

Alpha-1 Antitrypsin Deficiency

Disorder Also Known As: AAT Deficiency, AATD

Variant List: c.1096 C>T, p.E366K (Z allele) and c.863 T>A, p.E288V (S allele) in *SERPINA1*

Clinical Features:

Alpha-1 antitrypsin deficiency (AATD) is an inherited disorder affecting approximately 1 in 5,000 individuals of Caucasian ancestry, and is characterized by an increased risk to develop lung, liver, and skin disease.^{1,2} Adult-onset chronic obstructive pulmonary disease (COPD, e.g. emphysema, persistent airflow obstruction, and/or chronic bronchitis) is the most common manifestation of AATD, with symptoms typically presenting between the ages of 20-50 years.² Environmental factors, primarily smoking, are known to accelerate the onset and progression of respiratory disease. While the development of COPD among smokers with AATD typically occurs between the ages of 40-50 years, the onset in non-smokers can be delayed to the sixth decade or beyond, and some non-smokers with AATD never develop COPD.² Rarely, emphysema has been reported in children with AATD, although other genetic factors may be contributory. Manifestations of liver disease can occur in both children and adults with AATD. Neonatal or childhood onset of jaundice, hepatitis, and/or cirrhosis occurs in a small proportion of individuals with AATD. In one study of 120 Swedish children with homozygous Z allele (PI*ZZ) genotype, 18% developed clinically recognized liver abnormalities and 2.4% developed liver cirrhosis with death in childhood.³ Studies of adult-onset fibrosis and cirrhosis suggest that between 15-40% of adults with the homozygous Z allele genotype experience liver manifestations.^{4,5} Progression of liver disease to hepatocellular carcinoma is more common among individuals affected with AATD and homozygous Z allele genotype than what is typically expected among individuals with cirrhosis in the general population. Less frequent clinical findings associated with AATD include panniculitis and C-ANCA-positive vasculitis.²

A diagnosis of AATD is confirmed following demonstration of low serum concentration of alpha-1 antitrypsin (AAT) and detection of a functionally deficient AAT protein variant by protease inhibitor (PI) typing or detection of biallelic pathogenic variants in the *SERPINA1* gene. Prior to the identification of the *SERPINA1* gene, electrophoretic AAT protein variants were named using the prefix PI*. Thus, both historic and current nomenclature are utilized when describing genetic variants associated with AATD. PI*Z, or Z allele (c.1096 C>T, p.E366K), is the most common pathogenic variant resulting in functionally deficient AAT and is associated with severe manifestations of AATD when it occurs in the homozygous state (PI*ZZ). PI*S, or S allele (c.863 T>A, p.E288V), is another pathogenic variant resulting in functionally-deficient AAT, yet is typically only associated with clinical manifestations of AATD when it occurs in combination with another pathogenic variant (e.g. PI*SZ) and when the serum AAT level is <57mg/dL.² The Z allele and S allele account for 95% of the pathogenic variants identified in individuals affected with AATD; other variants are rare and/or have low penetrance.

Inheritance Pattern/Genetics: Autosomal Recessive

Test Methods:

Using genomic DNA from the submitted specimen, the relevant portion of the requested gene is PCR amplified and capillary sequencing is performed. Bi-directional sequence is assembled, aligned to reference gene sequences based on human genome build GRCh37/UCSC hg19 and analyzed for only the requested variant(s). Sequence alterations are reported according to the Human Genome Variation Society (HGVS) nomenclature guidelines. The methods used by GeneDx are expected to be greater than 99% sensitive in detecting variants identifiable by sequencing.

Clinical Test Sensitivity: Approximately 95% of individuals with AATD are found to harbor pathogenic variants, Z and/or S allele, in SERPINA1. Thus, the targeted genotyping analysis as performed by GeneDx is expected to identify pathogenic variants in 95% of cases.

References:

1. Nussbaum, RL, McInnes, RR, Willard, HF, Hamosh, A, & Thompson, MW (2007). *Thompson & Thompson Genetics in Medicine*. Philadelphia: Saunders/Elsevier.
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3. Sveger T. Liver disease in alpha-1 antitrypsin deficiency detected by screening of 200,000 infants. *N Engl J Med*. 1976;294:1316–21. (PMID: 1083485)
4. Cox DW, Smyth S. Risk for liver disease in adults with alpha-1 antitrypsin deficiency. *Am J Med*. 1983;74:221–7. (PMID: 6600583)
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