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α_1 -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 α_1 -antitrypsin deficiency, the PI*SZ genotype has been little studied, and many unknowns regarding its clinical significance remain unanswered. <https://bit.ly/3aut4ZE>

Cite this article as: Blanco I, Diego I. α_1 -antitrypsin PI*SZ genotype: a SERPINA1 deficiency haplotype with uncertain clinical and therapeutic implications. *Eur Respir J* 2020; 55: 2000713 [<https://doi.org/10.1183/13993003.00713-2020>].

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After the discovery of lung emphysema associated with α_1 -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”.