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

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<tr>
<th>Genotype/Phenotype Interpretation</th>
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<td>Allele Variants</td>
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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