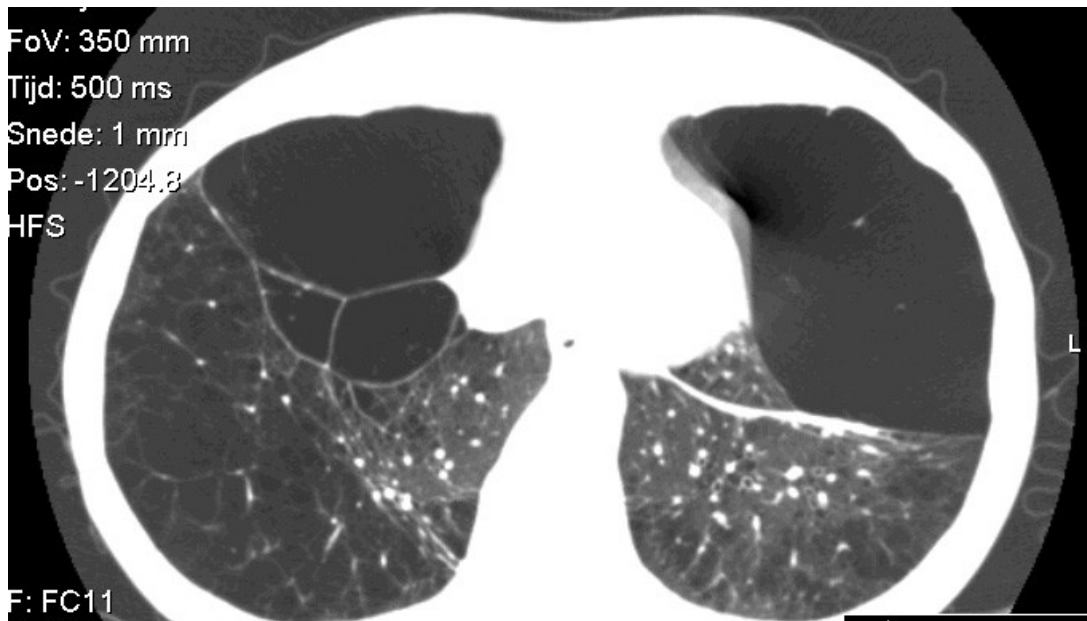


Alpha-1 Antitrypsin Deficiency — Etiology, Clinical Manifestations, and More

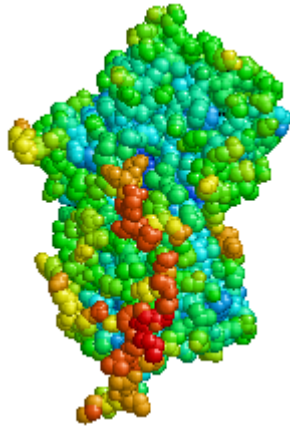
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Without the liver, we would not be able to metabolize certain components of the food, drinks, and medications we ingest. We would experience difficulties with hemostasis and would not be able to properly digest food, particularly fatty food. These are only a few of the many contributions the liver makes to homeostasis. However, a number of conditions can cause damage to the liver. Although the pathogenesis of liver diseases is most likely caused by a combination of many factors, there are well-studied disorders in which genetics plays the most crucial role in initiating disease. Alpha-1 antitrypsin deficiency is one of these disorders.



Overview

Biochemistry



[Image](#): "Alpha-1 antitrypsin" by PDB. License: [CC BY-SA 3.0](#)

Alpha-1 antitrypsin is a **single-chain glycoprotein that is produced by the hepatocytes, phagocytes, and epithelial cells of the lungs**. The liver is the dominant producer of alpha-1 antitrypsin. It is made up of a chain of 394 amino acids that demonstrate various glycoforms. It has a mass of 52 kDa and belongs to a superfamily of proteases called **serpins**. Alpha-1 antitrypsin is the most prominent of the protease inhibitors in this group.

"Serpins" stands for **serine protease inhibitor**. Serpins are a group of proteins that consists of proteins with similar structures as alpha-1 antitrypsin. These are known to irreversibly inactivate chymotrypsin-like proteases by causing a conformational change in the structure of the protease, thereby inhibiting the binding of the active site with its ligands.

The gene that is responsible for the expression of alpha-1 antitrypsin is found on **chromosome 14** and is very **pleomorphic**. To date, there are at least 75 known alpha-1 antitrypsin-expressing genes. The most common of these is **PiMM (protease inhibitor plus the genotype of an individual's 2 alleles)**. PiS variants produce a moderately lower amount of alpha-1 antitrypsin in the serum, while Pi-null does not produce any. A reduction in alpha-1 antitrypsin production caused by these variants does not necessarily cause manifestations in the affected individual, however.

Protective functions

Alpha-1 antitrypsin is known to inhibit the action of many serine proteases, including **neutrophil elastase, cathepsin G, and proteinase 3**. These proteases are usually produced by neutrophils during inflammatory processes. An absence of alpha-1 antitrypsin is known to have deleterious effects on the [liver](#) and lungs, as well as on small to medium-sized blood vessels.

Definition

Conditions Associated with Alpha-1 Antitrypsin Deficiency

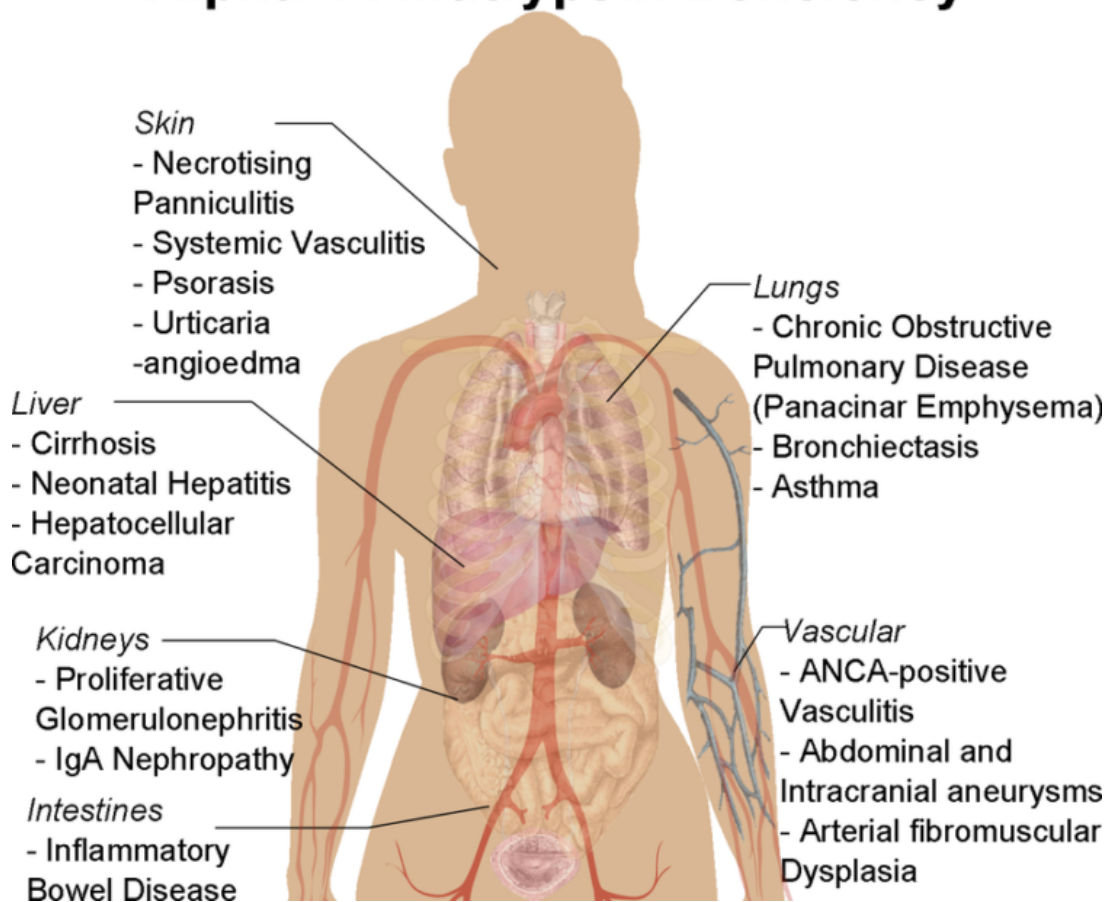


Image: "Human female shadow diagram with conditions associated with alpha-1 antitrypsin deficiency" by Mikael Häggström. License: Public Domain

Alpha-1 antitrypsin deficiency is a genetic disorder characterized by low serum levels of alpha-1 antitrypsin and a high risk of pulmonary disease and vasculitis in adults and liver disease in both children and adults.

Epidemiology

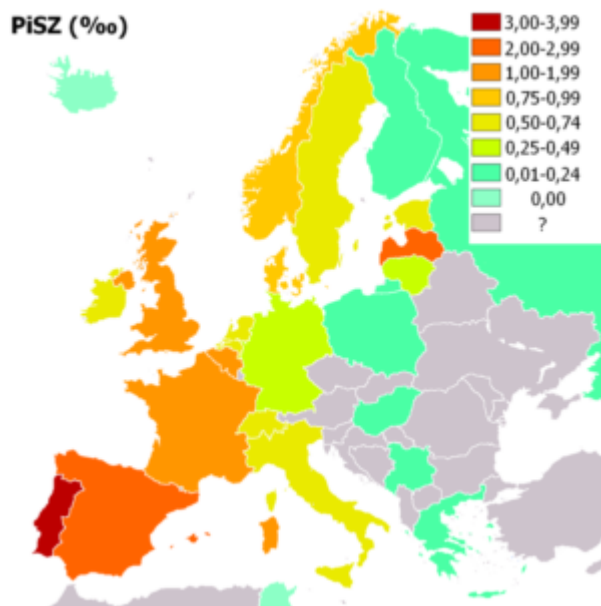


Image: "European distribution by country of genotype PiSZ — heterozygous alpha 1-antitrypsin deficiency" by Olve Utne.
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Alpha-1 antitrypsin deficiency was first diagnosed in an adult patient in 1963, and was generally seen at first in patients with emphysema. Later, it was also observed to occur alongside liver disease. The first diagnosis of the deficiency in neonates was in children who later developed liver disease.

Although the disease is prevalent in many populations around the world, it **occurs more frequently among Caucasians of European descent**. It occurs in almost 1 of every 1,600–2,000 live births and is the **most common genetic causative factor for juvenile liver problems**. Most children who require liver transplantation are diagnosed with alpha-1 antitrypsin deficiency.

Many epidemiological studies related to alpha-1 antitrypsin deficiency have been performed, and a number are still underway. Although certain problematic variants of the alpha-1 antitrypsin gene may cause some degree of alpha-1 antitrypsin deficiency, not all affected individuals develop significant liver disease. This fact confirms that, even with a genetic condition, environmental factors still play an important part in disease progression.

Etiology and Pathogenesis

The most commonly known genetic mutation associated with clinically significant alpha-1 antitrypsin deficiency is the **PiZ variant**. Individuals with 2 copies of the Z allele are known to exhibit clinical manifestations, as only up to 10% of the needed functional alpha-1 antitrypsin is produced. The same manifestations are sometimes present in homozygous individuals with the **PiMZ variant** because the allele acts in a dominant fashion and does not need a duplicate allele copy to exert its effects. Some individuals with clinically manifesting alpha-1 antitrypsin deficiency may also have the PiS variant. This disorder can present early in life and is frequently diagnosed among young children and infants with liver disease.

The mutation in the gene causes an abnormal folding of the alpha-1 antitrypsin protein. The resulting abnormality in structure leads to an **impairment in the mobility of the glycoprotein out from the secretory cell** such as the hepatocytes. A single amino

acid replacement (Glu342 to Lys342) in the chain is the cause of this impairment. The defective protein, **alpha-1-AT Z**, is then retained and accumulated in the endoplasmic reticulum, as it fails to move on to the Golgi apparatus. A deficiency of glycoprotein follows.

Aside from the impaired production of alpha-1 antitrypsin in the sera, point mutations in the gene ultimately lead to the damage of hepatocytes as the accumulated alpha-1-AT Z polymerizes and aggregates to cause liver inflammation. Many researchers have also theorized that this **gain of toxic mechanism** also predisposes the individual to liver cancer, as mitochondria tend to lose their function.

As noted, environmental factors play a key role in the development of this disease. This is because **certain exogenous factors** affect the intracellular mechanisms that attempt to eliminate the aggregated alpha-1-AT Z in the cells producing these defective proteins.

Mutations in the pathways that can alleviate the alpha-1-AT Z aggregation intracellularly have also been implicated in the development of the disease. For example, single nucleotide polymorphisms in the downstream flanking region of the endoplasmic reticulum mannosidase I can significantly affect the degree of alpha-1 antitrypsin deficiency and liver damage present. This pathway is one of the many that compose the intracellular clearing pathways for defective alpha-1 antitrypsin proteins.

Clinical Manifestations

Liver

Most if not all of the clinical presentations of alpha-1 antitrypsin deficiency result from a general **impairment of the functions of the liver**. The disease is often diagnosed early in childhood and can manifest as early as 2 months of age. However, signs and symptoms may also begin later in childhood, during the teenage years, or even as late as adulthood. Infants and young children may demonstrate various signs of impaired vitamin K synthesis, including bleeding at the umbilical stump, gastrointestinal tract, or intracranial space.

Unexplained bruising may also be evident, as may other signs such as a failure to gain weight. A condition called **neonatal hepatitis** with cholestatic jaundice may also be present in some newborns with alpha-1 antitrypsin deficiency. Newborns with this condition tend to go through acute bouts of hepatitis with complete recovery in between. However, there are also cases in which newborns undergo an episode of acute hepatitis and fail to recover. These cases usually progress to acute hepatitis.

As the affected individual ages, signs and symptoms of advanced liver disease may be seen, including:

- Hepatomegaly
- [Splenomegaly](#)
- Ascites
- [Bleeding esophageal](#) varices
- Scleral icterus

These manifestations are usually associated with cirrhosis in adults. In some cases, especially in individuals with the PiZZ genotype, hepatocellular carcinoma may develop, although not always in those with cirrhosis. Insufficient data exist about the ability of heterozygous genotypes to cause alpha-1 antitrypsin deficiency. However, some studies

have found that individuals with the PiSZ gene can show clinical manifestations of the deficiency because of its resemblance to the PiZZ gene.

Effects on the lungs and other systems



Image: "Emphysema due to alpha 1-antitrypsin deficiency"
by James Heilman, MD. License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

Alpha-1 antitrypsin deficiency is the most common genetic cause of [emphysema](#). However, this type of emphysema makes up only a small portion of all cases of the disease. The onset of manifestations of alpha-1 antitrypsin deficiency in the lungs usually starts in the 3rd or 4th decade of life. Clinical presentation begins with **coughing, difficulty breathing, and expectoration**. Pulmonary manifestations are variable, with basal panacinar emphysema as the classical phenotype. Some patients may present with centrilobular emphysema and bronchiectasis.

External factors such as occupational exposure to irritants and smoking accelerate the progression of the disease. These factors can reduce the median survival rate of alpha-1 antitrypsin deficiency-affected individuals by 20 years or more. Individuals with the PiS variant are even more prone to pulmonary complications than those with PiZZ.

Other inflammatory diseases associated with alpha-1 antitrypsin deficiency include:

- Necrotizing panniculitis
- Wegner's granulomatosis
- [Membranoproliferative glomerulonephritis](#)
- [IgA nephropathy](#)
- Other vasculitis syndromes

Pathologic Changes in the Liver

When viewed under a microscope, a liver biopsy sample shows **cytoplasmic globular inclusions in hepatocytes**. These round-to-oval-shaped inclusions stain magenta on eosin and hematoxylin. These are also periodic acid-Schiff (PAS)-positive and diastase-resistant. These inclusions represent the accumulated mutant alpha-1-AT Z proteins.

During the early stages of the disease, these inclusions are mostly found in the **periportal liver cells**, as disease progression tends to move in a peripheral to central direction. The presence of these inclusions in the hepatocytes does not, however, correlate with the severity of the disease in all cases.

In samples taken from neonates and infants with the PiZZ variant, changes in the hepatocyte may vary. Especially in very early cases, PiZZ alpha-1 antitrypsin deficiency may present with hepatitis, accompanied by cholestasis and fibrosis. Some infants may only exhibit steatosis.

Differential Diagnosis and Diagnostic Investigation

In all cases in which the signs and symptoms of abnormal liver functioning occur, such as **elevated transaminases** and **prolonged clotting and bleeding times**, alpha-1 antitrypsin deficiency should be considered. Differential diagnoses may vary depending on the patient's age (see table below).

Infancy	<ul style="list-style-type: none"> • Extrahepatic biliary atresia <ul style="list-style-type: none"> • Alagille syndrome <ul style="list-style-type: none"> • Cystic fibrosis • Choledochal cyst <ul style="list-style-type: none"> • Galactosemia • Tyrosinemia • Neonatal giant cell hepatitis • Progressive familial intrahepatic cholestasis <ul style="list-style-type: none"> • TORCH infection
Childhood/adolescence	<ul style="list-style-type: none"> • Autoimmune hepatitis <ul style="list-style-type: none"> • Wilson's disease • Infectious hepatitis • Toxic hepatitis
Adulthood	<ul style="list-style-type: none"> • Wilson's disease • Autoimmune hepatitis • Hepatocellular carcinoma <ul style="list-style-type: none"> • Hemochromatosis • Cryptogenic cirrhosis • Nonalcoholic steatohepatitis

Source: Adapted from Hawkey CJ, Bosch J, Richter JE, Tsao GG, and Chan FKL, ed. (2012). *Textbook of Clinical Gastroenterology and Hepatology*, 2nd ed. Wiley-Blackwell.

The diagnosis of alpha-1 antitrypsin deficiency can be confirmed by **measuring serum levels of alpha-1 antitrypsin** and determining the PI type by isoelectric focusing gel electrophoresis. Abnormal results will show approximately 10%-15% of normal levels of alpha-1 antitrypsin in the blood.

As an acute phase reactant, alpha-1 antitrypsin may also be elevated in the presence of inflammatory processes. This means that an elevated serum measurement should not be used as the sole basis for the exclusion of alpha-1 antitrypsin deficiency.

Although not indicated, **a liver biopsy** can help determine the extent of liver damage and the presence of hepatocellular carcinoma. The presence of PAS-positive and diastase-resistant inclusions is diagnostic of the disease.

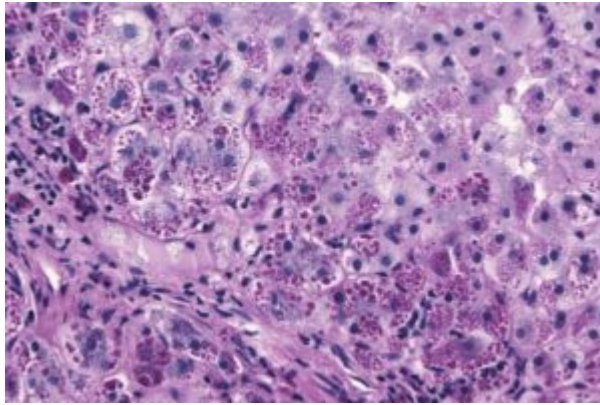


Image: "Photomicrograph of a liver biopsy from a patient with alpha-1 antitrypsin deficiency. The PAS with diastase stain shows the diastase-resistant pink globules that are characteristic of this disease" by Jerad M Gardner, MD. License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

Treatment and Prevention

The definitive treatment for alpha-1 antitrypsin deficiency, especially for advanced cases, is **liver transplantation**. For milder forms or in the early stages of the disease, supportive treatment is indicated.

Oxidative stress to the hepatocytes and bile stasis can be prevented by **administering vitamin E and ursodeoxycholic acid**, respectively. However, studies have shown that these 2 treatments do not exhibit efficacy for their indications. Other treatments such as gene therapy and the use of pharmacologic chaperones are also being developed.

Health education plays an important role in the treatment regimen for alpha-1 antitrypsin deficiency. It should be emphasized to patients with the disease that smoking will aggravate their condition and can cause fatal consequences. Vaccination against influenza, pneumococcus, and hepatitis A and B are also indicated to reduce the progression of the disease.

When lungs are the predominantly affected organ, replacement therapy with plasma containing alpha-1 antitrypsin is usually indicated. Lung transplantation may also be indicated in these cases, especially in patients with advanced lung involvement.

Complications and Prognosis

Usually, liver involvement in alpha-1 antitrypsin deficiency progresses slowly but can be accelerated in the presence of comorbidities and infections. Manifestations develop into severe forms, much like those seen in other chronic liver diseases. Other complications include **severe bleeding**, especially among newborns, and **malnutrition** as a result of poor food intake and malabsorption brought about by cholestasis.

As not all individuals with the homozygous gene variant present with signs and symptoms, it is important to understand that patients with alpha-1 antitrypsin gene variants may continue to live without any liver-related complications. In advanced cases, liver transplantations have demonstrated favorable results.

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