α₁-antitrypsin PI*SZ genotype: a SERPINA1 deficiency haplotype with uncertain clinical and therapeutic implications

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Despite its high prevalence and being one of the first genotypes identified in the field of α₁-antitrypsin deficiency, the PI*SZ genotype has been little studied, and many unknowns regarding its clinical significance remain unanswered.


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After the discovery of lung emphysema associated with α₁-antitrypsin (AAT) deficiency (AATD) in 1963 by Laurell and Eriksson [1], basic and clinical advances in the AATD field have been dramatic and relatively fast [2]. It was soon confirmed that AATD was an inherited codominant recessive condition, but it took seven more years to associate AATD-related lung emphysema with neutrophil elastase [3, 4], and between 7 to 10 years to discover its causal relationship with childhood and adult liver cirrhosis [5, 6], and with neutrophilic panniculitis [7]. In the 1970s, isoelectric focusing (IEF) became the technique of choice for diagnosis, capable of identifying more than 30 AAT variants [8]. In the 1980s, the AAT gene was sequenced and cloned, its locus located on the long arm of chromosome 14 [9], and the structure of the protein revealed [10]. In 1987, the US Food and Drug Administration approved augmentation therapy for pulmonary emphysema associated with AATD [11]. This fact was crucial to promote the creation of powerful associations and patient registries aimed to enhance diagnosis and research, and to rationalise the use of augmentation therapy. In the 1990s, granulomatosis with polyangiitis (also known as Wegener’s granulomatosis) was added to the list of diseases related to AATD [12]. In parallel, in the field of basic sciences, researchers from Malmö, Sweden, and other laboratories first observed the polymerisation of AAT protein, and later Lomas et al. [13, 14] demonstrated the polymerisation of AAT-Z proteins, and developed the hypothesis of AATD and other serpinopathies pathogenesis. In 1997, the World Health Organization, and later many other scientific societies, recommended investigating AATD in all COPD and blood relatives of index cases, as well as in individuals with other AATD-related pathologies [15]. Moving to basic sciences, DNA sequencing and PCR techniques came into play, increasing the number of known AAT variants by over a hundred. At the end of the 20th century, the computed tomography scan began to be used to measure lung density in several clinical trials, finally demonstrating the efficacy of augmentation therapy to slow emphysema progression [16]. Currently, inhaled AAT is a reality [17], the...
attainment of recombinant AAT suitable to be applied to humans seems feasible, and various modalities of gene therapy are taking firm steps with the purpose of “getting the cure of the Alphas”.

However, despite these remarkable achievements, there remain many unanswered questions on genetics, pathophysiology, penetrance, natural history, prognosis, therapy or, among others, risk associated with other non-ZZ genotypes, such as the PI*SZ type, the subject matter of this editorial.

In this issue of the European Respiratory Journal, the report by McELVANEY et al. [18] is timely for health professionals, AATD patients and their families. The estimated number of those with the PI*SZ haplotype worldwide is 1.5 million individuals in countries with reliable data [19]. This PI*SZ haplotype is not uncommon in white individuals of European ancestry living in Europe and in countries to where they migrated or their ancestors colonised (figures 1 and 2).

Despite being known since the beginning of the AATD discovery, the risk for lung disease of individuals with the PI*SZ genotype has not been well established yet, partly due to its less frequent clinical detection, underreporting in registries, and lack of studies with sufficient statistical power to reach sound conclusions. The PI*SZ associated risk to develop COPD has been described as slightly increased, especially in smokers. But in absence of smoking or exposure to other toxic factors, its risk has been quantified as low or practically insignificant. In addition, its causal relationship with liver diseases is even less defined, although in any case is much smaller than in PI*ZZ individuals. In addition, its causal relationship with pathologies other than lung emphysema and liver cirrhosis is much less well documented [20]. Therefore, although it seems likely that a small proportion of PI*SZ individuals may have an increased risk for lung and liver diseases, definitive evidence to sustain this assertion is lacking, and consequently the ambiguity of the available statements makes it difficult for practising physicians to feel confident enough to make decisions or give accurate advice when faced with PI*SZ individuals in clinical practice [18].

AAT proteinase inhibitor (PI*) SZ genotype (PI*SZ) results from a double mutation in the SERPINA1 (serine protease inhibitor, family A, member 1) gene, which changes its normal nucleotide sequence by that of the two most common AATD alleles: “S” (Glu264Val) and “Z” (Glu342Lys) [21]. These mutated alleles encode abnormally constituted “S” and “Z” glycoproteins that polymerise into the rough endoplasmic reticulum of the producing cells (mainly hepatocytes), forming homopolymers “S-S” and “Z-Z”, as well as heteropolymers “S-Z”, that accumulate within the liver without being secreted, thus provoking a decreased concentration of AAT in blood and tissues [22].

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**FIGURE 1** Inverse distance weighting (IDW) interpolation map of prevalence and number of PI*SZ genotypes in the world. It has been estimated that there may be approximately 1.5 million individuals PI*SZ genotypes in the world. Almost half of them (approx. 700,000) are in Europe, and the rest in America (approx. 600,000), Australia and New Zealand (roughly 35,000), in addition to about 165,000 irregularly distributed throughout Africa and Asia. Figure and text adapted from [19] with permission.

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Compared to the normal “M” protein, the mutated “Z” molecule has profound conformational changes causing a loss of around 80% of its inhibitory capacity, and a massive intrahepatic polymerisation (of about 85–90%) of mutated molecules, resulting in very low serum concentrations of 10–15% [23]. On the contrary, compared to the “Z”, the structural alterations of the “S” protein are much less pronounced, keeping its antielastase capacity practically unchanged, its polymerisation tendency less pronounced (approximately 55% of molecules), and serum levels moderately reduced to around 45% [24].

Reported Pi*SZ serum levels differ between studies [25], although at least 10–20% express serum values below the theoretical “protection threshold” of 11 μM·L\(^{-1}\) (equivalent to 57 mg·dL\(^{-1}\) measured by nephelometry), raising doubts about whether they should be considered at increased risk of developing AATD-related diseases [12]. However, since AAT is an acute phase reactant whose production can double during inflammation and its local production by lung resident cells can be multiplied up to 11 times [20], it is assumed that in these circumstances SZ levels may exceed the “protective threshold” reaching sufficient concentrations to neutralise neutrophil serine proteases and other inflammatory mediators released by microorganisms and activated cells.

Interestingly enough, it has been shown that the composition of circulating AAT in AATD heterozygotes is inversely proportional to the amount of liver polymerisation/retention of each type of AAT. For example, in a recent study the percentage of “Z” AAT in MZ individuals was only 18%, because it was mostly retained intracellularly, and that of “S” protein in MS subjects was just 37% for a similar reason [26]. In this regard, although the composition of circulating AAT in Pi*SZ patients has not been sufficiently studied, it could be approximately of 70% “S” and 30% “Z”. This would mean that some Pi*SZ
individuals with AAT levels around or below the lower limit, having around of two-thirds of circulating AAT of "S" type (i.e., efficient) and a third of "Z" type (i.e., poorly efficient) may actually be below the "protective threshold", and therefore at increased risk, especially if they suffer from frequent or intense inflammatory respiratory exacerbations, or if AAT is inactivated by tobacco smoke. However, it must be taken into account that AATD is not a disease, but a complex monogenic inherited condition that can promote the development of diseases, especially when other environmental and/or genetic factors, mostly poorly understood, associate with this condition. Thus, the empirically assigned ‘protective threshold’ value of 11 μM·L⁻¹ (or 57 mg·dL⁻¹), though it may provide some clinical guidance in defining risk, it may do so inaccurately or even erroneously [12].

Augmentation therapy has been approved for adults with emphysema associated with severe AATD (i.e. homo and heterozygous combinations of Z, S, null and rare alleles) showing AAT levels below the putative "protective level", and impaired lung function. But while the US Alpha 1 Foundation guidelines does not exclude from AAT therapy PI*SZ individuals that meet these or similar criteria [27], the European Respiratory Society statement does not support this indication, arguing lack of supporting evidence [28].

Apart from this unresolved question, the authors of the manuscript identified other several open research questions concerning to the natural history, prognosis, genetic penetrance, monitoring requirements, and other unmet needs that deserve more research. At present, according to the expert panel, the lack of studies with results of high-quality evidence hinders the implementation of accurate medical recommendations to grade the effectiveness of an intervention aimed at ensuring proper control. Thus, in order to adequately address the limitations identified by the international panel of experts, long-term longitudinal follow-up studies of larger samples of PI*SZ individuals may be needed to obtain reliable clinical, epidemiological, analytical, radiological and functional data from index and non-index cases, to identify risk factors, progression rate and healthcare costs, and assist in collection of other specific data to advance the scientific and medical knowledge about PI*SZ genotypes.

Augmentation therapy for PI*SZ patients requires further study; it will be necessary to perform well-designed randomised controlled clinical trials to verify tolerance, safety and effectiveness of AAT therapy, and to find the appropriate dose of exogenous "M" protein that added to the partially efficient circulating native SZ protein provides sufficiently high protective levels against proteinases in blood and alveolar fluid.

In this context, the European Alpha-1 Clinical Research Collaboration (EARCO), a newly created patient registry designed to elaborate a powerful standardised database for the follow-up of patients with AATD, will include a significant number of PI*SZ individuals. This will facilitate collection of the most-needed clinical data, which is expected to answer the open research questions raised by this expert panel [29, 30].

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References


