

# Alpha-1-antitrypsin (A1AT) deficiency secondary to *SERPINA1* mutations

**A1AT deficiency** is one of the most common genetic disorders in Caucasian populations. In North America, approximately one individual in every 5,000-7,000 has A1AT deficiency. Clinically significant alpha-1-antitrypsin deficiency is typically the result of homozygosity for the PI\*Z allele or compound heterozygosity for the PI\*S\*Z alleles, although other disease-causing alleles are identified in ~5% of affected individuals.

A1AT deficiency is characterized by liver disease from infancy and throughout adulthood and by lung disease in adults, particularly those who smoke cigarettes. A1AT is a serum protease inhibitor. In the adult liver, A1AT deficiency may lead to the accumulation of insoluble intracellular proteins in hepatocytes and bile ducts, leading to cirrhosis and fibrosis. However, the etiology of liver disease in children with A1AT deficiency is not well understood. In the lung, A1AT deficiency leads to a reduced inhibition of leukocyte elastase resulting in destruction of the elastin in the alveolae resulting in pulmonary disease. Hepatocellular carcinoma, panniculitis, and Wegener granulomatosis are rare complications of A1AT deficiency.

Approximately 2% of individuals with the PI\*S\*Z genotype develop severe liver disease in childhood while approximately 10% of adults over 50 years of age develop cirrhosis. In contrast, pulmonary disease is very rare in children with the PI\*S\*Z genotype, while adults with this genotype who smoke cigarettes have a significantly increased risk of developing chronic obstructive pulmonary disease (COPD). Heterozygotes for the Z allele are not at increased risk for liver disease, but may have a mildly increased risk of pulmonary dysfunction in adulthood, particularly among individuals who smoke. An individual's genotype and history of environmental exposures contribute to a highly variable phenotype, even among family members.

## Indications:

- Obstructive jaundice in infancy or childhood
- Cirrhosis, fibrosis or hepatocellular carcinoma in adults
- Chronic obstructive pulmonary disease (COPD) in adults
- Presymptomatic testing of at-risk siblings
- Prenatal diagnosis of at-risk pregnancies
- Carrier testing in relative of a patient with A1AT deficiency

## Specimen:

At least 2 mls of whole blood in purple top (EDTA) tube. Label tube with patient's name, birth date, and date of collection. Phlebotomist must initial tube to verify patient's identity.

## Methodology:

- TaqMan-based genotyping assay to detect Z and S alleles only

OR

- TruSeq Custom Amplicon enrichment followed by next-generation sequencing with > 20 fold coverage at every target base and Sanger confirmation of all variants OR PCR-based sequencing, of all exons and exon/ intron boundaries of the gene.

## Sensitivity and Specificity:

- Genotyping Assay: This test detects only the Z and S alleles which account for 95% of disease causing mutations.
- DNA sequencing: The sensitivity of DNA sequencing is over 99% for the detection of nucleotide base changes, small deletions and insertions in the regions analyzed. Multiple exon deletions and insertions may not be identified by this methodology.

- *SERPINA1* is the only gene associated with A1AT deficiency. If the patient has received a liver transplant or recent blood transfusion, donor DNA may be present in the blood along with patient DNA (chimerism). In this case, additional testing may be required to rule out chimerism.

### Turn-Around Times:

- **Genotyping Assay:** 2 business days
- ***SERPINA1* full gene sequence analysis:** 28 days

### Costs:

Please call 1-866-450-4198 for pricing or with any billing questions.

### CPT Codes:

- **Genotyping Assay:** 81332
- ***SERPINA1* sequence analysis:** 81479
- **Family specific analysis:** 81479

### Results:

Each test report includes a detailed interpretation of the genetic findings, the clinical significance of the result, and specific recommendations for clinical management and additional testing, if warranted. Results will be reported to the referring physician or health care provider as specified on the test requisition form.

### Shipping Instructions:

Please enclose **test requisition** with sample.

**All information must be completed before sample can be processed.**

Place samples in styrofoam mailer and ship at room temperature by overnight Federal Express to arrive Monday through Friday.

### Ship to:

Cytogenetics and Molecular Genetics Laboratories  
3333 Burnet Avenue NRB 1042  
Cincinnati, OH 45229  
513-636-4474