Gene 589 (2016) 118–122

Contents lists available at ScienceDirect

Gene

journal homepage: www.elsevier.com/locate/gene

Research paper

Historical role of alpha-1-antitrypsin deficiency in respiratory and hepatic complications

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ARTICLE INFO

Article history:
Received 17 September 2015
Received in revised form 11 November 2015
Accepted 3 January 2016
Available online 5 January 2016

Keywords:
COPD
Disease
Elastase
Lung
Therapy

ABSTRACT

Alpha-1-antitrypsin (AAT) deficiency is a heritable disease that is commonly associated with complications in the respiratory and hepatic systems. AAT acts as a regulatory enzyme that primarily inhibits neutrophil elastase activity thus protecting tissues from proteolytic damage after inflammation. This paper provides a historical review of the discovery, classification, phenotypic expression, and treatment of AAT deficiency. While its pattern of inheritance has been long understood, the underlying mechanism between AAT deficiency and related diseases remains to be elucidated. Most commonly, AAT deficiency is associated with the development of emphysema in the lungs as well as various liver injuries. Cigarette smoke has been shown to be particularly detrimental in AAT deficient individuals during the development of lung disease. Therefore, understanding familial history may be beneficial when educating patients regarding lifestyle choices. While numerous AAT deficient phenotypes exist in the human populations, only specific variants have been proven to markedly predispose individuals to lung and liver disorders. The exact relationship between AAT levels and the aforementioned diseases is an essential area of further research. It is imperative that clinicians and researchers alike strive to standardize diagnostic criteria and develop safe and effective therapies for this genetic disease.

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1. Introduction

Alpha-1-antitrypsin (AAT) deficiency is an inherited condition that commonly causes serpinopathy, a group of diseases associated with mutations in the serine protease inhibitor (serpin), particularly in the lungs and liver (Roussel et al., 2011). AAT deficiency is found to genetically predispose individuals to respiratory and hepatic complications such as emphysema and cirrhosis (Fairbanks and Tavill, 2008; Stoller and Aboussouan, 2012). Reduced circulating AAT proteins in the plasma as well as aberrant protein function are hallmarks of AAT deficiency (Fairbanks and Tavill, 2008; Stoller and Aboussouan, 2012). AAT is a 52 kDa glycoprotein belonging to the largest family of protease inhibitors, the serpin superfamily, with a serum level normally ranging between 1.5 and 3.5 g/l (Crowther et al., 2004). It is a natural antiprotease that mainly inhibits neutrophil elastase activity in order to protect tissue from proteolytic damage after inflammation (Nukiwa et al., 1986; Crowther et al., 2004; Stoller and Aboussouan, 2012). Most of the enzymes in the serpin superfamily share more than 25% of the same features as AAT, serving as regulators of proteolytic cascades (Roussel et al., 2011).

AAT deficiency and its clinical manifestation of emphysema, were first described by Laurell and Eriksson in 1963 (Laurell and Eriksson, 1963; Ghouse et al. 2014). Later in 1969, the association between AAT deficiency and liver disease was discovered (Sharp et al., 1969; Ghouse et al., 2014). AAT deficiency has been characterized as following an autosomal co-dominant pattern of inheritance (DeMeo and Silverman, 2004; Ghouse et al., 2014). Although much has been learned since the discovery of AAT and AAT deficiency in the last 50 years, advanced techniques continue to provide researchers with the opportunity to make significant breakthroughs in the understanding of this disease. In this review, we aim to provide a historical timeline of AAT deficiency and its discovery, classification, phenotypic expression, and treatment.

2. AAT deficiency genetics

2.1. Classification and nomenclature

AAT deficiency is classified according to variant phenotypes. Each allele is assigned a letter depending on how far it can migrate in the isoelectric focusing (IEF), an electrophoretic technique that separates proteins based on individual isoelectric points. The letters B to Z were

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Abbreviations: AAT, alpha-1-antitrypsin; IEF, isoelectric focusing; Pi, protease inhibitor; COPD, chronic obstructive pulmonary disease; BAL, bronchoalveolar lavage; PEG, polyethylene glycol.

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http://dx.doi.org/10.1016/j.gene.2016.01.004
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used with B being the most anodal and Z being the most cathodal positioned variants (Holmes et al., 1990).

Another classification is based on the evaluation of the risk in the development of AAT deficiency. The M allele is the "normal" or most common AAT variant and produces normal levels of functional AAT, while alleles S and Z represent the most common "at risk" variants (Crystal, 1989; Holmes et al., 1990). The protease inhibitor (Pi) system was implemented to describe each specific phenotype. For example, PiMM is the "normal" phenotype, while PiZZ presents the phenotype with the highest risk of developing lung disease (DeMeo and Silverman, 2004).

2.2. Allele isoforms identification

After Laurell and Eriksson first discovered AAT deficiency in 1963, many studies have been focused on increasing the knowledge regarding AAT deficiency and its associated diseases. AAT is known to play an essential role in providing protection to the lower respiratory tract against neutrophil elastases. It also functions as an acute phase reactant, which is produced by respiratory macrophages and neutrophils during infection and inflammation (Nukiwa et al., 1986; Crystal, 1989).

Agarose gel electrophoresis and IEF have both been widely used to differentiate between different forms of AAT. In 1988, it was reported that more than 75 AAT variants had been discovered (Brantly et al., 1988). As of 2010, more than 120 single nucleotide polymorphisms have been identified at the Pi locus (Kelly et al., 2010). Several attempts have been made to accurately characterize the AAT gene. With hybridization techniques, many studies have successfully located this gene on chromosome 14 (Darlington et al., 1982; Lai et al., 1983; Rabin et al., 1986; Cox and Coulson, 1987). By the late 1980s, there was a general consensus among researchers regarding the structure of the AAT gene. This 12.2 kb gene is located at chromosome 14 at q31–32.3. It consists of three 5′ noncoding exons (Ia–Ic) and four coding ones (II–V) (Takahashi and Crystal, 1990).

3. Variant expression of phenotypes

The standard phenotyping of AAT variants was previously carried out by separation according to protein charge in polyacrylamide gels (Wood and Stockley, 2007). Although this method provides a good separation of major alleles (F, fast; M, medium; S, slow; and Z, very slow) based on their migration speed in the gel, it is unable to clearly resolve the six most common M-subtypes (M1(ala^{213}), M1(val^{213}), and M2–M5) (Brooks and Iammarino, 1985; Gaillard et al., 1994; Wood and Stockley, 2007). The later development of the IEF technique with stationary pH gradients greatly improved the identification of microheterogeneity in each phenotype (Jeppsson and Franzen, 1982; Brooks and Iammarino, 1985). Accordingly, diverse allelic distributions of AAT have been observed among different populations. For example, the high frequency of PiM1 alleles was well present in African population. Particularly, the M1(ala^{213}) expression has been associated with inflammatory reactions possibly hinting at its role in asthma (Gaillard et al., 1994). In addition, the deficiency variant, PiZ, is more prevalent in persons of North European descent (Gooptu et al., 2014). Notably, a meta-analysis study performed by Blanco et al. showed that both PiZ and PiS alleles are present in all 21 European countries (Blanco et al., 2006).

3.1. PiZZ phenotype

Among the AAT variants, the Z allele is most significantly related to the pathology of AAT deficiency. Specifically, the PiZZ phenotype accounts for 96% of patients with AAT deficiency; while the remaining amount is associated with the PiSZ, PiMZ and other phenotypes (Blanco et al., 2006). Along with PiMS and PiSS, these five phenotypes are of the most interest in AAT deficiency (Blanco et al., 2006). The single nucleotide polymorphism for the PiZ mutation results in the substitution of lysine in the place of glutamic acid at position 342, leading to conformational changes in AAT and the insertion of inclusion bodies in the endoplasmic reticulum of hepatocytes (Wood and Stockley, 2007; Gooptu et al. 2014). The accumulation of the Z allele in hepatocytes can cause liver disease (Fairbanks and Tavill, 2008). In addition, low levels of circulating AAT in the plasma are observed in PiZZ individuals (Sandford et al., 1997). Indeed, Perlmutter et al. demonstrated a defect in the secretion of AAT in cells injected with PiZZ mRNA, possibly due to altered protein conformation and subsequent abnormalities (e.g., increased degradation and diminished solubility) (Perlmutter et al., 1985). Homozygous PiZZ and heterozygous PiSZ are generally considered to develop clinical manifestations, such as cryptogenic cirrhosis and early-onset lung emphysema (Malfait et al., 1985). Recently, it was estimated that approximately 10% of cases of chronic obstructive pulmonary disease (COPD) in the United States can be attributed to the deficiency alleles including PiZ and PiS (de Serres et al., 2006). Case studies of AAT deficiency have revealed a clear association between the homozygosity of the Z allele and the development of COPD. As an established genetic factor in COPD, the homozygous Z condition has long been shown to cause a higher risk in COPD development (Sandford et al., 1997).

3.2. PiMZ and other phenotypes

Besides the PiZZ phenotype, PiMZ has also been implicated in the increased risk of COPD (Sandford et al., 1997). Hall et al. observed an impaired maximal flow rate in PiMZ non-smokers (Hall et al., 1976). PiMZ subjects were previously seen to be genetically predisposed to pulmonary emphysema via aberrant pulmonary elastolysis (Pelham et al., 1985; Sandford et al., 1997). In 1994, Tarjan et al. further supported PiMZ as a risk factor for emphysema (Tarjan et al., 1994). In addition, PiMZ has been commonly associated with liver diseases (Smanadhikorn et al., 1995). Similar to PiMZ, the level of AAT in the serum of PiSS individuals is approximately 60% of predicted (McGee et al., 2010). Interestingly, McGee et al. were unable to identify a correlation between the PiSS phenotype and an increased risk of lung disease. Larger epidemiological studies are needed to fully address the association between lung disease and the PiSS phenotype (McGee et al., 2010).

4. AAT deficiency and diseases

Along with its discovery, AAT deficiency was quickly shown to be closely related to the development of pulmonary emphysema (Brantly et al., 1988). Kennedy et al. investigated AAT deficient monozygotic twins (ZZ homozygous) where one was a life-long smoker and the other was a non-smoker. By comparing test results (e.g., chest X-ray, forced expiratory volume in 1 s (FEV$_1$), and residual volume) between the two subjects, this study provided evidence suggesting that smoking can significantly hasten the pathogenesis of lung disease in AAT deficient patients. Therefore, homozygous (ZZ) individuals should be advised to avoid cigarette smoking (Kennedy and Brett, 1985). Interestingly, a different study was unable to find an association between the PiMZ phenotype and a predisposition to emphysema (Sutinen et al., 1985). This is likely due to the fact that individuals that are heterozygous for AAT deficiency are believed to have intermediate AAT levels, while homozygous ones have low AAT levels (Tarkoff et al., 1968). This is consistent with early studies that sought to evaluate the impact of AAT homozygous-deficiency in liver and lung disease (O'Brien et al., 1978).

A study performed in 1985 further confirmed that AAT deficient smoking individuals are very likely to develop emphysema at an early age (Janus et al., 1985). Although AAT deficient non-smokers were found to have a gradual decrease in lung function, they could have a normal life-span, not experiencing significant lung dysfunction for a while (Janus et al., 1985). Furthermore, it has been demonstrated that homozygous AAT deficiency evokes an increased risk for primary liver cancer and cirrhosis. This effect was greater in men than women

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