Clinical manifestations of the Mmalton alpha-1 antitrypsin deficiency variant

Alpha-1 antitrypsin (AAT) is a single-chain 52 kDa glycoprotein composed of 394 amino acid residues and 3 carbohydrate side chains. AAT is the most abundant protease inhibitor in human serum, and its coding gene, SERPINA1, is located on the long arm of chromosome 14 (14q32.1).

The AAT gene has a surprisingly high polymorphism rate with more than 120 allelic variants, at least 60 of which are related to decreased protein levels in plasma. A total of 95% of the clinical cases related to these deficiency variants are associated with the PI*ZZ genotype; the remaining 5% correspond to the PI*SZ and PI*MZ genotypes or combinations of PI*S and PI*Z with other, extremely rare deficiency or null alleles. This smaller set has been mainly connected to the development of pulmonary emphysema in early adulthood as well as liver disease in children and adults. In the Spanish population, the PI*S and PI*Z alleles are present in approximately 1/5 and 1/61 of general population, respectively.

Rare alleles constitute 4.6% of the deleterious variants recorded in the Spanish Register of alpha-1 antitrypsin deficiency (AATD) patients. Within this group, PI*Mmalton is the most frequently observed variant. However, a study published by Martinez Bugallo et al. emphasises that there is a higher rate of the deficiency variants PI*Mmalton and PI*Palermo in the Canary Islands than described for the rest of the Spanish population. The aim of this study was to describe the clinical impact of the PI*Mmalton variant in AATD, given the scarce literature on this question.

In our series, the respiratory system was affected in 31% of the subjects with the PI*Mmalton allele, whereas hepatic involvement was very rarely observed. The PI*Mmalton allele contains a deletion of the phenylalanine residue at position 52 (c.227_229delTCT; p.Phe52del), with a clinical behaviour similar to that of the PI*Z phenotype. Like the Z variant, the PI*Mmalton allele produces a poorly folded protein, 80–90% of which is polymerised in the hepatocyte, and an AAT content in blood of only 15% of that normally found. The clinical consequences in subjects with the PI*Mmalton allele are heterogeneous. Although the coexistence of emphysema and hepatic cirrhosis have been described in homozygous subjects, our group detected varying patterns of reactions to the exposure to tobacco smoke of comparable intensity in PI*Mmalton homozygous individuals. Likewise, the response to heterozygous alleles also seems to be difficult to predict. Lung function is not altered in most PI*M/Mmalton subjects, unlike the PI*Z/Mmalton genotype that appears to be related to an increased risk of developing emphysema. In our series, 17% of PI*M/Mmalton patients developed a chronic airflow obstruction. On the other hand, as to hepatic involvement, Canva et al. described a PI*M/Mmalton patient who developed terminal liver disease despite not having a history of hepatitis, alcohol abuse, or childhood liver disease.
Similarly, data on chronic liver disease have been reported in at least 13% of PI*Mmalton homozygous as well as heterozygous subjects. In our case, two of the patients presented alteration of the liver enzymes, although none presented signs of cirrhosis on abdominal ultrasonography.

In conclusion, subjects with the PI*Mmalton deficiency allele appear to be mostly affected at respiratory level, without detecting relevant hepatic involvement.

Conflicts of interest

The authors have no conflicts of interest to declare.

References


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