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Genetics of α1 Anti-Trypsin (AAT) Deficiency

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Introduction

Since the first description of alpha one antitrypsin deficiency (AATD) by Laurell and Eriksson in 1963, it has become a common but under-recognized genetic condition that predisposes to chronic obstructive pulmonary disease (COPD) and liver disease [1]. The prevalence of AATD is variable among different geographic areas and ethnic groups, where prevalence of the PiS allele is highest for countries in Southern Europe (Iberian Peninsula) and Sub-Sahara Africa. On the other hand, maximal PiZ frequencies (2-4%) are found in the southern regions of the Scandinavian countries [2].

Clinical presentation of AATD is diverse as it may affect different body systems. Liver disease is mainly attributed to gain-of-toxic function mechanism due to the accumulation of polymerized mutant AAT protein in endoplasmic reticulum of hepatocytes that trigger cell injury and death. Clinical liver disease may be presented as neonatal hepatitis syndrome, chronic hepatitis, cirrhosis, and hepatocellular carcinoma [3]. In an Egyptian study for molecular screening of the most common AATD mutations among children with unidentified liver diseases using amplification refractory mutation system (ARMS) technique, MM genotype was predominant in patients and control (64.5% vs. 96%). MS genotype was 4.4%, 4% in patients and control respectively. MZ and SZ genotypes were not detected in control but were present in 17.8%, 11.1% patients respectively. Homozygous ZZ was observed in only 2.2% of patients [4]. Lung diseases in AATD include early onset panacinar emphysema predominantly in lower lung lobes, bronchiectasis and increased susceptibility for childhood asthma; it is due to the uninhibited neutrophil elastase activity related to loss-of-function mediated by AAT molecules [1]. AATD has been also associated with skin disease called "panniculitis" that is mostly related to unopposed proteolysis of the subcutaneous tissues [5].

Genetics of Alpha One Antitrypsin Deficiency

The AAT is encoded by protease inhibitor (Pi) or serine protease inhibitor (*SERPINA1*) gene (OMIM 613490) that is mapped to the locus on chromosome 14q31-32.2 [6]. The gene is 12.2 kb in length with 4 coding exons (II, III, IV, and V), 3 non coding exons (IA, IB, and IC) and 6 introns (Figure 1). The region coding for the reactive loop and the active site methionine 358 is located within exon V, it is called P1. *SERPINA1* gene has been fully sequenced and cloned [7]; it shows a co-dominant pattern of inheritance as each allele contributes by 50% of the total circulating enzyme inhibitor [8]. It is a highly polymorphic gene with approximately 125 single nucleotide polymorphisms (SNPs) reported in public databases [9], a proportion of which have an effect on AAT level or function (Table 1 shows selected allelic variants with normal and abnormal gene functions). Traditionally, each variant is identified by its speed of migration on polyacrylamide gel electrophoresis called isoelectric focusing (IEF) in a pH 4-5, the most common forms being F (fast), M (medium), S (slow) and Z (very slow). Alteration in the speed of movement through a gel occurs because of variation in protein charge, due to the changes in amino acid composition [10].

Ten normal AAT alleles had been sequenced, Pi-M allele is the wild type, and is the most prevalent. At least there are four M alleles and over 95% of the population has one of these M alleles. Variants of AAT that are not associated with changes in serum concentration or functional activity from the normal range are termed as the normal allelic variants. When two alleles have an identical IEF pattern and the sequence difference is known, the relevant residue is specifically indicated [11]. For example; the two most common AAT alleles, M1 (Val213) and M1 (Ala213), have IEF patterns of M1, but differ at residue 213 by the neutral amino acids valine and alanine [12]. Some rare alleles are labeled by a letter indicating the IEF position together with the birth site of the allele (e.g. M procida). Variants may also be classified by their effect on AAT protein level and its function – normal, deficient, null or dysfunctional.

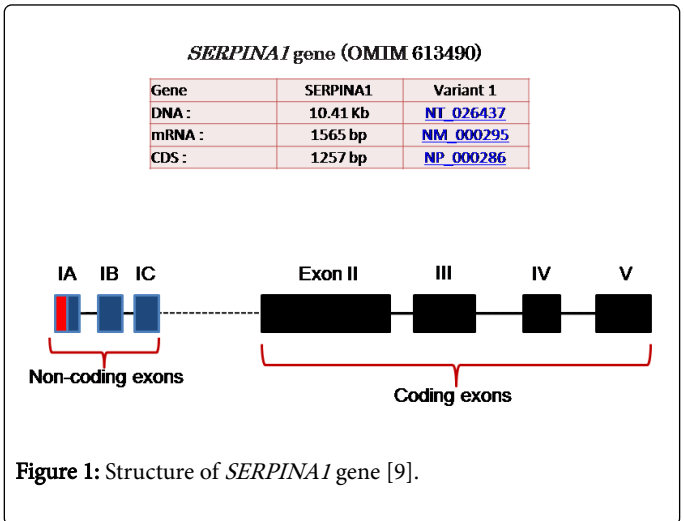

Figure 1: Structure of *SERPINA1* gene [9].

AAT 'at risk' alleles had been divided into 'deficiency' alleles and 'null' alleles [11]. The most common AATD allele is the Z allele (glu 342 lys), which occurs on an M1Ala213 haplotype [12]. Homozygous ZZ is at high risk of both emphysema and liver disease; Z allele is polymorphic in Caucasians but rare in Asians and blacks [13]. Another common AATD allele, which is also polymorphic in Caucasians but rare in Asians and blacks, is the S allele (glu 264 val); it occurs on the other isoform of M1 (M1Val213). Homozygous SS are at no risk of emphysema, but compound heterozygous with Z/null may have mild disease [14]. The molecular basis of homozygous null AAT phenotypes had been investigated; it is clinically associated with emphysema like ZZ and SZ but unlike them had no risk of liver disease. AAT gene in

null/null cases was found structurally intact but with no detectable mRNA; no epigenetic abnormality in promoter region or hyper-methylation of cytosine, so it was explained by failure of excretion of the abnormal AAT outside cells of origin [15]. Null (Granite Falls) results from a frame-shift mutation causing a stop codon [12]. Early onset emphysema was reported in three families presumed to be related to passive smoking, however they showed no detectable AAT protein with unexpectedly no major gene deletion [16]. Whatever the molecular basis of AATD, the severe protein deficiency is usually the cause for high risk of emphysema. Many SNPs had been reported to be associated with COPD; at least five were described among *SERPINA1* that increase the risk of COPD by 6-50 folds [17].

Number	Phenotype	Mutation	dbSNP
0.0001	PI M1-ALA213; PI, M1A	PI, Ala213	rs6647
0.0002	PI M1-VAL213; PI, M1V	PI, Ala213	rs6647
0.0003	PI M2	PI, Arg101His ON M3	rs709932
0.0004	PI M3	PI, Glu376Asp ON M1V	rs1303
0.0005	PI M4	PI, Arg101His ON M1V	
0.0006	PI B (Alhambra)	PI, Asp-Lys	
0.0007	PI F	PI, Arg223Cys ON M1V	rs28929470
0.0008	PI P (ST. Albans)	PI, Asp341Asn ON M1V	rs28929471,rs143370956
0.0009	PI X	PI, Glu204Lys ON M1V	rs199422208
0.001	PI Christchurch	PI, Glu363Lys	rs121912712
0.0011	PI Z	PI, Glu342Lys ON M1A	rs28929474
0.0012	PI M (Malton)	PI, Phe52Del ON M2	
0.0013	PI S	PI, Glu264Val ON M1V	rs17580
0.0014	PI M (Heerlen)	PI, Ppro369Leu ON M1A	rs199422209
0.0015	PI M (Mineral springs)	PI, Gly67Glu ON M1A	rs28931568
0.0016	PI M (Procida)	PI, Leu41Pro ON M1V	rs28931569
0.0017	PI M (Nichinan)	PI, Phe52Del & Gly148Arg	
0.0018	PI I	PI, Arg39Cys ON M1V	rs28931570
0.0019	PI P (Lowell); PI Null (Cardiff); PI Q0 (Carddiff)	PI, Asp256Val ON M1V	rs121912714
0.002	PI Null (Granite falls); PI Q0 (Granite falls)	PI, Tyr160Ter ON M1A	
0.0021	PI Null (Bellingham); PI Q0(Bellingham)	PI, Lys217Ter ON M1V	rs199422211
0.0022	PI Null (Mattawa)	PI, Leu353Phe ON M1V	rs28929473
0.0023	PI Null (Procida); PI Null (Isola Di Procida); PI Q0 (Procida)	PI, 17-KB Del	
0.0024	PI Null (Hong Kong 1); PI Q0 (Hong Kong 1)	PI, 2-BP Del, FS334TER	
0.0025	PI Null (Bolton); PI Q0 (Bolton)	PI, 1-BP Del	
0.0026	PI Pittsburgh;'Antithrombin Pittsburgh	PI, Met358Arg	rs121912713
0.0027	PI V (Munich)	PI, Asp2Ala ON M1V	rs199422212
0.0028	PI Z(Augsburg); PI Z(Tun)	PI, Glu342Lys ON M2	
0.0029	PI W (Bethesda)	PI, Ala336Thr ON M1A	rs1802959
0.003	PI Null (Devon); PI Q0 (Devon); PI Null (Newport); PI Q0 (Newport)	PI, Gly115Ser	rs11558261
0.0031	PI Null (Ludwigshafen); PI Q0 (Ludwigshafen)	PI, Ile92Asn	rs28931572

0.0032	PI Z(WREXHAM)	PI, Ser-19Leu	rs140814100
0.0034	PI Null (Hong Kong 2); PI Q0 (Hong Kong 2)	PI	
0.0035	PI Null (Riedenburg)	PI, Del	
0.0036	PI Kalsheker-Poller	PI, G-A, 3-Prime UTR Enhancer	
0.0037	PI P (Duarte)	PI, Asp256Val	
0.0038	PI Null (West) ;PI Q0 (West)	PI, IVS2DS, G-T, +1	
0.0039	PI S (IIYama)	PI, Ser53Phe	rs55819880
0.004	PI Z (Bristol)	PI, Thr85Met ON M1V	rs199422213

Table 1: Allelic variants of *SERPINA1* gene.

Gene Expression

Transcription is a complex process and involves a number of proteins that promote gene expression. Specifically, in AAT expression, two main promoters have been found; the major *hepatocyte promoter* driving expression in the liver and, further upstream, the *monocyte promoter* that drives expression in other cell types; transcription from the two promoters is mutually exclusive. Hepatocyte transcription start site resides within exon IC, while mononuclear phagocyte transcription start sites reside within exons IA and IB (Figure 1). These promoters are distinct and work via different mechanisms [18]. In addition to the liver, mononuclear phagocytes express the AAT gene. Analysis of mononuclear phagocytes of individuals with MM phenotype demonstrated spontaneously expression of a single AAT mRNA identical to that of liver. Relative quantification of the mRNA levels demonstrated 200-fold less than liver and that alveolar macrophage were 70-fold less than liver, thus suggesting low AAT expression in mononuclear phagocytes than liver but in process of maturation from monocytes, alveolar macrophages up-regulate expression [19].

It has been suggested that RNA stability also influences expression; in liver, there is a single mRNA transcript of 1.75 kb, however, in other cell types there are a number of alternative transcripts. Although most AAT is manufactured in the liver, the lung tissue has a huge capacity to make AAT; with appropriate stimuli, expression can be increased approximately 100-fold. Moreover, it has been estimated that, under inflammatory conditions, lung could produce as much as one third of the amount of AAT produced by the liver [20].

Factors Modifying Disease Severity

Individuals with similar AAT protein levels vary widely in their susceptibility to develop lung or liver disease, probably in part as a result of genetic and environmental modifiers. Although Pi Z individuals frequently develop airway obstruction at an early age, the characteristics and severity of the pulmonary disease are variable based on many factors; age of onset, variability of pulmonary function, asthma related phenotypes, other pulmonary phenotypes, disease related morbidity and disease related mortality [21].

Modifier genes could play a role at any stage of the disease from disease development to disease related mortality; nitric oxide synthetase (NOS) polymorphisms had been investigated as a modifier for gene expression in Pi Z individuals. Also IL10 was found as a potential modifier gene of COPD in individuals with severe AAT deficiency [21,22]. Environmental factors are also responsible for this difference observed in clinical presentation of AATD e.g. tobacco smoke or airway irritants [23].

Studies in animal models of AATD liver disease show that non-steroidal anti-inflammatory drugs (NSAIDS) may be uniquely toxic to the Pi ZZ liver. NSAIDS in model systems increase AAT mutant Z protein synthesis, increase the hepatic burden of accumulated mutant protein and potentiate liver injury [24]. Polymerization of purified AAT-Z in vitro had been observed when the temperature is increased from 37 to 42°C. Other researchers found enhanced secretion and diminished degradation of AAT-Z in vivo when the temperature is increased to 42°C, indicating that the temperature has multiple and complex effects on the fate of AAT-Z [25].

Heterozygotes as a Risk for Liver Disease

Compound heterozygous S and the Z alleles of AAT (Pi SZ) may develop liver disease identical to Pi ZZ patients [26]. Studies have shown that the AAT mutant S protein can heteropolymerize intracellularly only when it is co-expressed with the mutant Z protein, which may explain the occurrence of liver injury in Pi SZ patients while liver disease is absent in Pi SS individuals [27].

Heterozygous AAT (Pi MZ) are generally considered asymptomatic and healthy with regard to liver disease. The use of ARMS technique for molecular screening of AATD among pediatric patients with unidentified liver disease showed MZ and SZ genotypes in 17.8%, 11.1% respectively but none in the control. Homozygous ZZ was observed in only 2.2% of patients [4]. The most widely accepted explanation is that the Pi MZ heterozygous state likely represents a genetic modifier of other liver diseases as in cases of HCV chronic hepatitis. Graziadei and his colleagues investigated patients with end-stage liver disease, they found Pi MZ in 10 to 13% of HCV patients, compared with 2.8% in the control population. This suggests that an abnormal heterozygous phenotype is a co-factor in the development of chronic liver disease in HCV [28]. There are case reports of rare Pi MZ adults developing liver disease without other apparent risk factors for liver disease [29]. Pi MZ children appear to be completely healthy, and even in adults Pi MZ phenotype is not readily accepted as a cause of otherwise unexplained liver disease without extensive further evaluation [26].

Rare Disease –Associated Deficiency and Null Alleles

About 95% of individuals with severe AATD carry the Pi ZZ genotype. Little is known about the epidemiology of the remaining deficient AAT variants, which are called 'rare' due to their low prevalence (2-4%). A recent Spanish study found that 1.6% of registered AATD patients had rare AAT alleles with Pi I and Pi Mmalton representing 54% of them [30]. Null variants are variable and a novel one was detected firstly in an Egyptian family in Southern Italy and known as Q0 Cairo. This mutation is characterized by an A>T transversion at exon III, codon 259 (AAA?TAA) (GeneBank accession number AY 256958). The transversion results in a premature stop codon (Lys259AAA ? Stop259TAA) and undetectable serum AAT [31]. Adoption of allele specific PCR test (ASO) may increase the diagnosis of such under-estimated variants.

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