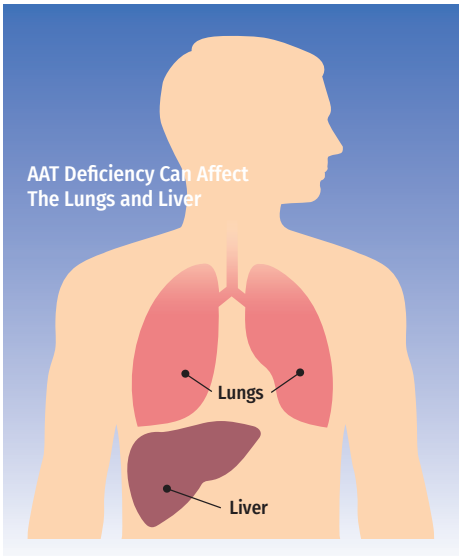
MZ Alpha-1 Antitrypsin Deficiency

Alpha-1 antitrypsin deficiency (AATD) is a hereditary condition that is passed on from parents to their children through genes. People with AATD have decreased levels of a protein called alpha-1 antitrypsin (AAT) in their blood. Low levels of AAT can lead to lung and/or liver problems. There are different types of AATD, and each of these types carry different degrees of risk. This fact sheet describes the MZ form of AATD. For more about AATD see the ATS Fact sheet at www.thoracic.org/patients.



How is MZ AATD inherited?

Genes carry the information that determines the features that are passed on to a person by their biological parents. Importantly, genes come in pairs. Each biological parent has two copies of each of their genes, and each parent passes along one of these copies to make up their children's genes. In other words, children get half their genes from each parent.

The gene responsible for the production of AAT protein is called the *SERPINA1* gene. Abnormalities or "mutations" in this gene lead to abnormal AAT being produced. Different types of *SERPINA1* mutations exist. Normal AAT protein is called "M" AAT. The most common abnormal types of AAT are the "Z" type and the "S" type. People can therefore have different combinations of normal or abnormal gene copies, depending on what genes their parents have. If a person gets an "M" from one parent and a "Z" from the other they are said to be "MZ". Similarly, people who get a "Z" from one parent and a "Z" from the other are said to be "ZZ". Those who get a normal "M" from each parent are "MM", and do not have AATD. If AATD is in your family, it is important to get tested to see whether you carry any abnormal genes.

I am an MZ, how low are my AAT levels?

If you are an MZ, you will have lower than normal levels of AAT in your blood. However, your levels are still slightly higher than those who have SZ AATD, and much higher than those with ZZ AATD, which is a severe form of the condition.

What is the risk of developing lung disease in MZ AATD?

Some people with MZ AATD will go on to develop a type of lung disease called chronic obstructive pulmonary disease (COPD). The likelihood of a person with MZ AATD developing lung disease is strongly influenced by whether or not that person smokes. Non-smoking MZ's do not have a higher risk of developing COPD compared to people without AATD. However, the risk of COPD is 5-10 times higher in MZs who smoke compared to people without AATD who smoke. Other lung injuries from marijuana or from vaping may carry similar risks. If you have MZ AATD you should:

- Know that you can develop lung problems. You are not just a 'carrier' of a mutation.
- Do not smoke or vape and avoid exposure from others. This will reduce your risk of developing lung problems and is something you can control.

How does this risk compare to other common types of AATD?

People who have ZZ AATD have severely decreased AAT levels, and are at increased risk of developing significant lung disease as early as their 30's and 40's. People who have SZ AATD and don't smoke are not at increased risk, making them more similar to people who have MZ AATD. It is important to remember that there is a difference between having a severely low AAT level and having severe lung disease—people with MZ AATD who smoke can develop severe lung disease even though their blood AAT levels are only moderately decreased.

What about liver disease?

The risk pattern for liver disease in people who have MZ AATD is similar to that described for lung disease. Liver disease is rarely seen in MZ AATD without having other coexisting factors that affect the liver, such as viral hepatitis, fatty liver disease, obesity and/or alcohol misuse. Similarly, people with alcoholic or nonalcoholic liver disease are at increased risk of

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progressing to cirrhosis if they carry a Z mutation.

In addition to the risks of lung and liver disease, MZ AATD is also associated with the development of gallstones and an inflammatory disorder affecting small vessels known as ANCA-positive vasculitis.

How is AATD managed?

The most important step in preventing and managing MZ AATD lung disease is stopping and/or avoiding cigarette smoking. At present, the treatment options available for people with MZ AATD who develop COPD are the same as for people with normal AAT levels who develop COPD. Management of COPD may include treatment with inhaled or nebulized medications that help decrease inflammation and keep the airways open. For people who have MZ AATD who have developed lung disease or who are of advanced age, vaccination against influenza and pneumococcus is strongly recommended.

Is there a role for "augmentation therapy" in the management of MZ AATD?

Augmentation therapy involves boosting, or augmenting, the blood levels of AAT by giving AAT purified from the blood of healthy donors through an intravenous (IV) line. This treatment has been shown to slow the progression of lung disease in people with the severe ZZ form of AATD. However, research studies to date have not shown a similar benefit for people with MZ AATD. As a result, augmentation therapy is not indicated for use in MZ patients at the present time.

How common is the "Z" mutation?

This depends on the population studied. For example, we know that about 1 in 25 people of European descent have a "Z" mutation, but this figure is lower in people of non-European descent. However, as the racial and ethnic characteristics of populations change, so too does the distribution of genetic mutations. This concept is particularly important in the United States, where the population of people who report having two or more racial backgrounds is due to be the fastest growing racial or ethnic group in the coming decades. This shift means that the number of people who have MZ mutations and are multiracial is likely to increase substantially.

My partner is also an MZ, what are the chances of our child having AATD?

Because your child receives one copy of the *SERPINA1* gene from each biological parent, they have a 50% chance of being an MZ, a 25% chance of being a ZZ and a 25% of being MM and having normal AAT levels (Figure 1). Importantly, a low AAT level in blood is not a guarantee of health problems. Most people with AATD, and in particular those with the MZ form, will live long and healthy lives provided they make the right lifestyle choices.

Action Steps:

- ✔ A person with MZ AATD should avoid all forms of smoking and vaping. Without smoking, lung function is likely to stay normal.
- ✔ Family members of people known to have "ZZ" or "MZ" AATD should consider genetic testing. Many people across multiple generations will likely have Z alleles.
- ✔ The risk of developing COPD is substantially higher in people with MZ AATD who smoke compared to people without AATD who smoke. At present, treatment of COPD in people with MZ AATD is the same as for MM individuals with COPD.
- ✔ Consider joining a support group or attending an AATD education day
- ✔ Consider seeing an AATD specialist.

Healthcare Provider's Contact Number:

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Resources:

American Thoracic Society

- www.thoracic.org
  - Alpha-1 antitrypsin deficiency
  - COPD
  - Lung Function Testing
  - Stopping Smoking and Vaping
  - E-cigarettes/vaping

Alpha-1 Foundation

- http://www.alpha1.org

Alpha-1 Alleles Website

- https://www.alpha1research.org/allele_search

Reference: Molloy K, Hersh CP, Morris VB, Carroll TP, O'Connor CA, Lasky-Su JA, Greene CM, O'Neill SJ, Silverman EK, McElvaney NG. Clarification of the risk of chronic obstructive pulmonary disease in alpha1-antitrypsin deficiency PiMZ heterozygotes. Am J Respir Crit Care Med 2014; 189: 419-427. doi: 10.1164/rccm.201311-1984OC