Alpha-1 Antitrypsin Deficiency Is Not a Rare Disease but a Disease That Is Rarely Diagnosed

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Articles in the literature on alpha-1 antitrypsin (AAT) deficiency have been interpreted as indicating that AAT deficiency is a rare disease that affects mainly Caucasians (whites) from northern Europe. In a recent publication on the worldwide racial and ethnic distribution of AAT deficiency, new data were presented demonstrating that it is also found in various populations of African blacks; Arabs and Jews in the Middle East; and Central, Far East, and Southeast Asians, as well as whites in Australia, Europe, New Zealand, and North America. The new data on the prevalence of AAT deficiency in other major racial groups worldwide will affect the standards for the diagnosis of AAT deficiency by the medical community, with the realization that is not a rare disease of whites in northern Europe and immigrants from these countries in the New World. In a total population of 4.4 billion in the 58 countries surveyed, there are at least 116 million carriers (those with Pi phenotypes PiMS and PiMZ) and 3.4 million with deficiency allele combinations (phenotypes PiSS, PiSZ, and PiZZ) for the two most prevalent deficiency alleles PiS and PiZ; therefore, the new data suggest that AAT deficiency may be one of the most common serious single-locus genetic diseases in the world. Particularly important is the unique susceptibility of AAT-deficient individuals to exposure to chemical and particulate environmental agents. Such exposures are known to result in both lung and liver disease as well as other adverse health effects. ***Key words:*** **alpha-1 antitrypsin deficiency, alpha-1 protease, alpha-1 protease inhibitor, genetic epidemiology, Pi phenotypes, Pi subtypes, population genetics.** ***Environ Health Perspect*** **111:1851–1854 (2003). doi:10.1289/ehp.6511 available via *http://dx.doi.org/* [Online 9 September 2003]**

Alpha-1 antitrypsin (AAT) deficiency is a common fatal genetic disease characterized by clinical manifestations primarily in the lung and liver [Brantly et al. 1988; Crystal 1996; World Health Organization (WHO) 1996]. It is commonly regarded as a disease of white northern Europeans. There are extensive data in the literature on the prevalence of the two most common deficiency alleles, indicated by Pi phenotypes PiS and PiZ, in countries all over Europe (Blanco et al. 2001; Hutchison 1988). Although AAT deficiency is thought to occur predominately in white northern Europeans of phenotype PiZZ, new data demonstrate that it affects major racial groups worldwide and that the numbers and phenotypic classes at risk in other countries are much greater than originally thought (de Serres 2002). Because of the differences in the population sizes of different countries, the highest numbers of individuals of phenotype PiZZ are actually found in North America, southern Europe, and Central Asia (de Serres 2002). These new data (de Serres 2002) indicate that in a total population of 4.4 billion in the 58 countries surveyed, there are at least 116 million carriers (PiMS and PiMZ) and 3.4 million with deficiency allele combinations (PiSS, PiSZ, and PiZZ).

There are no data on genetic epidemiologic studies of AAT deficiency in countries in the Caribbean such as Puerto Rico or countries in Central and South America where the numbers of immigrants from countries in southern Europe is high (de Serres 2002). Therefore, the numbers at risk for AAT deficiency worldwide are expected to be much higher. Furthermore, this database demonstrates that AAT deficiency is found in various populations of African blacks; Arabs and Jews in the Middle East; and Central, Far East, and Southeast Asians; as well as whites in northern Europe and their descendents in Australia, New Zealand, and North America. In addition, these new data indicate that there are marked racial and ethnic differences in the gene frequencies and prevalence of the PiS and PiZ alleles worldwide (de Serres 2002).

The impression that AAT deficiency is a rare disease has resulted in infrequent orders for tests for AAT deficiency even for many white patients who present with allergy, asthma, or pulmonary problems, and essentially no orders for tests for patients from other major racial groups. These findings on the prevalence of AAT deficiency worldwide are expected to affect the diagnosis of individuals with AAT deficiency by the medical community with the realization *a*) that it is not a rare disease worldwide, and *b*) that it does not affect only whites in northern Europe or immigrants from these countries living in other parts of the world.

In addition, based on the new data on the deficiency allele frequencies and prevalence for PiS and PiZ worldwide (de Serres 2002), we can conclude that AAT deficiency is a not a rare disease but is a disease that has been rarely diagnosed. The major conclusion of this study (de Serres 2002) was that AAT deficiency is not rare but actually may be one of the most common single-locus genetic diseases in the world.

Most important is the unique susceptibility of AAT-deficient individuals to exposure to chemical and particulate environmental agents (Mayer et al. 2000; Sigsgaard et al. 2000). Such exposures can result in both lung and liver disease as well as other adverse health effects.

Background

Molecular genetics. The AAT gene locus is located on the long arm of chromosome 14, has been mapped to chromosome 14q31–32.3 (Byth et al. 1994), and is organized in three noncoding (Ia, Ib, and Ic) exons and four (II, III, IV, and V) coding exons (Blank and Brantly 1994). AAT is a 52-kDa single-chain glycoprotein composed of 394 amino acid residues and three asparagine-linked complex carbohydrate side chains (Brantly et al. 1988). The normal gene is designated PiM, and at least 100 additional normal and deficiency alleles have been described (Brantly et al. 1988; Crystal et al. 1989). The two most common variant or deficiency alleles are PiS and PiZ (Brantly 1996). The PiS allele resulted from a single base-pair substitution in exon III of thymidine for adenine (Glu264G<u>A</u>A → Val G<u>T</u>A). The PiZ allele resulted from a single base-pair substitution in exon V of adenine for guanine (Glu342 <u>G</u>AG → Lys <u>A</u>AG) (Brantly 1996; Brantly et al. 1988).

The phenotypes of different *AAT* alleles are identified by determining their isoelectric point (IEF) on a thin-layer polyacrylamide gel in a pH gradient of 4–5. Major variation in the migration of various *AAT* alleles is the result of amino acid substitutions that alter the net charge of the protein and thus the IEF of the protein (Brantly 1996). This technique provides a reliable detection of individuals

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carrying either the PiS or PiZ variant alleles. It is important to note that the genotype of individual *AAT* alleles can only be determined by DNA sequencing.

The origin of PiS and PiZ deficiency alleles. Gene-mapping studies have shown that the PiZ allele probably arose in northern Europe (Cox et al. 1985; Seixas et al. 2001). Age estimates of AAT variants based on microsatellite variation suggest that the *Z* deficiency allele appeared 107–135 generations ago and could have been spread in Neolithic times. The PiS deficiency allele is older, occuring 279–470 generations ago; its high frequency in the Iberian Peninsula suggests that PiS could have originated in this region (Seixas et al. 2001). The presence of both of these deficiency alleles in countries in other parts of the world is yet to be explained. Does their presence result from independent mutations in the same two codons in the *AAT* gene, or have the original PiS and PiZ deficiency alleles been spread throughout the world by the migrations and explorations of different peoples?

Impact of the new data on carriers and deficiency allele combinations worldwide. AAT deficiency was discovered only in 1963 (Laurell and Eriksson 1963). The generally accepted feeling was that it was a disease of only white northern Europeans, where the prevalence of PiZ is the highest (Hutchison 1998); therefore, it was not a condition for which laboratory tests would be routinely ordered by physicians in clinical practice. The discovery that there are very large numbers of carriers and deficiency allele combinations for PiS and PiZ in the 11 geographic regions studied worldwide, as well as the fact that there are nonwhites affected by this disease, will have a major effect on the diagnosis of individuals with AAT deficiency by the medical community. The first consequence is that AAT deficiency may well affect diagnosis and treatment of nonwhites who seek medical treatment for allergies or asthma. The second consequence is that educational programs must be developed to train physicians in clinical practice to test patients for this disease.

Sources of information on AAT deficiency. Searches of the medical literature on AAT deficiency on PubMed (National Library of Medicine, Bethesda, MD) and Web of Science (Institute for Scientific Information, Phildelphia, PA) from 1965 to 2003 have resulted in the development of a bibliography of almost 12,500 references, which is available on the Alpha-1 Foundation website (Alpha-1 Foundation 2003). Particularly useful are four excellent reviews of AAT deficiency (Brantly 1996; Crystal 1996; Fagerhol and Cox 1981; WHO 1996). In this article, I present primary facts of this disease in order to improve understanding of AAT deficiency.

ATT Deficiency and Health

Physiology. AAT is a protein produced mainly by the liver and to a lesser extent by mononuclear phagocytes, which are present in blood and tissues throughout the body. Although named for its ability to inhibit the action of the protease trypsin, AAT is thought to function physiologically as a primary inhibitor of elastase, a powerful neutrophil-derived protease. AAT also inhibits other serine proteases (Crystal 1996) and consequently is also known as "alpha$_1$-proteinase inhibitor." This neutrophil elastase is an omnivorous protease that can result in "genetic emphysema" from damage primarily to the lower lobes of the lungs (Pierce 1988), as well as liver disease, which is expressed as neonatal cholestasis that may progress to juvenile cirrhosis and slowly progressive liver disease in the adult (Mahadeva and Lomas 1998).

Clinical manifestations. The clinical manifestations of AAT deficiency vary widely among individuals, ranging from asymptomatic in some to fatal liver or lung disease in others (Hutchison 1988). The lung manifestations of AAT deficiency include emphysema, chronic bronchitis, chronic obstructive pulmonary disease (COPD), bronchiectasis, and asthma. Emphysema usually develops by the fifth to sixth decade in affected individuals but commonly appears in the fourth decade in individuals who smoke (Brantly et al. 1988; Janus et al. 1985). The liver manifestations include hepatitis, cirrhosis, hepatocarcinoma, and liver failure. The presence of a particular abnormal *AAT* allelic variant, PiZ, is strongly associated with liver disease. However, how this genetic abnormality results in abnormalities in the liver is not known. In addition, the natural history and course of AAT deficiency–associated liver disease have not been adequately defined. In rare cases, AAT deficiency can result in necrotizing panniculitis (a skin disease resulting from an inflammatory response with typical necrotic lesions in the subcutis and dermis, which can be extensive), for which there is little or no effective treatment (O'Riordan et al. 1997), as well as vasculitis (Bazex et al. 2002).

Genetic epidemiology. The presumed incidence of AAT deficiency (e.g., phenotype PiZZ) has been estimated by others (Cox et al. 1987; Tobin et al. 1983) at about 1/4,000 live births among individuals in the United States. Thus, AAT deficiency was believed to be second in frequency only to cystic fibrosis, which occurs in approximately 1/2,500 live births among whites in this same population. New data based on control cohort data on the population of the United States indicate that the incidence of AAT deficiency for all five phenotypic classes of the PiS and PiZ deficiency alleles (PiMS, PiMZ, PiSS, PiSZ, and PiZZ) is 1 in 9.8 for Canada and 1 in 11.3 for the United States (de Serres et al. In press). Comparable studies of countries in southern Europe indicate marked variation in the total frequency of all five phenotypic classes: 1 in 3.8 for Portugal, 1 in 4.4 for Spain, 1 in 6.3 for France, and 1 in 13.4 for Italy (de Serres et al. 2003).

These new data support the general impression of the scientific community (WHO 1996) that AAT deficiency is significantly underestimated in North America and Europe as well as worldwide. Therefore, determination of the true gene frequencies and gene prevalences of PiS and PiZ, the most common abnormal AAT alleles, in addition to factors affecting phenotypic penetrance are high priorities of those groups that support screening and detection programs.

Pathogenesis. The pathophysiologic basis of emphysema in individuals with AAT deficiency is currently thought to be a secondary consequence of the reduction in serum and tissue AAT levels. In the lung, repeated exposure to microbial pathogens and/or other inflammatory stimuli that result in neutrophil recruitment and activation increases the burden of free neutrophil elastase activity in the lung. The consequence of the latter, unopposed by an effective antiprotease protective screen, is progressive destruction of normal lung tissue and, as a result, emphysema.

Plasma deficiency of AAT is most commonly due to the *Z* mutation (Glu342 GAG → Lys AAG) and is associated with early-onset panlobular emphysema. Reduced AAT levels (~10–15% of normal) result in a compromised "protective screen" of antiprotease activity. The local deficiency of *Z* AAT is exacerbated by the formation of polymers within the lung (Lomas 2000), and data now show that this polymerization not only inactivates AAT but also converts the molecule to a chemoattractant for human neutrophils (Parmar et al. 2002). The chemotactic properties of polymeric AAT may explain the excessive numbers of neutrophils found in the lungs of *Z* AAT homozygotes and suggest a new paradigm for the pathogenesis of emphysema in these patients (Parmar et al. 2002).

The liver is thought to be the predominant source of AAT in the blood and tissues, with a somewhat lesser contribution from circulating and tissue mononuclear phagocytes. In some forms of AAT deficiency, liver cells have reduced secretion of the abnormal AAT. However, the reduction in serum and/or tissue AAT protein levels has not been identified as a determinant of the liver pathology. Rather, the accumulation of abnormal AAT (i.e., in the case of the PiZ-type AAT allele) is thought to initiate the pathologic response leading to juvenile and adult cirrhosis as well as hepatocellular carcinoma as a result of its accumulation in the endoplasmic reticulum of hepatocytes (Lomas et al. 1992). The association of other abnormal

AAT alleles has not been demonstrated to be clearly associated with liver disease.

There are several current theories about how such abnormal accumulation might translate into hepatocellular damage (Marcus et al. 1998). A better understanding of the molecular biology of AAT gene expression and protein folding as well as intracellular and extracellular responses to expression of abnormal AAT has recently led to identification of novel potential targets of therapy (Carrell and Lomas 2002).

Adverse health effects of PiS and PiZ. Recent review articles (Feld 1989; Gourley et al. 1989) and research articles (Sandford et al. 1999; Sigsgaard et al. 2000) provide documentation that both carriers (PiMS and PiMZ) and deficiency allele combinations (PiSS, PiSZ, and PiZZ) are at risk for various adverse health effects. The adverse health effects associated with being a carrier of the PiS defective allele were reviewed in 1989 (Gourley et al. 1989), and they included cirrhosis (Lieberman et al. 1975), multiple sclerosis (Lolin and Ward 1995), chronic "cryptogenic" liver disease (Carlson and Eriksson 1985), and malignant hepatoma (Carlson and Eriksson 1985). In addition, there are more recent reports that the PiMS phenotype can be associated with hepatic dysfunction during the first 6 months of life (Pittschieler 1994), to cryptogenic cirrhosis between ages 1 month and 18 years (Lima et al. 2001), and intracranial arterial dissections (Schievink et al. 1998).

In other publications, PiMZ carriers were found to be more prone to the development of COPD (Lieberman et al. 1986) and to chronic liver failure as adults (Graziadei et al. 1998). In addition, carriers for both defective alleles have been found to be at risk for the development of asthma (Colp et al. 1993) and of alcoholic toxic cirrhosis (Spitsyn et al. 2001).The fact that carriers for various metabolic diseases such as early vascular disease in homocystinuria, hyperammonemic episodes in ornithine transcarbamylase deficiency, presenile cataracts in galactosemia, and so forth (Endres 1997), as well as for AAT deficiency (Feld 1989; Gourley et al. 1989), are at risk for adverse health effects has been well documented. Additional evidence for the risk of developing adverse health effects for carriers of AAT deficiency can also be found in more recent reviews (Gourley et al. 1989; Stoller et al. 2003).

New research initiatives are needed to gain a better understanding of the differences in the adverse health effects associated with the same five phenotypic classes of AAT deficiency in different individuals associated with the two most prevalent deficiency alleles, PiS and PiZ. Equally important is the need to investigate any differences associated with the expression of this genetic disease in different racial subgroups. Such an approach may well resolve apparent differences in the adverse health effects reported in the medical literature on each of the five phenotypic classes of the PiS and PiZ deficiency alleles.

Current therapy. The current approach to specific therapy for individuals with lung diseases related to AAT deficiency involves administration of the normal AAT protein. This replacement usually involves weekly or biweekly infusion with a derived pooled human blood product containing normal AAT (Dirksen et al. 1999; Lieberman 2001). Other therapeutic measures include nonspecific or supportive measures for the clinical manifestations of liver or lung disease. In severe cases of liver or lung disease, transplantation has been used successfully in selected cases (Fischer et al. 2002; Kayler et al. 2002). Moreover, liver transplantation is a therapeutic option for some patients with advanced liver disease.

Risk Factors

Smoking as a risk factor for emphysema. Smoking is the most important risk factor for the development of emphysema in AAT deficiency of the PiZZ type. In a British study (Hutchison and Cooper 2002), homozygotes for Pi type *Z* were identified among chest clinic patients and close relatives. Clinical and lung function data were obtained by means of a standardized questionnaire administered yearly for a maximum of 15 years. Forced expiratory volume in 1 sec (FEV_1) and vital capacity were studied in 194 PiZZ patients at registration. Past or present smoking history had the strongest relationship to reduction in FEV_1 ($p < 0.001$), but among those who had smoked, estimated total lifetime tobacco consumption (kilograms) was not significantly related to FEV_1.

In a Danish study on never-smoking nonindex cases of phenotype PiZZ, no abnormalities in lung function could be identified (Seersholm et al. 1994). The annual decline of FEV_1 in smokers with AAT deficiency is approximately 130 mL compared with 70 mL in ex-smokers (Seersholm et al. 1995). A later series (Piitulainen and Eriksson 1999) showed mean declines of 70 mL/year in current smokers, 47 mL in never-smokers, and 41 mL in ex-smokers, indicating similar decline rate in nonsmokers and ex-smokers.

In another British study, Hutchison et al. (1987) found an overall FEV_1 decline of 55 mL/year with no effect of smoking cessation. In a joint American and Swedish study, Buist et al. (1983) estimated the FEV_1 decline to be 100 mL/year, and Janus et al. (1985) found a FEV_1 decline of 316 mL/year in smokers and 80 mL/year in never smokers. These two studies did not evaluate the effect of smoking cessation, but concurred that smoking is the most important risk factor for adverse lung effects from AAT deficiency.

Environmental chemicals and particulates. The role of polymorphisms in the human genome in modifying the effects of exposures to toxic environmental agents has been discussed in a recent review in a broader context (Kelada et al. 2003).

Regarding AAT deficiency, questions exist as to whether there is an increased risk for adverse health effects when such individuals with AAT deficiency are exposed to toxic environmental agents (Mayer et al. 2000; Sigsgaard et al. 2000). Occupational exposures of concern may include a variety of work situations that expose workers with AAT deficiency to hazardous agents. Such agents (and worker groups exposed) could include chemical substances (beauticians, chemical plant workers, fumigators, gas station attendants, painters, and welders), toxic fumes (airport personnel; bus, cab, and truck drivers; dry cleaners; factory workers; industrial and household cleaners; and manicurists), and organic wastes and/or particulates (agricultural workers, dental workers, farmers, miners, and textile workers). Those at risk also may work in professions regularly exposed to pathogens and other readily transmissible diseases (doctors, school teachers, nurses and other health care professionals, sales personnel, and restaurant and hotel wait staffs). The collection of detailed information on occupation is critical for the effective management of individuals with AAT deficiency.

Conclusions

The new data on the incidence of AAT deficiency worldwide and the suggestion that it may be the most common single gene hereditary disease for humans mandate the development of better mechanisms for effective diagnosis and treatment. The large numbers of AAT deficiency carriers and those with deficiency allele combinations for the two most common alleles PiS and PiZ worldwide clearly indicate that most carriers and deficiency allele combinations for PiS and PiZ have not been diagnosed. The fact that this disease is not just a disease of white northern Europeans but affects essentially all racial subgroups worldwide impacts the commonly accepted standards for diagnosis of AAT deficiency by general practitioners and such specialists as allergists and pulmonary and hepatic physicians. Particularly important is the unique sensitivity of AAT-deficient individuals to exposure to chemical and particulate environmental agents.

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