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ORIGINAL RESEARCH

Alpha-1 Antitrypsin Genotype Distribution in Patients with Emphysema

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Purpose: Alpha-1 antitrypsin deficiency (AATD) is a rare inherited condition characterized by low serum levels of alpha-1 antitrypsin (AAT). In this study, we aimed to determine the frequency of AATD in patients with emphysema, to show the distribution of AATD genotypes according to the type and localization of emphysema, and to evaluate patients in terms of augmentation therapy.

Patients and Methods: This cross-sectional descriptive study included 794 patients with emphysema on high-resolution thoracic tomography (HRCT) between December 2022 and December 2024 at the chest disease clinic of the Samsun Training and Research Hospital. During screening, demographic characteristics (age and sex), smoking status (smoker, ex-smoker, and non-smoker), types of emphysema (centriacinar emphysema, panacinar emphysema, and paraseptal emphysema), and location (upper, middle, and lower lobes) were recorded. Dried blood spot samples collected from the fingertips of patients with emphysema were screened for Alpha-1 Antitrypsin (AAT) genotype deficiency. AAT levels and PFT were evaluated in patients with AATD.

Results: In the AAT genotyping results, no mutations were detected in 763 (96%) patients, while AATD mutations were detected in 31 (4%) patients. While AATD was more common in panacinar emphysema, no mutations were detected in paraseptal emphysema. The most common mutations were PI*M/M malton (n=9), PI*M/Z (n=7), PI*M/I (n=4), and PI*M malton/M malton (n=4). AAT level was found to be low in PI*Z/Z (n=3), PI*M malton/M malton (n=4) and PI*Z/M malton (n=1) genotypes (0.20±0.2 g/L). Six patients received augmentation therapy for AATD: three had PI*Z/Z, two had PI*M malton/M malton, and one had the PI*Z/M malton genotype.

Conclusion: As a result, analyzing AAT genotypes in patients with emphysema may provide an early diagnosis of AATD, allowing the application of preventive measures and augmentation therapy strategies.

Keywords: alpha-1 antitrypsin, emphysema, genotype, augmentation therapy

Introduction

Alpha-1 antitrypsin (AAT) is a serine proteinase inhibitor synthesized from hepatocytes in the liver that plays a protective role against proteolytic enzymes in the body. In particular, AAT inhibits neutrophil elastase (NE) secreted by activated neutrophils during infectious processes and helps to prevent tissue damage. It also inhibits the action of other proteolytic enzymes, such as cathepsin G and proteinase 3.[1]

Alpha-1 antitrypsin deficiency (AATD) is a genetic disorder caused by mutations in SERPINA1 and is characterized by decreased AAT levels. AATD is one of the most common inherited lung diseases. Patients with AATD typically present with symptoms of emphysema at a younger age than those with smoking-related COPD. Although some have a significant history of tobacco use, the disease may also occur in never-smokers. Emphysema, chronic obstructive pulmonary disease (COPD), asthma, and bronchiectasis are all lung diseases associated with AATD.[2,3]

Emphysema is a chronic disease of the lower respiratory tract characterized by the expansion of air spaces distal to the terminal bronchioles as a result of the destruction of alveolar walls.[4] Although this disease is associated with environmental factors such as smoking and air pollution, genetic factors also play an important role. AATD is a known genetic cause of emphysema.[5] Early findings of AATD in the lungs revealed emphysema. Currently, it is being diagnosed

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at a higher rate with the increasing use of computed chest tomography.[6] AATD-related emphysema classically involves the lower lobes and causes Panaciner-type emphysema.[7]

The frequency of AATD has been studied in different parts of the world in chronic lung diseases, such as COPD, asthma, and bronchiectasis, and its frequency has been determined at different rates. Less than 10% of individuals with AATD are diagnosed, and the time between symptom onset and diagnosis is often prolonged.[8] Few studies have been conducted on patients with emphysema, and patient characteristics have not been adequately defined.

In Turkey, the prevalence of AATD has been reported to range between 3% and 5% in patients with chronic lung diseases. Studies have identified both common mutations such as PIM/Z and PIZ/Z and rare alleles like PIM Malton and PIP Lowell in the Turkish population. These findings highlight the genetic variability in AATD across different regions of Turkey and underscore the importance of genotype-based evaluations in emphysema patients.[9–11]

This study was conducted to determine the frequency of AATD, a genetic cause of emphysema, in patients with emphysema, to show the distribution of AATD genotypes by the type and localization of emphysema, and to evaluate patients in terms of augmentation therapy.

Materials And Methods

This cross-sectional descriptive study included patients with emphysema on high-resolution chest tomography (HRCT) between 01.12.2022 and 31.12.2024 in the chest diseases clinic of the Samsun Training and Research Hospital.

Inclusion Criteria

Patients who agreed to participate in the study, provided informed consent, and had emphysema on HRCTwere included in the study.

Exclusion Criteria

Patients Who Refused to Give Fingertip Blood

Approval was obtained from the Samsun University Non-Interventional Clinical Research Ethics Committee (Date: 08.01.25, Decision No: 2025/1/10). This study was conducted in accordance with the principles of the Declaration of Helsinki.Written informed consent was obtained from all the patients after they were informed of their condition.

Based on the relevant literature, the AAT genotyping test simultaneously identified the 14 most common allele variants associated with AAT deficiency. This test is based on genomic DNA amplification using polymerase chain reaction (PCR) and subsequent hybridization with allele-specific probes by utilizing Luminex xMAP technology. Dried blood spot samples collected from the fingertips of patients with emphysema were screened for Alpha-1 Antitrypsin (AAT) genotype deficiency. Genotype analysis (AlphaKits®; GE Healthcare Ltd., Cardiff, CF147YT, UK) was conducted at the Progenika Clinical Diagnostics Laboratory in Spain. The alleles examined in the patients included PI*I, PI*M procida, PI*M malton, PI*S iiyama, PI*Q0 granite falls, PI*Q0 west, PI*Q0 bellingham, PI*F, PI*P lowell, PI*S, PI*Z, PI*Q0 mattawa, PI*Q0 clayton and PI*M heerlen.

During screening, demographic characteristics (age and sex), smoking status (smoker, ex-smoker, and non-smoker), types of emphysema (centriacinar emphysema, panacinar emphysema, and paraseptal emphysema), and location (upper, middle, and lower lobes) were recorded.

Smoking Status

Non-smokers; those who had never smoked

Ex-smokers; those who had quit smoking for at least one year

Current smokers; those who still smoke

Types of Emphysema[12] Figure 1.

A. Centriacinar emphysema: characterized by the destruction of the proximal respiratory bronchioles, while the distal alveolar sacs and ducts remain normal.

B. Panacinar emphysema: characterized by the destruction of proximal respiratory bronchioles, distal alveolar ducts, and sacs.

C. Paraseptal emphysema: Characterized by destruction of the distal alveolar sacs and ducts, while the proximal respiratory bronchioles are preserved.

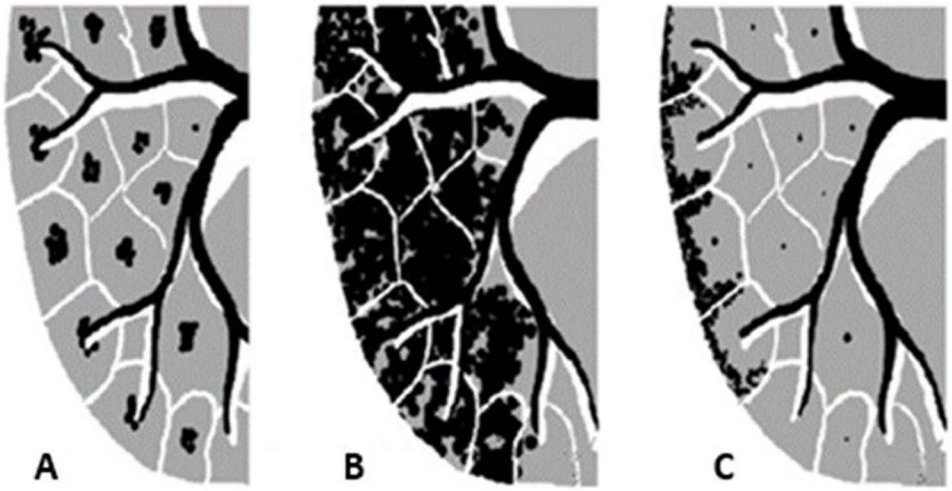

Figure 1 Types of emphysema (**A**). Centriacinar emphysema (**B**). Panacinar emphysema (**C**). Paraseptal emphysema.

AAT levels and pulmonary function tests were evaluated in patients with AAT genotype deficiency during stable periods (no exacerbation and normal CRP levels). Pulmonary function tests were performed to assess the clinical relevance and phenotypic expression of AAT genotype deficiencies.

Lung function tests were performed in accordance with European Respiratory Society (ERS) recommendations. Spirometry was conducted using standardized equipment, and the results were expressed as percentages of the predicted reference values based on ERS standards. Pre-bronchodilator values were used in the analysis. FEV_1, FVC, and FEV_1/FVC ratios were recorded and analyzed.

Patients were assessed for eligibility for augmentation therapy based on their AAT levels and clinical status.

Statistical Analysis

All statistical analyses were performed using SPSS version 22 for Windows program (SPSS Inc., Chicago, IL, USA). The frequencies and percentages of categorical variables and the mean, median, and standard deviation of the numerical variables were calculated.

Results

Between 01.12.2022 and 31.12.2024, 794 patients with emphysema with a mean age of 61.4±10.5/year (Male: 61.8±10.5, Female: 56.6±9.9) were evaluated. Sixty-six (8.3%) patients were female, and 728 (91.7%) were male. Regarding the smoking status, 586 (73.8%) were smokers, 165 (20.8%) were ex-smokers, and 43 (5.4%) were non-smokers. Upper lobe involvement (n=784, 98.7%) and panacinar emphysema (n=443, 55.8%) were most common (Table 1).

In the AAT genotyping results, no mutations were detected in 763 (96.1%) patients, while AATD mutations were detected in 31 (3.9%) patients. Although AATD was more common in panacinar emphysema (n=24, 3%), no mutations were observed in paraseptal emphysema (Table 2). In the PI*Z/Z and PI*Z/M malton genotypes, emphysema was observed in all lobes and panacinar types (Table 3).

The characteristics of patients with defects in SERPINA1 based on genotype distribution are presented in Table 4. Of the patients with detected mutations, 5 were female and 26 were male. Fourteen patients were smokers, 14 were ex-smokers, and 3 were non-smokers. Panaciner-type emphysema was detected in 2 non-smokers, while centriacinar-type emphysema was observed in 1 patient. The most common mutations were PI*M/M malton (n=9), PI*M/Z (n=7), PI*M/I (n=4), and PI*M malton/M malton (n=4). Serum AAT levels of the patients with AATD were found to be 0.85±0.44 g/L. AAT level was found to be low in PI*Z/Z, PI*M malton/M malton and PI*Z/M malton genotypes (0.20±0.2 g/L). In pulmonary function tests, the mean FEV_1 was 1.68±0.85 mlt (57±26.8%). None of the patients diagnosed with AATD were receiving augmentation

Table 1 Demographic Characteristics of Patients with Emphysema

Gender	**Female n (%) 66 (8.3)**	**Male n (%) 728 (91.7)**	**Total n 794**
Age	56.6±9.9	61.8±10.5	61.4±10.5
Smoking status			
Non-smoker	20 (2.5)	23 (2.9)	43 (5.4)
Smoker	30 (3.8)	556 (70)	586 (73.8)
Ex-smoker	16 (2)	149 (18.8)	165 (20.8)
Emphysema type			
Centriacinar	36 (4.5)	214 (27)	250 (31.5)
Panacinar	23 (2.9)	420 (52.9)	443 (55.8)
Paraseptal	7 (0.9)	94 (11.8)	101 (12.7)
Emphysema localization			
Upper lobe	61 (7.7)	723 (91.1)	784 (98.7)
Middle lobe or lingula	12 (1.5)	126 (15.9)	138 (17.4)
Lower lobe	13 (1.6)	124 (15.6)	137 (17.3)

Table 2 Genotype Distribution According to Emphysema Type

Genotype	**Centriacinar n (%)**	**Panacinar n %**	**Paraseptal n %**	**Total n %**
PI*M/M	243 (30.6)	419 (52.8)	101 (12.7)	763 (96.1)
PI*M/M malton	3 (0.4)	6 (0.8)	0	9 (1.2)
PI*M/Z	0	7 (0.9)	0	7 (0.9)
PI*M malton/M malton	1 (0.1)	3 (0.4)	0	4 (0.5)
PI*M/I	2 (0.3)	2 (0.3)	0	4 (0.6)
PI*Z/Z	0	3 (0.4)	0	3 (0.4)
PI*M/ P lowell	1 (0.1)	2 (0.3)	0	3 (0.4)
PI*Z/ M malton	0	1 (0.1)	0	1 (0.1)

Table 3 Genotype Distribution According to Emphysema Localization

Genotype	**Upper Lobe n (%)**	**Middle Lobe or Lingula n %**	**Lower Lobe n %**
PI*M/M	754 (98.8)	122 (16)	122 (16)
PI*M/M malton	9 (100)	3 (33.3)	3 (33.3)
PI*M/Z	7 (100)	5 (71.4)	4 (57.1)
PI*M malton/M malton	4 (100)	2 (50)	2 (50)
PI*M/I	4 (100)	1 (25)	0

(*Continued*)

Table 3 (Continued).

Genotype	Upper Lobe n (%)	Middle Lobe or Lingula n %	Lower Lobe n %
PI*Z/Z	3 (100)	3 (100)	3 (100)
PI*M/ P lowell	2 (66.7)	1 (33.3)	2 (66.7)
PI*Z/ M malton	1 (100)	1 (100)	1 (100)

Table 4 Characteristics of Patients with Alpha 1 Antitrypsin Deficiency

Genotype	Age Gender	Cigarete	Emphysema Type	AAT level N:0.9–2 g/L	FVC L (%)	FEV_1 L (%)	FEV_1/ FVC %	Augmentation Therapy
PI*Z								
Z/Z								
Case 1	49/M	Ex-smoker	Panacinar	0.20	2.33 (51)	1.17 (32)	50	Yes
Case 2	59/M	Ex-smoker	Panacinar	0.21	1.32 (41)	1.27 (49)	96	Yes
Case 3	57/F	Ex-smoker	Panacinar	0.18	1.01 (37)	0.88 (31)	87	Yes
M/Z								
Case 4	48/M	Smoker	Panacinar	1.02	3.88 (91)	3.34 (96)	86	No
Case 5	55/M	Smoker	Panacinar	0.97	2.78 (69)	2.78 (68)	100	No
Case 6	64/M	Ex-smoker	Panacinar	0.97	1.55 (42)	1.18 (41)	76	No
Case 7	65/M	Smoker	Panacinar	0.92	3.22 (86)	2.69 (93)	83	No
Case 8	66/M	Ex-smoker	Panacinar	1.21	1.88 (60)	1.2 (48)	64	No
Case 9	68/M	Smoker	Panacinar	0.86	0.86 (24)	0.49 (17)	57	No
Case 10	54/M	Ex-smoker	Panacinar	0.93	0.83 (20)	0.78 (23)	94	No
PI*M malton								
M/M malton								
Case 11	59/M	Smoker	Centriacinar	1.18	2.29 (63)	2.07 (72)	90	No
Case 12	59/M	Smoker	Centriacinar	0.98	2.41 (67)	2.30 (80)	95	No
Case 13	68/M	Smoker	Centriacinar	1.12	2.40 (77)	1.68 (68)	70	No
Case 14	53/M	Smoker	Panacinar	0.85	2.73 (73)	2.37 (78)	87	No
Case 15	63/M	Non-smoker	Panacinar	0.83	2.32 (81)	2.23 (96)	96	No
Case 16	64/M	Ex-smoker	Panacinar	0.72	3.32 (73)	2.86 (81)	86	No
Case 17	70/M	Ex-smoker	Panacinar	0.87	1.82 (42)	1.32 (39)	72	No
Case 18	72/M	Ex-smoker	Panacinar	0.95	1.40 (34)	1.23 (38)	88	No
Case 19	74/M	Ex-smoker	Panacinar	1.02	1.46 (43)	0.77 (29)	52	No
M malton/M malton								
Case 20	74/F	Ex-smoker	Panacinar	0.23	0.32 (10)	0.24 (11)	75	Yes
Case 21	58/F	Ex-smoker	Panacinar	0.20	0.88 (37)	0.40 (20)	45	Yes
Case 22	51/F	Non-smoker	Centriacinar	0.18	1.77 (68)	1.77 (80)	100	No
Case 23	49/M	Smoker	Panacinar	0.21	1.79 (43)	0.70 (21)	39	No
Z/ M malton								
Case 24	55/M	Smoker	Panacinar	0.26	2.01 (50)	1.13 (35)	56	Yes
PI*P lowell								
M/ P lowell								
Case 25	74/M	Smoker	Centriacinar	0.99	3.10 (83)	2.40 (82)	77	No
Case 26	71/M	Ex-smoker	Panacinar	1.30	2.94 (76)	1.96 (64)	67	No
Case 27	58/F	Non-smoker	Panacinar	1.15	1.88 (65)	1.8 (76)	96	No

(*Continued*)

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Table 4 (Continued).

Genotype	Age Gender	Cigarete	Emphysema Type	AAT level N:0.9–2 g/L	FVC L (%)	FEV $_1$ L (%)	FEV_1/ FVC %	Augmentation Therapy
PI*I								
M/I								
Case 28	40/M	Smoker	Centriacinar	1.41	2.30 (72)	2.09 (78)	90	No
Case 29	41/M	Smoker	Centriacinar	1.38	4.02 (94)	3.50 (101	87	No
Case 30	61/M	Smoker	Panacinar	1.52	2.46 (70)	1.94 (70)	79	No
Case 31	70/M	Ex-smoker	Panacinar	1.77	1.82 (49)	1.55 (53)	85	No

therapy. Six patients received augmentation therapy for AATD: three had PI*Z/Z, two had PI*M malton/M malton, and one had the PI*Z/M malton genotype. It was determined that 3 patients received treatment approval with off-label application.

Discussion

This cross-sectional descriptive study aimed to identify patients with mutations in SERPINA1, a potential genetic cause of emphysema. AATD was detected in 3.9% (n=31) of the patients with emphysema. AATD was associated with panacinar emphysema (3%) and with emphysema involving multiple lobes, predominantly affecting the upper lobes.

Although emphysema is an early finding in AATD, it is difficult to distinguish between non-hereditary emphysema and emphysema caused by AATD.[7] There is insufficient literature on the AAT genotypes in patients with emphysema. The prevalence and characteristics of these patients are not well known. When the studies were evaluated, AATD was examined in chronic lung diseases, such as COPD, asthma, and bronchiectasis, and the characteristics of patients with emphysema findings were given as sub-results. To the best of our knowledge, our study is the first to examine this number of emphysema cases and evaluate their genotypic characteristics and treatment indications.

Most AATD-related cases are diagnosed when symptoms become evident and at an advanced age, as genotype tests are performed at private centers.[13–15] In studies conducted worldwide[3,16,17] and in Türkiye[9–11] on chronic lung diseases such as COPD, asthma, and bronchiectasis, the age of AATD diagnosis was advanced. In our study, AATD was detected at an advanced age, similar to other studies (60.2±9.4 / year).

Notably, all individuals with the PiMZ genotype in our cohort were either current or former smokers. This supports previous findings indicating that the PiMZ genotype alone may not be sufficient to cause emphysema but becomes clinically significant when combined with tobacco exposure. Mild AAT deficiency may predispose individuals to disease progression under oxidative stress from cigarette smoke.[8] Therefore, Pi*MZ should be considered a genotype that warrants intervention, particularly in the context of active or past smoking.

The normal allele for AAT is PI × MM. More than 120 SERPINA 1 mutations have been reported in the literature for AATD, and the most common alleles consist of a combination of M, Z, and S alleles (PI*SS, PI*MZ, PI*SZ, and PI*ZZ).[2] In the study of Veith et al which examined the genotypes of 18736 patients diagnosed with COPD/emphysema, asthma and bronchiectasis, the genotype distribution in COPD/emphysema was determined as PI*MZ 2704 (22.01%), PI*ZZ 1120 (9.12%), PI*MS 557 (4.53%), PI*SZ 306 (2.49%), PI*Z/rare 202 (1.64%), PI*M/rare 142 (1.16%), PI*SS 33 (0.27%).[16] In this study, COPD and emphysema were not analyzed separately, and the type and localization of emphysema were not examined. Lopez-Campos et al evaluated materials collected from six countries between 2018 and 2022 in 15,230 COPD patients, 3,381 poorly controlled asthma patients, and 1,435 bronchiectasis patients, and the most common allele combinations were MS (14.7%), MZ (8.6%), SS (1.9%), SZ (1.9%), and ZZ (0.9%).[17] In a study conducted by Ale-Müniya et al on 1107 patients with COPD, AATD was detected in 144 patients (13.01%). Most mutations were PI*M/S (n=113, 78.5%) and PI*M/Z (n=14, 9.2%). Seventeen patients had at least one Z allele (11.8%) and one patient had a ZZ mutation.[3] A study by Çörtük et al on 196 patients with COPD and 14 patients (7.1%). Among the common allele combinations, PI*M/Z was detected in three patients (1.53%) and PI*Z/Z in one patient (0.51%), whereas the S allele combination was not detected. PIM/Malton was identified as a rare allele in 3 patients (1.53%), PIM/I in 3 patients (1.53%), PIM/Plowell in 2 patients (1.02%), PIM/procida in 1 patient (0.51%), and a single-point mutation

(GRCh38) g.94378611 in 1 patient (0.51%).[10] Onur et al evaluated 1,088 patients with COPD, asthma, and bronchiectasis and AATD was detected in 51 patients (5%). In 15 patients (29.4%), variants combining common S or Z alleles were detected in 36 patients (70.6%), whereas rare alleles (PIM Malton, PIP Lowell, PIM Heerlen, and PIS Iiyama). The most frequent combinations were PI*M/Z (n=12, 24%) and PI*M/M males (n=11, 22%). Among 51 patients with AATD, 19 had emphysema.[9] No information was available regarding the type and localization of emphysema.

In a study conducted by Onur et al on 596 patients with COPD, AATD was observed in 21 (3.52%). The most common mutations were PI*M/Plowell (23.8%, n=5), PI*M/S (23.8%, n=5), PI*M/I (19%, n=4), PI*M/Malton (14.3%, n=3), PI*Z/Z (9%, n=2), PI*M/Z (4.8%, n=1), and Kayseri/Kayseri (4.8%, n=1) mutations. Computed chest tomography revealed that 85.7% (n=18) of patients with AATD had emphysema, 55% (n=10) of patients with emphysema only had upper-lobe emphysema, and 83.3% (n=15) had emphysema in additional areas.[11] No information was available regarding the type of emphysema or genotype distribution.

In our study, the AATD genotypes in patients with emphysema were PI*M/M malton (n=9), PI*M/Z (n=7), PI*M/I (n=4), PI*M malton/M malton (n=4), PI*M/I (n=4), PI*Z/Z (n=3), PI*M/P low (n=3), and PI*Z/M malton (n=1). The frequency and genotype distribution of AATD in patients with emphysema in the present study were similar to those reported by Türkiye et al. Unlike other studies. Interestingly, the M Malton/M Malton genotype was identified in 4 out of 794 patients (0.5%), higher than the frequency of the PiZZ genotype in our sample. This unexpected finding suggests a possible regional or ethnic variation in rare SERPINA1 mutation frequencies. Such variation may have important implications for the design of genetic screening programs. In populations where rare mutations such as M Malton are more prevalent, targeted sequencing approaches may be more effective than focusing solely on the most common variants. AAT genotyping was performed based on the type of bronchiectasis. The most frequently observed alleles in panacinar emphysema were PIM/Z, PIM/M Malton, PIM Malton/M Malton, and PIZ/Z. In centriacinar emphysema, the PIM/M Malton and PIM/I alleles were detected, whereas no mutations were observed in paraseptal emphysema. In the PI*Z/Z and PI*Z/M malton genotypes, emphysema was observed in all lobes and panacinar types.

Augmentation therapy (a human Alpha-1-Proteinase inhibitor) in AATD has been used for approximately 38 years. The benefits of augmentation therapy in patients with chronic obstructive pulmonary disease (COPD) and pulmonary emphysema due to AATD have been well established. Augmentation therapy has been shown to increase the level of AAT in serum and lung tissue, increase pulmonary anti-neutrophil elastase capacity, slow the progression of emphysema, and reduce the decrease in FEV_1.[4,18–21] Augmentation therapy in Türkiye is paid when it is prescribed to patients with the homozygous PI*Z/Z allele with genetic examination and $FEV_1 > 30\%$ in a pulmonary function test or after it is evaluated by the Ministry of Health Board in off-label applications in patients with rare heterozygous mutations. Our study also evaluated patients with emphysema and AATD in terms of augmentation therapy. It was determined that 6 of the patients received augmentation therapy indication for AATD, and 3 patients received treatment approval with off-label admission. It was determined that 3 of Three patients had PI*Z/Z, 2 had PI*M malton/M malton, and 1 had PI*Z/M malton genotype. The AAT levels in patients receiving augmentation therapy were very low and they had panaciner-type emphysema.

The limitations of our study include its single-center retrospective design. In addition, because screening was conducted only in patients with emphysema, there is no possibility of detecting AATD in patients with COPD or asthma without emphysema. One of the main limitations of our study is that smoking exposure was recorded only categorically (current, former, or never smokers), without quantitative data such as cumulative pack-years. This restricts the ability to assess the dose-dependent effect of tobacco exposure on genotype–phenotype correlations.

Our results emphasize the importance of identifying AAT deficiency in emphysema patients. Measurement of serum AAT levels is recommended as the initial step. If levels are found to be low or borderline, genotyping can then be performed to identify specific mutations. Analyzing AAT genotypes in patients with emphysema may provide an early diagnosis of AATD, allowing the application of preventive measures and augmentation therapy strategies. This may slow the progression of the disease and improve quality of life.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Dasí F. Alpha-1 antitrypsin deficiency. *Med Clin*. 2024;162(7):336–342. doi:10.1016/j.medcli.2023.10.014
2. American Thoracic Society; European Respiratory Society. American Thoracic Society/European Respiratory Society statement: standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. *Am J Respir Crit Care Med*. 2003;168(7):818–900. doi:10.1164/rccm.168.7.818.
3. Alí-Munive A, Leidy P, Proaños NJ, et al. Prevalence of genetic mutations in alpha-1 antitrypsin deficiency (aatd) in patients with chronic obstructive pulmonary disease in Colombia. *BMC Pulm Med*. 2023;23(1):156. doi:10.1186/s12890-023-02453-0
4. Wewers MD, Casolaro MA, Sellers SE, et al. Replacement therapy for alpha 1-antitrypsin deficiency associated with emphysema. *N Engl J Med*. 1987;316(17):1055–1062. doi:10.1056/NEJM198704233161704
5. Janssen R, Piscaer I, Franssen FME, Wouters EFM. Emphysema: looking beyond alpha-1 antitrypsin deficiency. *Expert Rev Respir Med*. 2019;13(4):381–397. doi:10.1080/17476348.2019.1580575
6. Regan EA, Lynch DA, Curran-Everett D, et al. Clinical and radiologic disease in smokers with normal spirometry [published correction appears. *JAMA Intern Med*. 2015;175(9):1588. DOI:10.1001/jamainternmed.2015.4706
7. Strnad P, McElvaney NG, Lomas DA. Alpha1-antitrypsin deficiency. *N Engl J Med*. 2020;382(15):1443–1455. doi:10.1056/NEJMra1910234
8. Stoller JK, Brantly M. The challenge of detecting alpha-1 antitrypsin deficiency. *COPD*. 2013;10 Suppl 1:26–34. doi:10.3109/15412555.2013.763782
9. Tural Onur S, Natoli A, Dreger B, et al. An alpha-1 antitrypsin deficiency screening study in patients with chronic obstructive pulmonary disease, bronchiectasis, or Asthma in Turkey. *Int J Chron Obstruct Pulmon Dis*. 2023;18:2785–2794. doi:10.2147/COPD.S425835
10. Çörtük M, Demirkol B, Arslan MA, et al. Frequency of alpha-1 antitrypsin deficiency and unexpected results in COPD patients in Turkey; rare variants are common. *Turk J Med Sci*. 2022;52(5):1478–1485. doi:10.55730/1300-0144.5486
11. Önür ST. Initial alpha-1 antitrypsin screening in Turkish patients with chronic obstructive pulmonary disease. *Turk J Med Sci*. 2023;53(4):1012–1018. doi:10.55730/1300-0144.5665
12. Takahashi M, Fukuoka J, Nitta N, et al. Imaging of pulmonary emphysema: a pictorial review. *Int J Chron Obstruct Pulmon Dis*. 2008;3(2):193–204. doi:10.2147/copd.s2639
13. Miravitlles M, Nuñez A, Torres-Durán M, et al. The importance of reference centers and registries for rare diseases: the example of alpha-1 antitrypsin deficiency. *COPD*. 2020;17(4):346–354. doi:10.1080/15412555.2020.1795824
14. Gurevich S, Daya A, Da Silva C, Girard C, Rahaghi F. Improving screening for alpha-1 antitrypsin deficiency with direct testing in the pulmonary function testing laboratory. *Chronic Obstr Pulm Dis*. 2021;8(2):190–197. doi:10.15326/jcopdf.2020.0179
15. Tejwani V, Nowacki AS, Fye E, Sanders C, Stoller JK. The impact of delayed diagnosis of alpha-1 antitrypsin deficiency: the association between diagnostic delay and worsened clinical status. *Respir Care*. 2019;64(8):915–922. doi:10.4187/respcare.06555
16. Veith M, Tüffers J, Peychev E, et al. The Distribution of alpha-1 antitrypsin genotypes between patients with copd/emphysema, asthma and bronchiectasis. *Int J Chron Obstruct Pulmon Dis*. 2020;15:2827–2836. doi:10.2147/COPD.S271810
17. Lopez-Campos JL, Osaba L, Czischke K, et al. Feasibility of a genotyping system for the diagnosis of alpha1 antitrypsin deficiency: a multinational cross-sectional analysis. *Respir Res*. 2022;23(1):152. doi:10.1186/s12931-022-02074-x
18. Wencker M, Fuhrmann B, Banik N, Konietzko N. Wissenschaftliche Arbeitsgemeinschaft zur Therapie von Lungenerkrankungen. Longitudinal follow-up of patients with alpha(1)-protease inhibitor deficiency before and during therapy with IV alpha(1)-protease inhibitor. *Chest*. 2001;119(3):737–744. doi:10.1378/chest.119.3.737
19. Survival and FEV_1 decline in individuals with severe deficiency of alpha1-antitrypsin. the alpha-1-antitrypsin deficiency registry study group. *Am J Respir Crit Care Med*. 1998;158(1):49–59. doi:10.1164/ajrccm.158.1.9712017
20. Stockley RA, Parr DG, Piitulainen E, Stolk J, Stoel BC, Dirksen A. Therapeutic efficacy of α-1 antitrypsin augmentation therapy on the loss of lung tissue: an integrated analysis of 2 randomised clinical trials using computed tomography densitometry. *Respir Res*. 2010;11(1):136. doi:10.1186/1465-9921-11-136
21. McElvaney NG, Burdon J, Holmes M, et al. Long-term efficacy and safety of α1 proteinase inhibitor treatment for emphysema caused by severe α1 antitrypsin deficiency: an open-label extension trial (RAPID-OLE) [published correction appears. *Lancet Respir Med*. 2017;5(2):e13. doi:10.1016/S2213-2600(17)30004-8.]