

# Alpha-1-Antitrypsin Deficiency: Diagnosis, Pathophysiology, and Management

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Alpha-1-antitrypsin deficiency is a relatively common but under-recognized genetic disease in which individuals homozygous for the mutant Z disease-associated allele are at risk for the development of liver disease and emphysema. The protein product of the mutant Z gene is synthesized in hepatocytes but accumulates intracellularly rather than being appropriately secreted. The downstream effects of the intracellular accumulation of the mutant Z protein include the formation of unique protein polymers, activation of autophagy, mitochondrial injury, endoplasmic reticulum stress, and caspase activation, which subsequently progress in a cascade, causing chronic hepatocellular injury. The variable clinical presentations among affected individuals suggest an important contribution of genetic and environmental disease modifiers, which are only now being identified. The heterozygous carrier state for the mutant Z gene, found in 1.5% to 3% of the population, is not itself a common cause of liver injury but may be a modifier gene for other liver diseases.

## Introduction

Alpha-1-antitrypsin ( $\alpha$ 1AT) is a glycoprotein primarily synthesized in the liver and secreted into the serum, where its function is to inhibit nonspecific, neutrophil protease-induced host tissue damage [1,2•]. It is second only to albumin in total grams per day of a single protein synthesized in the liver and in abundance in serum. Homozygosity for the autosomal codominant Z mutant allele of  $\alpha$ 1AT ("PIZZ" in World Health Organization [WHO] nomenclature) represents the classical form of  $\alpha$ 1AT deficiency [3]. The protein product of the mutant

Z gene accumulates within hepatocytes rather than being efficiently secreted. PIZZ adults have a markedly increased risk of developing emphysema by a loss-of-function mechanism in which reduced levels of circulating  $\alpha$ 1AT are available in the lung to inhibit connective tissue breakdown. A subgroup of PIZZ homozygous children and adults may also develop liver disease and hepatocellular carcinoma by a gain-of-function mechanism whereby intracellular accumulation of  $\alpha$ 1AT mutant Z protein damages hepatocytes.

## Presentation and Natural History

The presentation of patients with PIZZ  $\alpha$ 1AT deficiency can be highly varied, ranging from chronic liver disease to fulminant hepatic failure to adult emphysema [1,2•]. In infancy, the typical presentation is one of neonatal cholestasis (neonatal hepatitis syndrome), and infants, toddlers, and older children may have the symptoms and signs of jaundice, abdominal distention, pruritis, poor feeding, poor weight gain, hepatomegaly, and splenomegaly [4,5]. Some older children come to medical attention only when asymptomatic hepatomegaly or splenomegaly are detected during routine check-ups. Many children appear to be completely healthy, without evidence of liver injury, except for mild and usually clinically insignificant elevations of serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT). PIZZ individuals generally do not develop clinically detectable emphysema in childhood, although they may be at increased risk for childhood asthma [1,6–8]. Laboratory evaluation may reveal elevated total and conjugated bilirubin, elevated serum AST and ALT, hypoalbuminemia, or in some infants a vitamin K deficient coagulopathy. Population-based studies indicate that 80% of PIZZ patients presenting with neonatal cholestasis are healthy and free of chronic disease by the age of 18 years [9]. These data also suggest that the overall risk of life-threatening liver disease in childhood may be as low as 3%, but that the risk of varying degrees of liver dysfunction in children may range from 15% to 60% [4].

There are few unbiased prospective data on the incidence or the rate of progression of significant liver injury

in PIZZ adults, although many authorities believe the development of life-threatening disease to be uncommon in the young and middle adult years [9,10•]. Liver disease in adults may present as chronic hepatitis, with or without cirrhosis, and the risk of clinically significant disease may increase with advancing age, as shown by recent and extensive autopsy studies [10•]. These data suggest that often clinically unapparent but histologically significant liver injury and cirrhosis may be present in 30% to 40% of elderly PIZZ adults [10•]. The biochemical and histopathologic findings may be similar to those of adult alcoholic liver disease, which may lead to diagnostic confusion. There is likely also an increased risk of hepatocellular carcinoma of unknown magnitude in PIZZ adults.

Liver biopsy findings may be highly variable, including giant cell transformation, bile duct paucity, or bile duct proliferation in infants, and lobular hepatitis, significant steatosis, fibrosis, and hepatocellular necrosis in infants, older children, or adults [1,11]. Globular, eosinophilic inclusions in some but not all hepatocytes under conventional hematoxylin and eosin stain are usually seen, which represent dilated endoplasmic reticulum (ER) membranes engorged with polymerized  $\alpha$ 1AT mutant Z protein [12]. Staining with periodic acid-Schiff (PAS) followed by digestion with diastase, a technique that labels glycoproteins red, is used to highlight the red, "PAS-positive" globules. Examination of liver biopsies for PAS-positive globules should be done with caution because similar structures have been described in other liver diseases, the globules are not present in all hepatocytes, and they are occasionally absent in very young infants [1]. Given the highly variable disease course observed between patients with the same genotype in what has been viewed traditionally as a "single gene defect" disease, it has been widely hypothesized that there must be important genetic and environmental disease modifiers involved in the pathophysiology of this condition. A variety of research studies are beginning to map the specific steps in the pathophysiology of this disease and to identify some of the modulating factors.

### Genetics and Pathophysiology

Classical PIZZ  $\alpha$ 1AT deficiency is caused by homozygosity for a point mutation at position 342 in the *a1AT* gene encoding the substitution of lysine for glutamate, although nearly 100 other, less common mutations have been described. The 12.2-kb gene is located on chromosome 14q and encodes a 55-kD product of 95 amino acids [2•]. PIZZ homozygotes are found at a frequency of 1 in 1500 to 3500 in North American and European populations, indicating a frequency of PIMZ carriers of approximately 1.5% to 3%, which is widely underappreciated [2•]. Recent data suggest that only 10% of the estimated 100,000 PIZZ individuals in the United States have been identified.

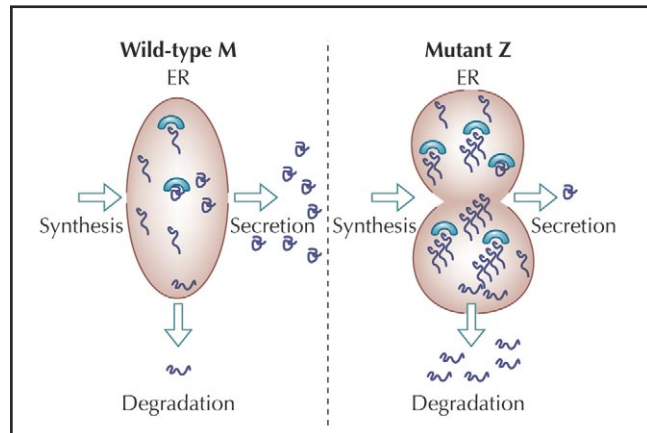
Alpha-1-antitrypsin is primarily synthesized in the liver but is also found in other tissues, including enterocytes and leukocytes [13]. The critical step in the pathophysiology of  $\alpha$ 1AT deficiency is retention of the newly synthesized mutant Z protein molecule within the ER of hepatocytes (Fig. 1) [14,15,16•]. During biosynthesis, the nascent mutant Z polypeptide chain is appropriately assembled on the ribosome and translocated into the ER lumen. However, in the ER the mutant Z protein molecule folds slowly and inefficiently into its final, secretion-competent conformation and may attain a variety of abnormal conformations, including a unique state in which multiple molecules aggregate to form large polymers [17,18]. A system of proteins within the ER, termed the "quality control" apparatus, recognizes these mutant Z molecules as abnormal and directs them to a series of proteolytic mechanisms rather than allowing progression down the secretory pathway [19–21,22•]. The result of these processes is significantly "deficient," approximately 15% of the normal serum level of  $\alpha$ 1AT. Accumulation of the retained mutant Z protein molecules within hepatocytes appears to cause liver injury [1,23•]. A small proportion of the retained molecules may remain in the polymerized conformation and accumulate as aggregates within dilated areas of ER. These accumulations may become so large that they are visible by light microscopy as the globules classically described within hepatocytes in this disease [12].

The exact mechanistic role of the polymerized conformation of  $\alpha$ 1AT mutant Z in the pathophysiology of this disease is controversial and still being investigated [16•,24]. The presence of the Z mutation in the  $\alpha$ 1AT molecule allows the protruding reactive site loop of one molecule to insert into a groove in the  $\beta$  sheet of a neighboring molecule. A conformational change then occurs, tightly binding the molecules together in the absence of covalent bonds. Long chains of  $\alpha$ 1AT mutant Z protein polymers are formed in this way, and physical-chemical studies suggest that this conformation is extremely stable and long-lived in biologic systems. Most authorities credit the formation of the polymerized conformation as the key mechanistic step in the intracellular retention of the molecule, although not all mutagenesis studies of the  $\alpha$ 1AT mutant Z molecule that disrupt the polymerized conformation have been shown to inhibit intracellular retention [25–27]. A series of detailed ongoing studies are documenting the complex series of conformations attained by the mutant Z molecule as it folds in the ER, and how chaperone binding and other actions during this process affect ER retention, secretion, protein degradation, and the pathophysiology of this so-called conformational disease [22•,28,29]. It has been suggested that manipulation of the enzymes responsible for quality control and degradation could be a useful therapeutic strategy in this disease. Therefore, investigation is proceeding into whether it is the actions of the cellular

quality control apparatus, the effect of the polymerized conformation, or both that causes intracellular retention of the molecule within hepatocytes.

Another series of new studies have greatly contributed to the understanding of the downstream mechanism(s) of hepatocellular injury resulting from  $\alpha$ 1AT mutant Z intracellular protein retention (Fig. 2). Multiple intracellular pathways are activated in response to the accumulation of the mutant protein within the ER [1,20,21,22•,23•,30–33]. These responses include activation of autophagy, ER stress pathways, and apoptosis. Autophagy is a highly conserved cellular function in which targets destined for proteolytic degradation, including senescent organelles such as mitochondria and cytoplasmic debris, are directed into a unique vacuolar degradation system during development, stress, or nutrient deprivation. Autophagy may be one mechanism for the intracellular disposal of the accumulated  $\alpha$ 1AT mutant Z protein. Studies have suggested that stimulation of hepatocellular autophagy may lead to damage to mitochondria as one mechanism for hepatocellular death in  $\alpha$ 1AT deficiency [23•]. There is also evidence for  $\alpha$ 1AT mutant Z protein-specific damage to mitochondria that does not involve autophagy, and for possible activation of apoptosis, which may also play a role in the hepatocellular death in  $\alpha$ 1AT deficiency [23•,30]. It is proposed that the chronic burden of hepatocellular death, whether from mitochondrial injury, apoptosis, or other mechanisms over time, leads to organ injury and cirrhosis in this chronic metabolic liver disease. Studies using models of  $\alpha$ 1AT Z liver injury have also been able to identify putative disease modifiers that might affect these pathways, including specific proteins involved in the degradation machinery, nutrient deprivation, sex hormones, and inflammation [23•,30,33,34]. Ongoing studies are examining the specific mechanistic steps in these processes, and how new treatments might be developed based on interruption of this injury cascade [23•]. Furthermore, newly developed biochemical methods to quantify the amount of  $\alpha$ 1AT mutant Z protein existing specifically in the polymerized conformation, within a human or animal liver, will for the first time allow direct quantitative examination of the relationship between polymer accumulation and liver injury [12]. Future studies may be able to identify a “dose effect” of  $\alpha$ 1AT mutant Z polymer accumulation and measure the efficacy of “anti-polymer” therapeutic strategies.

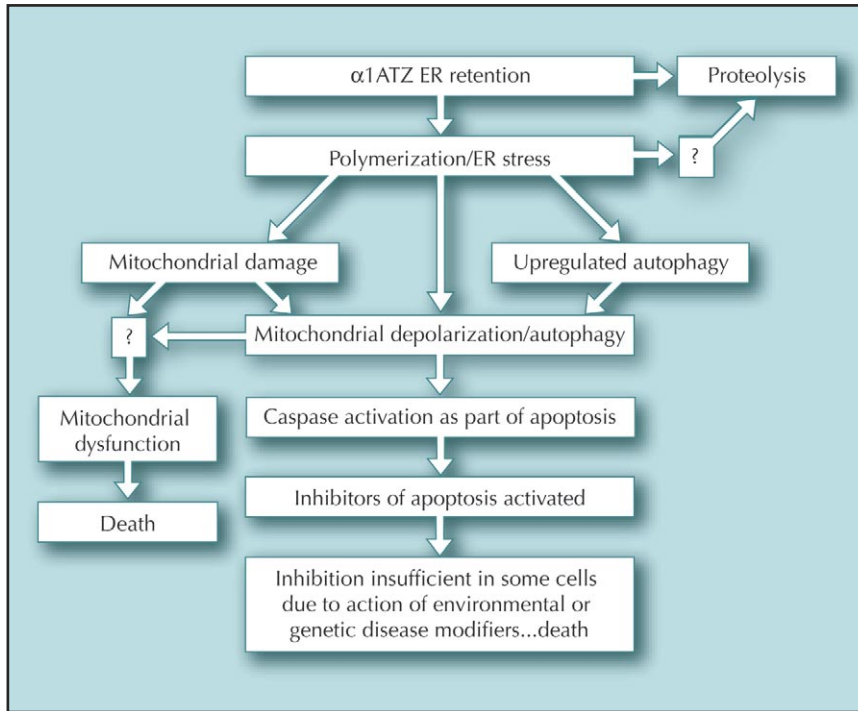
Several intracellular pathways have been described that are activated in response to “ER stress,” which is usually defined as accumulation of unfolded or misfolded proteins in the ER or inhibition of protein progression out of the ER down the secretory pathway. Although  $\alpha$ 1AT deficiency would seem an ideal candidate for a disease related to ER stress, in fact, the chronic nature of the mutant Z protein accumulation may modulate ER stress pathways in unpredicted ways. These pathways are likely



**Figure 1.** A conceptual model of  $\alpha$ 1AT mutant Z protein endoplasmic reticulum (ER) retention in  $\alpha$ 1AT deficiency is depicted. During the biosynthesis of the normal, wild-type M,  $\alpha$ 1AT, the nascent polypeptide chain (shown as long wavy lines) enters the ER lumen and binds with chaperone proteins (dark semicircles), which assist in folding into the final, secretion-competent conformation (compact knot). Some molecules do not fold appropriately and are directed to proteolytic degradation pathways. However, during biosynthesis of the  $\alpha$ 1AT mutant Z the nascent polypeptide in the ER lumen folds inefficiently, and very few molecules achieve a secretion-competent conformation. Some of the molecules polymerize and some are directed to degradation pathways. The accumulation of the  $\alpha$ 1AT mutant Z molecules within the ER deforms the ER architecture, leading to ER stress and triggering cell injury.

best suited to respond to acute stress and may be maladaptive or injurious if constantly active. Many studies are ongoing in this area, and some new data indicate that the best defined of the ER stress responses, the unfolded protein response (UPR), is not induced solely by the chronic retention of  $\alpha$ 1AT mutant Z protein in the ER. Rather, chronic retention of  $\alpha$ 1AT mutant Z protein appears to “prime” the UPR, making it more susceptible to activation by a second stimulus [22•,24,32]. This phenomenon may be an attractive cell biologic correlate to the clinical observation that many PIZZ individuals, even those with some degree of liver injury, often remain stable for many years before undergoing an episode of decompensation that, anecdotally, may be accompanied by an acute illness or inflammatory stress.

A series of studies have also examined the role of the proteasome and other proteolytic systems in explaining the considerable variability observed in the severity of liver disease among individual patients with  $\alpha$ 1AT deficiency. Some PIZZ individuals appear to be protected from liver disease because the quality control apparatus of the ER ensures relatively efficient degradation of the accumulated  $\alpha$ 1AT mutant Z protein [14,35]. However, in patients “susceptible” to liver injury subtle alterations in the quality control apparatus of the ER result in inefficient degradation of accumulated  $\alpha$ 1AT mutant Z protein, presumably a greater net burden in the ER and an increased potential for liver injury. Several genes and gene



**Figure 2.** The hypothetical hepatocellular injury pathway in PIZZ  $\alpha$ 1AT deficiency is depicted. The  $\alpha$ 1AT mutant Z protein is appropriately synthesized but then retained in the endoplasmic reticulum (ER) of hepatocytes rather than being secreted. “Quality control” processes within the cells direct most of the mutant Z protein molecules into intracellular proteolysis pathways. However, some of the mutant Z protein molecules escape proteolysis and may attain a unique, polymerized conformation, forming inclusions in the ER. This results in activation of a variety of cellular responses. Autophagy may be upregulated, resulting in damage to mitochondria; mitochondria may be damaged directly or may be involved in activation of caspases and the intrinsic pathway of apoptosis. Hepatocellular death may result from mitochondrial dysfunction or from an uninhibited apoptotic cascade. Given the variable nature of clinical liver injury between individuals with the same genotype, and the usually slow disease progression, there are likely to be important environmental and genetic disease modifiers affecting the rate and magnitude of hepatocellular death.

products critical to these processes have been identified within hepatocytes [15,19,22•,34,36]. Recent studies have also shown that the carbohydrate side-chains attached to the nascent polypeptide in the ER, and the enzymes that mediate the reactions, are critical to chaperone binding and to directing an abnormal molecule to a degradation pathway rather than allowing accumulation.

## Diagnosis

The gold standard for the diagnosis of  $\alpha$ 1AT deficiency is the phenotype (PI or PI-type) of the  $\alpha$ 1AT protein present in a sample of the patient’s serum as determined by isoelectric focusing gel electrophoresis [2•]. Although many different phenotype band patterns have been documented, the normal wild-type M and the mutants Z and S are by far the most common. If only the PI type Z band is present in the gel, it is usually inferred that the patient is carrying two copies of the mutant Z *a1AT* gene, whereas a heterozygote would have a combination of normal, wild-type M, and mutant Z protein bands (discussed further in following text). The phenotype gel analysis is technically demanding and is therefore best performed in a reference laboratory with experienced staff. Because the presentations of  $\alpha$ 1AT deficiency are quite variable, requests for serum phenotype testing from a reference facility are indicated in a wide variety of clinical situations (Table 1) [1,2•]. Measurement of the level of  $\alpha$ 1AT in peripheral blood can be used as a complementary test to compare the phenotype result against what would be an appropriate predicted level (Table 2) and to assist in the elucidation of unusual

alleles the protein products of which yield confusing phenotype results [37,38]. Liver biopsy is not required for the diagnosis of  $\alpha$ 1AT deficiency, although it is used in some cases to evaluate disease progression or to investigate the contribution of comorbid states. More recently, new commercial (LabCorp, Burlington, NC) and research tests have become available based on analysis of genomic DNA obtained from blood leukocytes, buccal mucosa, and other sources, although these tests usually detect only the most common S and Z mutant alleles [39]. Families of affected individuals should be offered optional testing in the context of appropriate education and genetic counseling. Prenatal diagnosis by amniocentesis or chorionic villus sampling can also be performed.

## Management

There is no specific treatment for the liver disease associated with  $\alpha$ 1AT deficiency. Management focuses on preventing the complications of chronic liver disease, such as bleeding, ascites, pruritis, malnutrition, fat-soluble vitamin deficiency, infection, and growth disturbances, or attenuating the systemic repercussions if they do occur [1]. Many patients have normal health and can be monitored conservatively with infrequent visits to a physician knowledgeable in liver disease. Some experienced clinicians use routine but infrequent hepatic imaging out of concern for the increased risk of hepatic carcinogenesis. However, some patients with significant degrees of liver injury, and even cirrhosis, often remain stable for many years with very little intervention. If life-threatening

**Table 1. Clinical presentation and indications for testing for alpha-1-antitrypsin deficiency**

Infant	Cholestatic jaundice
Child	Unexplained failure to thrive or poor feeding
Any age	Unexplained, asymptomatic hepatomegaly or elevated AST/ALT
Any age	Unexplained liver disease, cirrhosis, or hepatocellular carcinoma
Adult	Severe asthma, any emphysema in patients under age 50 years or at any age in nonsmokers

ALT—alanine aminotransferase; AST—aspartate aminotransferase.

liver disease does develop, liver transplantation is commonly employed with excellent published success rates. All pediatric and adult patients with  $\alpha$ 1AT deficiency should be urgently cautioned against personal smoking, secondhand smoke, and environmental lung exposures. Prospective studies indicate that identification of  $\alpha$ 1AT-deficient patients as children dramatically reduces their incidence of smoking as adults and therefore decreases morbidity and mortality from lung disease [40,41]. Exogenous  $\alpha$ 1AT protein replacement is available as a treatment for the adult emphysema associated with  $\alpha$ 1AT deficiency, although replacement has no effect on the development of liver disease because liver injury is not related to a lack of circulating anti-protease activity [2•]. Experimental therapies, including the use of so-called chemical chaperones such as 4-phenylbutyrate, hepatocyte transplantation, and gene therapy strategies, are being investigated but have not yet been shown to be clinically useful [1,42,43].

### Heterozygosity and Other Alleles

Individuals who are heterozygous for  $\alpha$ 1AT, carrying one normal M allele and one mutant Z allele (“PIMZ” or “MZ”) make up 1.5% to 3% of North American and European populations and are generally considered asymptomatic and healthy. However, data from referral center studies with significant selection bias suggest that there is an over-representation of PIMZ individuals (4%–15% vs the expected 1.5%–3%) in adult hepatology practices with cryptogenic cirrhosis and other chronic liver lesions. Inconsistent associations between PIMZ and hepatitis B, hepatitis C, and other conditions are described in some of these series [2•,44–50]. Many of these patients exhibit the PAS-positive hepatocellular inclusions on liver biopsy as seen in PIZZ patients. It is still unclear if there are rare PIMZ individuals who develop a primary liver injury related to their PIMZ status alone, or whether heterozygosity for the Z gene is acting as a disease modifier for alcohol, viral hepatitis, hemochromatosis, or some as yet unidentified hepatotoxin. There are reports of PIMZ

**Table 2. Alpha-1-antitrypsin phenotypes and corresponding typical alpha-1-antitrypsin serum levels**

Phenotype	Level, $\mu$ M*
PIMM	20–48
PIMZ	12–35
PISS	15–33
PISZ	8–19
PIZZ	2.5–7.0
Null-Null	0

\*Convert micromolar to mg/dL by multiplying by conversion factor of 5.2.

individuals developing liver injury who did not have PAS-positive globules identified on biopsies obtained early in their course but who had globules identified later [51]. This raises the question as to whether globules in a PIMZ liver are a marker for primary  $\alpha$ 1AT Z protein-related disease, or if a liver damaged by another cause then has difficulty coping with even the small “dose” of  $\alpha$ 1AT mutant Z protein synthesized and degraded within a PIMZ hepatocyte, which then forms a globule as a secondary marker of injury. In any case, PIMZ status is not readily accepted as the primary cause of otherwise unexplained liver injury without significant further investigation. The high prevalence of PIMZ carrier status in the population suggests that carrier status will commonly be found associated with other conditions by chance alone [2•,46–48].

Individuals have been described who are compound heterozygotes for the S and the Z alleles of  $\alpha$ 1AT (PISZ) and who have developed liver disease identical to that of PIZZ patients, including PAS-positive, diastase-resistant globules. Physical-chemical studies have shown that the  $\alpha$ 1AT mutant S protein is retained within hepatocytes and can heteropolymerize intracellularly when coexpressed with the mutant Z protein, which may give a pathophysiologic basis for the occurrence of liver injury in PISZ patients when liver disease is notably absent in PISS individuals [35,52]. PISZ individuals may also be at risk for adult emphysema. Nearly 100 other mutations have been described in the  $\alpha$ 1AT gene, some of which yield a normal M phenotype result but when present in the heterozygous state with a Z allele can accumulate within the liver and have been associated with liver disease [2•,38]. Such patients are usually recognized by a significantly lower  $\alpha$ 1AT level in peripheral blood than that predicted by the phenotype result.

### Conclusions

Alpha-1-antitrypsin deficiency is an underdiagnosed genetic disease with highly variable clinical presentations and variable disease severity. New studies of the cell biological consequences of the intracellular accumulation

and polymerization of the  $\alpha$ 1AT mutant Z protein are beginning to elucidate the specific mechanism of liver cell injury and the genetic and environmental factors that modulate this injury. As studies continue, especially toward an improved understanding of the role of the polymerized conformation of the Z protein in the injury cascade and the mechanisms involved in activating autophagy and mitochondrial injury, new highly focused and rational treatment approaches can be developed.

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