Alpha-1-Antitrypsin Deficiency

Indications for Ordering

Diagnostic testing for alpha-1-antitrypsin (AAT) deficiency or carrier screening for AAT deficiency

Test Description

- AAT genotyping with reflex to phenotyping
  - Protein concentration measured by immunoturbidimetric assay
  - Genotyping by PCR followed by fluorescence monitoring to detect the Z (c.1024G>A, p.E342K) and S (c.791A>T, p.E264V) alleles in the *SERPINA1* gene
  - Phenotyping performed by qualitative isoelectric focusing electrophoresis/immunoturbidimetric assay
- Reflexes to phenotyping when protein concentration <90 mg/dL and individual is not homozygous or compound heterozygous for the S or Z deficiency alleles by genotyping

Tests to Consider

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

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

Alpha-1-Antitrypsin 0050001

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

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

- 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
- Most common nonenvironmental cause of emphysema
- Cause of one in every six lung transplants performed

Age of onset

- Smokers develop lung disease in 40s
- Nonsmokers develop lung disease in 50s

Symptoms

- Adults
  - Pulmonary: dyspnea, wheezing, cough, and phlegm, early onset emphysema (panacinar)
  - Hepatic: liver dysfunction, cirrhosis
    - Occurs more often in individuals with Z allele
    - Hepatitis with jaundice
    - Chronic liver disease
  - Skin: panniculitis
    - Necrotic areas with spontaneous suppuration
- Neonates
  - 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
- 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 AAT protein, causing further AAT impairment
  - Symptoms in smokers begin ≥10 years earlier than in nonsmokers

Genetics

Gene: *SERPINA1*

Inheritance: autosomal recessive

Pathogenic 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
- Normal phenotype: PI*MM

Test Interpretation

Sensitivity/specificity

- Clinical sensitivity of genotyping: 95% (Stoller, 2017)
- Analytical sensitivity/specificity of genotyping: 99%

Positive result

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

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
- Ferrarotti I, Thun GA, Zorzetto M, Ottaviani S, Imboden M, Schindler C, von Eckardstein A, Rohrer L, Rochat T, Russi EW, Probst-Hensch NM, Luisetti M. Serum levels and genotype distribution of α1-antitrypsin in the general population. Thorax. 2012 Aug;67(8):669-74. PubMed
- Stoller JK, Lacbawan FL, Aboussouan LS. Alpha-1 Antitrypsin Deficiency. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, eds. GeneReviews, University of Washington, 1993-2019. Seattle, WA [Last Revision: Jan 2017; Accessed: Nov 2019]