ORIGINAL ARTICLE

Serum levels and genotype distribution of \(\alpha_1\)-antitrypsin in the general population

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ABSTRACT

\textbf{Rationale} \(\alpha_1\)-Antitrypsin (AAT) deficiency is one of the commonest rare respiratory disorders worldwide. Diagnosis, assessment of risk for developing chronic obstructive pulmonary disease (COPD), and management of replacement therapy require the availability of precise and updated ranges for protein serum levels.

\textbf{Objective} This paper aims to provide ranges of serum AAT according to the main genotype classes in the general population.

\textbf{Methods} The authors correlated mean AAT serum levels with the main SERPINA1 variants (M1Ala/M1Val (rs6647), M3 (rs1303), M2/M4 (rs709932), S (rs17580) and Z (rs28929474)) in 6057 individuals enrolled in the Swiss Cohort Study on Air Pollution and Lung Diseases in Adults (SAPALDIA) cohort.

\textbf{Results} The following ranges (5th—95th percentile) of AAT were found in the serum (g/litre): 1.050—1.640 for PI*MM, 0.880—1.369 for PI*MS, 0.730—1.060 for PI*SS, 0.660—0.997 for PI*MZ and 0.490—0.660 for PI*SZ.

\textbf{Conclusion} This work resulted in three important findings: technically updated and narrower serum ranges for AAT according to PI genotype; a suggestion for a population-based ‘protective threshold’ of AAT serum level, used in decision-making for replacement therapy; and more precise ranges framing the intermediate AAT deficiency area, a potential target for future primary prevention.

INTRODUCTION

One of the few unambiguously ascertained individual risk factors for chronic obstructive pulmonary disease (COPD) is the serum level of \(\alpha_1\)-antitrypsin (AAT), which in turn is strongly determined by the AAT genotype variant system, classically named PI type. A large body of evidence suggests that the degree of risk for COPD is inversely related to the serum AAT level according to the hierarchy PI NullNull > PI ZZ > PI SZ > PI MZ.1–4 Therefore, accuracy in AAT serum level determination is a relevant factor in COPD risk assessment. Above the area termed ‘severe’ AAT deficiency (AATD), bounded by the AAT protective threshold level of 11 \(\mu\)M5 and at high risk for developing COPD, lies the area of ‘intermediate’ AATD, whose threshold has not been determined but is currently used as a proxy for the PI*MZ genotype.

Key messages

\textbf{What is the key question?}

\begin{itemize}
  \item What are the ranges of serum \(\alpha_1\)-antitrypsin (AAT) level in the general population?
\end{itemize}

\textbf{What is the bottom line?}

\begin{itemize}
  \item State-of-the-art methodologies allowed identification of AAT ranges according to the major genotypes, narrower than those previously available. Moreover, the authors defined the intermediate AAT deficiency area (0.92—0.49 g/litre) of particular interest being a possible target for future interventional options and clarified the longstanding controversy in the conversion from \(\mu\)M to g/litre of the ‘protective threshold’ of AAT serum level, used in decision-making for replacement therapy.
\end{itemize}

\textbf{Why read on?}

\begin{itemize}
  \item It is important to clearly identify the protective threshold for AAT deficiency and, in turn, the serum level of AAT characterising patients with severe AAT deficiency. It is also important to correctly diagnose patients with intermediate AAT deficiency (mostly with the PI*MZ genotype).
\end{itemize}

Notably, the currently used standard reference values for AAT in serum\textsuperscript{6} show a broad and overlapping range of values for the PI MM, PI MZ, PI MS and PI SS classes and do not represent data from the general population. In the absence of such data, only AAT serum values below 11 \(\mu\)M are of use for the assessment of severe AATD and for COPD risk prediction, whereas meaningful reference values to classify intermediate AATD associated with different AATD genotypes are lacking. Careful evaluation of serum AAT concentration is the initial diagnostic test in patients with suspected AATD.\textsuperscript{7} This measurement can be routinely performed in any clinical chemistry laboratory, and it is the determining factor that justifies further analysis such as genotyping and sequencing, which are performed in dedicated laboratories.\textsuperscript{8} Thus, the need for updated reference intervals for AAT according to the different PI types is of clinical relevance. This is especially true for reference values related to PI MZ, which may also require clinical attention in the form of smoking counselling in light of evidence for an increased risk of developing airflow obstruction.\textsuperscript{4,9}
Alpha-1-antitrypsin deficiency

The aim of this paper was to correlate serum AAT levels with the main PI variants, using current standards of measurement and diagnosis, including the molecular characterisation of the SERPINA1 gene encoding AAT. To the best of our knowledge, this information has not been published for a large general population sample.

We took advantage of the first follow-up examination of the (Swiss) Cohort Study on Air Pollution and Lung Diseases in Adults) SAPALDIA cohort, which included 8047 people randomly selected from eight population registries representing the three major Swiss language regions, including both urban and rural areas. The SAPALDIA biobank, which includes blood and DNA samples for more than 6000 people, was used to perform a previous study on the SERPINA1 molecular characterisation of 1399 samples displaying reduced serum AAT levels. In this study all 6057 samples from subjects who gave consent for genetic analyses, including the 1399 mentioned above, were investigated for normal M and deficient Z and S SERPINA1 variants. The data presented were used to define the prevalence of those variants and the levels of serum AAT according to the main genotypes in the general population.

MATERIALS AND METHODS

Subjects

The SAPALDIA cohort has been previously described. At the baseline in 1991 the subjects, who were 18–60 years old and predominantly Caucasian of Swiss nationality, were randomly selected from eight population registries. The current cross-sectional investigation of serum AAT is restricted to follow-up data collected in 2002–2003 when the biobank was established and includes 6057 subjects who donated blood and consented to genetic analysis. The study was approved by the Central Ethics Committee of the Swiss Academy of Medical Science and Cantonal Ethics Committees for each of the eight examination areas.

Serum analysis

AAT (g/litre) and C-reactive protein (CRP, mg/litre) concentrations were determined by latex-enhanced immunoturbidimetric assay (COBAS Integra analyzer, Roche Diagnostics, Indianapolis, Indiana, USA), a robust assay with principles that are perfectly comparable to those of nephelometry. The interassay coefficient of variation (CV) was 3.6–4.6%; lower detection thresholds for the AAT and CRP assays were 0.21 g/litre and 8 mg/litre, respectively, and reference values were 0.9–2.0 g/litre and <3 mg/litre, respectively. Each new batch of antisera was compared with previous batches for value recovery and proportionality in actual assays. A clarified, delipidated, commercially available serum calibrant (Calibrator f.a.s. Proteins, Roche Diagnostics) was used during the study; the same calibration batch, buffers and other reagents were used throughout the entire study.

Single nucleotide polymorphism analysis

All subjects were typed for give SNPs: S (rs17580), Z (rs28929474), M1Ala/M1Val (rs6647), M5 (rs1305), M2/M4 (rs709932). Typing was performed by PCR with fluorescently labelled TaqMan probes (Vic or Fam labels) on a LightCycler480 (Roche Diagnostics). All single nucleotide polymorphisms (SNPs) were in Hardy–Weinberg equilibrium. Further details on SNP analysis are available in the online data supplement.

Detection of rare deficient variants

The presence of rare deficient mutations was determined by sequencing the coding region of the SERPINA1 gene, as previously described, on selected samples as reported by Zorzetto and coworkers.

Statistical analysis

AAT concentrations were normally distributed and analysis of variance (ANOVA) was applied to compare means in different subgroups. Reference values covered the range from the 5th to the 95th percentile of AAT serum values. Linear and quantile regression was used to calculate adjusted means and percentiles. Covariates in the regression models were selected according to a former publication and they were all significantly associated with AAT concentrations. The receiver operating characteristic (ROC) curve was used to estimate the predictive accuracy of serum AAT, and maximization of the Youden index (ie, the sum of sensitivity and specificity minus 1) defined the optimal threshold for discrimination of genotype classes. Bootstrapping procedures were used to estimate the 95% CIs of the optimal thresholds. Statistical analysis was performed with MedCalc 9.4.2.0 (MedCalc Software, Mariakerke, Belgium), Stata V.10.1 IC and SAS V9.2.

RESULTS

As a first step we identified the number of subjects belonging to different SERPINA1 genotype classes and determined their frequency in the general population (table 1). The PI*M M genotype accounted for 5598 individuals (89.12% of the overall population), whereas PI*M S was the second genotype in order of frequency (7.48%), followed by PI*M Z (2.36%). Only one subject carrying the PI*Z Z genotype (0.02%) was identified. The two classes defined in table 1 as rare variants and novel variants, accounting for 42 subjects (0.69%), were very heterogeneous groups of variants and were therefore excluded from further analyses on the relationship between AAT serum levels and SERPINA1 genotypes. Nevertheless, means and ranges of AAT serum levels did not notably change if rare and novel variants were not excluded (data not shown). The frequencies of S and Z alleles in the three main Swiss language groups (German, French, Italian) are shown in online table E1 and are further described in the online data supplement.

Table 1 Frequency of the SERPINA1 genotype classes detected in 6057 subjects from the Swiss Cohort Study on Air Pollution and Lung Diseases in Adults (SAPALDIA) cohort

<table>
<thead>
<tr>
<th>Genotype</th>
<th>PI*M M†</th>
<th>PI*M S</th>
<th>PI*S S</th>
<th>PI*M Z</th>
<th>PI*S Z</th>
<th>Rare variants‡</th>
<th>Novel variants§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>5398</td>
<td>453</td>
<td>10</td>
<td>143</td>
<td>10</td>
<td>34</td>
<td>8</td>
</tr>
<tr>
<td>Frequency (%)</td>
<td>89.12</td>
<td>7.48</td>
<td>0.16</td>
<td>2.36</td>
<td>0.17</td>
<td>0.02</td>
<td>0.56</td>
</tr>
</tbody>
</table>

† The PI*M M genotype class encompasses different combinations of normal M variants (M1Ala/Val, M3, M2/M4). Details are reported in the online data supplement.
‡ This class includes subjects heterozygous for rare deficient variants, such as L, P occurs, M leucine, M threonine, etc. These data were previously analysed in more detail.
§ This class includes novel putative deficient variants detected during SERPINA1 gene sequencing. These data were previously analysed in more detail.
Table 2  Unadjusted and adjusted means and intervals (5th and 95th percentiles) for α1-antitrypsin (AAT) serum concentration in the six main SERPINA1 genotype classes

<table>
<thead>
<tr>
<th>SERPINA1 genotype</th>
<th>Unadjusted AAT serum concentrations, N = 5981*</th>
<th>Adjusted AAT serum concentrations, † N = 5768‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean, SD (g/litre)</td>
</tr>
<tr>
<td>MM</td>
<td>5386</td>
<td>1.298, 0.18</td>
</tr>
<tr>
<td>MS</td>
<td>451</td>
<td>1.085, 0.16</td>
</tr>
<tr>
<td>SS</td>
<td>10</td>
<td>0.849, 0.10</td>
</tr>
<tr>
<td>MZ</td>
<td>143</td>
<td>0.805, 0.11</td>
</tr>
<tr>
<td>SZ</td>
<td>10</td>
<td>0.555, 0.06</td>
</tr>
<tr>
<td>ZZ</td>
<td>1</td>
<td>0.320, 0.00</td>
</tr>
</tbody>
</table>

*Subjects with rare variants (42) and samples with missing AAT levels (34) were excluded.
† Adjusted for age, sex, area, alcohol consumption (yes/no), systolic blood pressure, body mass index, smoking habit (never, former, current) and C-reactive protein levels.
‡ Additionaly excluded were subjects with missing covariate data (212) and ZZ genotype due to insufficient frequency (1).

Unadjusted and adjusted means and reference intervals for AAT serum concentration in the six main SERPINA1 genotype classes are presented in table 2. Adjusting for age, sex, study area, alcohol intake (yes vs no), systolic blood pressure, body mass index (BMI), smoking status (never, former, current) and CRP levels did not essentially alter the results. The 5th—95th percentiles were subsequently compared with previously reported American Thoracic Society (ATS)/European Respiratory Society (ERS) reference values5 (table 3). The AAT serum level ranges determined in our investigation are markedly more narrow than those previously reported. Data are also graphically reported in figure E1, in which AAT serum concentrations are mathematically converted to μM.

Since AAT is a acute phase protein, we recalculated the reference intervals of AAT serum concentrations in subgroups of subjects according to systemic inflammatory status. A CRP value of 8 mg/litre, which is the upper normal limit for this protein as suggested by the equipment used in the present study, was used as the cutoff to stratify subjects as being without (<8 mg/litre) or with (≥8 mg/litre) systemic inflammation (table E2). Comparison of AAT means between the two CRP strata revealed higher values in the systemic inflammation stratum for all genotype classes. This difference was statistically significant in the PI*MM subgroup (p<0.001).

As a next step we assessed the accuracy of predicting genotype classes which are not believed to represent a risk for developing emphysema (PI*MM and PI*MS) and those associated with intermediate AATD and arguably a slightly increased risk for developing emphysema (PI*SS and PI*MZ) from AAT serum concentrations using ROC statistics.4 14 For this analysis we included the rare variant carriers of the respective groups to get a representative sample for the general population. The findings were highly accurate for the area under the curve (AUC = 0.9907) (figure E2). The optimal threshold according to the Youden index provided a cutoff at 1.00 g/litre AAT level (95% CI 0.97 to 1.06), which presents a sensitivity of 95.8% and a specificity of 94.8%. For discrimination between PI*MM and any other genotype carrying at least one S or Z allele an optimal cutoff at 1.10 g/litre was determined (75.4% sensitivity, 88.5% specificity). The impact of sex, smoking status and CRP levels on these genotype discriminations are described in the online data supplement (table E3).

Finally we analysed the influence of the different PI*M subtypes on AAT serum level. This result is reported in the online data supplement (table E4 and figure E3).

DISCUSSION

This study ideally represents the most valid setting to date to derive reference values for serum AAT by genotype group in the general population. We applied state-of-the-art technology for the assessment of serum AAT and SERPINA1 genotypes in the Swiss population, which is a combination of three language groups that adequately represent the genetic structure of the European population.15 To the best of our knowledge, only a few studies have been performed in the general population that measure circulating AAT protein16 or SERPINA1 gene variants5 or both.17 18 The most comparable study is the Copenhagen City Heart study, a longitudinal survey of 7963 subjects from Copenhagen who were genotyped for PI*Z and PI*S but in whom only a small sample of AAT concentrations in blood were measured (n=592).7 In the study by Sveger,16 blood from 200 000 infants was drawn for simultaneous AAT determination by semi-quantitative electroimmunoassay and Pi typing with isoelectric focusing. However, the analytical methods used in this study were out of date and therefore these data can no longer be used as a reference. The study by Silverman et al17 applied an automated immunoassay to measure AAT in plasma samples from 20 000 blood donors from the St Louis area. Plasma samples that met criteria of <50% of plasma pool reactivity were examined by isoelectric focusing to determine PI type. The reported St Louis Z allele frequency was 0.0116, but no data on the reference values for the concentration of AAT in plasma were extrapolated. In summary, current AAT serum level—genotype relationships seem obsolete as updated diagnostic standards for AATD have never been applied to a general population sample.

Our work generated a number of outputs. First, a more precise allele and genotype frequency was identified for SERPINA1 variants in Switzerland’s general population. We calculated an updated PI*S gene frequency of 0.0401 whereas that of PI*Z was 0.0130. Compared with previous estimates for this population,18

Table 3  Comparison between two published ranges (5th—95th percentiles) of α1-antitrypsin serum levels according to different phenotypes (PI),7 one in μM and one in g/litre,8 and the range, according to different genotypes (PI*), as deduced by our analysis5

<table>
<thead>
<tr>
<th>Phenotype—genotype</th>
<th>Units</th>
<th>Reference ranges</th>
<th>Present paper</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI MM—PI*MM</td>
<td>μM</td>
<td>20–48</td>
<td>20.2–31.5</td>
</tr>
<tr>
<td></td>
<td>g/l</td>
<td>1.50–3.50</td>
<td>1.05–1.64</td>
</tr>
<tr>
<td>PI SS—PI*SS</td>
<td>μM</td>
<td>15–33</td>
<td>14.0–20.4</td>
</tr>
<tr>
<td></td>
<td>g/l</td>
<td>1.00–2.00</td>
<td>0.73–1.06</td>
</tr>
<tr>
<td>PI MZ—PI*MZ</td>
<td>μM</td>
<td>17–33</td>
<td>12.7–19.2</td>
</tr>
<tr>
<td></td>
<td>g/l</td>
<td>0.90–2.10</td>
<td>0.66–1.00</td>
</tr>
<tr>
<td>PI SZ—PI*SZ</td>
<td>μM</td>
<td>8–16</td>
<td>9.4–12.7</td>
</tr>
<tr>
<td></td>
<td>g/l</td>
<td>0.75–1.20</td>
<td>0.49–0.66</td>
</tr>
</tbody>
</table>

The g/litre values in our analysis were mathematically converted to μM, based on a molecular weight of 52 kDa. Note that the PI*MS data are not present because this genotype was not included in the original American Thoracic Society/European Respiratory Society guidelines.
PI’S frequency was similar whereas PI’Z frequency was slightly higher. Further discussion of this topic is provided in the online data supplement.

A second major outcome of the study was the analysis of AAT serum concentration and genotypes of the SERPINA1 gene in a large cohort representative of the general population. This enabled the extrapolation of updated protein ranges according to the main normal and deficient genotype classes and evaluation of whether reference values need to be specific for sex, smoking status and CRP level.

To date, no epidemiological data on AAT serum concentration according to the SERPINA1 genotype have been reported for the general population. Some studies identified mean values or reference intervals of AAT serum concentration but they were limited to target groups, mostly COPD cases or populations in which the frequency of AATD is low, such as Japanese19 and Korean populations,20 or in patients with a peculiar clinical phenotype, such as Peyronie’s disease,21 or characteristic cohorts, such as paediatric subjects7 and pregnant women.22 The use of advanced technologies makes this study innovative. These technologies include SNP detection for genotyping and the inclusion of potentially confounding genetic factors, that is, deficient variants other than S and Z alleles, from the final analysis. The presence of other variables that could affect the AAT concentration in serum were considered and adjusted for in an additional analysis. This resulted in much narrower serum AAT ranges than those presented in the ATS/ERS consensus document,6 with a drastic reduction in the overlap among genotypes (table 3). Moreover, the mean values of AAT concentration according to SERPINA1 genotypical classes (table 2), were lower than those reported so far,11 likely due to a smaller upper dispersion of measurements. Although 70–80% of the variation in total AAT serum concentration is explained by the Pi type (after age and sex adjustment),23 other factors can influence variation.15 Since AAT is an acute-phase reactant, inflammatory status may increase the serum level of AAT.11 15 24 As shown in table E2, when SAPALDIA subjects were stratified according to the presence or absence of an inflammatory condition, most SERPINA1 genotypes showed even narrower ranges, particularly those with CRP <8 mg/litre. However, ranges for individuals with elevated CRP were generally higher. In the real world of routine AAT serum measurement, our data do not justify systematic measurement of the inflammatory status and the stratified ranges can be used only in reference laboratories.8

Other factors that impact AAT concentration variability include active smoking26 and age.21 An in-depth analysis of the same SAPALDIA population has shown that an inter-relationship among circulating AAT, smoke exposure, gender and systemic inflammatory status exists.13 However, in this study with narrower diagnostic purposes, we demonstrated that inclusion of sex and current smoking status to predict intermediate deficiency genotypes was not necessary. We also addressed a further putative factor for AAT serum concentration variability, that is, the intrinsic effect of the different PI*M subtypes (figure E3). The effect of this variable seems to be negligible because only two PI*MZ haplotypes displayed significant changes in AAT serum concentration.

In this study, we also analysed the limits of the so-called ‘protective threshold’ and we tried to address the controversy and confusion about the expression of serum AAT concentration. The term ‘protective threshold’ derives from evidence that subjects with AATD and an AAT serum level above the threshold are at reduced risk of developing emphysema. This is not merely a theoretical cutoff because it is considered the decisional cutoff below which subjects with AATD are eligible for AAT replacement therapy.25 Therefore, it is a very important concept in AATD patient management. An excellent discussion on this topic by Tonelli and Brantly has recently been published.26 The concept was originally developed by Hutchinson et al27 and Stockley,28 based on evidence that subjects displaying the PI SZ phenotype had a reduced risk of developing emphysema compared with those displaying the PI ZZ phenotype3 and are therefore seldom suitable for replacement therapy. The threshold was fixed at the serum AAT level corresponding to 0.8 g/litre, measured by radial immunodiffusion. A few years later, to resolve the lack of standardisation among laboratories that caused so much confusion in the definition of the AAT measurements, a highly purified AAT standard, expressed as μM, was introduced.29 In the same report, the protective threshold using the highly purified AAT standard determined by nephelometry was fixed at 11 μM; that is, the 10th percentile of the AAT serum range for subjects with PI SZ, which is considered adequate to protect the lungs from proteolytic attack. Since then, in countries where the AAT concentration was expressed as g/litre, the 0.8 threshold was often considered equivalent to 11 μM. However, radial immunodiffusion cannot be considered equivalent to nephelometry because the former, obsolete method overestimates the real AAT concentration by about

Figure 1 Suggested areas corresponding to severe α1-antitrypsin (AAT) deficiency (below the protective threshold) and intermediate AAT deficiency (above the protective threshold and below the 10th percentile of the AAT range for subjects carrying the PI*M1S genotype). Bars represent 5th/95th percentiles of AAT serum levels.
50%. The value corresponding to the 10th percentile of AAT serum concentration for the PI*SZ group in SAPALDIA, which is suitable to derive threshold values in the general population, is 0.49 g/litre.

Intermediate deficiency is a term usually referred to as synonymous with the PI*MZ genotype, which may represent a slightly increased risk of developing COPD. We believe that correct diagnosis of subjects carrying the PI*MZ genotype is a critical issue for a number of reasons. First, having been identified as a group at risk of developing COPD, they are subjects particularly suitable for an effective prevention and smoking cessation campaign, as suggested by an increased rate of attempting to quit smoking following genetic testing. Second, correct diagnosis is mandatory for genetic counselling. Third, subjects with COPD carrying the PI*MZ genotype could be suitable for future, specific therapeutic interventions. Expressed as a range of serum levels, we propose that corresponding values stretch from the protective threshold (0.49 g/litre) to the 10th percentile of the AAT concentration range for subjects carrying the PI*MZ genotype, who are believed not to be at risk of developing emphysema, which would correspond to 0.92 g/litre in SAPALDIA. This area includes 87% of subjects carrying the PI*MZ genotype in our cohort. The reported thresholds and related areas are depicted in figure 1.

One of the aims of this paper was to provide a clear cutoff, below which suspicion of AATD is reasonable, and to resolve the controversy around this issue. The choice of the AAT cutoff, below which samples should be selected for PI pheno-genotyping, has important financial and clinical implications. The cutoffs determined by individual laboratories currently range between 1.00 and 1.50 g/litre and they strongly depend on specific requirements. For example, the clinical importance of PI*MZ detection is considered to be far less than PI*MZ detection due to the different risks for emphysema for the two genotypes. Therefore, we reported two different cutoffs, one focused on avoiding the omission of deficient S or Z alleles (1.10 g/litre) and the second set to identify genotypes at a likely increased risk of emphysema (1.00 g/litre). We also considered the previously reported cutoff of 1.15 g/litre, which is still useful since no Z alleles (and PI*SS) have been found in individuals with AAT blood levels above this level (100% sensitivity and 78.6% specificity for detecting AATD genotypes), while 31% of all assigned subjects with the PI*MZ genotype show AAT blood levels higher than 1.15 g/litre (78.6% sensitivity and 82.6% specificity for detecting any deficient S or Z allele).

In conclusion, we provided values for serum AAT level according to the major genotype classes in the general population. In addition, these data have helped us to address controversies related to the different opinions in the definition of limits for the ‘protective threshold’ and to define a useful range for intermediate AATD. We believe that these findings will be helpful in the future for the investigation of AATD-related risk for COPD and for a more precise definition of when to implement AAT replacement therapy. Finally, the reported data show that the gene-environmental analysis is critical in the ongoing SAPALDIA longitudinal assessment of the impact of SERPINA1 on pulmonary health.

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Patient consent Obtained.

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Alpha-1-antitrypsin deficiency

Serum levels and genotype distribution of α₁-antitrypsin in the general population

Ilaria Ferrarotti, Gian Andri Thun, Michele Zorzetto, Stefania Ottaviani, Medea Imboden, Christian Schindler, Arnold von Eckardstein, Lucia Rohrer, Thierry Rochat, Erich W Russi, Nicole M Probst-Hensch and Maurizio Luisetti

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