

Alpha-1 antitrypsin deficiency and lung disease – what it means for my patient during the COVID-19 era?

Written by: Dr Daniel Fraughen¹, Dr Tomás P. Carroll^{1,2}, Geraldine Kelly², Gerry McElvaney¹

Author Affiliations: ¹Irish Centre for Genetic Lung Disease, RCSI Education and Research Centre, Beaumont Hospital, Dublin 9.

²Alpha-1 Foundation Ireland.

Correspondence: danieldfraughen@rcsi.ie

Following on from a previous article in HPNI, we will look back over the basics of alpha-1 antitrypsin deficiency (AATD), and the associated risk of lung disease. We will also briefly discuss the new therapies on the horizon for AATD and look at what impact COVID-19 has on people with AATD.

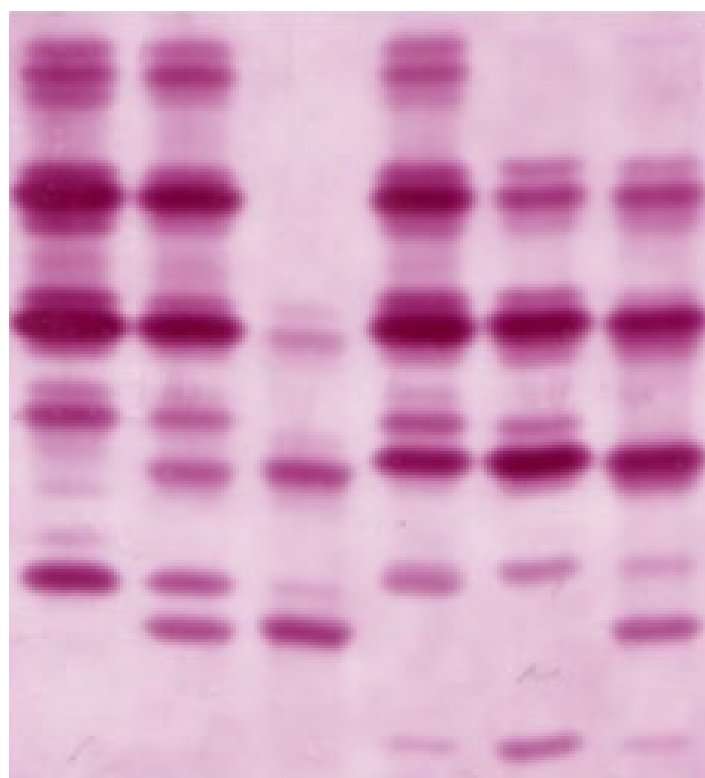
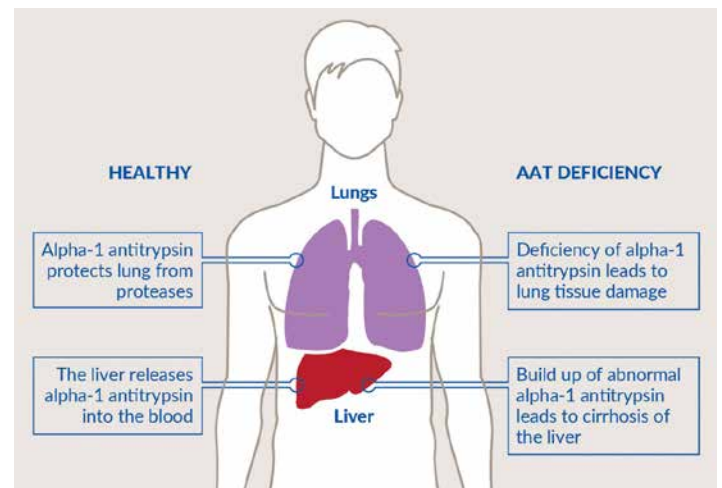
Alpha-1 antitrypsin (AAT) is an anti-protease produced predominantly in the liver that circulates in the blood and is responsible for inhibiting neutrophil elastase (NE). NE is a destructive protease released by activated neutrophils that can cause significant damage to lung tissue if left uninhibited.

Alpha-1 antitrypsin deficiency (AATD) is a genetic condition characterised by low circulating levels of AAT in the blood. The deficiency allows uncontrolled NE to cause irreversible lung damage and emphysema over time, a

Figure 1. The alpha-1 antitrypsin protein in healthy individuals and in those with the genetic deficiency

process accelerated dramatically by cigarette smoke (Figure 1).

AAT protein synthesis is controlled by the SERPINA1 gene. Every individual has 2 copies (alleles) of the SERPINA1 gene and each allele is equally responsible (co-dominant) for producing its share of AAT protein. The normal SERPINA1 allele is called M and produces fully functional M AAT protein. If a person inherits 2 normal SERPINA1 alleles, they produce sufficient AAT protein to protect their lungs and are referred to as having the “MM” phenotype. Over 100 alleles of the SERPINA1 gene exist resulting in abnormal variants of AAT. These include



MM MZ ZZ MS SS SZ

“I”, “S” and “Z” variants, which result in increasingly ineffective AAT protein. A person can have many different allele combinations resulting in various phenotypes such as MM, MS, MZ, SZ, IZ, and ZZ et cetera. This gives rise to a spectrum of deficiency phenotypes.

These phenotypes are determined in the laboratory by isoelectric focusing where the AAT protein variants are separated on agarose gel by an electrical current. Where the protein variant stops on the gel and the resulting banding pattern determines the phenotype (Figure 2).

Further genetic analysis may sometimes be required to determine the exact mutation in the SERPINA1 gene, but this usually only applies to rare or novel mutations. Through the national targeted detection programme for AATD, some ultra-rare mutations have been found to exist in the Irish population that produce no detectable AAT in blood. These are

Figure 2. Typical isoelectric focusing gel used to diagnose AATD. The 6 most common phenotypes are shown. ZZ causes the most severe serum AAT deficiency (reduced by 80-85%) and poses the highest disease risk

called “Q0” or “null” mutations. These mutations are named after the place of birth of the index or first case; examples include the novel Q0dublin and Q0cork mutations.

So, what do these different phenotypes actually mean for our patients?

Firstly, it should be noted that AATD is very prevalent in Ireland. A previous study of the Irish population by Carroll et al., noted that the “S” mutation appears in approximately 1 in 10 people in the general population. The “Z” mutation appears in 1 in 25 people in the general population. These numbers were derived by testing the Trinity Biobank samples for the presence of the 2 most common AATD mutations, Z and S. This biobank is a relatively representative sample of voting-age Irish adults from every county on the island (Figure 3).

The “Z” mutation confers a particularly high risk of disease due to the misfolding of the “Z” AAT protein. This misfolded protein has two effects in that it gains a toxic function in the liver where it polymerises but subsequently cannot be released into the bloodstream (loss of function) to carry out its protective function in the lung.

As previously stated, there is a spectrum of deficiency phenotypes from MS, SS, MZ, SZ to ZZ with increasingly ineffective AAT protein. This can lead to a number of health issues including emphysema, bronchiectasis, steatohepatitis, cirrhosis, panniculitis and ANCA positive vasculitis. The main determinant of lung disease is the presence of a smoking history (Figure 4).

Previously it was thought that SZ AATD lead to a severe deficiency and had clinical manifestations similar to that of ZZ AATD. A study by Franciosi et al, however, found that SZ AATD is a moderate deficiency state and that patients with this phenotype tend to follow a similar clinical course to MZ AATD, and not to ZZ AATD in people who have not smoked. It is imperative, therefore, that an early diagnosis is made so smoking can be stopped at an earlier stage. An early diagnosis is also important as it allows family screening to occur. This can identify additional at-risk individuals, perhaps smokers, among the wider family.

As outlined in Figure 4, it should be noted that patients are at risk of liver disease in addition to lung disease if the “Z” mutation is present. This is due to the hepatotoxic misfolding of the protein in the liver.

Are there any new therapies on the horizon for AATD?

Since the late 1980s, the only therapy routinely administered for severe AATD (ZZ phenotype) is intravenous purified alpha-1 antitrypsin protein. This is generally given as a weekly infusion, though different regimens exist. The cost associated with this therapy is significant and currently this treatment is not reimbursed by the government. This therapy, however, does not treat the underlying cause of AATD, and

Figure 3. Extrapolated data from the Trinity Biobank presented as prevalence of the different AATD phenotypes on the island of Ireland



merely replaces the deficient AAT protein and as such, slows the destruction of lung tissue over time, a hallmark of emphysema.

Unfortunately, for ZZ AATD patients, this means that there is no effective intervention available in Ireland beyond smoking cessation therapy and close medical surveillance for complications. These interventions become increasingly ineffective, the longer a person continues to smoke. As such, it is extremely important to arrive at the diagnosis of ZZ AATD at an early age, so as to minimise the risk of smoke exposure over that person's lifetime.

Over the past year, Vertex Pharmaceuticals has conducted phase two clinical trials to look at novel molecules that will aid in the treatment of ZZ AATD. One of these molecules is currently being studied in a clinical trial taking place in the RCSI Education and Research Centre, Beaumont Hospital. These are the first of, likely many, clinical trials that will take place over the next few years that will look at treating the underlying cause of AATD for the first time.

The swift identification of patients eligible for enrolment in clinical trials is facilitated by the national AATD registry, which is a registry of patients with AATD who have volunteered to take part in helping our understanding of AATD.

How does COVID-19 affect the AATD population?

In addition to being an anti-protease, AAT is also responsible for a number of immuno-modulatory effects. Intravenous AAT protein is currently being trialled in Beaumont Hospital as a treatment for the severe lung damage (ARDS) seen with COVID-19. AAT protein works to dampen down the body's own overactive immune response to COVID-19, particularly in the lungs.

It follows on from this, that if you have ZZ AATD (severe deficiency), then you have a particularly high risk of having an adverse outcome if you contract COVID-19. As such, we have advised that all patients with ZZ AATD should follow public health advice and consider cocooning for the period of the pandemic regardless of having COPD or emphysema.

Current advice from Alpha-1 Foundation Ireland is that the

following groups should consider cocooning:

- All people who are ZZ, whether healthy or not.
- People who are SZ or MZ type AATD with severe lung disease (e.g. COPD, emphysema, bronchiectasis) or severe liver disease (e.g. cirrhosis).
- People who are ZZ, SZ, or MZ and have received a lung or liver transplant.

People who have SZ or MZ AATD, but do not have severe lung, liver disease or a transplant, should follow the same government advice that applies to the general population.

It should be noted that Alpha-1 Foundation Ireland has sought to change the vaccination schedule for people with AATD, who are in the high-risk groups as they are particularly vulnerable due to the loss of the immuno-modulatory properties of AAT, when present in normal levels. The Foundation has asked that these patients be deemed very high-risk for this reason and should be a priority for the COVID-19 vaccine.

There is an undoubted and untold psychological toll suffered by those who have been advised to cocoon for the duration of this pandemic and hopefully, with early access to the vaccine, there may be a light at the end of this long and dark tunnel for all of those with lung disease, in particular those with AATD-associated lung disease.

If you, or anyone you know is affected by AATD, you can find out more information at www.alpha1.ie or by sending us an email at alpha1@rcsi.ie.

AAT Phenotype / AAT Genotype*	AAT Deficiency?	What does it mean?
MM	No	Does not have the disorder – has 2 normal copies of the AAT gene.
MS	Mild	No evidence of increased risk of lung or liver disease but does carry 1 altered AAT gene.
MZ	Moderate	Significantly increased risk of lung disease <u>in smokers</u> . Increased risk of liver disease.
SS	Moderate	Presumed increased risk of lung disease <u>in smokers</u> . No evidence for increased risk of liver disease.
SZ	Moderate	Significantly increased risk of lung disease <u>in smokers</u> . Increased risk of liver disease.
ZZ	Severe	Significantly increased risk of lung disease <u>in smokers and ever smokers</u> . Increased risk of liver disease.

Figure 4. A simple overview of the most common AAT phenotypes in Ireland and how this phenotype relates to disease severity in the presence of smoking