

ALPHA-1 ANTITRYPSIN DEFICIENCY: Why it is Important to Test for this Rare Disease

By Daniel T. Layish, MD



Alpha-1 Antitrypsin (AAT) deficiency is a genetic disorder which affects the lung, liver, and occasionally the skin. AAT is a protease inhibitor, and protects the lungs from damage caused by the proteolytic enzyme elastase. Elastase is essential in protecting the lungs from dust, smoke etc. However, AAT is also essential to regulate this process, essentially providing a “shut off mechanism” for the proteolytic degradation of elastase.

There have been over 100 alleles of AAT that have been identified. They have been given letter codes based upon electrophoretic mobility. The normal phenotype is MM. The most common deficient allele is the Z allele. The Z allele is carried by approximately 2-3% of the Caucasian population in the United States. This allele is associated with plasma AAT levels below 35% of the average normal level. The Null allele results in the absence of detectable AAT in the plasma. Although this phenotype is the least common, it results in the most severe form of lung disease. With plasma levels below 80 mg/dL, there is insufficient AAT to protect the lung (which causes an increased risk of emphysema).

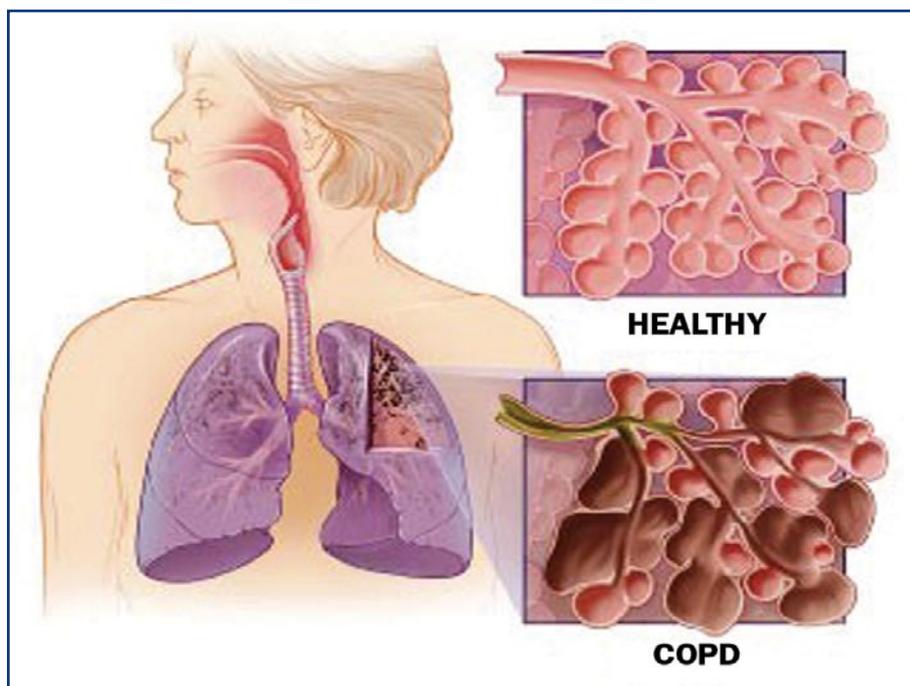
AAT deficiency is often felt to be rare, but it is estimated that about 100,000 people in the United States have severe AAT deficiency. However, most people that have this disease are currently not yet diagnosed. In one survey of over 300 people with Alpha-1 antitrypsin deficiency there was an average delay of over seven years between the first onset of symptoms and the diagnosis of AAT deficiency! There are also felt to be over 20 million Alpha-one carriers in the United States.

In the lung, AAT deficiency predisposes to COPD, particularly panacinar emphysema. Not every AAT deficient individual will develop emphysema. Risk factors include cigarette smoking and occupational exposures. The onset of emphysema in AAT deficient individuals may occur at a younger age than in non-AAT deficient individuals. The characteristic radiographic pattern is basilar predominant bullous changes, although those individuals who are also smokers may demonstrate the typical apical pattern. AAT deficiency has also been associated with bronchiectasis. Because there is specific therapy available for AAT deficiency, correct diagnosis is crucial. AAT deficiency should be suspected in a patient who develops emphysema before age 45, or in a patient who develops emphysema despite a non-smoking (or minimal smoking) history.

The American Thoracic Society recommends testing for AAT deficiency in ALL patients with COPD/emphysema (regardless of smoking history).

Testing is also recommended for people with asthma with fixed airway obstruction and siblings of individuals with AAT deficiency. Testing can be done in several ways. A serum level below 80 mg/dL would be consistent with the diagnosis, and should then lead to genotype analysis. Genotyping has the advantage of identifying heterozygotes. Serum testing thresholds can miss as many as 90 percent of carriers. AAT is an acute phase reactant so ideally a genotype/phenotype is recommended along with a serum level test. Obviously, genotype testing is a once-in-a-lifetime event.

Liver disease is the second most common health problem that results from AAT deficiency. The exact cause of the liver disease in AAT deficiency is not known, but it is felt to be caused by the accumulation of abnormal AAT in the liver. The liver is not able to metabolize this abnormal protein and it builds up and causes hepatotoxicity. Testing for AAT deficiency is therefore recommended for people with unexplained liver disease, people with a family history of liver disease, and relatives of a person diagnosed with AAT deficiency. Augmentation therapy (AAT replacement) does not help the liver disease caused by AAT deficiency. In fact, there is NO specific treatment for AAT deficiency related liver disease. Liver transplantation is currently the only option for these patients.



Diagnosis

- Simple to diagnose
 - Tube of blood → Serum AAT Level
 - Finger stick → Phenotyping
 - Buccal swab → Genotyping

Alpha-1 is a laboratory diagnosis, **NOT** a clinical diagnosis

- Normal AAT levels:	Severely deficient levels:
25-40 µM	≤ 11 µM
125-400 mg/dL	≤ 80 mg/dL

- **When you identify an individual with Alpha-1, you identify a family with Alpha-1**



AAT Mutations

Most Common Genotypes

- The most common genes for Alpha-1 are M (normal or "wild-type"), S, Z, and Null (produces no AAT)
- The two most frequent deficient alleles are:
 - PiS (50 -60 % of AAT)
 - PiZ (10 -20 % of AAT)
- Most labs test only for M, S, & Z genes

- MM ----- Normal
- MS ----- "Carriers"
- MZ ----- "Carriers"
- SS ----- "Severe Deficiency"
- SZ ----- "Severe Deficiency"
- ZZ ----- "Severe Deficiency"
- Z Null ----- "Severe Deficiency"
- Null Null ----- "Severe Deficiency"



Augmentation therapy is effective at raising alpha-one levels in people with AAT deficiency. This is the only therapy approved for adults with emphysema related to AAT deficiency. The goal of therapy is to correct the imbalance between neutrophil elastase and AAT. The therapy is administered intravenously once/week.

The Florida Department of Health and Human Services, the Alpha-1 Foundation and the University of Florida College of Medicine sponsor an awareness, screening and detection program for AAT deficiency. A free fingerstick test can be done at the physician's office. For more info on this program (or to receive free test kits) call Dr. Francisco Pena at the Alpha-1 Foundation at 1-888-825-7421 ext.250 or email to Fpena@alpha-one.org.

Daniel Layish, MD, graduated magna cum laude from Boston University Medical School in 1990. He then completed an Internal Medicine Residency at Barnes Hospital (Washington University) in St.Louis, Missouri and a Pulmonary/Critical Care Fellowship at Duke University in Durham, North Carolina. Since 1997, he has been a member of the Central Florida Pulmonary Group in Orlando. He currently serves as Medical Director of the Intensive Care Unit, Respiratory Therapy and Pulmonary Rehab at Winter Park Memorial Hospital. Dr. Layish serves as the director of the Orlando Clinical Resource Center for the Alpha-1 Foundation.

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