alpha-1 ORGANISATION AUSTRALIA INC

# Alpha Times

Newsletter of Alpha-1 Organisation Australia inc *Issue 12 Autumn 2023*

## From the President's Pen

Hi everyone.
Welcome to our Autumn Edition.

For most people a diagnosis with an unfamiliar genetic disorder like Alpha-1 Antitrypsin Deficiency (Alpha-1), with its unfamiliar terms and an unknown future - due to the lack of treatment options- is typically challenging. The condition is also challenging for many medical professionals as most have no, or only a few, Alpha-1 patients.

The disorder's name doesn't help as "Alpha-1" does not impart any immediate meaning while "Antitrypsin" implies the ability of an important protein to inhibit the enzyme "trypsin". Interestingly, since the seventies, an alternative name, "alpha-1 protease inhibitor", has been used interchangeably with Alpha-1 Antitrypsin, due to the recognition that other proteases are also inhibited. Despite this, the original name, Alpha-1 Antitrypsin Deficiency is generally used outside of research.

A further challenge relates to the fact that most Alpha-1 research has been undertaken on people with the ZZ phenotype who have low levels of antitrypsin (typically in the 10-15% range of normal). This has resulted in many unknowns about potential disease risk for people with other phenotypes including rare types and MZ (i.e., people with one normal gene and one faulty gene). Until we have a good body of research knowledge on all Alpha-1 populations, the general advice given for those severely deficient can be adopted e.g., avoid breathing in particulates, smoke (tobacco) and fumes, and protect the liver (e.g., avoid fatty liver).

While we wait for further research and novel therapies (including recombinant treatments and genetic interventions) that provide hope for those deficient in antitrypsin, our charity (Alpha-1 Organisation Australia) is delighted to advise that we are expanding our video series **"Alpha-1 Unwrapped".** This series is aligned with our strategic aim of "education" of patients, community members and health practitioners. Education is so important as we still hear that it takes an average of seven years to receive an accurate diagnosis of Alpha-1, after seeing many different doctors, and the associated unnecessary costs and mental anguish.

Our new videos will feature a range of health professionals discussing various aspects of Alpha-1 and their role in managing, supporting, and treating patients. These videos will appear on our recently revamped website (www.a1oa.org.au). Visitors to the website will find a vast range of useful resources and we trust that visitors find the website more user friendly and a place full of reliable information.

Wishing you all the best,
Gaynor Heading
President A1OA

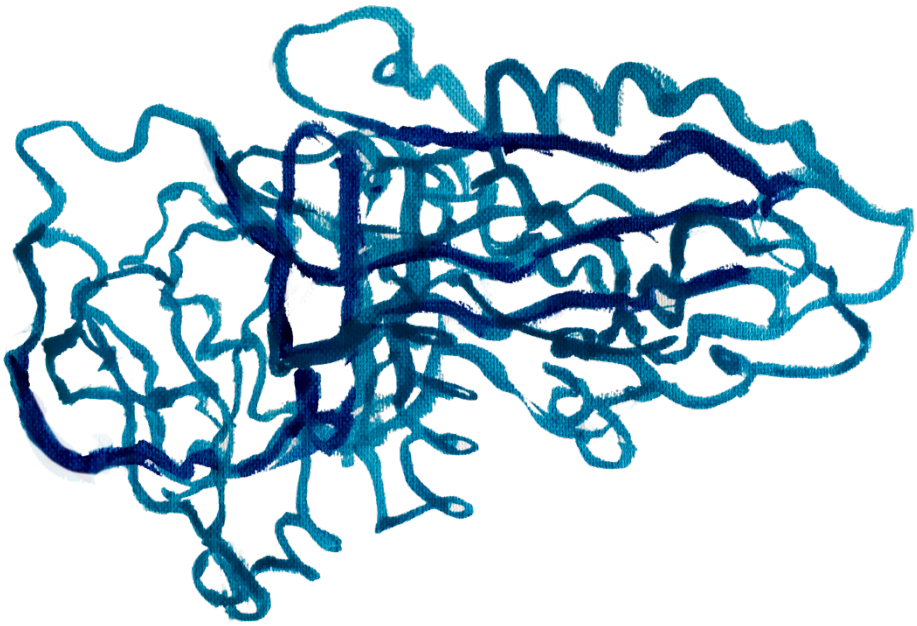
## I'm MZ, am I a carrier?

Without going off into scientific gobbledegook we'll try and answer this question – of course if you have any questions relating to this, get in touch and we'll try and answer them.

The simple answer to this question is yes, you are a carrier of the Z gene which you can then pass on to your children. The issue with using the term 'carrier', however, is that its normal use implies that you are not likely to suffer the symptoms or ill-effects of being so. Very often this language results in doctors who are not familiar with Alpha-1 Antitrypsin Deficiency using phrases such as 'you're just a carrier', with the implication being that this is not a problem for you.

Unfortunately, this is not the case – as we know, while MZ Alphas typically have a higher level of antitrypsin than other genotypes (such as SZ or ZZ), their level of antitrypsin is low enough to allow emphysema to develop if they smoke, and other lung disease including bronchiectasis due to mycobacterium (McElvaney 2023; Strange 2018). Many MZ alphas have been found to suffer from cirrhosis too, however, the absolute risk of liver disease in MZ carriers is unknown but the risk appears to be increased by additional coexisting conditions such as non-alcoholic fatty liver disease, alcohol misuse, and cystic fibrosis (Strnad 2020).

MZ genotype is a common form of Alpha-1 Antitrypsin Deficiency. This population appears to have a low absolute risk of emphysema but are susceptible to multiple disorders due to lower levels of circulating alpha-1 antitrypsin protein, and due to additional genetic and environmental factors (Strnad et al. 2023) which raises risk of disease.



Antitrypsin molecule *Artwork by Leonie Robison*

In summary if you have an MZ diagnosis you are a carrier, but you should also be considered as someone with alpha-1 antitrypsin deficiency. This means you should be tested for your level of alpha-1 antitrypsin and have regular lung and liver checks to look for signs of any ill-effects associated with the condition. You should also be aware of detrimental lifestyle factors and environmental factors (e.g., smoking, alcohol, diet, pollutants) which may increase the chances of organ damage.

A greater understanding of how antitrypsin is involved in immunity, inflammation and disease is being developed (McElvaney et al. 2023). As research reveals more about MZ risk, health professionals and those diagnosed with a MZ phenotype will benefit. We may even see a change in language use, from 'carrier' to 'moderately deficient' in recognition of disease risk.

**References:**

McElvaney O.F., Fraughen D.D, McElvaney OJ, Carroll TP, McElvaney NG. Alpha-1 antitrypsin deficiency: current therapy and emerging targets. *Expert Review of Respiratory Medicine*. 17, 3, 191-202.

Strnad P, McElvaney NG, Lomas DA. (2020) Alpha$_1$-Antitrypsin Deficiency. *N Engl J Med*. 382, 15.

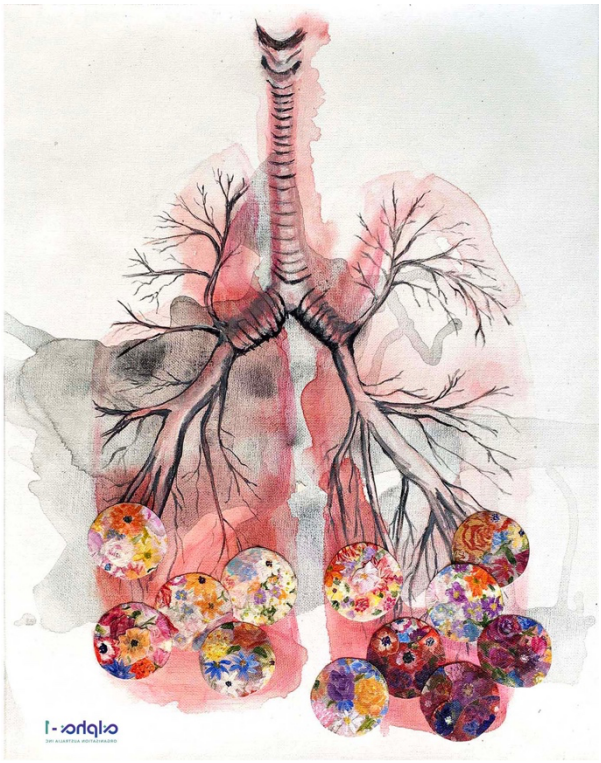
Strange C. (2018) Anti-Proteases and Alpha-1 Antitrypsin Augmentation Therapy. *Respiratory Care*. 63, 6, 690-698.

## Do you suspect that you or a loved one has Alpha-1 Antitrypsin Deficiency?

Maybe you have emphysema but have never smoked?

It's a simple blood test to find out.

Ask your GP for a test.



*Artwork by Leonie Robison*

## Research Partnerships

Did you know that Alpha-1 Organisation Australia is a potential research partner for Alpha-1 Antitrypsin Deficiency research and diseases related to this condition? We foster collaboration and partnerships that support treatment innovation and a cure for Alpha-1.

In recent times we wrote to Australian-based researchers with a research history or interest in Alpha-1, advising them of potential support and a research partnership opportunity. This has led to some research groups reaching out in a number of ways e.g. spreading the word about their research, letters of support, assisting with resource development, and invitations to formally partner on research grant submissions – an offer that we have accepted.

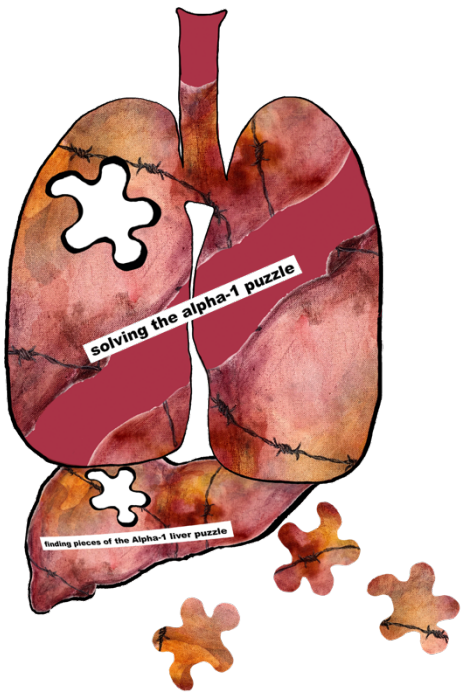
Alpha-1 Organisation Australia advocates for treatment and a cure. If you are involved in Alpha-1 research e.g. looking at innovative treatments or a cure, or work on related research topics e.g. COPD, emphysema, chronic bronchitis, bronchiectasis, inflammation, non-alcoholic liver cirrhosis, please let us know so we can explore potential partnerships or support.

Why partner with us:

- Experience with Alpha-1
- Board members hold degrees and higher degrees in medicine, health, nursing and science and understand the importance of research and innovation
- Experience designing, implementing and publishing research
- In-kind research support
- Communication channels to alpha-1 patients and health practitioners
- Rapid feedback and insight from potential end users of products and treatments
- Integrated knowledge translation
- Registered with the Australian Charities and Not-for-profits Commissions (ACNC)

Please contact the President (Gaynor Heading) at president@a1oa.org.au if you or one of your team would like to discuss potential research partnerships or support.

We are getting closer to solving the Alpha-1 puzzle. There are promising trials of different treatments being undertaking in different centres around the world.




*Artwork by Leonie Robison*

## Some AATD Treatments Currently Being Trialled.

*There are some promising trials into treatment for AATD being undertaken by several companies in centres around the world.*

The ESTRELLA study is being conducted at St Vincent's Hospital, Melbourne, Australia

This is a multiple dose, randomized, placebo-controlled, double-blind study of the drug *Belcesiran* delivered by subcutaneous injection to evaluate the safety, tolerability, PK (drug absorption and metabolism etc), and PD (biological processes in the body) in adult patients with PiZZ AATD-associated liver disease (AATLD).

Belcesiran is a drug developed by Dicerna (Novo Nordisk company). It is a targeted RNAi therapy designed to target the gene responsible for production of the abnormal AAT protein in order to reduce AAT production in the liver.

Takeda with Arrowhead Pharmaceuticals

Fazirsiran, similarly to Belcesiran, is designed to stop the hepatic production of mutant AAT protein (specifically the Z mutation), the cause of progressive liver disease in about 10% of AATD patients.

Reducing production of the inflammatory Z-AAT protein is expected to halt the progression of liver disease and potentially allow it to regenerate and repair.

Median reduction of 83% of Z-AAT accumulation in the liver

ASTRAEUS trial

The drug Alvelestat is being developed by *Mereo BioPharma*

The purpose of this study is to investigate the effect of Alvelestat (an oral neutrophil elastase inhibitor) on blood and sputum biomarkers in patients with PiZZ, null or rare variant phenotype/genotype alpha-1 anti-trypsin deficient lung disease. Change in a number of different blood and sputum biomarkers related to lung damage, inflammation and elastase activity will be measured over a 12 week period. The effect on lung function and respiratory symptoms will also be measured.

Kamada

Existing treatment for AATD require weekly intravenous infusions of AAT therapeutics. Kamada believes that Inhaled AAT for AATD will significantly improve the patient's disease condition and the quality of life of the patients versus current invasive weekly treatment that requires uncomfortable infusion, consumption of time and administration by a medical professional. If approved, Inhaled AAT for AATD is estimated to be the first AAT product that is not required to be delivered intravenously but, instead is administered by a user-friendly, lightweight and silent nebulizer in up to two short daily sessions.

## Did you know we have a Pinterest site?

You can click this link to take you there:
https://www.pinterest.com.au/alpha1ATD/_saved/
Websites of interest are saved on various Boards which include:

- Basics
- Liver Disease
- Lungs
- Exercise
- Hints
- Charity
- Commercial products (available but not endorsed).

Pinterest is great for visual learning or for when you can't remember the web address of a useful website or the name of a good YouTube video. If you come across a helpful video or website please send it to Sandra Baxendell. (comm1.a1oa@gmail.com) to add it to a Board.

## Aunty Alpha

Dear Aunty Alpha,
Every year I suffer from hay fever and allergies to pollen etc, and this tends to exacerbate breathing problems for me. I've read that masks (as used for Covid etc) can reduce the incidence of hay fever and am wondering what the best type of mask would be for this purpose.
Regards
Sylvia

Dear Sylvia,
Our research suggests that as pollen particles are fairly large (compared to smoke, viruses etc) most masks are reasonably effective, but N95 masks in particular have been found to filter 99%+ of pollen particles and are probably the most cost-effective solution. In terms of sourcing, the cheapest masks are available online (Amazon, eBay, Aliexpress etc), but some would be of dubious quality. Chemist Warehouse has packs of 10 N95 masks for $20 (as at April 2023) which are probably a good balance between quality and cost.
In addition to masks, in areas of heavy pollen it's also recommended to use an air purifier indoors – any reputable brand with a HEPA filter should be effective for this purpose.

Regards
Aunty

If you have a question about any of the issues raised

write to Aunty Alpha, who is always happy to answer your questions, or contact the A1OA through contactus.a1oa@gmail.com

## Mental Health First Aid

Alpha-1 Organisation Australia has an accredited Mental Health First Aider who is ready to help if you are not coping after a diagnosis of A1AD for yourself or a family member. A new diagnosis can cause mental distress, anxiety, or depression. Please reach out to mentalhealth.a1oa@gmail.com