Alpha1-Antitrypsin Deficiency

A Cause of Chronic Liver Disease

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KEYWORDS

• Alpha1-antitrypsin • Cirrhosis • *SERPINA1*

KEY POINTS

- Alpha1-antitrypsin deficiency (A1ATD) is a genetic disorder that can cause liver and lung disease that can present at any age but follows a bimodal age distribution.
- A1ATD seems to be more common than other liver diseases, such as autoimmune hepatitis or Wilson disease, but is still under-recognized.
- A1ATD has multiple alleles but the most important disease-causing genotypes are PI*ZZ and PI*SZ.
- Diagnosis of A1ATD requires measuring serum levels and the phenotype or genotype, although serum levels may be influenced by many factors and are therefore insufficient for diagnosis.
- Although no medical therapy for A1ATD-related liver disease is currently available, monitoring for complications of liver disease can be useful so diagnosis is critical.

INTRODUCTION

Alpha1-antitrypsin (A1AT) is a serum glycoprotein, encoded by the gene *SERPINA1*, that belongs to a family of proteins known as serine protease inhibitors, or serpins.[1] The major function of A1AT is to inhibit serine proteases secreted by neutrophils, such as neutrophil elastase, usually in response to inflammation.[1] The protein is produced in many cell types but principally in hepatocytes and then released into circulation where it performs its inhibitory function primarily in the blood and lungs.[1,2] A1AT deficiency (A1ATD) can lead to a constellation of disease states, with lung and liver disease being the most common.[1,2]

A1ATD is a genetic disorder caused by mutations in *SERPINA1* that lead to deficiency in the circulating levels of A1AT.[3] The decreased level of A1AT leads to unopposed proteolytic degradation of lung tissue and can cause emphysema and chronic

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bronchitis.[1] In contrast, the accumulation of abnormal A1AT polymers in hepatocytes is the key feature associated with the development of liver disease.[2] The development of liver disease seems to be independent of lung disease.[2] A1ATD-linked chronic liver disease is a frequently unrecognized and underdiagnosed cause of chronic liver disease.[1–4] The focus of this article is to aid gastroenterologists in the diagnosis and management of A1ATD-linked chronic liver disease.

GENETICS OF ALPHA1-ANTITRYPSIN DEFICIENCY

Genotypes and Phenotypes of Alpha1-Antitrypsin Deficiency

The gene *SERPINA1* is located on the long arm of chromosome 14 and is highly polymorphic with more than 100 germ-line mutations identified.[2,3,5] Despite the diversified nature of *SERPINA1*, the phenotypic expression of A1AT is generally in 4 different groups: normal, decreased, dysfunctional, or null variants based on circulating levels of A1AT.[2,6] The null phenotypic variant is associated with severe lung disease but not liver disease, because this variant is linked to an absence of A1AT, not just a deficiency,[2] because abnormal polymerization and accumulation of mutant A1AT is necessary to develop A1ATD-linked liver disease, which is absent in null phenotypic variants.[2,3,5,7] The dysfunctional variant has also not been associated with liver disease because, again, this variant does not seem to cause intrahepatic accumulation.[6] Therefore, A1ATD-linked liver disease has been mostly described in the decreased phenotypic variant.[2,3]

SERPINA1 is inherited in an autosomal codominant pattern, meaning that each allele plays a role in determining the final circulating levels of the protein.[3] The standard nomenclature used to describe the genotype and phenotype is denoted with the abbreviation PI (protease inhibitor), followed by the 2 alleles (ie, PI*MM). The normal wild-type allele is denominated with the letter M and the most common alleles associated with A1ATD are designated Z and S.[2] Most A1ATD-linked liver disease is seen in patients who are homozygous for the Z allele, or PI*ZZ.[1–3,5] The compound heterozygote phenotype, PI*SZ, is also implicated in A1ATD liver disease, although it is far less common.[7,8] There have been several other phenotypes associated with liver disease (**Table 1**), but these are notably rare.[7]

Compound Heterozygotes Without Alpha1-Antitrypsin Deficiency

Another phenomenon that has been well described is the association of the Z allele as a risk factor for progression of liver disease in patients with preexisting cirrhosis.[9–11] The phenotypes PI*MZ and PI*SZ are known to have decreased levels of A1AT, roughly 55% of normal and 40% of normal respectively, but may not be below the threshold used to diagnose A1ATD and therefore are not always associated with liver or lung disease.[12] Prior research seemed to show a link between heterozygosity of the Z allele increasing the risk for development of chronic liver disease,[9] but this was not borne out in follow-up studies.[10,11] Even so, data indicate that, in patients with

Table 1
Alleles associated with alpha-1 antitrypsin deficiency

Most common disease alleles[2,7]	Z[a], S[b]
Rare disease alleles[c]	M_{malton},[53] Siiyama,[54] King[55]

[a] The genotype/phenotype PI*ZZ accounts for roughly 95% of A1ATD.
[b] The genotype/phenotype PI*SZ accounts for roughly 4% of A1ATD.
[c] Rare phenotypes account for less than 1% of A1ATD.

cirrhosis from other causes, the Z allele seemed to increase the risk of liver disease progression.[10,11] A recent study conducted by Schaefer and colleagues[11] showed that patients with cirrhosis of any cause and with the PI*MZ phenotype had higher model for end-stage of liver disease (MELD) scores, were more likely to have decompensating events, and had higher rates of liver transplant or death. The implication of the Z allele in causing progression of liver disease is not entirely understood.[11] Furthermore, whether these data should lead to screening for the A1AT phenotype in patients with cirrhosis is unclear and not addressed by major guidelines.[1,12]

EPIDEMIOLOGY OF ALPHA1-ANTITRYPSIN DEFICIENCY

Prevalence of Select Alleles and Phenotypes

Data on the frequency of the myriad rare alleles are not readily available; however, several epidemiologic studies have examined the most common disease-causing alleles, Z and S, and the phenotypes PI*ZZ and PI*SZ.[13,14] Blanco and colleagues[13] compiled data from 93 countries to show that the frequency of the Z allele seems highest in countries with large white populations. More importantly, the prevalence of the PI*ZZ phenotype was noted to be from 1:2000 to 1:5000 in areas with the highest frequency of Z alleles.[13] For context, the PI*ZZ phenotype is significantly more common than other causes of liver disease, such as Wilson disease, which is noted to be close to 1:30,000 to 1:100,000,[15] or autoimmune hepatitis, with a prevalence of 1:5900 to 1:9100.[16] Furthermore, the PI*SZ phenotype seems to be even more common and not only includes white populations but also seems to include a Hispanic population, with prevalence data suggesting from 1:700 to 1:3000 have this phenotype in areas of highest allelic frequency.[14] Despite having phenotypes associated with disease, only a small proportion of patients develop chronic liver disease that can occur at any age.[2,3]

Neonatal and Pediatric Alpha1-Antitrypsin Deficiency

A1ATD-linked liver disease can present at any age and is the most common presentation in neonatal and pediatric populations because lung disease takes decades to develop.[17] Even so, not all children who have a disease-associated phenotype develop liver disease.[17] For example, a study in Sweden that identified children at birth with a phenotype that could result in A1ATD were followed up to 6 months, and liver abnormalities occurred in up to 50% of these children.[18] The liver abnormalities were variable, and ranged from mild increases in transaminase levels to neonatal jaundice up to and including significant portal hypertension and cirrhosis requiring pediatric liver transplant.[18] This same cohort was followed until age 12 years and most of the liver abnormalities among patients without cirrhosis resolved, and the overall risk of fibrosis and cirrhosis was noted to be only 2% to 3%.[19] A recent systematic review also suggested that cirrhosis develops in fewer than 10% of pediatric patients (0–18 years old) despite having an abnormal phenotype associated with A1ATD.[20] The most notable risk factors for progression of liver disease in the pediatric population were increased aspartate transaminase level, persistent or recurrent jaundice, and increased gamma-glutamyltransferase level.[20]

Adult Alpha1-Antitrypsin Deficiency

The prevalence of chronic liver disease in adults seems to mirror the prevalence in the pediatric population.[20,21] The systematic review done in children was also performed in adults and similarly noted that roughly 10% of adults with a phenotype associated with A1ATD developed complications of liver disease.[20] A newly released retrospective, longitudinal study conducted in Sweden by Tanash and Piitulainen[21] also

supported this conclusion.[21] The study included more than 1500 adult patients with the PI*ZZ phenotype and found that 7% had developed cirrhosis and an additional 2% had developed hepatocellular carcinoma (HCC) over a mean follow-up of 12 years.

Risk factors for progression of liver disease in adults varied from the pediatric population.[20] The most consistent risk factors found in the review were male gender and increased body mass index.[20,22] The study by Tanash and Piitulainen[21] concurred that male gender was a risk factor for progression but also noted that age greater than 50 years and diabetes also increased the risk. This finding suggests that A1ATD-linked chronic liver disease has an aggressive and an indolent form that can appear very early in age or much later in life and is consistent with a large body of evidence that shows A1ATD has a bimodal age distribution.[20]

PATHOPHYSIOLOGY

Polymerization and Accumulation of Alpha1-Antitrypsin Deficiency

As noted earlier, the polymerization of the mutant A1AT protein is necessary for development of liver disease, whereas the absence of the protein leads to lung disease.[1–3] To form polymers, the abnormal genes first make a normal nascent protein that then is translocated to the endoplasmic reticulum (ER).[2,3] In the ER, the mutant protein, especially in the case of the Z alleles, takes longer to fold properly compared with the normal M allele[2,3] (**Fig. 1**). The inefficiently folded protein is detected by the

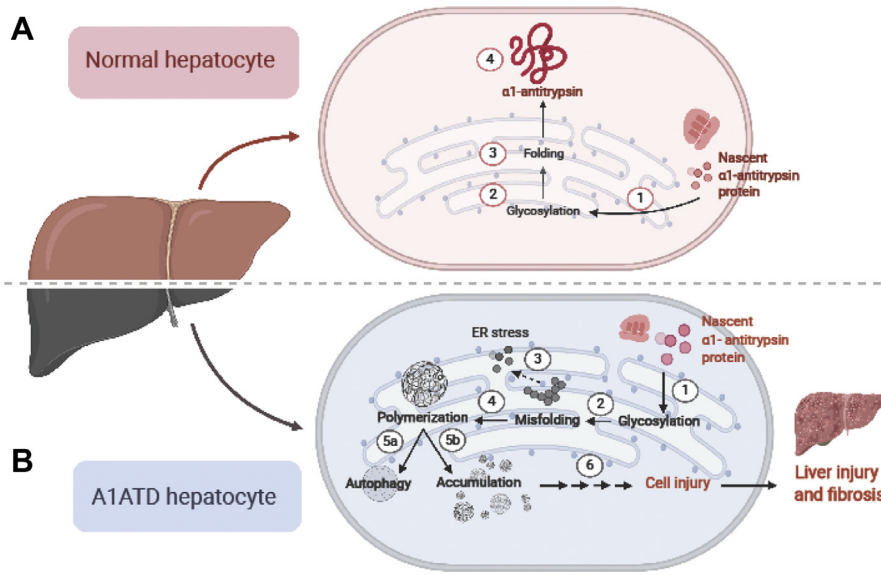

Fig. 1. Mechanism of liver injury in A1ATD. (*A*) The normal folding of the A1AT protein in the ER from (1) transport of nascent polypeptide to the ER, (2) glycosylation of the protein and entry into the ER, (3) normal folding, (4) transport of the protein out of the cell. (*B*) The abnormal nascent protein is (1) transported to the ER and (2) glycosylated. The protein undergoes abnormal folding leading to (3) ER stress and proteolytic degradation or (4) polymerization of multiple misfolded proteins. These proteins can either be further degraded by (5a) autophagy and other cellular mechanisms or (5b) continue to accumulate. The accumulation eventually leads to (6) cell injury and, thus, liver injury, fibrosis, and ultimately cirrhosis.

hepatocyte and is usually targeted for degradation, but some of the proteins escape this degradation by forming thermodynamically stable polymers with other mutant proteins.[23–25] These stable polymers can continue to accumulate and form characteristic globules that can be stained and seen under light microscopy[3] (**Fig. 2**). Other cell types can also produce the mutant A1AT and undergo the same pathophysiology as in hepatocytes, but the level of production is too low for these intracellular polymers to be seen.[26]

Rough Endoplasmic Reticulum Stress, Proteolytic Degradation, and Autophagy

The accumulation of inefficiently folded proteins and protein polymers within the ER causes ER stress.[2] The presence of ER stress activates a series of proteolytic degradation pathways[27–31] (**Fig. 1**). These pathways break down nonpolymerized mutant proteins and attempt to degrade the polymerized proteins, but not as adeptly, and variation in the efficiency of these multiple pathways is thought to be one reason for hepatocellular injury.[27,32] Another proteolytic pathway is a process known as autophagy.[33] This process involves specialized vacuoles that degrade abnormal proteins and larger structures, including large polymers of abnormal A1AT.[33–35] Experimental murine models have found that inducing autophagy may be one approach to degrade large polymers and reduce the likelihood of hepatocellular injury.[33–35]

DIAGNOSIS OF ALPHA1-ANTITRYPSIN DEFICIENCY–LINKED LIVER DISEASE

Under-Recognized Cause of Liver Disease

A1ATD is widely known to be under-recognized and underdiagnosed.[1–3,12,36] For example, the burden of A1ATD in the United States is estimated to be more than 70,000, and more than 250,000 people have the PI*ZZ and PI*SZ phenotypes, respectively.[13,14,37] Research indicates that fewer than 10% of the affected population have been diagnosed with A1ATD,[36] with the average delay in diagnosis being roughly 6 years.[38] These data are not specific to the United States and have mirrored research from other countries as well.[39]

Although it is not entirely clear why there is such a large gap in diagnosis, there are a few known problems. Awareness about A1ATD is increasing among providers but there are still several gaps in knowledge that can lead to under-recognition.[4] In addition, adherence to current guidelines may not be optimal.[39–41]

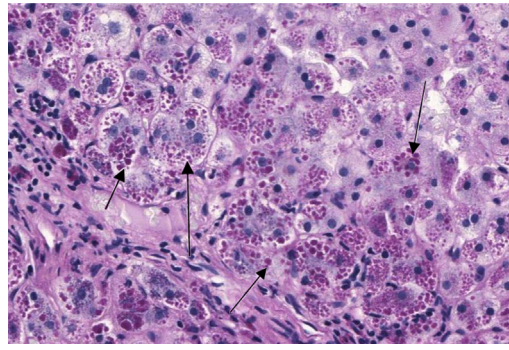

Fig. 2. Polymers of A1ATD in hepatocytes. Photomicrograph of a liver biopsy from a patient with A1ATD. The stain (*black arrows*) shows the diastase-resistant pink globules that are characteristic of this disease (periodic acid–Schiff with diastase, original magnification ×100). (*Courtesy of* Jerad M Gardner, MD.)

Screening

Current guidelines do not support screening for A1ATD in the pediatric population without overt signs of liver disease[1] because of a paucity of unbiased evidence.[1] Neonatal screening decreased long-term smoking rates in patients who tested positive for A1ATD.[42,43] Nevertheless, the cost-effectiveness of screening all newborns is unclear; therefore, it may be prudent to consider screening children who have persistent neonatal jaundice, other liver abnormalities, or parents who have been previously diagnosed with A1ATD.[17]

In adults, screening for A1ATD is supported by guidelines in all patients with unexplained increased aminotransferase levels or who have evidence of chronic liver disease.[1,12] The young adult population, between the ages of 18 and 40 years, generally do not manifest evidence of liver disease with A1ATD, but it may be useful to screen for A1ATD given that having a heterozygous phenotype with a Z allele seems to increase the risk of progression of preexisting liver disease.[10,11]

Diagnostic Studies

Diagnostic testing for A1ATD has evolved over the last few decades. Simply measuring A1AT levels is not sufficient to diagnose A1ATD.[1,12,44] A1AT is an acute phase reactant and circulating levels can vary dramatically based on genotype in acute illness.[1,44] Due to this variability, guidelines recommend adjunct testing for genotype or phenotype in addition to circulating levels.[1,44]

A routinely used test to identify the phenotype is isoelectric focusing.[12,44] This test uses speed of migration of the A1AT protein in gel electrophoresis to identify the different phenotypes.[44] Isoelectric focusing can identify the most common phenotypes, such as PI*MM or PI*ZZ, as well as some rarer phenotypes.[44] One limitation of this method is that certain rare deficient and null phenotypes have normal MM protein migration, giving discordant results, so clinical context is important when using this test.[44]

Genotyping of specific alleles can also be done using polymerase chain reaction. Because most A1ATD is seen in patients with the Z and S alleles, specific primers for these alleles have been developed for genotyping.[1] The main drawback of genotyping is the lack of primers for more rare phenotypes, although this will likely improve over time.[44] Whole-gene sequencing or expanded genotyping to test for known abnormal alleles is becoming more widely available, less expensive, and may become the standard of care for diagnosis in the future.[1,44]

Liver biopsy may also be a useful adjunct test for A1ATD, although this is not commonly recommended by guidelines.[1,12] The classic periodic acid–Schiff–positive and diastase-resistant granules of accumulated protein polymers (see **Fig. 2**) are not always seen on biopsy because of some of the granules being 1 μm or less.[12] Liver biopsy may be best used to rule out other causes of liver disease if there is uncertainty about the diagnosis.[45]

MANAGEMENT

Monitoring

Monitoring patients with A1ATD has proven benefits in patients with lung disease.[1,12,44] Its utility in patients without advanced liver disease is not well understood.[2] A study conducted by Tanash and colleagues[46] found that liver-related mortality in a Swedish population who were never-smokers was as high as 28% in adults. Most patients had passed away from complications of decompensated liver disease, with 38% having complications of HCC.[46] Of note, the rate of HCC in A1ATD is not increased compared with other causes of cirrhosis.[17,20,46] However, current

guidelines recommend monitoring laboratory tests and doing an ultrasonography scan annually given the high mortality associated with development of liver disease.[1,12] An additional benefit to monitoring patients with A1ATD is to prevent the development of another cause of liver disease. Vaccinating against hepatitis A and B, moderating alcohol consumption, and minimizing the risk of metabolic diseases are reasonable recommendations as well.[2]

Medical Therapies

At present, there are no approved medical therapies for the management of A1ATD-linked liver disease.[2,3] Several therapies are currently under investigation.[2,3] One pathway that shows promise is enhancement of cellular autophagy to degrade intracellular A1AT protein polymers.[33] In murine models, the antiepileptic medication carbamazepine has been shown to be effective in augmenting this process,[34,35] and a phase 2 clinical trial is currently underway to evaluate the effect of this medication in patients with severe A1ATD-linked liver disease.[47] Another therapy that has also shown promise uses small-interfering RNAs (siRNAs) to disrupt the transcription of messenger RNA generated from the *SERPINA1* gene leading to decreased levels of mutant proteins.[48] The caveat to this approach is that although it may help liver disease, it will continue to cause a deficiency of A1AT so it must be used in conjunction with other therapies to augment intravascular A1AT levels.[2]

Other potential targets include attempting to improve efficiency in folding of mutant proteins to prevent polymerization and trying to inhibit the polymerization process itself.[2] These targets are not as well studied and there is still more work needed to address the clinical application of these methods.[2]

Liver Transplant

In patients with cirrhosis and cirrhosis-related complications from A1ATD-linked liver disease, liver transplant is another potential option. Liver transplant in pediatrics for A1ATD is a common indication with excellent outcomes.[49] A 15-year follow-up study in 42 pediatric patients transplanted for A1ATD found survival to be more than 75%, which was notably better than liver transplant for biliary atresia in the same center.[49] Most deaths occurred within the first 6 months with infection, hemorrhage and graft failure being the most likely causes of death.[49]

Even in adults, liver transplant seems to have good outcomes for A1ATD-linked disease.[50] Transplant for A1ATD-linked cirrhosis accounts for only a small proportion of transplants, roughly 1%.[51] A retrospective study including 73 patients with A1ATD-linked cirrhosis from 1987 to 2012 conducted by Carey and colleagues[50] showed that the posttransplant outcomes at 1, 3, 5, and 10 years were 90%, 88%, 85%, and 78%, respectively. These results are on par with the most recent transplant outcomes for other causes of liver disease.[52] Some patients continued to have worsening lung function despite having a new liver that could produce normal A1AT.[50] The reasons for this are not yet fully understood but, overall, the use of liver transplant is a viable option for A1ATD-linked cirrhosis.

SUMMARY

A1ATD-linked liver disease is an under-recognized cause of chronic liver disease. It is hoped that improvements in education and awareness will improve diagnosis of this common disease. More work is necessary to recognize patients who are at risk earlier, especially because new and exciting therapies may be available in the near future for management of this disease.

DISCLOSURE

Nothing to disclose for V. Manne or K.V. Kowdley.

REFERENCES

1. Sandhaus RA, Turino G, Brantly ML, et al. The diagnosis and management of alpha-1 antitrypsin deficiency in the adult. Chronic Obstr Pulm Dis 2016;3(3):668–82.
2. Greene CM, Marciniak SJ, Teckman JH, et al. α1-antitrypsin deficiency. Nat Rev Dis Primers 2016;2:16051.
3. Teckman JH, Jain A. Advances in alpha-1 antitrypsin deficiency liver disease. Curr Gastroenterol Rep 2014;16(1):367.
4. Stoller JK, Brantly M. The challenge of detecting alpha-1 antitrypsin deficiency. COPD 2013;10(Suppl 1):26–34.
5. Blanco I, de Serres FJ, Carcaba V, et al. Alpha-1 antitrypsin deficiency PI*Z and PI*S gene frequency distribution using on maps of the world by an inverse distance weighting (IDW) multivariate interpolation method. Hepat Mon 2012;12(10 HCC):e7434.
6. Stoller JK, Aboussouan LS. A review of α1-antitrypsin deficiency. Am J Respir Crit Care Med 2012;185(3):246–59.
7. Gooptu B, Dickens JA, Lomas DA. The molecular and cellular pathology of α1-antitrypsin deficiency. Trends Mol Med 2014;20(2):116–27.
8. Mahadeva R, Chang WS, Dafforn TR, et al. Heteropolymerization of S, I, and Z alpha1-antitrypsin and liver cirrhosis. J Clin Invest 1999;103(7):999–1006.
9. Graziadei IW, Joseph JJ, Weisner RH, et al. Increased risk of chronic liver failure in adults with heterozygous alpha1-antitrypsin deficiency. Hepatology 1998;28:1058–63.
10. Regev A, Guaqueta C, Molina EG, et al. Does the heterozygous state of alpha-1 antitrypsin deficiency have a role in chronic liver disease? Interim results of a large case-control study. J Pediatr Gastroenterol Nutr 2006;43(Suppl 1):S30–5.
11. Schaefer B, Mandorfer M, Viveiros A, et al. Heterozygosity for the alpha1-antitrypsin Z allele in cirrhosis is associated with more advanced disease. Liver Transpl 2018;24(6):744–51.
12. American Thoracic Society, European Respiratory Society. American Thoracic Society/European Respiratory Society statement: standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. Am J Respir Crit Care Med 2003;168(7):818–900.
13. Blanco I, Bueno P, Diego I, et al. Alpha-1 antitrypsin PI*Z gene frequency and PI*ZZ genotype numbers worldwide: an update. Int J Chron Obstruct Pulmon Dis 2017;12:561–9.
14. Blanco I, Bueno P, Diego I, et al. Alpha-1 antitrypsin Pi*SZ genotype: estimated prevalence and number of SZ subjects worldwide. Int J Chron Obstruct Pulmon Dis 2017;12:1683–94.
15. Ala A, Walker AP, Ashkan K, et al. Wilson's disease. Lancet 2007;369(9559):397–408.
16. Heneghan MA, Yeoman AD, Verma S, et al. Autoimmune hepatitis. Lancet 2013;382(9902):1433–44.
17. Torres-Duran M, Lopez-Campos JL, Barrecheguren M, et al. Alpha-1 antitrypsin deficiency: outstanding questions and future directions. Orphanet J Rare Dis 2018;13(1):114.

18. Sveger T. Liver disease in alpha1-antitrypsin deficiency detected by screening of 200,000 infants. N Engl J Med 1976;294(24):1316–21.
19. Sveger T. The natural history of liver disease in alpha1-antitrypsin deficient children. Acta Paediatr Scand 1988;77(6):847–51.
20. Townsend SA, Edgar RG, Ellis PR, et al. Systematic review: the natural history of alpha-1 antitrypsin deficiency, and associated liver disease. Aliment Pharmacol Ther 2018;47(7):877–85.
21. Tanash HA, Piitulainen E. Liver disease in adults with severe alpha1-antitrypsin deficiency. J Gastroenterol 2019;54(6):541–8.
22. Bowlus CL, Willner I, Zern MA, et al. Factors associated with advanced liver disease in adults with alpha1-antitrypsin deficiency. Clin Gastroenterol Hepatol 2005;3(4):390–6.
23. Lomas DA, Evans DL, Finch JT, et al. The mechanism of Z alpha 1-antitrypsin accumulation in the liver. Nature 1992;357(6379):605–7.
24. Dafforn TR, Mahadeva R, Elliot PR, et al. A kinetic mechanism for the polymerization of alpha1-antitrypsin. J Biol Chem 1999;274(14):9548–55.
25. Lomas DA, Mahadeva R. Alpha1-antitrypsin polymerization and serpinopathies: pathobiology and prospects for therapy. J Clin Invest 2002;110(11):1585–90.
26. Van't Wout EF, Dickens JA, van Schadewijk A, et al. Increased ERK signaling molecules promotes inflammatory signaling in primary airway epithelial cell expressing Z α1-antitrypsin. Hum Mol Genet 2014;23(4):929–41.
27. Cabral CM, Choudhury P, Liu Y, et al. Processing by endoplasmic reticulum mannosidases partitions a secretion-impaired glycoprotein into distinct disposal pathways. J Biol Chem 2000;275(32):25015–22.
28. Teckman JH, Burrows J, Hidvegi T, et al. The proteasome participates in degradation of mutant alpha 1- antitrypsin Z in the endoplasmic reticulum of hepatoma-derived hepatocytes. J Biol Chem 2001;276(48):44865–72.
29. Teckman JH, Perlmutter DH. Retention of mutant alpha(1)- antitrypsin Z in endoplasmic reticulum is associated with an autophagic response. Am J Physiol Gastrointest Liver Physiol 2000;279(5):G961–74.
30. Sifers RN. Cell biology. Protein degradation unlocked. Science 2003;299(5611):1330–1.
31. Qu D, Teckman JH, Omura S, et al. Degradation of a mutant secretory protein, alpha1-antitrypsin Z, in the endoplasmic reticulum requires proteasome activity. J Biol Chem 1996;271(37):22791–5.
32. Cabral CM, Liu Y, Moremen KW, et al. Organizational diversity among distinct glycoprotein endoplasmic reticulum-associated degradation programs. Mol Biol Cell 2002;13(8):2639–50.
33. Marciniak SJ, Lomas DA. Alpha1-antitrypsin deficiency and autophagy. N Engl J Med 2010;363(19):1863–4.
34. Hidvegi T, Ewing M, Hale P, et al. An autophagy-enhancing drug promotes degradation of mutant alpha1-antitrypsin Z and reduces hepatic fibrosis. Science 2010;329(5988):229–32.
35. Kaushal S, Annamali M, Blomenkamp K, et al. Rapamycin reduces intrahepatic alpha-1- antitrypsin mutant Z protein polymers and liver injury in a mouse model. Exp Biol Med (Maywood) 2010;235(6):700–9.
36. Silverman EK, Sandhaus RA. Clinical practice. Alpha1-antitrypsin deficiency. N Engl J Med 2009;360(26):2749–57.
37. Howden L, Meyer J. Age and sex composition: 2010. 2010 census briefs [Internet]. C2010BR-03. c2011. Available at: http://www.census.gov/prod/cen2010/briefs/c2010br-09.pdf. Accessed November 29, 2019.

38. Stoller JK, Sandhaus RA, Turino G, et al. Delay in diagnosis of alpha1-antitrypsin deficiency: a continuing problem. Chest 2005;128(4):1989–94.
39. Greulich T, Ottaviani S, Bals R, et al. Alpha1-antitrypsin deficiency-diagnostic testing and disease awareness in Germany and Italy. Respir Med 2013;107(9): 1400–8.
40. Rubenfeld GD, Cooper C, Carter G, et al. Barriers to providing lung-protective ventilation to patients with acute lung injury. Crit Care Med 2004;32(6):1289–93.
41. Cabana MD, Rand CS, Powe NR, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. JAMA 1999;282:1458–65.
42. Thelin T, Sveger T, Mcneil TF. Primary prevention in a high-risk group: smoking habits in adolescents with homozygous alpha-1-antitrypsin deficiency (ATD). Acta Paediatr 1996;85(10):1207–12.
43. Wall M, Moe E, Eisenberg J, et al. Long-term follow-up of a cohort of children with alpha-1-antitrypsin deficiency. J Pediatr 1990;116(2):248–51.
44. Miravitlles M, Dirksen A, Ferrarotti I, et al. European Respiratory Society statement: diagnosis and treatment of pulmonary α1-antitrypsin deficiency. Eur Respir J 2017;50(5) [pii.1700610].
45. Nelson D, Teckman J, Di Bisceglie A, et al. Diagnosis and management of patients with a1-antitrypsin (A1AT) deficiency. Clin Gastroenterol Hepatol 2012; 10(6):575–80.
46. Tanash HA, Nilsson PM, Nilsson JA, et al. Clinical course and prognosis of never-smokers with severe alpha-1-antitrypsin deficiency (PiZZ). Thorax 2008;63(12): 1091–5.
47. Carbamazepine in severe liver disease due to alpha-1 antitrypsin deficiency (CBZ). Available at: https://clinicaltrials.gov/ct2/show/NCT01379469. Accessed November 29, 2019.
48. Guo S, Booten SL, Aghajan M, et al. Antisense oligonucleotide treatment ameliorates alpha-1 antitrypsin-related liver disease in mice. J Clin Invest 2014;124(1): 251–61.
49. Hughes MG Jr, Khan KM, Gruessner AC, et al. Long-term outcome in 42 pediatric liver transplant patients with alpha 1-antitrypsin deficiency: a single-center experience. Clin Transplant 2011;25(5):731–6.
50. Carey EJ, Iyer EN, Nelson DR, et al. Outcomes for recipients of liver transplantation for alpha-1-antitrypsin deficiency-related cirrhosis. Liver Transpl 2013;19(12): 1370–6.
51. Kemmer N, Kaiser T, Zacharias V, et al. Alpha-1 Antitrypsin deficiency: outcomes after liver transplantation. Transplant Proc 2008;40:1492–4.
52. Kim WR, Lake JR, Smith JM, et al. OPTN/SRTR 2017 annual data report: liver. Am J Transplant 2019;19(Suppl 2):184–283.
53. Miranda E, Perez J, Ekeowa UI, et al. A novel monoclonal antibody to characterize polymers in liver disease associated with alpha1-antitrypsin deficiency. Hepatology 2010;52(3):1078–88.
54. Lomas DA, Finch JT, Seyama K, et al. α1-Antitrypsin Siiyama (Ser53→Phe); further evidence for intracellular loop-sheet polymerization. J Biol Chem 1993; 268(21):15333–5.
55. Lomas DA, Elliot PR, Sidhar SK, et al. α1-Antitrypsin Mmalton (Phe52- deleted) forms loop-sheet polymers in vivo: evidence for the C sheet mechanism of polymerization. J Biol Chem 1995;270(28):16864–70.