α_1-Antitrypsin Deficiency

Introduction

α_1-antitrypsin (AAT) deficiency is one of the most common hereditary diseases in the world as it affects approximately 3.4 million people worldwide.[1,2] 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 adults[1] 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 include[6]:

- 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

α_1-antitrypsin (AAT) deficiency is inherited in an autosomal recessive manner.[3,4] 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.[2,3,6] 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.[2,3]

Table 1 — α_1-Antitrypsin Alleles*

M	This is the most common allele and is considered to be "normal."[6]
S	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]
Z	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.[6]
Null	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.[3,4]

*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

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

A = Genetic testing recommended.

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

References

1. de Serres FJ. Worldwide racial and ethnic distribution of alpha$_1$-antitrypsin deficiency: Summary of an analysis of published genetic epidemiological surveys. *Chest*. 2002 Nov; 122(5):1818-1829.

2. Kelly E, Greene CM, Carroll TP, McElvaney NG, O'Neill SJ. Alpha-1 antitrypsin deficiency. *Respiratory Medicine*. 2010 Jun; 104(6):763-772.

3. Schlade-Bartusiak K, Cox DW. Alpha1-antitrypsin deficiency. Available at: http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=alpha1-a. *GeneReviews*. Accessed September 9, 2010.

4. Perlmutter DH. α_1-Antitrypsin deficiency. In Walker WA, Durie PR, Hamilton JR, Walker-Smith JA, Watkins JB, eds. *Pediatric Gastrointestinal Disease: Pathophysiology, Diagnosis, Management*. 2nd ed. St Louis, Mo: C.V. Mosby-Year Book; 1994:chap 28.

5. Dahl M, Tybjærg-Hansen A, Lange P, Vestbo J, Nordestgaard BG. Change in lung function and morbidity from chronic obstructive pulmonary disease in alpha1-antitrypsin MZ heterozygotes: A longitudinal study of the general population. *Ann Intern Med*. 2002 Feb 19; 136(4):270-279.

6. American Thoracic Society, European Respiratory Society. American Thoracic Society/European Respiratory Society statement: Standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. *Am J Respir Crit Care Med*. 2003 Oct 1; 168(7):818-900.

α_1-Antitrypsin Deficiency, DNA Analysis 511881

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

Synonyms A_1-Antitrypsin; A_1AT; 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

Storage Instructions 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 α_1-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 α_1-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

American Thoracic Society, European Respiratory Society. American Thoracic Society/European Respiratory Society statement: Standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. *Am J Respir Crit Care Med*. 2003 Oct 1; 168(7):818-900. PubMed 14522813

de Serres FJ. Worldwide racial and ethnic distribution of alpha$_1$-antitrypsin deficiency: Summary of an analysis of published genetic epidemiological surveys. *Chest*. 2002 Nov; 122(5):1818-1829. PubMed 12426287

α_1-Antitrypsin, Serum 001982

CPT 82103

Synonyms AAT; Acute Phase Proteins; Alpha$_1$-Antitrypsin, Serum; Alpha$_1$ Protease Inhibitor; α_1AT

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.

Storage Instructions Maintain specimen at room temperature.

Stability

Temperature	Period
Room Temperature	14 days
Refrigerated	14 days
Frozen	14 days
Freeze/thaw cycles	Stable x3

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 α_1-antitrypsin (α_1AT). Decreased or nearly absent levels of α_1AT 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 α_1AT deficiency or Wilson's disease. Diagnosis of inflammatory states, if elevated (eg, rheumatoid arthritis, bacterial infection, vasculitis, neoplasia).

Limitations α_1AT 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 α_1AT 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 α_1AT in 10 to 14 days.

Methodology Immunologic

Additional Information Should be run when α_1-globulin in serum protein electrophoresis is low or when two bands are seen in the α_1-region. Heterozygous patients exhibit AAT levels, which are commonly about 60% of normal. Homozygous recessive α_1AT 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.

α_1-Antitrypsin Phenotyping 095653

CPT 82103; 82104

Synonyms A_1A Phenotyping; AAT Phenotype; AAT-Pi; $Alpha_1$-Antitrypsin Phenotyping; Pi Phenotype; Protease Inhibitors; α_1AT Phenotype

Test Includes α_1-antitrypsin, total, serum; phenotype

Related Information α_1-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 are designated. PiMM phenotype is normal; PiMZ is heterozygous, intermediate deficient; and PiZZ is homozygous, severely deficient. More than 75 alleles are described; biosynthesis of α_1AT is controlled at the Pi locus by a pair of genes. There is codominant expression. The phenotype is "Pi" for protease inhibitor. Z and S are mutant proteins. A null-null state occurs as well. In the dysfunctional type, α_1AT is found in normal amounts but does not function normally.

Use Definitive analysis of hereditary α_1-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 neonates with α_1AT deficiency.

Limitations α_1-antitrypsin therapy may alter the patient phenotype.

Methodology Phenotype: isoelectric focusing (IEF); total: immunologic

Additional Information Most pathologic is homozygous state ZZ. An M null genotype will have phenotype as MM, but low serum level of α_1AT. α_1-antitrypsin deficiency may eventuate in or be associated with cholestatic hepatopathy in infants, a chronic hepatitis, familial infantile cirrhosis, or familial emphysema.[1,2] The risks of cirrhosis and development of hepatoma are greater in males. α_1-antitrypsin (α_1AT) is a glycoprotein synthesized in the liver and is the main component of the α_1 globulins. α_1AT serves to counter the effects of several serine proteases, including elastase and trypsin. When α_1AT is deficient, unopposed activity of these enzymes results in emphysema. The age of occurrence of emphysema varies with the type of deficiency, ZZ being most severe, SZ less severe, and SS least severe. It often varies with the personal habits of the individual, especially regarding smoking. Individuals with α_1AT deficiency have PAS-positive diastase-negative granules accumulate in the periportal hepatocytes. Eventually, damage occurs to the liver resulting in cirrhosis. It is especially important to detect α_1AT deficiency early as a replacement therapy is now available which has received favorable review in a recent NIH study. Although the long-term effects of this therapy are still unknown, it does have great potential to decrease the severity of emphysema.

α_1AT is a positive acute phase protein because it rises whenever there is tissue injury, necrosis, inflammation, or infection; therefore, patients with α_1AT 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 "resting" α_1AT level, which is indicative of the heterozygous phenotypic deficiency.

Use of high-resolution electrophoresis, therefore, that would detect the slower electrophoretic migration of the Z and S variants is preferred over quantification of α_1AT by nephelometry or turbidimetry as a preliminary test for this deficiency. Further, a high-resolution electrophoretic system will detect heterozygotes that could lead to important family studies of potentially deficient first-degree relatives who may benefit from therapy.

Serum α_1AT may be increased in patients during normal pregnancy, chronic pulmonary diseases, hereditary angioneurotic edema, gastric diseases, liver diseases, pancreatitis, diabetes, carcinomas, renal diseases, and rheumatic diseases. It may also be decreased in patients with severe protein loss or in improper storage of specimen.

More than 95% of subjects who are severely deficient are homozygous for the Z allele (PiZZ). PiZZ subjects who smoke have a shorter life expectancy than do nonsmoking PiZZ persons. Variation in severity of clinical manifestations is recognized; some subjects with deficiency do not have significant impairment, but development of airway disease is partly a function of age.

α_1AT Concentration*		
Phenotype	**Population Incidence**	**%MM (Reference Interval) Mean (mg/dL)**
MM	86.5%	100% (90–200) 145
MS	8.0%	81% (73–162) 118
MZ	3.9%	60% (54–120) 87
FM	0.4%	97% (87–194) 141
SZ	0.3%	39% (35–78) 57
SS	0.1%	71% (64–142) 103
ZZ	0.05%	7% (6–14) 10
FS	0.05%	66% (59–132) 96
FZ	Unknown	Unknown
FF	Unknown	Unknown

*α_1AT concentration in the homozygous MM phenotype is taken as the reference normal. Deficiency in phenotypes is reported relative to this reference.

Footnotes

1. Buist AS. Alpha 1-antitrypsin deficiency in lung and liver disease. *Hosp Pract* (Off Ed). 1989 May 15; 24(5):51-59 (review). PubMed 2497126

2. Pierce JA. Antitrypsin and emphysema. Perspective and prospects. *JAMA.* 1988 May 20; 259(19):2890-2895 (review). PubMed 3285040

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