

Alpha-1-Antitrypsin GenotypR™

Mutation analysis of deficiency

Overview

Alpha-1 Antitrypsin Deficiency

Alpha-1 antitrypsin (AAT) deficiency is a common genetic cause of increased risk for cirrhosis and hepatocellular carcinoma in children and of emphysema in adults.^{1,2} In normal and healthy individuals, AAT protects connective tissue in the lungs from a natural enzyme (neutrophil elastase) that helps fight bacteria and remove cellular debris; a deficiency results in destruction of the connective tissue. In the liver, hepatocellular injury occurs due to polymerization of a mutant AAT protein in hepatic cells.¹⁻⁴ AAT is a protease inhibitor, and disease occurs when 2 protease inhibitor-deficient alleles are inherited from the AAT gene locus (*Pi*).⁵

Serum Testing

The primary diagnostic test for AAT deficiency is an immunoassay that measures AAT concentration in plasma or serum.⁶ Typically, AAT-deficient patients homozygous for the Z allele have plasma or serum concentrations 85%

below normal; whereas, patients who are heterozygous for both the Z and S alleles can have intermediate AAT concentrations (~40% below normal).^{4,6} Because of the significant overlap in concentrations between normal patients and heterozygote carriers of AAT deficiency, immunoassays cannot be used to detect carriers of AAT deficiency.⁶ Genotyping can identify carriers and individuals at risk for AAT-deficiency independent of AAT concentrations.⁶

AAT Deficiency Mutation Analysis

Although over 70 European alleles in the *Pi* gene are reported, most are private or rare. 95% of AAT-deficient patients are either homozygous for the Z allele or are heterozygous for both the Z and S alleles.^{2,7} This assay detects both of these common alleles and is thus diagnostic for the majority of AAT patients and also detects most carriers.

Clinical Utility

- ?? **Diagnosis** of AAT deficiency in the **symptomatic** patient and concomitant identification of familial mutation(s)
- ?? **Carrier risk revision** for an **at-risk relative** of a diagnosed patient known to have the ZZ or SZ genotype
- ?? **Prenatal diagnosis** of a fetus at 1-in-4 risk for AAT deficiency. Both parents must be previously and/or concurrently tested at *Specialty* and both demonstrated to be heterozygous for either the Z or the S mutation.
- ?? The World Health Organization (WHO) recommends screening for AAT deficiency at least once in all Chronic Obstructive Pulmonary Disease (COPD) patients and in adults and children with asthma⁵

Ordering Information & Specimen Requirements

Test Code	Test Name	Specimen Requirements
1513	Alpha-1-Antitrypsin - For serum concentrations of alpha-1-antitrypsin	1 mL Serum; Ambient, Refrigerated or Frozen.
1515	Alpha-1-Antitrypsin Deficiency GenotypR² - Detects the common Z & S alleles for diagnosis of alpha-1-antitrypsin deficiency	5 (3) mL Whole Blood EDTA or ACD; AMBIENT ONLY. Ship AMBIENT immediately by overnight courier. DO NOT FREEZE.
<p><i>The interpretation provided with the result is specific for a symptomatic patient. If an asymptomatic patient is referred for testing based on a positive family history of AAT deficiency, the ordering physician will be advised to request a re-interpretation of the results tailored to the specific family history of the patient.</i></p>		
1518	Alpha-1-Antitrypsin Deficiency Fetal Study - Detects the common Z & S alleles for prenatal	20 (10) mL Amniotic Fluid; Sterile; AMBIENT ONLY. Ship immediately by overnight courier.

Methodology

INVADER[®]-based detection of Pi Z and S alleles in genomic DNA

Related Assays**5822 Chromosome Analysis Amniotic Fluid**

Cell culture will be added at the laboratory. Ship flask at confluency, topped off with culture media. DO NOT REFRIGERATE OR FREEZE. For chorionic villus specimens, please contact Technical Services.

References

1. Marcus N, Teckman JH, Perlmutter DH. α_1 -antitrypsin deficiency: from genotype to childhood disease. *J Pediatr Gastroenterol Nutr* 1998;27:65-74.
2. Primhak RA, Tanner MS. Alpha-1-antitrypsin deficiency. *Arch Dis Child* 2001;85:2-5.
3. Carrell RW, Lomas DA. Alpha₁-antitrypsin deficiency – a model for conformational diseases. *N Engl J Med* 2002;346:45-53.
4. Lomas DA, Mahadeva R. α_1 -antitrypsin polymerization and the serpinopathies: pathobiology and prospects for therapy. *J Clin Invest* 2002;110:1585-90.
5. α_1 -Antitrypsin deficiency: memorandum from a WHO meeting. *Bull World Health Organ* 1997;75:397-415.
6. Campbell EJ. α_1 -antitrypsin deficiency: incidence and detection program. *Respir Med* 2000;94(Suppl C):S18-S21.
7. Dahl M, Tybjaerg-Hansen A, Lange P, Vestbo J, Nordestgaard BG. Change in lung function and morbidity from chronic obstructive pulmonary disease in α_1 -antitrypsin MZ heterozygotes: a longitudinal study of the general population. *Ann Intern Med* 2002;136:270-9.

For more information, please call Client Services at 800-421-4449 or visit our Web site at www.specialtylabs.com