Alpha-1-Antitrypsin Deficiency Testing

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Alpha-1-antitrypsin (AAT) deficiency is an inherited disorder associated with lung and liver disease. Alpha-1-antitrypsin (AAT) is the chief protease inhibitor (PI) in human serum. Alterations in the production of this PI may result in the degradation of the connective protein elastin in lung alveoli, which increases the risk for developing lung disease. AAT deficiency is the most common nonenvironmental cause of emphysema and is the fourth most common indication for lung transplantation worldwide. Additionally, severe AAT deficiency may cause improper folding of the AAT protein, leading to deposition in hepatocytes and corresponding liver disease.

Featured ARUP Testing

Alpha-1-Antitrypsin (SERPINA1) Enzyme Concentration and 2 Mutations with Reflex to Alpha-1-Antitrypsin Phenotype 0051256

Method: Immunoturbidimetry/Polymerase Chain Reaction (PCR)/Fluorescence Monitoring/Isoelectric Focusing

Preferred test to identify AAT deficiency and causative DNA and protein variants

Alpha-1-Antitrypsin 0050001

Method: Quantitative Immunoturbidimetry

Determines AAT enzyme plasma concentration for the initial evaluation of AAT deficiency

Alpha-1-Antitrypsin Phenotype (Includes Alpha-1-Antitrypsin) 0080500

Method: Qualitative Isoelectric Focusing/Immunoturbidimetry

Determines specific AAT protein variant(s) in individual with decreased concentration of AAT (<90mg/dL)

Disease Overview

Incidence

- 1/3,000-5,000 individuals of European ancestry

Age of Onset

- Smokers may develop lung disease in their 40s.
- Nonsmokers may develop lung disease in their 50s.
- Childhood-onset liver disease (neonatal cholestasis) may occur in early months of life.

Symptoms

- Adults
  - Pulmonary: dyspnea, wheezing, cough, and phlegm, early onset emphysema (panacinar)
  - Hepatic: liver dysfunction, cirrhosis
    - Occurs more often in individuals with the Z allele
    - Hepatitis with jaundice
    - Chronic liver disease
  - Skin: panniculitis
    - Necrotic areas with spontaneous suppuration
- Neonates
  - A small percentage of affected newborns have hepatitis with cholestatic jaundice (prolonged jaundice with conjugated hyperbilirubinemia).
  - Low AAT levels are also found in neonatal respiratory distress syndrome and severe protein-losing disorders.
- Rare associated diseases
  - Granulomatosis with polyangiitis, necrotizing panniculitis, aneurysms of aortic and brain arteries
- Complications
  - Hepatocellular carcinoma and cholangiocarcinoma

Physiology

- AAT is a glycoprotein mainly synthesized in the liver.
- Hepatic disease is secondary to accumulation of improperly folded AAT in hepatocytes.
- AAT deficiency results in uninhibited free neutrophil elastase, which leads to degradation of the connective protein elastin in the alveoli.
  - Increases the risk for developing severe lung disease during early adulthood
- Oxidants in cigarette smoke inactivate the AAT protein, causing further AAT impairment.
  - Symptoms in smokers begin ≥10 years earlier than in nonsmokers.

Genetics

Gene

SERPINA1

Variants

- AAT deficiency is caused by two pathogenic variants in the *SERPINA1* gene on opposite chromosomes.
- 100 allelic variants classified based on mobility (proteinase inhibitor [PI] typing)
  - Z and S alleles account for 95% of deficiency alleles
  - Other deleterious variants include I, F, P, and null variants
- Normal phenotype: PI*MM

Inheritance

Autosomal recessive

Test Interpretation

Clinical Sensitivity of Genotyping

95%[1]

Analytic Sensitivity/Specificity of Genotyping

99%

Results

Genotype/Phenotype Interpretation		
Allele Variants	**Emphysema Risk**	**Liver Disease Risk**
MM	Background	Background
MS	Background	Low
MZ	Background	Low
SS	Background	Low
SZ	20%-50%	Intermediate
ZZ	80%-100%	Moderately high to high
Null-Null	100%	Background

Limitations

- Acutely ill AAT-deficient patients may have falsely normal AAT concentrations.
- Only the Z (c.1024G>A, p.E342K) and S (c.791A>T, p.E264V) alleles are detected by genotyping.
- Diagnostic errors can occur due to rare sequence variations.
- Atypical electrophoretic patterns resulting from extremely rare AAT protein variants may not be interpretable by isoelectric focusing used in A1A phenotype.

References

1. Stoller JK, Hupertz V, Aboussouan LS. Alpha-1 antitrypsin deficiency. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. *GeneReviews*. University of Washington, Seattle. Updated May 2020; accessed Dec 2022.

Additional Resources

American Thoracic 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;168(7):818-900.

Ferrarotti I, Thun GA, Zorzetto M, et al. Serum levels and genotype distribution of α1-antitrypsin in the general population. *Thorax*. 2012;67(8):669-674.

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