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Perspective

Genetics and Treatment Options of Alpha-1 Antitrypsin Deficiency

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ABOUT THE STUDY

The lungs and liver are the main organs affected by the hereditary disease known as Alpha-1 Antitrypsin Deficiency (AATD). It is caused by mutations in the *SERPINA1* gene, leading to reduced levels or dysfunctional Alpha-1 Antitrypsin (AAT) protein. This deficiency predisposes individuals to various lung diseases, particularly emphysema, and liver diseases such as cirrhosis.

Genetics of alpha-1 antitrypsin deficiency

Alpha-1 Antitrypsin (AAT) is a serine protease inhibitor primarily produced in the liver and secreted into the bloodstream. It plays a important role in protecting tissues, especially the lungs, from enzymes released by inflammatory cells such as neutrophil elastase. The gene responsible for encoding AAT is called *SERPINA1*, located on chromosome 14q32.1.

In individuals with Alpha-1 antitrypsin deficiency, mutations in the *SERPINA1* gene lead to either reduced production of AAT or production of dysfunctional AAT protein. The most common mutation associated with severe deficiency is the Z allele (Glu342Lys mutation), which leads to polymerization of AAT molecules within hepatocytes, impairing their secretion into the bloodstream.

The inheritance pattern of AATD is autosomal codominant, meaning individuals with two deficient alleles (e.g., ZZ genotype) typically have more severe manifestations, while those with one deficient allele (e.g., MZ genotype) may exhibit milder symptoms or remain asymptomatic.

SERPINA1 gene

The *SERPINA1* gene, also known as Alpha-1 Antitrypsin (AAT) gene, is located on the long arm of chromosome 14 (14q32.1). It encodes the Alpha-1 antitrypsin protein, which is a key serine protease inhibitor primarily produced in the liver. Alpha-1 antitrypsin plays a critical role in protecting tissues, particularly the lungs, from damage caused by enzymes like neutrophil elastase.

Mutations in the *SERPINA1* gene are associated with Alpha-1 Antitrypsin Deficiency (AATD), a genetic disorder characterized by reduced levels or dysfunctional forms of the AAT protein. The most common and clinically significant mutations include the Z (Glu342Lys) and S (Glu264Val) alleles. These mutations lead to impaired secretion of AAT from hepatocytes and subsequent accumulation of misfolded protein within liver cells, contributing to liver disease and increasing susceptibility to lung conditions such as emphysema.

Structure and function: The AAT protein is a serine protease inhibitor primarily synthesized in the liver and secreted into the bloodstream. It acts to inhibit neutrophil elastase and other proteases, thereby preventing excessive degradation of lung tissue and maintaining pulmonary function. Proper folding and secretion of AAT are essential for its function; mutations in the *SERPINA1* gene can disrupt this process, leading to AATD.

Inheritance patterns: *SERPINA1* follows an autosomal codominant inheritance pattern, meaning that individuals inherit two copies of the gene one from each parent. The severity of AATD depends on the specific mutations in the *SERPINA1* gene and whether the affected alleles result in reduced production or impaired function of AAT protein.

Z allele (Glu342Lys)

Description: The Z allele is the most prevalent and clinically significant mutation in AATD.

Mutation: A single nucleotide substitution (c.1096G>A) leads to a change in amino acid sequence from glutamic acid (Glu) to lysine (Lys) at position 342 of the AAT protein.

Effect: The mutation causes misfolding of AAT protein in hepatocytes, leading to accumulation within the liver cells and reduced secretion into the bloodstream. This results in low circulating levels of functional AAT, increasing susceptibility to lung conditions such as emphysema and Chronic Obstructive Pulmonary Disease (COPD), as well as liver diseases like cirrhosis.

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S allele (Glu264Val)

Description: Another common mutation in the *SERPINA1* gene associated with AATD.

Mutation: A substitution mutation where glutamic acid (Glu) is replaced by valine (Val) at position 264 of the AAT protein.

Effect: Similar to the Z allele, the S allele leads to reduced secretion of functional AAT, though typically resulting in milder forms of AATD compared to the Z allele. Individuals with the S allele may still be at increased risk for lung and liver diseases, depending on the specific genotype (e.g., MS).