Alpha-1-Antitrypsin Deficiency Testing

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.

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%

Analytic Sensitivity/Specificity of Genotyping

99%

Results

<table>
<thead>
<tr>
<th>Genotype/Phenotype Interpretation</th>
<th>Emphysema Risk</th>
<th>Liver Disease Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allele Variants</td>
<td></td>
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</tr>
<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>
</tr>
<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.
- Atypical electrophoretic patterns resulting from extremely rare AAT protein variants may not be interpretable by isoelectric focusing used in A1A phenotype.

References


Additional Resources
