

# Alpha-1 Antitrypsin Deficiency

## What is alpha-1 antitrypsin deficiency?

Alpha-1 antitrypsin (AAT) deficiency, first described in 1963, is one of the most common inherited recessive disorders among Caucasians that may cause lung or liver disease. Its primary manifestation is early-onset emphysema. Unlike the common form of emphysema seen in otherwise healthy individuals who have smoked for many

years, the AAT deficiency form of emphysema occurs at a much younger age and after less exposure to tobacco smoke. It develops in the third to fourth decade of life in smokers and a decade later in non-smokers.



AAT is encoded by a gene located on chromosome 14. This gene is polymorphous, the alleles being classified as normal (M), deficient (Z, S) or null. Individuals with null-null, Z-null or ZZ phenotypes are at risk of developing the disease. The genetic defect alters the configuration of the AAT molecule and prevents its release from liver cells into the bloodstream. As a result, serum levels are decreased, leading to low concentrations in the lung, where the AAT molecule normally serves as a protective enzyme.

The major biochemical activity of the AAT molecule is directed against several proteases, e.g. trypsin, elastase, proteinase 3, and cathepsin G. In the case of illness or exposure they are released by a type of white blood cell also known as neutrophil granulocytes. Therefore, the compound is more accurately termed alpha-1 anti-protease. However, physicians and patients refer to the disorder as AAT deficiency.

The resulting protease excess in the lungs destroys alveolar walls and causes emphysema. About one to three per cent of patients with diagnosed chronic obstructive pulmonary disease (COPD) are estimated to have AAT deficiency. Slowly progressive dyspnoea is the primary symptom, though many patients initially have symptoms of cough, wheezing and sputum production. Similar to other forms of emphysema, the dyspnoea of AAT deficiency is initially evident only with strenuous exertion. Over several years, it eventually limits even mild activities.

The accumulation of excess AAT in hepatocytes can also lead to destruction of the cells and, ultimately, clinical liver disease. The enzyme deficiency is present from birth and can be an unusual cause of neonatal jaundice. AAT deficiency can also present in children and adults as hepatic cirrhosis or liver failure and is the leading cause of liver transplantation in children.

## Who does alpha-1 antitrypsin deficiency affect?

AAT deficiency has been identified in all populations, but it is most common in individuals of Northern European and Iberian descent. Similar rates are found among Caucasians worldwide, with an estimated gene frequency of AAT deficient alleles of 120 million and 3.5 million affected individuals. According to the World Health Organi-

sation (WHO) AAT deficiency affects approximately 100,000 people in Europe, although an estimated 90 per cent of these patients are undiagnosed.

In the US, AAT deficiency is one of the three most common fatal genetic diseases among adult Caucasians, affecting one in 3,000-5,000 individuals (the other two are cystic fibrosis and Down syndrome). Severe AAT deficiency affects an estimated 100,000 individuals, and approximately 25 million people are carriers of at least one deficient gene.

Racial groups other than whites are affected less frequently. There is no gender prevalence; women and men are affected in equal numbers. Specific morbidity and mortality rates are unknown. Not all patients with homozygous deficiency develop symptomatic emphysema or cirrhosis; however, among those who develop symptomatic disease, the mortality rate is high.

### Present treatments

To maximise lung function, short-acting beta-adrenergic agents and anti-cholinergic bronchodilators are given. Metered-dose inhalers are the preferred method of administration. Oral corticosteroids are reserved for acute exacerbations with increased cough and sputum and are limited to brief courses of one to two weeks. There is recommendation of early antibiotic therapy for all exacerbations with purulent sputum. Aggressive treatment of infections may help decrease additional lung injury from an influx of neutrophil granulocytes into the alveoli.

In cases with severe airflow obstruction and hypoxaemia, oxygen supplementation is warranted, as it increases exercise capacity, improves mental performance and sleep quality. Patients are also advised to follow physical rehabilitation in a programme similar to that designed for patients with smoking-related COPD. Certainly, quitting smoking is crucial. In addition, genetic testing of relatives may be recommended.

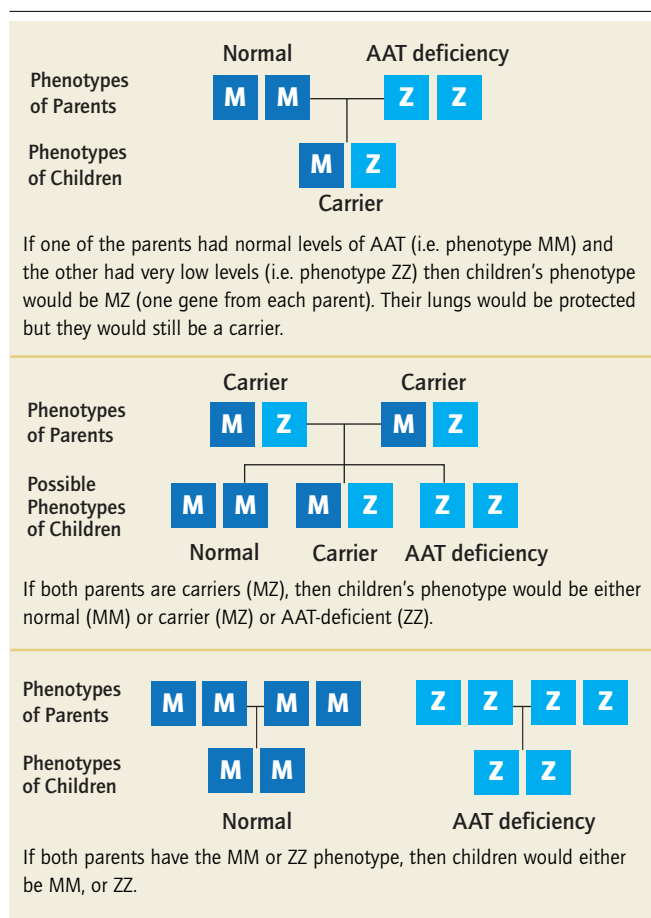
Since the late 1980s, AAT-deficient individuals with signs of developing significant emphysema have been treated with human plasma protein concentrate replacement for the missing enzyme. Several preparations are now available. Weekly intravenous infusions restore serum and alveolar AAT concentrations to protective levels. Metaanalysis of data from patient registries in Denmark, Germany and the US suggest that augmentation therapy has beneficial effects on overall survival rate and parameters of lung function.

Pneumococcal and annual influenza vaccine will help prevent respiratory infections. Lung transplantation may be an option for those patients who develop end-stage lung disease.

### What's in the development pipeline?

Scientists are studying the pharmacokinetic profile of an intravenous preparation of functionally intact human AAT in a phase 1 clinical trial. Investigators have also started a clinical trial to evaluate the effects of an inhaled recombinant AAT therapy. The objective is to determine short-term safety and tolerability of the preparation at three different dosage levels.

**Alpha-1-antitrypsin deficiency is an inherited genetic disorder that affects mainly the lungs. It limits even mild activity and can be fatal. Intensive research continues in order to find even better treatments.**



Heredity pattern

Another research group is conducting a multicentre phase 3 clinical trial to study the efficacy and safety of an AAT augmentation therapy on subjects with emphysema due to AAT deficiency. The effect of the compound on the progression of emphysema is assessed by the decline of lung density, measured by computed tomography.

Transgenic animals can produce biological products. It may be possible to use transgenic animals to make rare biological products for medical treatment. Human AAT is such a candidate, and research is going on to breed transgenic sheep which produce the glycoprotein in their milk.

### **The longer-term future**

It is known that there is considerable variation in the time of onset and clinical symptoms of individuals affected by AAT. Investigators are trying to find out the exact genetic reasons why some patients develop emphysema and COPD while other individuals do not. This research is trying to determine if there are any inherited factors that modify the development of lung disease in people who inherit the severe form of the disorder.

Work has been presented demonstrating the pro-inflammatory potential of AAT polymers in the lungs of patients with AAT deficiency. Research groups are studying the development of small molecule inhibitors to block the polymerisation of Z AAT. These advances in the understanding of the basic mechanisms of inflammation will allow the development of novel anti-inflammatory therapies for a variety of lung diseases.

AAT deficiency has been identified as being caused by the malfunctioning of an enzyme controlled by a single gene on chromosome 14. Gene therapy, i.e. the delivery of a normal gene to replace the non-functional one should be the ultimate goal to ameliorate or cure the disease. Pre-clinical safety studies in animals have been completed for two different potential formulations for a gene therapy treatment for AAT. Both formulations are currently in phase 1/2 clinical trials. Scientists are also evaluating plasmid-cationic liposome delivery of normal AAT genes to the respiratory epithelium of deficient patients to produce potentially therapeutic local AAT concentrations.

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