Susceptibility to ankylosing spondylitis: no evidence for the involvement of transforming growth factor β1 (TGFB1) gene polymorphisms


Background: Genetic factors are thought to be crucial in the pathogenesis of ankylosing spondylitis. Transforming growth factor β1 (TGFB1) is a multifunctional cytokine that plays a key role in inflammation. Two functional single nucleotide polymorphisms (SNPs) in the TGFB1 gene have been described: TGFB1 T869C and TGFB1 G915C.

Objective: To determine whether these SNPs contribute to ankylosing spondylitis susceptibility or its disease characteristics.

Methods: Genomic DNA was isolated from the peripheral blood of 134 patients with ankylosing spondylitis and 194 healthy blood donors. All subjects were unrelated and of white Dutch ethnicity. The diagnosis of ankylosing spondylitis was made according to the modified New York criteria. The TGFB1 T869C and TGFB1 G915C SNPs were genotyped by a polymerase chain reaction–single strand conformation polymorphism haplotyping method.

Results: No significant differences were found between patients and controls in genotype, allele, and haplotype frequencies or in the carrier rate of the rare alleles of the TGFB1 T869C and TGFB1 G915C SNPs.

Conclusions: TGFB1 T869C and TGFB1 G915C SNPs are not major factors in the susceptibility to ankylosing spondylitis or its disease characteristics.
and 72 °C for 60 seconds, with a final elongation at 72 °C for 10 minutes.

A polymerase chain reaction–single strand conformation polymorphism (PCR-SSCP) method was optimised for the polymerase chain reaction–single strand conformation polymorphism (PCR-SSCP) method was optimised for the

**Statistical analysis**

Allele and genotype frequencies were tested for Hardy–Weinberg equilibrium (HWE) by the χ² test. To compare

**Table 1** Demographic and clinical characteristics of patients with ankylosing spondylitis (n = 134)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>50.9 (12.9)</td>
</tr>
<tr>
<td>Age at first complaints (years)†</td>
<td>23.0 (19.0 to 31.5)</td>
</tr>
<tr>
<td>Age at diagnosis (years)*</td>
<td>34.7 (10.6)</td>
</tr>
<tr>
<td>Years between first complaints and diagnosis†</td>
<td>7.0 (2.0 to 12.5)</td>
</tr>
<tr>
<td>Women</td>
<td>18.7%</td>
</tr>
<tr>
<td>HLA-B27 positive</td>
<td>94%</td>
</tr>
<tr>
<td>Iridocyclitis</td>
<td>43%</td>
</tr>
<tr>
<td>Peripherial arthritis</td>
<td>41%</td>
</tr>
<tr>
<td>First degree relatives with AS</td>
<td>28%</td>
</tr>
</tbody>
</table>

*Mean (SD) (range).†Median (interquartile range). AS, ankylosing spondylitis.

**Table 2** TGFBI genotype and allele frequencies in patients with ankylosing spondylitis and controls

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Controls (n = 194)</th>
<th>Patients (n = 134)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>AF</td>
<td>n (%)</td>
</tr>
<tr>
<td>TGFB1 T869C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TT</td>
<td>80 (41.2)</td>
<td>65.5</td>
<td>57 (42.5)</td>
</tr>
<tr>
<td>TC</td>
<td>94 (48.5)</td>
<td>18.7</td>
<td>59 (44.0)</td>
</tr>
<tr>
<td>CC</td>
<td>20 (10.3)</td>
<td>34.5</td>
<td>18 (13.4)</td>
</tr>
<tr>
<td>TGFB1 G915C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GG</td>
<td>168 (86.6)</td>
<td>93.3</td>
<td>107 (79.9)</td>
</tr>
<tr>
<td>GC</td>
<td>26 (13.4)</td>
<td>6.7</td>
<td>26 (19.4)</td>
</tr>
<tr>
<td>CC</td>
<td>0</td>
<td>0.7</td>
<td>1 (0.7)</td>
</tr>
</tbody>
</table>

AF, allele frequency; CI, confidence interval; OR, odds ratio.
attributable to the rare variants TGFB1 C1632T and TGFB1 G915C.25

The TGFB1 polymorphism 713-8delC is more frequent in patients with osteoporosis than in normal controls and seems to be associated with very low bone mass in osteoporotic women and with low bone mass and increased bone turnover in both osteoropic and healthy women.26 As bone mineral density is often decreased in AS patients, TGFB1 polymorphisms seem to be of even more interest in this disease.

In a Japanese study, the frequency of the allele TGFB1 869T was found to be significantly higher in subjects with osteoporosis than in healthy individuals.27 On the other hand, the TGFB1 869C allele was associated with an increase in osteoporosis in white Australian women.28 The TGFB1 869C allele has also been associated with ossification of the posterior longitudinal ligament in the cervical spine and with spinal osteophytes in Japanese patients.29 The development of spinal osteophytes is also a characteristic feature of AS.

The TGFB1 915G allele is strongly associated with fibrotic lung disease.30 Apical pulmonary fibrosis is rare but well recognised in patients with AS.31 No association between Crohn’s disease or ulcerative colitis, which are clinically related to AS, and TGFB1 SNPs had been found in previous studies.32

The genotype TGFB1 915GG has been related to higher serum concentrations of TGFB1 in a previous study.33 A combined study from Finland and the United Kingdom found a weak association between age of symptom onset of AS and the TGFB1 G915C SNP.34 Furthermore, this study noted a weak positive association of the rare allele TGFB1 1632T with AS and also with a younger age at symptom onset of AS. These investigators concluded from their study that “the polymorphisms (G–800A, C–509T, T+869C, G+915C and C+1632T) in the TGFB1 gene play at most a small role in AS and that other genes on chromosome 19 are involved in the susceptibility to AS”.35

The results from our study do not show an association between the TGFB1 G915C SNP and AS, although the frequency of allele TGFB1 915G was greater in AS patients than in controls, but this difference did not reach significance (p = 0.09). In our group of AS patients no association between the TGFB1 G915C SNP and a younger age of symptom onset of AS could be found.

As TGFβ may play a crucial role in the pathogenesis of AS, especially in new bone formation, further research is necessary to elucidate the role of TGFβ1 in this disease, and possibly open the way towards new pharmacological approaches for preventing the most disabling phenomenon of this disorder, ankylosis.

### Table 3

<table>
<thead>
<tr>
<th>Haplotype</th>
<th>Controls (n = 194)</th>
<th>Patients (n = 134)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PF, n (%)</td>
<td>PF, n (%)</td>
</tr>
<tr>
<td>1.1</td>
<td>80 (41.2)</td>
<td>116 (86.6)</td>
</tr>
<tr>
<td>1.2</td>
<td>76 (39.2)</td>
<td>57 (42.5)</td>
</tr>
<tr>
<td>1.3</td>
<td>18 (9.3)</td>
<td>40 (29.9)</td>
</tr>
<tr>
<td>2.2</td>
<td>12 (6.2)</td>
<td>19 (14.2)</td>
</tr>
<tr>
<td>2.3</td>
<td>8 (4.1)</td>
<td>27 (20.1)</td>
</tr>
<tr>
<td>3.3</td>
<td>0</td>
<td>26 (13.4)</td>
</tr>
</tbody>
</table>

*Overall odds ratios for carriership of haplotypes 1–3.*

Haplotype 1: TGFB1 869T–TGFB1 915G; haplotype 2: TGFB1 869C–TGFB1 915C; haplotype 3: TGFB1 869C–TGFB1 915G. CI, confidence interval; PF, haplotype frequency; n, number of individuals; OR, odds ratio; PF, phenotype frequency.

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