μL. The reaction mix was added to capillary tubes, which were sealed, centrifuged, and placed in the LightCycler rotor. The PCR cycling program consisted of an initial denaturing step at 95°C for 7 min, followed by 45 amplification cycles at 94°C for 5 s, 55°C for 10 s, and 72°C for 10 s. Finally, following completion of the PCR, the PCR mixture was denatured and the temperature lowered to 40°C for 20 s to facilitate binding of the hybridization probes, and then slowly increased (0.1°C/s) to 87°C to permit melting curves of the detection probe. Melting curves were converted to melting peaks by software, allowing easy distinction of the wild type from mutant types by the different melting temperatures. Melting temperatures of the GSTP1 polymorphisms were 64.4°C for 105Val and 68.8°C for 105Ile. Individuals with two copies of the sequence for 105Val showed a single melting peak at 64.4°C, homozygous individuals with two copies of 105Ile showed a single peak at 68.8°C, and heterozygous individuals with 105Val and 105Ile showed two peaks in the analysis. To confirm the GSTP1 genotyped by melting peaks, 20 samples were regenotyped by a DNA sequencing method using primers A: 5′-GTGGTTT-GCCCCAAGGTCAG-3′ and B: 5′-ACCACCTGAGGGGTAAG-3′ for PCR amplification and sequencing. The reaction conditions and the PCR and sequencing procedure have been described previously.

**AAT Quantification and Phenotyping**

An immune nephelometry method (Array 360 System; Beckman; Altamont, NY) was used for quantitative determination of AAT in serum. The normal range for AAT was 105 to 170 mg/dL. Screening for variants was carried out by means of the isoelectric focusing technique using carrier ampholytes on flatbed polyacrylamide.

**Data Analysis**

Differences in allele distribution and allele frequency among the groups were examined for statistical significance by χ² analyses. Odds ratios (ORs) with their corresponding 95% con-
Table 1—Clinical and Functional Characteristics of the Populations Studied*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>COPD Patients With Normal AAT Levels (n = 99)</th>
<th>AAT-Deficient Patients (n = 65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender, No. (%)</td>
<td>91 (92.9)</td>
<td>36 (56.8)</td>
</tr>
<tr>
<td>Age, yr</td>
<td>56.4 (8.9)</td>
<td>48.9 (12.1)</td>
</tr>
<tr>
<td>Smoking status, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active smokers</td>
<td>30 (30.6)</td>
<td>10 (15.3)</td>
</tr>
<tr>
<td>Former smokers</td>
<td>68 (69.4)</td>
<td>30 (46.1)</td>
</tr>
<tr>
<td>Never-smokers</td>
<td>0</td>
<td>25 (38.4)</td>
</tr>
<tr>
<td>Pack-years</td>
<td>50.1 (22.3)</td>
<td>25.6 (13.7)</td>
</tr>
<tr>
<td>AAT levels, mg/dL</td>
<td>157.1 (47.3)</td>
<td>27.8 (10.9)</td>
</tr>
<tr>
<td>FVC, mL</td>
<td>2,408.6 (744.1)</td>
<td>2,960.1 (1,166)</td>
</tr>
<tr>
<td>FVC, %</td>
<td>55.8 (16.1)</td>
<td>77.4 (29.9)</td>
</tr>
<tr>
<td>FEV₁, mL</td>
<td>1,196.1 (474.6)</td>
<td>1,619.3 (994.6)</td>
</tr>
<tr>
<td>FEV₁, %</td>
<td>36.8 (12.3)</td>
<td>54.1 (33.5)</td>
</tr>
<tr>
<td>FEV₁/FVC, %</td>
<td>49.3 (10.7)</td>
<td>54.8 (21.1)</td>
</tr>
</tbody>
</table>

*Data are presented as mean (SD), unless otherwise specified.

Results
Characteristics of the Populations Studied

Most of the patients in the COPD group were men (92.9%) and heavy smokers (mean, 50.1 pack-years) with a mean age of 56.4 years. The mean predicted FEV₁ was 1,196 mL (SD, 474 mL) or 36.8% predicted. PI phenotypes were 79 PI MM, 16 PI MS, 2 PI MZ, and 1 PI SI. Patients in the AAT deficiency group were younger (mean age, 48.9 years; SD, 12.1 years), smoked less (mean, 25.6 pack-years), and had better-preserved lung function, with a mean FEV₁ percentage of predicted of 54.1% (SD, 33.5%). All except three patients were PI ZZ (2 PI MmaltonZ, 1 PI YbarcelonaYbarcelona23). The clinical and functional characteristics of both groups are shown in Table 1. Lung volumes and diffusing capacity of the carbon monoxide were not available for most of the patients with AAT deficiency because they were attended in different centers associated with the Spanish registry.

GSTP1 Alleles in the Different Study Groups

A total of 13 persons (6.6%) and 97 persons (49%) from the general population were homozygous for the GSTP1 105Val and 105Ile alleles, respectively (Table 2). A small nonsignificant increase in the proportion of individuals homozygous for the two alleles was observed in the COPD group compared with the general population. Of the 69 patients with AAT deficiency from whom blood samples were available, the proportion of individuals homozygous for the GSTP1 105Val allele was significantly higher (20.2%) than in COPD patients (10.2%; p = 0.012) or in the general population (6.6%; p = 0.001) [Table 2].

Table 2 shows the allele frequencies in the three groups studied. In the general population, the frequencies of 105Ile and 105Val were 0.712 and 0.288, respectively. The frequencies in the COPD group were almost identical. The distributions of GSTP1 105Ile and 105Val genotypes observed in both groups were in Hardy-Weinberger equilibrium when compared with those predicted by allele frequencies. However, in the AAT-deficient group, allele frequencies were significantly different (0.557 and 0.442, respectively). The OR for the 105Val allele was 2.09 (95% CI, 1.17 to 3.72) when comparing the AAT-deficient group with control subjects; and the OR was 2.41 (95% CI, 1.27 to 4.59) when comparing the AAT-deficient group with COPD patients.

Table 2—Distribution of GSTP1 Polymorphisms in Patients With COPD, AAT Deficiency, and in Healthy Volunteers*

<table>
<thead>
<tr>
<th>Patients</th>
<th>Ile/Ile</th>
<th>Ile/Val</th>
<th>Val/Val</th>
<th>p Value vs General Population†</th>
<th>p Value vs AAT Deficient†</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD (n = 98)</td>
<td>52 (53.1)</td>
<td>36 (36.7)</td>
<td>10 (10.2)</td>
<td>0.51</td>
<td>0.012</td>
</tr>
<tr>
<td>AAT deficient (n = 60)</td>
<td>22 (31.8)</td>
<td>33 (47.8)</td>
<td>14 (20.2)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>General population (n = 198)</td>
<td>97 (49)</td>
<td>88 (44)</td>
<td>13 (6.6)</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

*Data are presented as No. (%).
†χ² test.
Lung Function in Relation to GSTP1 Genotype

The association between the different GSTP1 genotypes and lung function measured by the FEV₁ as percentage of predicted was analyzed separately in the COPD group, all of whom were smokers or former smokers, and in the 40 smokers or former smokers with AAT deficiency. Patients with COPD showed a similar age and lung function impairment in the three groups (Ile/Val/Val, Ile/Ile/Vie, Ile/Ile), despite higher (but not significant) tobacco consumption in the Val/Val group (Table 4). In contrast, in the AAT-deficient patients, significant differences were observed in lung function (analysis of variance, p = 0.028). Homozygous Ile/Ile patients showed better preserved lung function (mean FEV₁ percentage of predicted, 59.9%; SD, 28.2%) compared to both the Ile/Val and Val/Val groups (37.2%; SD, 25.3%; and 33.6%; SD, 11.4%, respectively). The test had a calculated power of 77% to detect these significant differences. The three groups were of similar age (p = 0.37), and cumulative tobacco consumption was also similar (p = 0.34) [Table 4].

To investigate the association of the different genotypes with the impairment in FEV₁ percentage of predicted, a regression model was constructed adjusting for age and smoking history. No significant association was observed in the different genotypes of the GSTP1 with lung function in the group of patients with COPD. Furthermore, variables considered as independent were not sufficient to explain the variability in FEV₁ percentage of predicted (coefficient of determination, $R^2 = 6\%$; F test for global significance, p = 0.26). In contrast, the 105Ile/Ile genotype was independently and significantly associated with a better FEV₁ percentage of predicted in patients with AAT deficiency (p = 0.016) after adjusting for age and tobacco consumption. However, the presence of only one Ile allele was not associated with a better FEV₁ percentage of predicted (p = 0.62). In patients with AAT deficiency, age (p = 0.030) was also independently associated with impairment in lung function and tobacco consumption was of borderline significance (p = 0.053). Globally, GSTP1 genotypes, age, and tobacco smoking explained 41% of total FEV₁ percentage of predicted variability in patients with AAT deficiency ($R^2 = 41\%$; F test, p = 0.001) [Table 5].

**Discussion**

In this study, the distribution of GSTP1 polymorphisms in patients with smoking-related COPD was similar to that observed in the general population of our area. Individuals with AAT deficiency, however, presented a significant, twofold increase in 105Val allele frequency as compared to both COPD patients and the general population. Smokers with AAT deficiency and carriers of 105Val appeared to be at an increased risk for lung function impairment. However, the GSTP1 genotypes studied did not seem to influence the severity of lung function impairment in patients with COPD and normal AAT concentrations.

GSTP1 genotyping was performed with the LightCycler system, a unit that combines a microvolume fluorometer with a rapid thermal cycler approach to

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**Table 3—Allele frequencies of GSTP1 in Patients with COPD, Patients With AAT Deficiency, and Healthy Control Subjects**

<table>
<thead>
<tr>
<th>Participants</th>
<th>Ile allele</th>
<th>Val allele</th>
<th>OR (CI 95%) vs General Population</th>
<th>OR (CI 95%) vs AAT Deficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD patients (n = 98)</td>
<td>0.714</td>
<td>0.286</td>
<td>1.17 (0.72–1.91) [p = not significant]</td>
<td>2.41 (1.27–4.59) [p = 0.007*]</td>
</tr>
<tr>
<td>AAT-deficient patients (n = 69)</td>
<td>0.557</td>
<td>0.442</td>
<td>2.09 (1.17–3.72) [p = 0.01*]</td>
<td></td>
</tr>
<tr>
<td>General population (n = 198)</td>
<td>0.712</td>
<td>0.288</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*χ² test.

**Table 4—Clinical and Functional Characteristics of Patients (Smokers and Former Smokers) According to the Different Genotypes of GSTP1*  

<table>
<thead>
<tr>
<th>COPD Patients (n = 98)</th>
<th>AAT-Deficient Patients (n = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ile/Ile (n = 53)</td>
<td>Ile/Val (n = 36)</td>
</tr>
<tr>
<td>Age, yr</td>
<td>57.3 (9.2)</td>
</tr>
<tr>
<td>Pack-years</td>
<td>49.3 (18.7)</td>
</tr>
<tr>
<td>FEV₁, % predicted</td>
<td>37.9 (13.8)</td>
</tr>
</tbody>
</table>

*Data are presented as mean (SD).
†Analysis of variance.
The United Kingdom,16 the Netherlands,26 and Nor-
volunteers was similar to that of white populations in
COPD, and for screening AAT deficiency linked
hydrolase and susceptibility to development of
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-40-
that seen in African-Americans13 and higher than
However, the 105Val allele frequency was lower than
in earlier studies,21,24,25 we evaluated the association
formance of large molecular studies within a reason-
DNA amplification and provides simultaneous de-
tection of genetic polymorphisms, allowing easy per-
formance of molecular studies within a reason-
able length of time. With the use of this technology
in earlier studies,21,24,25 we evaluated the association
between polymorphisms of the microsomal epoxide
hydrolase and susceptibility to development of
COPD, and for screening AAT deficiency linked
with the PI Z and PI S alleles. In the present study,
the prevalent of the GSTP1 genotypes in healthy
volunteers was similar to that of white populations in
the United Kingdom,16 the Netherlands,26 and Nor-
way,27 and in European-American individuals.13
However, the 105Val allele frequency was lower than
that seen in African-Americans13 and higher than
that in Japanese populations (p < 0.05).28,29 The
comparative genotype frequencies suggest that there
may be racial or ethnic differences with respect to
the metabolism of chemicals detoxified by GSTP1
and, potentially, differences in susceptibility to spe-
cific exposure-induced diseases among these
populations. Studies in large series are required to ade-
quately investigate these interethnic differences in
normal populations.

The most important risk factor for the develop-
ment of COPD is cigarette smoking. Tobacco smoke
contains several thousand toxic chemical products,
some of which are capable of generating reactive
epoxides by direct combustion or metabolic conver-
sion.9 Many of these elements are detoxified by
phase II enzymes.13,27,29,30 One important class of
these enzymes is GSTP1, which has an important
role in protecting the lung against damage by elec-
trophilic substances, xenobiotic oxidants, and reactive
oxygen, modulating the detoxification of epox-
ides and other reactive intermediates. Two allelic
variants of the GSTP1 gene have been identified by
the codon 105 polymorphism. Molecular modeling
analyses of these variants have shown that substitu-
tions at this position change the GSTP1 active site
architecture, giving different kinetic properties to
both allelic variants.9 In this study, we investigated
the possible association between impaired lung func-
tion in smokers and without AAT deficiency and
GSTP1 genotypes. No statistically significant differ-
ences were found in the allelic frequency of the two
GSTP1 polymorphisms between COPD patients
without AAT deficiency and the general population.
Although this is not a proper case-control study,
these results suggest that these polymorphisms do
not confer increased susceptibility to smoking-in-
duced COPD in our population. However, there is a
potential for confounding by smoking history and
misclassification of younger healthy subjects who
may have subclinical COPD, both resulting in a
potential bias toward the null in the comparison
between COPD patients and the healthy population.
A well-designed case-control study is required to
confirm our findings.

In keeping with our results, a nonsignificant in-
crease in the proportion of homozygous 105Val
status among British patients with COPD as com-
pared to healthy control subjects has been report-
ed.16 In contrast, a Japanese study17 observed a
statistically significant increase in the frequency of
homozygous 105Ile status in a sample of COPD
patients, suggesting an association between the
GSTP1 Ile105 polymorphism and the development
of COPD. The authors suggested that the Ile105
allele may be less protective against xenobiotics in
tobacco smoking. However, it is important to note
that this study was performed with a small number of
healthy volunteers and the 105Ile allele frequency
observed was lower than that reported in two pre-
vious studies28,29 in healthy Japanese volunteers. In
studies with a limited control sample size, the results
should be interpreted with caution. In fact, a large
study31 involving 1,098 individuals with different
degrees of lung function impairment found a signif-
icant association of the 105Val allele and a rapid
decline in lung function in smokers with mild-to-
moderate airflow obstruction. These results,
together with ours, suggest that the 105Val mutation
is a risk factor for rapid decline of lung function in
smokers; however, the impact of this mutation is low
and studies in large populations, or individuals with
other risk factors such as AAT deficiency, may be
required to demonstrate this association.

Hereditary deficiency of AAT is strongly associ-
ated with an increased risk of developing COPD. It
has been described that reactive xenobiotics directly
inhibit antiproteases and increase protease secretion
from neutrophils. A combination of oxidative attack
and changes in antiprotease activity could amplify
the lung tissue damage of COPD. In this study, we
analyzed GSTP1 polymorphisms in individuals with

Table 5—Results of the Regression Models for the
Group of Patients With Smoking-Related COPD and
the Group of Smokers or Former Smokers With AAT
Deficiency*

<table>
<thead>
<tr>
<th>Variables</th>
<th>COPD Group (n = 98)†</th>
<th>AAT-deficiency Group (n = 40)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>p Value</td>
</tr>
<tr>
<td>Ile/Ile vs other genotypes</td>
<td>−0.098</td>
<td>0.591</td>
</tr>
<tr>
<td>Ile/Val vs other genotypes</td>
<td>−0.192</td>
<td>0.293</td>
</tr>
<tr>
<td>Age</td>
<td>−0.152</td>
<td>0.293</td>
</tr>
<tr>
<td>Pack-years</td>
<td>0.153</td>
<td>0.150</td>
</tr>
</tbody>
</table>

*Dependent variable is FEV1 percentage of predicted.
†R² = 6%; F test for global significance, p = 0.26.
‡R² = 41%; F test for global significance, p = 0.01.
AAT deficiency to determine whether the combination of these genetically determined factors influences the progression of lung disease. Our results show a significantly increased proportion of homozygous Val/Val in the group of AAT-deficient subjects. The frequency of the 105Val allele was twofold greater in this group than in the other two groups. Studies of genetic determinants of impairment of lung function in AAT-deficient individuals are scant. Novoradovsky et al. found a significantly increased frequency of 774T and 894T alleles of endothelial nitric oxide synthase in severely affected patients with the deficiency, whereas patients with less severe lung disease had similar allele frequencies compared with the control population. It is well recognized that the severity of lung function impairment is highly variable in AAT deficiency, a fact that is only partly explained by differences in smoking habits. Poly-morphisms in genes such as GSTP1 that codify other molecules involved in the detoxification of tobacco smoke compounds or environmental pollutants may modulate the degree of lung damage in AAT-deficient individuals.

Interestingly, in patients with COPD and normal AAT levels, lung function was not significantly different among the GSTP1 genotypes. However, patients with AAT deficiency carriers of 105Val exhibited significantly impaired FEV1, a fact that cannot be attributed to differences in age or tobacco consumption. These data suggest that 105Ile may be more protective against xenobiotics in tobacco smoke than 105Val, as reported previously. Moreover, the present results suggest that the protective effect of 105Ile may be low since the polymorphism is only expressed when inherited in the homozygous form in patients lacking AAT and there is no protective effect when AAT concentrations are normal, suggesting that the protection conferred by AAT is of higher magnitude or relevance. Since it was not possible to randomly select the sample of patients with AAT deficiency, the possibility of a selection bias in favor of the 105Val allele cannot be ruled out. However, it is remarkable that the same bias, if it really exists, does not affect the population of smoking-related COPD. Studies in larger populations of patients with AAT deficiency are required to confirm these findings.

In summary, patients with AAT deficiency had an increased prevalence of 105Val GSTP1 polymorphism compared with the general population and patients with smoking-related COPD. AAT-deficient patients who were homozygous for the 105Ile variant seemed to have a decreased risk for lung damage. The protective effect of the 105Ile variant was of lesser magnitude than that conferred by AAT, and was therefore not detected in patients with COPD and normal AAT concentrations.

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