

Seminal References – Alpha 1-Antitrypsin Deficiency 1963 - 2003

Anonymous (2003). "American Thoracic Society/European Respiratory Society Statement: Standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency." American Journal of Respiratory and Critical Care Medicine **168**(7): 818-855.

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alpha 1-Antitrypsin (AAT) deficiency, also known as alpha 1-antiprotease inhibitor deficiency, is a disease caused by genetically determined AAT deficiency. It occurs as a result of inheritance of two protease inhibitor (PI) deficiency alleles from the AAT gene locus (designated PI) on chromosomal segment 14q32.1. The most common deficiency allele is PI*Z and a large majority of individuals with severe AAT deficiency are PI type ZZ. The disease occurs predominantly in white persons of European origin and its frequency in Europe and North America is comparable to that of cystic fibrosis (1 in 2000 to 1 in 7000.) Persons with AAT deficiency may have no clinical manifestations. Chronic obstructive pulmonary disease (COPD) with a high frequency of panacinar emphysema is the most prevalent clinical disorder associated with AAT deficiency and the most frequent cause of disability and death. Tobacco smoking is the major risk factor for developing COPD, which generally begins by the third decade of life, much earlier than "usual" COPD that occurs in AAT-replete individuals. Liver disease, the second most frequent clinical manifestation of AAT deficiency, typically presents as cholestasis in infancy but is usually not severe and generally remits by adolescence. Chronic liver disease develops infrequently, although AAT deficiency is the commonest cause of chronic liver disease in childhood. Cirrhosis and carcinoma of the liver affect at least 25% of AAT-deficient adults over the age of 50 years. AAT deficiency appears to be widely underdiagnosed and based on predicted gene frequencies even in the most intensely studied populations, only a small proportion of those predicted to have AAT deficiency have been diagnosed. Human AAT is available in limited quantity for augmentation therapy. This Memorandum summarizes the discussions and recommendations made by participants at a WHO meeting held in Geneva on 18-20 March 1996 to review existing knowledge about this highly prevalent genetic disorder, develop a strategy for enhancing awareness of it among health-care-givers and the general public, and explore new case-finding and disease-prevention strategies.

Alpha-1-Antitrypsin Deficiency Registry Study Group (1998). "Survival and FEV1 decline in individuals with severe deficiency of alpha1-antitrypsin." Am J Respir Crit Care Med **158**(1): 49-59.

Blank, C. A. and M. Brantly (1994). "Clinical features and molecular characteristics of alpha 1-antitrypsin deficiency." Ann Allergy **72**(2): 105-20.

Abstract: Alpha-1-antitrypsin deficiency is a common, underrecognized disorder manifested by emphysema in adults and liver disease in children. Early diagnosis and subsequent prevention of lung inflammation due to cigarette smoking, infection, and airborne irritants form the most rational approach to slow the progression of the lung destruction associated with alpha 1AT deficiency. Currently, liver transplantation is the only therapy available to patients with severe liver disease due to alpha 1AT deficiency. Less commonly, many inflammatory and/or immune-mediated diseases have been described in association with alpha 1AT deficiency. These observations are probably related to the role that alpha 1AT plays in the immune response both as a target for modulation by cytokines and as a modulator of the immune response. At present, therapy for the emphysema associated with alpha 1AT is limited to weekly augmentation therapy with recombinant alpha 1AT. Future therapeutic modalities include aerosol alpha 1AT, secretory leukocyte proteinase inhibitor, low molecular weight inhibitors of neutrophil elastase, and gene transfer via viral vector.

Brantly, M., T. Nukiwa, et al. (1988). "Molecular basis of alpha-1-antitrypsin deficiency." *Am J Med* 84(6A): 13-31.

Abstract: Alpha-1-antitrypsin (A1AT) deficiency is an autosomal hereditary disorder associated with a major reduction in serum A1AT levels. Clinically, A1AT deficiency is associated with emphysema in adults and, less commonly, liver disease in neonates. A1AT is a 52-kDa, 394-amino acid, single-chain glycoprotein normally present in serum at 150 to 350 mg/dl. The A1AT gene, composed of seven exons dispersed over 12 kb of chromosomal segment 14q31-32.3, is expressed in hepatocytes and mononuclear phagocytes. The A1AT protein, a member of the class of protease inhibitor proteins known as serpins (serine protease inhibitors), is a globular molecule composed of nine alpha-helices and three beta-pleated sheets. The major function of A1AT is to inhibit neutrophil elastase; A1AT does so through an active site centered around Met358 contained within an external stressed loop on the surface of the molecule. A1AT is a highly pleomorphic protein with greater than 75 variants determined at the protein and/or gene level. These variants can be categorized into four groups according to their serum A1AT level and function: normal, deficient, dysfunctional, and absent. There are two important salt bridges within the A1AT molecule (Glu342-Lys290; Glu263-Lys387); a mutation in the A1AT gene causing disruption of either salt bridge causes distinct molecular pathology resulting in reduced serum A1AT levels. Clinically relevant variants can be distinguished by a combination of isoelectric focusing of serum, restriction fragment length analysis of genomic DNA, oligonucleotide probes, and direct sequencing of the variant A1AT genes.

Brantly, M. L., L. D. Paul, et al. (1988). "Clinical features and history of the destructive lung disease associated with alpha-1-antitrypsin deficiency of adults with pulmonary symptoms." *Am Rev Respir Dis* 138(2): 327-36.

Abstract: Alpha-1-antitrypsin (alpha 1AT) deficiency is a hereditary disorder characterized in adults by a high risk for the development of severe destructive lung disease at an early age. The present study was designed to draw conclusions concerning the characteristics of a referral population of 124 patients with alpha 1AT

deficiency and symptomatic emphysema. Typically, the alpha 1AT level was 30 mg/dl, and the alpha 1AT phenotype was almost always PiZZ. The individuals in this population were most often male, caucasian, and ex-smokers, and they had become dyspneic between 25 and 40 yr of age. Most routine blood tests were normal. The chest radiographs and ventilation-perfusion studies typically showed abnormalities with a lower zone distribution, and about one third of the study population had evidence suggestive of pulmonary hypertension. Lung function tests were typical for emphysema; the FEV1 and DLCO were the parameters most dramatically reduced, and the annual rate of decline of those parameters was greater than that of the general population. The cumulative probability of survival of this population indicated a significantly shortened lifespan with a mean survival of 16% at 60 yr of age compared with 85% for normal persons.

Cox D. W (1989). Alpha-1 antitrypsin deficiency. In: Scriber CR, Beaudet AL, Sly WS et al, eds. *The Metabolic Basis of Inherited Disease*, New York, NY: McGraw Hill; 1989:2409- 2437.

Cox, D. W. (1978). "Genetic variation of alpha 1-antitrypsin." *Am J Hum Genet* 30(6): 660-2.

Crystal, R. G., M. L. Brantly, et al. (1989). "The alpha 1-antitrypsin gene and its mutations. Clinical consequences and strategies for therapy." *Chest* 95(1): 196-208.

Eden, E., D. Mitchell, et al. (1997). "Atopy, asthma, and emphysema in patients with severe alpha-1-antitrypsin deficiency." *Am J Respir Crit Care Med* 156(1): 68-74.
Abstract: Bronchial asthma is characterized by episodic airway obstruction and associated with wheezing, a bronchodilator response, an elevation in total serum IgE, and atopy. To determine whether asthma is more common in subjects with severe alpha 1-antitrypsin deficiency (alpha 1-ATD) and airway obstruction, we compared 38 patients who had this condition (Group 1) with 22 control patients with chronic obstructive pulmonary disease (COPD) (Group 2) and with five subjects with alpha 1-ATD and normal spirometry (Group 3). Subjects were evaluated with a symptom questionnaire, pulmonary function testing, intradermal allergen testing, and serum IgE measurement. Self-reported wheezing was a common symptom in all patient groups, but attacks of wheezing with dyspnea were significantly more common in Group 1. Of those patients with airway obstruction, more than 50% showed a bronchodilator response whether suffering from alpha 1-ATD or not. Atopy was more common in Group 1 than in Group 2 (48% versus 27%). Mean serum IgE for all groups was similar but significantly greater in patients with atopy. We estimated the prevalence of asthma in the study groups on the basis of the criteria of attacks of wheezing, reversible airway obstruction, atopy, and that increased IgE. The proportion of patients with asthma in Group 1 was significantly greater than that in Group 2 (22% versus 5%, $p < 0.05$). Our study shows that with control for the degree of airway obstruction, asthma, as defined, is more common in patients with alpha 1-ATD than in those without it. We suggest that a lack of alpha 1-AT in airways increases the propensity to develop asthma.

Eriksson, S. (1989). "Alpha 1-antitrypsin deficiency: lessons learned from the bedside to the gene and back again. Historic perspectives." *Chest* 95(1): 181-9.

Eriksson, S. (1990). "Discovery of alpha 1-antitrypsin deficiency." *Lung* 168(Suppl): 523-9.

Abstract: The author reviews the early history of alpha 1-antitrypsin (AAT) deficiency; the biochemical characterization of this inborn error of metabolism, its pattern of inheritance, frequency and predisposition to early, panacinar emphysema. The importance of the destructive element in emphysema and the gradual focusing on neutrophil elastase as a key enzyme in the pathogenesis of emphysema in alpha 1-antitrypsin deficiency is emphasized. The deficiency state as a prototype of an endoplasmic reticulum storage disease is discussed.

Eriksson, S. (1994). "Alpha 1-antitrypsin deficiency and the liver." *Acta Paediatr* 83(4): 444-7.

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Gadek JE, Crystal, RG (1982). Alpha-1 antitrypsin deficiency. In: Stanbury JB, Wyngaarden JB, Fredrickson DS et al eds. *The Metabolic Basis of Inherited Disease*. New York NY: McGraw-Hill : 1450-1467.

Hutchison, D. C. (1988). "Natural history of alpha-1-protease inhibitor deficiency." *Am J Med* 84(6A): 3-12.

Abstract: Alpha-1-protease inhibitor (A1PI) exists in over 30 biochemical variants (the Pi system), inherited as autosomal codominant alleles. Homozygotes of Pi type Z have only 10 to 20 percent of the normal serum A1PI concentration and have a high risk of developing pulmonary emphysema. A1PI is an inactivator of polymorph lysosomal elastase, the unopposed action of which may damage the lung. Cigarette smoking is an important additional risk factor. Neonatal hepatitis occurs in 10 to 20 percent of Pi type Z persons, and cirrhosis develops in a number of them in later childhood or in adult life. In heterozygotes of Pi type MZ, pulmonary or hepatic disease may also develop, though they are at lesser risk than type Z homozygotes. Specific A1PI replacement therapy derived from human plasma is now available and has been administered to Pi type Z patients by weekly intravenous infusion without adverse effects. A controlled clinical trial would be desirable, though this would be attended by organizational and economic problems.

Hutchison, D. C. (1990). "The epidemiology of alpha 1-antitrypsin deficiency." *Lung* 168(Suppl): 535-42.

Abstract: Alpha 1-protease inhibitor can exist as over 70 different biochemical variants (the Pi system) which are inherited as autosomal-codominant alleles. The majority of these variants are of no clinical significance. Epidemiologically, the most abundant are Pi types M, S, and Z. Homozygotes of type Z have only 10%-20% of the normal serum concentration of the inhibitor and have an increased risk of developing pulmonary emphysema. Cigarette smoking is the most important risk factor. A minority of Pi Z homozygotes (10%-20%) develop a form of neonatal hepatitis and a proportion of these suffer from liver cirrhosis in adult life. Heterozygotes of Pi type SZ have about one third of the normal serum alpha 1-protease inhibitor concentration but this phenotype does not in itself appear to be a significant emphysema risk factor. Heterozygotes of Pi type MZ are thought to have a moderately increased risk of developing emphysema but only if they smoke; there is also evidence for an increased risk of cirrhosis among subjects of type MZ. No excessive risk appears to be attached to the MS phenotype. Cumulative survival curves have suggested that type Z homozygotes have a poor prognosis but such estimates are based on clinic or hospital patients who already have respiratory symptoms. Calculations based on population frequencies however, suggest that about 90% of the total number of type Z subjects are not accounted for in such surveys. Their whereabouts remains unclear at present; some will undoubtedly have died of liver or lung disease but it is possible that the majority escape and live undetected among the general population.

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Laurell C-B, Eriksson S (1963) "The electrophoretic alpha1-globulin pattern of serum in a1-antitrypsin deficiency" *Scan J Clin Lab Invest* 15: 132.

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Mayer, A. S., J. K. Stoller, et al. (2000). "Occupational exposure risks in individuals with PI*Z alpha(1)-antitrypsin deficiency." *Am J Respir Crit Care Med* 162(2 Pt 1): 553-8.

Abstract: We obtained questionnaire and spirometry data from 128 alpha(1)-antitrypsin (alpha(1)AT)-deficient individuals with phenotype PI*Z to examine the relationship between chronic respiratory symptoms, airflow limitation, treatment requirements, and semiquantitative estimates of occupational exposure to dust, fumes, smoke, and gas. After adjusting for age, smoking, and prior lower respiratory tract infections, increased prevalence of chronic cough (OR = 4.69, 95% CI = 1.57-13.74, p = 0.006) and having left a job due to breathlessness (OR = 2.72, 95% CI = 1.07-6.92, p = 0.036) were seen in individuals reporting high mineral dust exposure compared with those with no exposure. Subjects reporting high mineral dust exposure

also had significantly lower FEV(1) (31% predicted for high exposure versus 36% for low and 40% for unexposed, $p = 0.032$). The excess risk of chronic cough seen with occupational fumes or smoke exposure disappeared after adjusting for mineral dust exposure, but the association with lower FEV(1)/FVC ratio persisted ($p = 0.022$). Personal tobacco use was a significant risk factor for most outcome measures, but no interaction with occupational exposure was seen. These results suggest that occupational inhalational exposures are independently associated with respiratory symptoms and airflow limitation in severely alpha(1)AT-deficient individuals.

Pierce, J. A. (1988). "Antitrypsin and emphysema. Perspective and prospects." *Jama* 259(19): 2890-5.

Seersholm, N., M. Wencker, et al. (1997). "Does alpha1-antitrypsin augmentation therapy slow the annual decline in FEV1 in patients with severe hereditary alpha1-antitrypsin deficiency? Wissenschaftliche Arbeitsgemeinschaft zur Therapie von Lungenerkrankungen (WATL) alpha1-AT study group." *Eur Respir J* 10(10): 2260-3.

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