

12.13 α 1- Antitrypsin deficiency and the serpinopa

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ESSENTIALS α 1-Antitrypsin is an acute phase glycoprotein synthesized by the liver that functions as an inhibitor of a range of proteolytic enzymes, most importantly neutrophil elastase in the lung. Ninety-five per cent of severe plasma deficiency of α 1-antitrypsin results from homozygosity for the Z allele (Glu342Lys), which causes the protein to undergo a conformational transition and form ordered polymers that are retained within hepatocytes as periodic acid-Schiff-positive, diastase-resistant inclusions. Clinical features—all adults homozygous for the Z allele of α 1-antitrypsin have a minor degree of portal fibrosis that is often sub-clinical, but up to 50% have clinically evident cirrhosis and occasionally hepatocellular carcinoma. They also develop panlobular emphysema that typically affects the lung bases and is greatly exacerbated by smoking. Cor pulmonale and polycythaemia are late features. Diagnosis and management—severe genetic deficiency of α 1- antitrypsin is readily diagnosed by low plasma levels and the virtual absence of the α 1-band on protein electrophoresis. Patients should abstain from smoking and avoid agents that cause hepatic injury, such as excessive alcohol and obesity. Emphysema is treated along conventional lines. α 1-Antitrypsin replacement therapy is widely used in North America to slow the progression of the lung disease and has recently been licensed by the European Medicines Agency, but its clinical efficacy remains contentious and it has no effect on liver disease. Clinical trials are underway to ‘knock down’ the expression of mutant Z α 1-antitrypsin within hepatocytes to try to prevent cirrhosis. Other serpinopathies—the polymerization that underlies α 1- antitrypsin deficiency is found in other members of the serine protease inhibitor (or serpin) superfamily to cause diseases as diverse as thrombosis (antithrombin), angio-oedema (C1 inhibitor), and dementia (neuroserpin). Introduction α 1-Antitrypsin deficiency was first described by Carl-Bertil Laurell and Sten Eriksson in 1963 when they reported five individuals in whom there was a deficiency of the α 1 band on serum protein electrophoresis. Three of the individuals had emphysema and one had a family history of emphysema. α 1-Antitrypsin is a 394-amino acid, 52-

kDa acute phase glycoprotein synthesized by the liver, the lung and gut epithelial cells, neutrophils, and alveolar macrophages. It is present in the plasma at a concentration of between 0.9 and 1.8 g/litre and functions as an inhibitor of a range of proteolytic enzymes of which the most important is neutrophil elastase. α 1-Antitrypsin deficiency results from point mutations that cause the protein to misfold and be retained within hepatocytes which in turn causes liver disease. The lack of circulating α 1-antitrypsin causes uncontrolled tissue digestion within the lung and hence emphysema. Genetics and pathogenesis of disease Genetics α 1-Antitrypsin is subject to genetic variation resulting from mutations in the 12.2-kb, 7-exon SERPINA1 gene on the long arm of chromosome 14 (14q32.1) (OMIM 107400). Over 100 allelic variants have been reported and classified using the PI (protease inhibitor) nomenclature that assesses α 1-antitrypsin mobility in isoelectric focusing analysis. Normal α 1-antitrypsin migrates in the middle (M) and variants are designated A (anodal) to L if they migrate faster than M, and N to Z if they migrate more slowly. Many of these variants have been sequenced at the DNA level and shown to result from point mutations in the α 1-antitrypsin gene (Table 12.13.1). For example, the Z allele results from the substitution of a positively charged lysine for a negative glutamic acid at position 342. The S allele results from the substitution of a neutral valine for a glutamic acid at position 264. Point mutations are inherited as a simple Mendelian trait; the normal genotype is designated PI MM or PI M, a heterozygote for the Z gene is PI MZ, and a homozygote is PI ZZ or PI Z. α 1-Antitrypsin alleles are codominantly expressed, with each allele contributing to the plasma level of protein. Therefore each of the deficiency alleles results in a characteristic decrease in the plasma concentration of α 1-antitrypsin; the S variant forms 60% of the normal M concentration and the Z variant 10 to 15%. Thus combinations of alleles have predictable effects: the MZ heterozygote has an α 1-antitrypsin plasma level of 60% (50% from the normal M allele 12.13 α 1-Antitrypsin deficiency and the serpinopathies David A. Lomas

section 12 Metabolic disorders 2236 Table 12.13.1 Pathogenic alleles that cause α 1-antitrypsin deficiency. The letter represents the migration on isoelectric focusing and the name is typically the origin of the first reported individual Variant Mutation Molecular basis of disease Clinical features Epidemiology Deficiency alleles I Arg39Cys Protein misfolding; able to form heteropolymers with

Z α 1-antitrypsin Reduced serum protein No clear disease association Disease only reported in compound heterozygotes King's Hisp334Asp Rapid polymerization in hepatocyte endoplasmic reticulum, delayed secretion Neonatal jaundice. Presumed high risk of emphysema in homozygote/compound heterozygote Case report Mheerlen Pro369Leu Retained in the endoplasmic reticulum, none secreted High risk of emphysema in homozygotes/compound heterozygotes. Unknown liver disease risk Case report Mmalton Δ 52Phe (M2 variant) Intracellular degradation and polymerization; low serum concentration Well-established association with liver disease and emphysema in homozygotes Most common rare deficiency allele in Sardinia; seen sporadically in the UK and Canada Mmineral springs Gly67Glu Abnormal post-translational biosynthesis but no polymerization; low serum concentration Emphysema in homozygotes Unusual as described in a Afro-Caribbean individual in the United States Mnichinan Δ 52Phe and Gly148Arg Intracellular polymerization in hepatocytes and plasma deficiency Risk of liver disease and emphysema Case report (Japanese family with consanguineous origin) Mpalerma Δ 51Phe Serum deficiency High risk of emphysema in homozygotes Case report Mprocida Leu41Pro Unstable protein structure leading to intracellular degradation; reduced inhibitory activity of circulating protein High risk of emphysema in homozygotes Case report Mvall d'hebron (=Mwurzburg) Pro369Ser Retained in the

endoplasmic reticulum, none secreted Presumed risk of emphysema in homozygotes/compound heterozygotes; 50% normal serum α 1-antitrypsin level in M/vall d'hebron (/wurzberg) heterozygotes Case reports from Spain and Germany Mvarallo Δ 41-51, replaced with 22 bp sequence creating stop codon at 70-71 Unknown intracellular defect Presumed risk of emphysema in homozygotes/compound heterozygotes; 50% normal serum α 1-antitrypsin level in M/Mvarallo heterozygote Case report Pittsburgh Met358 Arg Function altered to an antithrombin Fatal bleeding disorder Case report Plowell (=QO Cardiff) and Pduarte Asp256Val (M1 and M4 alleles respectively) Intracellular degradation and plasma deficiency Increased risk of emphysema in Z/QO compound heterozygotes Case report S Glu264Val Protein misfolding and reduced secretion; able to form heteropolymers with Z α 1-antitrypsin Emphysema seen in SZ heterozygotes but less severe than in ZZ homozygotes. Cirrhosis reported in SZ heterozygotes Most common deficiency variant. Carrier frequency: 1:5 Northern Europe 1:30 USA 1:23 Australian Caucasian 1:26 New Zealand Caucasian Rare/non-existent in Asia, Africa and Australian Aboriginals Siiyama Ser53Phe Intracellular degradation and polymerization; low serum concentration Liver disease and emphysema in homozygotes Rare, but most common deficiency allele in Japan Wbethesda Ala336Thr Intracellular degradation, serum levels 50% normal Risk of liver disease and emphysema in compound heterozygotes Case report Ybarcelona Asp256Val and Pro391His Unknown intracellular defect; very low serum protein Severe emphysema reported in homozygote Case report Z Glu342 Lys Intracellular degradation and polymerization; low serum concentration Homozygotes: well-established association with liver disease and emphysema. MZ heterozygotes may be more susceptible to airflow obstruction and chronic liver disease Commonest severe deficiency variant. Carrier frequency: 1:27 Northern Europe 1:83 USA 1:75 Australian Caucasian 1:46 New Zealand Caucasian Not seen in China, Japan, Korea, Malaysia, Northern and Western Africa

2237 12.13 α 1-Antitrypsin deficiency and the serpinopathies Variant Mutation Molecular basis of disease Clinical features Epidemiology Zausburg (=Ztun) Glu342 Lys (M2 variant) Intracellular degradation and polymerization; low serum concentration Liver disease and emphysema in homozygotes/compound heterozygotes Case report Zwrexham Ser-19Leu and Glu342 Lys (Z mutation) Poor expression, low serum concentration Emphysema reported in compound Z/ Zwrexham compound heterozygotes. Unclear whether Ser-19 Leu would cause disease in absence of Z mutation Case report Null (QO) alleles QO Bellingham Lys217 stop codon No detectable α 1-antitrypsin mRNA High risk of emphysema in homozygotes/compound heterozygotes Case report QO Bolton Δ 1bpPro362 causing stop codon at 373 Truncated protein; intracellular degradation and no secreted protein High risk of emphysema in homozygotes/compound heterozygotes Case report QO Cairo Lys259 stop codon Unknown intracellular defect High risk of emphysema in homozygotes/compound heterozygotes Case report QO Clayton Pro362 insC causing stop codon at 376 Truncated protein; intracellular degradation and no secreted protein High risk of emphysema in homozygotes/compound heterozygotes Case report QO Devon (=QO Newport) Gly115Ser and Glu342 Lys (Z mutation) Intracellular degradation and polymerization; reduced serum concentration Risk of emphysema and liver disease in compound heterozygotes. Unclear whether Gly115Ser would cause disease in absence of Z mutation Case report QO Granite Falls Δ 1bpTyr160 causing stop codon No detectable α 1-antitrypsin mRNA Severe emphysema reported in Z compound heterozygote Case report QO Hong Kong Δ 2bpLeu318 causing stop codon at 334 Truncated protein; intracellular aggregation (no polymerization), degradation and no secreted

protein High risk of emphysema in homozygotes/compound heterozygotes Case reports (individuals of Chinese descent) QO Isola di Procida Δ 17 Kb inc. exons II-V No detectable α 1-antitrypsin mRNA Emphysema reported in Mprocida compound heterozygote Case report QO Lisbon Thr68Ile Truncated protein; not secreted High risk of emphysema in homozygotes. 50% normal serum α 1-antitrypsin in M/QO Lisbon heterozygotes Case report QO Ludwisghafen Ile92 Asn Disruption of tertiary structure; intracellular degradation and no detectable serum protein High risk of emphysema in homozygotes/compound heterozygotes Case report QO Mattawa (M1allele)/QO Ourém (M3 allele) Leu353Phe causing stop codon at 376 Truncated protein; misfolding and reduced serum levels Emphysema reported in homozygotes Case reports QO Riedenburg Whole gene deletion No gene expression High risk of emphysema in homozygotes/compound heterozygotes Case report QO Saarbueken 1158dupC causing stop codon at 376 Truncated protein; not secreted High risk of emphysema in homozygotes. 50% normal serum α 1-antitrypsin in M/QO Saarbueken heterozygotes Case report QO Trastevere Try194 stop codon Reduced mRNA, degradation of truncated protein; not secreted Emphysema reported in compound heterozygote Case report QO West Δ Gly164 Lys191 Aberrant mRNA splicing, intracellular degradation and no detectable serum protein Emphysema reported in compound heterozygote Case report Reproduced from Dickens, J.A. and Lomas D.A. (2011) Why has it been so difficult to prove the efficacy of alpha-1-antitrypsin replacement therapy? Insights from the study of disease pathogenesis. *Drug Des Devel Ther*, 5, 391-405 with permission. Table 12.13.1 Continued

section 12 Metabolic disorders 2238 and 10% from the Z allele), the MS heterozygote 80%, and the SZ heterozygote 40%. Rarely, point mutations can result in null alleles that express no functional α 1-antitrypsin and there is a case report of a dysfunctional α 1-antitrypsin that no longer inhibits neutrophil elastase but which can inhibit other serine proteases. The Pittsburgh mutant (Met358Arg) converted α 1-antitrypsin into an inhibitor of thrombin, thereby causing a fatal bleeding diathesis. The molecular basis of α 1-antitrypsin deficiency Liver disease α 1-Antitrypsin functions by presenting its reactive-centre methio- nine residue on an exposed loop of the molecule such that it forms an ideal substrate for the enzyme neutrophil elastase (Fig. 12.13.1). The conformational transition that ensues results in the formation of a stable complex that inhibits the enzyme and allows it to be elim- inated from sites of inflammation. The Z mutation (Glu342Lys) results in normal translation of the gene, but 85% of the Z α 1- antitrypsin is retained within the endoplasmic reticulum with only 10 to 15% entering the circulation. The Z mutation distorts the relationship between the loop and the A β -pleated sheet that forms the major feature of the molecule. The consequent perturbation in structure allows the reactive-centre loop of one α 1- molecule to lock into the A sheet of a second to form a dimer which then extends to form chains of loop-sheet polymers (Fig. 12.13.1). The forma- tion of these polymers is temperature and concentration dependent and is localized to the endoplasmic reticulum of the hepatocyte (Fig. 12.13.2). These chains of polymers become interwoven to P D M* M Z Fig. 12.13.1 Mutant Z α 1- antitrypsin is retained within hepatocytes as polymers. The structure of α 1-antitrypsin is centred on β -sheet A (green) and the mobile reactive-centre loop (red). Polymer formation results from the Z variant of α 1-antitrypsin (Glu342Lys at P17; arrowed) or mutations in the shutter domain (blue circle) that open β -sheet A to favour partial loop insertion and the formation of an unstable intermediate (M*). The patent β -sheet A can accept the loop of another molecule to form a dimer (D) which then extends into polymers. From Gooptu, B., Hazes, B., Chang, W.-S.W., Dafforn, T.R., Carrell, R.W., Read, R. & Lomas, D.A. (2000). Inactive conformation of the serpin α 1-antichymotrypsin indicates two stage insertion of the reactive loop; implications for inhibitory

function and conformational disease.

Proc. Natl. Acad. Sci (USA), 97, 67–72, with permission. (a) (b) (c) Fig. 12.13.2 Z α 1-antitrypsin is retained within hepatocytes as intracellular inclusions. These inclusions are PAS positive and diastase resistant (a) and are associated with neonatal hepatitis and hepatocellular carcinoma. (b) Electron micrograph of a hepatocyte from the liver of a patient with Z α 1-antitrypsin deficiency shows the accumulation of α 1-antitrypsin within the rough endoplasmic reticulum (arrow). These inclusions are composed of chains of α 1-antitrypsin polymers (c). (b) and (c) Reproduced from (i) Lomas, D.A., Evans, D.L., Finch, J.T. & Carrell, R.W. (1992). The mechanism of Z α 1-antitrypsin accumulation in the liver. *Nature*, 357, 605– 607. Copyright © 1992, Springer Nature. (ii) Lomas, D.A., Finch, J.T., Seyama, K., Nukiwa, T. & Carrell, R.W. (1993). α 1-antitrypsin Siiyama (Ser53→Phe); further evidence for intracellular loop-sheet polymerisation. *J. Biol. Chem.*, 268, 15333–15335, with permission.

2239 12.13 α 1-Antitrypsin deficiency and the serpinopathies form the insoluble intracellular aggregates that are the hallmark of α 1-antitrypsin liver disease. The process of intrahepatic polymerization also underlies the severe plasma deficiency of the rare Siiyama (Ser53Phe), Mmalton (deletion of residue 52) and King's (His334Asp) deficiency alleles and the mild plasma deficiency of the S (Glu264Val) and I (Arg39Cys) variants (Table 12.13.1). There is a strong genotype-phenotype correlation that can be explained by the molecular instability caused by the mutation and in particular the rate at which the mutant forms polymers. Those mutants that cause the most rapid polymerization cause the most retention of α 1-antitrypsin within the liver. This in turn correlates with the greatest risk of liver damage and cirrhosis, and the most severe plasma deficiency. Misfolded Z α 1-antitrypsin within hepatocytes is cleared by the proteosome but the ordered polymers are not detected by the unfolded protein response and are handled by less well understood pathways including autophagy. Lung disease The development of emphysema associated with α 1-antitrypsin deficiency is greatly accelerated by tobacco smoking. Emphysema results from uncontrolled enzymatic activity within the lung with those individuals with plasma α 1-antitrypsin levels of less than 40% of normal being most at risk. This is compounded by a fivefold reduction in association rate kinetics with neutrophil elastase caused by the Z mutation and the polymerization of secreted Z α 1-antitrypsin within the airways and alveoli. The formation of polymers inactivates α 1-antitrypsin (thereby further reducing the protein available to inhibit neutrophil elastase) and the polymers themselves are chemotactic for neutrophils and so may drive some of the excessive inflammation that characterizes the lung disease associated with α 1-antitrypsin deficiency. Epidemiology Two point mutations have been shown to explain the vast majority of cases of α 1-antitrypsin deficiency. The Z allele causes the most severe plasma deficiency and is most prevalent in southern Scandinavia and the north-western European seaboard where 4% of the population are MZ heterozygotes and 1 in 1700 are PI Z homozygotes. The gene frequency of the Z allele reduces towards the south and east of Europe. In contrast, the S allele causes only mild plasma deficiency and is most common in southern Europe where up to 28% of the population are MS heterozygotes. The S allele becomes less frequent as one moves north-east. The frequencies of the Z allele in the United States of America are similar to the lowest frequencies in Europe but the S allele is more common than in northern Europeans. α 1-Antitrypsin deficiency is infrequent in Asian, African, and Middle Eastern populations. It is also rare in Japan, but when present it is usually due to the Siiyama mutation (Ser53Phe). In the genetically isolated island of Sardinia, the commonest cause of severe α 1-antitrypsin deficiency is the Mmalton mutation (deletion of residue 52). The Z allele is believed to have arisen from a single origin 66 generations

or 2000 years ago. The high frequency in southern Scandinavia suggests that the mutation arose in the Viking population. The date of origin implies that the allele arose when the Vikings populated mid/northern Europe and before their migration to Scandinavia. It is likely that the Z allele of α 1-antitrypsin was then distributed across northern Europe by the Viking raiders between 800 and 1100 ad, and then to the United States of America and the rest of the world during migration over the past 200 years. The S allele appears to have arisen in the north of the Iberian peninsula, but the date of origin is uncertain. This mutation was similarly introduced into North America by mass migration.

Clinical features α 1-Antitrypsin deficiency and liver disease

The accumulation of abnormal protein starts in utero and is characterized by periodic acid-Schiff (PAS)-positive, diastase-resistant inclusions of α 1-antitrypsin in the periportal cells (Fig. 12.13.2). Seventy-three per cent of Z α 1-antitrypsin homozygote infants have a raised serum alanine aminotransferase in the first year of life but in only 15% of people is it still abnormal by 12 years of age. Similarly serum bilirubin is raised in 11% of PI Z infants in the first 2–4 months but falls to normal by 6 months of age. One in ten infants develops cholestatic jaundice and 6% develop clinical evidence of liver disease without jaundice. These symptoms usually resolve by the second year of life but approximately 15% of patients with cholestatic jaundice progress to juvenile cirrhosis. The overall risk of death from liver disease in PI Z children during childhood is 2 to 3%, with boys being at more risk than girls. All adults with the Z allele of α 1-antitrypsin have slowly progressive hepatic damage that is often subclinical and only evident as a minor degree of portal fibrosis. However, up to 50% of Z α 1-antitrypsin homozygotes present with clinically evident cirrhosis and occasionally with hepatocellular carcinoma.

α 1-Antitrypsin deficiency and emphysema

Patients with emphysema related to α 1-antitrypsin deficiency usually present with increasing dyspnoea with cor pulmonale and polycythaemia occurring late in the course of the disease. Emphysema associated with Z α 1-antitrypsin deficiency differs from 'usual chronic obstructive pulmonary disease (COPD)' with normal levels of M α 1-antitrypsin in that it affects predominantly the bases rather than the apices of the lungs, it is associated with panlobular rather than centrilobular disease, and it results from the expression of different genes when assessed by microarray analysis. However, in many cases the distribution of disease is indistinguishable from 'usual COPD'. High-resolution CT scans are the most accurate method of assessing the distribution of panlobular emphysema and for monitoring the progress of the pulmonary disease, although this currently has little value outside clinical trials. Lung function tests are typical for emphysema with a reduced FEV1/FVC ratio (forced expiratory volume in 1 s/forced vital capacity) and FEV1, gas trapping (raised residual volume/total lung capacity ratio), and a low gas-transfer factor. Partial reversibility of airflow obstruction (as defined by an increase of 12% and 200 ml in FEV1) is common in individuals with COPD secondary to α 1-antitrypsin deficiency as it is in many individuals with COPD. The most important factor in the development and progression of emphysema in α 1-antitrypsin deficiency is tobacco smoking.

section 12 Metabolic disorders 2240 Other conditions associated with α 1-antitrypsin deficiency

α 1-Antitrypsin deficiency is associated with an increased prevalence of asthma, panniculitis, granulomatosis with polyangiitis, and possibly pancreatitis, gallstones, bronchiectasis, and intracranial and intra-abdominal aneurysms. There appears to be a reduced risk of cardiovascular disease.

Clinical investigation

The severe genetic deficiency of α 1-antitrypsin is readily diagnosed by low plasma levels and the virtual absence of the α 1 band on protein electrophoresis. As α 1-antitrypsin is an acute phase protein, most laboratories will report levels with another acute phase reactant, such as α 1-antichymotrypsin or C-reactive protein, which allows an assessment of the

likelihood of deficiency in the context of the inflammatory response. The acute phase response raises the plasma level of α 1-antitrypsin, but the plasma level of the PI Z homozygote can never reach the normal range. The deficiency variant is then assigned a PI phenotype according to the migration of the protein on an isoelectric focusing gel. The mutation underlying the deficiency can be determined by sequencing the SERPINA1 gene. Commercial kits permit detection of the Z and S alleles but will not detect null or other rare alleles.

Treatment The treatment of α 1-antitrypsin deficiency depends largely on the avoidance of stimuli causing repeated pulmonary inflammation—primarily smoking. Patients with α 1-antitrypsin deficiency-related emphysema should receive conventional therapy with trials of bronchodilators and inhaled corticosteroids, pulmonary rehabilitation, and, where appropriate, assessment for long-term oxygen therapy and lung transplantation. The role of lung volume-reduction surgery in this group is less clear as the disease is basal rather than apical and resections of this region are technically more difficult. Any benefits are shorter lasting than in individuals with COPD and normal levels of α 1-antitrypsin. The lung disease results from a deficiency in the anti-elastase screen. This may be rectified biochemically by intravenous infusions of α 1-antitrypsin. Registry data suggest that individuals with α 1-antitrypsin deficiency and an FEV1 of 35 to 49% predicted may derive benefit from replacement therapy. One controlled trial has shown reduced progression of CT markers of emphysema in individuals receiving intravenous α 1-antitrypsin, but none has been powered to detect an effect on patient-reported outcomes or mortality. α 1-Antitrypsin replacement therapy is widely used in North America and has recently been licensed by the European Medicines Agency but its clinical efficacy remains contentious. All Z homozygotes have some liver damage and, as such, would be wise to avoid alcohol abuse and obesity. PI Z homozygotes should be monitored for the persistence of hyperbilirubinaemia as this, along with deteriorating results of coagulation studies, indicates the need for liver transplantation. Clinical trials are underway to ‘knock down’ the expression of mutant Z α 1-antitrypsin within hepatocytes to prevent the protein overload that causes cirrhosis. Parents with a child with severe Z α 1-antitrypsin liver disease may require genetic counselling. The likelihood of similar severe liver damage in a subsequent Z homozygote sibling is approximately 20%.

The uncommon α 1-antitrypsin deficiency-associated panniculitis usually responds to dapsone, 100 to 150 mg daily, for 2 to 4 weeks, but occasionally it necessitates the administration of intravenous α 1-antitrypsin replacement therapy.

Prognosis Estimates of the annual rate of decline in FEV1 range from 41 to 109 ml in individuals with α 1-antitrypsin deficiency although one study reported a rate of decline of 316 ml/year in current smokers. The fastest rate of decline is in current smokers (and, to a lesser extent, ex-smokers), men, individuals aged 30–44 years, those with FEV1 values between 35 and 79% predicted, and those with a bronchodilator response. Respiratory failure accounts for 50 to 72% of deaths in individuals with α 1-antitrypsin deficiency with the second most common cause of death being liver cirrhosis (10–13%). Most children avoid significant liver damage in childhood but are still at risk of disease in adult life. The factors that predict progressive liver disease are unclear but males and the obese appear to be most at risk. The only significant cohort study has followed 184 individuals with α 1-antitrypsin deficiency (127 PI Z, 2 PI Znull, 54 PI SZ, 1 PI Snull) from birth to 34 years of age. One PI SZ and five PI Z children died in early childhood (two of liver disease and two of other causes but were found to have histological signs of cirrhosis or fibrosis at post-mortem) and 12% and 6% of PI Z subjects had abnormal liver function tests at 18 and 26 years respectively but no clinical evidence of liver disease. All the 34-year-olds had normal liver and lung function (including the 14% of individuals who were current or ex-smokers) but smoking frequency was significantly lower among individuals with α 1-antitrypsin deficiency than in the controls. A logical follow-on from the

association of α 1-antitrypsin deficiency with emphysema is an assessment of the risk of COPD in heterozygotes who carry an abnormal Z allele and a normal M allele. These individuals have plasma α 1-antitrypsin levels that are approximately 60% of normal. A population-based study demonstrated that PI MZ α 1-antitrypsin heterozygotes do not have a clearly increased risk of lung damage. However, if groups of patients are collected who already have COPD, then the prevalence of PI MZ individuals appears to be elevated. In addition, a longitudinal study has demonstrated that among COPD patients, the PI MZ heterozygotes have a more rapid decline in lung function. These data suggest that either all PI MZ α 1-antitrypsin individuals are at slightly increased risk for the development of COPD, or that a subset of the PI MZ α 1-antitrypsin subjects are at substantially increased risk of pulmonary damage if they smoke. Other 'serpinopathies' α 1-Antitrypsin is the archetypal member of a superfamily of proteins termed the serine protease inhibitors, or serpins, that have closely related structures and functions. These inhibitors control various inflammatory cascades, including coagulation (antithrombin), complement activation (C1-inhibitor), and fibrinolysis (α 2-antiplasmin).

2241 12.13 α 1-Antitrypsin deficiency and the serpinopathies Pathological processes that underlie the deficiency of one member may account for deficiency of others. Indeed, the process of polymer formation has also been reported in deficiency mutants of antithrombin, C1-inhibitor, α 1-antichymotrypsin, and heparin cofactor II. These polymers are inactive as proteinase inhibitors and so predispose the individual to thrombosis (antithrombin) and angio-oedema (C1-inhibitor). The plasma deficiency that results from the polymerization of mutants of α 1-antichymotrypsin has been associated with COPD in some (but not all) association studies, but the plasma deficiency of heparin cofactor II has yet to be associated with a clinical phenotype. Perhaps the most striking serpinopathy results from the polymerization of mutants of a neuron-specific serpin, neuroserpin, to cause the novel inclusion-body dementia known as familial encephalopathy with neuroserpin inclusion bodies (FENIB; OMIM 604218). This is inherited as an autosomal dominant trait with the inclusions of neuroserpin in the brain being PAS positive and diastase resistant, identical to those of Z α 1-antitrypsin in the liver. The six mutations that have been described show a striking inverse correlation between the rate that the protein forms polymers and the age of onset/severity of the dementia. New and emerging treatments Other treatments at earlier stages of development include gene and stem cell therapy and chemical chaperones. Vectors carrying the α 1-antitrypsin gene have been targeted to liver, lung, and muscle in animals. There is good expression of α 1-antitrypsin but further data are required to assess whether this can be achieved in humans. In particular, it is important to determine the length of time of protein expression and whether the levels of α 1-antitrypsin in the epithelial lining fluid of the lung are sufficient to prevent ongoing proteolytic damage. Genomic correction of fibroblast-derived, induced pluripotent stem cells provides a novel strategy to generate 'corrected hepatocytes' from individuals with α 1-antitrypsin deficiency, but further development is required before these can be used as 'hepatocyte replacement therapy' in humans. The antiepileptic drug carbamazepine increases autophagy and so promotes the degradation of Z α 1-antitrypsin in cell lines and mouse models of disease. Clinical trials are underway to evaluate the efficacy of this agent in α 1-antitrypsin deficiency-related liver disease in humans. The long-term aim is to exploit our understanding of the pathogenesis of α 1-antitrypsin deficiency to develop small molecules to block polymerization and so treat the associated liver and lung disease. FURTHER READING Chapman KR, et al. (2015). Intravenous augmentation treatment and lung density in severe α 1-antitrypsin deficiency (RAPID): a randomised, double-blind, placebo-controlled trial. *Lancet*, 386, 360–8. Davis RL, et al. (2002).

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