



REVIEW

The discovery of α 1-antitrypsin and its role in health and disease

Sabina M. Janciauskiene ^{a,*}, Robert Bals ^b, Rembert Koczulla ^c,
Claus Vogelmeier ^c, Thomas Köhnlein ^a, Tobias Welte ^a

^a Department of Respiratory Medicine, Hannover Medical School, Feodor-Lynen Str. 23, D-30625 Hannover, Germany

^b Department of Pulmonology, Hospital of the University of the Saarland, Kirrbergerstr. 1, Building 91, D-66421 Homburg/Saar, Germany

^c Department of Pulmonology, Philipps University Marburg, Baldingerstrasse, D-35043 Marburg, Germany

Received 13 October 2010; accepted 7 February 2011

Available online 1 March 2011

KEYWORDS

α 1-Antitrypsin;
Deficiency;
Chronic obstructive
pulmonary disease;
Augmentation therapy;
Inflammation

Summary

α 1-Antitrypsin (AAT) is the archetype member of the serine protease inhibitor (*SERPIN*) supergene family. The AAT deficiency is most often associated with the Z mutation, which results in abnormal Z AAT folding in the endoplasmic reticulum of hepatocytes during biogenesis. This causes intra-cellular retention of the AAT protein rather than efficient secretion with consequent deficiency of circulating AAT. The reduced serum levels of AAT contribute to the development of chronic obstructive pulmonary disease (COPD) and the accumulation of abnormally folded AAT protein increases risk for liver diseases. In this review we show that with the discovery of AAT deficiency in the early 60s as a genetically determined predisposition to the development of early-onset emphysema, intensive investigations of enzymatic mechanisms that produce lung destruction in COPD were pursued. To date, the role of AAT in other than lung and liver diseases has not been extensively examined. Current findings provide new evidence that, in addition to protease inhibition, AAT expresses anti-inflammatory, immunomodulatory and antimicrobial properties, and highlight the importance of this protein in health and diseases. In this review co-occurrence of several diseases with AAT deficiency is discussed.

© 2011 Elsevier Ltd. All rights reserved.

* Corresponding author. Department of Respiratory Medicine, Hannover Medical School, Carl-Neuberg Str. 1, 30625 Hannover, Germany. Tel.: +49 511 532 7297; fax: +49 511 532 7294.

E-mail address: Janciauskiene.Sabina@mh-hannover.de (S.M. Janciauskiene).

Contents

α 1-Antitrypsin (AAT)	1130
AAT synthesis and regulation	1130
Protease inhibitory activity of AAT	1130
Other biological activities of AAT	1130
Discovery of α 1-antitrypsin deficiency (AATD)	1131
Prevalence of AATD	1131
Diagnosis of AATD	1132
Clinical manifestations of AATD	1133
Lung disease in AATD	1133
Liver disease in AATD	1133
Disease manifestations other than the lung and liver	1134
Conclusions	1135
Conflict of interest	1135
References	1135

α 1-Antitrypsin (AAT)

The protease inhibitor activity of human plasma was first discovered by Fermi and Pernossi in 1894.¹ However, the isolation and characterization of individual proteins have only emerged much later with the availability of new techniques. Ultimately, the so-called serum trypsin inhibitor responsible for antiprotease activity was first isolated in 1955 by Schultze and named α 1-antitrypsin because of its occurrence in the α 1-globulin fraction and its ability to inhibit trypsin.²

α 1-Antitrypsin (AAT), also referred to as α 1-proteinase inhibitor or *SERPINA1*, and is the prototypical member of the *SERPIN* (an acronym for *serine proteinase inhibitor*) family of protease inhibitors. The term *SERPIN* was introduced as by Carrell and Travis in 1985 to describe a superfamily of serine protease inhibitors of mammalian plasma.³ Serpin-like genes have subsequently been identified in animals, poxviruses, plants, bacteria and archaea, and over 1500 members of this family have been described to date.⁴

AAT synthesis and regulation

AAT is mainly produced (70–80%) by liver cells, but it is also synthesized by monocytes, macrophages, pulmonary alveolar cells, and by intestinal and corneal epithelium.^{5–8} De novo synthesis of AAT has also been demonstrated in human cancer cells.⁹

The normal plasma concentration of AAT ranging from 0.9 to 1.75 g/L and the protein is cleared with a half-life of 3–5 days.¹⁰ AAT is also present in saliva, tears, milk, semen, urine and bile^{11–15}. The distribution of the protein is not uniform: for example, in the epithelial lining fluid of the lower respiratory tract its concentration is suggested to be about 10% of plasma levels.¹⁶ As an acute-phase reactant, plasma AAT levels increase rapidly (3–4 fold) in response to inflammation or infection. The concentration of AAT in plasma also increases during oral contraceptive therapy and pregnancy. During an inflammatory response, tissue concentrations of AAT may increase as much as 11-fold as a result of local synthesis by resident or invading inflammatory cells.^{16,17} For example, human alveolar macrophages can contribute to

tissue AAT levels in response to inflammatory cytokines (IL-6, IL-1 and TNF α) and endotoxins.^{18,19} The expression of AAT by alpha and delta cells of human islets²⁰ and intestinal epithelial cells²¹ is also enhanced by cytokines. AAT synthesis by corneal epithelium, on the other hand, appears to be under the influence of retinol, IL-2, fibroblast growth factor-2, and insulin-like growth factor-1. Interestingly, AAT expression also shows some degree of substrate and/or auto-regulation with enhanced synthesis following exposure to elastase alone or as a complex of AAT.²²

Protease inhibitory activity of AAT

Until recently it was thought that inhibition of neutrophil elastase and proteinase 3 (PR3) is the primary function of AAT.²³ Current studies demonstrate that AAT is an irreversible inhibitor for kallikreins 7 and 14²⁴, and that AAT also inhibits intra-cellular and cell-surface proteases. Matriptase, a cell-surface serine protease involved in the activation of epithelial sodium channels, is one such protease. Findings that AAT inactivates the catalytic domain of matriptase *in vitro* and inhibits epithelial sodium transport both *in vitro* and *in vivo*^{25–27} support the notion that the inhibition of matriptase by AAT may offer a pharmacologic target for improving mucociliary clearance in both COPD and cystic fibrosis. Several studies have shown that AAT inhibits the activity of caspase-3, an intra-cellular cysteine protease which plays an essential role in cell apoptosis.^{28,29} A recent study by Bergin and collaborators, provides new evidence that AAT modulates neutrophil chemotaxis in response to soluble immune complexes by inhibiting ADAM-17 activity, also called TACE (tumor necrosis factor- α -converting enzyme).³⁰

Other biological activities of AAT

AAT has been reported to play an immunoregulatory role,^{31,32} to inhibit neutrophil superoxide production,³³ to enhance insulin-induced mitogenesis in various cell lines,³⁴ and to induce a IL-1 receptor antagonist expression.³⁵ *In vivo*, AAT has been shown to protect against TNF α or endotoxin-induced lethality.^{36,37} Findings that AAT enhances the

synthesis of both transferrin receptor and ferritin revealed a role of AAT in iron metabolism.³⁸ AAT has also been found to bind to the secreted enteropathogenic *Escherichia coli* proteins (EspB, EspD), thereby reducing their hemolysis of red blood cells.³⁹ An interaction between AAT and *Cryptosporidium parvum*,⁴⁰ a protozoan parasite, has been shown to inhibit *Cryptosporidium parvum* infection, suggesting a potential role for AAT in cryptosporidiosis. Aerosolized AAT also suppressed bacterial proliferation in a rat model of chronic *Pseudomonas aeruginosa* lung infection and in patients with cystic fibrosis.⁴¹ It has recently been demonstrated that a specific 20-residue fragment of AAT (C-terminal peptide, residues 377–396, referred to as VIRIP) binds to the gp41 fusion peptide of HIV-1 and prevents the virus from entering target cells, thereby inhibiting HIV-1 infection.⁴² These findings suggest that AAT may play a protective role in HIV-1-infected individuals.⁴³

In vitro, AAT was demonstrated to inhibit endotoxin-stimulated TNF α and to enhance IL-10 expression in human monocytes, mediated by signaling through the cAMP-dependent protein kinase A pathway which is targeted by a number of anti-inflammatory drugs used and/or currently under development for COPD.⁴⁴ AAT also expresses a broad anti-inflammatory profile in gene expression studies on primary human lung microvascular endothelial cells, including the suppression of self-induced TNF α expression.⁴⁵ Animal studies provide further evidence that AAT therapy prolongs islet graft survival in transplanted allogeneic diabetic mice.^{46,47} Current findings show that AAT stimulates insulin secretion and protects β -cells against cytokine-induced apoptosis, and these effects of AAT also seem to be mediated through the cAMP pathway. In view of these novel findings, it is suggested that AAT may represent an anti-inflammatory compound to protect β -cells under immunological attack in type 1 diabetes and also therapeutic strategy to potentiate insulin secretion in type 2 diabetes.⁴⁸

Interestingly, complexes between AAT and other proteins have been associated with specific diseases. In sera from patients with myeloma, Bence-Jones proteinemia complexes between AAT and the kappa light chain of immunoglobulins were detected.⁴⁹ In plasma from diabetic subjects, complexes of AAT with factor XIa and with heat shock protein-70 (HSP70), as well as glycosylated forms of AAT were found.^{50,51} Moreover, complexes between immunoglobulin A and AAT have been detected in the sera and synovial fluid of patients with rheumatoid arthritis, systemic lupus erythematosus and ankylosing spondylitis.⁵² Human tissue kallikrein 3, known as a prostate-specific antigen which correlates with prostate hypertrophy and malignancy, is also found to bind to AAT in sera of subjects with high prostate-specific antigen concentrations.⁵³ Localization of AAT and AAT-low-density-lipoprotein complexes in atherosclerotic lesions, and enhanced degradation of AAT-low-density-lipoprotein by macrophages suggested the involvement of the complex in atherogenesis.⁵⁴ So far, the factors driving assembly of AAT with other proteins and the biological roles of such complexes warrant further investigations.

Discovery of α 1-antitrypsin deficiency (AATD)

In 1952, C-B Laurell at Malmö University Hospital made outstanding contributions to protein research by introducing

plasma protein electrophoresis as a tool for clinical investigations. By using electrophoresis, clinicians in respiratory medicine in Malmö unexpectedly noted the absence of the alpha1 band in two patients, both of whom suffered from severe respiratory insufficiency caused by emphysema. This observation, published in 1963 by C-B Laurell and S Eriksson, established that AAT deficiency (AATD) is inherited and linked to emphysema. In the following years, several research groups in Europe and the USA demonstrated that AAT is an effective inhibitor of neutrophil elastase, thereby implicating elastase in the pathogenesis of emphysema. Based on these developments, it was generally accepted that the protease-anti-protease balance is an essential requirement for respiratory health.⁵⁵ Later, in a classical paper from 1978 by Larsson and collaborators, it was convincingly demonstrated that the age of onset of emphysema in AATD persons who were also current or ex-smokers was very rapidly reduced.⁵⁶

Since AAT is produced mainly in the liver, investigators in Malmö expected to find abnormal liver function in AATD patients. Eriksson wrote that in 1962 they had seen a patient with cryptogenic, decompensated cirrhosis who also lacked the AAT band in the electrophoresis strip. Unfortunately, the finding was misinterpreted in the belief that the patient had developed an acquired AATD secondary to a severely impaired liver function.⁵⁶ The association between liver diseases and inherited AATD was documented in the USA by Sharp and colleagues in 1969.⁵⁷ These observations were explained in the 1990s when Lomas and his group in Cambridge showed that the mutant AAT in deficient patients forms intra-hepatic polymers due to the insertion of the reactive center loop of one molecule into the opened B-sheet of the next.⁵⁸

The detection of AAT variants became the greatest challenge from 1963 to 1978. The Pi-system was developed, based on the migration of the AAT variants in an electric field. The position of the migrated proteins is identified by a letter, where M is normal, while the positions of the slower-moving proteins are marked by letters before M in the alphabet and these of the faster-moving proteins are denoted by letters after M. Soon it became apparent that the underlying abnormalities of the AAT variants were due to single amino acid substitutions. By 1975, Carrell and co-workers were able to show that the S variant is due to the substitution of a glutamic acid by a valine at position 264 in AAT.⁵⁹ Soon after this, the abnormality of Z AAT (glutamic acid substitution by lysine) was explained by Jeppson in Malmö.⁶⁰ Moreover, it was shown that the mutation in Z AAT does not affect protein synthesis, but causes a perturbation of structure that results in defective secretion of the protein.^{61,62} Thus, cases of inherited AATD traceable to genetic mutations firmly demonstrated the clinical importance of AAT in determining susceptibility to chronic inflammatory conditions, including COPD and liver diseases (Fig. 1).

Prevalence of AATD

The highest prevalence of the Z deficiency variant of AAT is recorded in Northwest European countries and North America⁶³ (Table 1). The Swedish neonatal screening performed in 1972–74 greatly contributed to our knowledge of AATD epidemiology,⁶⁴ and permitted determination of a Z

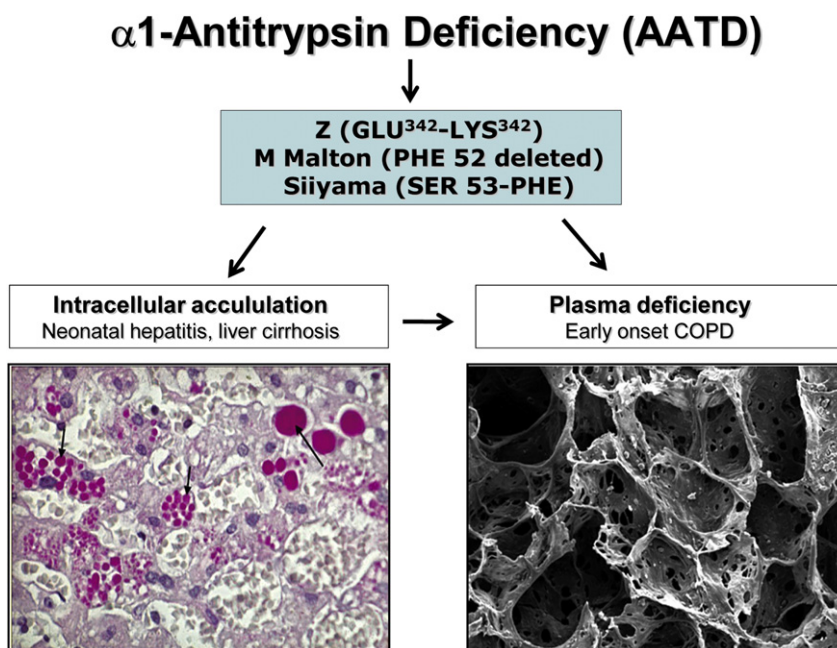


Figure 1 α-1 Antitrypsin deficiency (AATD) is an inherited disorder affecting mainly the liver and lung. Today it is well established that the Z, and also Siiyama (Ser53Phe) and Mmalton (52Phe del) variants of AAT form polymers and retain in the endoplasmic reticulum of the hepatocytes. The retention of AAT within hepatocytes results in protein overload that in turn is associated with juvenile hepatitis, cirrhosis, and hepatocellular carcinoma. Individuals with AATD have about 90% reduced levels of serum AAT and are at greatly increased risk for early-onset COPD, especially if they are cigarette smokers.

Table 1 Estimated percentages of individuals with α-1 Antitrypsin genotypes SZ, ZZ, and SS among the total population of selected countries.

Country	α1-Antitrypsin genotype		
	SZ	ZZ	SS
Austria	0.053	0.018	0.041
Belgium	0.181	0.028	0.295
Denmark	0.151	0.073	0.078
Estonia	0.061	0.061	0.016
Finland	0.010	0.004	0.005
France	0.195	0.017	0.578
Germany	0.041	0.010	0.044
Hungary	0.034	0.005	4.762
Italy	0.075	0.027	0.052
Latvia	0.282	0.204	0.098
Lithuania	0.051	0.023	0.028
The Netherlands	0.044	0.010	0.046
Poland	0.012	0.002	0.022
Portugal	0.356	0.019	1.667
Russia	0.007	0.001	0.009
Spain	0.360	0.030	1.087
Sweden	0.113	0.053	0.060
UK	0.065	0.014	0.075
US African American	0.006	0.002	0.022
US Caucasian	0.022	0.036	0.052

Table is based on the study published by Blanco I et al., 2006.⁶³

gene frequency of 0.026. Another survey in Denmark yielded a Z frequency of 0.049.⁶⁵ The prevalence of the Z AAT genotype decreases throughout Europe along a north-west→south-east gradient.⁶⁶ The distribution of the S variant of AAT differs markedly from that of Z, the highest frequency being reported in Southern Europe, and peaking in the Iberian Peninsula (frequency > 0.1400).⁶⁷ On the other hand, these mutant gene frequencies are very low in the Far East (0.00002 in Japan, 0 in China, and 0.0061 in South Korea).⁶⁸ The frequencies of Z and S AAT variants in North America, Australia and New Zealand are very similar (0.012 and 0.035, respectively), which is further support for the hypothesis that AATD arose in European population. Some scientists estimate that the Z AAT mutation arose between 7000 and 4000 years ago⁶⁹ in Southern Scandinavia, and subsequently was spread to other European countries. In contrast, the high prevalence of the S mutation in the Iberian peninsula indicates that this variant most likely arose in the Portuguese population.⁷⁰

Diagnosis of AATD

To date, approximately 100 different alleles of the AAT gene (*SERPINA1*; MIM# 107400) have been identified and named according to the Pi classification scheme.⁷¹ Moreover, available AAT variants have been categorized as normal (M), deficient (most common Z and S), dysfunctional or null variants.^{69,72} With regard to AATD, the “null” alleles are associated with no detectable AAT in the serum, while the “deficient” alleles lead to a decrease in plasma AAT. The AAT genes are inherited as co-dominant alleles (products of both

genes can be found in the circulation). Therefore, individuals heterozygous for the Z allele (MZ) have 50–60% while individuals homozygous for the Z allele (ZZ) have only 10–15% of the normal MM AAT value (≤ 0.8 mg/ml or ≤ 11 μ mol/L).⁷³

Guidelines for the diagnostic strategies and management of AATD were published by the ERS/ATS in 2003.⁷⁴ In general, measurement of the serum AAT concentration is the first step in the algorithm for diagnosis of AATD. However, AAT is an acute-phase protein and its synthesis may be up-regulated during inflammation. Therefore, it is recommended that C-reactive protein (CRP) levels are determined simultaneously and that AAT concentration results are rejected if CRP levels are abnormal. On the other hand, if the serum concentration of AAT is below normal, characterization of AAT geno- and phenotype is recommended. All newborns with prolonged jaundice or nonspecific signs of liver disease should be screened for AATD. Adults with chronic respiratory diseases, such as COPD, not fully reversible bronchial asthma, bronchiectasis, immotile cilia syndrome, frequent airway infections or indeterminate liver disease, should be tested once in their lives. In addition to the index case, relatives need to be screened in order to identify symptom-free carriers, and, if necessary, to recommend prophylactic measures.

Clinical manifestations of AATD

Lung disease in AATD

It is generally accepted that ZZ AATD comprises about 1–2% of all COPD cases, and that heterozygous MZ and MS have no risk for development of COPD. However, a recent German study using a targeted screening program including 2696 subjects identified 268 (ZZ), 488 (MZ), 97 (MS) and 53 (SZ) with AATD, and 16 with rare genotypes.⁷⁵ The data from the study carried out in Denmark showed that the frequency of AATD among COPD patients is 0.8% for ZZ and 2.4% for MZ genotype.⁶⁵ In the Lithuanian cohort, consisting of 1167 patients with moderate to severe COPD, it was found that 40 (3.4%) are MZ, 39 (3.3%) MS, 1 (0.1%) SS, 3 (0.3%) SZ and 8 (0.7%) ZZ.⁷⁶ Current literature indicates that asthma signs and symptoms are common in AATD with or without COPD and that bronchodilator response is a risk factor for FEV₁ decline.¹³ The British Registry of patients with AATD reported the presence of asthma in about 11% of cases, and an increased prevalence of the MS (18%) and MZ (7%) genotypes. AATD was found in Puerto Rican children attending an asthma clinic.⁷⁷ These findings suggest that not only severe ZZ, but also mild, heterozygous (MS, MZ, SZ) AATD may be a risk factor for developing airways pathology.

Severe pulmonary impairment, manifesting as COPD and panacinar lung emphysema (Fig. 2), may be expected if the AAT serum concentration is below the protective threshold of 35% of the normal mean value (≤ 0.8 mg/ml or ≤ 11 μ mol/L). Pulmonary symptoms, such as cough, sputum expectoration, and dyspnea may occur by the age of 30–40 years. Up to 20% of symptomatic patients develop bronchial hyperreactivity. The course of the disease is progressive and may lead to severe respiratory insufficiency. As in COPD, which is unrelated to AATD, typical findings are repeated acute exacerbations with increase of symptoms and worsening of the general condition. In the majority of cases, the



Figure 2 Computed tomography of the thorax of a patient with severe emphysema. Large bullae in both lungs and severe panlobular emphysema, rarefaction of pulmonary parenchyma and pulmonary vessels.

cause of exacerbations is believed to be airway infection. The frequency of exacerbations seems to be associated with the progression of pulmonary emphysema and correlates with the decline of pulmonary function. The disease may progress faster if additional risk factors are present, such as tobacco smoking or (occupational) air pollutants. The mean life expectancy of ZZ AATD patients is 48–52 years for smokers and 60–68 years for nonsmokers.⁷⁸ Today it is widely accepted that the most important problem behind AATD-related emphysema is a reduction in anti-elastase defense. Either an increase in elastase burden (which might happen with cigarette smoking or pulmonary infection) or the quantitative deficiency of an inhibitor of neutrophil elastase (inherited AATD) can lead to an elastase/anti-elastase imbalance that accelerates lung tissue breakdown. Most recent experimental data show that cigarette smoke accelerates polymerization of Z AAT by oxidative modification, which in so doing further reduces pulmonary defenses and increases neutrophil influx into the lungs (Fig. 3). These novel findings provide a molecular explanation for the striking observation of premature emphysema in ZZ AATD subjects who smoke and raise the prospect of anti-oxidant therapy in AATD-related COPD.⁷⁹

Liver disease in AATD

Today it is well established that the Z, and also Siiyama (Ser53Phe) and Mmalton (52Phe del) variants of AAT, form polymers and are retained in the endoplasmic reticulum (ER) of hepatocytes.⁶¹ The polymers of Z-mutant AAT can be identified by microscopy in diastase resistant inclusion bodies reacting positively with PAS-staining (Periodic acid-Schiff). This accumulation of abnormally folded AAT protein is thought to be associated with increased risk for liver diseases. Research from several laboratories has identified a possible role for ER stress in Z AAT-induced hepatocyte

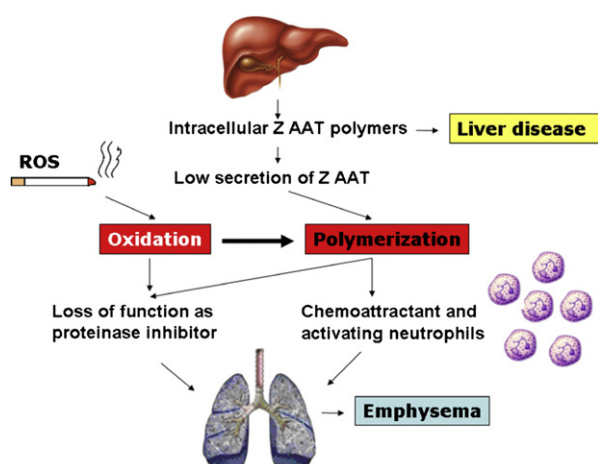


Figure 3 Schematic diagram depicting the role of Z α -1-Antitrypsin (AAT) in the development of liver and lung diseases. The pathogenesis of AATD-related liver disease is based on the aberrant folding and polymerization of AAT protein in the hepatocytes. Polymeric Z AAT is also found in the plasma, bronchoalveolar lavage fluid and in the alveolar walls of Z AATD individuals. Cigarette smoke accelerates polymerization of Z AAT by oxidative modification,⁷⁹ and further reduces anti-elastase defense and increases neutrophil influx into the lungs.

injury; however, the causative role of ER stress in human liver diseases has yet to be proven.^{80,81} Interestingly, current studies provide new evidence that ERManI, a putative ER mannosidase, plays a critical role in distinguishing and targeting misfolded glycoproteins for ER-associated degradation.⁸² Therefore, genetically low levels of ERManI in subjects with AATD may impair the liver's capacity to deal with the accumulation of misfolded Z AAT and accelerate the development of end-stage liver disease.^{83,84}

In infants liver disease associated with ZZ AATD typically presents as neonatal cholestatic jaundice, which often subsides spontaneously after a few months. However, the outcome in childhood and adolescence varies a lot, ranging from normalization of liver test results to early cirrhosis requiring liver transplantation.^{64,85} Even in children with an apparently favorable outcome, a significant degree of liver fibrosis may be present.⁸⁶ It is well known that ZZ AATD individuals, who do not develop liver disease in childhood, have increased risk of liver cirrhosis and hepatocellular carcinoma later in adulthood. Notably, AATD may be a relevant cause for liver cirrhosis, after viral hepatitis, alcohol abuse, and chronic cholangitis. From retrospective studies it is known that up to 25% of those with ZZ AATD may suffer from liver cirrhosis or liver cancer in late adulthood.⁸⁷ However, in adults the association between the ZZ genotype and liver disease is still unclear, and the incidence of such an association varies considerably.⁸⁸ Cirrhosis in ZZ AATD individuals may become clinically apparent at any age, with the peak incidence typically occurring in elderly never-smokers who have survived without developing severe emphysema. Aside from low plasma AAT levels, laboratory and other clinical features of affected individuals are indistinguishable from those with cirrhosis of any etiology.⁸⁹ Therefore, in the absence of specific biomarkers and lack of firm evidence regarding optimal follow-up and preventive

strategies, the regular assessment of simple liver function tests is typically recommended in elderly individuals with AATD who lack liver symptoms.

Disease manifestations other than the lung and liver

Diseases other than lung and liver diseases have been associated with AATD, but their association with AATD is less clear. Indeed, the multiple protective role(s) of AAT described above suggest that the deficiency of that protein may worsen the pathogenesis of other diseases rather than causing them. To date fewer than 50 cases of panniculitis associated with various phenotypes of AATD have been reported.⁹⁰ Panniculitis characteristically presents as red, painful nodular lesions^{91,92} and clinical features that distinguish the AATD-associated panniculitis include higher frequency of ulceration, a vigorous neutrophilic response and histological evidence of both necrosis and elastin breakdown.⁹³ In support of AATD as a contributor to the inflammatory pathogenesis of panniculitis, a few case reports provide evidence that the infusion of purified pooled human AAT induces a rapid clinical resolution of panniculitis.^{94–96}

The putative association between AATD and vasculitis (Wegener's granulomatosis) is based on the fact that AATD variants occur more frequently among individuals with multisystem vasculitis anti-neutrophilic cytoplasmic antibodies (C-ANCA) or anti-protease-3 (PR-3) and glomerulonephritis.^{97,98} Moreover, since AAT plays an important role in inhibiting PR3, it has been suggested that AATD could trigger an autoimmune response due to increased extracellular exposure to PR3.⁹⁹ Alternatively, although unproven, it is conceivable that circulating Z AAT polymers could prompt a vascular response.

Several reports have described AATD patients having both liver disease and rheumatoid arthritis¹⁰⁰ and larger studies

Table 2 Disease manifestations in α -1 Antitrypsin deficiency other than the lung and liver.

Disease	Reference number
Panniculitis	106· 107
ANCA-positive vasculitis	72· 108
Rheumatoid arthritis	100· 109
Chronic rhinosinusitis	110· 111
Acute Uveitis	112
Pancreatitis	113–115
Inflammatory bowel disease	116· 117
Celiac disease	118· 119
Peptic ulcer disease	120· 121
Diabetes	105· 122
Islet cell hyperplasia	6· 123
Renal disease	124–126
Fibromyalgia	127· 128
Idiopathic granulomatous mastitis	129
Peripheral neuropathy	130
Aneurisms	131–134
Coronary atherosclerosis	135
Cancer	136–139

from Canada and Sweden have shown an increased frequency of AATD phenotypes in patients with rheumatoid arthritis compared to population frequencies.^{101,102} In addition, in the setting of AATD-associated chronic liver disease, renal disease is often seen in children and young adults.^{103,104} Numerous reports have also associated AATD and pancreatitis, inflammatory bowel disease, celiac disease, peptic ulcer disease, fibromuscular dysplasia, aneurysms and coronary atherosclerosis. AATD association with psoriasis, chronic urticaria, multiple sclerosis, fibromyalgia, ocular allergy, acute uveitis and other conditions have been reported (Table 2). However, further investigations are needed before these putative associations between AATD and various diseases are confirmed. In general, one can predict that in AATD, the protective effects of AAT protein are much lower and therefore a more aggressive inflammatory course of disease can be seen in AATD carriers.

Finally, recent studies have raised the possibility of an association between AAT and diabetes. In support of this, a few clinical studies demonstrated that plasma AAT levels and activity are lower in diabetic patients than in non-diabetic controls.¹⁰⁵ It has also been demonstrated that over-expression of AAT significantly reduces insulinitis and prevents the development of overt hyperglycemia in non-obese diabetic (NOD) mice.⁴⁶ In addition, it has been shown that administration of clinical-grade human AAT prolongs pancreatic islet allograft survival and exhibits cytoprotective effects.²⁹ Studies examining the role of AAT in diabetes are an area of intense and ongoing investigation.

Conclusions

Despite tremendous progress made in the field of AATD since its first description by Laurell and Eriksson,¹⁴⁰ key challenges still remain. Clearly the role of AAT in inflammatory processes in the lung has until recently been oversimplified. Although we believe that the effects of AAT are predominantly anti-inflammatory, the actual impact of AAT on inflammatory disease may depend not only on the relative concentration of native, inhibitory and non-inhibitory, modified forms of AAT, but also on the inflammatory context in which they are expressed. The formation of post-translational modified forms of AAT may lead to a functional deficiency of AAT, even if the individual has a normal level of AAT, and the modified forms of AAT may themselves express biological activities. Studies characterizing the inhibitor-independent activity of AAT and its modified forms are incomplete, particularly with regard to an understanding of the signaling mechanisms involved. Delineation of these will not only help us to further understand the role of AAT in the pathogenesis of inflammatory disease, but may also facilitate the identification of new and effective anti-inflammatory therapies.

Conflict of interest

All authors received lecture fees and SJ has received unrestricted research grant from Talecris Biotherapeutics GmbH.

References

1. Fermi C, Pernossi L. Untersuchungen über die enzyme, Vergleichende Studie. *Z Hyg Infektionskr* 1894;18:83–9.
2. Schultze HE, Goitner I, Heide K, Schoenenberger M, Schwick G. Zur Kenntnis der alpha-globulin des menschlichen normal serums. *Naturforsch* 1955;10:463.
3. Carrell R, Travis J. α 1-Antitrypsin and the serpins: variation and counter-variation. *Trends Biochem Sci* 1985;10:20–4.
4. Silverman GA, Bird PI, Carrell RW, Church FC, Coughlin PB, et al. The serpins are an expanding superfamily of structurally similar but functionally diverse proteins. Evolution, mechanism of inhibition, novel functions, and a revised nomenclature. *J Biol Chem* 2001;276:33293–6.
5. Perlmutter DH, Kay RM, Cole FS, Rossing TH, Van Thiel D, et al. The cellular defect in alpha 1-proteinase inhibitor (alpha 1-PI) deficiency is expressed in human monocytes and in xenopus oocytes injected with human liver mRNA. *Proc Natl Acad Sci U S A* 1985;82:6918–21.
6. Ray MB, Geboes K, Callea F, Desmet VJ. Alpha-1-antitrypsin immunoreactivity in gastric carcinoid. *Histopathology* 1982;6:289–97.
7. Geboes K, Ray MB, Rutgeerts P, Callea F, Desmet VJ, et al. Morphological identification of alpha-1-antitrypsin in the human small intestine. *Histopathology* 1982;6:55–60.
8. Bosković G, Twining SS. Local control of alpha1-proteinase inhibitor levels: regulation of alpha1-proteinase inhibitor in the human cornea by growth factors and cytokines. *Biochim Biophys Acta* 1998;27:37–46.
9. Higashiyama M, Doi O, Kodama K, Yokouchi H, Tateishi R. An evaluation of the prognostic significance of alpha-1-antitrypsin expression in adenocarcinomas of the lung: an immunohistochemical analysis. *Br J Cancer* 1992;65:300–2.
10. Kalsheker N, Morley S, Morgan K. Gene regulation of the serine proteinase inhibitors alpha1-antitrypsin and alpha1-antichymotrypsin. *Biochem Soc Trans* 2002;30:93–8.
11. Chohanadisai W, Lönnnerdal B. Alpha(1)-antitrypsin and antichymotrypsin in human milk: origin, concentrations, and stability. *Am J Clin Nutr* 2002;76:828–33.
12. Berman MB, Barber JC, Talamo RC, Langley CE. Corneal ulceration and the serum antiproteases. I. Alpha 1-antitrypsin. *Invest Ophthalmol* 1973;12:759–70.
13. Eden E. Asthma and COPD in alpha-1 antitrypsin deficiency. Evidence for the Dutch hypothesis. *COPD* 2010;7:366–74.
14. Huang C. Comparative proteomic analysis of human whole saliva. *Arch Oral Biol* 2004;49:951–62.
15. Janciauskiene S, Toth E, Sahlin S, Eriksson S. Immunochemical and functional properties of biliary alpha-1-antitrypsin. *Scand J Clin Lab Invest* 1996;56:597–608.
16. Janciauskiene S. Conformational properties of serine proteinase inhibitors (serpins) confer multiple pathophysiological roles. *Biochim Biophys Acta* 2001;1535:221–35.
17. Boskovic G, Twining SS. Retinol and retinaldehyde specifically increase alpha1-proteinase inhibitor in the human cornea. *Biochem J* 1997;322:751–6.
18. Perlmutter DH, Punsal PI. Distinct and additive effects of elastase and endotoxin on expression of alpha 1 proteinase inhibitor in mononuclear phagocytes. *J Biol Chem* 1988;263:16499–503.
19. Knoell DL, Ralston DR, Coulter KR, Wewers MD. Alpha 1-antitrypsin and protease complexation is induced by lipopolysaccharide, interleukin-1beta, and tumor necrosis factor-alpha in monocytes. *Am J Respir Crit Care Med* 1998;157:246–55.
20. Bosco D, Meda P, Morel P, Matthey-Doret D, Caille D, et al. Expression and secretion of alpha1-proteinase inhibitor are regulated by proinflammatory cytokines in human pancreatic islet cells. *Diabetologia* 2005;48:1523–33.

21. Faust D, Hormann S, Friedrich-Sander M, Milovic V, Stein J. Butyrate and the cytokine-induced alpha1-proteinase inhibitor release in intestinal epithelial cells. *Eur J Clin Invest* 2001;31:1060–3.
22. Perlmutter DH, Travis J, Punsal PI. Elastase regulates the synthesis of its inhibitor, alpha 1-proteinase inhibitor, and exaggerates the defect in homozygous PiZZ alpha 1 PI deficiency. *J Clin Invest* 1988;81:1774–80.
23. Goopu B, Lomas DA. Conformational pathology of the serpins: themes, variations, and therapeutic strategies. *Annu Rev Biochem* 2009;78:147–76.
24. Luo LY, Jiang W. Inhibition profiles of human tissue kallikreins by serine protease inhibitors. *Biol Chem* 2006;387:813–6.
25. Tseng IC, Chou FP, Su SF, Oberst M, Madayiputhiya N, et al. Purification from human milk of matriptase complexes with secreted serpins: mechanism for inhibition of matriptase other than HAI-1. *Am J Physiol Cell Physiol* 2008;295:C423–31.
26. Janciauskiene S, Nita I, Subramaniam D, Li Q, Lancaster Jr JR, et al. Alpha1-antitrypsin inhibits the activity of the matriptase catalytic domain in vitro. *Am J Respir Cell Mol Biol* 2008;39:631–7.
27. Lazrak A, Nita I, Subramaniam D, Wei S, Song W, et al. Alpha(1)-antitrypsin inhibits epithelial Na⁺ transport in vitro and in vivo. *Am J Respir Cell Mol Biol* 2009;41:261–70.
28. Petrache I, Fijalkowska I, Medler TR, Skirball J, Cruz P, et al. Alpha-1 antitrypsin inhibits caspase-3 activity, preventing lung endothelial cell apoptosis. *Am J Pathol* 2006;169:1155–66.
29. Zhang B, Lu Y, Campbell-Thompson M, Spencer T, Wasserfall C, et al. Alpha1-antitrypsin protects beta-cells from apoptosis. *Diabetes* 2007;56:1316–23.
30. Bergin DA, Reeves EP, Meleady P, Henry M, McElvaney OJ, et al. α -1 Antitrypsin regulates human neutrophil chemotaxis induced by soluble immune complexes and IL-8. *J Clin Invest* 2010;120:4236–50.
31. Arora PK, Miller HC, Aronson LD. Alpha1-antitrypsin is an effector of immunological stasis. *Nature* 1978;274:589–90.
32. Dabbagh K, Laurent GJ, Shock A, Leoni P, Papakrivopoulou J, et al. Alpha-1-antitrypsin stimulates fibroblast proliferation and procollagen production and activates classical MAP kinase signalling pathways. *J Cell Physiol* 2001;186:73–81.
33. Bucurenci N, Blake DR, Chidwick K, Winyard PG. Inhibition of neutrophil superoxide production by human plasma alpha 1-antitrypsin. *FEBS Lett* 1992;300:21–4.
34. She QB, Mukherjee JJ, Crilly KS, Kiss Z. Alpha(1)-antitrypsin can increase insulin-induced mitogenesis in various fibroblast and epithelial cell lines. *FEBS Lett* 2000;473:33–6.
35. Tilg H, Vannier E, Vachino G, Dinarello CA, Mier JW. Anti-inflammatory properties of hepatic acute phase proteins: preferential induction of interleukin 1 (IL-1) receptor antagonist over IL-1 beta synthesis by human peripheral blood mononuclear cells. *J Exp Med* 1993;178:1629–36.
36. Libert C, Van MW, Brouckaert P, Fiers W. Alpha1-antitrypsin inhibits the lethal response to TNF in mice. *J Immunol* 1996;157:5126–9.
37. Churg A, Dai J, Zay K, Karsan A, Hendricks R, et al. Alpha-1-antitrypsin and a broad spectrum metalloprotease inhibitor, RS113456, have similar acute anti-inflammatory effects. *Lab Invest* 2001;81:1119–31.
38. Graziadei I, Weiss G, Bohm A, Werner-Felmayer G, Vogel W. Unidirectional upregulation of the synthesis of the major iron proteins, transferrin-receptor and ferritin, in HepG2 cells by the acute-phase protein alpha1-antitrypsin. *J Hepatol* 1997;27:716–25.
39. Knappstein S, Ide T, Schmidt MA, Heusipp G. Alpha 1-antitrypsin binds to and interferes with functionality of EspB from atypical and typical enteropathogenic *Escherichia coli* strains. *Infect Immun* 2004;72:4344–50.
40. Forney JR, Yang S, Healey MC. Interaction of the human serine protease inhibitor alpha-1-antitrypsin with cryptosporidium parvum. *J Parasitol* 1996;82:496–502.
41. Griese M, Latzin P, Kappler M, Weckerle K, Heinzlmaier T, et al. Alpha1-antitrypsin inhalation reduces airway inflammation in cystic fibrosis patients. *J Eur Respir* 2007;29:240–50.
42. Münch J, Ständker L, Adermann K, Schulz A, Schindler M, et al. Discovery and optimization of a natural HIV-1 entry inhibitor targeting the gp41 fusion peptide. *Cell* 2007;129:263–75.
43. Forssmann WG, The YH, Stoll M, Adermann K, Albrecht U, et al. Short-term monotherapy in HIV-infected patients with a virus entry inhibitor against the gp41 fusion peptide. *Sci Transl Med* 2010;2:63. re3.
44. Janciauskiene SM, Nita IM, Stevens T. Alpha1-antitrypsin, old dog, new tricks. Alpha1-antitrypsin exerts in vitro anti-inflammatory activity in human monocytes by elevating cAMP. *J Biol Chem* 2007;282:8573–82.
45. Subramaniam D, Virtala R, Pawlowski K, Clausen IG, Warkentin S, et al. TNF-alpha-induced self expression in human lung endothelial cells is inhibited by native and oxidized alpha1-antitrypsin. *Int J Biochem Cell Biol* 2008;40:258–71.
46. Koulmanda M, Bhasin M, Hoffman L, Fan Z, Qjpo A, et al. Curative and beta cell regenerative effects of alpha1-antitrypsin treatment in autoimmune diabetic NOD mice. *Proc Natl Acad Sci U S A* 2008;105:16242–7.
47. Lewis EC, Mizrahi M, Toledano M, Defelice N, Wright JL, et al. Alpha1-antitrypsin monotherapy induces immune tolerance during islet allograft transplantation in mice. *Proc Natl Acad Sci U S A* 2008;105:16236–41.
48. Kalis M, Kumar R, Janciauskiene S, Salehi A, Cilio CM. α 1-antitrypsin enhances insulin secretion and prevents cytokine-mediated apoptosis in pancreatic β -cells. *Islets* 2010;2:185–9.
49. Laurell CB, Thulin E. Complexes in plasma between light chain kappa immunoglobulins and alpha 1-antitrypsin respectively prealbumin. *Immunochemistry* 1974;11:703–9.
50. Austin GE, Mullins RH, Morin LG. Non-enzymic glycation of individual plasma proteins in normoglycemic and hyperglycemic patients. *Clin Chem* 1987;33:2220–4.
51. Finotti P, Pagetta A. A heat shock protein70 fusion protein with alpha1-antitrypsin in plasma of type 1 diabetic subjects. *Biochem Biophys Res Commun* 2004;315:297–305.
52. Scott LJ, Evans EL, Dawes PT, Russell GI, Matthey DL. Comparison of IgA-alpha1-antitrypsin levels in rheumatoid arthritis and seronegative oligoarthritis: complex formation is not associated with inflammation per se. *Br J Rheumatol* 1998;37:398–404.
53. Zhang WM, Finne P, Leinonen J, Stenman UH. Characterization and determination of the complex between prostate-specific antigen and alpha 1-protease inhibitor in benign and malignant prostatic diseases. *Scand J Clin Lab Invest Suppl* 2000;233:51–8.
54. Donners MM, Verluyten MJ, Bouwman FG, Mariman EC, Devreese B, et al. Proteomic analysis of differential protein expression in human atherosclerotic plaque progression. *J Pathol* 2005;206:39–45.
55. Eriksson S. A 30-year perspective on alpha 1-antitrypsin deficiency. *Chest* 1996;110:2375–42S.
56. Larsson C. Natural history and life expectancy in severe alpha1-antitrypsin deficiency, Pi Z. *Acta Med Scand* 1978;204:345–51.
57. Sharp HL, Bridges RA, Krivit W, Freier EF. Cirrhosis associated with alpha-1-antitrypsin deficiency: a previously unrecognized inherited disorder. *J Lab Clin Med* 1969;73:934–9.

58. Lomas DA. Loop-sheet polymerization: the structural basis of Z alpha 1-antitrypsin accumulation in the liver. *Clin Sci (Lond)* 1994;**86**:489–95.
59. Owen MC, Carrell RW, Brennan SO. The abnormality of the S variant of human alpha-1-antitrypsin. *Biochim Biophys Acta* 1976;**453**:257–61.
60. Jeppsson J. Amino acid substitution Glu leads to Lys alpha1-antitrypsin PiZ. *FEBS Lett* 1976;**65**:195–7.
61. Carrell RW, Lomas DA. Alpha1-antitrypsin deficiency—a model for conformational diseases. *N Engl J Med* 2002;**346**:45–53.
62. Potempa J, Korzus E, Travis J. The serpin superfamily of proteinase inhibitors: structure, function, and regulation. *J Biol Chem* 1994;**269**:15957–60.
63. Blanco I, de Serres FJ, Fernandez-Bustillo E, Lara B, Miravittles M. Estimated numbers and prevalence of Pi*S and Pi*Z alleles of alpha1-antitrypsin deficiency in European countries. *Eur Respir J* 2006;**27**:77–84.
64. Sveger T. Liver disease in lapha1-antitrypsin deficiency detected by screening of 200,000 infants. *N Engl J Med* 1976;**294**:1316–21.
65. Dahl M, Tybjaerg-Hansen A, Lange P, Vestbo J, Nordestgaard BG. Change in lung function and morbidity from chronic obstructive pulmonary disease in alpha1-antitrypsin MZ heterozygotes: a longitudinal study of the general population. *Ann Intern Med* 2002;**136**:270–9.
66. Ferrarotti I, Baccheschi J, Zorzetto M, Tinelli C, Corda L, et al. Prevalence and phenotype of subjects carrying rare variants in the Italian registry for alpha1-antitrypsin deficiency. *J Med Genet* 2005;**42**:282–7.
67. Martin JP, Sesboue R, Charlionet R, Ropartz C, Pereira MT. Genetic variants of serum alpha1-antitrypsin (Pi types) in Portuguese. *Hum Hered* 1976;**26**:310–4.
68. Seyama K, Nukiwa T, Takabe K, Takahashi H, Miyake K, et al. Siiyama (serine 53 (TCC) to phenylalanine 53 (TTC)). A new alpha 1-antitrypsin-deficient variant with mutation on a predicted conserved residue of the serpin backbone. *J Biol Chem* 1991;**266**:12627–32.
69. Luisetti M, Seersholm N. Alpha1-antitrypsin deficiency. 1: epidemiology of alpha1-antitrypsin deficiency. *Thorax* 2004;**59**:164–9.
70. Seixas S, Garcia O, Trovoada MJ, Santos MT, Amorim A, et al. Patterns of haplotype diversity within the serpin gene cluster at 14q32.1: insights into the natural history of the alpha1-antitrypsin polymorphism. *Hum Genet* 2001;**108**:20–30.
71. Fagerhol MK, Hauge HE. The Pi phenotype MP. Discovery of a ninth allele belonging to the system of inherited variants of serum alpha 1 antitrypsin. *Vox Sang* 1968;**15**:396–400.
72. Ranes J, Stoller JK. A review of alpha-1 antitrypsin deficiency. *Semin Respir Crit Care Med* 2005;**26**:154–66.
73. Wittes J, Wu MC. Natural history of alpha-1 antitrypsin deficiency. In: Crystal RG, editor. *Alpha-1 antitrypsin deficiency*. New York: Marcel Dekker; 1996. p. 281–91.
74. 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**:818–900.
75. Bals R, Koczulla R, Kotke V, Andress J, Blackert K, et al. Identification of individuals with alpha-1-antitrypsin deficiency by a targeted screening program. *Respir Med* 2007;**101**:1708–14.
76. Sitkauskiene B, Serapinas D, Blanco I, Fernández-Bustillo E, Janciauskiene S, et al. Screening for alpha1-antitrypsin deficiency in lithuanian patients with COPD. *Respir Med* 2008;**102**:1654–8.
77. Colp C, Pappas J, Moran D, Lieberman J. Variants of alpha 1-antitrypsin in Puerto Rican children with asthma. *Chest* 1993;**103**:812–5.
78. Dowson LJ, Guest PJ, Stockley RA. Longitudinal changes in physiological, radiological, and health status measurements in alpha(1)-antitrypsin deficiency and factors associated with decline. *Am J Respir Crit Care Med* 2001;**164**:1805–9.
79. Alam S, Li Z, Janciauskiene S, Mahadeva R. Oxidation of Z {alpha}1-antitrypsin by cigarette smoke induces polymerization: a novel mechanism of early-onset emphysema. *Am J Respir Cell Mol Biol*; 2010 [Epub ahead of print].
80. Hidvegi T, Ewing M, Hale P, Dippold C, Beckett C, et al. An autophagy-enhancing drug promotes degradation of mutant alpha1-antitrypsin Z and reduces hepatic fibrosis. *Science* 2010;**329**:229–32.
81. Fairbanks KD, Tavill AS. Liver disease in alpha 1-antitrypsin deficiency: a review. *Am J Gastroenterol* 2008;**103**:2136–41.
82. Perlmutter DH, Brodsky JL, Balistreri WF, Trapnell BC. Molecular pathogenesis of alpha-1-antitrypsin deficiency-associated liver disease: a meeting review. *Hepatology* 2007;**45**:1313–23.
83. Avezov E, Frenkel Z, Ehrlich M, Herscovics A, Lederkremer GZ. Endoplasmic reticulum (ER) mannosidase I is compartmentalized and required for N-glycan trimming to Man5-6GlcNAc2 in glycoprotein ER-associated degradation. *Mol Biol Cell* 2008;**19**:216–25.
84. Pan S, Huang L, McPherson J, Muzny D, Rouhani F, et al. Single nucleotide polymorphism-mediated translational suppression of endoplasmic reticulum mannosidase I modifies the onset of end-stage liver disease in alpha1antitrypsindeficiency. *Hepatology* 2009;**50**:275–81.
85. Primhak RA, Tanner MS. Alpha-1 antitrypsin deficiency. *Arch Dis Child* 2001;**85**:2–5.
86. Francavilla R, Castellaneta SP, Hadzic N, Chambers SM, Portmann B, et al. Prognosis of alpha-1-antitrypsin deficiency-related liver disease in the era of paediatric liver transplantation. *J Hepatol* 2000;**32**:986–92.
87. Fleming LE, Oquendo S, Bean JA, Tamer R, Finn S, et al. Pilot detection study of alpha(1) antitrypsin deficiency in a targeted population. *Am J Med Genet* 2001;**103**:69–74.
88. Kalsheker NA. Alpha1-antitrypsin deficiency: best clinical practice. *J Clin Pathol* 2009;**62**:865–9.
89. Ellis G, Goldberg DM, Spooner RJ, Ward AM. Serum enzyme tests in diseases of the liver and biliary tree. *Am J Clin Pathol* 1978;**70**:248–58.
90. Stoller JK, Fromer L, Brantly M, Stocks J, Strange C. Primary care diagnosis of alpha-1 antitrypsin deficiency: issues and opportunities. *Cleve Clin J Med* 2007;**74**:869–74.
91. Hendrick SJ, Silverman AK, Solomon AR, Headington JT. Alpha 1-antitrypsin deficiency associated with panniculitis. *J Am Acad Dermatol* 1988;(4 Pt 1):684–92.
92. Requena L, Sánchez Yus E. Panniculitis. Part II. Mostly lobular panniculitis. *J Am Acad Dermatol* 2001;**45**:325–61 [quiz 62–4].
93. Smith KC, Su WP, Pittelkow MR, Winkelmann RK. Clinical and pathologic correlations in 96 patients with panniculitis, including 15 patients with deficient levels of alpha 1-antitrypsin. *J Am Acad Dermatol* 1989;**21**:1192–6.
94. Gross B, Grebe M, Wencker M, Stoller JK, Bjursten LM, et al. New Findings in PiZZ alpha1-antitrypsin deficiency-related panniculitis. Demonstration of skin polymers and high dosing requirements of intravenous augmentation therapy. *Dermatology* 2009;**218**:370–5.
95. O’Riordan K, Blei AT, Rao MS, Abecassis MM. Alpha 1-antitrypsin deficiency-associated panniculitis: resolution with intravenous alpha1-antitrypsin administration and liver transplantation. *Transplantation* 1997;**63**:480–2.
96. Furey NL, Golden RS, Potts SR. Treatment of alpha-1-antitrypsin deficiency, massive edema, and panniculitis with alpha-1 protease inhibitor. *Ann Intern Med* 1996;**125**:699.

97. Esnault VL, Testa A, Audrain M, Rogé C, Hamidou M, et al. Alpha 1-antitrypsin genetic polymorphism in ANCA-positive systemic vasculitis. *Kidney Int* 1993;43:1329–32.
98. O'Donoghue DJ, Guickian M, Blundell G, Winney RJ. Alpha-1-proteinase inhibitor and pulmonary haemorrhage in systemic vasculitis. *Adv Exp Med Biol* 1993;336:331–5.
99. Esnault VL, Audrain MA, Sesboué R. Alpha-1-antitrypsin phenotyping in ANCA-associated diseases: one of several arguments for protease/antiprotease imbalance in systemic vasculitis. *Exp Clin Immunogenet* 1997;14:206–13.
100. Teh LG, Steven MM, Capell HA. Alpha-1-antitrypsin associated liver disease in rheumatoid arthritis. *Postgrad Med J* 1985;61:171–2.
101. Cox DW. Transmission of Z allele from heterozygotes for alpha1-antitrypsin deficiency. *Am J Hum Genet* 1980;32:455–7.
102. Beckman G, Beckman L, Bjelle A, Dahlqvist SR. Alpha-1-antitrypsin types and rheumatoid arthritis. *Clin Genet* 1984;25:496–9.
103. Davis ID, Burke B, Freese D, Sharp HL, Kim Y. The pathologic spectrum of the nephropathy associated with alpha 1-antitrypsin deficiency. *Hum Pathol* 1992;23:57–62.
104. Noble-Jamieson G, Thiru S, Johnston P, Friend P, Barnes ND. Glomerulonephritis with end-stage liver disease in childhood. *Lancet* 1992;339:706–7.
105. Sandström CS, Ohlsson B, Melander O, Westin U, Mahadeva R, et al. An association between type 2 diabetes and alpha-antitrypsin deficiency. *Diabet Med* 2008;25:1370–3.
106. Valverde R, Rosales B, Ortiz-de Frutos FJ, Rodríguez-Peralto JL, Ortiz-Romero PL. Alpha-1-antitrypsin deficiency panniculitis. *Dermatol Clin* 2008;26:447–51.
107. Lyon MJ. Metabolic panniculitis: alpha-1 antitrypsin deficiency panniculitis and pancreatic panniculitis. *Dermatol Ther* 2010;23:368–74.
108. Esnault VL. ANCA-positive vasculitis and alpha 1-antitrypsin deficiency: could free ANCA antigens released by neutrophils mediate vasculitic lesions? *Nephrol Dial Transplant* 1997;12:249–51.
109. Breit SN, Wakefield D, Robinson JP, Luckhurst E, Clark P, et al. The role of alpha 1-antitrypsin deficiency in the pathogenesis of immune disorders. *Clin Immunol Immunopathol* 1985;35:363–80.
110. Kilty SJ, Desrosiers MY. Chronic sinusitis and alpha1-antitrypsin deficiency: potential role for protease in rhinosinusitis? *J Otolaryngol Head Neck Surg* 2008;37:E179–82.
111. Maune S, Rath NF, Görögh T, Steinert R. Genetic disposition to chronic polypoid sinusitis and alpha 1-proteinase inhibitor deficiency types. *HNO* 1995;43:537–9.
112. Fearnley IR, Spalton DJ, Ward AM, Slavin B, Muncey F. Alpha 1-antitrypsin phenotypes in acute anterior uveitis. *Br J Ophthalmol* 1988;72:636–9.
113. Needham M, Stockley RA. Alpha 1-antitrypsin deficiency. 3: clinical manifestations and natural history. *Thorax* 2004;59:441–5.
114. Witt H, Kage A, Luck W, Becker M. Alpha1-antitrypsin genotypes in patients with chronic pancreatitis. *Scand J Gastroenterol* 2002;37:356–9.
115. Rabassa AA, Schwartz MR, Ertan A. Alpha 1-antitrypsin deficiency and chronic pancreatitis. *Dig Dis Sci* 1995;40:1997–2001.
116. Gambichler T, Reich S, Banasch M, Altmeyer P. Complex extra-intestinal complications of ulcerative colitis in a patient with alpha1-antitrypsin deficiency. *Eur J Med Res* 2006;11:135–8.
117. Folwaczny C, Urban S, Schröder M, Hofmann B, Noehl N, et al. Alpha1-antitrypsin alleles and phenotypes in patients with inflammatory bowel disease. *Scand J Gastroenterol* 1998;33:78–81.
118. Pons Romero F, Casafont F, Rodriguez de Lope C, San Miguel G, Artiñano E, et al. Could alpha 1 antitrypsin deficiency have any role in the development of celiac sprue after gastric operations? *J Clin Gastroenterol* 1986;8:559–61.
119. Klasen EC, Polanco I, Biemond I, Vazquez C, Peña AS. Alpha 1-antitrypsin and coeliac disease in Spain. *Gut* 1980;21:948–50.
120. Elzouki AN, Tóth E, Florén CH, Lindgren S, Fork FT, et al. Alpha1-antitrypsin deficiency may be a risk factor for duodenal ulcer in patients with helicobacter pylori infection. *Scand J Gastroenterol* 2000;35:32–5.
121. Andre F, Andre C, Lambert R, Descos F. Prevalence of alpha1-antitrypsin deficiency in patients with gastric or duodenal ulcer. *Biomedicine* 1974;21:222–4.
122. Lisowska-Myjak B, Pachecka J, Kaczyńska B, Miszkurka G, Kadziela K. Serum protease inhibitor concentrations and total antitrypsin activity in diabetic and non-diabetic children during adolescence. *Acta Diabetol* 2006;43:88–92.
123. Callea F, Fevery J, Desmet VJ. Simultaneous alpha-1-antitrypsin accumulation in liver and pancreas. *Hum Pathol* 1984;15:293–5.
124. Ting SM, Toth T, Caskey F. Alpha1-antitrypsin (A1AT) deficiency presenting with IgA nephropathy and nephrotic syndrome: is renal involvement caused by A1AT deposition? *Clin Nephrol* 2008;70:159–62.
125. Dieriks B, Hoorens A, Vanden Houte K, Verbeelen D. Alpha-1-antitrypsin deficiency and mesangio-capillary glomerulonephritis in an elderly patient. *Nephrol Dial Transplant* 2006;21:2027.
126. Szönyi L, Dobos M, Vásárhelyi B, Héninger E, Vas T, et al. Prevalence of alpha1-antitrypsin phenotypes in patients with IgA nephropathy. *Clin Nephrol* 2004;62:418–22.
127. Ablin JN, Bar-Shira A, Yaron M, Orr-Urtreger A. Candidate-gene approach in fibromyalgia syndrome: association analysis of the genes encoding substance P receptor, dopamine transporter and alpha1-antitrypsin. *Clin Exp Rheumatol* 2009;27:S33–8.
128. Blanco I, Bérizte N, Argüelles M, Cárcaba V, Fernández F, et al. Abnormal overexpression of mastocytes in skin biopsies of fibromyalgia patients. *Clin Rheumatol* 2010;29:1403–12.
129. Schelfout K, Tjalma WA, Cooremans ID, Coeman DC, Colpaert CG, et al. Observations of an idiopathic granulomatous mastitis. *Eur J Obstet Gynecol Reprod Biol* 2001;97:260–2.
130. Frederick WG, Enriquez R, Bookbinder MJ. Peripheral neuropathy associated with alpha 1-antitrypsin deficiency. *Arch Neurol* 1990;47:233–5.
131. Elzouki AN, Rydén Ahlgren A, Länne T, Sonesson B, Eriksson S. Is there a relationship between abdominal aortic aneurysms and alpha1-antitrypsin deficiency (PiZ)? *Eur J Vasc Endovasc Surg* 1999;17:149–54.
132. Elzouki AN, Eriksson S. Severe alpha 1-antitrypsin deficiency and intracranial aneurysms. *Lancet* 1994;343:1037.
133. Pezzini A, Magoni M, Corda L, Pini L, Medicina D, et al. Alpha-1-antitrypsin deficiency-associated cervical artery dissection: report of three cases. *Eur Neurol* 2002;47:201–4.
134. Schardey HM, Hernandez-Richter T, Klueppelberg U, Tutsch-Bauer E, Lauterjung L. Alleles of the alpha-1-antitrypsin phenotype in patients with aortic aneurysms. *J Cardiovasc Surg (Torino)* 1998;39:535–9.
135. Talmud PJ, Martin S, Steiner G, Flavell DM, Whitehouse DB, et al. Diabetes atherosclerosis intervention study investigators. Progression of atherosclerosis is associated with variation in the alpha1-antitrypsin gene. *Arterioscler Thromb Vasc Biol* 2003;23:644–9.
136. Yang P, Sun Z, Krowka MJ, Aubry MC, Bamlet WR, et al. Alpha1-antitrypsin deficiency carriers, tobacco smoke, chronic obstructive pulmonary disease, and lung cancer risk. *Arch Intern Med* 2008;168:1097–103.

137. Li Y, Krowka MJ, Qi Y, Katzmann JA, Song Y, et al. Alpha1-antitrypsin deficiency carriers, serum alpha 1-antitrypsin concentration, and non-small cell lung cancer survival. *J Thorac Oncol*; 2010 [Epub ahead of print].
138. Topic A, Ljujic M, Nikolic A, Petrovic-Stanojevic N, Dopudja-Pantic V, et al. Alpha-1-antitrypsin phenotypes and neutrophil elastase gene promoter polymorphisms in lung cancer. *Pathol Oncol Res*; 2010 [Epub ahead of print].
139. Lindor NM, Yang P, Evans I, Schowalter K, De Andrade M, et al. Alpha-1-antitrypsin deficiency and smoking as risk factors for mismatch repair deficient colorectal cancer: a study from the colon cancer family registry. *Mol Genet Metab* 2010;**99**: 157–9.
140. Laurell CB, Eriksson S. The electrophoretic alpha-1-globulin pattern of serum in alpha1-antitrypsin deficiency. *Scan J Clin Lab Invest* 1963;**15**:132–40.