Alpha1 MZ Foundation - Information & Research

News and Research Update

Understanding Alpha-1: why not all MZ's are equal

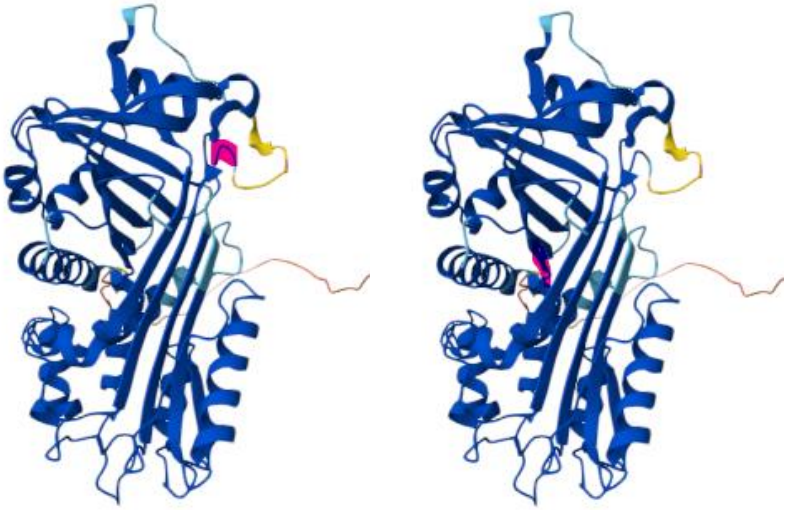
Reinoud Doeschot, December 2025

Most people with alpha-1 antitrypsin deficiency know the labels MM, MZ, ZZ, SZ and FZ. These labels suggest that Alpha-1 comes in only a few forms. But the truth is: the Alpha-1 protein can change in many ways, and some of these changes can be more harmful than the common types we test for.

The Alpha-1 protein is a long chain of 394 building blocks, called amino acids — like beads on a string. There are only 20 different amino acids. Sometimes one of the beads changes. Two things matter: where in the chain a change occurs and which amino acid replaces the original one. These two factors determine whether a mutation is harmless, mild, or harmful.

Where the change happens

Some positions in the protein are crucial, like key parts of a machine. A mutation in such an important spot can cause serious problems. A change in a less important area may do little harm.



Position of the Z-mutation (in pink) Position of the Mmalton-mutation (in pink)

Which amino acid replaces the original one

A replacement amino acid may be similar, causing little or no effect. But if the amino acid is very different, the protein may fold incorrectly, get stuck in the liver, or lose its function partly or completely. So, both the location and the type of change matter.

A well-known example: the Z-mutation

In the Z-mutation, position 342 changes from glutamic acid to lysine. This makes the protein fold badly, causing it to build up in the liver. It is the single most frequent mutation. This is why the Z-type is well known and often discussed. But some other mutations can be just as harmful.

We now know of about 200 rare mutations that influence how Alpha-1 works. Some of these behave just like the Z-mutation — or even worse — but they do not show up as Z-type on the usual lab test.

The limits of the test

Many laboratories use a test to classify Alpha-1 types that is not conclusive for a number of rare mutations. For many mutations, we do not actually know how rare — or common — they are.

The problem is that some harmful mutations appear in the test as a normal M-type protein, even though the protein is not normal. If your M-type is actually a 'hidden' rare mutation (for example Mmalton), your true combination is not MZ — it may be a pairing that is more harmful than the standard MZ. A person may appear to be MZ, but the "M" can actually be Mmalton, Mwurzburg, or Mprocida, which are especially harmful together with the Z-mutation. These combinations can lead to even more severe liver disease or lower Alpha-1 levels than in true MZ individuals.

Why this matters for patients

If your symptoms seem worse than expected for your test result — or if you experience unexplained fatigue, repeated infections, inflammation, or unusual liver concerns — it may be worth considering DNA-based testing to check for one of the many rare mutations.

A "normal M" result does not always mean the Alpha-1 protein is truly normal.

Reference:

Foil KE. Variants of SERPINA1 and the increasing complexity of testing for alpha-1 antitrypsin deficiency. *Ther Adv Chronic Dis*. 2021;12:20406223211015954. doi:10.1177/20406223211015954.

A relatively cheap, anonymous test is offered by iGene:
https://www.igene.eu/choose-your-country