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Review

ALPHA 1-ANTITRYPSIN DEFICIENCY: FROM GENETIC ROUTES TO BEDSIDE

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Alpha 1-antitrypsin (A1AT) deficiency is a one of the most common genetic disorders in Caucasians. It is characterised by low serum levels of A1AT and a high risk of pulmonary emphysema and liver disease at a young age. The disease is caused by mutations in the SERPINA1 *gene, which belongs to a cluster of protease inhibitor genes, with the main protein function of reducing the activity of serine-type endopeptidases, like neutrophil elastase. The most common mutation is E342K (Z), which is frequently found in northern Europeans. This mutation most probably arose in southern Sweden; however, the highest frequency of the Z mutation reported so far is in western Latvia. A1AT deficiency is not a widely recognised clinical problem. Disease onset most probably occurs in early adulthood with non-specific symptoms, like dyspnoea and recurrent pulmonary events, and it is triggered by certain risk factors, like smoking and working in an unfavourable environment.*

Key words: *alpha 1-antitrypsin deficiency, Z mutation.*

INTRODUCTION

Alpha 1-antitrypsin (A1AT) deficiency is an autosomal recessive genetic disorder characterised by low serum levels of A1AT and a high risk of pulmonary emphysema and liver disease at a young age (Anonymous, 1997). A1AT deficiency is frequent in Caucasians, and allelic frequency for the most common mutation E342K (Z) of the *SERPINA1* gene leading to A1AT deficiency is 1–2% in Caucasians of northern European descent (Anonymous, 1997).

C.B. Laurell (1919–2001), from Malmo in Sweden, had a special interest in protein biochemistry and discovered absence of the alpha 1-globulin band in some individuals after paper electrophoresis of a large series of blood samples from volunteers (Laurell *et al*., 1963). The alpha 1-globulin region has the strongest trypsin inhibition features; therefore, the band was named alpha 1-antitrypsin. His medical resident, Sten Eriksson, found that three of the volunteers with an absent alpha-1 band had developed emphysema at a young age (Eriksson, 1989).

The *SERPINA1* gene product A1AT is a 52 kDa large protein, and it functions as the main serine protease inhibitor in humans. A1AT stops, prevents or reduces the activity of serine-type endopeptidases, with a serine residue at the active centre of the enzyme. Lack of the A1AT enzyme leaves proteases, such as neutrophil elastase, trypsin, chymotrypsin, and catepsin G, uncleaved and consequently disturbs the balance of proteolytic activity, which severely affects the lungs. Production of A1AT mainly occurs in hepatocytes; smaller amounts are synthesised in macrophages (Potempa, 1994; Permutter, 1998).

A1AT protein is coded by the gene *SERPINA1* (former PI) on the long arm of chromosome 14 at locus 32, belonging to the serine protease gene cluster. Lai *et al.* (1987), who described three introns in the peptide-coding region, cloned the *SERPINA1* gene for the first time in 1983.

The genomic length of *SERPINA1* is 10.2 kb with a 1.4 kb coding region. The gene has four introns and five exons; exon 1, the 5_ portion of exon 2, and the 3_ portion of exon 5 are non-coding regions (Long, 1984) (Fig. 1).

A1AT deficiency is detected by direct measurement of A1AT level in blood, but phenotyping is performed in isoelectric focusing (IEF) gels. A1AT protein in IEF gel separates in distinct bands according to phenotype: M (from M1–M4) — attributed to the normal A1AT variants; the S type, which shows a slower migration pattern; and the Z type, which is the most cathodal.

The most frequent allele of the gene in Caucasians leading to A1AT deficiency is the E342K (Z) mutation. Z mutation is caused by a single base substitution in exon 5 of the normal M1 allele leading to a glycine-to-lysine amino acid change at position 342 in the molecule. This amino acid

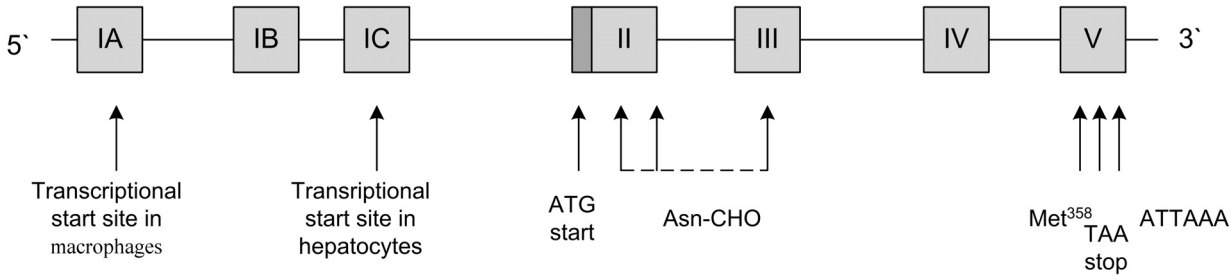

Fig. 1. SERPINA1 gene structure. Boxes IA to V donate exons. Exons IA, IB, and IC have regulatory elements for normal A1AT expression. ATG start codon is localised in the second exon. Asn-CHOs are three carbohydrate attachment sites. Active site Met^{358}, the TAA stop site, and polyadenylation signal are localised in the fifth exon.

change causes a loss of the normal internal salt bridge between the two amino acids, Gly342 and Lys290, in the A1AT molecule (Long, 1984; Nukiwa, 1986)

The homozygous Z mutation leads to A1AT protein forming a two-dimensional Z form, which folds at a slow rate, allowing A1AT molecules to aggregate. Spontaneous conformation of A1AT promotes insertion of the reactive centre loop of one molecule into the A β-pleated sheet of another to form chains of polymers (Elliot, 1998; Carell, 2002; Lomas, 2002).

Conformational changes of a mutated A1AT molecule lead to development of several pathological pathways. Because ZZ homozygotes secrete only 15% of A1AT in plasma, this decreased amount of A1AT leads to an increased proteolytic activity in tissues. The remaining 85% accumulates in the endoplasmic reticulum of hepatocytes (Lomas, 2002).

Phenotypic expression of A1AT and its serum levels depends on deficient alleles (Elliot, 1998) (Table 1).

S mutation is caused by a substitution of valine for glutamic acid at position 264 in the molecule (Nukiwa, 1986). This amino acid change causes intracellular A1AT degradation before secretion. Homozygous individuals do not have a risk of emphysema, but compound heterozygotes with the Z or a null allele have a mildly increased risk of emphysema development. Because of the high frequency of the *SERPINA1* gene S mutation in Europe, such compound heterozygotes are relatively common (Anonymous, 1997).

Table 1

PHENOTYPIC EXPRESSION AND SERUM LEVELS OF A1AT[1]

SERPINA1 variant	Frequency (in northern European populations)	mg/dl	Emphysema risk
MM	90%	150–350	No increase
MZ	4%	90–210	No increase
SS	1.5%	100–200	No increase
SZ	0.2%	75–120	Mild risk
ZZ	0.02%	20–45	High risk
Null-Null	very rare	0	High risk

[1] Anonymous, 1997; Elliot, 1998

GENETIC ROUTE OF *PI* Z AND S ALLELES

Cox *et al.* (1985; 1987) identified several polymorphic restriction sites for the *SERPINA1* gene with the RFLP and Southern blotting techniques. Linkage disequilibrium was found with the *SERPINA1* Z mutation, thus, leading to the conclusion that the *SERPINA1* Z occurred mainly with one haplotype, indicating a single, relatively recent origin in Caucasians. This origin was in an individual who lived in northern Europe some 6,000 years, or 216 generations, ago (Cox, 1987). Using microsatellite analysis, Byth *et al.* (1994) recently recalculated the age of the PI Z allele to be 2,000 years or 66 generations, but they did not eliminate the possibility of a high recombination rate within this region.

Genetic studies of the distribution of the alleles *SERPINA1* S and Z in Europe showed that they occur mainly among those of European descent. Hutchinson *et al.* (1998) reported that the frequency of *SERPINA1* Z is the highest on the north-western seaboard of Europe and that the mutation seems to have arisen in the southern part of Sweden, probably some 14,000 years ago.

A1AT deficiency in people of northern European descent is most commonly caused by the *SERPINA1* Z mutation (Cox, 1987). More recently, based on protein analysis with isoelectric focusing on samples from different populations. Beckman *et al.* (1980; 1999) observed that the frequency of mutation Z in ethnic Latvians is the highest reported so far.

The *SERPINA1* Z variant between Swedish and Latvian *SERPINA1* Z mutation carriers shared a unique genotype that was not present in the control population (Fig. 2). The analysed SNPs showed a high degree of similarity between the *SERPINA1* Z mutation carriers in both Latvian and Swedish populations, indicating a common ancestor. The population pairwise Fst value for homozygous *SERPINA1* ZZ individuals from Latvia and Sweden is 0.024 with a *P* value equal to 0.0109 (Lace, 2008).

The age of the *SERPINA1* Z mutation was calculated using the method of Rannala and Slatkin (Rannala, 2001). The analysed SNPs revealed that the Z mutation appeared 2,902 years ago in Latvia (SD, 1983) and 2362 (SD, 1614) years ago in Sweden (Lace, 2008).

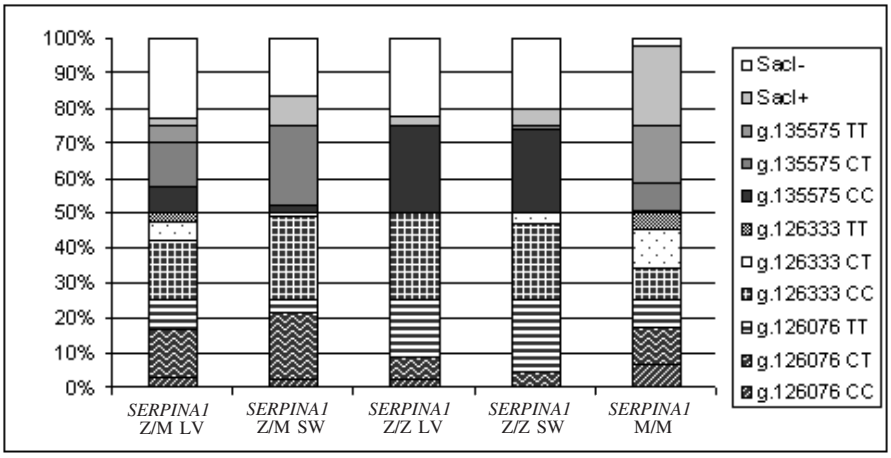

Fig. 2. SERPINA1 gene selected SNP frequencies in heterozygous and homozygous individuals from Latvia and Sweden in comparison with a control group.

Four selected *SERPINA1* gene SNPs (c.126333C>T, c.126076C>T, c.135575T>C, and 2134 +45delG): frequency in heterozygous (PIZ/M LV) individuals from Latvia and Sweden (PIZ/M SW), homozygous individuals from Latvia (PIZ/Z LV) and Sweden (PI Z/Z SW), and a control group (PI M/M) showed considerable similarity between Latvian and Sweden homozygous individuals (Lace *et al*., 2008).

Microsatellite genotyping of the *SERPINA1* gene in four populations with different historical backgrounds (Basque, Portuguese, Canadian of British origin, and Gulf of Guinea inhabitants) showed a common genotype variation. Samples from Portuguese and northern European populations are roughly concordant, and the estimated average *PI* Z allele age is 4,070 years, assuming 30 years per generation (Seixas, 2001).

The distribution of *SERPINA1* S is quite different. The S mutation is frequent in southern Europe and gradually decreases in frequency towards the north. The frequency of the PI S is highest on the Iberian Peninsula. The PI S mutation most probably arose there (Blanco, 2001).

A1AT DEFICIENCY

Clinical symptoms of A1AT deficiency are dependent on the A1AT type, the age of the patient, environmental factors, and lifestyle. Most likely, other, thus far unknown, modifying factors influence development of the disease.

The main impact of A1AT deficiency in human serum leads to the development of chronic obstructive pulmonary disease (COPD) and emphysema later in life. COPD is the sixth leading cause of death in the Western world. WHO data indicate that COPD will be the third most prevalent reason for death in the world in 2020 (Lopez, 1998). In 2–3% (depending on the population) of COPD cases, patients have A1AT deficiency (Anonymous, 1997).

The most typical clinical manifestations of A1AT deficiency in adults are dyspnoea, chronic bronchitis, COPD, and bronchial asthma (Tobin, 1983). Morphologically, emphysema in the lower lobes of the lungs is observed on chest computed tomography. Occasionally, the only symptom of A1AT deficiency is bronchiectasis (Tobin, 1983).

The British Thoracic Society studied 166 patients with A1AT deficiency having the *SERPINA1* ZZ genotype. They found that the mean time for dyspnoea onset is 40 years, and grade 2, 3, or 4 dyspnoea was observed in 86% of patients. Chronic bronchitis is usually also present by age 40 in 50% of cases (Tobin, 1983). Certain environmental factors (dust, smoke) and smoking will induce clinical symptoms much earlier and with more severity. Approximately 80% of cases had some radiological evidence of lower zones of emphysema. In a study by Piitulainen, 124 PI ZZ subjects were examined, and nearly 20% of them had wheezing and bronchial asthma (Piitulainen, 2002).

In 1972, Berg and Eriksson estimated that 80% of people with the *SERPINA1* ZZ genotype will develop emphysema and will probably die in their fifties (Berg, 1972). In 1999, at the Annual Meeting of the European Association for the Study of the Liver, Eriksson presumed that in non-smokers, only 20% will develop severe emphysema at an early age. In patients with A1AT deficiency, even a few years of moderate smoking is enough to start the disease process and progression.

In most of the conducted studies, the conclusion was made that smoking reduces lifespan and life quality significantly in all patients with A1AT deficiency, and it is a main risk factor for the development of disease.

Accumulation of A1AT Z polymers in hepatocytes causes liver disease, mostly in childhood. The clinical picture may vary from no symptoms to congenital biliary atresia.

Elevated liver enzymes, hyperbilirubinaemia, and jaundice are the most typical clinical symptoms of A1AT deficiency in childhood. A1AT deficiency may also be a reason for failure to thrive in early childhood. In a Swedish neonatal screening study, 127 children were identified as having the Z mutation in a homozygous state, of whom 22 (17%) had clinical signs of neonatal liver disease, and subsequently two of them developed liver cirrhosis before adolescence (Sveger, 1976; 2000). Sveger *et al.* (1995) performed a follow-up study at the ages of 16 and 18 years, when no clinical liver damage symptoms were observed, except for a mild elevation of liver enzymes in around 17% at the age of 16 years in identified *SERPINA1* ZZ homozygous individuals and in approximately 12% at the age of 18 years (Sveger, 1976; 2000).

A1AT deficiency symptoms in adults often present with idiopathic hepatitis, which in some of the cases (2.2–20.0% depending on the study) progresses to liver cirrhosis.

Atypical clinical presentation of A1AT deficiency often misguides physicians; therefore, the World Health Organisation (WHO) recommends measuring the A1AT level in blood for all cases of cholestatic hepatitis with unknown aetiology (Anonymous, 1997).

During the early stage of inflammation in the lungs, when neutrophils release proteases, A1AT produces a 1:1 complex with its target protease and cleaves it. A lack of A1AT causes the concentration of proteases to increase. Increased amounts of protease PR3 cause significant production of antinuclear antibodies (ANCA). There are some controversial data showing that A1AT deficiency may be associated with systemic diseases like Wegener's granulamatosis, Henoch–Schonlein purpura, and systemic vasculitis in about 10% of cases. A1AT deficiency alone is not sufficient to cause disease symptoms, but it can be a contributing factor (Callea, 1997).

CLINICAL MANAGEMENT

Despite the term "A1AT deficiency", it is not widely recognised as a common genetic disorder. Some of the reasons lie in the clinical variability of the disease, which masks disorders of a frequent occurrence, and an overestimated expected number of A1AT deficiency patients based on molecular studies. Less than 1% (0.35%) of expected patients in most countries are diagnosed (Luisetti, 2004). In Latvia, the calculated frequency of PI ZZ homozygous individuals, who are at risk of developing A1AT deficiency, is 230 patients. Since 2001, A1AT deficiency diagnosis had been confirmed for 17 patients, which is less than 8% of the theoretical estimate. The worldwide percentage of clinically recognised A1AT deficiency patients differs even further from theoretical expectations, and in Sweden alone it barely reaches 3% (Table 2).

Diagnosis of A1AT deficiency is based on a reduced level of A1AT in human serum analysed by immunological or calorimetric methods such as radial immunodiffusion or nephelometry (Walker, 2006). The normal range of A1AT level in blood detected by radial immunodiffusion is 1.50–3.3 mg/l, and the protective threshold is 0.80 mg/l; by nephelometry, the normal A1AT level range is 0.83–2.20 mg/l, and the protective threshold is 0.50 mg/l (Brantly, 1991).

Table 2

EXPECTED AND DIAGNOSED CASES OF A1AT DEFICIENCY (*SERPINA1* ZZ AND PI ZS) IN SELECTED COUNTRIES[1]

Country	A1AT deficiency expected	A1AT deficiency diagnosed	Percentage of diagnosed from expected
Spain	86,899	90	0.10
UK	79,456	324	0.40
Italy	46,068	100	0.21
Canada	42,372	144	0.34
New Zealand /Australia	33,707	93	0.28
Sweden	6,717	181	2.7
Latvia	230	17	8
Total	305,009	1068	0.35

[1] Luisetti, 2004

Quantitative testing of A1AT level in blood is recommended for individuals who meet the following criteria (Anonymous, 1997):

1) early onset pulmonary emphysema,

2) family members of known A1AT deficiency patients,

3) dyspnoea and cough occurring in at least 3 close relatives,

4) liver disease of unknown cause,

5) COPD, and

6) bronchial asthma non-responsive to therapy evaluated by spirometry.

Approval of diagnosis of A1AT deficiency should be made by A1AT typing methods, either with protein analysis methods such as isoelectric focusing and ELISA or DNA analysis methods (Anonymous, 1997).

There was an attempt to perform a newborn screening for A1AT deficiency in the USA and Sweden as a pilot project. In Sweden, 98 infants from 108,000 newborns were identified as *SERPINA1* Z mutation carriers in the heterozygous or homozygous state. The effectiveness of these projects is still under discussion (Sveger, 2000). WHO recommends considering screening for the risk groups in selected populations (Anonymous, 1997).

PREVENTION

The cornerstone for preventing complications from A1AT deficiency is cessation of smoking for adults and recommending the avoidance of smoking in the future for children. Non-smokers have a good chance of escaping a serious lung disease at early age (Seersholm, 1995).

It is recommended that A1AT-deficient patients avoid air pollution of particles smaller than 10 μm indoors and outdoors; therefore, they should be careful of dust and irritating gasses as found in occupational exposures (Mayer, 2000).

A1AT-deficient patients are at risk of developing liver cirrhosis; therefore, avoidance of alcohol consumption reduces the risk of severe liver injury (Bowlus, 2005).

Because lungs are vulnerable to any infection, vaccinations against influenza and pneumonia are highly recommended (Techman, 2006).

THERAPY

SERPINA1 Z polymers fold at a higher rate at increased temperature; therefore, patients are encouraged to use antipyretics (Ferguson, 2000).

Symptomatic therapy for the lung disease includes:

– bronchodilators,

– corticosteroids, and

– supplemental oxygen.

Augmentation or enzyme replacement therapy is limited only for A1AT-deficient patients with emphysema. It can be prescribed only for patients with severe dyspnoea and A1AT serum level less than 0.9 mg/l. Enzyme replacement therapy together with avoidance of smoking improves the health status of A1AT-deficient patients (Wencker, 1998; Dirksen, 1999; Bowlus, 2005).

Surgery is recommended for those patients who do not have a response to drug therapy and who have severe lung or liver damage. Liver transplantation because of A1AT deficiency is the second most common reason for liver transplantation in the USA (Strange, 2006).

Lung transplantation is possible for patients with the end stage of disease.

Outcomes of surgical therapy depend on several aspects and are unique to individuals (Strange, 2006).

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ALFA 1-ANTITRIPSĪNA NEPIETIEKAMĪBA

Alfa 1-antitripsīna (A1AT) nepietiekamība eiropiešiem ir viena no visbiežākajām ģenētiskajām slimībām. A1AT raksturīgs samazināts A1AT līmenis serumā un paaugstināts emfizēmas un plaušu slimību risks. Slimību izraisa *SERPINA1* gēna mutācijas. *SERPINA1* gēns pieder pie serīna proteāžu kopas, kuru galvenā funkcija ir serīna veida endopeptidāžu, piemēram, neitrofīlās elastāzes, aktivitātes samazināšana. Ziemeļeiropas izcelsmes pacientiem ar A1AT nepietiekamību visbiežākā mutācija ir E342K (Z), kas, iespējams, ir radusies Zviedrijas dienvidu daļā, lai gan visbiežāk Z mutācija ir sastopama Kurzemē, Latvijā. A1AT nepietiekamība pasaulē ir maz atpazīta slimība, tā parasti sākas pieaugušajiem ar nespecifiskiem plaušu simptomiem un aizdusu, ko saasina tādi riska faktori kā smēķēšana vai darbs piesārņotā vidē.