Case Report

# Description of a new rare alpha-1 antitrypsin mutation in Naples (Italy): PI*M S-Napoli

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**Abstract:**

Alpha-1 antitrypsin deficiency is a rare and often underdiagnosed hereditary disorder, which mainly affects the Caucasian population. We report a case of a noncystic fibrosis bronchiectasis patient in the absence of emphysema associated with low serum alpha-1-antitrypsin (AAT) level, in the absence of the most common defective alleles associated with AAT deficiency (PI*S and PI*Z) but with a new mutation in heterozygosis. This mutation is characterized by the substitution in the coding region of exon 3, of a guanine (G) for a thymine (T), generating the replacement of a glutamine (Gln) by a histidine (His) in codon 212 (cod 212 GlnCAG > HisCAT), corresponds to a new S allelic variant. This mutation, never identified before, is called S-Napoli.

**Keywords:**

Alpha-1 antitrypsin deficiency, bronchiectasis, emphysema

Alpha-1 antitrypsin deficiency (AATD) is a hereditary disorder, which affects mainly the Caucasian population.[1] This is a rare and often underdiagnosed disease[2] and most of the potential patients are yet to be identified.[3] AATD is known to cause panacinar emphysema, liver disease, or skin disorders. Among other pulmonary manifestations, bronchiectasis without emphysema has also been described.[4] The normal AAT protein is synthesized by the liver and is produced in sufficient quantity to perform a protective antiprotease action in the lung. Normal alpha-1 antitrypsin (AAT) alleles are called M, and genotype for the most common defective alleles are PiS and PiZ.[3] PI*ZZ homozygote is associated with a severe AATD and results in a critically low level of AAT that reduce the ability to protect tissues from the damage caused by proteolytic enzymes from the neutrophil, including neutrophil elastase and proteinase 3.[3] Z variant is incorrectly folded into the hepatocytes that produce it and is released in smaller amounts in the plasma causing hepatic disease. There are also at least 50 rare deficiency variants, such as I, P, F, Mlike, and Null (Q0), which confer various degrees of deficit associated with pulmonary and/or hepatic risk.

## Case Report

We report a case of a 52-year-old man native of Naples (Italy), nonsmoker, with no history of pulmonary infections in pediatric age and no occupational exposure to irritating inhalants, with liver steatosis, splenomegaly, and atopy. He was admitted to our Respiratory Medicine Care Unit for persistent cough accompanied by low-grade fever and dyspnea. Chest X-ray shows bilateral lamellar and interstitial thickening. Laboratory tests shows white blood cell 15.90 × $10^3$/μL, red blood cell 5.34 × $10^6$/μL, hemoglobin 16.0 g/dL, hematocrit 47.9%, platelet 241 × $10^3$/μL, erythrocyte sedimentation rate 15 mm 1 h,

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C-reactive protein 8 mg/dL (0–0.3), glutamic oxaloacetic transaminase 20 U/L, glutamic pyruvic transaminase 22 U/L, gamma-glutamyl transpeptidase 19 U/L. His spirometry showed a mild restrictive pattern (forced vital capacity [FVC] 3.45 L, FVC 73%, forced expiratory volume-1 s [$FEV_1$] 3.01 L $FEV_1$ 80%, $FEV_1$/FVC 87.4%, total lung capacity [TLC] 5.94 L TLC 81%), and the carbon monoxide diffusing capacity and transfer coefficient (KCO) were 97% and 117%, respectively. The arterial blood gas analysis was normal (partial pressure of oxygen $PaO_2$ 81 mmHg, partial pressure of carbon dioxide $PCO_2$ 36 mmHg). He was prescribed oral antibiotic, antihistaminic, and inhaled corticosteroids therapy, but due to the persistence of symptoms, we decided to submit him to the second-level clinical investigations, including immunology tests (antinuclear antibodies, extractable nuclear antigens, and antineutrophil cytoplasmic antibodies), which were all within the normal range. Serum immunoglobulins (Ig) A, IgM, IgG, as well as IgG subclasses, were in the normal range.

Sweat test to rule out cystic fibrosis was negative. High-resolution computed axial tomography showed upper right lobe and medium lobe bronchiectasis [Figure 1]. The microbiological analysis of sputum indicated the presence of *Pseudomonas aeruginosa* 1.000.000 ufc/mL. After the treatment for the acute phase of lung infection, we performed two nephelometric measurements of serum AAT concentrations, which showed an average AAT concentration of 85 mg/dL (reference value: 90–200) while the gene coding portion sequencing revealed the presence of heterozygosity of a new mutation likely to be responsible for the S bandage obtained by isoelectrophocalization. This mutation was characterized by the substitution in the coding region of exon 3, of a guanine (G) for a thymine (T), generating the replacement of a glutamine (Gln) by an histidine (His) in codon 212 (cod 212 GlnCAG > HisCAT), which corresponded to a new S allelic variant.

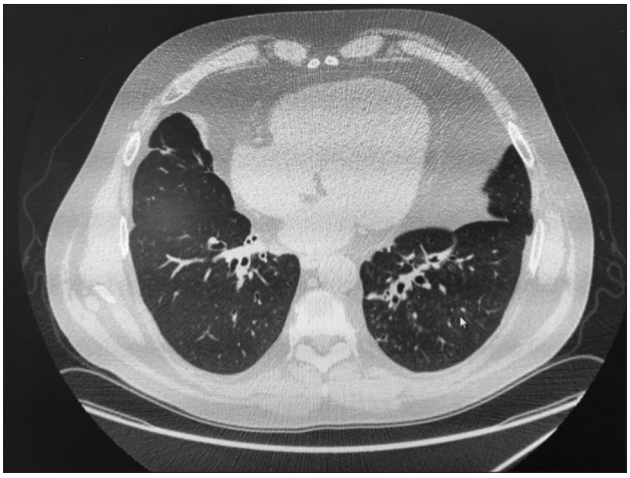

**Figure 1:** Computed tomography-scan section showing upper right lobe and medium lobe bronchiectasis

This variant has not been previously described and has not been previously reported in the human gene mutation database. Furthermore, there are no frequency data in the Exome Sequencing Project, Exome Aggregation Consortium, and dbSNP databases. The new mutation was called S-Napoli.

## Discussion

In our report, we have described in a patient with bronchiectasis a novel missense mutation in the heterozygous state, characterized by the substitution in the coding region of exon 3, of a guanine (G) for a thymine (T). This has generated the replacement of a glutamine (Gln) by a histidine (His) in codon 212 (cod 212 GlnCAG > HisCAT), which corresponded to a new S allelic variant, probably leading to a dysfunctional protein.

Interestingly, this is the second case in South Italy showing an AATD in a patient with bronchiectasis in the absence of emphysema. In fact, in a recent report, Carpagnano *et al*.[4] described a patient with a novel missense mutation Ile74Asn (c. 221T[A]) in heterozygous state on a M3 allele, affected by bronchiectasis in the absence of emphysema. This condition is not frequent as only a few case reports have been reported so far,[5,6] and a novel SERPINA-1 mutation causing alpha-1 antitrypsin deficiency in a patient with severe bronchiectasis and pulmonary embolism has been identified.[7] Furthermore, the association between bronchiectasis and AATD is not common as in a study on 1258 patients, only 0.6% of the population was affected.[8]

However, we can only speculate on the association between AATD and bronchiectasis as in our case, the AAT was at lower limit. The hypothesis is that the low level of AAT or alternatively the low efficiency of the enzyme might determinate an unbalance of the equilibrium between protease and antiprotease promoting the destruction of the epithelium and the development of bronchiectasis.[9]

Interestingly, our report presented both atopy and liver steatosis both conditions highly characterizing AAT deficiency, which can increase the susceptibility to the loss of lung function.[10]

Another important issue is about the therapy of this patient. The patient was not treated as in Italy the strict indication for therapy in AAT deficiency is AAT <80 mg/dl with a spirometric $FEV_1$ value between 35% and 60%. Although it was demonstrated that

augmentation of therapy reduces the progression of emphysema,[11] no studies on the effects of augmentation therapy in patients with bronchiectasis has been reported.

The last issue is on the diagnosis of AATD. AATD is considered a rare genetic disease, having a prevalence of around 1/5000 in Europe. However, due to the large subdiagnosis, it is reasonable to assume that it is not so rare. The AATD laboratory diagnosis is based on the use of biochemical and genetic methods for the identification of AAT protein deficiency, and the characterization of SERPINA1 gene mutations that cause it. The spread of a sample collection management system that is simple and easy to use, such as AlphaKit®, allows to simplify the diagnostic process by extending the survey to young people who are not yet affected by any symptoms, and fosters a systematic focused family screening.

We believe that it is necessary to carry out a molecular investigation whenever there is clinical suspicion of disease to identify rare mutations that could express themselves in homozygous, causing severe pathological conditions.

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## Conflicts of interest
There are no conflicts of interest.

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