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Clinical implications of the SERPINA1 variant, $M_{Palermo}$, and alpha-1 antitrypsin deficiency in Türkiye

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Abstract

Background Alpha-1 antitrypsin deficiency (AATD) is associated with increased susceptibility to chronic obstructive pulmonary disease (COPD). AATD results from mutations in the *SERPINA1* gene and over 500 rare mutations have been identified. Despite these findings and recommendations from major healthcare organizations, testing of COPD patients and their family members for AATD remains inadequate.

Methods We examined genotypes and clinical characteristics of COPD patients (index cases; $n=14$) treated at Recep Tayyip Erdoğan University Chest Diseases Department and their relatives ($n=17$).

Results When index cases were compared with screened relatives positive for AATD ($n=14$), index cases were older and more predominantly male than screened relatives. Both groups had extensive smoking histories. All of the index cases and one of the screened relatives had been diagnosed with COPD. Clinical characterization of the COPD cases (14 index cases; 1 screened relative) showed that they had moderate to severe COPD with pre-treatment AAT levels of 0.59 ± 0.40 g/L (mean ± SD) and a COPD Assessment Test (CAT) score of 16.0 ± 8.12. The majority of these patients (73.3%) had panlobular emphysema. Five of the patients were treated with AAT augmentation which led to a decrease in the number of COPD exacerbations. Genotyping revealed that the most common rare allele identified in this population was $M_{Palermo}$ (c.227_229delTCT mutation on the M1(Val^{213}) allelic background).

Conclusions More testing and research need to be done to identify the relative prevalence of rare AATD variants. Earlier identification could lead to more effective treatment of affected individuals and improvement in their quality of life.

Keywords Alpha-1 antitrypsin deficiency, $M_{Palermo}$, M_{Malton}, COPD, Screening, Tobacco

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Introduction

Until recently, there has been little or no data on patients in Türkiye regarding alpha-1 antitrypsin deficiency (AATD) in chronic obstructive pulmonary disease (COPD). With the approval of reimbursement for alpha-1 antitrypsin (AAT) augmentation treatment in Türkiye in 2019, interest in AATD has increased. In addition, recent review articles have described over 500 rare mutations in the *SERPINA1* gene [1, 2].

These results support the view that AATD is not a rare disease but is under-diagnosed [1]. The best described and most common mutations in the *SERPINA1* gene (95%) are c.1096G>A and c.863 A>T that correspond to the Z and S alleles, respectively. But it is becoming increasingly clear that the so-called rare AATD mutations are of great relevance in AATD. The mutation that is the subject of this study, c.227_229delTCT, is a rare pathologic variant. This is named as the M_{Malton} or $M_{Palermo}$ allele depending on the genetic background in which it is present. M_{Malton} is derived from a M2 base allele, whereas $M_{Palermo}$ is on an M1(Val^{213}) background [3]. Given that the molecular genetic analysis used to determine AATD mutations identifies the c.227_229delTCT mutation, but not the base allele, and, that M_{Malton} was found more frequently than $M_{Palermo}$ [4], results are usually reported as M_{Malton}, even though the base allele has not been identified.

Recently, it was determined that the majority of COPD patients with AATD in Türkiye, especially in the Eastern Black Sea Region, have the p.Phe52del (c.227_229delTCT) mutation, reported as Pi* M_{Malton} [4] since the allelic background was unknown.

The clinical implications of rare variants have not been adequately examined. The aim of this study was to examine the characteristics of COPD patients with the c.227_229delTCT mutation (Pi* M_{Malton} or Pi* $M_{Palermo}$ allele), the most frequently detected variant in Türkiye, and the characteristics of their family members whose mutation was detected by AATD screening.

Methods

Patient selection

Patients were selected among COPD patients that were screened for AATD by genotyping in Recep Tayyip Erdoğan University Chest Diseases Department between 2019 and 2024. Based on current COPD guidelines [5], every COPD patient in Türkiye is tested for AATD at least once in their lifetime. Female or male patients were eligible for inclusion in the study if they were aged 18 years and older, were admitted to the Department of Chest Diseases, RTEU Training and Research Hospital and diagnosed with COPD. Patients were also included if they had the c.227_229delTCT mutation detected as a result of family screening and COPD in a first degree relative. Patients were excluded if they did not have a confirmed diagnosis of COPD or the c.227_229delTCT mutation was not detected.

Patients were treated in the normal course of practice. No specific interventions were made for this study.

Genetic testing

Genetic testing was conducted as previously described [6]. Patients with a spirometrically confirmed COPD diagnosis and their first-degree relatives with a mutation detected during screening were included in the study. Genetic screening was conducted by collecting whole blood samples as dried blood spots and testing them by allele-specific genotyping (A1AT Genotyping Test, Progenika Biopharma, SA, Derio, Spain). This test detects 14 allelic variants associated with 20 alleles. Full *SERPINA1* gene sequencing was also conducted on these samples to confirm the specific alleles present (Progenika Biopharma, Derio, Spain).

Demographic and clinical data

The patients' demographic information and clinical characteristics (including respiratory complaints, respiratory function tests, and serum AAT levels) were collected. Any treatments for COPD were recorded in detail. These assessments included the COPD Assessment Test (CAT) [7, 8], and the modified Medical Research Council Dyspnea Scale (mMRC) [9, 10]. Generally, a score of 10 or above indicates symptomatic COPD [11]. For mMRC scores, "0" corresponds to dyspnea only with strenuous exertion, "1" corresponds to dyspnea when rushing or going up a slight incline, "2" corresponds to walking slower than an age-matched people due to dyspnea or having to stop to catch one's breath while walking at their own pace on level ground, "3" corresponds to stopping to catch one's breath after walking 91 m or a few minutes on level ground and "4" which corresponds to being too short of breath the leave the house or becoming short of breath while dressing [12].

Results

*Out of a total of 234 patients with COPD seen on an inpatient or outpatient basis at our clinic, 86.8% did not have any mutation in SERPINA1, i.e., they were genotype Pi*MM, 8.9% had $M_{Palermo}$ mutations in at least one allele, 1.7% were PiMZ, 1.2% were Pi*ZZ. The rest were rare null mutations. Fourteen COPD patients with $M_{Palermo}$ mutations were identified and included in the study as index cases.*

Table 1 shows the demographic data and clinical status of patient and relatives included in this study. For the index cases, 85.7% were male and 28.6% were current smokers.

Table 1 Baseline demographics, clinical findings and genetic analysis for index COPD cases and their screened relatives positive for the c.227_229delTCT mutation: comparison between index cases and screened relatives

	Index cases (*n*:14)	Screening (*n*:17)	*p*
Age, mean ± SD	62.8 ± 9.5	46.1 ± 14.6	0.002
Sex, *n*(%)			0.029
Male	12 (85.7%)	6 (35.3%)	
Female	2 (14.3%)	11 (64.7%)	
Smoking status, *n*(%)			0.010
Never smoker	0 (0%)	6 (35.3%)	
Former smoker	10 (71.4%)	4 (23.5%)	
Current smoker	4 (28.6%)	7 (41.2%)	
Smoking pack/year, mean ± SD	27.1 ± 15.4	17.8 ± 14.6	0.058
COPD diagnosis. *n*(%)	14 (100)	1 (5.8)	< 0.001
Serum AAT level, (g/L)	0.62 ± 0.40	0.73 ± 0.19	0.887
Genotypes, *n*(%)			
$M/M_{Palermo}$	4 (25.0)	9 (52.9)	-
$Z/M_{Palermo}$	4 (25.0)	1 (5.9)	-
$M_{Palermo}/M_{Palermo}$	3 (18.8)	2 (11.8)	-
M/Z	0 (0)	2 (11.8)	-
$M/M_{Palermo}$ + c.-428G > A + c. -10T > C	1 (6.2)	3 (17.6)	-
M/M_{Malton}or $M/M_{Palermo}$	1 (6.2)	0 (0.0)	-
$M_{Wurzburg}/ M_{Palermo}$	1 (6.2)	0 (0.0)	-

SD = standard deviation; COPD = chronic obstructive pulmonary disease; AAT = alpha-1 antitrypsin

Table 2 Clinical characteristics of patients with COPD diagnosis (n:15)

	n(%) or mean (SD)
CAT, mean (SD)	16.0 (8.12)
At least one hospitalization in last year, *n*(%)	5 (33.3)
mMRC, *n*(%)	
2	4 (26.7)
3	7 (46.7)
4	4 (26.7)
FEV1/FVC, mean (SD)	62.1 (5.95)
FEV1%, mean (SD)	39.6 (26.9)
FEV1(L), mean (SD)	1.76 (0.69)
Panlobular emphysema, *n*(%)	11 (73.3)
Centriacinar emphysema, *n*(%)	2 (13.3)
Pre-treatment serum AAT (g/L), mean (SD)	0.59 (0.40)
Under augmentation therapy, *n*(%)	5 (33.3)
LABA + LAMA, *n*(%)	6 (40.0)
LABA + LAMA + ICS, *n*(%)	3 (20.0)
LAMA, *n*(%)	2 (13.3)
As needed SABD, *n*(%)	5 (33.3)
LTOT, *n*(%)	4 (26.6)
Single lung transplantation, *n*(%)	1 (6.7)

CAT = Chronic Obstructive Pulmonary Disease Assessment Test; mMRC = modified Medical Research Council Dyspnea Scale; FEV1 = forced expiratory volume in 1 s; FVC = forced vital capacity; AAT = alpha-1 antitrypsin; LABA = long-acting beta agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid; SABD = short-acting bronchodilator; LTOT = long-term oxygen therapy

The index cases were significantly older ($p=0.002$) and more predominantly male than the screened relatives positive for the c.227_229delTCT mutation ($p=0.029$). The majority of COPD patients were former (71.4%) or current smokers (28.6%) as were the screened relatives (23.5% former smokers and 41.2% current smokers) with significant difference between the groups ($p=0.010$). The index cases had an average cumulative smoking exposure that was longer than the screened relative group, but the difference was not statistically significant ($p=0.058$). As noted in the Methods section, all of the index cases have COPD. One of the screened relatives has been diagnosed with COPD.

The clinical attributes of the COPD patients in the study are summarized in Table 2.

These data include the 14 index cases and the one screened relative diagnosed with COPD. The mean CAT score for these patients was 16.0 ± 8.12 (mean ± SD). The mMRC scores ranged from 2 to 4.

SERPINA1 mutations were found in 14 index cases and 17 of the 23 screened family members. The A1AT Genotyping test showed the presence of the variant c.227_229delTCT (M_{Malton} or $M_{Palermo}$) in the initial genotyping test. Full sequencing data allow us to identify base allele and confirmed that the samples from the index cases and the screened relatives had the $M_{Palermo}$ allele ($M1(Val^{213})$ background) (Table 1). There were four samples in which the sequencing results did not allow confirmation of the allele ($M_{Palermo}$ versus M_{Malton}). Three of these four individuals were screened relatives of index cases and the presence of the $M_{Palermo}$ allele can be inferred from the index case. For the remaining case no information on relatives was available so this patient was listed as M/M_{Malton} or $M/M_{Palermo}$.

The most frequently detected genotypes in the index cases were as follows: Pi* $M/M_{Palermo}$ (25.0%), Pi* $Z/M_{Palermo}$ (25.0%), Pi* $M_{Palermo}/M_{Palermo}$ (18.8%). Of the screened relatives, 52.9% had the Pi* $M/M_{Palermo}$ genotype. A total of 15 patients were diagnosed with COPD, and augmentation therapy was started in 5 of them. One patient with the $Pi^*Z/M_{Palermo}$ genotype had a history of single lung transplantation in 2014, and 2 patients with the $Pi^*M_{Palermo}/M_{Palermo}$ genotype were using long-term oxygen therapy.

Lung function testing showed moderate to severe COPD for the cohort in this study (Table 2). Panlobular emphysema was present in the majority of patients (73.3%) while centriacinar emphysema was uncommon in this group (13.3%). The mean pre-treatment serum AAT level in this group of patients was 0.59 ± 0.40 g/L which is below the protective threshold against lung damage (80 mg/dL or 0.8 g/L) [13]. About 33.3% of the patients in

this group ($n=5$) were being treated with AAT augmentation therapy.

> *There was a significant positive correlation between AAT levels and FEV1% predicted for the entire study population ($r=0.496$, $p=0.005$) (Fig. 1). When the relationship was assessed for the index cases and the screened relatives the correlations were similar (Fig. 2). Individual values for AAT in index cases and screened relatives showed considerable variation. Several of the index cases and screened relatives had serum AAT values that were below the protective threshold against lung damage (0.8 g/L) as shown in Fig. 3 [13].*

Routine screening did not indicate liver involvement in any of the COPD patients. No addition testing of hepatic function was conducted.

Symptomatic treatment of the COPD patients in this study included the use of long-acting beta agonists (LABA), long-acting muscarinic antagonists (LAMA), inhaled corticosteroids (ICS) and short-acting bronchodilators (SABD) (Table 2). A small number of patients ($n=4$, 26.6%) were on long-term oxygen therapy (LTOT) and one patient had a single lung transplant.

Individual patient characteristics of the patients treated with AAT augmentation therapy are shown in Table 3. The five patients receiving augmentation ranged in age from 48 to 76 years. Four of the five patients were male, and all had severe AATD and very low serum AAT levels prior to therapy (0.2–0.9 g/L). All five were also former smokers with a use history of 5–40 pack/years. Four of the five are continuing augmentation therapy with a marked decrease in exacerbations after initiation of this therapy.

A representative chest x-ray and representative CT scans are shown in Fig. 4. Figure 4A and B show CT scans from Patient A in Table 3 with the homozygous genotype Pi*$M_{Palermo}$/$M_{Palermo}$ and an AAT level of 0.2 g/L prior to starting augmentation therapy. The sagittal section in Fig. 4A shows diffuse panlobular emphysema. The coronal section in Fig. 4B also shows diffuse emphysema and peribronchial wall thickening. Hospitalizations due to COPD exacerbations decreased from over 15 per year prior to augmentation therapy to once a year after initiation of therapy.

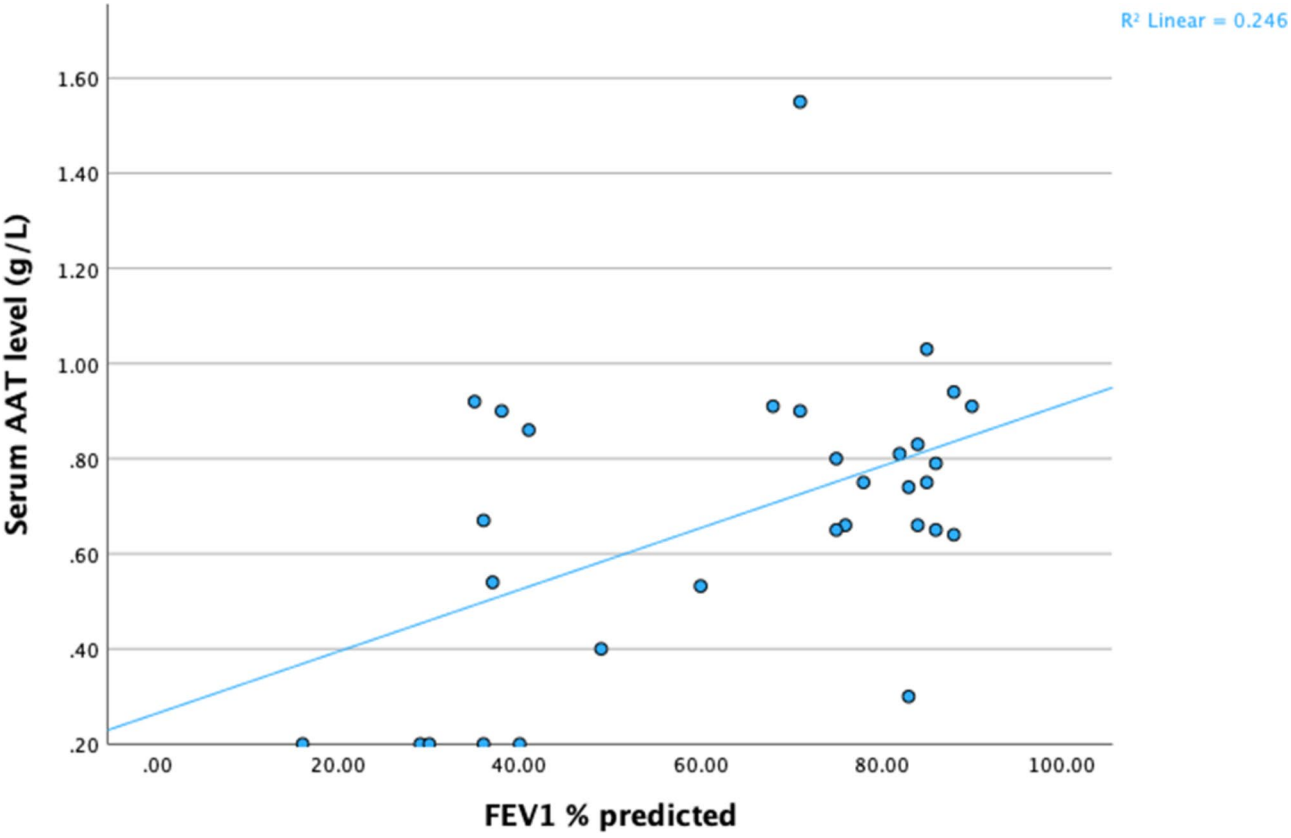

Fig. 1 Correlation of serum alpha-1 antitrypsin (AAT) levels with FEV1% predicted in the complete study population (index cases plus screened relatives with AATD)

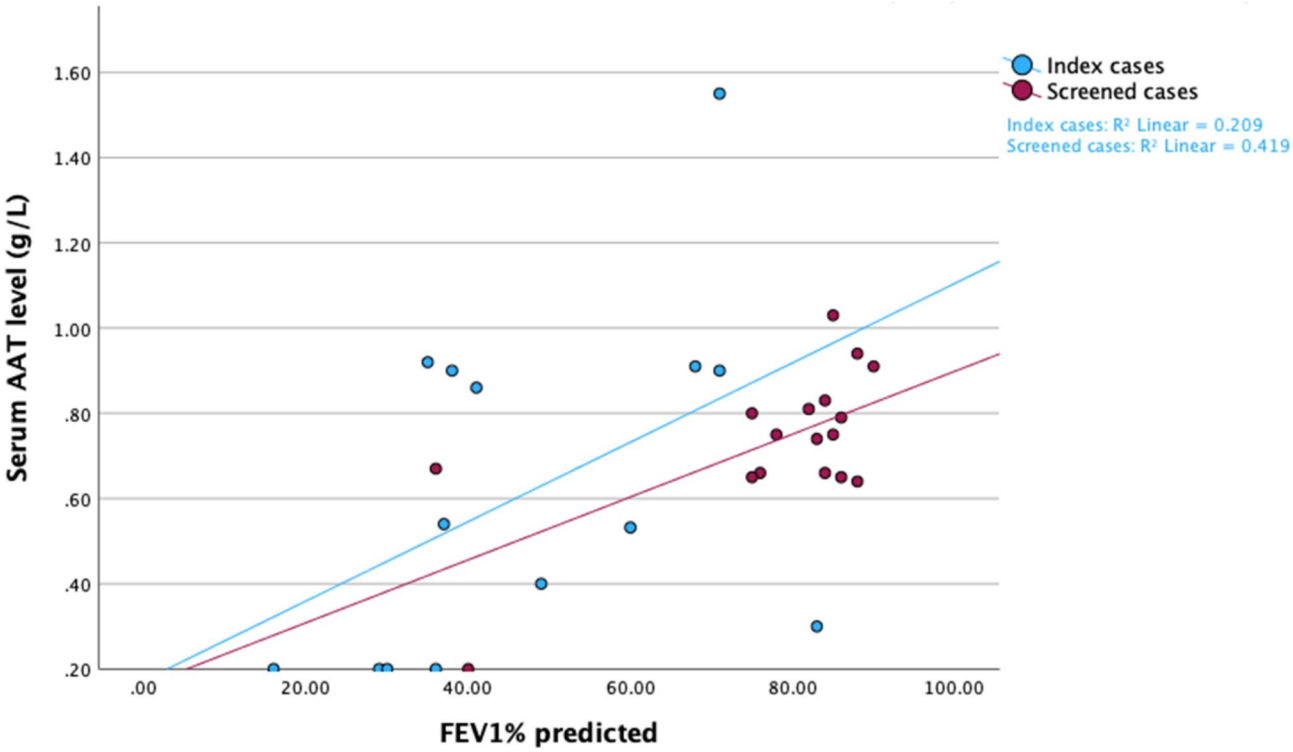

Fig. 2 Correlation of serum alpha-1 antitrypsin (AAT) levels with FEV1% predicted according to subgroups (index cases and screen relatives)

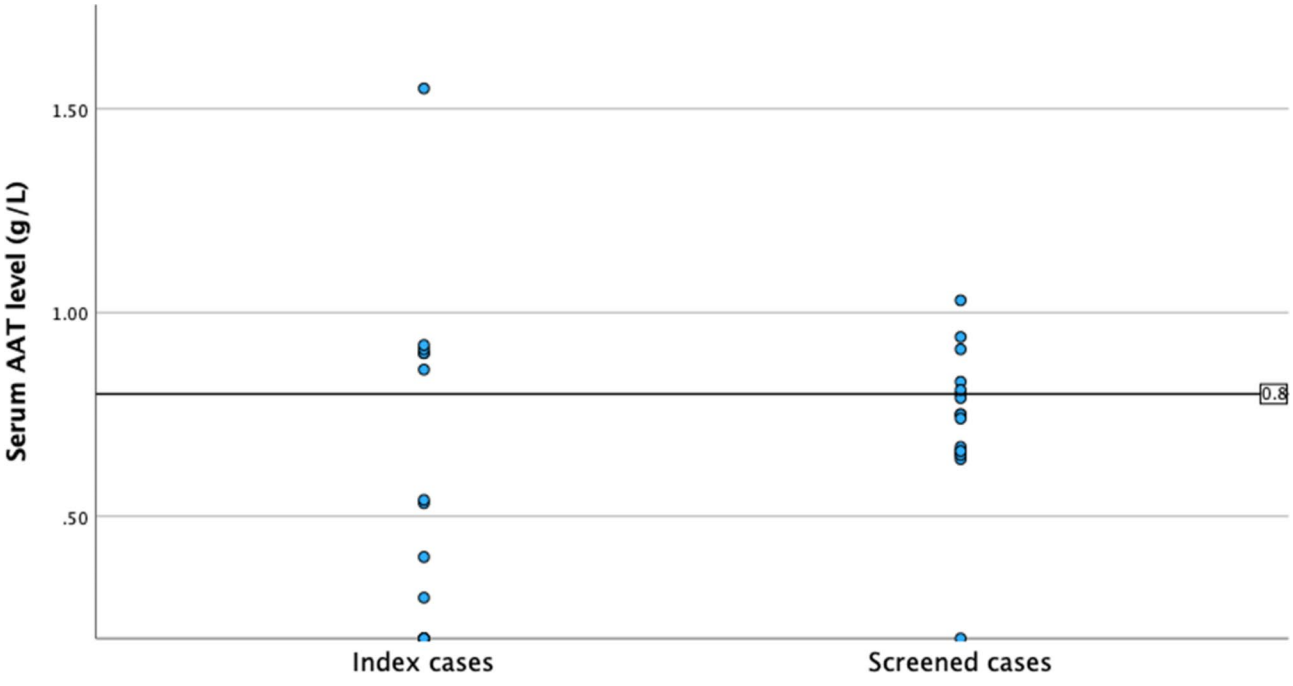

Fig. 3 Scatter plot of serum alpha-1 antitrypsin (AAT) levels of index and screened cases. The gray horizontal line indicates the protective level of serum AAT (0.8 g/L)

Discussion

M_{Malton}, $M_{Nichinan}$ and $M_{Palermo}$ are rare variants linked to the same mutation p.Phe52del (c.227_229delTCT) but present on different allele backgrounds – M2 for M_{Malton} [14], M1(Val^{213}) for $M_{Nichinan}$ [15] and $M_{Palermo}$ [3]. M_{Malton} has been found to leave AAT synthesis in hepatocytes unaffected but causes around 70% of the protein to be degraded within the endoplasmic reticulum and 15%

Table 3 Clinical characteristics of COPD patients prior to initiation of AAT augmentation therapy

										Before augmentation	After augmentation
Pt	**Age**	**Sex**	**AAT level (g/L)**	**Genotype**	**Smoking History**	**mMRC**	**CAT**	**FEV1%**	**Duration of augmentation therapy (months)/status**	**Exacerbations in the last year**	**Exacerbations**
A	59	Male	0.2	$M_{Palermo}$/ $M_{Palermo}$	Former 30 p/y	4	28	16	16 /continuing	> 15 (6 hospitalizations, 10 ED)	2 (1 ED, 1 hospitalization)
B	57	Male	0.9	$M_{Palermo}$ /$M_{Palermo}$	Former 5 p/y	1	3	30	3 /discontinued, for 6 months; re-started	3 (ambulatory exacerbation)	0
C	76	Male	0.9	$M_{Palermo}$/ $M_{Palermo}$	Former 40 p/y	4	18	35	16 /continued, died May 2024)	3 (2 ED, 1 hospitalization)	1 (ED)
D	48	Female	0.2	Z/$M_{Palermo}$	Former 15 p/y	3	20	36	10 /continuing	3 (hospitalizations due to pneumonia)	1 (hospitalization due to pneumonia)
E	55	Male	0.3	Z/$M_{Palermo}$	Former 20 p/y	3	7	35	44 /continuing	Single lung transplant in 2014	0

AAT = alpha-1 antitrypsin; mMRC = Modified Medical Research Council Dyspnea Scale; CAT = Chronic Obstructive Pulmonary Disease Assessment Test Score; p/y = pack years. ED: Emergency department admission

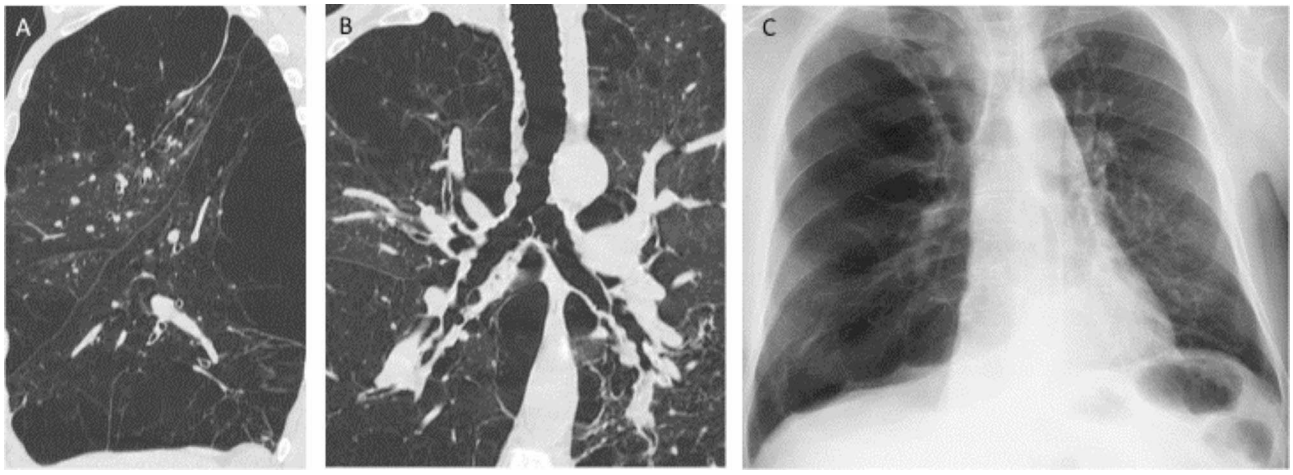

Fig. 4 Representative CT scans and X-ray of study patients with AATD. **A and B.** CT scans of the lungs of a 57-year-old patient with genotype PI*$M_{Palermo}$/ $M_{Palermo}$ and AATD (AAT 0.2 g/L) prior to initiation of AAT augmentation therapy (Patient A in Table 3). **A.** This sagittal section shows diffuse areas of panlobular emphysema. **B.** A coronal section show diffuse emphysema and peribronchial wall thickening. Patient is an ex-smoker with a 30 pack/year history. Patient is currently on augmentation therapy which has dramatically decreased hospitalizations due to COPD exacerbations. **C.** Chest x-ray of a 59-year-old male patient with genotype Pi*Z/$M_{Palermo}$ prior to initiation of AAT augmentation therapy (Patient E in Table 3). The right lung shows hyperinflation consistent with emphysema and the left lung appears normal. The left lung was transplanted in 2014. This patient is an ex-smoker with a 20 pack/year history of tobacco use and AATD (pre-treatment serum AAT level 0.3 g/L). This patient has been on AAT augmentation therapy since 2019

to form polymers, leaving on 15% to be secreted [16]. This mutation has been clearly associated with hepatic dysfunction and emphysema especially in homozygous individuals [3, 14–16].

A recent systematic review of the literature on rare variants associated with AATD found useful information on 216 types of rare variants in 80 countries. This study confirmed that AATD extends well beyond the well-known Z and S variants and re-emphasized that AATD likely to be a widely undiagnosed and untreated disease [17]. The review also noted that different geographical regions (Africa, Asia, Europe, North America, South America and Oceania) had distinct prevalence patterns for AATD variants. M_{Malton} was among the 20 most common variants in Europe, Asia and North America and $M_{Palermo}$ was among the top 20 variants in Europe [17]. It should be noted that null or rare variants that were not specifically identified in the source publication were among the top five rare variants in all global geographic regions.

In index patients in the current study, there was a direct proportional increase in the development of emphysema and COPD with cumulative tobacco use. In addition, in the small number of patients that received AAT augmentation therapy ($n=5$), there appeared to be an improvement in their pulmonary health based on a decrease in COPD exacerbations after the initiation of augmentation therapy. Family members who were identified to

have variants associated with AATD before the development of significant pulmonary disease provide an excellent opportunity for early and potentially more effective interventions. Lifestyle interventions (smoking cessation, avoidance of secondhand smoke and avoidance of environmental exposure to dust or other pulmonary hazards), monitoring for disease development and early application of treatment could alter the course of their disease.

When compared to the index cases, the screened AATD cases were younger, predominantly female and had a higher frequency of heterozygous mutations. The screened cases also had a higher rate of current smokers and never smokers compared to index cases. A previous study that evaluated index and screened cases with the PiZZ genotype found that index and screened cases had similar lifetime smoke exposure and attributed the observed reduction in lung function to the older average age of the index cases [18].

Screening programs that include not only COPD patients but also their relatives may provide multiple opportunities for medical and behavioral interventions. A 2007 study showed that diagnosis of the AATD status in individuals with PiZZ genotype increased the number of attempts to quit smoking in the three-month period following diagnosis [19]. More recently, 3506 patients with AATD-associated lung disease were surveyed during enrollment in a program for patients being treated with AAT augmentation therapy. This study found that heterozygotes, MZ and SZ were more likely to smoke and have an unhealthy lifestyle (sedentary and overweight) than patients that were homozygous ZZ [20]. These studies suggest that disease awareness may have positive behavioral effects especially in patients with severe AATD.

Screening programs also allow for emphasis on education that even moderate AATD commonly seen in heterozygotes (MZ and with rare mutations) can result in more severe COPD especially in smokers [21]. Identification of rare patients with severe AATD (ZZ or homozygous null mutations) is undoubtedly important in providing the most effective therapy for those individuals. A greater public health benefit may be realized from finding, educating and treating the larger group of individuals with intermediate AATD. Smoking cessation in these individuals may not only help them directly but also help their progeny due to decreased second-hand smoke exposure and decreased inheritance of smoking habits [21].

Conclusions

The results of these genetic studies and the current study clearly indicate that more testing and more research are needed to clearly identify the relative prevalence and clinical relevance of rare AATD variants. This could allow for earlier and more effective treatment of affected individuals and improvement in their quality of life.

Abbreviations

AAT	Alpha-1 antitrypsin
AATD	Alpha-1 antitrypsin deficiency
CAT	Chronic obstructive pulmonary disease assessment test
COPD	Chronic obstructive pulmonary disease
FEV1	Forced expiratory volume in 1 s
FVC	Forced vital capacity
ICS	Inhaled corticosteroid
LABA	Long-acting beta agonist
LAMA	Long-acting muscarinic antagonist
LTOT	Long-term oxygen therapy
MMRC	Modified Medical Research Council Dyspnea Scale
SABD	Short-acting bronchodilator

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Author contributions

DK, BD, and LO participated in the conceptualization of the study and genetic analysis. DK, EA, SO, BYK, NH, TGT and US analyzed and interpreted the clinical information regarding the patients' pulmonary disease. LO performed the genetic analyses. TGT performed the statistical analysis. DK, BD, and LO participated in the creation of the first draft and subsequent revisions. DK, BD, LO, EA, SO, BYK, NH, TGT and US read and approved the final manuscript.

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Data availability

The data that support the findings of this study are not openly available dueto reasons of confidentiality and are available from the corresponding authorupon reasonable request. Data are located in controlled access data storageat Recep Tayyip Erdoğan University, School of Medicine, Department of ChestDiseases.

Declarations

Ethics approval and consent to participate

Written informed consent was obtained from the patients described herein for their anonymized information to be published in this article. Ethical approval was provided from Recep Tayyip Erdoğan University Ethical Committee, date: 28.09.2023 and number: 2023/224. This study was completed in accordance with the Helsinki Declaration as revised in 2013.

Consent for publication

Written informed consent was obtained from the patients described herein for their anonymized information to be published in this article.

Competing interests

DK, EA, SO, BYK, NH, TGT and ÜS have no competing interests related to this work. BD was an employee of Grifols Deutschland at the time this study was conducted, and LO is an employee of Progenika.

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