



## RESEARCH LETTERS

## 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.<sup>1</sup> 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.<sup>2</sup> 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.<sup>3</sup> 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.<sup>2</sup> However, a study published by Martinez Bugallo et al.<sup>4</sup> 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.<sup>5,6</sup>

We reviewed cases with AAT plasma levels <100 mg/dl, which had been referred to the clinical analysis service of our hospital between 2009 and 2016 for clinical suspicion of AATD. Serum AAT values were determined by nephelometry (BN ProSpec System, Siemens Healthcare Diagnostics). Genomic DNA was purified from EDTA whole blood (QIAamp DNA Blood Mini Kit, Qiagen, Hilden, Germany). The two most frequent deficiency alleles, PI\*S and PI\*Z, were genotyped by real-time PCR with FRET probes (LightCycler 2.0, Roche Diagnostics, Mannheim, Germany). The resulting genotypes were correlated with the plasma AAT values according to a protocol previously established.<sup>7</sup> In cases where the genotype did not match with AAT plasma levels, *SERPINA1* gene was sequenced (BigDye v3.1 Terminator cycle sequencing kit, Thermo Fisher Scientific, Waltham, MA). Electrophoresis was performed using an AB 3500 capillary sequencer (Applied Biosystems, Carlsbad, CA) and the results compared

with the reference sequence NM\_000295.4 (SeqScape 3.0, Applied Biosystems).

The computerised clinical record of each subject was retrospectively analysed for existing liver or respiratory disease at the moment of diagnosis. Hepatic disease was defined as elevated levels of transaminases (ALT >40 U/l, AST >45 U/l), GGT >40 U/l or both, conjugated bilirubin >1.5 mg/dl, and alkaline phosphatase >350 U/l. In order to determine possible chronic airflow obstruction, respiratory functional parameters were evaluated through forced spirometry.

We found AAT levels <100 mg/dl in 1081 samples, 340 out of which were genotyped. The characteristics of the 16 subjects with the PI\*Mmalton variant are given in Table 1. A severe AATD, defined as plasma levels <50 mg/dl, was only confirmed in four cases, two of them in their homozygous and two in a compound heterozygous form, associated with the deficiency alleles PI\*Z or PI\*S. From the clinical point of view, two of the subjects had severe (one of them Mmalton/Mmalton) and one moderate airflow obstruction (S/Mmalton); mild obstruction was observed in another two cases (M/Mmalton and Z/Mmalton). Only two patients (Mmalton/Mmalton and M/Mmalton) exhibited an altered hepatic profile.

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,<sup>5</sup> our group detected varying patterns of reactions to the exposure to tobacco smoke of comparable intensity in PI\*Mmalton homozygous individuals.<sup>6</sup> 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.

**Table 1** Characteristics of subjects with the Mmalton alpha-1 antitrypsin deficiency variant.

Sex	Age	Smoker	AAT levels	Genotype	Forced spirometry	Liver function
M	47	Yes	16 mg/dl	Mmalton/Mmalton	Severe airflow obstruction	Altered
F	42	Yes	19 mg/dl	Mmalton/Mmalton	Normal	Normal
M	42	Yes	19 mg/dl	Z/Mmalton	Mild airflow obstruction	Normal
M	51	Yes	25.9 mg/dl	S/Mmalton	Moderate airflow obstruction	Normal
M	5	No	66 mg/dl	M/Mmalton	Normal	Normal
F	49	Yes	74 mg/dl	M/Mmalton	Normal	Normal
M	86	No	77.3 mg/dl	M/Mmalton	Mild airflow obstruction	Normal
F	14	No	78 mg/dl	M/Mmalton	Normal	Normal
M	7	No	81 mg/dl	M/Mmalton	Normal	Normal
F	52	Yes	82 mg/dl	M/Mmalton	Severe airflow obstruction	Altered
F	23	No	83.4 mg/dl	M/Mmalton	Normal	Normal
F	49	No	84.3 mg/dl	M/Mmalton	Normal	Normal
F	39	Yes	85 mg/dl	M/Mmalton	Normal	Normal
F	83	No	85.8 mg/dl	M/Mmalton	Normal	Normal
M	53	No	90.3 mg/dl	M/Mmalton	Normal	Normal
F	45	No	94 mg/dl	M/Mmalton	Normal	Normal

F: Female; M: Male; AAT: alpha-1 antitrypsin; age given in years.

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.

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