






Pulmonary Function and Respiratory Diseases in Different Genotypes of Alpha-1 Antitrypsin Deficiency

José María Hernández Pérez¹, Juan José Suárez Sánchez², Claudia Viviana López Charry¹, Yolanda Ramallo Fariña^{3,4,5}, José Antonio Pérez Pérez⁶

¹Department of Pulmonology, Hospital Universitario Nuestra Señora de Candelaria [Our Lady of Candelaria University Hospital], Santa Cruz de Tenerife, Canary Islands, Spain

²Faculty of Health Sciences, Universidad de Las Palmas de Gran Canaria [Las Palmas de Gran Canaria University], Canary Islands, Spain

³Foundation of the Canary Islands Health Research Institute (FIISC), Santa Cruz de Tenerife, Spain

⁴Health Services Research on Chronic Patients Network (REDISSEC), Madrid, Spain

⁵Research Network on Chronic Disease, Primary Care, and Health Promotion (RICAPPS), Madrid, Spain

⁶Department of Biochemistry, Microbiology, Cellular Biology and Genetics, Canary Islands, Spain

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Abstract

OBJECTIVE: Respiratory disease is the major cause of morbidity and mortality in patients with alpha-1 antitrypsin deficiency, mainly in homozygous *PI*ZZ* individuals. However, this association is uncertain in subjects with other deficiency genotypes. The objective of this study was to assess, in the context of alpha-1 antitrypsin deficiency, the existence of further risk factors that have been associated with respiratory diseases.

MATERIAL AND METHODS: Lung function was assessed by spirometry in a sample of 1334 patients with a known genotype for the *SERPINA1* gene whose serum alpha-1 antitrypsin levels had been previously determined. Patients with a normal genotype (*PI*MM*) were compared to 389 patients carrying a deficiency allele.

RESULTS: Statistically significant associations were detected between (i) *PI*ZZ* genotype and abnormal FEV₁ values ($\chi^2 = 26.45$; $P < .0002$), FEV₁/FVC ($\chi^2 = 14.8$; $P < .02$) or forced mid-expiratory flow 25%-75% ($\chi^2=22.66$; $P < .0009$); (ii) chronic obstructive pulmonary disease and *PI*ZZ* odds ratio: 26.5; 95% CI: (2.6-265.9); $P < .005$ and or *PI*SS* genotype odds ratio: 9; 95% CI: (2-40.1); $P < .004$; (iii) prevalence of COPD in *PI*MZ* subjects and smoking habit ($P < .01$), low body weight ($P < .01$) or older age ($P < .0001$).

CONCLUSION: The *PI*ZZ* and *PI*SS* genotypes seem to be associated with the prevalence of chronic obstructive pulmonary disease. Tobacco use, low body weight, and older age are risk factors that increase the probability of prevalence of chronic obstructive pulmonary disease by up to 70% in *PI*MZ* individuals.

KEYWORDS: Alpha-1 antitrypsin deficiency, spirometry, lung function, chronic obstructive pulmonary disease, respiratory disease

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INTRODUCTION

Alpha-1 antitrypsin deficiency (AATD) is a genetic condition that predisposes a person to certain diseases over their lifetime, including lung disease (in the form of emphysema), liver disease (liver cirrhosis), panniculitis, and vasculitis.¹ Alpha-1 antitrypsin deficiency-related lung disease usually occurs in adulthood. It is the most common cause of morbidity and mortality in patients with severe AATD and accounts for around 2% of all patients with chronic obstructive pulmonary disease (COPD).^{2,3} Spirometry in AATD shows an obstructive pattern and the degree of involvement is related to the severity of the disease and survival.⁴ Patients with the *PI*ZZ* genotype, particularly those who smoke, are at higher risk of developing emphysema.⁵ The relationship is not so clear in subjects with the *PI*MZ* genotype, although some authors have found a larger drop in forced expiratory volume in the first second (FEV₁), especially among active and former smokers.⁶ Ortega et al⁷ observed that patients with *PI*MZ* showed had lower postbronchodilator FEV₁, FEV₁/FVC, and greater computed tomography-based emphysema compared with White individuals without *PI Z, S*, or additional rare variants. Foreman et al⁸ demonstrated that *PI*MZ* heterozygous individuals who smoke are at increased risk for COPD and obstructive lung function impairment compared with *Z*-allele noncarriers, regardless of race. Our objectives were to determine if there are other deficient genotypes other than the *PI*ZZ* genotype, which may be associated with the development of COPD. To identify the characteristics of patients with the *PI*MZ* genotype who have developed COPD.

Corresponding author: José Antonio Pérez Pérez, e-mail: joanpere@ull.edu.es

MATERIAL AND METHODS

Study Design

This was an observational, cross-sectional, analytic study in which a total of 1510 patients who consecutively attended the respiratory medicine outpatient clinic for any reason were included and analyzed. They were divided into 2 comparable groups: 1 group of subjects with a normal genotyping result (Pi^*MM -control group) and another group of subjects with a different genotyping result ($Pi^*\neq MM$). The objectives of the study were to see if genotypes other than Pi^*ZZ have increased in the prevalence of COPD and the percentage of alteration of spirometry values. The study was conducted in accordance with the Declaration of Helsinki. This study was approved by the ethics committee of the Hospital [HGLaPalma_2010_7], and all patients were informed of the study objectives and signed an informed consent. In the case of minors, their parent or guardian signed the consent.

Inclusion criteria were patients who properly performed the spirometry technique, patients who had undergone genotyping of the SERPINA1 gene, patients whose alpha-1 antitrypsin (AAT) levels had been measured via blood clinical chemistry, and patients who expressed their agreement to participate in the study by signing the informed consent form.

Exclusion criteria were patients diagnosed with at least 2 respiratory diseases, patients who could not perform spirometry for various reasons, and patients whose spirometry did not meet the reproducibility criteria.

Patients

After the SERPINA1 gene was genotyped by real-time polymerase chain reaction with HybProbe probes and/or DNA sequencing,^{9,10} the patients were divided into 2 groups: those with normal genotyping (Pi^*MM ; 945 individuals) and those carrying a deficient allele (Pi^*S , Pi^*Z or rare variants; 389 individuals). Measurement of each patient's serum AAT levels was performed by immunonephelometry.

Determination of Lung Function by Spirometry

Forced spirometry was performed using the Dataspir 600 spirometer (Silbimed®). Each individual performed at least 3 maneuvers in the pre-bronchodilator and post-bronchodilator tests, with a deviation of less than 200 mL in the measurements of forced vital capacity (FVC) and FEV_1 established as a reproducibility criterion. Acceptability criteria were determined in the analysis of the curve performed by assessing the start (FEV_1 and maximum expiratory flow), the morphology of the flow-volume (FV) curve, the volume-time (VT) curve, and the end with a minimum duration of 6 seconds of forced expiration, following standard quality criteria.¹¹

Four variables were used to define an impaired respiratory function: FEV_1 , abnormal if less than 80%; FVC, abnormal if below 80%; FEV_1/FVC ratio, abnormal if below 70%; forced mid-expiratory flow at 25% and 75% of the pulmonary volume ($FEF_{25\%-75\%}$), defined as abnormal if less than 60%.¹¹

Definition of Respiratory Disease

The following respiratory diseases were diagnosed based on a range of different investigations and tests: bronchial asthma, defined according to the criteria of the Guía Española para el Manejo del Asma [Spanish Asthma Management Guidelines] (GEMA)¹²; COPD, defined according to the criteria of the Guía Española de Diagnóstico y Tratamiento de la Enfermedad Pulmonar Obstructiva Crónica [Spanish Guidelines for Diagnosis and Treatment of Chronic Obstructive Pulmonary Disease] (GesEPOC)¹³; sleep apnea-hypopnea syndrome (SAHS), defined according to the criteria of the Spanish guidelines for diagnosis and treatment of SAHS¹⁴; obesity hypoventilation syndrome (OHS), also defined according to the Spanish guidelines for SAHS¹⁴; non-specific bronchial hyperresponsiveness, defined as the excessive narrowing of the airway lumen in response to physical or chemical stimuli that usually only cause little or no reduction in the lumen, which can be detected, temporarily or permanently, accompanying other situations (exposure to environmental contaminants and irritants, viral infections of the respiratory tract, chronic bronchitis, rhinitis, sarcoidosis, mitral stenosis, bronchopulmonary dysplasia, etc.), or even in apparently healthy subjects.¹⁵

In other diseases, small percentages of other pathologies of the respiratory system were grouped, for example, diffuse interstitial lung diseases, bronchiectasis, pulmonary neoplasms, neurological diseases with pulmonary involvement (amyotrophic lateral sclerosis), alterations of the rib cage, non-specific pleural effusions, and pneumothorax.

Statistical Analysis

Qualitative variables were summarized as frequencies and percentages and continuous variables as means and standard deviations (SD). For continuous normal variables, bivariate comparisons between independent samples were made using Student's *t*-test or ANOVA depending on the number of groups to compare. Qualitative variables were tested by means of chi-square or Fisher's exact test, as applicable. To compare the frequency between 2 samples, Z test was used. To study the association of the sample characteristics with the diagnosis of COPD, a multivariate logistic regression was implemented, including the variables with *P*-value <.1 in the bivariate analysis. Odds ratio (OR) and its 95% CI were obtained as a measure of association and Nagelkerke's *R* squared as a measure of goodness of fit. A *P*-value of <.05 was considered statistically significant. Analyses were performed using the Statistical Package for Social Sciences version 21.0 software (IBM Corp.; Armonk, NY, USA).

RESULTS

Baseline Characteristics

Out of the sample of 1510 patients, 176 were excluded because they did not meet the inclusion criteria. The final study sample consisted of 1334 patients; the majority were

MAIN POINTS

- In addition to the Pi^*ZZ genotype, Pi^*SS has also been associated with the prevalence of chronic obstructive pulmonary disease (COPD).
- In patients with the Pi^*MZ genotype, being underweight, a smoker, and being older are also risk factors that increase the prevalence of COPD.

Table 1. Baseline Characteristics of the Patients

	No Respiratory Pathology (n = 158)	Asthma (n = 455)	COPD (n = 383)	SAHS/OHS (n = 164)	HBR (n = 85)	Others (n = 89)	Total (n = 1334)	P
Sex, women, n (%)	89 (56.3)	286 (62.9)	55 (14.4)	41 (25)	50 (58.8)	43 (48.3)	564 (42.3)	<.001 ¹
Age, mean (SD)	43.6 (15.8)	47.5 (19.3)	67.7 (12.4)	61.7 (11.8)	58 (17.2)	65.4 (15.6)	56.4 (18.5)	<.001 [¥]
Weight, kg	75.6 (17.5)	78.8 (18.2)	80.6 (17.4)	98 (17.3)	83.4 (14.2)	75.6 (16)	81.4 (18.6)	<.001 [¥]
BMI, kg/m ² , mean (SD)	27.2 (5.4)	28.7 (6)	28.3 (5.8)	34.2 (5.9)	31 (4.9)	28.6 (5.7)	29.2 (6.1)	<.001 [¥]
Smoking, n (%)								<.001 ¹
Non-smokers	103 (65.2)	299 (65.7)	14 (3.7)	68 (41.5)	50 (58.8)	44 (49.4)	578 (43.3)	
Former smokers	31 (19.6)	106 (23.3)	238 (62.1)	66 (40.2)	23 (27.1)	29 (32.6)	493 (37)	
Smokers	24 (15.2)	50 (11)	131 (34.2)	30 (18.3)	12 (14.1)	16 (18)	263 (19.7)	
Genotype, n (%)								<.001 ¹
<i>Pi</i> *MM	57 (36.1)	334 (73.4)	288 (75.2)	133 (81.1)	63 (74.1)	70 (78.7)	945 (70.8)	
<i>Pi</i> *MS	44 (27.8)	73 (16)	60 (15.7)	26 (15.9)	14 (16.5)	11 (12.4)	228 (17.1)	
<i>Pi</i> *SS	1 (0.6)	5 (1.1)	12 (3.1)	0 (0)	1 (1.2)	1 (1.1)	20 (1.5)	
<i>Pi</i> *MZ	35 (22.2)	30 (6.6)	16 (4.2)	4 (2.4)	4 (4.7)	5 (5.6)	94 (7)	
<i>Pi</i> *SZ	10 (6.3)	8 (1.8)	2 (0.5)	1 (0.6)	2 (2.4)	2 (2.2)	25 (1.9)	
<i>Pi</i> *ZZ	2 (1.3)	0 (0)	4 (1)	0 (0)	0 (0)	0 (0)	6 (0.4)	
Rare variants	9 (5.7)	5 (1.1)	1 (0.3)	0 (0)	1 (1.2)	0 (0)	16 (1.2)	
Altered genotype (S o Z), n (%)	92 (61.7)	116 (25.8)	94 (24.6)	31 (18.9)	21 (25)	19 (21.3)	373 (28.3)	<.001 ¹
Serum AAT, mg/dL, mean (SD)	98.1 (27)	125.7 (29)	134.9 (34.8)	124 (23.3)	119.9 (26)	134.1 (32)	125.1 (31.9)	<.001 [¥]
FVC (mL), mean (SD)	4043.1 (1053.8)	3591 (1154.1)	3021.9 (950.5)	3599.3 (1051.1)	3332.1 (1037.5)	2691.2 (1144.4)	3405.6 (1128.7)	<.001 [¥]
FVC (%), mean (SD)	96.4 (12.2)	89 (15.8)	70.6 (18.8)	83.1 (15.2)	88.1 (16.4)	71.8 (19)	82.6 (19)	<.001 [¥]
FEV ₁ (mL), mean (SD)	3375 (882.1)	2847.4 (973)	1934.4 (767.6)	2953.8 (855.8)	2671.2 (882.6)	2135.4 (896.6)	2602.1 (1012)	<.001 [¥]
FEV ₁ (%), mean (SD)	104 (13.5)	91.3 (17.2)	62.5 (20.8)	93.2 (16.5)	95.4 (17.7)	79 (20.4)	84.2 (2.3)	<.001 [¥]
FEV ₁ /FVC (mL), mean (SD)	83.6 (6.3)	78.9 (8.9)	63.4 (12.3)	82.3 (6.7)	80.2 (6.6)	79.9 (9.1)	75.6 (12.3)	<.001 [¥]
MEF25-75 (mL), mean (SD)	3664.7 (1236.6)	2784.2 (1342.3)	1277 (929.4)	3196.7 (1220.1)	2630 (1216.8)	2198.5 (1130.2)	2457.6 (1443.6)	<.001 [¥]
MEF25-75 (%), median (SD)	117.7 (37.6)	95.2 (39.5)	50.7 (32)	123.3 (45.9)	114.8 (59.2)	105.9 (54.1)	90.5 (49)	<.001 [¥]
Altered FVC, n (%)	16 (10.1)	118 (25.9)	263 (68.7)	73 (44.5)	20 (23.5)	57 (64)	547 (41)	<.001 [¥]
Altered FEV ₁ , n (%)	6 (3.8)	106 (23.3)	304 (79.4)	37 (22.6)	15 (17.6)	42 (47.2)	510 (38.2)	<.001 [¥]
Altered FEV ₁ /FVC, n (%)	3 (1.9)	65 (14.3)	269 (70.2)	6 (3.7)	6 (7.1)	12 (13.5)	361 (27.1)	<.001 [¥]
Altered MEF25-75, n (%)	5 (3.2)	79 (17.4)	269 (70.2)	7 (4.3)	5 (5.9)	14 (15.7)	379 (28.4)	<.001 [¥]

Data are presented as median ± SD, n (%).

¹Chi-square test.[¥]ANOVA.

P-value of <.05 was considered statistically significant.

BMI, body mass index; AAT, alpha-1 antitrypsin; COPD, chronic obstructive pulmonary disease; SAHS/OHS, sleep apnoea-hypopnoea syndrome; HBR, non-specific bronchial hyperresponsiveness. FEV₁, forced peak expiratory volume in the first second; FVC, forced vital capacity; FEF 25%-75%, forced mid-expiratory flow rate at 25% and 75% of the forced vital capacity; SD, standard deviation.

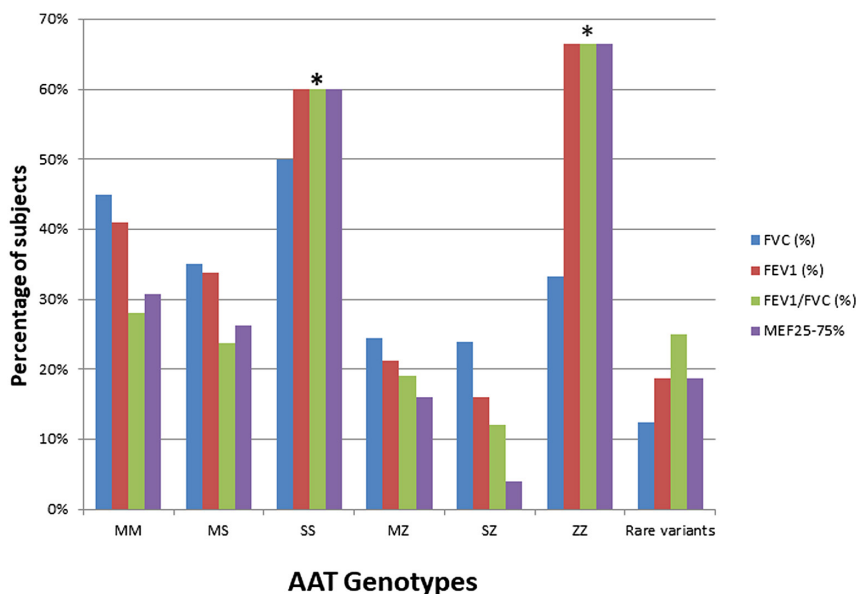


Figure 1. Association between AAT genotypes and abnormal lung function parameters: FVC (<80%), FEV₁ (<80%), (FEV₁/FVC <70%), and FEF at 25%-75% of the pulmonary volume (25%-75% <60%). There is a statistically significant association between the *Pi**ZZ and *Pi**SS genotype and impaired lung function (chi-square test (**P* < .05)). AAT, alpha-1 antitrypsin; FVC, forced vital capacity; FEV₁, forced expiratory volume in the first second; FEF, forced mid-expiratory flow.

males (57.7%) and non-smokers, with a mean age of 56.4 and a mean body mass index (BMI) of 29.2 kg/m² (±SD: 6.1). Of these patients, 34.1% were diagnosed with bronchial asthma and 28.4% with COPD. In addition, 27.1% of the patients in the sample had an obstructive pattern (FEV₁/FVC <70%), and forced vital capacity was abnormal in 41.08%. FEV₁ and MEF 25%-75% were decreased in 38.2% and 28.4% of the patients, respectively. A summary of the other characteristics of the patients is shown in Table 1.

Association Between Genotypes and Lung Function Parameters

In our sample, a statistically significant association was found between the *Pi**ZZ genotype and the different lung function parameters, with a chi-squared statistic value for FEV₁ = 26.45, *P* < .0002; FEV₁/FVC = 14.8, *P* < .0002; and FEF 25%-75% = 22.66, *P* < .0009, also *Pi**SS genotype and the different lung function parameters, with a chi-squared statistic value for FEV₁ = 34.96, *P* < .024; FEV₁/FVC = 23.95, *P* < .001; and FEF 25%-75% = 28.79, *P* < .001 (Figure 1).

Association Between Genotypes and Respiratory Disease

In Table 2, in studying the association with COPD independently for each of the variables, we observe that being male, being older, and being a smoker or ex-smoker, all genotypes except *Pi**MS, level of ATT, and lung function parameters are more associated with patients with COPD than patients free of the disease.

Multivariate logistic regression shows that *Pi**ZZ and *Pi**SS were found to be predictors of having COPD with value OR: 26.5; 95% CI: (2.6-265.9); *P* < .005 and OR: 9; 95% CI: (2-40.1); *P* < .004, respectively (Table 3). The association with COPD of the rest of the variables is maintained once the ORs have been adjusted in the multivariate analysis.

We also wanted to know if there were risk factors for increasing the prevalence of COPD in patients with the *Pi**MZ

genotype, so we examined patients with COPD in this genotype group to try to determine which variables could predict the increase of the disease. The results showed that patients with a *Pi**MZ genotype who are smokers (*P* < .01), underweight (*P* < .01), and older (*P* < .0001) have a likelihood of prevalence of a respiratory disease of more than 70% (Table 4).

DISCUSSION

This study assessed lung function in patients with AATD genotypes and identified risk factors for the increase in the prevalence of lung disease. In the vast majority of cases, patients with the *Pi**ZZ allele developed lung disease in the form of emphysema, as reported in the literature^{2,16} Previous studies associated impaired lung capacity assessed by FEV₁ spirometry with both disease severity and survival,⁴ particularly when accompanied by smoking,^{2,16,17} yielding an obstructive pattern characteristic of these patients. In our cohort, this association was statistically significant in the parameters FEV₁, FEV₁/FVC, and FEF 25%-75% (Table 2); our data were in line with previously reported data.^{16,18}

First of all, there was a statistically significant association between the *Pi**ZZ genotype and the prevalence of COPD. In this study, patients with *Pi**ZZ genotypes and those with rare variants have not been added because rare variants were published in another article in more detail.¹⁹ We also found that the patients with the highest percentage of an obstructive pattern were those with the lowest AAT levels, rendering this association equally statistically significant (*P* < .005). Moreover, we detected another genotype, *Pi**SS, which has been linked to an increase in prevalence of COPD (*P* < .004) (Figure 2). In our cohort, no statistically significant association was found between the *Pi**MZ genotype and COPD. However, when performing logistic regression to identify the characteristics of patients with the *Pi**MZ genotype who had an increased prevalence of COPD, we found a statistically significant association between being

Table 2. Comparison of Characteristics of Patient's Presence or Absence of COPD

	No COPD (n = 951)	COPD (n = 383)	P
Sex, women, n (%)	509 (53.5)	55 (14.4)	<.001 [¥]
Age, mean (SD)	51.9 (18.7)	67.7 (12.4)	<.001 ¹
Weight, mean (SD)	81.7 (19)	80.6 (17.4)	.302 ¹
BMI, kg/m ² mean (SD)	29.6 (6,2)	28.3 (5.8)	<.001 ¹
Smoking, n (%)			<.001 [¥]
Non-smokers	564 (59.3)	14 (3.7)	<.001 [£]
Former smokers	255 (26.8)	238 (62.1)	<.001 [£]
Smokers	132 (13.9)	131 (34.2)	<.001 [£]
Genotype, n (%)			<.001 [¥]
<i>Pi*MM</i>	657 (69.1)	288 (75.2)	.026 [£]
<i>Pi*MS</i>	168 (17.7)	60 (15.7)	.38 [£]
<i>Pi*SS</i>	8 (0.8)	12 (3.1)	.002 [£]
<i>Pi*MZ</i>	78 (8.2)	16 (4.2)	.009 [£]
<i>Pi*SZ</i>	23 (2.4)	2 (0.5)	.021 [£]
<i>Pi*ZZ</i>	2 (0.2)	4 (1)	.039 [£]
Rare variant	15 (1.6)	1 (0.3)	.046 [£]
Altered genotype (S o Z), n (%)	279 (29.8)	94 (24.6)	.057 [¥]
Serum ATT, mg/dL, mean (SD)	121 (29.8)	134.9 (34.8)	<.001 ¹
FCV (mL), mean (SD)	3560.2 (1158)	3021.9 (950.5)	<.001 ¹
FVC (%), mean (SD)	87.5 (16.8)	70.6 (18.8)	<.001 ¹
FEV ₁ (mL), mean (SD)	2871 (973.7)	1934,4 (767.6)	<.001 ¹
FEV ₁ (%), mean (SD)	92.9 (18)	62.5 (20.8)	<.001 ¹
FEV ₁ /FVC (mL), mean (SD)	80.5 (8.2)	63.4 (12.3)	<.001 ¹
MEF25-75(mL), mean (SD)	2933 (1337.5)	1277 (929.4)	<.001 ¹
MEF25-75 (%), mean (SD)	106.5 (45.4)	50.7 (32)	<.001 ¹
Altered FVC, n (%)	284 (29.9)	263 (68.7)	<.001 [¥]
Altered FEV ₁ , n (%)	206 (21.7)	304 (79.4)	<.001 [¥]
Altered FEV ₁ /FVC, n (%)	92 (9.7)	269 (70.2)	<.001 [¥]
Altered MEF25-75, n (%)	110 (11.6)	269 (n = 70.2)	<.001 [¥]

Data are presented as median ± SD or n (%).
¹Student's *t*-test.
[¥]Chi-square test.
[£]Z test.
 P-value of <.05 was considered statistically significant.
 BMI, body mass index; AAT, alpha-1 antitrypsin; COPD, chronic obstructive pulmonary disease; SAHS/OHS, sleep apnoea-hypopnoea syndrome; BHR, non-specific bronchial hyperresponsiveness. FEV₁, forced peak expiratory volume in the first second; FVC, forced vital capacity; FEF 25%-75%, forced mid-expiratory flow rate at 25% and 75% of the forced vital capacity; SD, standard deviation.

Table 3. Multivariate Logistic Regression for the Presence or Absence of COPD

	Beta	Wald	OR (95% CI)	P
Sex (ref: women)	0.93	18.5	2.53 (1.66-3.86)	<.001
Age	0.07	84.0	1.07 (1.05-1.08)	<.001
BMI	-0.06	17.5	0.94 (0.91-0.97)	<.001
Smoking habit (ref: non smokers)				
Former smokers	2.7	72.3	15.41 (8.21-28.95)	<.001
Smokers	3.8	121.4	46.54 (23.5-92.14)	<.001
Serum ATT	0.01	8.8	1.01 (1-1.02)	.003
Genotype (ref: <i>Pi*MM</i>)		15.0	0 (0-0)	.020
<i>Pi*MS</i>	0.10	0.17	1.1 (0.69-1.76)	.680
<i>Pi*SS</i>	2.2	8.3	8.98 (2.01-40.12)	.004
<i>Pi*MZ</i>	0.16	0.14	1.18 (0.51-2.72)	.704
<i>Pi*SZ</i>	0.10	0.01	1.1 (0.18-6.81)	.917
<i>Pi*ZZ</i>	3.3	7.8	26.5 (2.64-265.99)	.005
Rare variant	0.86	0.55	2.35 (0.24-22.81)	.460
Constant	-7.4	76.7	--	<.001
R square of Nagelkerke =				0.563

BMI, body mass index; AAT, alpha-1 antitrypsin; COPD, chronic obstructive pulmonary disease.

underweight ($P < .05$), smoking ($P < .0001$), and older age ($P < .05$) and there is a likelihood of an increase in the prevalence of respiratory disease of more than 70%. These results were in line with previous studies conducted by Molloy et al²⁰ and Cazolla et al²¹ in which patients with the *Pi*MZ* genotype and smokers had poorer lung function and a higher risk of increase in prevalence of COPD than patients with the normal *Pi*MM* genotype. We believe that the patients having only 1 Z allele would develop disease in more time, have to be heavier smokers, and need to be predisposed (underweight) to develop disease than patients homozygous for the Z allele, who would develop disease

Table 4. Multivariate Logistic Regression for the Presence or Absence of COPD in Patients with Genotype *Pi*MZ*

	Beta	Z Value	OR (95% CI)	P
Intercept	-2.306 ^{ns}	-1.038	0.100 (0.000-7.370)	.299
Smoking	1.110*	0.498	3.034 (1.197-8.882)	.026
Age	0.102***	3.652	1.108 (1.056-1.181)	.000
BMI	-0.214*	-2.457	0.808 (0.664-0.940)	.014

BMI, body mass index; ns: Not significant. Signif. codes: 0 "****" 0.001 "**" 0.05. Multivariate Logistic Regression in Patients with Genotype *Pi*MZ* for the Presence of COPD.

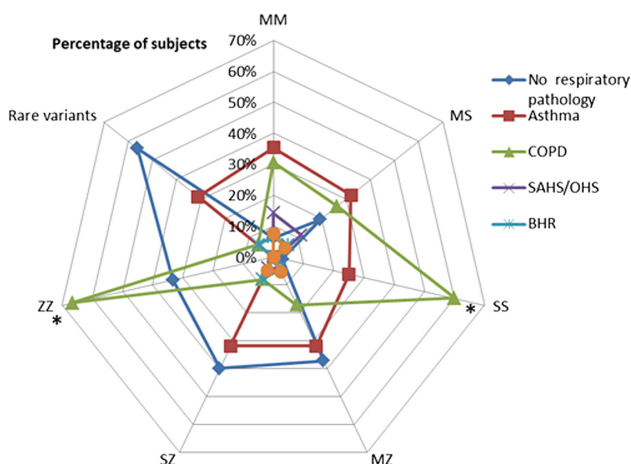


Figure 2. Association between AAT genotypes and respiratory disorders. A statistically significant association was found between the genotypes Pi^*ZZ and Pi^*SS and patients diagnosed with COPD (chi-square test ($*P < .05$)). SAHS/OHS, sleep apnoea-hypopnoea syndrome; BHR, non-specific bronchial hyperresponsiveness; AAT, alpha-1 antitrypsin; COPD, chronic obstructive pulmonary disease.

in less time with a lesser degree of smoking. Longitudinal studies over time would be needed to confirm this theory.

In a study of patients with AATD with Pi^*ZZ , Pi^*SZ and rare variants who had developed disease, Tirado-Conde et al²² showed that underweight patients (BMI <18.5 mg/kg²) had a worse prognosis than those of normal weight. Celli et al²³ showed in their study of the BODE (Body-Mass Index, Airflow Obstruction, Dyspnea and Exercise Capacity Index) cohort in patients with COPD that patients with both COPD and low weight had a worse prognosis, for which reason weight was included in the BODE scale; having a BMI <21 mg/kg² was scored with 1 point on the scale, while having a BMI is >21 was not scored.

Our study found an association between the Pi^*SS genotype and COPD, with the increase in prevalence of respiratory disease being statistically significant ($P < .004$). This suggests a relationship between the previous genotype and this type of respiratory disease, but due to the size of our sample, we must take it with caution. Other studies have found different results, such as the one carried out by Nakanishi et al²⁴ with an important sample size, they found that the Pi^*SS genotype did not show an association with COPD, but nevertheless, the authors themselves acknowledge that having extracted their sample of “healthy” subjects may have influenced the results since the proportion of subjects diagnosed with COPD is much lower than expected. Furthermore, in this study, unlike ours, up to 30% of subjects did not have lung function data, which could underestimate the number of patients with COPD, especially in this specific genotype.

Hobbs et al²⁵ reported a great deal of heterogeneity in the lung function of patients with AATD, and they believed that, despite the existence of external risk factors, certain added genetic modifiers can also promote the development of lung problems.

Our study has the limitations of a cross-sectional observational study. The temporal sequence of the variables studied

could not be established, making it difficult to separate risk factors from prognostic factors. Having extracted our population from a clinical consultation may have influenced our results, although our objective was not to evaluate the incidence or prevalence of AATD but to find possible factors that could favor the increase in prevalence of COPD in patients with different AATD genotypes. The variable of smoking intensity (pack years) was not available and therefore could not be included in the regression study and this may be a factor to take into account in our results. Even so, our data indicated that, in addition to the Pi^*ZZ genotype, other genotypes can also increase the prevalence of respiratory disease in the presence of other associated risk factors.

Ethics Committee Approval: This study was approved by Thics committe of Hospital General de La Palma (HGLaPalma_2010_7).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

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