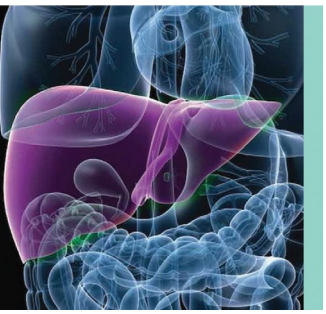

Update on Alpha-1 Antitrypsin Deficiency in Liver Disease

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Alpha-1-Antitrypsin (A1AT) deficiency (A1ATD) is typically discussed in the context of lung disease as a major cause of panacinar emphysema because of impaired inhibition of neutrophil elastase. *SERPINA1*, the gene encoding A1AT, has an autosomal recessive inheritance with codominant expression. Large numbers of mutations in the gene are associated with lung disease and a subset with liver disease. Mutations in *SERPINA1* causing liver disease do so by the formation of harmful aggregates of mutant A1AT protein within hepatocytes, which results in diverse manifestations, from devastating neonatal cholestasis to late-onset cirrhosis and hepatocellular carcinoma (HCC) in adults. Here, we summarize advances in our understanding and management of A1ATD liver disease with particular focus on the significance of A1ATD heterozygosity and its putative role as a cofactor in common causative factors for liver disease.

MOLECULAR BASIS AND PATHOPHYSIOLOGY

A1AT is a large, 52-kDa serum glycoprotein abundantly produced by the liver. It is a serine protease inhibitor whose primary function depends on its secretion from the liver and its physiological action in the lungs to prevent excessive tissue destruction by neutrophil elastase. A1AT is also an acute-phase reactant with a presumed inflammatory role.[1]

Certain missense mutations in A1AT result in the accumulation of toxic aggregates of misfolded protein in hepatocytes and, consequently, deficiency in the circulation. These A1AT aggregates appear as periodic acid–Schiff (PAS)-positive, diastase-resistant inclusions, the pathological hallmark of A1ATD liver disease (Fig. 1, right).

Abbreviations: A1AT, alpha-1-antitrypsin; A1ATD, alpha-1-antitrypsin deficiency; AASLD, American Association for the Study of Liver Diseases; AAV, adenovirus-associated vector; ALD, alcoholic liver disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CFTR, cystic fibrosis transmembrane conductance regulator; COPD, chronic obstructive pulmonary disease; ER, endoplasmic reticulum; ESLD, end-stage liver disease; GGT, gamma-glutamyltransferase; H&E, hematoxylin and eosin; HCC, hepatocellular carcinoma; INR, international normalized ratio; iPSC, induced pluripotent stem cell; NAFLD, nonalcoholic fatty liver disease; NF-κB, nuclear factor-κB; NSAID, nonsteroidal anti-inflammatory drug; PAS, periodic acid–Schiff; siRNA, small interfering RNA; TGF-β, transforming growth factor-β; UPR, unfolded protein response.

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Potential conflict of interest: Nothing to report.

Received May 12, 2019; accepted October 23, 2019.

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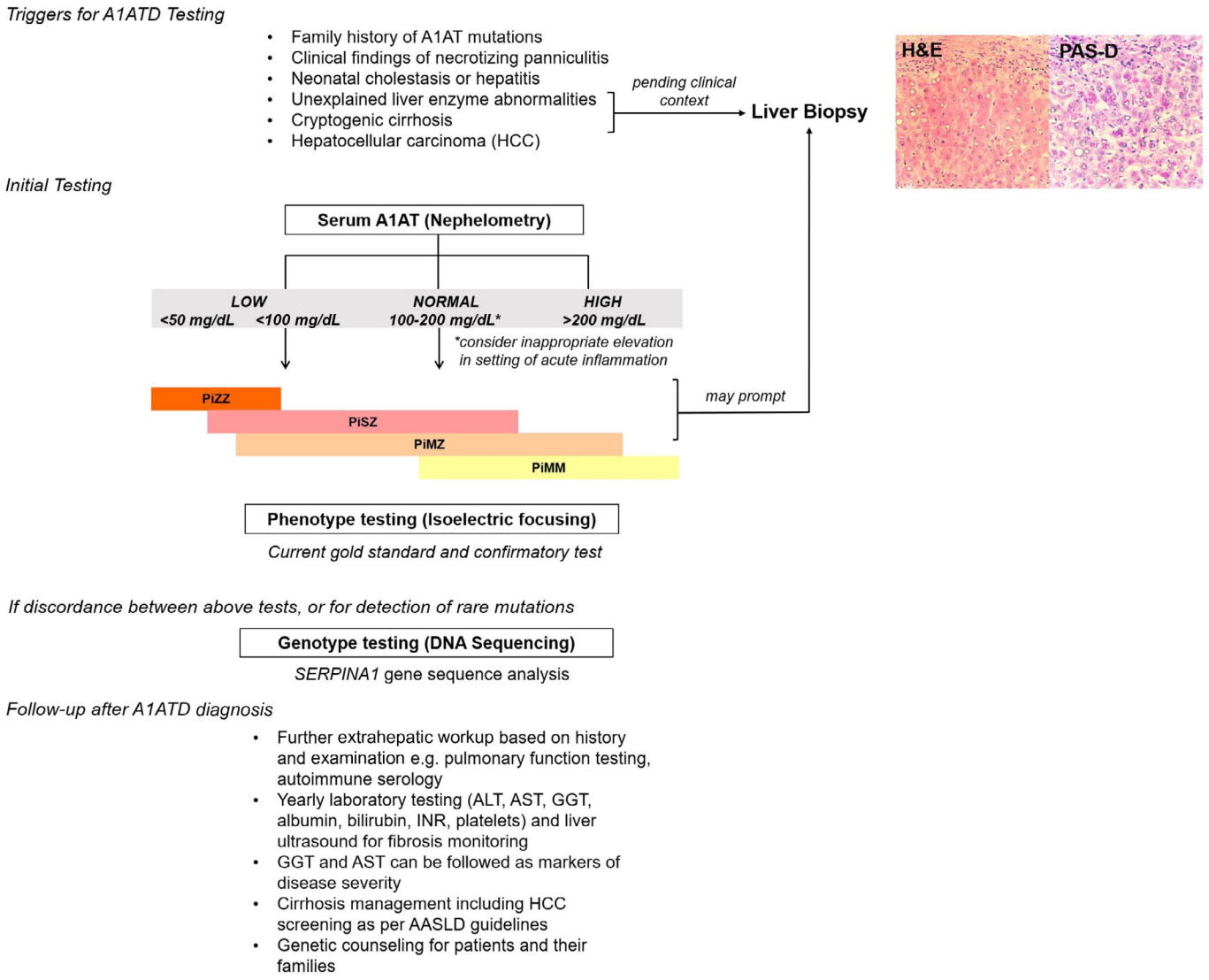

FIG 1 Algorithm for diagnosis of suspected A1ATD in liver disease. Serum testing should be limited to screening because it carries low sensitivity and specificity. Because of its role as an acute-phase reactant, A1AT can be elevated up to 4-fold in settings of inflammation, and thus normal levels cannot exclude PiMZ or PiMS heterozygous carriers. Very low levels carry high sensitivity and specificity for deficiency.[2,3] Serum level ranges for different phenotypes are graphically depicted. Phenotype testing is done by isoelectric focusing migration and is the current diagnostic gold standard and should be performed concomitantly with serum testing for confirmation. Increasingly, *SERPINA1* genotype testing is performed on dried blood spots, whole blood, or saliva, and can be a useful adjunct to phenotyping results, especially when they may be discordant with serum concentrations or for detection of the rare deficiency alleles. Liver biopsy is not required for diagnosis, although often part of the work-up for cryptogenic cirrhosis helps to reveal pathognomonic PAS-positive, diastase-resistant inclusions. Extrahepatic testing may be warranted and guided by thorough clinical and family history. For follow-up, once A1ATD is identified, yearly blood work and FibroScan are recommended to screen for fibrosis. In patients with cirrhosis caused by A1ATD, routine laboratory assessment and imaging for HCC should be done according to AASLD guidelines. (Left) Adapted with permission from *American Journal of Clinical Pathology*.[8] Copyright 2012, American Society for Clinical Pathology. (Right) Courtesy Xuchen Zhang, M.D., Ph.D., Department of Pathology, Yale School of Medicine, New Haven, CT.

The prototype mutation is associated with the misfolded protein pGlu342Lys. It is classified as the PiZ allele based on its distinctive migration on isoelectric focusing, with the normal allele designated PiM. When both mutant PiZ alleles are inherited, the severe homozygous PiZZ form of A1ATD results, compared with the heterozygous PiMZ presentation, which is of mild-to-intermediate severity (Tables 1 and 2). Although hundreds of polymorphisms have been identified within the SERPINA1 gene, it is predominantly the Z mutant allele and, to a lesser extent, the S mutant allele that are attributed to clinically significant liver disease.

TABLE 1. GENETIC VARIANTS OF A1ATD INVOLVED IN LIVER DISEASE

	Alleles	Mutation
Normal	M	
Most common mutations	S	Glu264Val
	Z	Glu342Lys

PiZZ A1ATD "loss of function" results in pulmonary manifestations because aggregated mutant A1AT protein cannot be secreted from the endoplasmic reticulum (ER) of the hepatocyte. Because misfolded A1AT is trapped in the hepatocytes, serum levels become low, predisposing to lung disease; this aspect of phenotype can be aggravated by exposures such as smoking. Meanwhile, a "gain-of-function" phenotype is exhibited when the rate of accumulation of polymerized mutant A1AT protein overwhelms the hepatocyte's protective mechanisms of recognizing, degrading, and exporting excess or misfolded proteins. Over time, this dysregulation of ER homeostasis spurs a reactive cascade that can progress clinically to the development of fibrosis, cirrhosis, and HCC[4,5] (Fig. 2).

Clinical Manifestations

The highest prevalence of homozygous PiZZ A1ATD is seen in Northern Europe, where 1/2000 individuals are affected. Because heterozygous PiMZ carriers can also experience development of disease, the at-risk population is much greater, with an estimated 4 million individuals worldwide carrying any disease-causing allele.[6] Males appear to be affected more than females, and murine studies suggest that hormonal effects contribute to increased A1AT expression and liver injury in male PiZ carriers.[7]

The natural history of A1ATD liver disease deserves further research; however, like many single-gene disorders, A1ATD displays marked clinical variability from infancy to adulthood.[8] In children, acute presentation with cholestatic liver disease progressing to end-stage liver disease is recognized. Modifiers that lead a minority of children to follow this rapidly progressive course have not been delineated.[9,10] This contrasts with adults, for whom it is more common to have a silently progressive liver disease for several decades until signs of portal hypertension develop or there is hepatic decompensation including HCC.[5] Interestingly, adults may have minimal liver enzyme elevations disproportionate to their severity of liver injury, perhaps reflecting that the mode of liver cell injury in PiZZ A1ATD liver disease is predominantly driven by apoptosis.[1]

It is well observed that patients with A1ATD with liver disease, especially ESLD, typically do not have emphysema. Certainly, PiZZ A1ATD can lead to both obstructive lung disease and liver disease; however, because the pathogenesis differs for each organ disease, it becomes the patient's risk factors and disease modifiers that trigger one over the other.[11] A1ATD patients with emphysema and a significant smoking history may experience mortality before experiencing signs of liver disease. Regardless, patients with A1ATD liver disease are strictly counseled on smoking cessation, especially as part of candidacy for transplantation.

DIAGNOSIS

A1ATD remains a disappointedly underreported, underdiagnosed condition often with a diagnostic delay of 5 to 10 years, by which time patients already have ESLD. Studies suggest that more than 80% to 90% of individuals with A1ATD are unaware of their condition because of lack of clinical symptoms or misdiagnosis with other cirrhosis causes, such as alcoholic liver disease (ALD) or nonalcoholic fatty liver disease (NAFLD).[6]

TABLE 2. GENETIC VARIANTS OF A1ATD INVOLVED IN LIVER DISEASE

	Phenotype/Genotype	Serum A1AT Level	Phenotype Range	Phenotype Modifiers
Normal	PiMM	100%		
Heterozygote	PiMZ	60%	Asymptomatic Cryptogenic cirrhosis Decompensated liver disease/HCC	Age >50 years Male sex Diabetes
Severe deficiency	PiSZ PiZZ	35% <15%	Neonatal Cholestasis Fulminant hepatitis Adult Cryptogenic cirrhosis Decompensated liver disease/HCC	Steatosis (ALD, NAFLD) Viral hepatitis Cystic fibrosis (CFTR) COPD NSAIDs Febrile episodes Infections

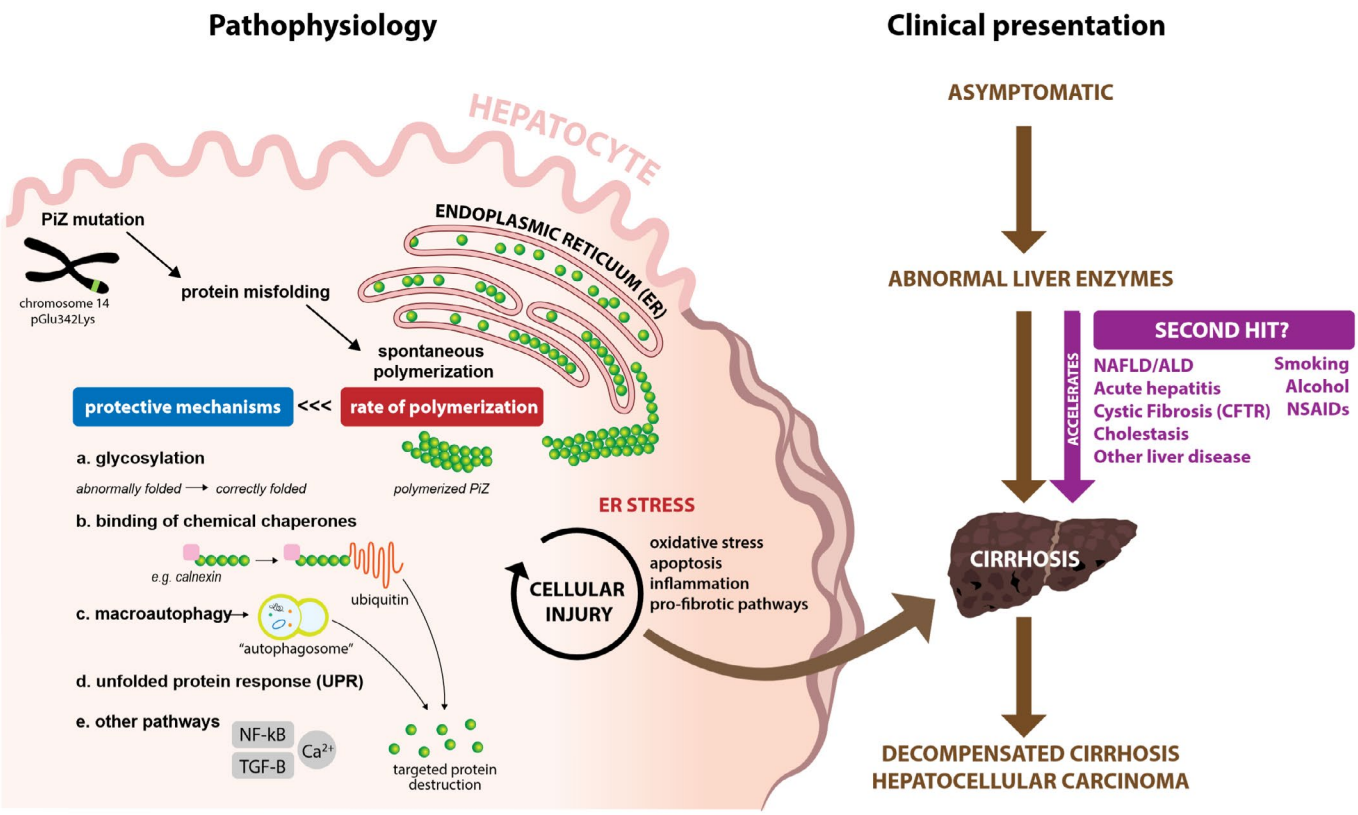

FIG 2 Pathophysiology with correlating clinical presentation of A1ATD in liver disease. Formation of PiZ A1AT starts with the base pair mutation that prompts protein misfolding and polymerization within the ER of the hepatocyte. Protective mechanisms for detecting and destroying mutant protein, such as PiZ A1AT, within the hepatocyte including the following: (a) glycosylation, the normal process of protein modification, which allows time for misfolded proteins to be identified and properly folded; (b) ER-associated destruction (ERAD), such as binding to chemical chaperones like calnexin, which can target for destruction via ubiquitin-mediated pathways; (c) formation of lysosome-fused phagosome that can also target for destruction of mutant protein; (d) UPR, typically another defense mechanism of the cell, but often not triggered in A1ATD because PiZ polymers are not recognized as abnormal[1]; and (e) many other pathways, including those that are calcium mediated, such as NF-κB and TGF-β, also exist. A1ATD is characterized by a rate of polymerization that exceeds these protective mechanisms and leads to unregulated formation, ultimately triggering a cycle of inflammation. Clinical manifestations are variable, and ESLD may be accelerated by the presence of other risk factors.

Figure 1 summarizes the current accepted testing algorithm for A1ATD liver disease.[12,13]

Following diagnosis, patients found to have A1ATD are largely managed supportively with close monitoring for progression of liver disease (Fig. 1). In comparison with A1ATD lung disease for which intravenous enzyme replacement therapy is available, treatments to correct misfolding in liver disease are currently the subject of several clinical trials (Tables 1 and 2), but they are not yet commercially available or shown to improve outcomes.

Routine screening for fibrosis, as well as HCC, is recommended, although it remains unclear how much the risk for HCC development differs in A1ATD from other etiologies of liver disease. In the original Swedish cohort studies by Eriksson et al.,[14] the relative risk was 5, with 28% of autopsy livers revealing HCC, much more than would be expected for cirrhosis alone. Further studies have presented conflicting data reporting both increased and decreased risk for HCC.[8,14] As a general observation, however, inherited metabolic diseases do carry an increased risk for HCC,[15] which overall supports the need for surveillance.

Liver transplantation remains the sole curative option for A1ATD liver disease, with the healthy donor liver both eliminating the mutant phenotype and restoring normal circulating levels of A1AT. Reassuringly, patients transplanted for A1ATD, who represent 1% of all liver transplants performed, have excellent 5-year graft and patient survival rates.[1]

Because of the lack of medical treatment options, there is an emphasis on efforts to prevent progression

TABLE 3. SUMMARY OF A1ATD TREATMENT TARGETS UNDER INVESTIGATION

Target Pathway	Treatment	Studies	Current Status	Limitations
Prevent polymerization	siRNA to downregulate endogenous Z mutant A1AT*	Cruz et al. 2007[23] Guo et al. 2014[24]	Clinical trials phases 1 and 2 (Alnylam Pharmaceuticals and Arrowhead Research Corporation)	Will suppress all A1AT production and require lifelong supplementation or augmentation therapy unless concurrent gene therapy is done to transfect patients with normal A1AT
	AAV-gene vector transfer of normal A1AT to muscle cells*	Multiple studies	Clinical trials phases 1 and 2	
	Autologous grafting of iPSC from Pi*ZZ individuals reprogrammed using CRISPR technology to correct Z mutation	Rashid et al. 2010[25] Yusa et al. 2011[26] Tafaleng et al. 2015[27] Wilson et al. 2015[28]	*In vitro* studies using iPSCs	
Detect and improve protein misfolding	Histone deacetylase 7 inhibitor suberoylanilide hydroxamic acid can restore secretion of Z-type A1AT from epithelial cells	Bouchecareilh et al. 2012[29]	*In vitro* study	Difficulties creating medicine molecules for use in animal models
Use of chemical chaperones stabilizes native A1AT and combats misfolded proteins	4-Phenylbutyric acid*	Burrows et al. 2000[30] Teckman et al. 2004[31]	Clinical trials phase 2	
	Trimethylamine N-oxide	Devlin et al. 2001[32]	*In vitro* study	
Increase degradation via autophagy	Carbamazepine*	Hidvegi et al. 2010[33]	Clinical trials phase 2, PiZZ-associated cirrhosis	Lowest effect doses needed to impact A1ATD exceed safety profiles for humans
	Bile acid 24-norursodeoxycholic acid	Tang et al. 2016[34]	*In vivo* study in PiZ mice	
	Sirolimus	Kaushal et al. 2010[35]	*In vivo* study in PiZ mice; appears to be more effective when given in weekly doses rather than daily	
	Ezetimibe	Yamamura et al. 2014[36]	*In vitro* study	
	Other agents: lithium, valproic acid, pimozide, fluphenazine, fluspirilene, cantharidin, tamoxifen, glucosamine, *N*-acetylglucosamine	Gosai et al. 2010[37]	*In vivo* study in *C. elegans*	
	Tat-beclin 1 peptide	Mallya et al. 2007[38]		
	Gene transfer of transcription factor TFEB using adenovirus-mediated approaches	Pastore et al. 2013[39]	*In vivo* study in PiZ mice	
Increase clearance of accumulated protein	Small-molecule therapy using bile duct ligation	Khan et al. 2017[40]	*In vivo* study in PiZ mice	
	Glucosidase inhibitors: castanospermine			
	Mannosidase inhibitors			
Reducing hepatic injury/ inflammation	Cyclosporin A reduces mitochondrial injury	Teckman et al. 2004[41]	*In vitro* study with HeLa cells *In vivo* study in PiZ mice	
	Immunosuppressants (cyclophosphamide, cyclosporine) with variable results	Multiple studies		

*Treatments undergoing clinical trial.

of A1ATD-related liver injury by reduction of modifiable risk factors. These include weight loss, cessation of tobacco and alcohol use, avoidance of nonsteroidal anti-inflammatory drugs (NSAIDs; because their properties may increase synthesis of mutant A1AT protein in the liver), prompt treatment of febrile illness, and up-to-date hepatitis vaccinations.[16]

EMERGING TREATMENTS

The advances in delineation of disease mechanisms have revealed promising molecular therapeutic targets. Disease models for A1ATD include human PiZZ transgenic mice and *Caenorhabditis elegans* expressing Z allele, which have been informative for understanding disease mechanisms and screening molecules as potential therapies. Although most of these potential treatments are in early stages of clinical development, some are using established US Food and Drug Administration–approved medications that may be repurposed for use in A1ATD and could, therefore, bypass the laborious regulatory process for new drugs. One such example is carbamazepine, which appears to enhance autophagy and clearance of mutant Z protein aggregates. It is currently in clinical trial. Another promising approach is RNA interference therapy to reduce production of mutant A1AT.[17]

Table 3 summarizes the major target pathways for treatment, therapies under study, and their potential limitations.

RELEVANCE IN COMMON LIVER DISEASES

A1ATD has gained recognition as a comodifier to other liver diseases. A longitudinal study by Tanash and Piitulainen[8] found that risk factors for progression of A1ATD liver disease included male sex, age older than 50 years, viral hepatitis, and diabetes. Recent studies have also linked the PiMZ phenotype to a higher risk for development of cirrhosis in patients with NAFLD or chronic alcohol use,[18] as well as cystic fibrosis.[19] Perlmutter et al. were among the first to recognize from retrospective studies that a large proportion of patients transplanted for A1ATD were heterozygous and appeared to have a "second hit" that accelerated progression to ESLD.[20] Putative modifiers of A1ATD liver disease include single-nucleotide polymorphisms in *SERPINA1* and in genes involved in the unfolded protein response (UPR) to control accumulation of mutant misfolded protein and environmental factors. In a 2018 study by Schaefer et al.[20], the PiMZ genotype was found to be an independent risk factor for advanced cirrhosis, decompensation by hepatic encephalopathy, and ascites, as well as a higher risk factor for death and need for transplantation. Although the mechanisms behind these associations are not well understood, the additive effect of multiple stressors on the hepatocellular system are likely contributing factors for increased inflammation and cell death. Therefore, A1ATD is emerging as a genetic modifier that predisposes to clinically significant liver disease akin to the role of Patatin-like phospholipase domain-containing protein 3 (PNPLA3) polymorphism in NAFLD and alcoholic liver disease (ALD). Given the high prevalence of the PiZ carrier state, identification of individuals and appropriate genetic counseling should be prioritized and offered.

FUTURE DIRECTIONS

The precise mechanisms underlying the variability in clinical presentations of patients with A1ATD have not been delineated. To date, no studies exist on the liver transplant outcomes for recipients with A1AT heterozygosity. More robust studies are also needed to confirm the degree of risk associated with the PiMZ phenotype and faster development of cirrhosis. A better definition of the natural history of A1ATD is also needed and would be beneficial in the pursuit of new detection strategies and biomarkers for the disease. Certainly, as established treatments emerge for A1ATD, its early and accurate diagnosis will become more of a priority. Furthermore, an in-depth understanding of the variants of A1ATD will facilitate precision medicine for individuals not only with this genetic disorder but with cirrhosis from other causative factors.

Acknowledgment: The authors thank Dr. Xuchen Zhang for providing pathology images included in Fig. 1 and Mikko Sallinen for significant contributions to Fig. 2. P.N. would also like to thank Dr. Kymberly D. Watt for serving as a longitudinal mentor, as well as a mentor for the 2018 Emerging Liver Scholars program from which stemmed the invitation for this submission.

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