α1-Antitrypsin-levels and phenotypes in Crohn’s
disease in the Netherlands

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Summary A group of 310 unrelated patients suffering from Crohn’s disease has been screened for quantitative and electrophoretic variations of α1-antitrypsin (α1AT). A comparison was made between patients and healthy controls. The distribution of electrophoretic α1AT variants in the patients showed no significant deviation from the controls. The α1AT quantities are significantly higher in the Crohn’s disease population than in the controls.

Crohn’s disease, a chronic inflammatory disease of
the intestine, is an uncommon condition mainly
affecting young adults.

Ever since it was first described,1 attempts have
been made to determine precise clinical and patho-
logical criteria for the diagnosis and to look for
factors which could influence or be the direct cause
of the disease. Studies on the role of infectious and
immunological factors in Crohn’s disease have not
yet provided clear answers concerning the cause of
the disease. Although genetic factors have been
implicated in its pathogenesis, neither a genetic
marker nor a biochemical parameter correlated with
Crohn’s disease has so far been identified.2

α1-Antitrypsin (α1AT, locus Pi) is the main
member of a species of inhibitors of proteolytic
enzymes occurring in human serum. Genetic
polymorphism was discovered by Fagerhol and
Braend.3 The alleles PiP, PiS, PiZ, PiW1, and Pinull
are associated with decreased levels of α1AT.

A deficiency of α1AT was found to be associated
with a variety of clinical conditions such as chronic
obstructive lung disease (COLD),4 chronic cirrhosis
of the liver,5 coeliac disease,6 arthritis,7 uveitis,8 and
ankylosing spondylitis.8 These last three clinical
conditions have been found to be associated with
Crohn’s disease. Linkage is shown between α1AT
and immunoglobulin G(Gm),9 whereas other
markers revealed no linkage.10–12

We have screened a population of thoroughly

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value. The standard serum was a mixture of several sera from healthy blood donors with the phenotype M. The \( \alpha_1 \) AT quantity of our standard serum was compared by Dr M K Fagerhol with his serum pool and found to be the same. For comparing the \( \alpha_1 \) AT levels in the Crohn’s disease patients the quantitative data of the healthy controls of Fagerhol were used.

**Results and discussion**

**Typing**

Seven phenotypes with six different alleles were found in the Crohn’s disease population and, they were shown to be in Hardy-Weinberg equilibrium (Table 1).

The Crohn’s disease and blood donor populations showed similar frequencies of electrophoretic variants of \( \alpha_1 \) AT; none of the seven phenotypes showed a significant difference compared with the controls (Table 2).

**Quantification**

The level of \( \alpha_1 \) AT rose in the Crohn’s disease patients in all phenotypes, as can be seen in Table 3. In the phenotypes FM, M, and MS the difference reached significance.

**Table 1** Hardy-Weinberg analysis of electrophoretic variants of \( \alpha_1 \) AT in 310 unrelated patients suffering from Crohn’s disease

<table>
<thead>
<tr>
<th>( \alpha_1 ) AT allele</th>
<th>( \alpha_1 ) AT gene frequency</th>
<th>( \alpha_1 ) AT phenotype</th>
<th>Number</th>
<th>( \chi^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observed</td>
<td>Expected</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>0.00806</td>
<td>FM</td>
<td>5</td>
<td>4.73</td>
</tr>
<tr>
<td>I</td>
<td>0.00323</td>
<td>IM</td>
<td>2</td>
<td>1.89</td>
</tr>
<tr>
<td>M</td>
<td>0.94516</td>
<td>M</td>
<td>277</td>
<td>276.93</td>
</tr>
<tr>
<td>S</td>
<td>0.03065</td>
<td>MS</td>
<td>17</td>
<td>17.96</td>
</tr>
<tr>
<td>X</td>
<td>0.00161</td>
<td>MX</td>
<td>1</td>
<td>0.95</td>
</tr>
<tr>
<td>Z</td>
<td>0.01129</td>
<td>MZ</td>
<td>7</td>
<td>6.62</td>
</tr>
<tr>
<td>S</td>
<td>0.02129</td>
<td>MZ</td>
<td>7</td>
<td>6.62</td>
</tr>
<tr>
<td>Others</td>
<td>0</td>
<td>0.64</td>
<td>0.6411</td>
<td></td>
</tr>
</tbody>
</table>

For 1 degree of freedom: \( p = 0.12 \).

**Table 2** Distribution of electrophoretic variants of \( \alpha_1 \) AT among patients and controls

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Patients (N=310)</th>
<th>Controls (N=708)</th>
<th>( \chi^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no.</td>
<td>%</td>
<td>no.</td>
</tr>
<tr>
<td>FM</td>
<td>5</td>
<td>1.6</td>
<td>8</td>
</tr>
<tr>
<td>IM</td>
<td>2</td>
<td>0.6</td>
<td>5</td>
</tr>
<tr>
<td>M</td>
<td>277</td>
<td>89.4</td>
<td>647</td>
</tr>
<tr>
<td>MS</td>
<td>17</td>
<td>5.5</td>
<td>40</td>
</tr>
<tr>
<td>MX</td>
<td>1</td>
<td>0.3</td>
<td>0</td>
</tr>
<tr>
<td>MZ</td>
<td>7</td>
<td>2.3</td>
<td>7</td>
</tr>
<tr>
<td>S</td>
<td>1</td>
<td>0.3</td>
<td>1</td>
</tr>
</tbody>
</table>

\( \chi \) Chi square with Yates correction.

Table 3 also shows that the phenotypes MS, S and MZ in the controls had a lower average \( \alpha_1 \) AT quantity than the other phenotypes, especially the M phenotype. This means that the average quantity is compared between patients and controls the phenotypes should also be taken into account.

**Conclusion**

The search for linkage or associations of other genetic markers including HLA-DR with Crohn’s disease has not so far led to positive results. The present study reveals no association. Patients suffering from Crohn’s disease do not differ from the normal controls in their \( \alpha_1 \) AT phenotype distribution. As \( \alpha_1 \) AT is an acute phase reactant, the overall increase of the level of \( \alpha_1 \) AT in the patients is likely to be related to the activity of the disease.

The authors gratefully acknowledge Dr L F Bernini, Dr P Meera Khan, Dr A S Peña, and Professor Dr A J Ch Haex for their helpful discussions.

**References**


**Table 3** Quantitation of \( \alpha_1 \) AT in Patients and controls

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Patients</th>
<th>Controls</th>
<th>( \chi^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Mean %</td>
<td>St. dev. %</td>
</tr>
<tr>
<td>FM</td>
<td>5</td>
<td>124</td>
<td>30.1</td>
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<tr>
<td>IM</td>
<td>2</td>
<td>111</td>
<td>0</td>
</tr>
<tr>
<td>M</td>
<td>277</td>
<td>127</td>
<td>33.1</td>
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<tr>
<td>MS</td>
<td>17</td>
<td>104</td>
<td>27.3</td>
</tr>
<tr>
<td>MX</td>
<td>11</td>
<td>183</td>
<td></td>
</tr>
<tr>
<td>MZ</td>
<td>7</td>
<td>81</td>
<td>36.5</td>
</tr>
<tr>
<td>S</td>
<td>1</td>
<td>81</td>
<td></td>
</tr>
</tbody>
</table>

\*Student T test.
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