The Distribution of Alpha-1 Antitrypsin Genotypes Between Patients with COPD/Emphysema, Asthma and Bronchiectasis

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Purpose: Alpha-1-antitrypsin deficiency (AATD) is a rare hereditary condition characterized by low circulating levels of alpha-lantitrypsin (AAT). While the association between AATD and COPD/emphysema is undisputed, the association between AATD and asthma or bronchiectasis is still a matter of debate.

Aims and Objectives: Our study aimed to investigate the distribution of AAT genotypes between patients with COPD/emphysema, asthma and bronchiectasis. To back up the diagnostic labels, we described symptoms associated with the diagnosis.

Methods: Between September 2003 and March 2020, 29,465 testing kits (AlphaKit®) were analyzed in the AAT laboratory, University of Marburg, Germany. The diagnosis of AATD has been made based on the measurements of AAT serum levels, followed by genotyping, phenotyping or whole gene sequencing depending on the availability and/or the need for more detailed interpretation of the results. The respiratory symptoms were recorded as well.

Results: Regarding the distribution of the wild type allele M and the most frequent mutations S (E264V) and Z (E342K), no significant differences could be found between COPD/emphysema [Pi*MM (58.24%); Pi*SZ (2.49%); Pi*ZZ (9.12%)] and bronchiectasis [Pi*MM (59.30%) Pi*SZ (2.81%); Pi*ZZ (7.02%)]. When COPD/emphysema and bronchiectasis were recorded in the same patient, the rate of Pi*ZZ (14.78%) mutations was even higher. Asthma patients exhibited significantly less deficient genotypes [Pi*MM (54.81%); Pi*SZ (2%); Pi*ZZ (2.77%)] than two other groups. Associated respiratory symptoms confirmed the diagnosis.

Conclusion: COPD/emphysema and bronchiectasis, but not asthma patients, exhibit higher frequency of AATD genotypes. Our data suggest that AATD testing should be offered to patients with COPD/emphysema and bronchiectasis.

Keywords: SERPINA1, alpha-1-antitrypsin deficiency, bronchiectasis, asthma, diagnosis

Introduction

Alpha-1 antitrypsin deficiency (AATD) is an autosomal codominant condition caused by mutations of the SERPINA1 gene characterized by low serum level of AAT. Since the discovery of AATD in early 1960s has become apparent that the emphysematous form of chronic obstructive pulmonary disease (COPD) is the most frequent clinical manifestation in individuals with AATD. Other common clinical manifestations of AATD include hepatic diseases, and less frequently panniculitis and other skin diseases. Despite of being one of the most common inherited conditions worldwide (AATD occurs in approximately 1:3,000–5,000 people), it
remains significantly under-diagnosed. Data show that less than 10% of individuals with AATD identified and with delays of more than 5 years between initial symptoms and diagnosis. This is also in part related to the fact that many people with AATD are asymptomatic during the life time.

The clinical spectrum of AATD-related lung diseases is variable. AATD pulmonary involvement might include emphysema with variable functional and radiological impairments, asthma and bronchiectasis. In addition, the unusual associations between AATD and idiopathic pulmonary fibrosis have also been reported. Therefore, an early detection of AATD is a crucial to define indicator diseases that should prompt physicians to screen for AATD. While according to recent guidelines-all patients with COPD and/or emphysema recommended for AATD screening, the importance of routinely screening of patients with asthma and bronchiectasis remains controversial. This is due to the conflicting epidemiological results concerning the association between AATD and those diseases. Regarding asthma, several investigators have suggested an increased risk of asthma among certain genotypes of AATD whereas others did not find an association. Nevertheless, few studies suggested that AATD patients with concomitant asthma have a worse prognosis. The recent ERS Statement of few years ago refer to the WHO recommendation to test all patients with COPD and all patients with adult-onset asthma. Thus also asthma patients (at least those with adult onset) should be tested. Likewise, the causal relationship between AATD and bronchiectasis is controversial. Some studies have found a high prevalence of bronchiectasis among AATD patients while others found no association. Although data document the role of AATD as an underlying etiology of bronchiectasis, the majority of patients are not tested for AATD. It is likely that the estimation of AATD prevalence in bronchiectasis population remains poor. Because of the high prevalence of COPD/emphysema, asthma, and bronchiectasis and the common pathophysiological pathways, some AATD patients with different diseases may present with similar symptoms. For example, common pathophysiological features of AATD-related bronchiectasis and emphysema include elevated elastin degradation as an indicator of elevated levels of desmosine and isodesmosine in both diseases. Considering latter, the investigations for the presence of chronic respiratory conditions, as asthma or bronchiectasis, in AATD are of great clinical importance. Hence, to elucidate the importance of COPD/emphysema, asthma, and bronchiectasis as indicator diseases for AATD, we compared the frequency and distribution of the different AAT alleles in patients with each of those three conditions.

Materials and Methods

Patients and Methods

Between September 2003 and March 2020, 29,465 testing kits (AlphaKit®) were analyzed in the AAT laboratory, University of Marburg, Germany. The diagnosis of AATD was made through a measurement of AAT serum levels, followed by genotyping, phenotyping or whole gene sequencing depending on availability and/or the need for more detailed interpretation of the AAT results. Respiratory symptoms were recorded.

Clinical Samples

We used serum samples and dried blood spot (DBS) samples (AlphaKits® GE Healthcare Ltd, Cardiff, CF147YT, UK) for screening and testing for AATD. The AlphaKits® consists of an instruction manual that outlines the purpose of the testing and the procedure how to obtain a blood specimen. Blood is applied to a filter paper, dried and shipped to our laboratory at the University of Marburg for the routine diagnosis of AATD. The AlphaKits® includes a text field for patient and physician’s identification. Clinical characteristics are recorded on the AlphaKit® (acute bronchitis, asthma, bronchiectasis, COPD, dyspnoea on exertion, dyspnea attacks, emphysema, chronic bronchitis, cough, sputum, wheezing), and also the smoking history and substitution therapy for AAT are asked for. The physician’s signature on the AlphaKit® confirms that patients approved and signed informed consent for the samples shipped to our laboratory for genetic analysis. Because our study reflects a retrospective analysis of those routine data, a formal ethics approval for this summary statistics of anonymized data was not necessary.

Nephelometry was used for the semi-quantitative determination of the plasma AAT levels and polymerase chain reaction (PCR) for genotyping, which was eventually followed by isoelectric focusing (IEF) (phenotype) and gene sequencing. Two independent readers validated the results of PCR and IEF. For the sequencing, the DBS samples were shipped to a reference laboratory (Eurofins Genomics Germany GmbH or Progenika Biopharma, S.A. A Grifols
### Table 1 Baseline Characteristics of Probands

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>COPD/Emphysema</th>
<th>Asthma</th>
<th>Bronchiectasis</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>18736</td>
<td>12283</td>
<td>4041</td>
<td>285</td>
<td></td>
</tr>
<tr>
<td><strong>Age (Median [IQR])</strong></td>
<td>62.72</td>
<td>64.78</td>
<td>48.59</td>
<td>59.85</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(51.2–71.76)</td>
<td>(56.13–74.03)</td>
<td>(30.17–60.52)</td>
<td>(42.72–70.46)</td>
<td></td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>47%</td>
<td>55.2%</td>
<td>46.5%</td>
<td>38.2%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>52.2%</td>
<td>43.8%</td>
<td>53%</td>
<td>60%</td>
<td></td>
</tr>
<tr>
<td><strong>Smokers</strong></td>
<td>25.7%</td>
<td>29.6%</td>
<td>12.2%</td>
<td>7.7%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>40.4%</td>
<td>44.7%</td>
<td>20.4%</td>
<td>19.6%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>33.9%</td>
<td>20.7%</td>
<td>61.8%</td>
<td>62.5%</td>
<td></td>
</tr>
<tr>
<td><strong>Augmentation therapy</strong></td>
<td>1%</td>
<td>1.1%</td>
<td>0.3%</td>
<td>0.7%</td>
<td></td>
</tr>
</tbody>
</table>

**Notes:** Table 1 displays the baseline characteristics of patients according to the chronic respiratory diseases. Patients with asthma were of the youngest age (median 48.59 years) when compared to patients with bronchiectasis (59.85 years) and COPD/emphysema (64.78 years). Patients with bronchiectasis or asthma were predominantly female (60% and 53%), whereas more patients with COPD/emphysema were men (55.2%). Smoking habits were different among the three groups, too: Patients with bronchiectasis or asthma were mainly non-smokers (62.5% and 61.8%) in contrast to COPD/emphysema patients, who had a history of smoking in 44.7% and were currently smoking in 29.6%. Patients with COPD/emphysema received augmentation therapy most frequently (1.1%) when compared to patients with bronchiectasis or asthma (0.7% and 0.3%). ***p<0.001, **p<0.01, *p<0.05 significant between bronchiectasis and asthma. ***p<0.001 significant between asthma and COPD/emphysema.

### Results

#### Study Population

In total, 29,465 AlphaKit® were analyzed between September 2003 and March 2020. According to the transferred information, 18,736 patients had been diagnosed with COPD/Emphysema, 285 (1.52%) asthma, and bromchectasis (1.84%) COPD/emphysema, asthma and bronchiectasis, 92 (0.52%) cases of COPD/emphysema, asthma, and bronchiectasis, and 98 (0.52%) cases of combined with COPD/emphysema and asthma. Additionally, we found 1,592 (8.30%) cases of COPD/emphysema, asthma, and bronchiectasis. The baseline characteristics of the respective group were presented in Table 1. We identified patient having only COPD/Emphysema 12,283 (65.56%), asthma 4,101 (21.57%) or bronchiectasis 285 (1.52%).

#### Statistical Analysis

For the comparison of continuous variables, Kruskal–Wallis test was applied. Microsoft Excel 2010 (Microsoft Corporation, Redmond, Washington, USA), IBM SPSS statistics version 24 (IBM, Armonk, New York, USA) and GraphPad version 7 (GraphPad, San Diego, CA, USA) were used for all calculation graphs. AlphaKit® (acute bronchitis, asthma, bronchiectasis, COPD, dyspnea on exertion, dyspnea attacks, emphysema, chronic bronchitis, cough, sputum, wheezing) and were documented in a database.
was most often recorded in COPD/emphysema, wheezing was most often recorded in asthma, and productive cough (cough, phlegm, chronic bronchitis) were the leading symptoms in bronchiectasis (Figure 2).

Distribution of Genotypes

The distribution of the AAT alleles of the 18,736 individuals is illustrated in Figure 3. In total 10,829 (57.80%) Pi*MM, 944 (5.04%) Pi*MS, 4,437 (23.68%) Pi*MZ, 49 (0.26%) Pi*SS, 432 (2.31%) Pi*SZ, 1,432 (7.64%) Pi*ZZ, 253 (1.35%) Pi*M and rare, 47 (0.25%) Pi*S and rare, 268 (1.43%) Pi*Z and rare, 45 (0.24%) Pi*rare and rare have been identified.

The distribution of the AAT alleles among patients with COPD/emphysema or asthma, or bronchiectasis yielded the following results (illustrated in Figure 4 and Table 2): Regarding the distribution of the wild type allele M and the most frequent mutations S (E264V) and Z (E342K), no significant differences could be found between COPD/emphysema [Pi*MM (58.24%); Pi*SZ (2.49%); Pi*ZZ (9.12%)] and bronchiectasis [Pi*MM (59.30%); Pi*SZ (2.81%); Pi*ZZ (7.02%)]. In contrast, asthma patients exhibited significantly less deficient genotypes [Pi*MM (54.81%); Pi*SZ (2%) ; Pi*ZZ (2.77%)] than two other groups.

We also analyzed the distribution of these genotypes in a number of combinations of the three diagnostic groups (Table 3). Adding patients with the diagnostic label COPD/emphysema or bronchiectasis to any other group increases the frequency of Pi*ZZ samples while the addition of the diagnostic label asthma decreases the detection rate.

In Figure 5 the detection rate is shown over a period of 17 years of normal genotype, intermediate genotype and severe genotype of patients with COPD/emphysema, bronchiectasis, asthma. The genotypes have been grouped in: normal genotype (Pi*MM); intermediate genotype (Pi*MS, Pi*MZ, Pi*M/Rare) and severe genotype
(Pi*ZZ, Pi*SS, Pi*SZ, Pi*S/Rare, Pi*S/Rare, Pi*Rare/ Rare). A decline of the detection rate of the normal genotype can be seen in Figure 5. The detection rate of the intermediate genotype however increases. Over the 17 years, the detection rate of the severe genotypes remained unchanged.

Ten thousand seven hundred and twenty-nine samples were analyzed out of which none of the three indications (COPD/emphysema, bronchiectasis, asthma) were ticked off on the AlphaKit®. Dividing those samples into a group of samples with at least one symptoms and a second group without symptoms, the symptomatic patients exhibited a lower percentage of at least one mutation (43.44% vs 56.83%) and also a lower percentage of Pi*ZZ samples (4.87% vs 6.37%). We assume that the AlphaKits® have not been ticked off correctly. For this reason, we omitted further analyses of those samples.

**Discussion**

In our database of almost 30,000 samples, which had been tested for AATD for different reasons, we analyzed the distribution of three important respiratory diseases, namely COPD/emphysema, asthma, and bronchiectasis. Furthermore, we described the distribution of different AAT genotypes in this cohort. To the best of our knowledge, this is one of the largest cohorts comparing the distribution of AAT genotypes among different respiratory diseases. We found COPD/emphysema to be the most frequent reason for testing, followed by asthma and bronchiectasis. Remarkably, 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 COPD/emphysema was by far the most prevalent disease entity in our study population (65.56%), followed by asthma (21.57%) and bronchiectasis (1.52%). This is likely relates to the facts that: i) early onset emphysema known as a typical manifestation of AATD and ii) COPD is a highly prevalent internationally and nationally. The bronchiectasis is gaining importance and awareness, however, it still remains a rare and underdiagnosed disease. Therefore, the low prevalence of samples in which bronchiectasis was the reason for testing, was expected.

Figure 2 Frequency of symptoms among the chronic respiratory diseases: COPD/emphysema, asthma and bronchiectasis. Figure 2 displays the frequency of clinical symptoms (dyspnea, dyspnea attacks, cough, phlegm, wheezing, acute bronchitis and chronic bronchitis) among the chronic respiratory diseases (COPD/emphysema, asthma and bronchiectasis). Chi-square test was used for statistical analyses. This information has been evaluated on the basis of the information on the AlphaKit®. Dyspnea appeared most frequently in patients with COPD/emphysema, whereas dyspnea attacks were more often in patients with asthma. Cough and phlegm could be observed most frequently in patients with bronchiectasis. Acute and chronic bronchitis occurred more often in patients with asthma or bronchiectasis than in patients with COPD/emphysema. $p<0.001$ significant between bronchiectasis and asthma; $p<0.01$, $p<0.05$ significant between bronchiectasis and COPD/emphysema. $p<0.001$, $p<0.01$ significant between asthma and COPD/emphysema.
bronchiectasis and absence of asthma or COPD/emphysema), and is in line with what has been reported by the NHLBI registry (2% of 1,129 participants).

By analyzing the association between recorded symptoms and the leading diagnosis, we gained confirming findings. While in COPD/emphysema was most often recorded dyspnea, wheezing was most often in asthma, and productive cough (cough, phlegm, chronic bronchitis) was most often in bronchiectasis. The combination of symptoms and the main diagnosis made us confident that the reported diagnoses were correct, even though lung function data and/or CT data are not part of the information that is transferred with the AlphaKit®.

Most interesting in our analysis is that we found a similar distribution of AAT genotypes between bronchiectasis and COPD/emphysema. The Pi*ZZ genotype was found significantly more often in patients with COPD/emphysema or bronchiectasis (9.12% in COPD/emphysema, 7.02% in bronchiectasis) than in patients with asthma (2.77%). The literature on AAT genotypes in patients with bronchiectasis is scarce. In a case-control study of 2000, Cuvelier and colleagues recorded no difference in the distribution of AAT alleles between bronchiectatic patients and 1,030 control subjects (unrelated healthy blood donors). Very recently, investigators from two hospitals in the UK screened 1600 patients with bronchiectasis, which resulted in the detection of only eight individuals (0.5%) with AATD. The authors concluded that routine screening for AATD in bronchiectasis in the UK has a low rate of detection. One can agree that 0.5% is certainly a low number; however, it is in the same range as the percentage of AATD patients within the overall COPD population, in which screening for AATD is accepted.

Furthermore, these numbers come from rather unselected disease populations, while our results are from a pre-filtered population. Nevertheless, it is reassuring that in our as well as in UK study the frequency of severe AATD in bronchiectasis was comparable to that in COPD.

The recommendation of the WHO, the ERS and the ATS about the need to test all COPD patients (and all patients with adult-onset asthma) have been emphasized

Figure 3 Distribution of the AAT alleles.
repeatedly. Despite this, the recommendation is clearly not followed by any health-care system throughout the world. One could argue that adding bronchiectasis as another rare (or believed to be rare) condition to the reasons for AATD screening could “dilute” the message of testing for AATD in routine screening. In our opinion, the recommendations depend on the clinical setting: While COPD should be a reason for AATD screening in every clinical setting, screening for AATD in bronchiectasis should be implemented in the workup of bronchiectasis patients in specialist centers.

One could argue that COPD and emphysema we need to analyze separately. In a subgroup analysis, we looked at the symptom and genotype distribution in patients with “COPD only” patients and compared them to “emphysema only”. In general, COPD patients were more symptomatic (supplement Figure 1) while emphysema patients more often exhibited a genotype compatible with severe

![Graph showing distribution of AAT alleles among chronic respiratory diseases: COPD/emphysema, asthma, and bronchiectasis.](image)

**Figure 4 Distribution of AAT alleles among the chronic respiratory diseases: COPD/emphysema, asthma, and bronchiectasis.** Figure 4 displays the distribution of AAT alleles among the chronic respiratory diseases bronchiectasis, asthma and COPD/emphysema. The distribution of the wild type (Pi*MM) was roughly comparable between the three groups (significant only between asthma and COPD/emphysema). The same applied to the distribution of the genotypes Pi*M5, Pi*M/rare and Pi*Z/rare, while the genotypes Pi*SS, Pi*SZ and Pi*S/rare were not distributed significantly different. A higher percentage of asthma patients exhibited the Pi*MZ genotype, whereas more COPD/emphysema and bronchiectasis patients exhibited the Pi*ZZ genotype when compared to asthma patients. ***p<0.001, **p<0.01 significant between bronchiectasis and asthma; #p<0.001, *p<0.05 significant between asthma and COPD/emphysema.

### Table 2 Distribution of the AAT Alleles Among Patients with COPD/Emphysema or Asthma, or Bronchiectasis

<table>
<thead>
<tr>
<th>Allele</th>
<th>COPD/Emphysema</th>
<th>Asthma</th>
<th>Bronchiectasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pi*MM</td>
<td>7,154 (58.24%)</td>
<td>2,215 (54.81%)</td>
<td>169 (59.3%)</td>
</tr>
<tr>
<td>Pi*MS</td>
<td>557 (4.53%)</td>
<td>261 (6.46%)</td>
<td>14 (4.91%)</td>
</tr>
<tr>
<td>Pi*MZ</td>
<td>2,704 (22.01%)</td>
<td>1,238 (30.64%)</td>
<td>61 (21.4%)</td>
</tr>
<tr>
<td>Pi*SS</td>
<td>33 (0.27%)</td>
<td>12 (0.3%)</td>
<td>2 (0.7%)</td>
</tr>
<tr>
<td>Pi*SZ</td>
<td>306 (2.49%)</td>
<td>81 (2%)</td>
<td>8 (2.81%)</td>
</tr>
<tr>
<td>Pi*ZZ</td>
<td>1,120 (9.12%)</td>
<td>112 (2.77%)</td>
<td>20 (7.02%)</td>
</tr>
<tr>
<td>Pi*M/rare</td>
<td>142 (1.16%)</td>
<td>76 (1.88%)</td>
<td>6 (2.11%)</td>
</tr>
<tr>
<td>Pi*S/rare</td>
<td>31 (0.25%)</td>
<td>10 (0.25%)</td>
<td>2 (0.7%)</td>
</tr>
<tr>
<td>Pi*Z/rare</td>
<td>202 (1.64%)</td>
<td>32 (0.79%)</td>
<td>1 (0.35%)</td>
</tr>
<tr>
<td>Pi*rare/rare</td>
<td>34 (0.28%)</td>
<td>4 (0.1%)</td>
<td>2 (0.7%)</td>
</tr>
</tbody>
</table>
deficiency (supplement Figure 2), both confirming earlier findings.26,34

Discussing the limitations of our analysis, we have to acknowledge that targeting preselected individuals (which is the basis for the vast majority of our analyses) might result in missing asymptomatic subjects with severe AATD, because a significant proportion of severe AATD patients do not develop pulmonary diseases.35,36 Secondly, our laboratory population only reflects a small and preselected part of the overall populations of the three diseases that we looked at. Thirdly, the retrospective nature of our analysis resulted in a high number of samples in which the reason for the analysis was not recorded. The reasons for that remain speculative. Finally, only limited information about the clinical characteristics was available, and the diagnostic accuracy of

<table>
<thead>
<tr>
<th>COPD/Emphysema and Asthma</th>
<th>COPD/Emphysema and Bronchiectasis</th>
<th>COPD/Emphysema and Bronchiectasis and Asthma</th>
<th>Asthma and Bronchiectasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pi*MM</td>
<td>986 (61.93%)</td>
<td>184 (53.33%)</td>
<td>56 (57.14%)</td>
</tr>
<tr>
<td>Pi*MS</td>
<td>84 (5.28%)</td>
<td>19 (5.51%)</td>
<td>4 (4.08%)</td>
</tr>
<tr>
<td>Pi*MZ</td>
<td>321 (20.16%)</td>
<td>72 (20.87%)</td>
<td>23 (23.47%)</td>
</tr>
<tr>
<td>Pi*SS</td>
<td>1 (0.06%)</td>
<td>1 (0.29%)</td>
<td>0 (%)</td>
</tr>
<tr>
<td>Pi*SZ</td>
<td>33 (2.07%)</td>
<td>4 (1.16%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Pi*ZZ</td>
<td>114 (7.16%)</td>
<td>51 (14.78%)</td>
<td>13 (13.27%)</td>
</tr>
<tr>
<td>Pi*M/3</td>
<td>24 (1.51%)</td>
<td>2 (0.58%)</td>
<td>1 (1.02%)</td>
</tr>
<tr>
<td>Rare</td>
<td>3 (0.19%)</td>
<td>1 (0.29%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Pi*S/3</td>
<td>25 (1.57%)</td>
<td>7 (2.03%)</td>
<td>1 (1.02%)</td>
</tr>
<tr>
<td>Rare</td>
<td>1 (0.06%)</td>
<td>4 (1.16%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Pi*Rare/3</td>
<td>1 (0.06%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Figure 5 Detection rate of patients with COPD/Emphysema, bronchiectasis, asthma.
the disease entity remains unknown. Nevertheless, our analysis provides important insights into the distribution of ATTD among diseases, which are regularly screened for AAT genotypes. Overall, in our population the COPD/emphysema and bronchiectasis exhibited very similar distributions of AAT genotypes. Hence, screening of patients with bronchiectasis for the presence of AATD is of importance.

**Abbreviations**

AAT, alpha 1 antitrypsin; AATD, alpha 1 antitrypsin deficiency; COPD, chronic obstructive pulmonary disease; DBS, dried blood spot; IEF, isoelectric focussing; PCR, polymerase chain reaction.

**Ethics Approval and Informed Consent**

Because our study reflects a retrospective analysis of those routine data, an ethics approval is not necessary.

**Acknowledgments**

We thank all employees of the alpha-1 antitrypsin laboratory at the University of Marburg for their continuous effort they put into this project. The alpha-1 antitrypsin laboratory at the University of Marburg has been supported by Grifols and Progenika Biopharma (A Grifols Company).

**Disclosure**

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**References**


