Alpha-1 Antitrypsin Deficiency (AATD)
“Precision Medicine for COPD”

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LabCon, Galway, March 31st 2017
Alpha-1 Antitrypsin

- Alpha-1 antitrypsin (AAT) is a 52kDa glycoprotein

- Key antiprotease produced by the liver
  - Regulates harmful serine proteases (SERPIN family member)

- Second most abundant protein in blood, easy to measure

- Evidence to suggest many other functions
  - Anti-inflammatory
  - Anti-viral
  - Anti-bacterial

Main job is to protect the lungs
Alpha-1 Antitrypsin Deficiency

- Alpha-1 antitrypsin deficiency (AATD) first described in 1963 by Laurell & Eriksson

- Caused by mutations in the AAT gene
  - most common are Z and S

- Low serum AAT levels
  - unchecked enzyme activity
  - lung and liver disease
  - leading cause of lung/liver transplantation

- Misdiagnosis all too common
Genetics of Alpha-1

• Everyone inherits 2 copies of a gene
  - 1 from mother
  - 1 from father

• If both parents are carriers
  - 1 in 4 chance each child will be ZZ
  - 1 in 2 chance each child will be MZ (a carrier)
How does Alpha-1 present?

- Recurrent respiratory infections, SOB
- Lung disease 4th or 5th decade (COPD)
  - Rapid deterioration of lung function (+/- history of smoking/environmental exposures)
- Persistently elevated liver enzymes → cirrhosis (→hepatocellular carcinoma)
- Panniculitis
- Vasculitis
- Lung/liver transplantation or death

DIAGNOSIS USUALLY TOO LATE!
COPD and Alpha-1 Antitrypsin Deficiency

- AATD under-recognised & misdiagnosed as chronic obstructive pulmonary disease (COPD) or severe asthma

- US studies show it can take up to 5 doctors and 7 years from time of first symptoms to diagnosis

- Environmental risk factors for COPD well known but AATD only known genetic risk factor for COPD

- Originally thought ~250 Irish citizens had severe AAT deficiency (Irish Medical Journal, 1993)
How many Alpha-1 individuals do we have in Ireland?
Biobank DNA Collection at Trinity College

- Mouth swab collection kits provided to ESRI random-sampling unit and kits posted to potential donors
- Age, gender, educational status and county of birth recorded for 1100 individuals
- Collection irreversibly anonymised

Searched for the S and Z variants
Prevalence of AATD on the Island of Ireland

- 3,000 ZZ individuals (1/2,100) with a carrier rate of 1 in 25
- Estimated 12,000 SZ and over 250,000 MZ carriers
- ZZ individuals in Ireland 8 times more numerous than previously estimated

Table 1 Estimated Prevalence of AAT Genotypes in Ireland

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Prevalence [%]</th>
<th>Numbers in Ireland</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS</td>
<td>1/10 [10.00%, 9.70 - 10.30%]</td>
<td>423,947</td>
</tr>
<tr>
<td>MZ</td>
<td>1/25 [4.03%, 3.97 - 4.09%]</td>
<td>170,832</td>
</tr>
<tr>
<td>SS</td>
<td>1/341 [0.29%, 0.20 - 0.40%]</td>
<td>12,409</td>
</tr>
<tr>
<td>SZ</td>
<td>1/424 [0.24%, 0.23 - 0.25%]</td>
<td>10,001</td>
</tr>
<tr>
<td>ZZ</td>
<td>1/2,104 [0.05%, 0.04 - 0.06%]</td>
<td>2,015</td>
</tr>
</tbody>
</table>

Data from the Trinity Biobank presented as prevalence [% of total population, 95% confidence interval (CI)]. These figures are based on an Irish population of 4.24 million in the Republic of Ireland (www.cso.ie).
National Alpha-1 Targeted Detection Programme
Who do we test?

ATS/ERS & WHO Guidelines

- All COPD patients
- All non-responsive asthmatics (adults/adolescents)
- All patients with cryptogenic cirrhosis/liver disease
- All first degree relatives of patients/carriers with AAT deficiency

The roots of COPD are in your family tree
How do we test for Alpha-1?

- Blood collected & serum/plasma isolated
- Two tests: quantitative & qualitative

1. Measure levels of AAT in the blood
   - AAT < 1.0 g/litre
2. Analyse the type of AAT present (by isoelectric focusing, called “phenotyping”)

- Genetic analysis sometimes required
  - **DNA sequencing of AAT gene** if rare mutation suspected
Not just ZZ?

Relationship between AAT level and AAT mutation

Risk of disease

AAT as % of normal: 100 80 60 60 40 15

Normal range

“Protective threshold”
Laboratory Red-flag on Low AAT Reports

MRH @ Mullingar. Immunology Dept Phone 044 9394339

NAME: FOR UNASSIGNED  LAB NO.: 123456
CHART #:  DOB: 23/02/1927  SEX: MALE
CONS:  WARD: UNSPECIFIED
HOSP: Mullingar  GP:
PT ADDR:  Sample Type: Serum
GP ADDR:  Printed on 16/07/14 at 11:48  Received: 08/03/2013 11:48

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

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

Sample Date: 08/03/13  Run Date: 16/07/14 11:48  Authorised by Martina M Collins

System adopted in 9 Hospitals to date: Goal is National Implementation
Are we busy?
Reasons for Testing

- Screened over 17,000 at risk individuals
- Receiving >200 samples per month from over 26 hospitals + GP clinics
Screening for Alpha-1 in Ireland to date

- Almost 17,500 tested; ~ 30% possess at least one abnormal AAT gene
- 294 ZZ and 255 SZ individuals (severe AATD) identified
- Over 2,500 MZ carriers also identified (~15% detection rate)
Distribution of Severe Alpha-1 in Ireland

ZZ AATD

Total Number of Cases

>30
10–15
6–9
1–5
0

350...and counting
The testing cycle...
What happens at the Alpha-1 Clinic?

• Newly diagnosed & existing Alpha-1 patients can be referred to Alpha-1 Clinic in Beaumont for assessment
• Variety of tests carried out including;
  – Breathing tests (spirometry)
  – HRCT scan of the lungs
  – Blood profile
  – Liver ultrasound scan & liver function test
• Genetic counseling
• People are often asked to participate in the National Alpha-1 Registry or in a research project
What difference does a diagnosis of Alpha-1 make in COPD?
1. Specific Treatment – Augmentation Therapy

- Weekly intravenous infusions of plasma-purified alpha-1 antitrypsin protein (approved by US FDA in 1987)
- RAPID clinical trial published in Lancet in 2015 (180 patients, 13 countries)
  - 21 Irish Alpha-1 patients took part in 4 year study where CT lung density was primary endpoint

Best evidence yet that Aug Tx slows the progression of emphysema by 34%
1. Specific Treatment – Augmentation Therapy

- A survey of the 21 Irish Alphas who took part in the RAPID study revealed patients felt that chest infections and hospital admissions were dramatically reduced by treatment.

- Hospitalisations per year ↓ 69%
- Chest infections per year ↓ 68%

HSE decision pending on reimbursement of this therapy
1. Specific Treatment – Augmentation Therapy: Impact on Mortality **AND** Infections

Efficacy data on Aug Tx is not new

*Source: Lieberman, J. Chest 2000;118:1480-1485*
2. Family or Cascade Screening

Severe Alphas identified through family screening have better lung function (Carroll et al, 2013)
3. Smoking Cessation Rates

- The small amount of AAT reaching the lung in ZZ individuals is knocked out by cigarette smoke
- AAT deficient individuals who smoke develop lung disease much earlier
- Early Swedish study saw median survival time for ZZ smokers of 40 years (Larsson C, 1978)

- COPD patients diagnosed with Alpha-1 twice as likely to attempt to quit smoking (Carpenter et al., Ann Behav Med 2007)
- At the National Centre of Expertise for AATD at Beaumont, the active smoking rate in severe AATD is 1.5% (2 active smokers out of 210 cases). The ever smoking rate is 69%.

The single most important decision an Alpha-1 can make is to stop smoking
4. Occupational Exposures

- Never-smoking ZZs show significant lung function decline after 50 yrs

Occupational and environmental exposures must be considered (e.g. farming, welding, painting)

*Effect of age and occupational exposure to airway irritants on lung function in non-smoking individuals with alpha 1-antitrypsin deficiency (PiZZ). Thorax. 1997 Mar;52(3):244-8.*
Rarer Variants
Diagnostic advances in AAT phenotyping

Advances have improved ability & accuracy to detect rare AAT variants
Rare AAT Mutations: IEF

Common

I Variants

F Variants

Ultra Rare
What else do we do?
Alpha One Foundation Team:
Kitty O’Connor – CEO
Dr. Tomás Carroll – Chief Scientist
Laura Fee – Clinical Research Associate
Margaret Molloy – Research Nurse
Professor Gerry McElvaney – Chairman
The MZ (Heterozygote) Question

- Unique family-based study with AOF, RCSI & Harvard University
- 51 Irish families and over 250 subjects studied
- Best evidence yet that MZ is a risk factor for COPD if a smoker (Odds Ratio 5.0)

One in 25 at risk of chronic obstructive pulmonary disease

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

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

The debilitating lung condition is linked to alpha-1 antitrypsin deficiency, an inherited condition affecting almost 280,000 people in Ireland.

Increased risk

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

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

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

Doctors leading the research urge people diagnosed with COPD – an estimated 440,000 – to get tested for alpha-1 antitrypsin deficiency through a free screening programme. Dr Kevin Molloy of the RCSI, lead author of the study, said alpha-1 deficiency was massively underdiagnosed both in Ireland and internationally.

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

The Irish Times 10th February 2014

TV3 News, February 2014
• Information guides available for both patients and healthcare professionals
  o Ever thankful to the US Alpha-1 Foundation for sharing their resources

• Produce Annual Report every year
THE ALPHA ONE FOUNDATION
...to promote research into Alpha-1 Antitrypsin Deficiency...

Latest News from the Alpha One Foundation

Annual Alpha-1 Patient Conference 2016: Agenda
Monday, September 26th 2016 10:10

We are delighted to announce the Annual Alpha-1 Conference will take place on Friday 7th October 2016 beginning at 9.30am in Marino Institute of Education, Griffith Avenue, Dublin 9. We would like to invite all Alpha-1 patients and their families to attend, with a special welcome for newly diagnosed Alpha-1 individuals and...

Three Bronze Medals for Ireland at European Transplant Games
Monday, September 5th 2016 14:21

Hearty congratulations to Stephen Smith who won 3 bronze medals for Team Ireland at the European Transplant Games. Stephen had a successful double lung transplant in the Mater Hospital in 2013 and was a member of a large team of athletes who represented Ireland at the games in Finland. In July, Stephen won his first bronze medal...

www.alpha1.ie

We are delighted to release our new educational film on Alpha-1 which was officially launched at the Annual Alpha-1 Conference on October 7th. Funded by an educational grant from the Health Research Board and developed in conjunction with COPD Support Ireland, RCSI, and DCU, we must give very special thanks to the O’Donnell and Gormley families, Anne Gormley and Orla Keane. The film opens and closes with poetry written by the late John O’Donnell and if you would like to buy a book of his poems please visit http://eprint.ie/Window-To-My-World. All proceeds go to the Alpha One Foundation.

https://www.youtube.com/watch?v=kAOlRAim648

Please share this film with as many people as possible and get people talking about Alpha-1!
Why Bother Test for Alpha-1?

- AAT is the original and best COPD biomarker
  - Inexpensive & easy to measure
  - Lower the level, higher the risk
Every single person with COPD should be tested for Alpha-1
Acknowledgements

- Kitty O’Connor, Laura Fee & Margaret Molloy (Alpha One Foundation)
- Professor Gerry McElvaney & Respiratory Research Department (RCSI Beaumont Hospital)
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- Dr. Ilaria Ferrarotti and Dr. Stefania Ottaviani (University of Pavia)
- Joe McPartlin & Professor Dermot Kelleher (TCD)
- John Walsh RIP and Angela McBride of the US Alpha-1 Foundation
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