

Alpha-1-Antitrypsin & AAT Genotype with Reflex to Phenotype

PLASMA CONCENTRATION OF ALPHA 1-ANTITRYPSIN (AAT) AND DNA TEST FOR THE S AND Z ALLELES

Disease Overview

- AAT, a glycoprotein mainly synthesized in the liver, is the chief protease inhibitor in serum. The most important role of AAT is the inhibition of the protease neutrophil elastase. In cases of AAT deficiency, uninhibited free neutrophil elastase results in the degradation of the connective protein elastin in the alveoli of the lungs.
- Common symptoms of severe AAT deficiency include dyspnea (84 percent), wheezing (65 percent), increased cough and phlegm (50 percent), and emphysema/chronic obstructive lung disease (COPD) (30–40 percent). Fifteen to nineteen percent of individuals over age 50 develop cirrhosis. The risk of liver disease at age 20–40 years is about 2 percent; at age 41–50 years it is about 4 percent. The risk for developing severe liver disease in childhood is generally low (~2 percent).
- AAT deficiency is the most common non-environmental cause for emphysema and is responsible for one-sixth of all lung transplants.
- Cigarette smoke contains oxidants capable of inactivating the AAT protein, further impairing a quantitatively and/or qualitatively less functional AAT.
- Affected nonsmokers usually develop lung disease in the sixth decade of life, while smokers usually become symptomatic between the ages of 40 and 50.
- Protein-replacement therapy, utilizing purified AAT protein, and smoking cessation can dramatically slow disease progression.

Epidemiology

The frequency of severe AAT deficiency in the United States is approximately one in 6,000 Caucasians. It is less frequent in other ethnicities.

Genetics

- Autosomal recessive.
- The *AAT* gene is located on chromosome 14q31-q32.3 and has over 100 identified allelic variants classified based on their mobility using isoelectric focusing (PI typing).

- The most common normal genotype is designated PI*MM.
- The presence of two *AAT* deficiency alleles can dramatically reduce the concentration of circulating AAT. As a result, individuals with homozygous or compound heterozygous deficiency alleles that result in serum AAT concentrations below approximately 60 mg/dL are believed to be at substantial risk for AAT deficiency-related disorders.
- The common Z and S alleles are believed to account for 95 percent of deficiency alleles in the general population.
- Homozygotes for the Z allele have AAT serum concentrations 10–15 percent of normal, whereas homozygotes for the S allele have AAT serum concentrations 60 percent of normal.
- Although homozygosity for the Z allele is associated with the most severe phenotype, individuals with the SZ and SS genotypes are at risk for developing lung disease. In fact, SZ smokers have rates of emphysema similar to ZZ smokers.
- Two to four percent of Caucasians have the MZ genotype. Individuals heterozygous for a deficiency allele are only at a slightly increased risk for AAT deficiency-related disorders. Compared with the wild type (MM) genotype, MZ heterozygotes are twice as likely to be hospitalized for chronic obstructive pulmonary disease.

Indications for Use

- To confirm affected or carrier status in individuals with a serum AAT concentration less than 100 mg/dL.
- To determine affected or carrier status in individuals with a family history of AAT caused by the S or Z alleles.
- Prenatal diagnosis in fetuses whose parents are both known carriers of the Z allele.

Additional Ordering Notes

If there is a positive family history of AAT deficiency, please provide information on the relationship of the proband to the individual being tested, as well as the proband's specific mutations, PI type, and serum AAT protein concentration.

Interpretation

- AAT protein concentration and A1A genotyping are performed on all specimens for proper test interpretation.
- If protein concentration is less than 100 mg/dl and only one or no deficiency allele is detected by A1A genotyping, then phenotyping will be performed.
- Results are reported as homozygous, heterozygous, or negative for both the S and Z alleles; the serum AAT protein concentration is also provided.
- Homozygosity for the Z allele is consistent with AAT deficiency.
- Homozygosity for the S allele and SZ compound heterozygosity corresponds to an intermediate phenotype.

Methodology

- PCR followed by fluorescence monitoring to detect the Z (c.1024 G>A, p.E342K) and S (c.791 A>T, p.E264V) alleles in the AAT gene (Genbank accession number AL132708).
- AAT protein level is measured using an immunoturbidimetric assay.
- The analytic sensitivity and specificity of genotyping are 99 percent.
- The clinical sensitivity and specificity of genotyping are 95 and 99 percent, respectively.

Limitations

- *AAT* null alleles or deficiency alleles, other than S and Z, will not be detected.
- Rare diagnostic errors can occur due to probe-site mutations.

Related Tests

- Alpha-1-Antitrypsin– AAT plasma concentration. (0050001)
- Alpha-1-Antitrypsin Phenotype– AAT plasma concentration and protein phenotyping (0080500)

References

1. American Thoracic Society/European Respiratory Society Statement. Standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. *Respiratory and Critical Care Medicine* 2003;168:818–900.
2. Alpha-One Foundation. <http://www.alphaone.org> (accessed on July 24, 2008).

Test Information

0051256

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For specific collection, transport, and testing information, refer to the ARUP Web site at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.