AIR
Alpha-1 International Registry

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**Alpha\textsubscript{1}-antitrypsin Deficiency (AATD)**

- **Autosomal, codominant genetic disorder**
- **First recognized in 1963 in Sweden**
- **Increased risk of developing COPD (mostly pulmonary emphysema) early in life and chronic liver disease in later phases**
Alpha$_1$-Antitrypsin Deficiency (AATD)

- Characterized by a reduction in serum levels of AAT$^{1,2}$
  - Typically below 11 µM (0.5 to 0.8 g/L- dependent upon assay)$^1$
  - Severe deficiency associated with serum concentrations below 35% of normal mean value in symptomatic homozygous patients$^1$

- Early-onset obstructive lung and liver disease$^2$
  - Symptomatic lung disease may occur by the age of 30 to 40 years in individuals with a history of smoking$^1$
    - Panacinar emphysema with basal predominance
  - Liver disease (neonatal cholestasis, cirrhosis, carcinoma) in children and adults

Alpha1-antitrypsin Deficiency PI*Z Gene Frequency

Blanco I et al Hepat Mon 2012;2:e7434
Prevalence of AATD Surpasses Other Well Known Diseases Affecting the Lungs
(per 100,000 population in EU)

- **Alpha-1 antitrypsin deficiency** (includes carriers): 33
- Amyloidosis: 30
- Idiopathic pulmonary fibrosis: 20
- Pulmonary arterial hypertension: 19.5
- Sarcoidosis: 15
- Cystic fibrosis: 12.6

AAT Deficiency is Globally Underdiagnosed

• Of the ~100,000 in the US with AAT deficiency, 95% are undiagnosed\textsuperscript{1}
• Many nonsmokers with the ZZ phenotype remain undiagnosed because of significant delay in onset of symptoms\textsuperscript{2}
• AAT deficiency is viewed as an uncommon cause of lung and liver disease\textsuperscript{2}
• Early diagnosis may enable earlier interventions\textsuperscript{1,2}
  – Lifestyle modifications
  – Augmentation therapy for symptomatic patients
  – Genetic counseling to help identify affected relatives

Who Do You Test and Who Are You Missing?

FEV$_1$ Percentage Predicted by Age for 378 Pi ZZ Patients Stratified by Smoking Status$^{1,2}$

* Stage III severe COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.

COPD, chronic obstructive pulmonary disease; FEV$_1$, forced expiratory volume in 1 second.
Who Should be Tested?

Patients at Risk

**Category A recommendations**
- All adults with symptomatic emphysema regardless of smoking history
- All adults with symptomatic COPD regardless of smoking history
- All adults with symptomatic asthma whose airflow obstruction is incompletely reversible after bronchodilator therapy
- Asymptomatic patients with persistent obstruction on pulmonary function tests with identifiable risk factors
- Siblings of individuals with Pi ZZ
- ATS also recommends diagnostic testing for all patients with unexplained liver disease and adults with necrotizing panniculitis

**Category B recommendations**
- Family history of any of the following: emphysema, bronchiectasis, liver disease or panniculitis
- Bronchiectasis without evident etiology

Recommend Testing for AATD

Local AAT Testing

- AAT Level Testing

Specialized AATD Testing

- Alpha-1 protease inhibitor (Pi)-"Phenotyping"
- Genotyping

ATS, American Thoracic Society; ERS, European Respiratory Society
AIR registry

1997
7 European countries (UK, Germany, , Sweden, the Netherlands, Italy, Spain and Switzerland), New Zealand, South Africa, Canada, U.S.A.

Austria
Poland
Belgium
Denmark
Finland
Latvia,
Lithuania

Argentina
Brazil
Australia

2005
21 countries from 4 continents
Mission

To share and disseminate results of the original research in the field of AATD

To this aim:

Council Meeting twice per year

Biannual scientific meeting
Activities

Web-based database
Clinical phenotype of patients with alpha-1-antitrypsin deficiency, including baseline characteristics of demography, smoking status, lung function results, health status SGRQ total score, socio-economic status, clinical profiles

Research activities
5 projects conducted funded by EU and successfully finished, currently 7 projects

Large-scale international phase II clinical trials
2 RCTs completed, 2 ongoing
General Introduction & Background

Alpha-1-antitrypsin (α1AT) is produced in the liver and is secreted into the circulation. It is the major serum and critical lung inhibitor of serine proteases, particularly neutrophil elastase. Inadequately controlled neutrophil elastase has been implicated as a cause of tissue destruction in the lung, resulting in emphysema and bronchial disease, which are the two major features of chronic obstructive pulmonary disease (COPD). Inherited deficiency of α1AT (α1ATD) is predominantly a European disorder originating in Scandinavia, and emigrants have carried the trait to other parts of the world. It is as common as cystic fibrosis and affects between 1 in 1700 and 1 in 5000 individuals, depending upon the local prevalence of individuals from Scandinavian origin. Although affected individuals have a predisposition to the development of cirrhosis, liver cancer or vasculitis, they most commonly present with early onset of rapidly progressive emphysema. The management of this disease is at present largely empirical with supportive bronchodilator therapy and oxygen supplementation and eventually lung volume reduction surgery or lung transplantation.

No clinical trial to prove the efficacy of α1AT Infusion has succeeded to date because factors influencing disease progression (with the exception of smoking) are largely unknown. It is currently impossible to prospectively select individuals in this population to identify who will develop disabling lung disease, and who have a critical need for early preventive therapy.
Cumulative inclusion (date of assessment) - baseline

Annual accumulation of patient numbers in the AIR database.

Stockley RA et al. COPD 2013
AATD subjects enrolled 4,938
(Update 20th August 2013)

<table>
<thead>
<tr>
<th>Genotype</th>
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<td>PI*ZZ</td>
<td>3,667</td>
<td>85.4</td>
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<tr>
<td>PI*SZ</td>
<td>494</td>
<td>11.4</td>
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<tr>
<td>PI*ZR §</td>
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<td>1.4</td>
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<tr>
<td>PI*RR</td>
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<td>PI*NullNull</td>
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<tr>
<td>PI*ZNull</td>
<td>15</td>
<td>0.4</td>
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§ R denotes non-Z and non-S deficiency variants

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<tr>
<td>Australia</td>
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Frequency of lung and/or liver disease at diagnosis

<table>
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<tr>
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<tr>
<td>Lung disease</td>
<td>59.62</td>
</tr>
<tr>
<td>Lung and liver disease</td>
<td>19.28</td>
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<tr>
<td>Liver disease</td>
<td>6.25</td>
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<td>Healthy</td>
<td>14.85</td>
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Frequency of lung and/or liver disease at diagnosis according to different genotypes

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<thead>
<tr>
<th>Genotype</th>
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<th>Lung disease</th>
<th>Lung AND liver disease</th>
<th>no disease</th>
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<tbody>
<tr>
<td>SZ</td>
<td>212</td>
<td>57</td>
<td>125</td>
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<tr>
<td>RR*</td>
<td>11</td>
<td>4</td>
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<td>17</td>
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<tr>
<td>Null/Null</td>
<td>17</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

* R denotes non-Z and non-S deficiency variants

* Abnormal liver function tests
DISTRIBUTION OF DIFFERENT CLINICAL RESPIRATORY PHENOTYPES ACCORDING TO GENOTYPES

* R denotes non-Z and non-S deficiency variants
**FEV$_1$ pre br (%)**

SZ vs Null/Null $p=0.0001$

**Range of Serum AAT Levels by Phenotype (μM)**

SZ vs ZZ $p=0.0001$

SZ vs Null/Null $p=0.0001$
FEV$_1$/FVC pre br (%)

SZ vs ZZ p=0.0001
SZ vs Null/Null p=0.0001
ZZ vs ZR p=0.03

FEV$_1$/FVC post br (%)

SZ vs ZR p=0.05
SZ vs ZZ p=0.0001
SZ vs Z/Null p=0.001
SZ vs Null/Null p=0.0001
Key Points

∗ AIR is an multinational, transcontinental independent organisation assembling the largest series worldwide of subjects with AATD

∗ It is a powerful tool for a better understanding of disease epidemiology, disease presentation, and disease natural history