Alpha One Foundation

ANNUAL REPORT 2014

MISSION STATEMENT

The Alpha One Foundation is a charity dedicated to raising awareness, increasing diagnosis, promoting research, and improving the treatment of Alpha-1 Antitrypsin Deficiency (Alpha-1).

CORE ACTIVITIES OF THE ALPHA ONE FOUNDATION

STAFF OF THE ALPHA ONE FOUNDATION

Ms Kitty O'Connor, CEO

Dr Tomás Carroll, Chief Scientist

Ms Laura Fee, Clinical Research Associate

Ms Patricia Ryan, Research Nurse

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1. Executive Summary

This year marks the 10th anniversary of the National Alpha-1 Antitrypsin Deficiency Targeted Detection Programme. To date this is the only national screening programme for Alpha-1 in the world. From small beginnings in Beaumont where we began testing on a pilot basis, we expanded to include Mullingar, Drogheda and Mater Hospitals in the first 18 months.

Today the screening programme has tested over 12,500 Irish people for Alpha-1 in 32 Irish hospitals. As a result, more than 400 people have been diagnosed with severe forms of Alpha-1 (ZZ and SZ), and almost 1,800 people have been diagnosed as carriers of the Z Alpha-1 gene (MZ). Recognition for the screening programme came in March when it was awarded "Department Initiative of the Year" at the Irish Healthcare Centre Awards.

Early 2014 saw the publication of an important Alpha-1 research study of 51 Irish families carried out by the Alpha One Foundation, RCSI, and Harvard University. The study provides the best evidence yet for an increased risk of the lung disease chronic obstructive pulmonary disease (COPD) in MZ carriers who smoke (see Chapter 4). The research was reported by TV3 News, Irish Examiner, Irish Times, Irish Independent, regional newspapers and local radio stations in Donegal, Cork, Kildare, Cavan, and Monaghan. The publicity gave our efforts to increase awareness a huge boost, and as a result many people starting talking about Alpha-1 for the first time. Alpha-1 was also covered during the year by The Irish Daily Mail, Dr Pixie McKenna on the Ray D'Arcy show, and in a series of three excellent articles on TheJournal.ie. Finally, in an exciting development "The Science Squad" a series dedicated to scientific and medical research is highlighting Alpha-1 in an episode to be broadcast on RTE in autumn 2014. We are grateful to all those patients who gave time to be interviewed by radio, TV, and print media and spoke so bravely about their condition.

Throughout the year other awareness activities included presentations at the Irish Thoracic Society (ITS) conference in Derry, ANÁIL's respiratory nurse conference in Dublin, UCD School of Medicine, the 3rd National Meeting for COPD Support Groups in Waterford, as well as presentations to respiratory and laboratory staff in Peamount, St James's, Mater, Wexford, and Navan hospitals. Our annual Alpha-1 conference was held in October 2013 in Marino Institute of Education. As usual this was a well-attended conference and provided an excellent opportunity for Alpha-1 patients and family members to meet other Alphas in a relaxed and informal environment. The Alpha One Foundation has continued to work with the Medical Research Charities Group (MRCG), the Irish Donor Network, Irish Platform for Patient Organisations, Science and Industry (IPPOSI), the Irish Lung Health Alliance, the European Organisation for Rare Diseases (EURORDIS) and most recently COPD Support Ireland.

Like many organisations in the country our core funding has been cut again this year, and we are striving to maintain the current level of service. For this reason we are very thankful to everyone involved in fundraising in the last 12 months. The efforts have been amazing and varied, mini-marathons, full marathons, table quizzes, Zumbathons, coffee mornings and triathlons. The money raised has been used to fund a vital upgrade of all our IT systems, which includes our new look website www.alpha1.ie.

Hopefully this brief synopsis gives the reader an idea of the progress made by the Alpha One Foundation over the past 12 months. This work is a team effort and I wish to thank all my colleagues for their hard work and dedication throughout the year, particularly Kitty O'Connor, Laura Fee, and Patricia Ryan.

Dr Tomás Carroll
Chief Scientist, Alpha One Foundation

2. Ten Years of the National Alpha-1 Antitrypsin Deficiency Targeted Detection Programme

WHO SHOULD BE TESTED FOR ALPHA-1?

Guidelines from the World Health Organisation (WHO), American Thoracic Society (ATS), and European Respiratory Society (ERS) advocate targeted detection programmes for AATD. Together these guidelines recommend targeted screening of patients with COPD, severe non-responsive asthma, cryptogenic (unexplained) liver disease and first-degree relatives of individuals with AATD (Table 2.1).

TABLE 2.1: *ATS/ERS recommendations for diagnostic testing for AATD (type A recommendations)*

Who Should Be Tested?
Adults with symptomatic emphysema or COPD (regardless of age or smoking history)
Adults with asthma with airflow obstruction that is incompletely reversible after aggressive treatment with bronchodilators
Asymptomatic individuals with persistent obstruction on pulmonary function tests with identifiable risk factors (e.g. cigarette smoking, occupational exposure)
Adults with necrotising panniculitis
Siblings of individuals with AATD
Individuals with unexplained liver disease, including neonates, children, and adults, particularly the elderly

AATD can be diagnosed by a simple blood test, but sadly it remains vastly under-diagnosed in Ireland and worldwide. A diagnosis of AATD gives the clinician a unique opportunity for early medical intervention and the possible prevention of lung disease in both the affected individual and first-degree relatives. Unfortunately, despite huge strides in awareness and understanding of this condition, this opportunity is often missed. Large variability exists in the clinical course of lung disease in AATD and therefore all COPD patients should be tested for AATD, regardless of age or smoking history. In May 2004, a national targeted detection programme for AATD was launched by the Alpha One Foundation, based at the RCSI Education and Research Centre at Beaumont Hospital.

HOW DO WE TEST FOR ALPHA-1?

Our method of diagnosis analyses blood from suspected individuals using a technique called isoelectric focusing (Sebia). This method identifies variants of alpha-1 antitrypsin (AAT) circulating in human blood, known as phenotyping (Figure 2.1). It is the most accurate method of testing for AATD and identifies not only the most common but also rare AAT phenotypes.

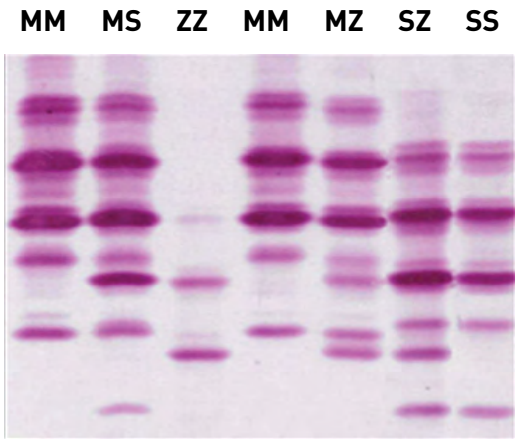


FIGURE 2.1: *Typical isoelectric focusing gel for AAT phenotype identification with the most common phenotypes included*

Since September 2010 the quantification of serum AAT by the Alpha One Foundation has been performed in collaboration with Dr Bill Tormey, Consultant Chemical Pathologist, Pat O'Brien, and Emma Pentony of the Department of Chemical Pathology in Beaumont Hospital. Measurement of AAT levels is performed by immune turbidimetry on the Olympus AU4500 instrument, an automated system for plasma protein determinations. The Department of Chemical Pathology in Beaumont Hospital has attained CPA accreditation which means that AAT measurements are performed to the highest standards. In addition, we have been participating in the UKNEQAS quality assurance scheme for AAT phenotyping since 2007, achieving 100% compliance to date.

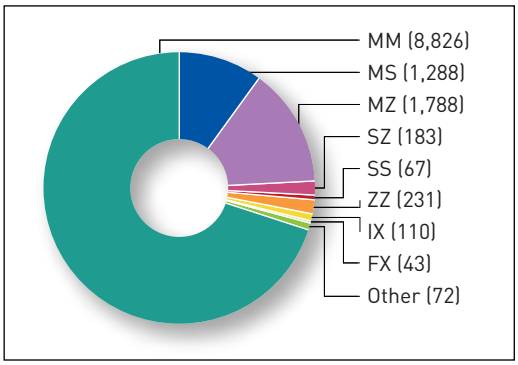
WHAT HAVE WE FOUND IN IRELAND?

Over 12,500 individuals with COPD, asthma, and liver disease, as well as first-degree relatives of known AATD individuals have been screened in our national AATD targeted detection programme since 2004. We receive blood samples from over 30 hospitals in Ireland as well as directly from GP practices. In addition, over 500 tests have been requested because a family member has AATD.

A total of 231 ZZ (severe AATD) individuals have been identified, as well as 183 SZ (moderate AATD) individuals, who are also at risk of developing lung and liver disease (Figures 2.2 and 2.3). In addition, a large number of other clinically significant phenotypes have been detected including 1788 MZ, 67 SS, 17 IZ, and 9 IS phenotypes. The percentage of deficiency alleles (approximately 30%) detected has been quite high, even allowing for the targeted nature of screening. A number of rare AAT mutations

were also identified in the Irish population, including I, F, $M_{wurzburg}$, $Z_{bristol}$, M_{malton} and three different Null mutations ($Null_{bolton}$, $Null_{cork}$, and $Null_{dublin}$).

FIGURE 2.2: *AAT phenotypes identified in National Targeted Detection Programme*



The primary outcome of the screening programme is the opportunity to receive specialist care. Newly diagnosed individuals can avail of rapid referrals to our dedicated Alpha-1 clinic in Beaumont Hospital under the care of Professor McElvaney. In addition, family screening allows the identification of younger relatives with AATD in whom no significant lung damage has occurred. These individuals benefit from lifestyle changes such as smoking cessation and closer medical observation which can help prevent or postpone the development of lung disease.

FIGURE 2.3: *Total ZZ and SZ cases detected since the beginning of the screening programme in 2004*

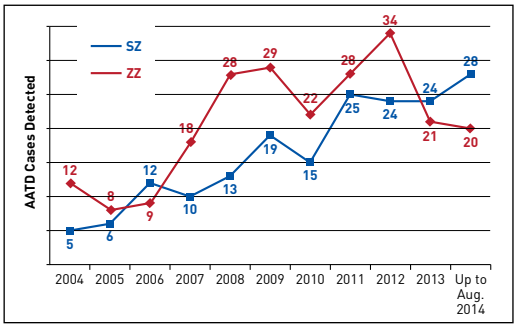


TABLE 2.2: *Requests from Dublin Area Hospitals*

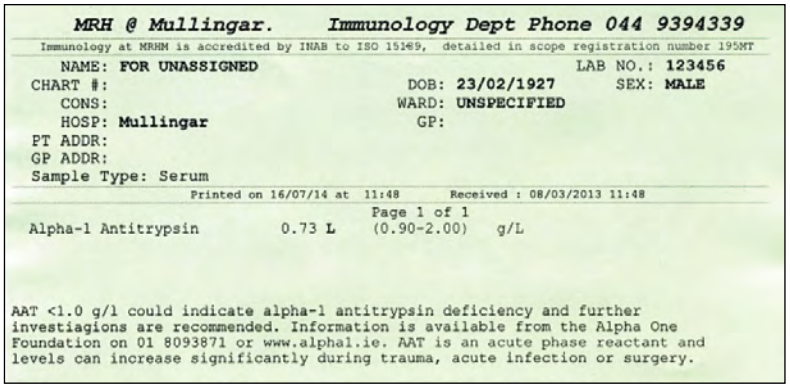
Dublin	Requests
Beaumont Hospital	2200
St Vincent's University Hospital	2041
Bon Secours Dublin	613
Connolly Hospital Blanchardstown	519
St James's Hospital	496
Peamount Hospital	236
Our Lady's Children's Hospital, Crumlin	146
The Adelaide and Meath Hospital, Dublin	139
Mater Misericordiae University Hospital	130
Temple St Children's University Hospital	34
The Coombe	18
St Columcille's Hospital	14
Rotunda Hospital Dublin	7
Blackrock Clinic	7
Mount Carmel Hospital	3
National Maternity Hospital, Holles Street	1

Nationwide	Requests
Cork University Hospitals	998
Sligo General Hospital	981
Letterkenny General Hospital	919
Cavan General Hospital	601
Bon Secours Tralee	366
Galway University Hospitals	258
Naas General Hospital	216
Midland Regional Hospital Mullingar	194
Mid-Western Regional Hospital Limerick	140
Our Lady of Lourdes Hospital Drogheda	137
Waterford Regional Hospital	103
Midland Regional Hospital Tullamore	84
Roscommon County Hospital	80
Mayo General Hospital	18
Monaghan General Hospital	8
Kerry General Hospital	7
Midland Regional Hospital, Portlaoise	4
Louth County Hospital	3
Navan Hospital	3
Clane General Hospital	1
Bon Secours Galway	1

TABLE 2.3: *Requests from Hospitals Nationwide (excluding Dublin)*

In the past 12 months we have presented results from our screening programme to the respiratory and biochemistry departments in St James's, Mater, and Peamount hospitals in Dublin, Our Lady's Hospital in Navan, and Wexford General Hospital. The main aim of these presentations is to increase awareness of AATD amongst the respiratory and paramedical community. While the respiratory (and liver) teams are dealing with patient populations most at risk due to AATD, Immunology, Biochemistry, and Clinical Chemistry Departments measure AAT levels as a routine test during normal blood investigations.

Furthermore, in an excellent example of joined-up thinking several laboratories have adopted a "red flag" system for AAT testing. This system means that if AAT concentrations are measured by a laboratory and found to be below a threshold of 1.0 g/L, an automatic "red flag" is included on the laboratory report to recommend testing for AATD (Figure 2.4). This value was found to achieve the greatest sensitivity, specificity, and cost-efficiency in the detection of deficient phenotypes in a large US study (Donato L.J. et al 2012). It is hoped that an electronic prompt system will lead to earlier diagnosis of AATD. The ultimate goal would be the adoption of this red flag system on AAT reports in every hospital in Ireland.



MRH @ Mullingar. Immunology Dept Phone 044 9394339

Immunology at MRHM is accredited by INAB to ISO 15189, detailed in scope registration number 195MT

NAME: FOR UNASSIGNED LAB NO.: 123456
CHART #: DOB: 23/02/1927 SEX: MALE
CONS: WARD: UNSPECIFIED
HOSP: Mullingar GP:
PT ADDR:
GP ADDR:
Sample Type: Serum

Printed on 16/07/14 at 11:48 Received : 08/03/2013 11:48

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Alpha-1 Antitrypsin	0.73 L	(0.90-2.00)	g/L

AAT <1.0 g/l could indicate alpha-1 antitrypsin deficiency and further investiagions are recommended. Information is available from the Alpha One Foundation on 01 8093871 or www.alpha1.ie. AAT is an acute phase reactant and levels can increase significantly during trauma, acute infection or surgery.

FIGURE 2.4: *Example of an electronic prompt on a laboratory AAT report*

NATIONAL ALPHA-1 ANTITRYPSIN DEFICIENCY PATIENT REGISTRY

The National AATD Registry is a confidential database that records medical information from individuals with alpha-1 antitrypsin deficiency. This database stores valuable clinical and demographic information such as lung and liver test results, smoking history, and symptom details which improves our understanding of the condition, facilitates clinical research, and helps in the design of clinical trials (Figures 2.6 and 2.7).

There are currently 258 Alpha-1 individuals from 29 counties in Ireland included on the registry to date. The process is ongoing and we hope to include as many Alpha-1 individuals as possible. Participation in the registry is voluntary; in order to be included in the registry a patient must give their written consent which is collected on a consent form with the patient retaining a copy. Patients are provided with an information leaflet about the registry and can withdraw their consent at a later date.

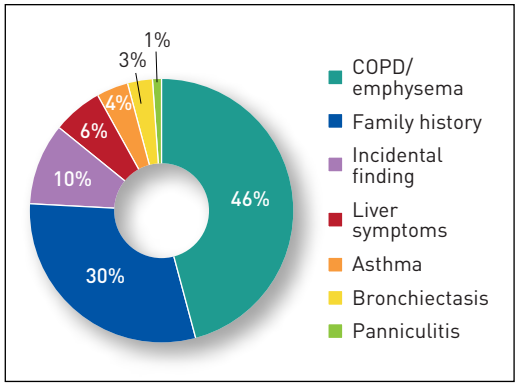


FIGURE 2.6: *Reason for Diagnosis of ZZ Individuals on the National Registry*

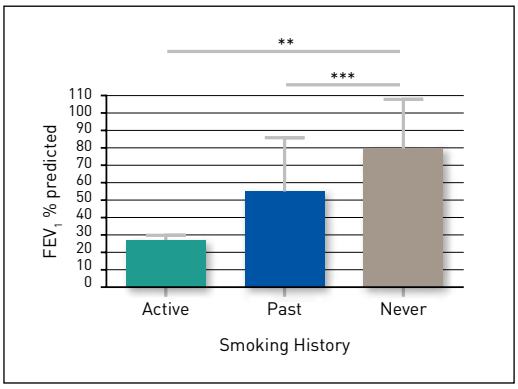
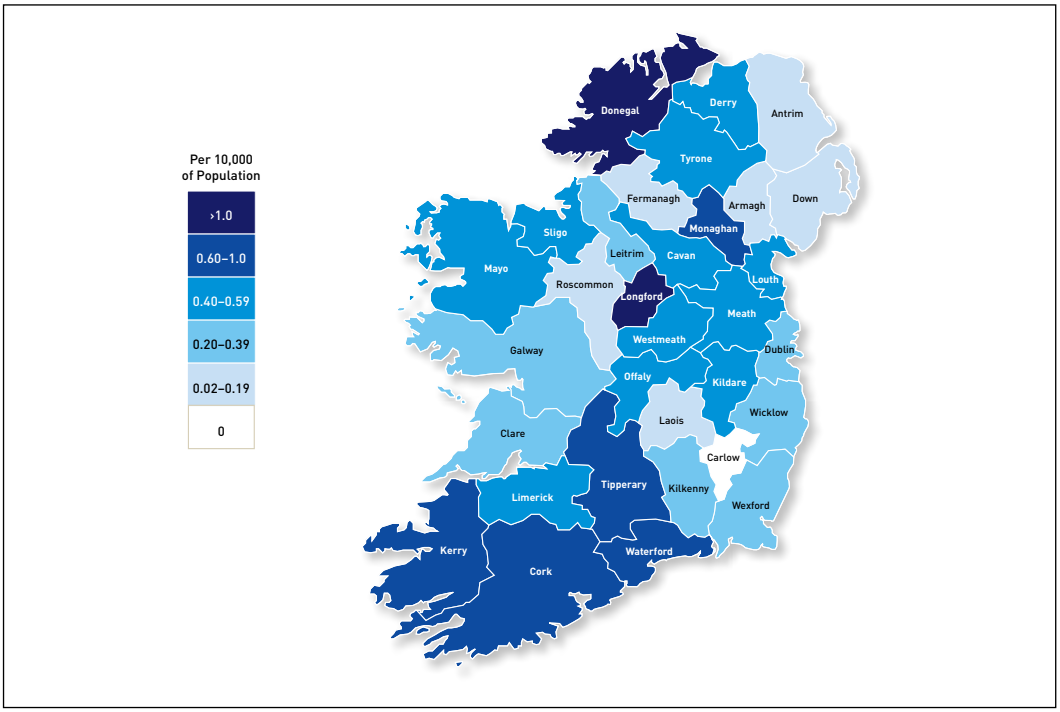


FIGURE 2.7: *Effect of smoking status on lung health (as measured by FEV1, % predicted) in ZZ AATD individuals on the National Registry*

If you have any questions relating to the national AATD registry please contact:
Laura Fee, Clinical Research Associate, Alpha One Suite, Beaumont Hospital, Dublin 9.
Telephone: 01-8093702. Email: *alpha1@rcsi.ie*

FIGURE 2.5: *Geographical distribution of ZZ AATD cases detected per 10,000 of population (a bias may exist for some counties depending on the number of samples received for testing)*



3. Current Research Developments in Alpha-1

CLINICAL TRIALS

A new **Alpha-1 antitrypsin *intravenous* augmentation therapy clinical trial** is starting in the RCSI Clinical Research Centre at Beaumont Hospital later this year. The trial, known as SPARTA, will be the first clinical trial to evaluate the efficacy of PROLASTIN-C at the standard 60/mg/kg dose and the 120 mg/kg dose vs. placebo. The international multicentre SPARTA study will use CT scans of the lung to measure the degree of lung damage over time in individuals with the ZZ phenotype. Recruitment for the study will commence towards the end of 2014.

Currently, a placebo-controlled, double-blinded, multicentre, phase III/IV trial is underway at the RCSI Clinical Research Centre at Beaumont Hospital. The aim of this study is to assess the safety and efficacy of the drug Zemaira® given *intravenously* to patients with emphysema due to alpha-1 antitrypsin deficiency. This study was initially conducted over a two year period. **Twenty-four patients** were enrolled in this study and recruitment has now closed.

Professor McElvaney and his team have also conducted a clinical trial looking at the safety and efficacy of *inhaled* alpha-1 antitrypsin (AAT) replacement therapy. **Nineteen patients** were recruited onto this study. The data collected during the study is now being assessed.

For further information on our clinical trials please contact the Alpha-1 nurse on 01-809 3864.

RESEARCH STUDIES

Earlier this year researchers from the Royal College of Surgeons in Ireland (RCSI) and Beaumont Hospital made an important breakthrough in the understanding and treatment of alpha-1 antitrypsin deficiency (AATD). Their study was published in Science Translational Medicine, a prestigious journal that highlights medical advances resulting from scientific research. Their exciting findings show how the Alpha-1 protein plays an important role in controlling inflammation caused by white blood cells that circulate throughout the body. For the first time it was revealed that a lack of the Alpha-1 protein causes an increase in the release of white blood cell proteins into the bloodstream. This leads to an autoimmune process in the body that mistakenly recognises these proteins as foreign and causes the production of harmful oxidants. Their research findings also revealed how augmentation therapy, where the Alpha-1 protein is given intravenously, alleviates the disease associated with autoimmunity in AATD.

More recent research is investigating the ability of different forms of Alpha-1 to control the activity of white blood cells. What does this mean? Well, when Alpha-1 is produced by liver cells a variety of sugars are attached to it. The process of adding sugars to Alpha-1 is called glycosylation. These different sugar coated forms of Alpha-1 are referred to as glycoforms. The unique research that is being performed is aimed at understanding whether different glycoforms of Alpha-1 are produced by the liver to dampen down inflammation. The ultimate goal of this research is to understand whether different glycoforms of Alpha-1 can be manufactured as a new Alpha-1 augmentation product with specific anti-inflammatory properties.

RCSI researchers working on Alpha-1 projects have received a number of awards over the last year. Ciara O'Dwyer, research scientist, was the winner of the PhD category of the RCSI Research Day and her project received funding from the US Alpha-1 Foundation. Dr Emmet O'Brien was awarded the Beaumont Hospital Sheppard Medal. Another team member Dr Cormac McCarthy received the prestigious European Alpha-1 Antitrypsin Laurell Training Award (eALTA). This award supports basic and clinical research into AATD and helps to identify new therapeutic avenues.

Dr Cormac McCarthy (L) and Dr Emmet O'Brien (R)

This clinical and scientific research is being carried out by a dynamic team in the Department of Medicine in RCSI including scientists, doctors and nurses under the leadership of Professor McElvaney. The results of the many research projects give a greater understanding of Alpha-1 and allow us to develop new therapies, design better clinical trials, improve the care of patients, and ultimately lead to better health outcomes for Alpha-1 patients.

4. Family Screening – Why is this Important?

We often hear the expression that something "runs in the family". This can be said of Alpha-1. As it is a genetic condition, it runs in families because the variant genes that cause Alpha-1 can be passed from one generation to the next. So if there is a strong family history of emphysema or COPD in your family, this could be a sign that you need to get tested for Alpha-1.

Following the World Health Organisation (WHO), American Thoracic Society (ATS) and the European Respiratory Society (ERS) the Alpha One Foundation advocates targeted screening of patients with COPD regardless of age or smoking history, patients with non-responsive asthma, cryptogenic liver disease and *the screening of first-degree relatives of known AATD individuals.*

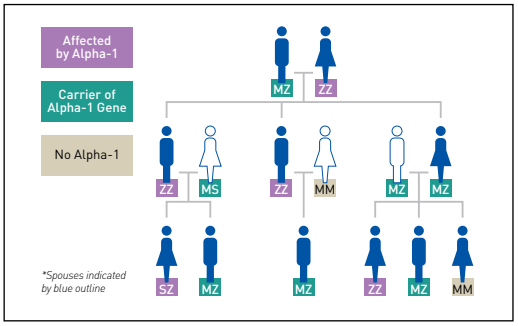


FIGURE 4.1: How Alpha-1 is Inherited. *From Alpha-1 Antitrypsin Deficiency: A Guide for the Recently Diagnosed Individual (courtesy of the US Alpha-1 Foundation)*

GENETICS OF ALPHA-1

In each of us, the normal AAT protein is made from a pair of genes obtained from one's parents. Each parent donates one alpha-1 gene from the two they have available. The normal AAT protein is made from the M variant of the gene. For unknown reasons, there are close to 100 altered or abnormal variants of the alpha-1 gene, also called alleles, but only a few can cause serious lung, liver or skin disorders. Two of the most common alleles are the S and Z gene variants. An individual with different gene variant pairs, such as the MZ combination, is called a heterozygote or carrier. Someone with similar gene variant pairs, such as the ZZ combination, is called a homozygote. Individuals with one normal and one abnormal alpha-1 gene are called carriers. ZZ Alphas can have parents who are both carriers, one parent who is a carrier and one who is severely deficient, or two parents who are severely deficient.

WHY DOES FAMILY SCREENING MATTER?

The area of family screening offers the greatest possibility for the prevention or at least postponement of lung disease, particularly COPD. An early diagnosis of AATD provides opportunities for behaviour modification and lifestyle changes, the most important of which is smoking cessation. Data from the Irish National AATD Registry demonstrates that ZZ individuals detected by family screening tend to have preserved lung function compared to those identified by symptomatic screening.

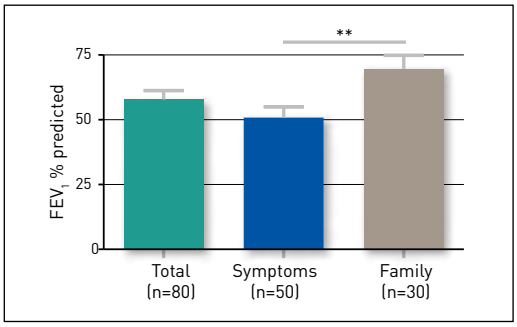


FIGURE 4.2: *FEV1 (% predicted) in ZZ individuals diagnosed by symptomatic screening versus those diagnosed by family screening enrolled in Irish National AATD Registry (**p < 0.001, t-test)*

An excellent example of the family screening possibilities opened up by a diagnosis of AATD is presented in a family study from the National AATD Registry. In this example, the index (or first) case was diagnosed with AATD because of lung disease. Six of the other nine siblings were subsequently tested revealing 3 ZZ individuals, 2 MZ individuals, and 1 MM individual.

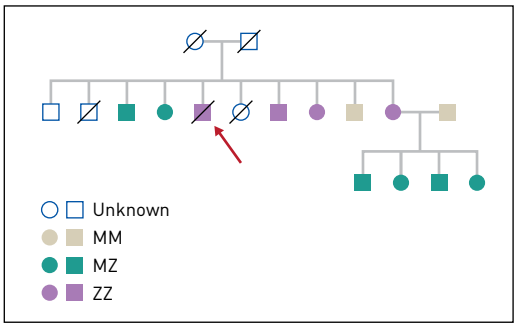


FIGURE 4.3: *Identification of ZZ index case (red arrow) and subsequent diagnosis of at risk relatives by family screening*

Members of this family have benefited from family screening in a variety of ways including increased motivation for lifestyle changes and behaviour modification (for example smoking cessation), screening of their own children, closer medical observation, the opportunity to be seen in the specialist Alpha-1 clinic in Beaumont Hospital, and having the opportunity to partake in clinical trials if suitable.

For more information on family screening and getting tested contact the Alpha One Foundation on 01-8093871 or alpha1@rcsi.ie.

5. The MZ Carrier Question – Finally Some Answers

Early this year, a joint Irish-American study by the Alpha One Foundation, RCSI, and Harvard University provided the best evidence yet to support the belief that being an MZ carrier is linked to increased risk for chronic obstructive pulmonary disease or COPD, a debilitating lung condition. The work was published in the prestigious American Journal of Respiratory and Critical Care Medicine. Alpha-1 antitrypsin is a protein which protects the lungs and deficient individuals with lower than normal amounts of this protein are at an increased risk of developing COPD. Previously, the increased COPD risk as a result of Alpha-1 was only definitively known to affect people who inherit two abnormal alpha-1 genes (for example ZZ individuals).

Study design: 250 individuals from 51 Irish families took part in the research study which set out to determine the risk of COPD for people who carry one normal Alpha-1 gene (M) and one abnormal Alpha-1 gene (Z). This study took a unique approach by specifically examining all the first degree relatives in families who had a family member who was both an MZ carrier and had also a diagnosis of COPD. This allowed the removal of a lot of the doubt that clouded previous attempts to answer this question once and for all.

Methods & Results: 89 MZ carriers were compared to 99 individuals who didn't have an abnormal alpha-1 gene (MM individuals). All participants were tested for alpha-1 antitryspin deficiency, had their lung function measured and completed a lung health questionnaire. It was shown that MZ carriers who smoke had worse lung function and are therefore at greater risk of developing COPD compared to people who had no abnormal Alpha-1 genes (MM individuals). In fact, smoking MZ carriers had an estimated 5 to 10 fold increased risk of developing COPD compared to MM individuals. MZ carriers who didn't smoke were at no apparent increased risk of lung disease compared to MM individuals. This means that lung disease in MZ carriers is completely preventable by avoiding cigarette smoke exposure.

Conclusion: The research has proven for the first time that the estimated 1 in 25 people on the island of Ireland who are MZ carriers have an increased risk of COPD if they smoke. Cigarette smoke is the most influential factor in determining whether these individuals who carry this combination of genes are at a greater risk of COPD compared to MM individuals.

Clarification of the risk of chronic obstructive pulmonary disease in alpha-1 antitrypsin deficiency PiMZ heterozygotes. Molloy K, Hersh CP, Morris VB, Carroll TP, O'Connor CA, Lasky-Su JA, Greene CM, O'Neill SJ, Silverman EK, McElvaney NG. *Am J Respir Crit Care Med.* 2014 Feb 15;189(4):419-27. PMID: 24428606.

Clockwise from top left:

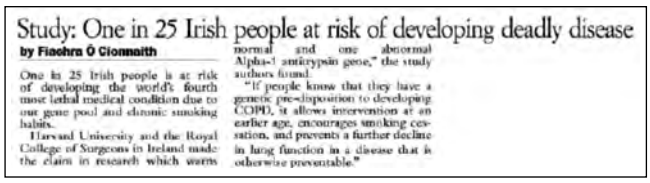
Irish Examiner

Donegal News, Derry People

Letterkenny Post

Irish Independent

Irish Times Health Plus



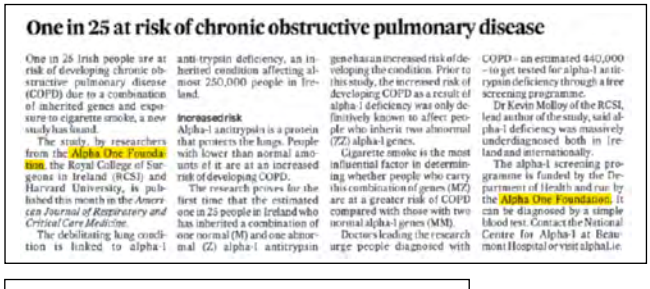
Study: One in 25 Irish people at risk of developing deadly disease

by Fiachra Ó Cionnaith

One in 25 Irish people is at risk of developing the world's fourth most lethal medical condition due to our gene pool and chronic smoking habits.

Harvard University and the Royal College of Surgeons in Ireland made the claim in research which warns normal and one abnormal Alpha-1 antitrypsin gene," the study authors found.

"If people know that they have a genetic predisposition to developing COPD, it allows intervention at an earlier age, encourages smoking cessation, and prevents a further decline in lung function in a disease that is otherwise preventable."



One in 25 at risk of chronic obstructive pulmonary disease

One in 25 Irish people are at risk of developing chronic obstructive pulmonary disease (COPD) due to a combination of inherited genes and exposure to cigarette smoke, a new study has found.

The study, by researchers from the Alpha One Foundation, the Royal College of Surgeons in Ireland (RCSI) and Harvard University, is published this month in the *American Journal of Respiratory and Critical Care Medicine*.

The debilitating lung condition is linked to alpha-1 anti-trypsin deficiency, an inherited condition affecting almost 250,000 people in Ireland.

Increased risk

Alpha-1 antitrypsin is a protein that protects the lungs. People with lower than normal amounts of it are at an increased risk of developing COPD.

The research proves for the first time that the estimated one in 25 people in Ireland who has inherited a combination of one normal (M) and one abnormal (Z) alpha-1 antitrypsin gene has an increased risk of developing the condition. Prior to this study, the increased risk of developing COPD as a result of alpha-1 deficiency was only definitively known to affect people who inherit two abnormal (ZZ) alpha-1 genes.

Cigarette smoke is the most influential factor in determining whether people who carry this combination of genes (MZ) are at a greater risk of COPD compared with those with two normal alpha-1 genes (MM).

Doctors leading the research urge people diagnosed with COPD – an estimated 440,000 – to get tested for alpha-1 antitrypsin deficiency through a free screening programme.

Dr Kevin Molloy of the RCSI, lead author of the study, said alpha-1 deficiency was massively underdiagnosed both in Ireland and internationally.

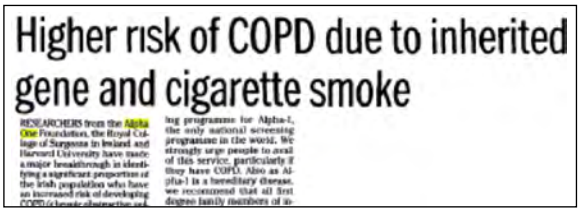
The alpha-1 screening programme is funded by the Department of Health and run by the Alpha One Foundation. It can be diagnosed by a simple blood test. Contact the National Centre for Alpha-1 at Beaumont Hospital or visit alpha1.ie

Donegal man helps develop link between genes and smoking

COPD ›› LINK WITH INHERITED GENE AND EXPOSURE TO CIGARETTE SMOKE

One in 25 has 'genetic risk' of getting lung disease

Brothers are proof of link



Higher risk of COPD due to inherited gene and cigarette smoke

RESEARCHERS from the Alpha One Foundation, the Royal College of Surgeons in Ireland and Harvard University have made a major breakthrough in identifying a significant proportion of the Irish population who have an increased risk of developing

SO WHAT DOES IT MEAN TO BE AN MZ CARRIER?

1

Q. WHAT IS MY RISK OF LUNG DISEASE IF I SMOKE? HOW DAMAGING IS IT IF I CONTINUE TO SMOKE?

A. MZ carriers who smoke are approximately 5–10 times more likely to develop COPD compared to MM individuals. Cigarette smoke is the most important factor in determining whether MZ carriers get lung disease and therefore avoidance of cigarette smoke is the single most important intervention in treating this otherwise preventable disease. Continuing to smoke if you are an MZ carrier is likely to significantly damage your lungs given that we have shown from our research that MZ carriers who smoke have significantly worse lung function compared to MM individuals.

2

Q. WHAT IS MY RISK OF LUNG DISEASE IF I DON'T SMOKE?

A. There is no apparent increased risk of lung disease in MZ carriers who don't smoke. However, more work is needed to determine whether non-smoking MZ carriers are at an increased risk of COPD, particularly the effect of passive cigarette smoke exposure and the effect of other irritants in the environment such dust, fumes, or sprays etc. in the workplace.

3

Q. ARE THERE ANY FOODS I NEED TO AVOID?

A. There are no foods you need to avoid if you are an MZ carrier but avoidance of excessive alcohol intake is very important to protect your liver. Men should not regularly drink more than 3–4 units of alcohol a day and women should not regularly drink more than 2–3 units a day.

4

Q. WHAT IS MY RISK OF LIVER DISEASE?

A. Current research suggests the risk of developing liver disease is increased in MZ carriers only if they are exposed to other risk factors for liver disease in their environment such as viral hepatitis or excessive alcohol intake.

5

Q. IS THERE ANYTHING I CAN DO TO PROTECT MY LUNGS?

A. Most importantly avoid cigarette smoke or stop smoking if you already are. We advise all of our patients to try and prevent lung infection by getting the flu vaccine every year and the pneumonia vaccine every five years. If you develop an infection in your lungs, it is important to treat it early and aggressively with antibiotics to prevent any damage to the lungs.

6

Q. SHOULD I GET MY CHILDREN TESTED?

A. If you have been diagnosed as an MZ carrier there is a 50/50 chance that your child has inherited your Z alpha-1 gene. Your child's other alpha-1 gene is inherited from the other parent. You may have to consider getting the other parent tested to see what other alpha-1 genes are present. Additional factors may need to be considered for example, age, smoking history, lung and liver problems, or other medical conditions. We would advise you contact the genetic counselling service in the Alpha One Foundation to discuss the best course of action for you and your family.

6. Organ Donation

STEPHEN'S STORY

My name is Stephen and I'm 35 years old. This time last year I wrote a very different letter, one which couldn't be further from the one I begin to write now. I had spoken about my wait for a lung transplant from June 2010 and how debilitated my life had become as my condition gradually deteriorated.

My wife and I had lived with years of false alarms, routine hospital appointments, bouts in hospital, cancelled holidays and limited social and sports activities due to my illness. However finally in November 2013, I received my gift of life when I received my double lung transplant. It was a gift I doubted I would ever receive at times but my wife and family never let me dwell on the negative for too long, constantly reassuring me that my day would come and I needed to be ready for it. When the call came that day, we both naturally assumed that it would be another false alarm and I would be back home in my bed before morning. That wasn't the case this time though, our transplant co-ordinator Zita came and told us the news at about 4am that this time the lungs were good and they were for me. I don't think you can ever be prepared for a moment like that. I remember coming around after my surgery and the doctor asking me how I felt and I said "This is awesome". To be able to take a full breath for the first time in so many years was a surreal experience. Of course I was still very sore and tender from the surgery but even then I knew how special this gift was. I recovered extremely well and was back at home in my own bed after just 15 days. Being at home was amazing, to be able to do the simplest things again like taking a shower without oxygen or climbing the stairs to play pool in my house was unreal. I thought I understood how limited my life had been when I was waiting on the transplant but I only truly realise what I missed out on, now that I'm feeling so well. I have started going to the gym 3-4 times a week now, training with my local Gaelic football team and training the juveniles on a Saturday morning. Gaelic is a big passion in my life and to be back involved with my club means more to me than I can ever put into words. If you ask anyone who knows me they'd say I'm like a new man, and that's exactly how I feel. I cannot wait to go back to work full time and make plans to travel next year now that I have the opportunity and I know my wife wouldn't say no to a holiday. We can finally take the honeymoon we never got to take when we got married.

Due to the generosity of one donor and the fortitude of their family to carry out their wishes, I am standing here today a much healthier man than I was last year. I remember when my own amazing aunt donated her organs in 2011, her children felt some sense of comfort knowing her donated organs had changed the lives of the people who received them. I can only hope that my donor's family can feel the same sense of comfort. I can see a future now and there are no words in the English language to express my gratitude for being given that gift. I pray for my donor every day and I thank them for making the decision to give me the gift of life. My favourite quote nowadays is "The greatest hero I never knew was an organ donor who saved my life" and it's so true. My donor is my hero and I will never be able to repay them for what they have done. I can only hope that I honour them by being the healthiest I can be and living life to the full.

Thank you,
Stephen

ORGAN TRANSPLANTATION IN IRELAND

The HSE's National Organ Donation and Transplantation Office recently launched its Annual Report for 2013. It was a record year for organ transplantation in Ireland, with 294 transplants carried out in Irish hospitals compared to 275 in 2011. Of particular interest for the Alpha-1 community are the lung and liver transplant programmes. Importantly, 2013 saw the allocation of an additional €2.9 million in the HSE service plan for 2014 for the creation of 19 whole-time equivalent (WTE)

posts in transplantation. Increased funding for transplantation has been a key demand of the Irish Donor Network (of which the Alpha One Foundation is an active member) for several years. Key points from the 2013 Annual Report are outlined below with more detail available on www.nodto.ie.

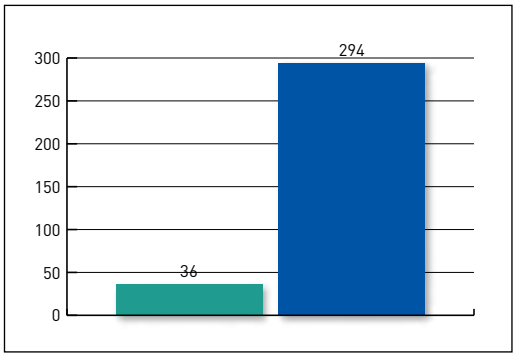


FIGURE 6.1: *Total Organ Donors and Transplants for 2013. Ratio of donors to transplants was 3.4:1*

ORGAN DONATION AND RETRIEVAL IN IRELAND

Organ donation in Ireland is currently based on a voluntary donation system (opt in) and occurs in 32 intensive care units throughout Ireland. Currently there are no organ donation personnel deployed in Irish Intensive Care Units. There is a voluntary "Link Nurse" in a proportion of Intensive Care Units across the country, who, laudably foster organ donation. The three transplant centres at Beaumont, Mater and St Vincent's Hospitals have developed independently of each other and have different requirements in relation to organ donation. Each transplant centre has its own organ retrieval team, which provides 24/7 service and travels nationwide to retrieve organs.

ORGAN PROCUREMENT SERVICE

Currently no independent organ procurement service exists in Ireland. The renal transplant coordinators have historically provided procurement (donor) coordination services for liver, lung and heart transplantation as well as its original primary function of coordinating renal and pancreas transplantation. They deliver a 24 hour on-call service for the three transplant centres and deal with all organ donor referrals.

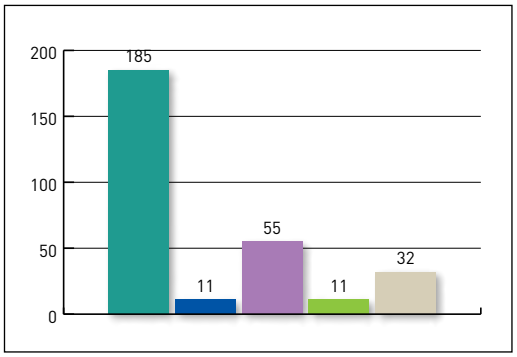


FIGURE 6.2: *Organ Specific Transplant Activity in 2013*

THE NATIONAL LUNG TRANSPLANT PROGRAMME

The lung transplant programme is located at the Mater Misericordiae University Hospital. The paediatric transplantation programme is conducted in various UK hospitals on behalf of the Irish Republic. The first lung transplant in Ireland was performed in 2005 on an Alpha-1 patient and since then the programme has grown incrementally. In 2006 the first double lung transplant was undertaken, again on an Alpha-1 patient. In 2007 the first lung transplant for a cystic fibrosis patient occurred. Performing a record 32 adult lung transplants in 2013 has allowed for repatriation of commissioned transplant services from Newcastle. The Irish programme has demonstrated its ability to provide care for even the most critically ill and complex patients requiring lung transplants. In 2013 the first lung transplant on a patient with primary pulmonary hypertension was performed and the first lobar (surgical downsizing) lung transplant was successfully undertaken. The national extra-corporeal life support (ECLS) service has supported such patients through the perioperative period.

NATIONAL LIVER TRANSPLANT PROGRAMME

The Liver Transplant Programme in Ireland was launched in January 1993, with the official opening of the Liver Unit in St Vincent's University Hospital by Mr Brendan Howlin, then Minister for Health. The development of the programme in Ireland was phased over several years and included an initial two-year liaison with King's College Hospital in London, who already had a fully developed programme in liver transplantation. During this period, all members of the future irish transplant team – medical, nursing and paramedical – spent time training at King's College Hospital. The links with King's College Hospital have been maintained over the years to provide a second opinion for complex cases.

In the initial years of the programme small numbers of liver transplants were carried out, with just 17 in the first year. These numbers have increased significantly over the years with 50–65 transplants being carried out annually over the last number of years. At the end of 2013, 845 liver transplants had been performed, with success rates very much in keeping with the best results achieved in UK and European centres. The continued success of the liver transplant programme and the comprehensive multidisciplinary approach to liver disease, has resulted in an increased rate of referral of patients for consideration for liver transplantation, including Alpha-1 patients. Paediatric liver transplant is conducted in the UK.

7. Recent Events

Alpha-1 Support Group presenting cheque

Professor McElvaney speaking at the Alpha-1 Patient Conference

ANNUAL ALPHA-1 CONFERENCE, OCT. 2013

The annual Alpha-1 conference took place in October 2013 once again in the Marino Institute of Education in Dublin. Our speakers included Professor McElvaney who spoke on forthcoming clinical trials, Dr Gianpiero Cavalleri who discussed human genetics and Alpha-1, Michael McGloin who talked about the Sligo COPD support group, and Michelle O'Brien, a physiotherapist in the pulmonary rehabilitation programme in St Michael's Hospital in Dun Laoghaire. The Alpha-1 Support Group presented a cheque for €2000 to fund a much-needed upgrade of the IT system used by the foundation to record every sample received for Alpha-1 testing.

'DANCE FOR A CAUSE' ZUMBATHON, OCT. 2013

A big thank you to all at Fitsmile in Celbridge who organised a 'Dance for a Cause' zumbathon last October in Celbridge and Maynooth. All donations were divided between three charities, one of which was the Alpha One Foundation. €1,350 was raised in total for each charity on the day. Congratulations and many thanks again to all involved.

Speakers at the Lung Health Talks in Dublin

LUNG HEALTH TALKS, NOVEMBER 2013

A series of public information lectures on lung health took place around the country in November of last year. These took place in Dublin, Galway, Cork, Limerick and Sligo and were well attended by members of the public. Talks included information from medical and sports experts as well as patient perspectives.

CHRISTMAS CARDS, DECEMBER 2014

We had yet another successful year with our Christmas cards last year. Many thanks to all who bought these lovely cards and shared with family and friends. We will have more cards on sale this year, please contact the Alpha One Foundation or check our website for more details.

Articles from the RTE News website and the Irish Times

NEW ALPHA-1 RESEARCH, JANUARY 2014

In January the Alpha-1 research group in RCSI in Beaumont published in Science Translational Medicine, a journal which highlights medical advances resulting from scientific research. Their findings show how the alpha-1 protein plays an important role in controlling inflammation from white blood cells and its importance for good health (see chapter 3). This research was highlighted in many national, local and online papers.

Stephen Smith interview on TV3 news in February

TV3 NEWS VISIT, FEBRUARY 2014

A substantial amount of media interest in Alpha-1 was created following on from a joint Irish/American research study which found that carriers of the Z alpha-1 gene have an increased risk of developing COPD when exposed to cigarette smoke (see Section 4). The study featured on TV3 news in February and was also covered by a variety of local and national radio stations and newspapers helping to raise awareness of Alpha-1 nationwide.

Dr Tomás Carroll and Patricia Ryan of the Alpha One Foundation being presented with the 'Community Care Services – Department Initiative of the Year' award at the Irish Healthcare Centre Awards

IRISH HEALTHCARE CENTRE AWARDS, MAR. '14

The Alpha One Foundation won a prestigious award for the National Alpha-1 Antitrypsin Deficiency Screening Programme at the Irish Healthcare Centre Awards held at the Royal Marine Hotel in Dún Laoghaire on March 7th. The Foundation was nominated in the competitive "Community Care Services – Department Initiative Of The Year" category along with 8 other organisations, and were awarded first prize. The judges described the national screening programme as an excellent cost effective initiative which addresses a significant medical issue.

(Top:) Harry English and Mike Keating and (Bottom:) Harry English with cheque from his table quiz in April

TABLE QUIZ IN TIPPERARY, APRIL 2014

A big thank you to Harry English from Ballyporeen in Co. Tipperary who for the third year running held a very successful table quiz in April of this year. Again Harry managed to raise a staggering amount for the Alpha One Foundation. Also pictured is Mike Keating, a close friend and brother in law of Harrys. Mike ran the Dublin marathon for Alpha-1 in October of last year. Many thanks to both Harry and Mike and well done on your accomplishments.

Britta competing in half ironman in Mallorca

HALF IRONMAN IN MALLORCA, MAY 2014

A big thank you and well done to Britta Luebbert an Alpha-1 patient who completed a half Ironman in Mallorca in aid of the Alpha One Foundation in May of this year. The half Ironman consisted of a 1.9k Swim, 90km Cycling and 21km running. Congrats to Britta on this fantastic achievement!

Tara Martin and friend

LADIES MINI MARATHON, JUNE 2014

A big thank you to all the ladies who took part in the Flora Women's Marathon this June. It is always a fun (and tough!) day out and we are always delighted to have people participating in aid of the Alpha One Foundation.

Carine Maher and friends

Bernie Moore and sister in law Anne Marie Clancy

Orla Keane and friends at coffee morning in Maynooth

COFFEE MORNING IN MAYNOOTH, JUNE 2014

Many thanks to Orla Keane an Alpha-1 patient who held a coffee morning in Maynooth in June and managed to raise €600 for the Alpha One Foundation.

www.alpha1.ie

NEW ALPHA ONE FOUNDATION WEBSITE LAUNCH, JUNE 2014

The new Alpha One Foundation website was launched in June of this year. Thanks to Stephen Cashell, IT student for his help with this important project. The entire website was redesigned for ease of use and improved access to information including news and events, alpha-1 research, resources for healthcare providers, and information for patients. If you have any ideas for the new website please let us know.

SCIENCE SQUAD VISIT, JULY 2014

Alpha-1 will feature on an episode of RTE's The Science Squad this autumn. A camera crew spent a day filming in the Alpha One Foundation and Beaumont in July and interviewed Professor McElvaney and two Alpha-1 patients.

Members of the Irish Lung Health Alliance pictured with Minsiter for Health Leo Varadkar at the launch of Lung Health Awareness Week 2014.

LUNG HEALTH WEEK, SEPTEMBER 2014

Ireland's first-ever National Lung Health Awareness Week, from September 22 to 29, saw a national roadshow offering free lung testing alongside an exciting science exhibition to highlight the importance of healthy lungs for life. The initiative, undertaken by the Irish Lung Health Alliance which is a coalition of 15 leading Irish charities, will see an interactive health and well-being exhibition – "BodyWorks on Tour" in partnership with the Glasgow Science Centre – visit Dublin, Cork, Galway and Portlaoise, Ireland's Healthy Town 2014. For information on the campaign and what people can do to safeguard their lung health, visit www.lunghealth.ie.

THANK YOU

The Alpha One Foundation wish to thank all Alpha-1 patients and family members who have helped with fundraising and been involved in events throughout the year some of which we haven't been able to mention here. Please contact us on alpha1@rcsi.ie or 01-8093871 if you wish to get involved in any way in the coming year.

8. Acknowledgements

We would like to thank the following:

- The Alpha-1 Patient Support Group
- Pat O'Brien, Emma Pentony, Helen Moore, Dr Bill Tormey and the Beaumont Hospital Chemical Pathology Department for their continued support and advice
- John Walsh and Angela McBride of the Alpha-1 Foundation (USA)
- Professor Maurizio Luisetti, Dr Ilaria Ferrarotti and Dr Stefania Ottaviani, Centre for Diagnosis of Inherited Alpha-1 Antitrypsin Deficiency, University of Pavia, Italy
- The Health Research Board (HRB), The Medical Research Charities Group (MRCG), and the Irish Platform for Patients' Organisations, Science & Industry (IPPOSI)
- Dr Paula Byrne and Dr Amanda McCann of the UCD School of Medicine
- Professor Dermot Kenny and the RCSI Clinical Research Centre (*www.rcsicrc.ie*)
- The McCausland family, Josephine McGuirk, Orla Keane, Stephen Smith, and Michael McNamee for all their help with raising awareness throughout the year
- All patients, family members and friends who have taken part in or organised fundraising events throughout the year
- Blair Murray, 3rd Year Medical Student, RCSI, who carried out a research project with the Alpha One Foundation in 2014
- Stephen Cashell, IT student at Stillorgan College of Further Education who carried out a summer placement with the Alpha One Foundation in June 2014 helping to re-develop our website *www.alpha1.ie*

We would also like to thank the Department of Health and Children and the Health Service Executive for their continued financial support.

We would also like to acknowledge the participation of the following hospitals;

- Adelaide and Meath Hospitals, including National Children's Hospital Tallaght
- Blackrock Clinic
- Bon Secours Hospital Tralee
- Bon Secours Hospital Dublin
- Cavan General Hospital
- Children's University Hospital, Temple Street, Dublin
- Coombe Women and Infants University Hospital
- Cork University Hospitals
- Galway University Hospitals
- James Connolly Memorial Hospital Blanchardstown
- Letterkenny General Hospital
- Mater Misericordiae University Hospital, Dublin
- Mayo General Hospital
- Midland Regional Hospitals: Tullamore, Mullingar, and Portlaoise
- Midwestern Regional Hospital, Limerick
- Naas General Hospital, Co. Kildare
- Our Lady's Children's Hospital, Crumlin
- Our Lady of Lourdes Hospital, Drogheda
- Our Lady's Hospital, Navan
- Peamount Hospital, Dublin
- Rotunda Hospital, Dublin
- Sligo General Hospital
- St James's Hospital, Dublin
- St Luke's General Hospital Carlow/Kilkenny
- St Vincent's University Hospital, Dublin
- Waterford Regional Hospital
- Wexford General Hospital

Recent Irish Research Publications in Alpha-1

Alpha-1 Antitrypsin Deficiency - A Missed Opportunity in COPD? Tomás P. Carroll, M. Emmet O'Brien, Laura T. Fee, Kevin Molloy, Blair Murray, Seshma Ramsawak, Oisín McElvaney, Catherine O'Connor and Noel G. McElvaney (2014). In: *COPD Clinical Perspectives*, Prof. Ralph Panos (Editor), ISBN: 978-953-51-1624-0, InTech, DOI: 10.5772/58602. Download from: *http://www.intechopen.com/books/copd-clinical-perspectives/alpha-1-antitrypsin-deficiency-a-missed-opportunity-in-copd-*.

The role and importance of glycosylation of acute phase proteins with focus on alpha-1 antitrypsin in acute and chronic inflammatory conditions McCarthy C, Saldova R, Wormald MR, Rudd PM, McElvaney NG, Reeves EP. *Journal of Proteome Research*. 2014 Jul 3;13(7):3131-43. PMID: 24892502.

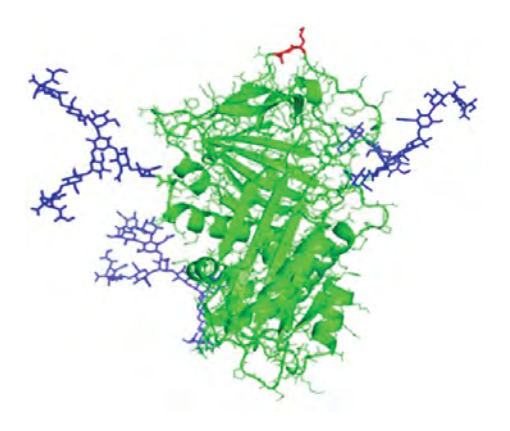
Circulating polymers in alpha-1 antitrypsin deficiency Tan L, Dickens JA, Demeo DL, Miranda E, Perez J, Rashid ST, Day J, Ordonez A, Marciniak SJ, Haq I, Barker AF, Campbell EJ, Eden E, McElvaney NG, Rennard SI, Sandhaus RA, Stocks JM, Stoller JK, Strange C, Turino G, Rouhani FN, Brantly M, Lomas DA. *European Respiratory Journal*. 2014 May;43(5):1501-4. PMID: 24603821.

Clarification of the risk of chronic obstructive pulmonary disease in alpha-1 antitrypsin deficiency PiMZ heterozygotes Molloy K, Hersh CP, Morris VB, Carroll TP, O'Connor CA, Lasky-Su JA, Greene CM, O'Neill SJ, Silverman EK, McElvaney NG. *American Journal of Respiratory & Critical Care Medicine.* 2014 Feb 15;189(4):419-27. PMID: 24428606.

Increased outer arm and core fucose residues on the N-glycans of mutated alpha-1 antitrypsin protein from alpha-1 antitrypsin deficient individuals McCarthy C, Saldova R, O'Brien ME, Bergin DA, Carroll TP, Keenan J, Meleady P, Henry M, Clynes M, Rudd PM, Reeves EP, McElvaney NG. *Journal of Proteome Research*. 2014 Feb 7;13(2):596-605. PMID: 24328305.

miR-199a-5p silencing regulates the unfolded protein response in chronic obstructive pulmonary disease and alpha-1 antitrypsin deficiency Hassan T, Carroll TP, Buckley PG, Cummins R, O'Neill SJ, McElvaney NG, Greene CM. *American Journal of Respiratory & Critical Care Medicine.* 2014 Feb 1;189(3):263-73. PMID: 24299514.

The circulating proteinase inhibitor alpha-1 antitrypsin regulates neutrophil degranulation and autoimmunity Bergin DA, Reeves EP, Hurley K, Wolfe R, Jameel R, Fitzgerald S, McElvaney NG. *Science Translational Medicine.* 2014 Jan 1;6(217):217ra1. PMID: 24382893.



Glycosylated Alpha-1 Antitrypsin
From: McCarthy et al, Journal of Proteome Research, February 2014

Timeline: Alpha One Foundation

2001	Alpha One Foundation Ireland is established
2004	Testing starts in national alpha-1 antitrypsin deficiency screening programme
2004	Ireland becomes the first country in the world to ban smoking in the workplace
2004	2nd International Alpha-1 Patient Congress takes place in Dublin
2005	Irish Government publishes Disability Act protecting against genetic discrimination
2005	First single lung transplant in Ireland (performed in Alpha-1 patient)
2005	First Irish clinical trial for intravenous augmentation therapy begins in Alpha-1 Centre at Beaumont Hospital
2006	First double lung transplant in Ireland (performed in Alpha-1 patient)
2009	National Alpha-1 clinic commences on weekly basis in Beaumont Hospital
2011	1 in 25 Irish people found to carry the Z gene, the most common cause of Alpha-1
2011	100th ZZ case diagnosed in national screening programme
2011	Clinical trial for inhaled augmentation therapy begins in Alpha-1 Centre at Beaumont Hospital
2012	Two new Null Alpha-1 mutations discovered in Ireland
2013	Record number of lung transplants performed in Ireland (including 3 Alpha-1)
2014	Alpha One Foundation wins healthcare award for national screening programme

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