α₁-Antitrypsin Deficiency

Introduction

α₁-antitrypsin (AAT) deficiency is one of the most common hereditary diseases in the world as it affects approximately 3.4 million people worldwide.¹² Chronic obstructive pulmonary disease (COPD), specifically emphysema, is the most common disease associated with AAT.³ AAT deficiency is also the most common nonenvironmental cause of emphysema in adults.⁴ AAT deficiency is associated with slow, progressive liver cirrhosis in adults¹ and in childhood can cause neonatal or juvenile liver disease.¹ It is the most common metabolic disorder for which children require liver transplantation.⁴

Characteristics of AAT Deficiency

AAT is a protease inhibitor, named for its role in inhibiting trypsin, but its primary function is to inhibit neutrophil elastase (NE).¹ When AAT is deficient, tissue is unprotected from NE and elastic tissue is destroyed.⁵ Common features of AAT deficiency include⁶:

- Early onset (<45 years) or idiopathic emphysema
- Idiopathic bronchiectasis
- COPD (chronic obstructive pulmonary disease) asthma
- Unexplained liver disease
- Necrotizing panniculitis
- C-ANCA (antineutrophil cytoplasmic antibody) positive vasculitis
- Family history of emphysema, COPD, bronchiectasis, liver disease, or panniculitis

Individuals who smoke and are AAT-deficient are at even greater risk for lung disease. The oxidants in cigarette smoke further reduce the effectiveness of AAT,⁶ and smokers have a more rapid decline in lung function.⁴ The median age for survival is 20 years less for AAT-deficient smokers compared to AAT-deficient nonsmokers.⁴ Treatment for AAT deficiency is available through intravenous augmentation therapy.⁶

Genetics of AAT Deficiency

α₁-antitrypsin (AAT) deficiency is inherited in an autosomal recessive manner.³⁴ Both parents of an affected individual are at least carriers. Siblings and children of an affected person are also at risk for being carriers or affected with disease.

The gene for AAT (called SERPINA1) is located on chromosome 14, and more than 100 different alleles, or gene variants, have been identified to date.²³⁶ The variants are classified alphabetically according to protein plasma isoelectric (Pi) focusing analysis, also called Pi typing.⁶ The common alleles are listed in table 1 below.

It is estimated that in North America, 1 in 12 individuals is a carrier of AAT deficiency, and 1 in 477 individuals has an S- or Z-deficient genotype (SS, SZ, or ZZ).¹ AAT has a highly variable clinical presentation with AAT deficiency, and other genetic and environmental factors are suspected to be involved in how an individual manifests this condition.²³

<table>
<thead>
<tr>
<th>Table 1 — α₁-Antitrypsin Alleles*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>M</strong> This is the most common allele and is considered to be “normal.”⁶</td>
</tr>
<tr>
<td><strong>S</strong> The S allele is the most common deficiency allele,⁴ and while some data suggest S may be associated with a possible increased risk of asthma,⁶ it is generally not associated with clinical disease.⁴</td>
</tr>
<tr>
<td><strong>Z</strong> The Z allele is the variant most commonly associated with disease, and ZZ homozygous individuals have AAT serum levels about 10% to 15% of normal.⁴ ZZ individuals are at increased risk for developing lung and liver diseases, as well as the rarer complications of vasculitis and panniculitis. MZ individuals may be at increased risk for COPD.⁵</td>
</tr>
<tr>
<td><strong>Null</strong> Variants causing no discernible levels of AAT in the serum are termed “null” alleles.⁶ Null/null individuals develop early onset emphysema, but to date, no case report of liver disease has come to our attention.³⁴</td>
</tr>
</tbody>
</table>

*Null alleles are not detected by LabCorp’s DNA analysis.
**Guidelines for Testing**

Most cases of AAT deficiency can be diagnosed through DNA testing or AAT phenotyping for the S and Z alleles. General population testing is not recommended at this time; however, the American Thoracic Society and the European Respiratory Society recommend diagnostic testing for individuals meeting the criteria listed in Table 2 below.6

### Table 2 — Criteria for Diagnostic Testing

<table>
<thead>
<tr>
<th>Presenting Conditions</th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic adults with emphysema, COPD, or asthma with airflow reduction unresponsive to bronchodilators</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Individuals with unexplained liver disease</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic individuals with persistent obstruction on pulmonary function tests with identifiable risk factors, such as smoking</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic individuals with persistent obstruction on pulmonary function tests without identifiable risk factors, such as smoking</td>
<td></td>
<td>●</td>
</tr>
<tr>
<td>Adults with necrotizing panniculitis</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Adults with idiopathic bronchiectasis</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Adolescents with persistent airflow obstruction</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Adults with C-ANCA-positive vasculitis</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Siblings of an individual known to have AAT deficiency, either heterozygous or homozygous</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Offspring of an individual known to have AAT deficiency, either heterozygous or homozygous</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Parents of an individual known to have AAT deficiency, either heterozygous or homozygous</td>
<td></td>
<td>●</td>
</tr>
<tr>
<td>Other relatives of an individual known to have AAT deficiency, either heterozygous or homozygous</td>
<td></td>
<td>●</td>
</tr>
<tr>
<td>Individuals with a family history of COPD or liver disease</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Individuals at increased risk of having AAT deficiency-related diseases</td>
<td></td>
<td>●</td>
</tr>
<tr>
<td>Partners of homozygous or heterozygous AAT-deficient individuals</td>
<td></td>
<td>●</td>
</tr>
</tbody>
</table>

A = Genetic testing recommended.

B = Genetic testing should be discussed and could reasonably be accepted or declined.

### References


**α1-Antitrypsin Deficiency, DNA Analysis**

**CPT** 83891; 83894; 83900; 83901(x2); 83912

**Synonyms** 1-Antitrypsin; α1AT; AAT; Alpha-1-Antitrypsin Deficiency; Genotype; Protease Inhibitor (PI)

**Specimen** Whole blood, amniotic fluid, chorionic villus sample (CVS) (submission of maternal blood is required for fetal testing), or LabCorp buccal swab kit (buccal swab collection kit contains instructions for use of a buccal swab)

**Volume** 7 mL whole blood, 10 mL amniotic fluid, 20 mg CVS, or LabCorp buccal swab kit

**Minimum Volume** 3 mL whole blood, 5 mL amniotic fluid, 10 mg CVS, or two buccal swabs

**Container** Lavender-top (EDTA) tube, yellow-top (ACD) tube, sterile plastic conical tube, or two confluent T-25 flasks for fetal testing, or LabCorp buccal swab kit

**Stability** Maintain specimen at room temperature or refrigerate.

**Causes for Rejection** Frozen specimen; hemolysis; quantity not sufficient for analysis; improper container; one buccal swab

**Use** DNA-based determination of the two common alleles underlying α1-antitrypsin deficiency that is associated with chronic obstructive pulmonary disease (COPD) and childhood-onset liver disease. Prenatal testing is available.

**Limitations** Tests for the two most common mutations, S and Z. Rare alleles, null or otherwise, are not detected by this assay.

**Methodology** Multiplex allele-specific polymerase chain reaction (PCR) and gel electrophoresis

**Additional Information** α1-antitrypsin deficiency (AATD) (OMIM 107400) is a genetic disorder, inherited in a codominant manner. It is associated with COPD (chronic obstructive pulmonary disease), early onset emphysema, unexplained liver disease, panniculitis, cANCA+ vasculitis, and a family history of any of these conditions. The clinical expression can be highly variable. Individuals who smoke and are affected with AATD accumulate lung damage at an accelerated rate over those who do not smoke or have stopped smoking. Two mutations, Z (E342K) and S (E264V), account for >95% of the mutant alleles. In North America, it is estimated that 1 in 12 individuals have either an S or Z allele, and 1 in 477 individuals have some form of deficiency (SS, SZ, ZZ).

**References**


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**α1-Antitrypsin, Serum**

**CPT** 82103

**Synonyms** AAT; Acute Phase Proteins; Alpha-Antitrypsin, Serum; Alpha, Protease Inhibitor; a1AT

**Specimen** Serum (preferred) or plasma

**Volume** 1 mL

**Minimum Volume** 0.5 mL (Note: This volume does not allow for repeat testing.)

**Container** Red-top tube, gel-barrier tube, lavender-top (EDTA) tube, or green-top (heparin) tube

**Collection** Separate serum or plasma from cells.

**Stability**

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Room Temperature</td>
<td>14 days</td>
</tr>
<tr>
<td>Refrigerated</td>
<td>14 days</td>
</tr>
<tr>
<td>Frozen</td>
<td>14 days</td>
</tr>
<tr>
<td>Freeze/thaw cycles</td>
<td>Stable x3</td>
</tr>
</tbody>
</table>

**Patient Preparation** Overnight fasting is preferred.

**Causes for Rejection** Chylous serum

**Reference Interval** 90-200 mg/dL

**Use** Detection of hereditary decreases in the production of α1-antitrypsin (α1AT). Decreased or nearly absent levels of α1AT can be a factor in chronic obstructive lung disease and liver disease. An increased prevalence of non-MM phenotypes is found with cryptogenic cirrhosis and with CAH. Cirrhosis in a child should raise consideration of α1AT deficiency or Wilson’s disease. Diagnosis of inflammatory states, if elevated (eg, rheumatoid arthritis, bacterial infection, vasculitis, neoplasia).

**Limitations** α1AT may be elevated into normal range in heterozygous deficient patients during concurrent infection, pregnancy, estrogen therapy, steroid therapy, cancer, and during postoperative periods. Homozygous deficient patients will not show such elevation. Normal α1AT levels may occur in patients with liver disease who are heterozygotes. In normals, pregnancy and contraceptive medication may elevate levels. Levels are normally low at birth but rise soon thereafter.

**Contraindications** If CRP is positive, retest α1AT in 10 to 14 days.

**Methodology** Immunologic

**Additional Information** Should be run when α1-globulin in serum protein electrophoresis is low or when two bands are seen in the α1-region. Heterozygous patients exhibit AAT levels, which are commonly about 60% of normal. Homozygous recessive α1AT patients exhibit levels at about 10% of normal. Phenotyping is desirable on patients with low values and on all patients being worked up for AAT-deficient liver disease. Most pathologic is homozygous state ZZ. An M null genotype will have phenotype as MM but low serum level. AAT is one of the alpha globulins that together are called “acute phase reactants.” These rise rapidly, but nonspecifically, in response to inflammatory insults.
α1-Antitrypsin Phenotyping .......................... 095653
CPT 82103; 82104

Synonyms A, A Phenotyping; AAT Phenotype; AAT-Pi; Alpha1-
Antitrypsin Phenotyping; Pi Phenotype; Protease Inhibitors; α1-AT Phenotype

Test Includes α1-antitrypsin, total, serum; phenotype

Related Information α1-Antitrypsin Deficiency, DNA Analysis

Specimen Serum

Volume 2 mL.
Minimum Volume 0.7 mL.

Container Red-top tube

Collection Separate serum from cells.

Storage Instructions Refrigerate; stable for two weeks at 2°C to
8°C.

Patient Preparation Overnight fasting is preferred.

Causes for Rejection Hemolysis; specimen at room temperature

Reference Interval Interpretation accompanies report; phenotypes

Hemolysis; specimen at room temperature

Patient Preparation Overnight fasting is preferred.

Storage Instructions Refrigerate; stable for two weeks at 2°C to
8°C.

Patient Preparation Overnight fasting is preferred.

Methodology Phenotype: isoelectric focusing (IEF); total: immu-

nologic type, α1-A1 is found in normal amounts but does not function normally.

Use Definitive analysis of hereditary α1-antitrypsin deficiency,

which is associated with chronic obstructive pulmonary disease
(COPD) (panacinar emphysema), hepatic cirrhosis, and hepatoma.

Cholestasis with neonatal hepatitis is found in a minority of neo-

nates with α1-AT deficiency.

Limitations α1-antitrypsin therapy may alter the patient phenotype.

Phenotype Population Incidence %MM (Reference Interval) Mean

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Incidence</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>MM</td>
<td>86.5%</td>
<td>100%</td>
</tr>
<tr>
<td>MS</td>
<td>8.0%</td>
<td>81%</td>
</tr>
<tr>
<td>MZ</td>
<td>3.9%</td>
<td>60%</td>
</tr>
<tr>
<td>FM</td>
<td>0.4%</td>
<td>97%</td>
</tr>
<tr>
<td>SZ</td>
<td>0.3%</td>
<td>39%</td>
</tr>
<tr>
<td>SS</td>
<td>0.1%</td>
<td>71%</td>
</tr>
<tr>
<td>ZZ</td>
<td>0.05%</td>
<td>7%</td>
</tr>
<tr>
<td>FS</td>
<td>0.05%</td>
<td>46%</td>
</tr>
<tr>
<td>FZ</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>FF</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

α1-AT is a positive acute phase protein because it rises whenever
there is tissue injury, necrosis, inflammation, or infection; there-
fore, patients with α1-AT deficiency who suffer from bronchitis,
pneumonia, or similar respiratory inflammation may have falsely
normal levels during acute illness. After the acute phase of illness
has passed, repeat determinations often reveal the “true” or “rest-
ing” α1-AT level, which is indicative of the heterozygous pheno-
typic deficiency.

Footnotes