Alpha1-antitrypsin deficiency and asthma

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Abstract

α1-antitrypsin deficiency (AATD) is a genetically inherited autosomal-codominant disease with a variable clinical spectrum of lung-related diseases. Pulmonary involvement of α1-antitrypsin deficiency may also include emphysema with variable functional and radiological abnormalities, asthma, and bronchiectasis. Asthma and AATD are mutually exclusive disease entities, but the commonality of neutrophil inflammation across the diseases might suggest common underlying mechanisms of effect. The diseases share many clinical and functional features: patients with AATD commonly first present with asthma-like symptoms; functional alterations may be common to both, such as bronchial hyperresponsiveness or fixed obstruction after bronchial remodeling. It has been recognized that allergy and asthma often coexist with AATD, but the relationship between allergy, asthma and AATD is not clear. Distinguishing AATD from asthma based on presentation and clinical evaluation is not possible. The clinician must assess each of the elements in the context of the whole patient, any patient with difficult-to-manage asthma should be screened for AATD. From the clinician's point of view, improving diagnosis in this population is fundamental to optimize clinical management. Genetic studies will probably be needed in the future to unequivocally establish the causal link between AATD and asthma.

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Introduction

α1-antitrypsin (α1-AT) is a serine proteinase inhibitor protecting alveoli against the effects of neutrophil elastase (NE), proteinase 3 (PR3) and cathepsin G, which cause destruction of pulmonary parenchyma [1,2] α1-antitrypsin deficiency (AATD) is an underrecognized genetic disorder [3] and, although it was initially thought of as a rare disease, it has proven to be underdiagnosed in many countries [4,5] .AATD is a genetically inherited autosomal-codominant disease [6] and more than 100 genetic variants have been described and those associated with severe plasma deficiency of α1-AT (<11 μM or 0.5 $g \cdot L^{-1}$) are recognized as increasing susceptibility to the development of emphysema even in never-smokers [7]. The variants are classified into three major categories: i) normal, with genotype M, with α1-AT normal ranges; ii) deficient (genotypes Z, S and M-like), with reduced but detectable α1-AT plasma levels; and iii) null (Q0), without detectable α1-AT plasma levels [8]. The most common deficient alleles are protease inhibitor Pi*S and Pi*Z. Pi*ZZ individuals have severe AATD, with only 10% of normal serum levels as compared to Pi*MM subjects. Individuals homozygous for the PI*S (PI*SS) alleles have approximately 60% of normal serum α1-AT levels [4,9]. AATD is the most common hereditary disorder in adults causing an increased risk of developing pulmonary emphysema and liver disease. AATD clinical impact is characterized by a high heterogeneity, only partly explained by exposure to risk factors. Lung disease in AATD generally presents at a younger age than "usual" chronic obstructive pulmonary disease (COPD) and it may be misdiagnosed as asthma [7], but its relationship with asthma remains controversial [10]. The most important preventable risk factor for the progression of lung disease in AATD is cigarette smoking, which is often associated with a lower FEV_1 and earlier development of COPD [11]. Prognosis is poor for patients with the Pi*ZZ phenotype who smoke because they have significantly lower survival rates than their nonsmoking counterparts and are expected to die up to 20 years sooner [12].

Current international guidelines, including the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [13] and the World

Health Organization (WHO) [14] recommend AATD screening in patients with obstructive lung disease. The consensus statement on AATD by the American Thoracic Society (ATS) and the European Respiratory Society (ERS) specifically recommends genetic screening in all symptomatic adults with emphysema, in patients with asthma who have airflow obstruction not completely reversible after aggressive treatment with bronchodilators, and in individuals with unexplained liver disease [15].

The purpose of this review is to explore the interactions and overlap between AATD and asthma. We examine the clinical consequences of AATD and discuss the rationale for extending AATD screening to patients with asthma based on currently available evidence. If patients with symptoms of asthma are targeted for AATD screening, research suggests that the disease might be detected sooner, and disease-specific interventions could be implemented.

Materials and Methods

Eligibility criteria

This review was performed on full-text original English articles published in international journals from January 1, 2000 to December 31, 2020. Articles were selected from PubMed.

Literature search

Articles were selected from PubMed database using keywords including: "α1-antitrypsin", "α1-antitrypsin deficiency", "early-onset emphysema", "asthma".

A total of 148 articles were initially reviewed. 92 articles were fully read, 39 were not relevant, 17 were in languages other than English, and finally 42 articles were included.

AATD associated lung diseases

The clinical spectrum of AATD-related lung diseases is a variable one. AATD pulmonary involvement may include emphysema with variable functional and radiological abnormalities, asthma, and bronchiectasis.

In one of the largest cohorts comparing the distribution of AAT genotypes among different respiratory diseases, Veith *et al.* [16] found COPD/emphysema to be the most frequent reason for testing patients with suspected AATD, followed by asthma and bronchiectasis. COPD/emphysema and bronchiectasis exhibited very similar distribution of the AAT genotypes. Both diseases exhibited higher percentages of severe deficient AAT genotypes as compared to asthma.

The cardinal clinical features of AATD were thereby established: early-onset emphysema and a genetic predisposition both associated with a protein deficiency [17]. But AATD predisposes to liver disease too, and patients with AATD might also be affected by other chronic respiratory disorders, granulomatosis with polyangiitis, and panniculitis [18]. Patients may present a severe airflow limitation often disproportionate to their smoking history. Furthermore, they do not always present airflow obstruction and parenchymal destruction concurrently. Often airflow limitation is not fixed and, consequently, there is a wide variation in bronchodilator response in these patients. The degree of lung function impairment can vary among patients with the same phenotype for AATD and can be significantly different in siblings with the same phenotype. The risk factors that can affect the rate of change in lung function in AATD are similar to those identified for COPD (smoking, exacerbations, environmental exposures, bronchodilator reversibility, age and basal lung function) [19]. Differential diagnosis of AATD-related COPD *versus* COPD from other etiologies and even asthma with fixed obstruction is complicated by shared signs and symptoms. Nevertheless, while not unique to AATD-related COPD, several characteristics indicate that AATD may be the cause of COPD [20]. When asthma co-occurs with AATD, it exacerbates COPD symptoms and it's a risk factor for more severe COPD [21]. Due to this heterogeneity, the paradigm of pure emphysematous patients has changed by the understanding that the clinical spectrum of AATD lung disease might include different phenotypes [22]. To characterize the clinical features of patients with AATD, Piras *et al*. [8] proposed clinical phenotyping of Pi*ZZ AATD patients in three categories: predominant emphysema, chronic bronchitis and overlap with asthma. They analyzed the data of adult patients with severe AATD enrolled in the Spanish and Italian national registries. Patients with chronic bronchitis were younger, they had better preserved lung function and lower tobacco consumption. Overlap patients (COPD/asthma) were mainly females, more frequently never-smokers and received respiratory medications more often [8].

AATD and asthma

Although asthma and AATD are mutually exclusive disease entities, several reports indicated that asthma is common in AATD patients [23,24] Asthma is currently interpreted as an inflammatory disease in which different subpopulations of cells (mast cells, lymphocytes, and eosinophils) play a decisive role [25]. Asthma is also a heterogeneous disease that may present at any age, but it often becomes apparent during childhood and occurs more frequently in youth.

On the other hand, AATD clinical manifestations rarely begin before 25 years of age and more often occur as hepatic illness when presenting in childhood [15]. Prior work suggests an association between AATD and asthma. The Alpha-1-Antitrypsin Deficiency Registry Study Group studied 1129 patients with AATD (α1-AT levels <=11 microM or a ZZ genotype). The authors described a self-reported diagnosis of asthma to be present in 35% of severely deficient participants [26]. Eden *et al*. [27], in a cohort of 60 patients, reported that asthma was more common in patients with AATD than in those without it suggesting that α1-AT paucity in airways increases the propensity to develop asthma. Several reports described an association between asthma prevalence or severity and the presence of phenotypic and functional abnormalities of AATD in screened populations [28-31].

In literature the prevalence of AAT deficiency alleles in asthmatic population is still an open question. In a study of patients with poorly controlled asthma, Eden *et al*. [32] demonstrated that the prevalence of AATD is over 2% and carriage of a deficiency gene is over 10%. In this cohort, mild deficiency as defined is associated with a propensity to greater bronchodilator responsiveness. Miravitlles *et al.* [33] studied the distribution of deficient α1-AT phenotypes in a non-selected population of adult patients with bronchial asthma. No significant differences were found in clinical and functional characteristics, or in asthma morbidity between Pi*MM and Pi*MS patients or the heterozygote group (Pi*MS and Pi*MZ) [33]. In an asthmatic population of 5629 9-11 aged children, von Eherestein *et al.* [34] studied relation between the prevalence and severity of asthma and allergic disorders and Pi heterozygosity and α1-AT plasma levels. They proposed that heterozygous Pi genotypes (MS or MZ) or low levels of α1-AT in plasma do not enhance the risk of children developing asthma or hay fever. The findings suggest, however, that an impaired α1-AT

balance may potentially increase the vulnerability for decrements in lung function and BHR in asthmatic children [34].

Common clinical features across asthma and AATD

In most individuals with severe AATD, asthma is diagnosed after COPD symptoms have developed. *Eden E.* estimated that physician-diagnosed asthma is present in up to 50% of patients with AATD once the symptoms of COPD have developed [35]. Asthma also can occur alone before COPD is diagnosed. Whether asthma precedes or results from AATD, the presence of coexisting asthma significantly affects the course of AATD, because it is associated with more severe lung disease. The prognosis for individuals who have asthma and AATD is poor [11,36].

It is of note that α1-AT inhibits neutrophil elastase-induced airway inflammation, and its loss may predispose to increased release of powerful chemotactic agents acting on neutrophils and the development of chronic airway hyperresponsiveness [37]. α1-AT plays relevant anti-infective, anti-inflammatory and antioxidant activities too. An increased inflammatory mediator release because of the lack of α1-AT inhibition may lead to the development of chronic airway hyperreactivity and asthmatic state [38]. This could suggest that AATD itself might predispose to airway hyper-reactivity and participate to asthma pathophysiology. While the underlying biological mechanism is not understood, data from basic research have in fact suggested that α1-AT has also immunomodulatory functions and it might affect eosinophilic cells [39].

Although the etiology and disease mechanisms of asthma and AATD are different, patients with AATD commonly first present with asthma-like symptoms [34]. That is why it is sometimes difficult to differentiate between these conditions. The symptoms include dyspnea (84%), wheezing (65%), cough without upper respiratory tract infection (42%), cough with mucus production (50%) [37] and the patients receive initially asthma treatment. Adding to the confusion, it has been recognized that allergy and asthma often coexist with AATD [34,35]. To complicate matters, AATD is frequently seen in patients with asthma and, conversely, patients with AATD are susceptible to developing asthma owing to increased underlying lung inflammation, leading asthma to coexist with AATD and emphysema. AATD can coincide with asthma, and patients with both AATD and asthma are more susceptible to developing an accelerated and progressive loss of lung function because of constant unchecked inflammation [27].

Common mechanisms across asthma and AATD

In literature there are many similarities in neutrophilic inflammation across airway diseases. First, an airway neutrophilia is common. Second, there are often markers of neutrophil degranulation and in particular reactive oxygen species (ROS) and proteinase activity which are associated with disease presentation and progression. Third, aspects of neutrophil function appear altered. The commonality of neutrophil inflammation across different diseases might suggest common underlying mechanisms of effect, and studies have suggested potential themes as to how this might occur. Neutrophils play a central role in the pathophysiology of AATD, and pulmonary disease is thought to develop from an imbalance of proteinases and α1-AT, although α1-AT has many non-proteolytic functions which protect against infection and inflammation, including immunomodulation and anti-microbial activity [40]. It is well known that AATD is associated with a reduced ability to neutralize NE and PR3 adequately, leading to more tissue damage. In response to NE activity, epithelial cells and macrophages also release pro-inflammatory mediators such as CXCL8 and leukotriene B4 (LTB4), respectively. This chemoattractant production is perpetuated, further increasing neutrophil influx and increased NE activity within the lung, forming a vicious cycle of damage [41,42]. ROS in AATD are increased, and α1-AT modulates neutrophil O^{2-} production elicited by N-formylmethionineleucyl-phenylalanine (fMLP) and CXCL8 in a dose-dependent manner. However, α1-AT is known to bind to several products with oxidative potential, and the burden of ROS in AATD may be multi-faceted [43,44]. Airway inflammation and remodeling in asthma involves degradation of the extracellular matrix, most prominently elastin, and is characterized by an imbalance between elastase and its primary inhibitor α1-AT [45]. Vignola *et al*. [46] documented that neutrophil elastase is significantly increased in the induced sputum from asthma patients compared with control subjects, and neutrophil elastase levels in asthmatic patients are correlated with a FEV_1 decline. Gharib *et al*. documented, computationally intensive analysis of induced sputum proteome, that SERPINA1 gene (whose mutations lead to a dysfunctional α1-AT protein production) is significantly upregulated in asthma [47]. In particular, in "non-eosinophilic asthma", neutrophils represent 40-76% of total sputum cells. This phenotype of asthma classically correlates with steroid resistance, acute exacerbations, occupational asthma, and more treatment-resistant forms of the disease. These characteristics suggest that the neutrophil plays a role in asthma pathophysiology [48]. In patients with asthma peripheral and airway neutrophils may exhibit functional defects [49], and, as in other airway diseases, there is some evidence of increased, ROS generation and reduced neutrophil phagocytosis [50]. In patients with neutrophilic asthma, as in those with COPD, systemic inflammation (C-reactive protein and IL-6) is increased compared with both patients with non-neutrophilic asthma and healthy controls [51] .Although neutrophils are associated with tissue damage in asthma, they have also been shown to have a role in controlling inflammation, restoring tissue homeostasis and promoting tissue repair, highlighting the delicate balance between protective and destructive functions of neutrophils in airway disease, a common feature across asthma and AATD [48].

Airflow limitation in asthma and AATD

Airflow limitation in AATD patients can be severe and disproportionate to their smoking history. Often airflow limitation is not fixed and, consequently, there is a wide variation in bronchodilator response in these patients. Furthermore, they do not always present airflow obstruction and parenchymal destruction concurrently [52]. The degree of lung function impairment can vary greatly among patients with the same phenotype for AATD and can be significantly different in siblings with the same phenotype. The risk factors that can affect the rate of change in lung function in AATD are like those identified for COPD (smoking, exacerbations, environmental exposures, bronchodilator reversibility, age, and basal lung function) [19.] Persistent airflow limitation is commonly found (up to 50%) in adult patients with severe asthma and it is demonstrated that the patients with asthma have a faster decline in FEV_1 in comparison with healthy subjects. Several factors (smoking, adult onset of asthma severe airway hyperresponsiveness and persistent eosinophilic airway inflammation) have been suggested to contribute to the decline in lung function in asthma [53].

Nevertheless, although fixed or nonreversible obstruction in patients with asthmatic symptoms in most cases is secondary to remodeling, in some cases it may result from AATD [54].

Evidence explains that patients with AATD who have bronchial hyper-reactivity have poorer outcomes and a more rapid decrease in lung function [55,56], with steeper rates of decreased FEV_1 compared

with subjects who had no hyper-reactivity (64.6 *vs* 40.2 mL/year) [26]. AATD itself might predispose to airway hyperresponsiveness, that is essential for reversible airflow obstruction, and participate in asthma pathophysiology [35]. Van Veen *et al*. showed that α1-AT heterozygosity does not seem to be an important risk factor of persistent airflow limitation in patients with asthma. Thus, routine assessment of the α1-AT phenotype is not indicated in asthmatic patients even if they exhibit fixed airflow limitation [53].

Allergy, asthma and AATD

It has been recognized that allergy and asthma often coexist with AATD. Atopy which predisposes to asthma has also been reported to be more prevalent in patients with AATD. But the relationship between allergy, asthma and AATD is not clear. Atopy confers a genetic predisposition to asthma [57] and in a previous study [27], positive skin reactions to common aeroallergens occurred in 48% in a group with severe AATD and COPD compared with 28% in COPD controls. In atopy, a reduced level of AAT may also enhance the severity of airway hyperresponsiveness [58]. Aiello *et al*. [38] studied a cohort of 58 asthmatic outpatients divided in AATD patients (n=22) and non AATD patients (n=36), according to genotype. They hypothesized that asthmatic patients with pathological gene mutations on SERPINA1 gene may exhibit peculiar clinical features that differentiate them from asthmatic patients without gene mutations. The presence of atopy was significantly higher in patients with AATD than in those without AATD (91% *vs* 64%; p=0.031). AATD patients reported allergic manifestations more than non AATD patients (77 % *vs* 47%; p=0.030), demonstrating that atopy in asthmatic patients with AATD is considerably increased than in asthmatic patients without gene mutation. Furthermore, AATD can differently characterize the asthmatic population through a higher prevalence of allergic manifestations and atopy in these patients, compared to those without AATD [38].

In the National Heart, Lung and Blood Institute's Registry of α1-AT Deficient Individuals (NHLBI), a network of 37 centers across USA and Canada for a total of 1219 subjects, 55% of patients reported a significant response to bronchodilation, while concomitant asthma and respiratory allergy were reported in 31% and 23% of cases, respectively [26]. Kelbel *et al.*, involving 500 patients with severe AATD, confirmed that clinical manifestations of uncontrolled asthma or asthma with fixed obstruction are frequent in AATD; however, among the 34% participants undergoing allergological evaluation, only 5% were diagnosed with AATD [59]. It has therefore been suggested that if a patient enters the healthcare system through allergists, this often delays the appropriate diagnosis and treatment [52]. Suárez-Lorenzo *et al*. [60]studied the α1-AT distribution in an allergic asthmatic population. They reported that 22.4% of asthmatic patients had at least one mutated allele (S or Z). Nevertheless, they found no association between the different genotypes and asthma severity and they observed no significant differences in all clinical and functional tests, as well as nasal eosinophils, IgA and IgE serum levels. Peripheral eosinophils were significantly lower in patients with the Pi*MS genotype. Neither association between deficient α1-AT genotypes or serum AATD and development of severe asthma, nor correlation between α1-AT levels and FEV_1 were observed [60]. *Miravitless et al*. studying influence of deficient α1-AT phenotypes on clinical characteristics and severity of asthma in adults, described that the asthmatics with PiMS phenotype for α1-AT did not present differential characteristics compared with the asthmatic carriers of the non-deficient PiMM phenotype, although AATD values were significantly lower. Neither did they observed differences in the results of respiratory function tests, blood eosinophil values or plasma IgE concentrations. These results were like those of other series in the literature, which failed to find a greater prevalence of the PiMS phenotype in asthmatic patients [33].

Discussion

Although AATD is one of the most prevalent diseases that can lead to significant morbidity and mortality, it continues to be underdiagnosed in patients with airflow obstruction [10]. Despite fixed or nonreversible obstruction in patients with asthmatic symptoms in most cases is secondary to remodeling, in some cases it may result from AATD and the presence of symptoms, onset in the fourth decade, nonreversible airways obstruction and panlobular emphysema should raise suspicion and promote further investigations to check for AATD [54]. Owing to overlapping clinical features, AATD is often overlooked in the differential diagnosis of asthma and can be misdiagnosed as asthma. According to the ATS/ERS and the WHO, diagnosis of asthma is one of the clinical indications for genetic AATD testing [14,15]. The use of genetic profiling of asthma in the clinic is current absent [61].With respect to asthma, there is an absence of any systematic recommendation for AATD screening in current guideline on the prevention and management of asthma, thus contributing to lack of recognition of AATD in patients with asthma [62].

The therapeutic options and outcomes differ significantly between asthma and AATD, which underscores the importance of making the correct diagnosis. Distinguishing AATD from asthma based on presentation and clinical evaluation is not possible. Baseline pulmonary function tests and asthma scores have been shown to be no different in patients with poorly controlled asthma with and without AATD [32]. Although a family history of liver and lung disease may lend support to its presence, diagnosis of AATD relies exclusively on laboratory assays [62].

In distinguishing AATD from asthma, the clinician must assess each of the elements in the context of the whole patient, particularly one who does not adhere to a typical clinical profile or course or who has recalcitrant disease. Regardless of overlapping clinical characteristics, any patient with difficult-to-manage asthma should be screened for AATD. When the patient with asthma shows a lack of improvement after receiving the usual therapeutic interventions, there can be several factors involved, including problems with adherence to the medication regimen, environmental avoidance measures, and comorbid disease. These may be cases of recurrent exacerbations, a chronic bronchitis, steroid dependence, and "brittle" asthma. Non-adherence to medication, comorbid disease and AATD are more common than corticosteroid resistance in patients with treatment-resistant asthma, although insensitivity to corticosteroids is more commonly contemplated by physicians [63]. Final, AATD patients with concomitant asthma have worse prognosis. Bronchodilator response has been associated with greater FEV_1 decline and poorer clinical outcomes [11,26,56]. From the clinician's point of view, improving diagnosis in this population is fundamental to optimize clinical management and further clinical trials are needed to investigate patient's response to available treatments [22].

Even though AATD is strongly associated to the development of COPD, GOLD document edited in 2021 mentioned AATD in only two occasions. First, as a known genetic risk factor for COPD and an example of gene-environment interaction; second, as a step in COPD assessment that WHO guidelines recommended to screen

once in all patients with a diagnosis of COPD, especially in areas with high AAT prevalence [13]. On the other hand, the Global Initiative for Asthma Management and Prevention (GINA) document has only one mention of AATD as a possible differential diagnosis in patient with suspected asthma in presence of family history of emphysema and aged between 12 and 39 years. Notably, no indication for AATD testing in asthmatic patients can be found in this document [64].

The laboratory tests are based on initial quantitation of the AAT level in blood together with a measure of C-reactive protein to determine whether the AAT level could be higher than usual due to a possible acute phase response. Thereafter, protein phenotyping by isoelectric focusing or genotyping, where specific primers for known mutations are available, will identify the most common variants. Whole exon sequencing can be undertaken especially if null variants are expected [65].

The AATD testing involves the collection of blood sample into a filter paper. Then, the dried blood is sent to a specialized laboratory that performs all necessary tests. The full panel of diagnostic tests for AATD involves serum level quantification, phenotyping, and genotyping. For high throughput screening, polymerase chain reaction-based methods are available, whereas DNA sequencing can be used to define specific genotypes, including rare alleles. A spectrum of disease exists for AATD and low to normal serum levels might provide false reassurance. Testing of α1-AT levels alone may result in mild or moderate cases of AATD being overlooked and carriers of a deficiency-related allele (e.g. PiMZ) to be missed: in patients with lung disease with frequent exacerbations or infections, α1-AT levels increase because it is an acute phase protein, thus giving the idea that this concentration is normal. A further limitation of serum testing alone is that α1-AT can be elevated when infection, cancer, thyroid disorders, and other forms of inflammation are present and may be increased by oral contraceptives, pregnancy, and stress [66]. Screening patients with COPD for AATD have greater impact than population screening because it shows a much higher prevalence of AATD genotypes [67]. Targeted screening of patients with asthma may expose a similar situation. Screening rates might be improved further by involving the wider multidisciplinary team, i.e., respiratory therapists and pulmonary function technicians, in testing candidate patients for AATD [68].

Three approaches to select individuals for diagnosis testing of AATD exist. First, the diagnostic testing of individuals with signs or symptoms consistent with AATD, such as early-onset, primarily lower-lobe emphysema. In the past, this paradigm led to underdiagnosis and late diagnosis of AATD. Second, predisposition testing of those who might be at high risk for AATD, such as asymptomatic individuals carrying a genetic mutation in SERPINA1 and who have low levels of α1-AT and a family member with AATD. Development of symptoms is likely for these patients, but it is not certain. Third, targeted detection in patients with a clinical reason to suspect AATD, including all patients with conditions associated with increased prevalence of AATD, such as COPD, poorly responsive asthma, cryptogenic liver disease, granulomatosis with polyangiitis, bronchiectasis of unknown aetiology and panniculitis, in addition to first-degree relatives of patients with AATD [69].

Conclusions

AATD is a condition with a high prevalence compared to other genetic diseases. The increase in awareness of AATD could be implemented through changes in clinical practice guidelines for the diagnosis and management of asthma, in particular in cases of severe bronchial asthma.

Although diagnostic testing is available, it is very rarely performed during asthma diagnostic investigations, even in patients with highly suggestive AATD symptoms. In addition, the availability of epidemiological data on the coexistence of asthma and AATD could raise the profile of this genetic condition among clinicians, as they could consider it as a differential diagnosis in their patients. There may be higher rates of detection, earlier diagnosis of the disease and better onset of disease management strategies, with a positive impact on long-term outcomes for patients.

Genetic studies will probably be needed in the future to unequivocally establish the causal link between AATD and asthma.

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