

## Alpha-1-Antitrypsin Deficiency - AAT

### Clinical Background

Alpha-1-antitrypsin (AAT, alpha-1-protease inhibitor) is the major protease (trypsin, chymotrypsin and elastase) inhibitor in human serum. The loss of this protease inhibitor increases the risk for developing emphysema in early adulthood.

#### Epidemiology

- Prevalence
  - Estimated that 2-3% of 2-3 million patients with chronic obstructive pulmonary disease (COPD) in the U.S. have AAT deficiency
  - 1/3,000 for severe deficiency
- Age – 30s-40s with early-onset COPD
- Ethnicity – highest prevalence in Caucasians of North American and European descent

#### Risk Factors

- Genetics
  - Over 100 AAT allelic variants have been classified according to their electrophoretic mobility using isoelectric focusing; most have no clinical significance
  - Common phenotypes include: MM, MS, SS, MZ and ZZ, associated with 100, 80, 60, 57.5 and 15% AAT activity, respectively
  - MM, present in 95% of Caucasians, is considered the normal phenotype
  - 95% of deficiency alleles in the general population are either S or Z
  - Z allele is associated with severe liver and lung disease, and the S allele is associated with milder lung disease
  - Heterozygotes for a deficiency allele are only at slightly increased risk for AAT deficiency-related disorders
- Concomitant tobacco use increases the risk of emphysema and lowers the age of onset

#### Pathophysiology

- AAT is an acute phase reactant synthesized by the liver; its inherited deficiency is associated with liver and lung disease
  - Most important role is inhibition of protease neutrophil elastase
- Decreased quantities of AAT allow elastase to degrade lung parenchyma
- Hepatic disease is secondary to accumulation of unsecreted AAT in hepatocytes

#### Clinical Presentation

- Adults
  - Pulmonary – early onset emphysema (panacinar)
  - Hepatic – liver dysfunction, cirrhosis
    - Occurs more often in individuals with a Z allele
    - Hepatitis with jaundice
    - Chronic liver disease
  - Skin – panniculitis
    - Necrotic areas with spontaneous suppuration
- Neonates

- 10% 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
  - Wegener granulomatosis, necrotizing panniculitis, aneurysms of aortic and brain arteries
- Complications
  - Hepatocellular carcinoma and cholangiocarcinoma

#### Treatment

- Enzyme replacement treatment is available, so early diagnosis is crucial

## Diagnosis

- Indications for testing
  - Adult with early-onset COPD (<45 years)
  - Necrotizing panniculitis (unexplained)
  - Sibling or family member with known AAT deficiency
  - Bronchiectasis without known etiology
  - Unexplained liver disease
  - Newborns with bleeding disorder or prolonged jaundice
  - ANCA vasculitis (anti-PR3 type)
- Laboratory testing
  - Initial testing – serum AAT concentrations usually low in disease
    - Because AAT is an acute phase reactant, it may be elevated
      - Plasma concentration can be elevated into the normal range in PI MZ heterozygotes
      - Up to fourfold increase observed in inflammatory conditions, cancer, and liver disease
  - Phenotyping and genotyping
    - Phenotype determination to identify AAT protein variants if concentration is <100 mg/dL
    - Molecular testing of *SERPINA1* (serpin peptidase inhibitor) gene for S and Z alleles

#### Differential Diagnosis

- Adults
  - Non-AAT COPD
  - Cirrhosis from other etiologies
- Pediatric
  - Viral infection
  - Hemochromatosis
  - Wilson disease
  - Autoimmune hepatitis
  - Inborn errors of metabolism

## Screening

- Screening tests available prior to testing for levels
  - Pulmonary function studies (irreversible airflow obstruction)
  - Chest x-ray/CT scan

## Lab Tests

### Indications for Laboratory Testing

Tests generally appear in the order most useful for common clinical situations. For test-specific information, refer to the test number in the ARUP Laboratory Test Directory on the ARUP Web site at [www.aruplab.com](http://www.aruplab.com).

Test Name and Number	Recommended Use	Limitations	Follow Up
Alpha-1-Antitrypsin & A1A Genotype with Reflex to Phenotype <b>0051256</b> Method: Immunoturbidimetric Polymerase Chain Reaction/Fluorescent Resonance Energy Transfer	Detects the presence of S and Z deficiency alleles and A1AT deficiency; includes reflex to phenotyping if A1AT concentration is not consistent with genotype 95% clinical sensitivity for DNA testing; 99% analytical sensitivity	An acutely ill AAT-deficient patient may have a falsely normal AAT concentration because AAT is an acute phase reactant	
Alpha-1-Antitrypsin Phenotype (includes Alpha-1-Antitrypsin) <b>0080500</b> Method: Isoelectric Focusing/ Immunoturbidimetric	Identifies AAT protein variants and AAT deficiency	An acutely ill AAT-deficient patient may have a falsely normal AAT concentration because AAT is an acute phase reactant	
Alpha-1-Antitrypsin <b>0050001</b> Method: Immunoturbidimetric	Detects AAT deficiency	An acutely ill AAT-deficient patient may have a falsely normal AAT concentration because AAT is an acute phase reactant	
Immunohistochemistry Stain Offering <b>arup005</b> Method: Immunohistochemistry	For fixed tissue samples, consultative services as well as immunohistochemical staining for Alpha-1-antitrypsin (AAT) are available		

### General References

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