



Alpha One Foundation

ANNUAL REPORT 2009



Contents

1. Executive Summary	ii
2. Prevalence of Alpha-1 Antitrypsin Deficiency in Ireland	1
3. National Targeted Detection Programme.....	6
4. National Alpha-1 Patient Registry	7
5. Priorities for the Alpha-1 Community: the Physician's Perspective	10
6. Research Programmes	19
7. Patient Support Group	28
8. Doctor's Corner.....	31
9. Acknowledgements	34

1. Executive Summary

In 2009 the Alpha One Foundation maintained its commitment to increase awareness of alpha-1 antitrypsin deficiency. Our endeavours to raise public awareness are linked to the promotion of basic and clinical research into alpha-1 antitrypsin deficiency.

Our research and experience with Alpha-1 patients point to the fact that there is a need for a National Respiratory Strategy to co-ordinate the proper diagnosis and treatment of Alpha-1 and other respiratory conditions. Our studies clearly show it is vital for the health and welfare of our patients that they are diagnosed as early as possible, before they develop symptoms of disease.

The Alpha One Foundation continues our active collaborations with the Medical Research Charities Group, Irish Donor Network, Irish Platform for Patient Organisations Science and Industry and the European Organisation for Rare Diseases (EURORDIS). We hosted an information stand and presented novel research at the Irish Thoracic Society (ITS) conference in November 2008 in Belfast. Our research was also presented at the American Thoracic Society meeting in San Diego in May 2009. This research demonstrated a much higher incidence of Alpha-1 on the island of Ireland, with an estimated 3,000 individuals at risk of developing this severe disease and highlighted the potential increased health risks to MZ carriers.

Our active patient support group held a meeting in Cork earlier this year, which received much positive feedback from patients. The patient support group was represented by John Hannan and Orla Keane at the Alfa Europe Annual meeting in Vienna this past May. Patients from Europe shared their experiences, views, and ideas in relation to Alpha-1. This meeting proved to be a useful and enriching experience for all attendees and for the medical personnel. The patient support group also successfully raised funds through the Women's Mini Marathon.

The Alpha One Foundation, held a Chopin Anniversary Recital in the Mansion House, in October 2008. During Chopin's life he suffered from chronic respiratory illness and probably Alpha-1. We felt it appropriate to celebrate Chopin's life and draw attention to respiratory research especially into alpha-1 antitrypsin deficiency. We would like to thank all those who were involved.

This year our CEO and co-founder of the Alpha One Foundation, Larry Warren retired. We wish to extend our gratitude for his dedication and tremendous contribution in improving Alpha-1 awareness, and gaining the recognition and financial support to promote and highlight research and care for Alpha-1 patients. We also wish to welcome Geraldine O'Brien, Clinical Research Associate, to the Alpha One Foundation.

This brief overview may give you some idea of the work being done and the progress being made by the Alpha One Foundation. This work is collaborative and I wish to thank my team colleagues for their diligence and cooperation which made the past year such a success for the Foundation.

Kitty O'Connor
CEO, Alpha One Foundation

2. The Prevalence of Alpha-1 Antitrypsin Deficiency in Ireland

INTRODUCTION

Alpha-1 antitrypsin (AAT) is the archetype of the serine protease inhibitor or serpin superfamily, members of which have closely related structures and functions.

The family includes alpha1-antichymotrypsin, C1 inhibitor, antithrombin and neuroserpin, which are all linked by a common molecular structure and a similar "mousetrap" mechanism for inhibiting their target enzymes. The main function of AAT is to protect fragile alveolar tissue from serine proteases including neutrophil elastase (NE), cathepsin G and proteinase 3 [Carrell 1986]. The majority of serum AAT is derived from hepatic production, however, AAT is expressed by other cells, including neutrophils, mononuclear phagocytes, enterocytes, renal parenchymal cells and intestinal epithelium [Carlson et al 1988; Perlmutter et al 1989; Rogers et al 1983].

Alpha-1 antitrypsin (AAT) deficiency is a hereditary disorder first described in the early 1960s when the association was made between low plasma levels of AAT protein and emphysema [Laurell & Eriksson 1963]. The condition is associated with a substantially increased risk for the development of pulmonary emphysema by the third or fourth decades of life and is also associated with risks for development of hepatic disease [Sveger 1976], cutaneous panniculitis [Edmonds et al 1991], arterial aneurysm [Schievink et al 1996], bronchiectasis [King et al 1996], lung cancer [Yang et al 2005] and renal disease [Davis et al 1992]. AAT deficiency is a genetic disorder characterised by misfolding of the AAT protein and it belongs to a class of genetic diseases associated with aberrant protein folding which are collectively known as conformational diseases [Greene et al 2008]. Conformational diseases are caused by mutations altering the folding pathway or the final conformation of a protein. Many such diseases are caused by mutations in secretory proteins and range from metabolic diseases such as diabetes, to

neurological conditions such as Alzheimer's disease. Other conformational diseases include cystic fibrosis, Parkinson's and Huntington's diseases, each of which is associated with intracellular accumulation of misfolded proteins and ER stress.

The AAT gene is highly pleiomorphic, with over 100 alleles identified to date [DeMeo & Silverman 2004]. Variants are inherited in an autosomal co-dominant fashion and the protein phenotype is classified according to the 'Pi' system, defined by plasma isoelectric focusing. AAT mutations which confer an increased risk of developing pulmonary emphysema and/or liver disease are those in which deficiency alleles are combined in homozygous or heterozygous states, yielding AAT serum levels below a putative protective threshold of 11µmol/L [Crystal 1990]. The most common variants associated with disease are the Z [Glu342Lys] and S [Glu264Val] mutations, caused by a single amino acid replacement of glutamic acid at positions 342 and 264 of the polypeptide respectively [Curiel et al 1989; Lomas et al 1992]. The class of SERPINA1 variants termed "null" mutations lead to a complete absence of AAT production and while extremely rare, confer a particularly high risk of emphysema [Fregonese et al 2008].

The distribution of AAT mutations most likely reflects the genetic origins of the disorder. Approximately 6% of people of northern European descent carry the S gene and 3-4% carry the Z variant [Blanco et al 2006]. The highest prevalence of the Z allele is in northern and western European countries, peaking in southern Scandinavia, and the mutation may have first arisen in the Viking population [Lomas 2006; Luisetti & Seersholm 2004]. The highest

frequency of the S allele is found in the Iberian Peninsula, and decreases along a southwest to northeast axis, suggesting that the mutation is likely to have arisen in the region (Hutchison 1998). Throughout Europe the frequency of the S and Z mutations varies widely between countries, geographic regions, and ethnic groups (de Serres 2002).

AATD is a notoriously under-diagnosed condition with most cases misdiagnosed as COPD or non-responsive asthma. As a result, long delays between presentation of first symptoms and correct diagnosis are commonplace (Stoller et al 2005). Guidelines issued by both the World Health Organisation and the American Thoracic Society/European Respiratory Society recommend the establishment of targeted screening programmes for the detection of patients with AATD (2003). In addition, while a large number of cohorts have been investigated, many of these studies were based on screening symptomatic patients, and performed on small groups of less than 500 individuals with an accompanying high risk of error. Apart from a few notable exceptions, such as the Swedish neonatal screening study (Sveger 1976), the lack of large population based studies means the true incidence of AATD in many European countries remains unknown. To date no studies have been performed to investigate the incidence of AATD in Ireland, however, a study in the 1970s did analyse AAT phenotypes in Northern Ireland (Blundell & Frazer 1975). To address the paucity of data relating to AATD in the Irish setting, we examined a targeted population of symptomatic individuals and a sample of the general population. The main objective of our study was to determine the true prevalence of AATD in Ireland.

METHODS

Measurement of AAT

AAT levels were measured by radial immunodiffusion using a commercial kit (NOR Partigen). Briefly, 5µl of serum was dispensed into each well of a Partigen plate, with a protein control also included. After the required diffusion time (48 hours) the diameter of each

precipitin ring was measured using an eye-piece. The diameter of the precipitin ring was directly proportional to the concentration of AAT in the sample and was calculated using a table of reference values.

Phenotyping

Phenotyping of AAT was carried out using the Sebia HydraSys electrophoresis platform and the Hydragel 18 A1AT Isofocusing kit (Sebia) (Zerimech et al 2008) (Figure 2.1).

Genotyping

Genotyping was performed using a genotyping mix for PCR (Roche) on a LightCycler 480 System (Roche) with specific primers and probes (Metabion) for the S and Z mutations as described in a previous publication (Rodriguez et al 2002) (Figure 2.1).

Targeted Detection Programme

A total of 3,000 individuals were screened for AATD as part of a national targeted detection programme. This detection programme is ongoing and began in May 2004 supported by generous funding from the Irish Government. From the screening programme 430 MZ heterozygotes, 263 MS heterozygotes, 44 SZ compound heterozygotes, 42 ZZ homozygotes, and 14 SS homozygotes were identified (Figure 2.2). This yields allele frequencies of 0.056 for the S mutation and 0.094 for the Z mutation in the targeted population. In addition to the S and Z mutations, 20 individuals with the I mutation (Arnaud et al 1978) were identified with an allele frequency of 0.007, as well as two individuals with the extremely rare AAT mutations, V (Faber et al 1994), and Zbristol (Lovegrove et al 1997).

Biobank Genotyping

A collection of DNA from 1,000 individuals comprising the St. James's Hospital/Trinity College Dublin Biobank was genotyped for the S and Z mutations. This collection represents a random sample of the general Irish population and is in Hardy-Weinberg equilibrium. In this group, 98 MS heterozygotes, 46 MZ heterozygotes, 2 SZ compound heterozygotes, and 1 SS homozygote were identified (Figure 2.3).

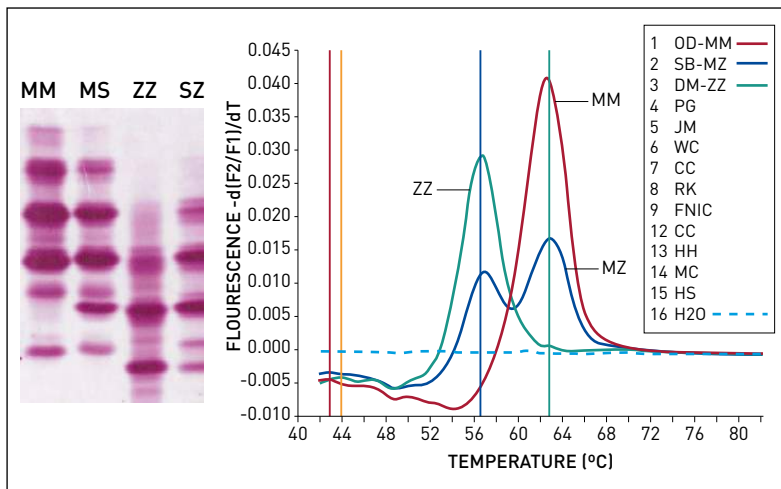


Figure 2.1 Typical phenotyping gel and a Z mutation genotyping assay.

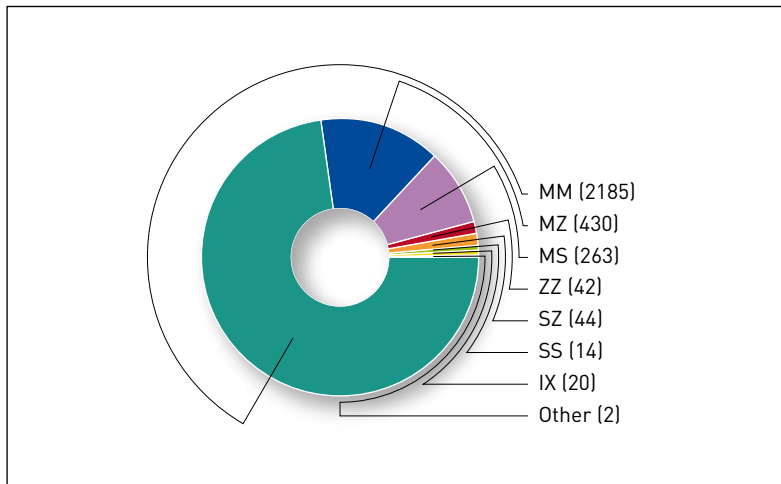


Figure 2.2 Targeted detection programme data.

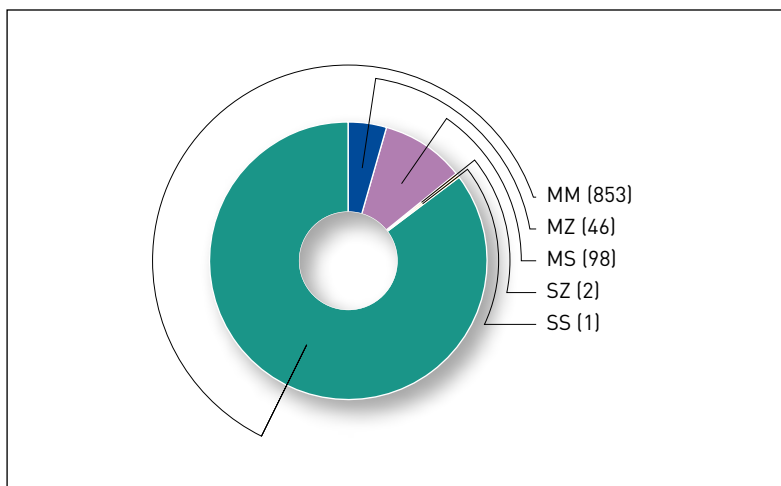


Figure 2.3 Biobank data.

This yields a frequency of 0.051 for the S mutation and 0.024 for the Z mutation in the Irish population. Assuming Hardy-Weinberg equilibrium and based on a population of 4.24 million inhabitants (Census of Ireland 2006, www.cso.ie) these allele frequencies would yield 2,442 ZZ individuals, 10,379 SZ individuals and 11,028 SS individuals. This means that the prevalence of severe AATD (ZZ homozygotes) in Ireland is 1/1736, meaning the disease is more common than previously estimated with one of the highest incidences in Europe. In addition to ZZ AATD, the prevalence of moderate AATD (SZ compound heterozygote) is 1/408, with this phenotype also at increased risk of lung and liver disease, while the prevalence of mild AATD (SS homozygote) is 1/384. Finally, the prevalence of carriers is 4.6% or 1/21 for MZ and 9.8% or 1/10 for MS.

DISCUSSION

Our study describes for the first time the true prevalence of AATD in a randomly selected sample of the general Irish population, specifically with regard to the two most common alleles associated with AATD, S and Z. We found that the S mutation occurs at a frequency of 0.051, while the Z mutation occurs at a frequency of 0.024. In simple terms, 9.8% of the Irish population carries a copy of the S allele, with 4.6% of the population carrying a copy of the Z allele. Combining the two, 15% of the Irish population possess one copy of either S or Z mutation, with an overall carrier rate of 1/6.7. Furthermore, we demonstrate that the allele frequency for Z is almost four-fold higher in the targeted population compared to the general Irish population represented by the Biobank cohort. Interestingly, the allele frequency for S was not significantly increased in the targeted population compared to the Biobank group (Figure 2.4).

The findings of our study have significant consequences. Placing our results in a European context, we observe that the allele frequency for the S mutation is among the highest in Europe. The frequency of the Z mutation in Ireland is also quite high. The high

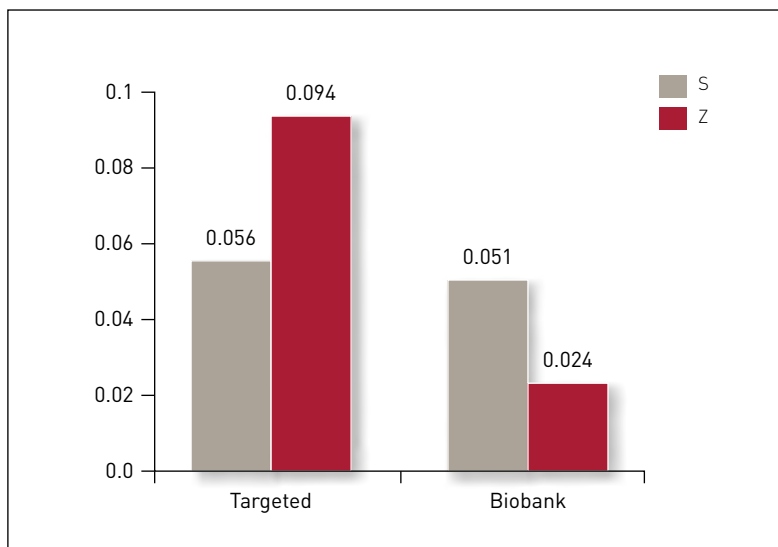


Figure 2.4 Comparison of the S and Z mutation frequencies in the targeted group and the Biobank cohort.

prevalence of AATD in Ireland is not without precedent. Ireland has the highest incidence of cystic fibrosis (Devaney et al 2003; Farrell 2008) and haemochromatosis (Byrnes et al 2001) in Europe. This can be partly explained by the geographical isolation of an island on the fringes of Western Europe, with the genetic background of the population remaining largely undisturbed by the demographic movements that have prevailed on the mainland. Another intriguing reason for the high incidence of AATD that has been postulated is that it confers a survival advantage on carriers for the mutated genes (Lomas 2006).

NOTE: This research forms part of a study which will be published in a peer-reviewed respiratory journal in early 2010.

REFERENCES

2003. American Thoracic Society/European Respiratory Society statement: standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. *Respir Crit Care Med* 168:818-900

Arnaud P, Chapuis-Cellier C, Vittoz P, Fudenberg HH. 1978. Genetic polymorphism of serum alpha-1-protease inhibitor [alpha-1-antitrypsin]: Pi i, a deficient allele of the Pi system. *J Lab Clin Med* 92:177-84

Blanco I, de Serres FJ, Fernandez-Bustillo E, Lara B, Miravittles M. 2006. Estimated numbers and prevalence of PI*S and PI*Z alleles of alpha1-antitrypsin deficiency in European countries. *Eur Respir J* 27:77-84

Blundell G, Frazer A. 1975. Alpha1 antitrypsin phenotypes in Northern Ireland. *Ann Hum Genet* 38:289-94

Byrnes V, Ryan E, Barrett S, Kenny P, Mayne P, Crowe J. 2001. Genetic hemochromatosis, a Celtic disease: is it now time for population screening? *Genet Test* 5:127-30

Carlson JA, Rogers BB, Sifers RN, Hawkins HK, Finegold MJ, Woo SL. 1988. Multiple tissues express alpha 1-antitrypsin in transgenic mice and man. *J Clin Invest* 82:26-36

Carrell RW. 1986. alpha 1-Antitrypsin: molecular pathology, leukocytes, and tissue damage. *J Clin Invest* 78:1427-31

Crystal RG. 1990. Alpha 1-antitrypsin deficiency, emphysema, and liver disease. Genetic basis and strategies for therapy. *J Clin Invest* 85:1343-52

Curiel DT, Chytil A, Courtney M, Crystal RG. 1989. Serum alpha 1-antitrypsin deficiency associated with the common S-type [Glu264---Val] mutation results from intracellular degradation of alpha 1-antitrypsin prior to secretion. *J Biol Chem* 264:10477-86

Davis ID, Burke B, Freese D, Sharp HL, Kim Y. 1992. The pathologic spectrum of the nephropathy associated with alpha 1-antitrypsin deficiency. *Hum Pathol* 23:57-62

de Serres FJ. 2002. Worldwide racial and ethnic distribution of alpha1-antitrypsin deficiency: summary of an analysis of published genetic epidemiologic surveys. *Chest* 122:1818-29

DeMeo DL, Silverman EK. 2004. Alpha1-antitrypsin deficiency. 2: genetic aspects of alpha[1]-antitrypsin deficiency: phenotypes and genetic modifiers of emphysema risk. *Thorax* 59:259-64

Devaney J, Glennon M, Farrell G, Ruttledge M, Smith T, et al. 2003. Cystic fibrosis mutation frequencies in an Irish population. *Clin Genet* 63:121-5

Edmonds BK, Hodge JA, Rietschel RL. 1991. Alpha 1-antitrypsin deficiency-associated panniculitis: case report and review of the literature. *Pediatr Dermatol* 8:296-9

Faber JP, Poller W, Weidinger S, Kirchgesser M, Schwaab R, et al. 1994. Identification and DNA sequence analysis of 15 new alpha 1-antitrypsin variants, including two PI*Q0 alleles and one deficient PI*M allele. *Am J Hum Genet* 55:1113-21

- Farrell PM. 2008. The prevalence of cystic fibrosis in the European Union. *J Cyst Fibros* 7:450-3
- Fregonese L, Stolk J, Frants RR, Veldhuisen B. 2008. Alpha-1 antitrypsin Null mutations and severity of emphysema. *Respir Med* 102:876-84
- Greene CM, Miller SD, Carroll T, McLean C, O'Mahony M, et al. 2008. Alpha-1 antitrypsin deficiency: a conformational disease associated with lung and liver manifestations. *J Inherit Metab Dis* 31:21-34
- Hutchison DC. 1998. Alpha 1-antitrypsin deficiency in Europe: geographical distribution of Pi types S and Z. *Respir Med* 92:367-77
- King MA, Stone JA, Diaz PT, Mueller CF, Becker WJ, Gadek JE. 1996. Alpha 1-antitrypsin deficiency: evaluation of bronchiectasis with CT. *Radiology* 199:137-41
- Laurell CB, Eriksson SE. 1963. The electrophoretic alpha-globulin pattern of serum in alpha1-antitrypsin deficiency. *Scand. J. Clin. Lab. Invest.* 15:132-40
- Lomas DA. 2006. The selective advantage of alpha1-antitrypsin deficiency. *Am J Respir Crit Care Med* 173:1072-7
- Lomas DA, Evans DL, Finch JT, Carrell RW. 1992. The mechanism of Z alpha 1-antitrypsin accumulation in the liver. *Nature* 357:605-7
- Lovegrove JU, Jeremiah S, Gillett GT, Temple IK, Povey S, Whitehouse DB. 1997. A new alpha 1-antitrypsin mutation, Thr-Met 85, (PI Zbristol) associated with novel electrophoretic properties. *Ann Hum Genet* 61:385-91
- Luisetti M, Seersholm N. 2004. Alpha1-antitrypsin deficiency. 1: epidemiology of alpha1-antitrypsin deficiency. *Thorax* 59:164-9
- Perlmutter DH, Daniels JD, Auerbach HS, De Schryver-Kecsckemeti K, Winter HS, Alpers DH. 1989. The alpha 1-antitrypsin gene is expressed in a human intestinal epithelial cell line. *J Biol Chem* 264:9485-90
- Rodriguez F, Jardi R, Costa X, Cotrina M, Galimany R, et al. 2002. Rapid screening for alpha1-antitrypsin deficiency in patients with chronic obstructive pulmonary disease using dried blood specimens. *Am J Respir Crit Care Med* 166:814-7
- Rogers J, Kalsheker N, Wallis S, Speer A, Coutelle CH, et al. 1983. The isolation of a clone for human alpha 1-antitrypsin and the detection of alpha 1-antitrypsin in mRNA from liver and leukocytes. *Biochem Biophys Res Commun* 116:375-82
- Schievink WI, Puumala MR, Meyer FB, Raffel C, Katzmann JA, Parisi JE. 1996. Giant intracranial aneurysm and fibromuscular dysplasia in an adolescent with alpha 1-antitrypsin deficiency. *J Neurosurg* 85:503-6
- Stoller JK, Sandhaus RA, Turino G, Dickson R, Rodgers K, Strange C. 2005. Delay in diagnosis of alpha1-antitrypsin deficiency: a continuing problem. *Chest* 128:1989-94
- Sveger T. 1976. Liver disease in alpha1-antitrypsin deficiency detected by screening of 200,000 infants. *N Engl J Med* 294:1316-21
- Yang P, Bamlet WR, Sun Z, Ebbert JO, Aubry MC, et al. 2005. Alpha1-antitrypsin and neutrophil elastase imbalance and lung cancer risk. *Chest* 128:445-52
- Zerimech F, Hennache G, Bellon F, Barouh G, Jacques Lafitte J, et al. 2008. Evaluation of a new Sebia isoelectrofocusing kit for alpha 1-antitrypsin phenotyping with the Hydrasys System. *Clin Chem Lab Med* 46:260-3

3. National Targeted Detection Programme

WHO (World Health Organisation) guidelines advocate targeted detection programmes for AATD in patients with COPD, non-responsive asthma or cryptogenic liver disease.

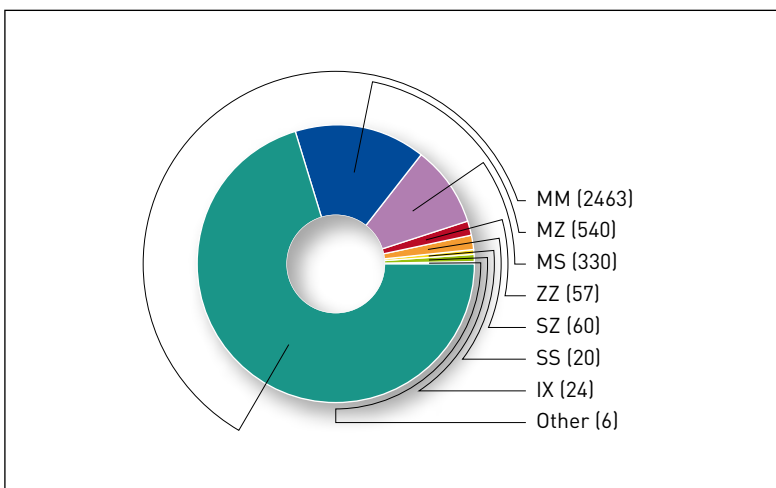


Figure 3.1 Targeted detection programme results.

In May 2004, a national targeted detection programme for AATD was launched by the Alpha One Foundation in Beaumont Hospital. The programme employs a full time clinical research nurse who attends respiratory outpatient clinics where patients are targeted for screening. AATD can be diagnosed from a venous sample drawn during a blood test, or alternatively a finger-prick test can be used to collect a dried blood spot (DBS) sample on specially treated filter paper for DNA isolation. In the last year a DNA genotyping system has been developed which can detect the two mutations (S and Z) responsible for almost 98% of all cases of AATD. After a short questionnaire is filled out for each patient, a lancet is used to obtain a small blood sample which is collected on specially treated filter paper. DNA isolated from this paper is then used to genotype the patient by RT-PCR (Real-Time Polymerase Chain Reaction), using primers and probes specific to each mutation. The major advantage of implementing the genotyping method is that the ease of sample collection and storage has allowed for self-

testing in the home, and the finger-prick kit test is particularly useful for family screening.

So far 3,500 individuals with COPD, asthma or asymptomatic first-degree relatives of known AATD individuals have been screened since the inception of the screening programme over five years ago. A total of 137 AATD individuals have been identified including 57 ZZ, 60 SZ, and 20 SS (Figure 1). Over 850 AATD carriers were detected including 540 MZ, 330 MS and 15 rare MI phenotypes. The percentage of deficiency alleles (>20%) detected has been quite high and the S variant, more prevalent in the Iberian Peninsula, has been detected with an unusually high frequency. Several rare phenotypes were also identified and further analysis will reveal whether these phenotypes predispose individuals to lung or liver disease.

4. National Alpha-1 Patient Registry

The National Alpha-1 Patient Registry was established in 2007. This secure database of patients and their comprehensive clinical details is a vital tool for basic and clinical research into alpha-1 antitrypsin deficiency.

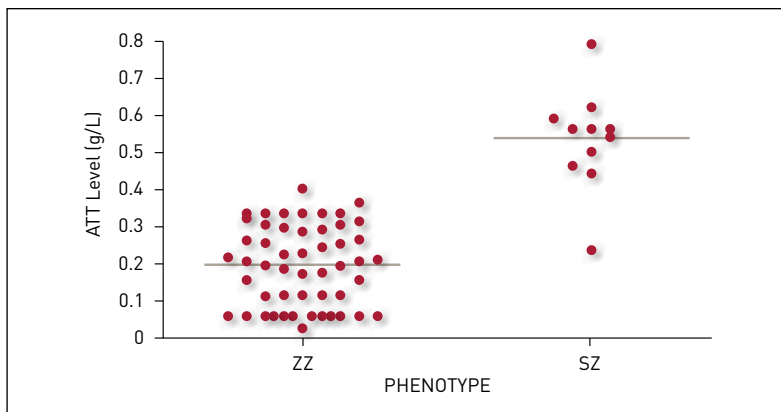


Figure 4.1 AAT levels in ZZ versus SZ phenotypes.

The registry is also beneficial in promoting awareness of Alpha-1. Parameters analysed included AAT phenotype, pulmonary function tests, radiological imaging, smoking status/pack year history, complications and hospitalisations.

Clinical and biochemical data were taken from the registry and analysed for ZZ and SZ patients.

DEMOGRAPHIC CHARACTERISTICS

Of the total number of individuals on the national registry as ZZ phenotype (n=56) 66% (n=37) were male and 34% (n=19) were female, while for SZ patients 50% (n=7) were male and 50% were female (n=7).

The mean age at diagnosis for ZZ patients was 43.6+/-2.0 years for males and 42.2+/-2.6 years for females, while for SZ patients mean age was 41.29+/-6.3 for males and 46.6+/-7.2 for females.

The presence of pulmonary symptoms (48%) and also family history (37%) were the major reasons for subsequent diagnosis of ZZ AATD (Figure 4.2).

Similarly in the SZ phenotype pulmonary symptoms accounted for 42% and family history 20%. However abnormal liver tests accounted for 30% of the reason diagnosis was made (Figure 4.3).

High resolution CT data was available for 50 ZZ and 9 SZ individuals. Emphysema was the predominant finding in the ZZ cohort. Emphysema and/or bronchiectasis was the predominant finding in the SZ population (Figure 4.4).

PULMONARY FUNCTION TESTS

ZZ individuals identified by family screening have significantly increased FEV1 (78.5+/-6.9%, mean age 47.3+/-2.4 years) compared to ZZ

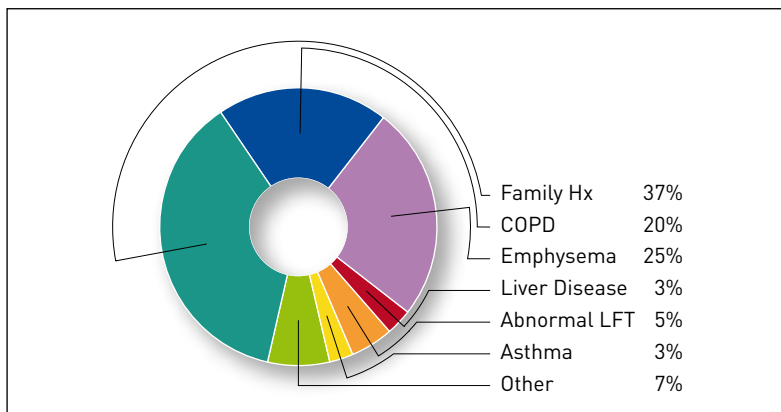


Figure 4.2 Reasons for diagnosis of ZZ patients.

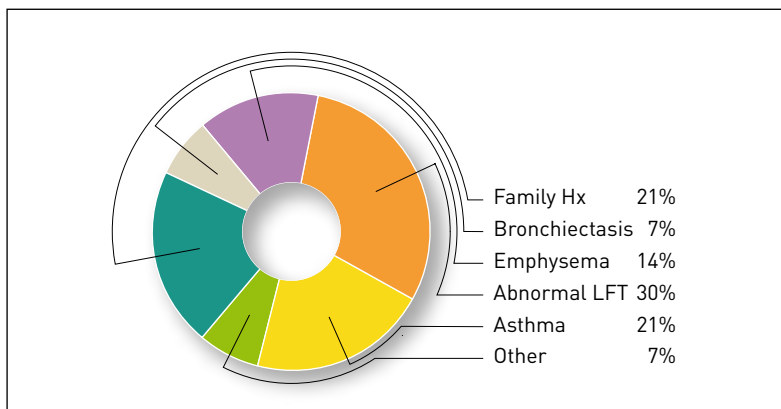


Figure 4.3 Reasons for diagnosis of SZ patients.

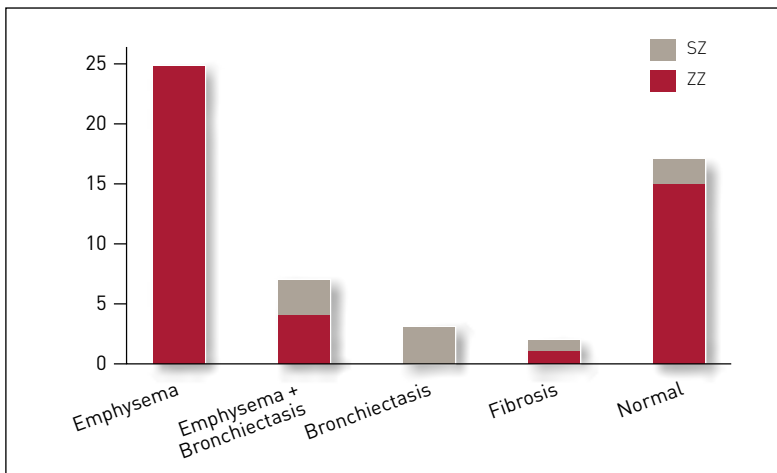


Figure 4.4 HRCT findings in ZZ and SZ patients.

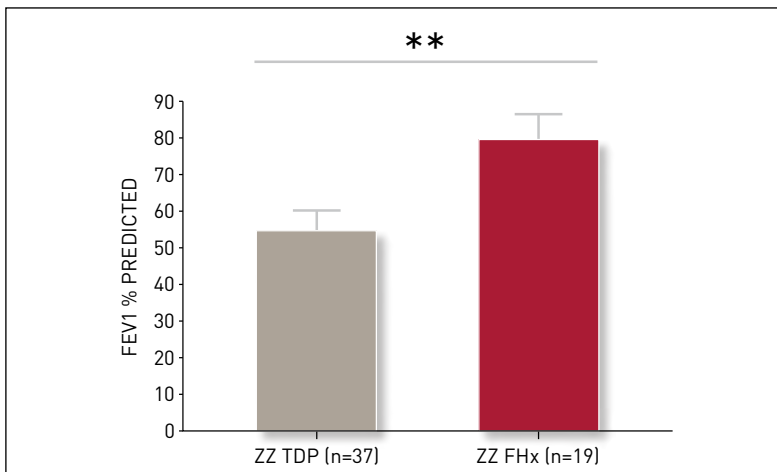


Figure 4.5 FEV1 of ZZ patients identified by symptomatic screening compared to family screening.

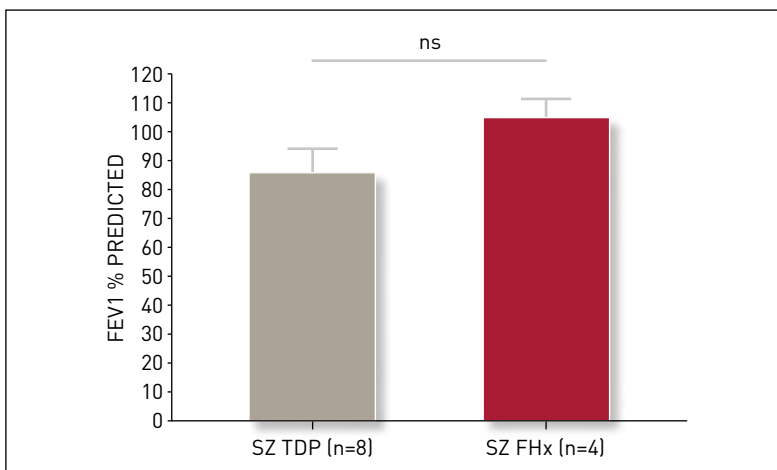


Figure 4.6 FEV1 of SZ patients identified by symptomatic screening compared to family screening (n=12).

patients identified by targeted screening (55.0+/-4.8%, 52.0+/-1.3 years, p=0.0062) (Figure 4.5).

SZ individuals identified by family screening tended to have an increased FEV1 compared to SZ identified by targeted screening (Figure 4.6). This trend was not-significant and is most likely due to the small numbers (n=12) in this analysis.

ZZ patients who smoked had significantly decreased lung function compared to non-smoking ZZ (mean FEV1 of ZZ smokers 52.7+/-4.5% v non-smokers 82.6+/-6.7%, p=0.0002) (Figure 4.7). This observation was also made in an SZ population where the mean FEV1 of SZ smokers was 81.4+/-6.0% compared to 106.3+/-5.4% in non-smokers (p=0.005) (Figure 4.8)

CLINICAL TRIALS

The Alpha-1 Foundation has coordinated clinical trials and research studies for Alpha-1 patients throughout the country; these are discussed in more detail in our 'Research Programmes' section. Figure 4.9 gives an indication of patients on the registry involved in research studies conducted in collaboration the Alpha-1 Foundation and the pharmaceutical industry.

Our results emphasize the need for increased awareness and early detection, particularly of asymptomatic AATD cases. ZZ individuals identified by family screening have significantly increased FEV1 when compared to ZZ patients identified by targeted symptomatic screening. The registry data shows that smoking correlates quantitatively with decreased lung function in both ZZ and SZ phenotypes. Identification of patients from a targeted detection programme should include aggressive screening of family members of known AATD patients and allow the initiation of preventative measures before significant lung disease has occurred.

In summary, the national Alpha-1 patient registry is a vital tool for monitoring disease progression and provides a wealth of valuable data. We strongly recommend the enrolment of all Alpha-1 patients on the national registry.

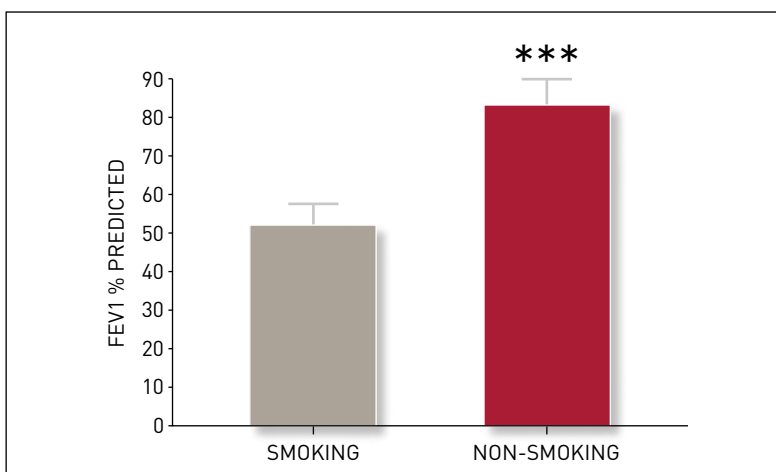


Figure 4.7 FEV1 versus smoking status in ZZ patients (n=56, p=0.0002).

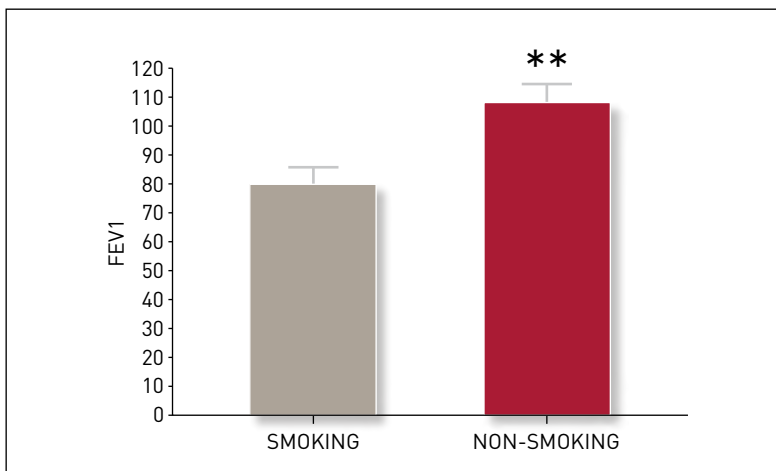


Figure 4.8 FEV1 versus smoking status in SZ patients (n=14, p=0.005).

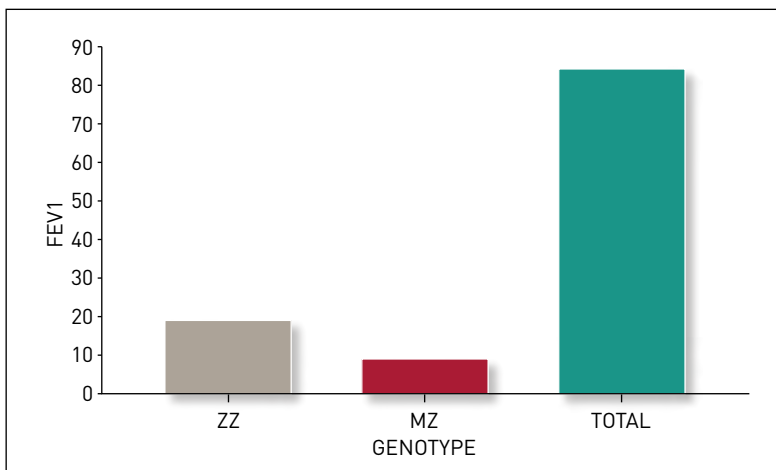


Figure 4.9 Research studies involving ZZ and MZ patients.

5. Priorities for the Alpha-One Community: the Physician's Perspective

Sanjay Haresh Chotirmall, Tomás Carroll, Muirne Spooner and Noel Gerard McElvaney

Respiratory Research Division, Beaumont Hospital, Dublin, Republic of Ireland

INTRODUCTION

Alpha-1 antitrypsin (AAT) deficiency is a clinically under-recognized hereditary disorder with multi-system manifestations, most prominently in the lungs and liver. A rare skin manifestation is also described. The AAT protein is synthesized in the liver and to a lesser extent in macrophages and neutrophils. AAT is the physiological inhibitor of a variety of proteases most notably neutrophil elastase (NE). Unopposed, NE and other proteases attack the lung matrix causing structural damage and markedly impairing host defence. In the commonest form of AAT deficiency the mutated Z AAT is improperly folded, polymerises and aggregates in the liver. As a result less AAT is secreted into the bloodstream and gets to the lungs. This results in liver disease due to AAT aggregation in the liver and pulmonary damage due to the deficiency in the lung rendering it unable to protect against NE-mediated damage. In this review we will discuss AAT deficiency in detail, outlining the pathogenesis, and the clinical manifestations of the condition.

THE ALPHA-1 GENE AND SUBSEQUENT DEFICIENCY DISEASE STATE

AAT deficiency was first described by Laurell and Eriksson in 1963 who noted a clinical link with emphysema (1). Just over 6 years later Sharp *et al* first associated the protein deficiency with liver disease (2).

Since then, our understanding has advanced significantly. The AAT gene, located on the long (q) arm of chromosome 14 is a member of the serpin gene family which encode a group of serine protease inhibitors. Inheritance is monogenic and autosomal co-dominant where products of both alleles are expressed. There are numerous AAT alleles, and their nomenclature is based on their migration on electrophoresis, with those exhibiting high isoelectric points being allocated letters from the beginning of the alphabet, and those with low isoelectric points conferred letters from the end of the alphabet. At least 100 alleles have been identified; however they can be widely classified into four main clinical groups, based on serum levels and function (Table 5.1).

Both null and dysfunctional mutations are rarely encountered in clinical practice with the majority of patients with AAT deficiency either homo- or heterozygous for 'Z' or 'S' variants which subsequently correlate with severity of pulmonary or hepatic manifestations of disease. The highest disease incidence is within Europe (4, 5).

Base substitutions, in-frame and exon deletions and frame-shift mutations can all occur within the AAT gene. The most common and clinically important variants (S, Z) result from single amino acid substitutions: a valine for glutamate at position 264 (Glu264Val) in the case of the 'S' variant and lysine for glutamate at position 342 (Glu342Lys) for the 'Z' variant (6). The S protein is less polymerogenic than Z and results in reduced accumulation of S AAT within hepatocytes, yielding a milder serum deficiency. However, if the S variant is inherited with the rapidly polymerising Z variant, the two forms interact within hepatocytes, forming inclusions and in some cases, cirrhosis (7-10).

VARIANT	ALLELE OR MUTATION	
Normal	M	Normal plasma levels (>20µmol/L); 95% of alleles in Caucasian populations
Deficient	Z or S	Common deficiency variants: 'Z' (5-6µmol/L) & 'S' (8-11µmol/L) plasma levels
Null	QOLisbon, Thr68Ile exon II	No detectable circulating protein; no associated liver disease
Dysfunctional	Met358Arg	Unique Pittsburgh mutation (3): converts protein into thrombin rather than elastase inhibitor

Table 5.1 Table showing genotype variants in alpha-1 antitrypsin protein level & function.

Hepatic polymerisation of Z AAT results in minimal secretion into the bloodstream and hence the lung. Consequently, a pulmonary protease-antiprotease imbalance occurs where proteases such as NE are relatively unopposed in causing lung destruction and hampering immune responses by effects on complement receptors (11, 12), immunoglobulins (13), ciliary motility (14), and antiproteases such as secretory leucoprotease inhibitor (SLPI) and elafin (15, 16). The polymerisation of Z AAT in the liver also goes some way to explaining liver disease associated with the condition. Normally cells have a mechanism by which abnormally folded proteins are recognised and removed. In AAT deficiency there is an imbalance between protein folding load and the cell's ability to process this load. The result is endoplasmic reticulum (ER) stress which manifests in a variety of individual but not exclusive intracellular responses including the ER overload response (EOR), the unfolded protein response (UPR) and apoptosis (17).

CLINICAL MANIFESTATIONS OF AAT DEFICIENCY LUNG DISEASE

The hallmark of AAT pulmonary disease is early onset panacinar emphysema in a predominantly basal distribution (18, 19). Obstructive lung disease presents at a mean age of 32 to 41 in subjects with a current or previous history of smoking (20-24). In a study of 246 PI*ZZ individuals, chronic obstructive pulmonary disease (COPD) was present in 74.8% at a median age of 52 years (25). True natural history of this condition remains uncertain; many individuals with AAT deficiency remain undiagnosed or misdiagnosed as non-hereditary emphysema. Most individuals with AAT deficiency have a smoking history (NHLBI Registry). Smoking is estimated to shorten survival of AAT-deficient individuals by up to 20 years (20).

The National Heart, Lung and Blood Institute Registry (NHLBI) of individuals with AAT deficiency utilised standardized symptom questionnaires to quantify symptom frequency. Exertional dyspnoea was predominant (84%), followed by self-reported wheezing (65%), cough

with phlegm (50%) and coughing alone (42%). Frequency of wheeze is important as 35% of subjects self-reported a history of asthma, while 50% had a significant bronchodilator-associated reversibility of airflow obstruction on serial testing (26). Eden *et al* assessed for the presence of asthma through wheezing, bronchodilator responsiveness, atopy, and increased serum IgE. They demonstrated the presence of three or more of these markers in 22% of AAT-deficient patients compared with 5% of COPD patients without AAT deficiency (27).



Figure 5.1 High Resolution Computed Tomography (HRCT) of lung bases from patient with Alpha-1 antitrypsin deficiency. Widespread emphysematous changes are seen bilaterally.

Pulmonary function in established disease shows decreased expiratory flow rates (FEV1 & FEV₂₅₋₇₅) but preserved forced vital capacity (FVC). Flow volume curves show "classic coving" on expiration (Figure 5.1). Plain chest radiography (CXR) in early disease shows minimal change. Changes are seen earlier and are more easily quantified on computed tomography (CT) scans of the thorax (Figure 5.2). There has been an increased use of CT scanning in AAT deficiency for two main reasons; to detect early disease before appreciable loss of lung function and to assess efficacy of therapeutic interventions such as augmentation therapy. This has led to the detection of other associated lung conditions such as bronchiectasis. Guest *et al* (28) demonstrated that in an AAT deficiency population, radiological features consistent with bronchiectasis were observed in 41%. King *et al* (29) demonstrated a similar prevalence of bronchiectasis (43%). An early

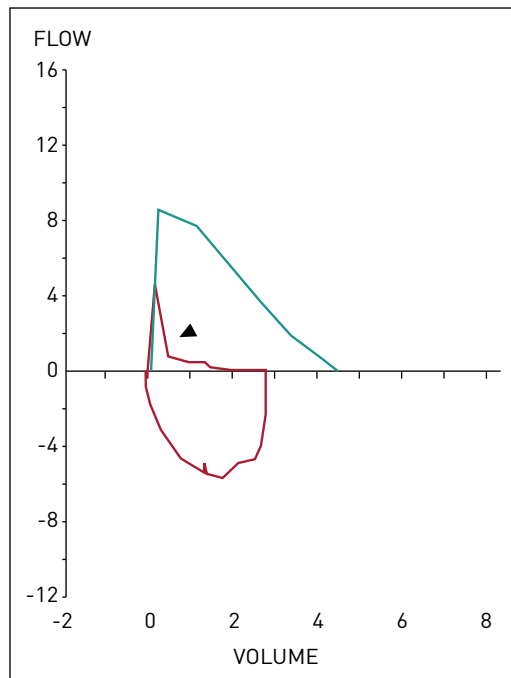


Figure 5.2 Flow-volume loop of a patient with Alpha-1 antitrypsin deficiency. Coving of the expiratory portion of the curve is seen (arrow), reflecting flow limitation. A normal expiratory curve is shown in green.

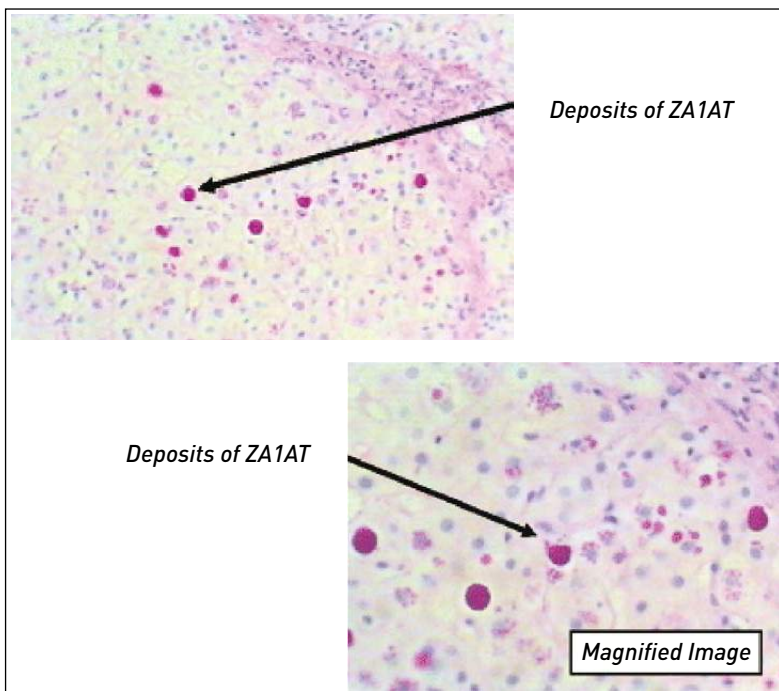


Figure 5.3 Diastase-resistant periodic acid-Schiff stained liver section from a ZA1AT-deficient individual showing A1AT deposits.

series however, by Larsson *et al* (21) showed that bronchiectasis was present in just 11.3% of 246 PI*Z homozygotes investigated. Arterial blood gases (ABG) show normoxia or hypoxia at rest although hypercapnia is seen in advanced disease associated with markedly decreased FEV1 (26).

CLINICAL MANIFESTATIONS OF AAT DEFICIENCY LIVER DISEASE

Sharp and colleagues (2) first described cirrhosis in AAT deficiency in 10 children from six families and later reported intra-hepatocyte periodic acid-Schiff diastase-resistant inclusions, which occur owing to polymer formation of Z AAT in the ER (Figure 5.3). In PiZZ individuals, 10–15% show clinically significant liver disease in their first 20 years of life (30).

Hepatic disease associated with A1AT deficiency is most common in children. Of the 127 newborn PiZZ infants studied by Sveger *et al* (31), all showed increased liver enzyme concentrations. Eleven percent had prolonged neonatal jaundice (the most common presentation of AAT deficiency in early childhood), of whom 29% developed cirrhosis. Sveger *et al* (31) also showed that infants with a PiSZ phenotype had no signs of liver disease. A follow-up study (30) performed at age 16 of neonates screened in Sweden showed elevated liver enzymes in 17% of PiZZ and 8% of PiSZ adolescents. Adults with liver disease in infancy were later clinically healthy (30).

In adults, liver damage can manifest as chronic liver disease or hepatocellular carcinoma with reported incidences of the latter ranging from 5-30% (30, 32). Five to ten percent of AAT-deficient patients over 50 will develop cirrhosis. A study of 19 adult patients with AAT deficiency and chronic liver disease revealed a late onset of symptomatic hepatic abnormalities. Thirteen patients (68%) were 60 years or older when the liver disease was discovered. Mean age of the patients with the PiZZ, PiSZ, and PiMZ phenotypes were 58, 66, and 72.5 years when liver disease was diagnosed, suggesting later onset liver disease in heterozygotes.(33)

OTHER CLINICAL MANIFESTATIONS OF AAT DEFICIENCY

An association has been described with Wegener's granulomatosis which is not surprising given that anti-neutrophil cytoplasmic antibody; the hallmark of this condition is raised against proteinase 3 which is naturally inhibited by AAT. There exists several case series (33, 34) describing an excess of AAT phenotypes in cohorts with ANCA positive vasculitis. Necrotizing panniculitis is the characteristic skin lesion described in AAT deficiency. Clinical responses to augmentation therapy and dapsone have been described (36-38).

Reports of aneurysms (intra-cranial/abdominal) and fibromuscular dysplasia demonstrate predilections for AAT deficient patients exist (39) but formal association remains unproven. Renal disease has been implicated in AAT deficiency, with a heterogenous series of manifestations ranging from IgA nephropathy to membranoproliferative glomerulonephritis. There is also a reported association with the development of renal disease in patients with cirrhosis (40,41).

CURRENT AND FUTURE TRANSLATIONAL AND THERAPEUTIC ASPECTS TO DISEASE

In 1987 Wewers *et al* (42) demonstrated that plasma purified AAT could be safely administered by intravenous infusion to AAT deficient individuals maintaining plasma levels above a putative protective threshold of 11 μ m. This protective level was based on typical levels of AAT in SZ individuals, who if non-smokers are at minimal risk of developing emphysema (43). Additionally, there were concomitant increases in both AAT and anti-NE capacity on the lung's epithelial surfaces. This evidence of biochemical efficacy is as yet unaccompanied by evidence of clinical efficacy. A number of studies suggest that intravenous AAT augmentation therapy may have some beneficial clinical effects. Seersholm *et al* (44) compared a group of Danish ex-smokers with AAT deficiency to a similar German group who received augmentation therapy. In individuals with forced expired volume in one second (FEV1) ranging

from 31-65% predicted there was a significant difference in FEV1 decline of approximately 21 cc/year between those receiving augmentation therapy and those who did not. Similar results were found on evaluation of the NHLBI registry data (45). These data additionally showed a mortality risk reduction in those receiving AAT augmentation therapy. Further work by Dirksen *et al* (46) evaluated radiographic changes (CT) in those receiving augmentation therapy and although no significant difference (p=0.07) was observed the study provided adequate information to develop a power statistic and determine how many AAT individuals were needed in future trials to conclusively show a clinical effect by CT scan. Consequently, spirometry measurements are now regarded as secondary efficacy endpoints. Once monthly and bi-weekly administration of AAT has also been evaluated but most data presently supports a once-weekly regimen (47).

Worries about potential transmission of infectious agents by a human plasma-derived product have led to the development of transgenic and recombinant sources of human AAT. Transgenic production of human AAT protein has been achieved in goats (48) and sheep (49), and human AAT has also been produced in yeast using recombinant technology (50). Unfortunately, all these proteins are cleared more rapidly than plasma purified AAT from the circulation following intravenous administration. Consequently, the inhaled route has been investigated for these products. These have an acceptable half-life on the epithelial surface following aerosolisation. The conceptual concern with this route is that while it can be argued that increasing the level of AAT in blood and subsequently measuring it in epithelial lining fluid (ELF) gives some reassurance that the interstitium of the lung is being protected the same argument is not necessarily applicable with aerosolisation. A number of gene therapeutics for AAT deficiency has been developed. For example, the normal AAT gene has been successfully introduced into striated muscle cells in animals using an adeno-associated virus vector (51) but clinical trials are awaited.

In terms of hepatic manifestations, liver transplantation provides the only effective intervention. Liver transplantation achieves successful serum conversion and acceptable survival rates of over 80% in both adults and children. Its benefit and application is hampered by the lack of donors and negative aspects of life-long immunosuppressive therapy. With regards potential medical interventions Miller et al (17) have shown that the bile acid tauroursodeoxycholic acid (TUDCA) targets the newly delineated apoptotic pathway in the liver and as such may hold therapeutic promise in promoting survival of hepatocytes in Z AAT expressing cells.

KEY CHALLENGES AND OPPORTUNITIES FACED BY AATD PATIENTS WORLDWIDE

There are a number of major questions, challenges and opportunities facing AAT deficient patients worldwide and these include; What is the natural history of the condition? How to diagnose individuals before appreciable organ damage?

1. How to determine whether current treatment modalities are effective and if not to investigate more effective therapeutics?
2. How to determine whether MZ carriers are at increased risk of lung disease?
3. How to utilise lessons from over 50 years research to better understand the pathogenesis of non-AAT related lung and liver disease?

THE NATURAL HISTORY OF AAT DEFICIENCY

The natural history of this condition still requires elucidation. We do not know how many people there are with the condition and how many will be clinically affected by it if they do not smoke or have other significant liver disease. Most published data suggesting a bleak outcome are based mainly on symptomatic index cases (52). With new larger pan-national registries and targeted detection programs inclusive of studying family members, a clearer picture should emerge in the coming decades.

DIAGNOSES OF INDIVIDUALS BEFORE APPRECIABLE ORGAN DAMAGE

This has been a major problem particularly in the early years of the condition. The diagnostic algorithms for lung disease have tested individuals with obstruction at an early age. The new diagnostic algorithms widen the net considerably (Table 5.2) to include first degree relatives, poorly responsive asthmatics, and individuals with cryptogenic cirrhosis and vasculitis, inevitably leading to earlier detection rates.

Determine efficacy of current treatments
We are still uncertain whether augmentation therapy has any clinical effect. This disappointing fact, twenty years after the original Wewers et al paper (41) is not surprising given the numbers of patients who would have to be studied to prove efficacy. It is estimated that approximately 550 AAT deficient individuals would need to be studied over a 2 year period to show a significant impact of intravenous AAT augmentation therapy on spirometry. However only 130 would have to be studied to show impacts on CT based indices of emphysema. This has been one of the major breakthroughs in recent years and such parameters are now accepted by the Food and Drugs Administration (FDA) (53).

ARE MZ CARRIERS AT INCREASED RISK OF DISEASE MANIFESTATIONS?

Many studies of the PI MZ population and COPD risk have been performed with inconsistent results. In general, studies comparing COPD with healthy controls have found an excess of PI MZ individuals among COPD cases, but studies assessing FEV1 in PI MZ and PI MM subjects from population-based samples have not found significant differences (54). Our group in collaboration is currently assessing this question. We are performing this in the setting of National Registries and in specific studies utilising the MZ population detected by our targeted detection program.

TYPE A RECOMMENDATION FOR DIAGNOSTIC TESTING
Symptomatic adults with emphysema, chronic obstructive pulmonary disease (COPD), or asthma with airflow obstruction that is incompletely reversible after aggressive treatment with bronchodilators.
First degree relatives of AATD patients
Individuals with unexplained liver disease, including neonates, children, and adults, particularly the elderly
Asymptomatic individuals with persistent obstruction on pulmonary function tests with identifiable risk factors (e.g. cigarette smoking, occupational exposure)
Adults with necrotizing panniculitis
TYPE B RECOMMENDATION FOR DIAGNOSTIC TESTING
Adults with bronchiectasis without evident etiology
Adolescents with persistent airflow obstruction
Asymptomatic individuals with persistent airflow obstruction and no risk factors
Adults with C-ANCA-positive (anti-proteinase 3-positive)

Table 5.2 Guidelines for diagnostic testing of AAT deficiency (adapted from ATS AAT Task Force Recommendations); A: Genetic testing is recommended B: Genetic testing should be discussed and could reasonably be accepted or declined.

UTILISE LESSONS FROM OVER 50 YEARS OF RESEARCH TO UNDERSTAND THE PATHOGENESIS OF NON-AAT RELATED LUNG AND LIVER DISEASE

AAT deficiency is the only hereditary condition directly related to development of COPD. As such it gives invaluable insight into COPD pathogenesis and its treatment. This deficiency has inspired studies into the effects of oxidants from cigarette smoke [55-58] and their ability to inactivate normal M AAT causing a functional deficiency in the lungs of smokers [59]. This suggests possible therapeutic options such as antiproteases or antioxidants. While hepatic manifestations have been less studied many of the mechanisms elucidated in AAT liver disease can be applied to other conditions such as viral

liver disease and haemochromatosis. Most recently our understanding of AAT deficiency as a conformational disorder has paved the way to a better understanding of pathogenesis of conditions as disparate as Alzheimer's, Parkinson's and Huntington's disease.

EXAMPLES OF PHYSICIAN INITIATIVES IN THE EU AND/OR INTERNATIONALLY

There have been increasing numbers of physician-inspired initiatives within the realm of AATD in the last decade. For example within the European Union several augmentation and lung transplant programmes exist along with the AIR registry. The Alpha One Foundation and the University of Florida screening programmes in the United States provide further evidence of this trend. For the purposes of this chapter, we will highlight our national initiative that has been developed over the last five years: "The National Alpha-1 Antitrypsin Deficiency Targeted Detection Programme and Registry".

In the Republic of Ireland, we established in 2004 a national detection programme for suspected alpha-1 antitrypsin deficiency patients and a website (<http://www.alpha1.ie/>) that provides a resource for physicians, patients and the general public.

The Irish national targeted detection programme is directly funded by the Department of Health and provides testing for AAT deficiency at no cost to patients at risk according to ATS guidelines.

Based on a genetic screening study on 1000 random samples by our group, we estimate that 3,000 Irish citizens have the deficiency and up to 700,000 are carriers, yet only a fraction of these has been identified to date. The targeted detection program is into its fifth operational year and during the period we have tested 3,000 individuals throughout Ireland. Thus far, we have identified over 90 severely deficient individuals (ZZ, SZ) and over 700 moderately deficient individuals (carriers, mainly MZ).

Following diagnosis, the foundation provides multiple ancillary services to patients including counselling, expert advice through clinics,

information packs and leaflets for patients and relatives. Through this initiative, we also offer patients opportunities for enrolment in clinical trials including an augmentation therapy trial and membership of the alpha-1 patient support group. In the last year, we have established a National Alpha-1 Registry to track the health status of patients with the deficiency throughout Ireland. The type of information collected includes height, weight, gender, genotype, pulmonary function, liver tests, hospitalisations and complications related to lung and liver disease manifestations. Such information will help clinicians and researchers to identify new trends, design clinical trials and improve care delivery for patients.

Alpha-1 antitrypsin deficiency is more prevalent in Ireland than was previously thought, even after making allowances for the targeted symptomatic population investigated through our national initiatives. The importance of an early and accurate diagnosis cannot be over-emphasised as the consequential medical follow-up and lifestyle changes help to prevent and at least postpone the development of related lung and liver disease.

REFERENCES

1. Laurell CB ES. "The electrophoretic alpha 1-globulin pattern of serum in alpha 1-antitrypsin deficiency". *Scand J Clin Lab Invest* 1963;15:132-40.
2. Sharp HL, Bridges RA, Krivit W, Freier EF. Cirrhosis associated with alpha-1-antitrypsin deficiency: a previously unrecognized inherited disorder. *J Lab Clin Med.* 1969 Jun;73(6):934-9.
3. Owen MC, Brennan SO, Lewis JH, Carrell RW. Mutation of antitrypsin to antithrombin. alpha 1-antitrypsin Pittsburgh (358 Met leads to Arg), a fatal bleeding disorder. *N Engl J Med.* 1983 Sep 22;309(12):694-8.
4. de Serres FJ. Worldwide racial and ethnic distribution of alpha1-antitrypsin deficiency: summary of an analysis of published genetic epidemiologic surveys. *Chest.* 2002 Nov;122(5):1818-29.
5. Hutchison DC. Alpha 1-antitrypsin deficiency in Europe: geographical distribution of Pi types S and Z. *Respir Med.* 1998 Mar;92(3):367-77.
6. Curiel DT, Chytil A, Courtney M, Crystal RG. Serum alpha 1-antitrypsin deficiency associated with the common S-type (Glu264---Val) mutation results from intracellular degradation of alpha 1-antitrypsin prior to secretion. *J Biol Chem.* 1989 Jun 25;264(18):10477-86.
7. Lomas DA, Evans DL, Finch JT, Carrell RW. The mechanism of Z alpha 1-antitrypsin accumulation in the liver. *Nature.* 1992 Jun 18;357(6379):605-7.
8. Elliott PR, Bilton D, Lomas DA. Lung polymers in Z alpha1-antitrypsin deficiency-related emphysema. *Am J Respir Cell Mol Biol.* 1998 May;18(5):670-4.
9. Janciauskiene S, Dominaitiene R, Sternby NH, Piitulainen E, Eriksson S. Detection of circulating and endothelial cell polymers of Z and wild type alpha 1-antitrypsin by a monoclonal antibody. *J Biol Chem.* 2002 Jul 19;277(29):26540-6.
10. Mulgrew AT, Taggart CC, Lawless MW, Greene CM, Brantly ML, O'Neill SJ, et al. Z alpha1-antitrypsin polymerizes in the lung and acts as a neutrophil chemoattractant. *Chest.* 2004 May;125(5):1952-7.
11. McElvaney NG, Hubbard RC, Birrer P, Chernick MS, Caplan DB, Frank MM, et al. Aerosol alpha 1-antitrypsin treatment for cystic fibrosis. *Lancet.* 1991 Feb 16;337(8738):392-4.
12. Tosi MF, Zakem H, Berger M. Neutrophil elastase cleaves C3bi on opsonized pseudomonas as well as CR1 on neutrophils to create a functionally important opsonin receptor mismatch. *J Clin Invest.* 1990 Jul;86(1):300-8.
13. Fick RB, Jr., Naegel GP, Squier SU, Wood RE, Gee JB, Reynolds HY. Proteins of the cystic fibrosis respiratory tract. Fragmented immunoglobulin G opsonic antibody causing defective opsonophagocytosis. *J Clin Invest.* 1984 Jul;74(1):236-48.
14. Smallman LA, Hill SL, Stockley RA. Reduction of ciliary beat frequency in vitro by sputum from patients with bronchiectasis: a serine proteinase effect. *Thorax.* 1984 Sep;39(9):663-7.
15. Guyot N, Butler MW, McNally P, Weldon S, Greene CM, Levine RL, et al. Elafin, an elastase-specific inhibitor, is cleaved by its cognate enzyme neutrophil elastase in sputum from individuals with cystic fibrosis. *J Biol Chem.* 2008 Nov 21;283(47):32377-85.

16. Taggart CC, Lowe GJ, Greene CM, Mulgrew AT, O'Neill SJ, Levine RL, et al. Cathepsin B, L, and S cleave and inactivate secretory leucoprotease inhibitor. *J Biol Chem*. 2001 Sep 7;276(36):33345-52.
17. Miller SD, Greene CM, McLean C, Lawless MW, Taggart CC, O'Neill SJ, et al. Tauroursodeoxycholic acid inhibits apoptosis induced by Z alpha-1 antitrypsin via inhibition of Bad. *Hepatology*. 2007 Aug;46(2):496-503.
18. Eriksson S. Pulmonary emphysema and alpha1-antitrypsin deficiency. *Acta Med Scand*. 1964;175:197 [Manual].
19. Gishen P, Saunders AJ, Tobin MJ, Hutchison DC. Alpha 1-antitrypsin deficiency: the radiological features of pulmonary emphysema in subjects of Pi type Z and Pi type SZ: a survey by the British Thoracic Association. *Clin Radiol*. 1982 Jul;33(4):371-7.
20. Brantly ML, Paul LD, Miller BH, Falk RT, Wu M, Crystal RG. Clinical features and history of the destructive lung disease associated with alpha-1-antitrypsin deficiency of adults with pulmonary symptoms. *Am Rev Respir Dis*. 1988 Aug;138(2):327-36.
21. Larsson C. Natural history and life expectancy in severe alpha1-antitrypsin deficiency, Pi Z. *Acta Med Scand*. 1978;204(5):345-51.
22. Eriksson S. Studies in alpha 1-antitrypsin deficiency. *Acta Med Scand Suppl*. 1965;432:1-85.
23. Tobin MJ, Cook PJ, Hutchison DC. Alpha-1 antitrypsin deficiency: the clinical and physiological features of pulmonary emphysema in subjects homozygous for Pi type Z. A survey by the British Thoracic Association. *Br J Dis Chest*. 1983 Jan;77(1):14-27.
24. Janus ED, Phillips NT, Carrell RW. Smoking, lung function, and alpha 1-antitrypsin deficiency. *Lancet*. 1985 Jan 19;1(8421):152-4.
25. McElvaney NG, Stoller JK, Buist AS, Prakash UB, Brantly ML, Schluchter MD, et al. Baseline characteristics of enrollees in the National Heart, Lung and Blood Institute Registry of alpha 1-antitrypsin deficiency. Alpha 1-Antitrypsin Deficiency Registry Study Group. *Chest*. 1997 Feb;111(2):394-403
26. N Seersholm and A Kok-Jensen Survival in relation to lung function and smoking cessation in patients with severe hereditary alpha 1-antitrypsin deficiency. *Am. J. Respir. Crit. Care Med.*, Vol 151, No. 2, 02 1995, 369-373.
27. Eden E, Mitchell D, Mehlman B, Khouli H, Nejat M, Grieco MH, et al. Atopy, asthma, and emphysema in patients with severe alpha-1-antitrypsin deficiency. *Am J Respir Crit Care Med*. 1997 Jul;156(1):68-74.
28. Guest PJ, Hansell DM. High resolution computed tomography (HRCT) in emphysema associated with alpha-1-antitrypsin deficiency. *Clin Radiol*. 1992 Apr;45(4):260-6.
29. King MA, Stone JA, Diaz PT, Mueller CF, Becker WJ, Gadek JE. Alpha 1-antitrypsin deficiency: evaluation of bronchiectasis with CT. *Radiology*. 1996 Apr;199(1):137-41.
30. Sveger T, Eriksson S. The liver in adolescents with alpha 1-antitrypsin deficiency. *Hepatology*. 1995 Aug;22(2):514-7.
31. Sveger T. Liver disease in alpha1-antitrypsin deficiency detected by screening of 200,000 infants. *N Engl J Med*. 1976 Jun 10;294(24):1316-21.
32. Eriksson S. Alpha 1-antitrypsin deficiency and liver cirrhosis in adults. An analysis of 35 Swedish autopsied cases. *Acta Med Scand*. 1987;221(5):461-7.
33. Rakela J, Goldschmiedt M, Ludwig J. Late manifestations of chronic liver disease in adults with alpha 1-antitrypsin deficiency. *Dig Dis Sci*. 1987 Dec;32(12):1358-62
34. Savige JA, Chang L, Cook L, Burdon J, Daskalakis M, Doery J. Alpha 1-antitrypsin deficiency and anti-proteinase 3 antibodies in anti-neutrophil cytoplasmic antibody (ANCA)-associated systemic vasculitis. *Clin Exp Immunol*. 1995 May;100(2):194-7.
35. Esnault VL, Testa A, Audrain M, Roge C, Hamidou M, Barrier JH, et al. Alpha 1-antitrypsin genetic polymorphism in ANCA-positive systemic vasculitis. *Kidney Int*. 1993 Jun;43(6):1329-32.
36. Geraminejad P, DeBloom JR, 2nd, Walling HW, Sontheimer RD, VanBeek M. Alpha-1-antitrypsin associated panniculitis: the MS variant. *J Am Acad Dermatol*. 2004 Oct;51(4):645-55.
37. Pittelkow MR, Smith KC, Su WP. Alpha-1-antitrypsin deficiency and panniculitis. Perspectives on disease relationship and replacement therapy. *Am J Med*. 1988 Jun 24;84(6A):80-6.
38. Edmonds BK, Hodge JA, Rietschel RL. Alpha 1-antitrypsin deficiency-associated panniculitis: case report and review of the literature. *Pediatr Dermatol*. 1991 Dec;8(4):296-9.

39. Schievink WI, Puumala MR, Meyer FB, Raffel C, Katzmann JA, Parisi JE. Giant intracranial aneurysm and fibromuscular dysplasia in an adolescent with alpha 1-antitrypsin deficiency. *J Neurosurg*. 1996 Sep;85(3):503-6.
40. Davis ID, Burke B, Freese D, Sharp HL, Kim Y. The pathologic spectrum of the nephropathy associated with alpha 1-antitrypsin deficiency. *Hum Pathol*. 1992 Jan;23(1):57-62.
41. Noble-Jamieson G, Thiru S, Johnston P, Friend P, Barnes ND. Glomerulonephritis with end-stage liver disease in childhood. *Lancet*. 1992 Mar 21;339(8795):706-7.
42. Wewers MD, Casolaro MA, Sellers SE, Swayze SC, McPhaul KM, Wittes JT, et al. Replacement therapy for alpha 1-antitrypsin deficiency associated with emphysema. *N Engl J Med*. 1987 Apr 23;316(17):1055-62.
43. RG C. Alpha-1-antitrypsin deficiency, emphysema and liver disease: genetic basis and strategies for therapy. *J Clin Invest*. 1998;85:1343-52.
44. Seersholm N, Wencker M, Banik N, Viskum K, Dirksen A, Kok-Jensen A, et al. Does alpha1-antitrypsin augmentation therapy slow the annual decline in FEV1 in patients with severe hereditary alpha1-antitrypsin deficiency? Wissenschaftliche Arbeitsgemeinschaft zur Therapie von Lungenerkrankungen (WATL) alpha1-AT study group. *Eur Respir J*. 1997 Oct;10(10):2260-3.
45. Survival and FEV1 decline in individuals with severe deficiency of alpha1-antitrypsin. The Alpha-1-Antitrypsin Deficiency Registry Study Group. *Am J Respir Crit Care Med*. 1998 Jul;158(1):49-59.
46. Dirksen A, Dijkman JH, Madsen F, Stoel B, Hutchison DC, Ulrik CS, et al. A randomized clinical trial of alpha(1)-antitrypsin augmentation therapy. *Am J Respir Crit Care Med*. 1999 Nov;160(5 Pt 1):1468-72.
47. Wencker M, Banik N, Buhl R, Seidel R, Konietzko N. Long-term treatment of alpha1-antitrypsin deficiency-related pulmonary emphysema with human alpha1-antitrypsin. Wissenschaftliche Arbeitsgemeinschaft zur Therapie von Lungenerkrankungen (WATL)-alpha1-AT-study group. *Eur Respir J*. 1998 Feb;11(2):428-33.
48. Ziomek CA. Commercialization of proteins produced in the mammary gland. *Theriogenology*. 1998 Jan 1;49(1):139-44.
49. Wright G, Carver A, Cottom D, Reeves D, Scott A, Simons P, et al. High level expression of active human alpha-1-antitrypsin in the milk of transgenic sheep. *Biotechnology (N Y)*. 1991 Sep;9(9):830-4.
50. Casolaro MA, Fells G, Wewers M, Pierce JE, Ogushi F, Hubbard R, et al. Augmentation of lung antineutrophil elastase capacity with recombinant human alpha-1-antitrypsin. *J Appl Physiol*. 1987 Nov;63(5):2015-23.
51. Kolodka TM, Finegold M, Kay MA, Woo SL. Hepatic gene therapy: efficient retroviral-mediated gene transfer into rat hepatocytes in vivo. *Somat Cell Mol Genet*. 1993 Sep;19(5):491-7.
52. Sveger T, Piitulainen E, Arborelius M, Jr. Lung function in adolescents with alpha 1-antitrypsin deficiency. *Acta Paediatr*. 1994 Nov;83(11):1170-3.
53. Proceedings of Meeting of Blood and Plasma Advisory Committee. Federal Drug Administration; 1998; Rockville, Maryland.
54. Hersh CP, Dahl M, Ly NP, Berkey CS, Nordestgaard BG, Silverman EK. Chronic obstructive pulmonary disease in alpha1-antitrypsin PI MZ heterozygotes: a meta-analysis. *Thorax*. 2004 Oct;59(10):843-9.
55. Rahman I, MacNee W. Oxidant/antioxidant imbalance in smokers and chronic obstructive pulmonary disease. *Thorax*. 1996 Apr;51(4):348-50.
56. Taylor JC, Madison R, Kosinska D. Is antioxidant deficiency related to chronic obstructive pulmonary disease? *Am Rev Respir Dis*. 1986 Aug;134(2):285-9.
57. Pryor WA, Stone K. Oxidants in cigarette smoke. Radicals, hydrogen peroxide, peroxyxynitrate, and peroxyxynitrite. *Ann N Y Acad Sci*. 1993 May 28;686:12-27; discussion -8.
58. Nakayama T, Church DF, Pryor WA. Quantitative analysis of the hydrogen peroxide formed in aqueous cigarette tar extracts. *Free Radic Biol Med*. 1989;7(1):9-15.
59. Hubbard RC, Ogushi F, Fells GA, Cantin AM, Jallat S, Courtney M, et al. Oxidants spontaneously released by alveolar macrophages of cigarette smokers can inactivate the active site of alpha 1-antitrypsin, rendering it ineffective as an inhibitor of neutrophil elastase. *J Clin Invest*. 1987 Nov;80(5):1289-95.

6. Research Programmes

ALPHA-1 AUGMENTATION THERAPY CLINICAL TRIAL

This study is being conducted in Beaumont Hospital by Professor McElvaney and his team.

This is a placebo-controlled, double blind, multicentre phase III/IV study to compare the efficacy and safety of the drug Zemaira® in patients with emphysema due to Alpha 1 proteinase inhibitor deficiency. The duration for each patient is 2 years.

We have recruited 18 patients so far and they are all at various stages in the trial. The trial involves having weekly intravenous infusions of Zemaira®, an Alpha-1 proteinase inhibitor or a placebo which is a dummy treatment that looks like the real thing but has none of the activity. As the study is double-blinded, neither the participating patients nor our study staff know which therapy has been assigned to them. There is an equal chance of receiving either treatment. As of July 2009 we have 11 patients who have continued onto the extension phase of the study. This is where each patient receives Zemaira® for at least two years.

The infusions are given either in Beaumont Hospital or in the patient's home and take on average 20 minutes once a week.

Every three months patients are required to attend Beaumont Hospital so that routine tests can be carried out. These include:

- Monitoring of vital signs, i.e. blood pressure, weight etc.
- Blood tests.
- Pulmonary function tests.
- Physical examination by physician.
- Cotinine test (urine test that detects nicotine).

During certain visits a Quality of Life questionnaire and CT scan are performed. These help to investigate the effect of Zemaira® on the development of emphysema within the patient.

The main inclusion criteria for all patients that enter onto the study are:

- Diagnosis of alpha-1 antitrypsin deficiency.
- Non smokers or ex-smokers who have stopped at least 6 months prior to screening.
- Age range of 18 – 65 years of age, male and female.
- Emphysema with an FEV1 of 35-70% predicted range.

In previous clinical studies, Zemaira® has been shown to be generally well tolerated and provides patients with half or less the infusion time of other available Alpha-1 augmentation therapies available.

If you would like any further information on Zemaira® or you are interested in taking part in the trial, please feel free to contact:

Grace Mullins

Research Nurse & Study Co-Coordinator,
Beaumont Hospital, Dublin 9.
Tel: +353-1-809 3864

CLARIFICATION OF THE RISK OF COPD IN ALPHA-1 ANTITRYPSIN (MZ) INDIVIDUALS

Funding Body: Alpha-1 Foundation USA

Project Description: This clinical research study, to clarify the risk of COPD in MZ individuals, commenced in July 2007 and is supervised by Professor Gerry McElvaney, Department of Medicine RCSI, Smurfit Building, Beaumont Hospital, Dublin 9, Ireland.

The purpose of this study is to obtain information about individuals (and their family members) that are carriers of alpha-1 antitrypsin (AAT). Acquisition of an abnormal alpha-1 gene from each parent leads to severe deficiency in alpha-1 protein levels which may result in serious lung disease in adults and/or liver disease in infants, children and adults. If an individual inherits an abnormal alpha-1 gene from only one parent, they are a carrier and may be predisposed to developing lung disease.

The main objective of this study is to determine whether carriers of alpha-1 antitrypsin deficiency

are at an increased risk of developing lung disease. We aim to identify subtle changes in lung function especially in close family members that may allow earlier intervention and treatment. We also aim to investigate whether there are any environmental factors that interact with the abnormal alpha-1 gene that predisposes some but not others to serious lung disease. If identified correctly, such environmental factors may then be avoided thus preventing the development of serious lung disease in carriers of alpha-1 antitrypsin deficiency.

Our aim is to enroll 400 parents and siblings of 100 alpha-1 antitrypsin carriers (PIMZ) with diagnosed GOLD Stage 3 or 4 COPD into this study. The inclusion criteria for PIMZ carriers are as follows:

- Age >30
- GOLD Stage 3 or 4 COPD (post-bronchodilator FEV1 <50% predicted; FEV1/FVC ratio 0.7)
- Confirmed PIMZ genotype
- No other lung diseases that would affect pulmonary function testing (PFT)

The exclusion criteria for relatives of the above PIMZ carriers are as follows:

- Any interstitial lung diseases
- PI types other than PIMM or PIMZ
- Non-biological siblings of the PIMZ COPD proband

Each individual will perform a lung function test (using a portable spirometer), complete a detailed questionnaire (respiratory and liver questions, family history, smoking history etc) and provide blood samples to confirm their carrier status and allow DNA extraction.

Our goal is to include as many siblings and parents from each family to participate in this ground-breaking clinical research study. We will determine whether the PI MZ carrier status is associated with an increased risk of COPD and whether cigarette smoking confers an increased risk of COPD in carriers of Alpha-1 antitrypsin deficiency.

If there are patients that fulfill the above criteria and are interested in partaking in this clinical research study, please contact:

Geraldine O'Brien

Clinical Research Associate
Alpha One Foundation, RCSI Building,
Beaumont Hospital, Dublin 9.
Tel: +353-1-809 3702
Email: geraldineobrien@rcsi.ie

ANTI-INFLAMMATORY EFFECT OF ALPHA-1 ANTITRYPSIN ON THE PHAGOCYTTIC NEUTROPHIL.

Funding Body: Health Research Board (HRB)/ Medical Research Charities Group (MRCG)

Project Abstract: Alpha-1 antitrypsin (A1AT) is a secretory protease inhibitor produced primarily in the liver. The functional A1AT molecule is found in abundance within human plasma, with normal concentrations in the range of 20-53µmol/L. Despite its name, A1AT is the major physiological inhibitor of a range of serine proteases and within the lung it can protect the alveolar matrix from destruction by neutrophil elastase (NE) and thus maintains a protease-antiprotease balance. A1AT deficiency is a lethal hereditary disorder characterized by low plasma levels of A1AT and accumulation of the misfolded protein within hepatocytes and colangiocytes. Polymerised aggregates of A1AT are implicated in liver cirrhosis and chronic hepatitis and loss of natural anti-protease screen results in early onset and pathogenesis of emphysema. A clear understanding of the molecular mechanisms that regulate inflammation in the lung in A1AT deficiency is a priority.

The anti-inflammatory effects of A1AT are generally thought to be mediated by its anti-protease activity, however recent data indicate alternative functions. A1AT has been reported to inhibit neutrophil NADPH oxidase activity, control lipopolysaccharide (LPS)-induced cytokine and chemokine release in monocytes and regulate IgE and IgG4 production by human B cells. In addition, an in vivo murine study revealed that, A1AT can protect against TNF α or endotoxin induced lethality. The aim of this study is to understand the relationship between A1AT and the phagocytic neutrophil. We propose that neutrophil-associated A1AT exerts immunomodulatory activities and in the

context of tissue homeostasis A1AT moderates neutrophil activation. Our preliminary data clearly show that A1AT is a genuine membrane/secretory vesicle protein of neutrophils, which is released from the cell immediately in response to physiologically relevant concentrations of pro-inflammatory cytokines with increased levels of molecular A1AT detected in the extracellular milieu. The relevance of A1AT binding to the neutrophil membrane will be investigated in respect to its ability to moderate the NADPH oxidase cascade of the circulating cell. Our initial studies have shown that A1AT exhibits distinct inhibitory effects on fMLP receptor-mediated O₂⁻ production. Ensuing experiments will shed light on the signalling steps affected by A1AT. Experiments will centre on testing whether A1AT prevents targeting of the NADPH oxidase components p67phox, p47phox, p40phox and p21rac to the membrane bound flavocytochrome b558 thereby averting oxidase activation. Alternatively, inhibition may occur via the cAMP pathway. Recently it has been shown that A1AT exerts in vitro anti-inflammatory activity in human monocytes by elevating intracellular cAMP. For this reason experiments will investigate whether the inhibitory effect of A1AT on fMLP-induced O₂⁻ production runs in parallel with altered intracellular cAMP levels.

There is a tremendous need to understand the molecular and cellular events that influence the course of lung disease within A1AT deficient patients. We propose to characterise in depth the anti-inflammatory effect of A1AT on neutrophil activity and study the implications of A1AT deficiency with respect to neutrophil regulation. This study will enhance and develop our knowledge of the role of the phagocytic neutrophil in pulmonary inflammation, and will not only provide a further understanding of the essential steps in neutrophil immunity but ultimately may lead to the identification of new therapeutic targets for A1AT deficiency.

CAN REPLACEMENT THERAPY INFLUENCE THE NEUTROPHIL?

Funding Body: Alpha-1 Foundation USA

Project Abstract: Individuals with severe hereditary alpha-1 antitrypsin (AAT) deficiency

(AATD) are at risk of developing early-onset emphysema. Replacement (augmentation) therapy has become a standard treatment for lung disease associated with AATD. Clinical studies have shown that augmentation therapy is associated with a reduction in frequency and severity of lung infections and a marked slow down in the course of lung deterioration. Neutrophils are the primary effector cells responsible for the pathological manifestations of AATD lung disease and for this reason the important translational research of this project will investigate the effect of AAT augmentation therapy on neutrophil function and activity. Our central hypothesis is that neutrophil membrane-associated AAT exerts immunomodulatory activities by sequestering neutrophil cellular processes. Our compelling preliminary data clearly show that AAT is a genuine outer membrane protein of neutrophils associated with lipid raft micro-domains via binding to a glycosylphosphatidyl-inositol (GPI) linked membrane protein. Physiological concentrations of AAT were found to modulate formyl-methionine-leucine-phenylalanine induced NADPH oxidase activity and interleukin-8 chemotactic responses of normal neutrophils. In contrast, neutrophils of AATD individuals illustrated enhanced NADPH oxidase and migratory activity, indicative of a primed or sub-activated cellular state. This innovative study will focus on the clinical relevance of AAT augmentation therapy and with respect to assigning an AAT anti-inflammatory role, will challenge the hypothesis that infused AAT in AATD individuals effectively binds circulating neutrophils in vivo efficiently modulating cellular activity. Technically we aim to combine a well developed clinical framework with quantitative proteomics specifically of neutrophil membranes pre- and post- AAT augmentation therapy and marry the results of the proteomic studies examining the proteins comprising the outer cellular membrane with modifications to cellular activity. The long-term objective of this research is to develop the means to control lung disease associated with AATD. The potential ramifications of AAT as a modulator of neutrophil activity will add a new understanding to the role of AAT in health and disease.

COUPLING ENDOPLASMIC RETICULUM STRESS TO NEUTROPHIL DYSFUNCTION IN ALPHA-1 ANTITRYPSIN DEFICIENCY.

Funding Body: Talecris Biotherapeutics.

Project Abstract: For patients with alpha-1 antitrypsin (AAT) deficiency (AATD), an autosomal recessive disorder characterized by serum AAT levels below 35 percent of normal, the alveolar structure possess little protection against proteolytic enzymes released by neutrophils in the lower respiratory tract. The resulting chronic destruction of the lung, or emphysema, typically affects individuals with AATD in middle age and progresses slowly. Ninety polymorphic alleles of AAT have been identified with the 'Z' variant held responsible for >95% cases of AATD. The Z mutation disrupts the secondary structure of the AAT protein causing it to adopt an aberrant conformation. This results in accumulation and polymerization of the protein within the endoplasmic reticulum (ER). The consequences of ZAAT ER retention can include impaired secretion of ZAAT and activation of three ER stress responses - the ER overload response (EOR) leading to proinflammatory cytokine expression, the unfolded protein response (UPR) and cellular apoptosis. This research project shall undertake a biochemical approach to determine whether polymerization and ER accumulation of ZAAT occurs within circulating neutrophils. The ultimate goal of this project is to identify ER stress responses associated with ZAAT ER retention and to examine disruption of ER calcium (Ca²⁺) homeostasis in the context of aberrant AATD neutrophil activity.

PRESENTATIONS

American Thoracic Society International Conference, May 2009.

Category: Poster Discussion.

Presenters: DA Bergin, EP Reeves, M Henry, P Meleady, M Clynes, SJ O'Neill, NG McElvaney.

TITLE: THE NEUTROPHIL AND ALPHA-1 ANTITRYPSIN: RELATIONSHIP AND REGULATION

Project Abstract: Introduction: Alpha 1 antitrypsin (A1AT) deficiency is a disease that is characterized by severe lung inflammation, in which neutrophils and neutrophil-derived factors play a crucial pathological role. The effect of A1AT on neutrophil function is poorly understood. In this study we examined the interaction of A1AT with the neutrophil and identified A1AT immuno-modulatory effects.

Methods: Localization of A1AT was performed by sub cellular fractionation, confocal immunofluorescence and detergent free lipid raft isolation. Membrane bound A1AT was evaluated by FACs and western blot analysis. FPLC, immunoprecipitation and mass spectrometry, was performed to identify the A1AT membrane binding partner. The effect of A1AT on neutrophil chemotaxis was performed employing a Boyden chamber.

Results: We have established that A1AT is localized to neutrophil membrane lipid rafts via interaction to the GPI linked protein, Fc β RIIIb. Release of Fc β RIIIb is a requirement for neutrophil chemotaxis and is modulated by A1AT binding to the receptor. In this regard we demonstrate that A1AT has the ability to prevent neutrophil IL-8 induced chemotaxis in dose dependant manner.

Conclusion: This study has determined a role A1AT with the neutrophil cell. It clearly demonstrates the critical role A1AT plays in regulation of neutrophil function. This work has re-evaluated and redefined the pivotal role which A1AT plays in neutrophil cell biology. Funding: Alpha One Foundation Ireland, US Alpha 1 Foundation, Medical Research Charities Group, Health Research Board.

American Thoracic Society International Conference, May 2009.

Category: Posters

TITLE: CLARIFICATION OF THE RISK OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) IN ALPHA-1 ANTITRYPSIN PIMZ INDIVIDUALS.

Author: VB Morris, MB BCH BAO¹, CP Hersh, MD PHD², EK Silverman, MD PHD² and NG McElvaney, MB BCH BAO¹.

Institution: ¹Pulmonary Research Division, Beaumont Hospital, Dublin 9, Ireland; ²Brigham and Women's Hospital, Boston, MA 02115, United States; ³Brigham and Women's Hospital, Boston, MA 02115, United States and ⁴Pulmonary Research Division, Beaumont Hospital, Dublin 9, Ireland.

Background: A major interest in Alpha-1 Antitrypsin Deficiency (AATD) research is whether PIMZ genotype increases COPD risk. Previous studies comparing PIMZ genotype and COPD risk have been inconsistent. We hypothesized that a subset of PIMZ individuals have lower FEV1 levels compared to their PIMM siblings and higher COPD risk due to additional genetic and environmental factors.

Method: PIMZ probands aged ≥ 30 with stage 3/4 COPD and full biological siblings and parents (MM/MZ genotype) without any interstitial lung disease were recruited. Spirometry testing, AAT genotype analysis and detailed respiratory questionnaire were performed.

Results: Ages were similar amongst the 26 PIMZ probands (mean \pm standard deviation, 57.7 \pm 13.9), 37 PIMM (53.5 \pm 14.7) and 41 PIMZ (54.8 \pm 15) relatives. Pack-years smoking was highest in PIMZ probands (52.4 \pm 34.3) compared to PIMM (34.12 \pm 20.1) and PIMZ (32.3 \pm 26.5) relatives. Analyses of spirometry were adjusted for age, sex, height and pack-years smoking. Including probands, PIMZ genotype was strongly associated with reduced values for FEV1 and FEV1/FVC ratio ($p < 0.0001$). Excluding probands, PIMZ \geq genotype was associated with lower FEV1/FVC (adjusted difference 0.06, $p = 0.001$); FEV1 was also reduced, but the difference was not significant. Family based association tests in PBAT confirmed these results ($p = 0.04$ for FEV1/FVC ratio).

Conclusion: These results demonstrate reduced lung function, specifically FEV1/FVC, in AAT PIMZ carriers. This ongoing study will determine genetic and environmental factors that may be associated with an increased risk of COPD in a subset of PIMZ individuals.

American Thoracic Society International Conference, May 2009.

Abstract: Poster Presentation

TITLE: PREVALENCE OF ALPHA-1 ANTITRYPSIN DEFICIENCY IN IRELAND

Author: T Carroll², O Floyd², C O'Connor², J Mcpartlin¹ and NG McElvaney²

Institution: ¹Trinity Biobank, Institute of Molecular Medicine, Trinity Centre, St James's Hospital, Dublin. ²Department of Respiratory Research, RCSI Education and Research Centre, Beaumont Hospital, Dublin 9, Ireland.

Rationale: AAT deficiency is a hereditary autosomal codominant disorder, resulting from mutations in the AAT gene, and classically presents with emphysema and liver disease. The most common phenotype presenting with clinical evidence of AAT deficiency is the Z phenotype, resulting in decreased levels of circulating AAT due to retention of the aberrantly folded protein in the liver. AAT deficiency is under-diagnosed and prolonged delays in diagnosis are common. World Health Organisation guidelines advocate targeted detection programmes of patients with COPD and asthma.

Methods: A combination of serum AAT measurement by radial immunodiffusion (RID) or nephelometry, phenotyping by isoelectric focussing (IEF), and genotyping of DNA isolated from dried blood spot samples was used to identify AAT variants.

Results: 2,600 individuals with COPD, asthma, or cryptogenic liver disease were screened in a national targeted detection programme. 1,000 healthy anonymised individuals from the Trinity College Biobank were genotyped for S and Z alleles.

Targeted screening identified 33 ZZ, 37 SZ, 12 SS, 358 MZ, 228 MS, and 12 MI individuals, yielding gene frequencies of 0.055 and 0.09 for

S and Z respectively. Screening of 1,000 healthy individuals identified 98 MS, 46 MZ, 2 SZ and a single SS case, yielding gene frequencies of 0.053 and 0.022 for S and Z.

Conclusions: The Z mutation is more clinically significant with a higher penetrance than S in the groups we have evaluated. The allele frequencies for S and Z in Ireland were previously estimated at between 0.02-0.04 and 0.005-0.015. Our pilot study shows S and Z alleles occur at higher frequencies, suggesting 2,900 ZZ individuals, 10,000 SZ cases and over 700,000 carriers on the island of Ireland.

Acknowledgements: Alpha One Foundation Ireland, Alpha One Foundation U.S., Department of Health and Children, the Royal College of Surgeons in Ireland and Talecris Biotherapeutics.

Irish Thoracic Society Annual Scientific Meeting Belfast, Ireland, November 2008.

Category: Poster Presentation

TITLE: ALPHA-1 ANTITRYPSIN DEFICIENCY ZZ COPD COMPARED TO MM COPD

Authors: O Floyd², T Carroll², C O'Connor², C Taggart¹, R Costello², SJ O'Neill² and NG McElvaney².

Institution: ¹School of Dentistry, Queens University, Belfast. ²Department of Respiratory Research, RCSI Education and Research Centre, Beaumont Hospital, Dublin.

AAT deficiency (AATD) is a hereditary disorder, resulting from mutations in the SERPINA1 gene, classically presenting with early-onset emphysema and liver disease. The most common mutation associated with AAT deficiency is the Z mutation, with the S mutation also associated with lung disease. AAT deficiency is under-diagnosed and prolonged delays in diagnosis are common. World Health Organisation guidelines advocate screening patients with COPD, asthma, cryptogenic liver disease and first degree relatives of known AATD patients.

ZZ AATD patients on the National Alpha-1 Registry (n=61, 49.3+/-1.3 years, 39 male, 22 female) were

compared to a cohort of MM COPD patients (n=100, 60.4+/-1.3 years, 40 male, 60 female).

Mean AAT levels in the ZZ group were 0.127+/-0.013g/L compared to 1.393+/-0.03g/L in the MM COPD cohort. The mean FEV1 for all ZZ patients was 63.0+/-4.2% compared to 62.8+/-2.6% for MM COPD patients. However, when ZZ cases identified by family screening were removed, the mean FEV1 of the ZZ cohort was lower than the MM group (55+/-4.8%, p=0.005, compared to MM group). When MM and ZZ groups were stratified by smoking status, ZZ smokers had mean FEV1 of 51.0+/-4.4% compared to 82.6+/-6.7% for never smokers, while MM smokers had mean FEV1 of 60.9+/-3.7% compared to 65.6+/-3.5% for never smokers. These findings underline the clinical significance of the ZZ phenotype and cigarette smoke in the development of COPD.

Irish Thoracic Society Annual Scientific Meeting Belfast, Ireland, November 2008.

Category: Poster Presentation.

Presenters: EP Reeves, DA Bergin, SJ O'Neill and NG McElvaney.

TITLE: ALPHA-1 ANTITRYPSIN MODIFIES NEUTROPHIL NADPH OXIDASE ACTIVITY BY REDUCING LEVELS OF INTRACELLULAR CYCLIC AMP (cAMP).

Abstract: Alpha-1 antitrypsin (AAT) deficiency classically presents with emphysema, in which neutrophils play a dominant role. Exposure of neutrophils to a variety of stimuli activates a membrane bound NADPH-oxidase to catalyse the generation of reactive oxygen species, including superoxide anion radical (O₂⁻). In the present study we examined the immunomodulatory activity of AAT and investigated whether NADPH-oxidase activation via the G-protein coupled N-formyl-methionyl-leucyl-phenylalanine (fMLP) receptor was inhibited by AAT.

Oxygen (O₂) consumption was quantified using a Clark-type oxygen electrode and O₂⁻ production was determined by superoxide dismutase (SOD)-inhibitable reduction of cytochrome c.

Both the rate of O₂ consumption and O₂⁻ production elicited by fMLP (10⁻⁶M) was

significantly inhibited in the presence of AAT (1 μ M). In addition, inhibition of O₂⁻ production was dose dependent and almost completely inhibited by 7.7 μ M AAT. Mechanisms of inhibition were investigated and found to be mediated through a decrease in intracellular cAMP. Levels of cAMP at 15 seconds post fMLP stimulation were elevated to 1.3 \pm 0.2 pmol/10⁷ neutrophils, whilst co-treatment with AAT (7.6 μ M) reduced cAMP levels to 0.06 \pm 0.1 pmol/10⁷ cells.

Conclusions: The observed inhibition of neutrophil NADPH-oxidase activity by AAT, is further evidence supporting a role for this molecule as an anti-inflammatory mediator.

Irish Thoracic Society Annual Scientific Meeting Belfast, Ireland, November 2008.

Category: Oral Presentation.

Presenters: DA Bergin, EP Reeves, SJ O'Neill and NG McElvaney

TITLE: A COATING OF ALPHA-1 ANTITRYPSIN MODULATES NEUTROPHIL ACTIVITY.

Abstract: Alpha-1 antitrypsin (A1AT) deficiency predisposes individuals to early onset emphysema and is a debilitating disease in which neutrophils play a central role. It is becoming more evident that A1AT possess key anti inflammatory properties and the aim of this project was to examine the possible role of A1AT in modulating neutrophil chemotaxis.

Western blot and FACS analysis was utilised to examine the effect of A1AT on release of CD16b, a key molecule in chemotaxis and adhesion, from the neutrophil membrane. The effect of A1AT on neutrophil migration using IL-8 (1-40ng/2.5x10⁵ cells) was quantified employing a multiwell chemotaxis chamber.

Our experimental results revealed that A1AT (27.5 μ M) prevented the release of CD16b from the neutrophil membrane. Inhibition of IL-8 chemotaxis was dose dependent and almost completely inhibited by 3.4 μ M AAT. In addition, neutrophils of A1AT deficient (ZZ) individuals displayed decreased levels of CD16b.

This study highlights the importance of serum levels of A1AT for modulating neutrophil activity and aims to evaluate whether infused A1AT

possess the ability to bind and govern the activity of circulating neutrophils in vivo.

Irish Thoracic Society Annual Scientific Meeting Belfast, Ireland, November 2008.

Category: Oral Presentation.

Presenters: DA Bergin, EP Reeves, SJ O'Neill and NG McElvaney.

TITLE: ALPHA-1 ANTITRYPSIN ASSOCIATES WITH CHOLESTEROL-ENRICHED MICRODOMAINS IN NEUTROPHIL MEMBRANES.

Abstract: Alpha-1 antitrypsin (A1AT) is a glycoprotein synthesised chiefly in the liver and functions as the most important antiprotease in the lung and also demonstrates anti inflammatory properties. It has previously been demonstrated that A1AT is packaged along with neutrophil elastase within the primary granules of these cells (1). Thus there remains a paradox as to why an enzyme and cognate inhibitor would simultaneously compartmentalize, potentially impeding protease antimicrobial activity. This aim of this study was to reevaluate the localisation of A1AT within the neutrophil.

Compartmentalisation of A1AT within the neutrophil was established by sub-cellular fractionation, western blot analysis and confocal immunofluorescence.

Our data clearly show that A1AT is a genuine outer membrane protein of neutrophils associated with cholesterol- and sphingolipid-enriched membrane domains called lipid rafts. We have observed that treatment of neutrophil membranes with phosphatidylinositol-specific phospholipase C (PIPLC) or high NaCl concentrations removed A1AT from the neutrophil membrane indicating that localization of A1AT in lipid rafts is mediated by electrostatic interactions to a glycosylphosphatidyl-inositol (GPI) linked membrane protein.

Further studies will address the relevance of neutrophil associated A1AT and may support the theory that the anti inflammatory effects of A1AT are not simply related to modulation of serine proteases activity.

References:

1. Mason DY et al. 1991. Am J Pathol 139:623 .

Ulster Immunology Group, Queen's University Belfast, June 2009 and the Royal Academy of Medicine in Ireland National University of Ireland Maynooth, June 2009.

Presenters: DA Bergin, EP Reeves, M Henry, P Meleady, C Condron, M Clynes, SJ O'Neill and NG McElvaney.

TITLE: THE NEUTROPHIL AND ALPHA-1 ANTITRYPSIN: RELATIONSHIP AND REGULATION.

Abstract: Alpha-1 antitrypsin (AAT) deficiency is a disease that is characterized by severe lung inflammation, in which neutrophils and neutrophil-derived factors play a crucial pathological role. The effect of AAT on neutrophil function is poorly understood. In addition to anti-protease activity it is becoming more evident that AAT possesses key anti-inflammatory properties. In this study we examined the interaction of AAT with the neutrophil and identified AAT immuno-modulatory effects.

Localization of AAT was performed by sub cellular fractionation, confocal immunofluorescence and detergent free lipid raft isolation. Membrane bound A1AT was evaluated by FACs and western blot analysis. FPLC, immunoprecipitation and mass spectrometry, was performed to identify the AAT membrane binding partner. The effect of AAT on neutrophil chemotaxis was performed employing a Boyden chamber.

We have established that AAT is localized to neutrophil membrane lipid rafts via interaction with the glycosylphosphatidyl-inositol linked protein, Fc β RIIIb. Release of Fc β RIIIb is a requirement for neutrophil chemotaxis and this process is modulated by AAT binding to the receptor. In this regard we demonstrate that AAT has the ability to prevent neutrophil IL-8 induced chemotaxis in a dose dependant manner.

This study has re-evaluated and redefined the role of AAT in neutrophil physiology. Results demonstrate the critical new role of AAT in the regulation of neutrophil chemotaxis and highlight the potential effect of AAT as a therapeutic agent.

Irish Thoracic Society Annual Scientific Meeting Belfast, Ireland, November 2008.

Category: Oral presentation

Presenters: TB Low, CM Greene, SJ O'Neill and NG McElvaney

TITLE: ANTI-PGP OR ANTI-ELASTIN AUTOANTIBODIES ARE NOT EVIDENT IN CHRONIC INFLAMMATORY LUNG DISEASE

Institution: Respiratory Research Division, Department of Medicine, Royal College of Surgeons in Ireland, Education and Research Centre, Beaumont Hospital, Dublin 9, Ireland.

In patients with chronic inflammatory lung disease pulmonary proteases can generate neoantigens from elastin and collagen with the potential to fuel autoreactive immune responses. Anti-elastin peptide antibodies have been implicated in the pathogenesis of tobacco-smoke induced emphysema. Collagen-derived peptides may also have a role.

We aimed to determine whether autoantibodies directed against elastin- and collagen-derived peptides are present in plasma from three groups of patients with chronic inflammatory lung disease compared to a non-smoking healthy control group, and to identify whether autoimmune responses to these peptides may be an important component of the disease process in these patients

124 patients or healthy controls were recruited for the study (Z-A1AT deficiency, n=20; cystic fibrosis, n=40; chronic obstructive pulmonary disease, n=31; healthy control, n=33). C reactive protein, interleukin-32 and anti-nuclear antibodies were quantified. Anti-elastin and anti-N-Acetylated-proline-glycine-proline autoantibodies were measured by reverse ELISA.

All patients were deemed stable and non-infective on the basis of absence of clinical or radiographic evidence of recent infection. There were no significant differences in levels of autoantibodies or IL-32 in the patients groups compared to the healthy controls. In summary, anti-elastin or anti-N-Acetylated proline-glycine-proline autoantibodies are not evident in chronic inflammatory lung disease.

We congratulate Dr. David Bergin on winning the prestigious eALTA award from Talecris Pharmaceutical at the European Respiratory Society meeting in Vienna, September 2009.



Dr David Bergin accepting the eAlta award

THE AWARD-WINNING STUDY

TITLE: COUPLING ENDOPLASMIC RETICULUM STRESS TO NEUTROPHIL DYSFUNCTION IN ALPHA-1 ANTITRYPSIN DEFICIENCY

Alpha-1 antitrypsin (AAT) deficiency (AATD) is a genetic disorder that affects approximately one in 2000 individuals in Ireland. AATD is clinically associated with early-onset emphysema and severe hepatic disease. AAT is mainly produced in the liver and disease symptoms arise due to accumulation of misfolded AAT in the endoplasmic reticulum (ER) of hepatocytes. The most frequent mutation that causes severe AATD arises in the SERPINA 1 gene and gives rise to the Z-allele. The 'Z' variant is responsible for >95% cases of AATD. Misfolded ZAAT is also expressed by cells of the lung and is a contributory factor to the lung inflammation experienced by those with AATD. Our preliminary data supports previous observations that circulating blood neutrophils express the AAT gene. As neutrophils play an important role in the pathological manifestations of

AATD lung disease, the primary goal of this innovative project is to determine the functional importance of polymerization and ER localization of ZAAT in circulating neutrophils.

Cytosolic free calcium (Ca^{2+}) concentration, in circulating neutrophils is an important determinant of cellular activity. In resting neutrophils Ca^{2+} is low (approximately 100 nM), but in response to occupation of cell surface receptors, it rises to micromolar levels, thereby activating a variety of cellular functions. To date we have observed quantitative changes in AATD (ZZ) neutrophil function and have recorded enhanced NADPH-oxidase and migratory activity, indicative of a sub-activated cellular state. We believe these to be important results as increased chemotaxis and reactive oxygen species production can contribute to more rapid lung disease progression. As the ER functions as a Ca^{2+} storage organelle, we hypothesize that ER accumulation of misfolded ZAAT impacts upon Ca^{2+} regulation in circulating AATD (ZZ) neutrophils. Accordingly, the aim of this project is to evaluate whether efflux of Ca^{2+} from ZAAT-sensitive endoplasmic reticulum plays a role in the observed defective activation of AATD (ZZ) neutrophils.

There is a tremendous need to understand the molecular and cellular events that influence the course of lung disease within AATD patients. We propose to characterise in depth ER accumulation of misfolded ZAAT in AATD (ZZ) neutrophils. In addition we will also study possible implications of ER Ca^{2+} efflux resulting in excessive levels of neutrophil activation. This study will enhance and develop our knowledge of the role of the circulating neutrophil in pulmonary inflammation and will provide a further understanding of the essential steps in neutrophil immunity. While the research described in this study is not a therapeutic intervention, it will elucidate more fully the role of the neutrophil in AATD related lung disease and will impact on the treatment options.

7. Patient Support Group

The main aims of the Alpha-1 Patient Support Group are to improve understanding of alpha-1 antitrypsin deficiency and increase awareness among medical professionals and patients.

The group held a very successful patient meeting in Cork in May of this year. Patients and family members participated in the Women's Mini Marathon this June and raised substantial funds.

To contact or even participate in the patient support group please email alpha1@rcsi.ie or call 01-809 3871.

Patient representatives contact details:

East representatives Josephine McGuirk: 086 606 1708 and Orla Keane: 087 260 2874

South representative John Hannan: 087 230 4369

North representative Anna Cassidy: 074 973 6157

WOMEN'S MINI MARATHON



Patients and fundraiser's participating in the Women's Mini Marathon this year.



Professor Gerry McElvaney, Larry Warren and guests attending the Chopin Recital in the Mansion House October 2008

CHOPIN ANNIVERSARY RECITAL

Fredric Chopin suffered from chronic respiratory disease, probably Alpha-1, during his short but very productive life. We in the Alpha One Foundation, wished to celebrate his life and draw attention to respiratory research especially into Alpha-1 Antitrypsin Deficiency with a Chopin Anniversary Recital.

As his condition greatly influenced his music we thought it appropriate to celebrate Chopin's life and music annually on the eve of the anniversary of his death.

The Lord Mayor Cllr. Eibhlin Byrne had kindly invited us to use her residence, in the Mansion House, for the occasion. We gratefully acknowledged her kindness.

The programme consisted of the works of Chopin and also included compositions of other composers.

The pianist for the night was Mr. Lance Coburn.

THE CONCERNS AND PROBLEMS FACING ALPHA-1 ANTITRYPSIN DEFICIENCY PATIENTS

Alpha-1 Antitrypsin Deficiency (AATD) is one of the most common life threatening inherited diseases in Europe. It is estimated that in excess of 100,000 individuals suffer from this condition, which can affect the lungs (emphysema) and liver (cirrhosis). As the only therapy for liver disease associated with AATD is transplantation and as the lung disease is far more common, I shall confine my remarks to lung-related AATD for which replacement (augmentation) therapy has been developed and is widely used. This is a plasma-derived product and is delivered intravenously, with an inhaled product in development.

Crucially, most individuals remain unaware that they have AATD as many doctors do not test for this condition. This is true even with symptomatic patients as they are usually diagnosed as asthma or chronic obstructive pulmonary disease (COPD).

AATD is a deficiency of a vital lung-protecting protein. Therefore, it would seem that the obvious therapy is to replace or augment the protein that is missing. This therapy has been developed and is now widely used in the USA and in Europe. In Europe it is licensed and prescribed in the following countries:

- Germany
- Austria
- France
- Spain
- Italy
- Portugal
- Ireland

It is important to note that its prescription and use varies from country to country, so we cannot say that it is universally available to patients in Europe. It is available on a named-patient basis in some other EU countries.

Some physicians will not prescribe the therapy because they believe that its efficacy has not been proven in a double-blinded placebo-controlled clinical trial. Studies are currently being carried out by CSL Behring. Countries involved in this international study include Ireland, Poland, Nordic countries and Australia. One of the main producers of replacement therapy for Europe is Talecris Biotherapeutics (Prolastin). It is also being produced by companies in France and Spain.

National patient groups and institutions as well as Alfa Europe are urgently promoting detection programmes. Currently there are numerous screening and detection programmes in progress in various countries. Lobbying is also being used to raise awareness of the need for screening and detection among various groups such as patient families, medical practitioners, statutory healthcare providers, local politicians and ministers, and the EU Parliament.

Financial support from governments and pharmaceutical companies has enabled the initiation of many research studies and screening programmes e.g. Ireland's Targeted Detection Programme, Germany's Screening Programme and Italy's Area Screening Programme.

As AATD is a genetic condition it is vital that family members of AATD patients are also tested for the condition. The Alpha One Foundation in Ireland provides advice and support to families requiring screening. The consideration of any potential problems including psychological issues, genetic discrimination anxieties, and financial concerns is also necessary. People fear the effect a diagnosis of AATD will have on their and their children's health insurance premiums, mortgage availability and life assurance. It is essential that accurate information, advice and support are made available to newly diagnosed patients and their families.

It is clear that Alpha-1 Antitrypsin Deficiency must be considered and properly addressed in national health plans and in EU directives on health. There are three immediate requirements to be prioritised in the diagnosis and treatment of AATD patients.

1. Availability of a full package of therapies and remuneration in all European countries.
2. Adequate counselling services for newly diagnosed patients and their families.
3. Accredited national screening or detection programmes for Alpha-1 patients.

It is incumbent on all states in the EU to afford equal access to adequate services and therapies to people with Alpha-1 Antitrypsin Deficiency.

In the meantime we need to:

- Continue political lobbying
- Raise awareness in the general population
- Raise awareness among General Practitioners
- Inform pulmonary healthcare providers
- Continue working closely with the healthcare industry.

Larry Warren

Former CEO, Alpha One Foundation (Ireland),
President, Alfa Europe

AN ALPHA-1 PATIENT CHECKS IN!

Since I was first diagnosed with Alpha-1 Antitrypsin Deficiency in Jan 1990 my life has been a bit of a roller coaster. Initially it did not bother me much but as time went on and my pulmonary function results began to go down I started to get concerned. Periodically I was depressed but luckily I was able to shake it off pretty quickly. Now I am almost 66 ...twenty years on and I have survived well.

My lung functions are down considerably. I attend Beaumont Hospital for my out-patients check-ups. I am under the care of Dr. James Doody, GP in Balbriggan Medical Centre, and Professor Gerry McElvaney in Beaumont Hospital. Both are brilliant doctors and are very understanding of Alpha-1.

Winters for me are not easy. Over the last New Year, I was hospitalised with pneumonia and pleurisy. I was in for two weeks and on returning home acquired another infection. I was also involved in the hospital in the home care service, which I found extremely beneficial and have participated in various research studies for Alpha One. The local health centre in Skerries have been extremely helpful in my care and provided essential support.

Home oxygen was prescribed in April 2005, which I take regularly... 16 hours daily, and find very helpful. I am very active mentally, read a bit, write a bit, talk a lot, laugh a lot and watch TV sport a lot. I have suffered from depression from time to time and commenced medication for this a while ago. I have had no dips in my mood for a long period of time. I am still learning to cope with my breathing difficulties. I have a large circle of friends who call in all the time. I love going out for a 'spin' with some of my visitors, which I do at least twice a week. The weather has been difficult this summer again and the winter, all too soon upon us, does not excite me much. But it is important to face it one day at a time and not to worry now about December or January. Maintaining a positive outlook, while not easy, is vital!!

I had great time for Larry Warren, now moved on. Also am regularly in contact with a Walter Mannhertz in Germany. He is head of the patient support for the whole of Germany. Walter believes that regular communications between patients is important. I do keep in contact with a number of people with various lung disease and talk to them all the time. This is mutually beneficial. I am available all the time to talk to you at 01-8491528 for 'an ould chat'.

Joe Clinton

3rd September 2009



8. Doctor's Corner

FREQUENTLY ASKED QUESTION

Is haemochromatosis related to alpha 1 as both affect the liver and there are a good few alpha 1 patients who suffer from the disease?

Haemochromatosis and alpha-1 antitrypsin deficiency are both genetically acquired illnesses. Both conditions are most common in North Europe, particularly England, Ireland and Scandinavia. However there is no evidence that there is an association between the two conditions. The reason why some patients have both conditions is due to the fact that they are both very prevalent in the same population. It is not due to an underlying link between the two illnesses. Having both illnesses may lead to faster progression of disease and /or increased severity of disease.

Is dry and itchy skin a symptom of alpha 1 antitrypsin deficiency and is so why?

There are a number of skin conditions reported to be associated with alpha -1 antitrypsin deficiency, but most of them are rare. These range from panniculitis – inflammation of the hair follicles to vasculitic – inflammation of the blood vessels. All of these can result in a rash which is typically red, raised and can be itchy. It can be quite painful. It is most commonly seen in PiZ individuals. The exact mechanism for the development of these skin manifestations is unknown, but it generally responds to treatment with replacement therapy – there are several studies to show this, can provide if required.

Some MZ levels of A1AT are quite low. Can they have symptoms as bad as ZZ abs they be monitored more?

The A1AT levels do not necessarily correlate with disease severity. The strongest predictor of disease is smoking history – if someone smokes this has much more of an influence on their risk of developing symptoms than their A1AT levels. There are no long-term studies that provide definitive evidence about whether MZ patients would develop respiratory symptoms if they never smoked, the A1AT foundation have now developed a targeted detection programme which aims to closely monitor all these patients to provide early intervention if they do develop symptoms and to increase our knowledge of the risk for MZ patients to improve future management.

PLAIN ENGLISH GUIDE

The Medical Research Charities Group (MRCG)

is an umbrella group of medical research and patient support charities, many of which are involved in with rare diseases. In order to support patients and those interested in medical research. MRCG has decided to compile a "Plain English Guide" to common research terms. This guide has brought together information from a variety of sources as a central and accessible resource.

Adverse reaction:

(Adverse event / side effect) An unwanted effect caused by the administration of drugs. Onset may be sudden or develop over time.

Baseline:

1. Information gathered at the beginning of a study from which variations found in the study are measured.
2. A known value or quantity with which an unknown is compared when measured or assessed.
3. The initial timepoint in a clinical trial, just before a participant starts to receive the experimental treatment which is being tested. At this reference point, measurable values such as those relating to the strength of the immune system are recorded. Safety and efficacy of a drug are often determined by monitoring changes from the baseline values.

Bias:

When a point of view prevents impartial judgment. In medical science it is important to avoid bias affecting the interpretation of data. In clinical studies, bias is controlled by blinding (see Blind below) and randomization.

Blind:

A clinical trial is "Blind" if participants are unaware on whether they are in the experimental or control arm of the study; also called masked.

Cohort:

Refers to a group of subjects who have some defining characteristic in common and who remain part of this group over an extended period of time. The common characteristic in a medical cohort may be a risk factor for a disease or health effect.

Clinical:

Pertaining to or founded on observation and treatment of participants, as distinguished from theoretical or basic science.

Clinical investigator:

A medical researcher in charge of carrying out a clinical trial's protocol.

Clinical trial:

A clinical trial is a research study to answer specific questions about vaccines or new therapies or new ways of using known treatments. Clinical trials are used to determine whether new drugs or treatments are both safe and effective. Carefully conducted clinical trials are the fastest and safest way to find treatments that work in people.

Trials are in four phases:

- Phase I tests a new drug or treatment in a small group;
- Phase II expands the study to a larger group of people;
- Phase III expands the study to an even larger group of people;
- Phase IV takes place after the drug or treatment has been licensed and marketed.

Control group:

The standard against which experimental observations are evaluated. In many clinical trials, the control group receives a placebo treatment.

FDA:

The Food and Drug Administration is the regulatory body in the United States with responsibility for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs; biological products; medical devices; food supply; cosmetics; and products that emit radiation.

Peer review:

Review of a scientific paper or clinical trial by experts in the field. These experts review the paper or trials for scientific merit, participant safety and ethical considerations.

Pharmacokinetics:

The processes (in a living organism) of absorption, distribution, metabolism and excretion of a drug or vaccine.

Placebo effect:

A physical or emotional change, occurring after a substance is taken or administered, that is not the result of any special property of the substance. The change may be beneficial, reflecting the expectations of the participant and, often, the expectations of the person giving the substance.

Protocol:

A study plan on which all experimental studies or clinical trials are based. A protocol for clinical trials is carefully designed to safeguard the health of the participants as well as answer specific research questions. A protocol describes what types of people may participate in the trial; the schedule of tests, procedures, medications, and dosages; and the length of the study. While in a clinical trial, participants following a protocol are seen regularly by the research staff to monitor their health and to determine the safety and effectiveness of their treatment.

Toxicity:

An adverse effect produced by a drug that is detrimental to the participant's health.

**USEFUL CONTACTS FOR PATIENTS
TRAVELLING ABROAD**

COUNTRY/ORGANISATION	CONTACT
Australia	www.alpha1.org.au/
Austria	www.alpha1-oesterreich.at/
Denmark	www.alfa-1.dk/ and www.lunge.dk
Europe	<i>European Organisation for Rare Diseases</i>
Europe - alpha-1	<i>Alfa Europe Federation</i>
Finland	www.kolumbus.fi/markku.laasonen/alfa/
France	alpha1-france.org/
Germany	www.alpha1-deutschland.de/
Ireland	www.alpha1.ie/
Italy	www.alfa1at.org and info@alfa1at.org
Netherlands	www.astma-copd.nl/content/copd/alpha1.asp
Spain	www.alfa1.org/
Sweden	www.alfa-1.se/news.php
Switzerland (French-speaking)	www.alpha-1swiss.ch/ and gvautier@worldcom.ch
Switzerland (German-speaking)	www.alpha-1swiss.ch/ and vlahovic@tele2.ch
United States	www.alphaone.org/

9. Acknowledgements

We would like to thank the following:

- The Alpha-1 Foundation in the US
- Maurizio Luisetti MD and Ilaria Ferrarotti, Centre for Diagnosis of Inherited Alpha-1 Antitrypsin Deficiency, Laboratory of Biochemistry and Genetics Institute for Respiratory Disease, University of Pavia, Italy
- Marc Miravittles, Servei de Pneumologia (ICPCT), Hospital Clínic Villarroel, Barcelona, for protocols and technical information
- Pat O'Brien and the Beaumont Hospital Biochemistry Department for their continued support
- Dr Joseph McPartlin, Trinity Biobank, Institute of Molecular Medicine, St James's Hospital, Dublin
- ECOM – Ireland who continue to consult, programme, advise and develop our website and database to the highest international standards

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

- Alpha-1 is not a rare disease, but a disease that is rarely diagnosed.
- Our national targeted detection programme screens all COPD, asthma, liver disease patients and relatives of Alphas. Early diagnosis is essential. Alpha-1 individuals diagnosed early have fewer symptoms and significantly better lung function.
- The Foundation's research demonstrates a much higher incidence of Alpha-1 in Ireland than previously thought, with over 2,100 individuals at risk of developing severe disease.
- In addition we have shown there are over 200,000 Alpha-1 carriers in Ireland who possess one copy of the harmful gene. These patients are also at increased risk of developing emphysema, particularly if they smoke.
- Identification of patients from a targeted detection programme should include aggressive family screening and allow the initiation of preventative measures before significant lung disease has occurred.