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-Antitrypsin (SERPINA1) Enzyme Concentration and 2 Mutations with Reflex to Alpha-Antitrypsin Phenotype 0051256
  - Preferred test to identify AAT deficiency and causative DNA and protein variants
- Alpha-Antitrypsin 0050001
  - Determines AAT enzyme plasma concentration for the initial evaluation of AAT deficiency
- Alpha-Antitrypsin Phenotype (Includes Alpha-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

<table>
<thead>
<tr>
<th>Genotype/Phenotype Interpretation</th>
<th>Emphysema Risk</th>
<th>Liver Disease Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>MM</td>
<td>Background</td>
<td>Background</td>
</tr>
<tr>
<td>MS</td>
<td>Background</td>
<td>Low</td>
</tr>
<tr>
<td>MZ</td>
<td>Background</td>
<td>Low</td>
</tr>
<tr>
<td>SS</td>
<td>Background</td>
<td>Low</td>
</tr>
<tr>
<td>SZ</td>
<td>20%-50%</td>
<td>Intermediate</td>
</tr>
<tr>
<td>ZZ</td>
<td>80%-100%</td>
<td>Moderately high to high</td>
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<tr>
<td>Null-Null</td>
<td>100%</td>
<td>Background</td>
</tr>
</tbody>
</table>

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