The effect of transforming growth factor β1 gene polymorphisms in ankylosing spondylitis

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Objectives. To determine whether genetic polymorphisms in or near the transforming growth factor β1 (TGFB1) locus were associated with susceptibility to or severity of ankylosing spondylitis (AS).

Methods. Five intragenic single-nucleotide polymorphisms (SNP) and three microsatellite markers flanking the TGFB1 locus were genotyped. Seven hundred and sixty-two individuals from 212 English and 170 Finnish families with AS were genotyped for all five intragenic SNPs. A structured questionnaire was used to assess the age of symptom onset, disease duration and disease severity scores, including the BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) and BASFI (Bath Ankylosing Spondylitis Functional Index).

Results. A weak association was noted between the rare TGFB1 +1632 T allele and AS in the Finnish population (P = 0.04) and in the combined data set (P = 0.03). No association was noted between any other SNPs or SNP haplotype and AS, even among those families with positive non-parametric linkage scores. The TGFB1 +1632 polymorphism was also associated with a younger age of symptom onset (English population, allele 2 associated with age of onset greater by 4.2 yr, P = 0.05; combined data set, allele 2 associated with age of onset greater by 3.2 yr, P = 0.02). A haplotype of coding region SNPs (TGFB1 +869/+915 +1632 alleles 2/1/2) was associated with age of symptom onset in both the English parent–case trios and the combined data set (English data set, haplotype 2/1/2 associated with age of onset greater by 4.9 yr, P = 0.03; combined data set, haplotype 2/1/2 associated with greater age of onset by 4.2 yr, P = 0.006). Weak linkage with AS susceptibility was noted and the peak LOD score was 1.3 at distance 2 cM centromeric to the TGFB1 gene. No other linkage or association was found between quantitative traits and the markers.

Conclusion. This study suggests that the polymorphisms within the TGFB1 gene play at most a small role in AS and that other genes encoded on chromosome 19 are involved in susceptibility to the disease.

KEY WORDS: Genetic aetiology, Microsatellites, Cytokines, Spondyloarthropathy, Polygenic.

Ankylosing spondylitis (AS) exhibits a strong genetic component determining both the susceptibility to and the severity of the disease; except for HLA B27, the genes responsible have not been definitely identified [1, 2]. Non-major histocompatibility complex (MHC) genes are estimated to account for at least half of the genetic variance of AS susceptibility [3]. The male:female ratio for AS is between 2.5:1 and 5:1 [4], but the gender bias is not explained by the linkage to the X chromosome [5]. The gene (TGFB1) for transforming growth factor (TGF) β1 is located on chromosome 19q13, where suggested evidence of linkage was reported in both our whole-genome screen [6] and the North American Spondylitis Consortium genome screen [7]. The peak of linkage on chromosome 19 in our genome screen was observed with the marker D19S420 [LOD (log of the odds) score 3.58], which is located 1.8 Mb from the TGFB1 gene. Strong evidence of linkage to chromosome 19 was also identified in a genome-wide scan for loci for susceptibility to inflammatory bowel disease (IBD) [8], a disease that is clinically associated with spondyloarthritis.

TGF-β1 plays a crucial role in inflammatory processes, extracellular matrix synthesis, bone remodelling and fibrosis and may be important in the biological pathways related to the expression of AS [9]. TGF-β1 is profibrotic and is possibly also responsible for late-stage fibrosis and ankylosis. TGF-β1 acts in the formation and repair of cartilage and bone [10], which are the major targets of the immune response in AS. TGF-β1 promotes immunoglobulin A (IgA) class-switching in B cells. Increased levels of serum IgA against Gram-negative bacteria have been reported among AS patients [11–13]. AS is associated with an impaired Th1 cytokine profile [14], and TGF-β1 can inhibit the production of and response to cytokines associated with both Th1 and Th2 cells [15]. TGF-β1 suppresses the expression of class II MHC antigens induced by interferon-γ [16]. TGF-β1 has multiple suppressive actions on T cells, B cells and macrophages, and increased TGF-β1 production has been shown to inhibit autoimmune and chronic inflammatory diseases [17]. In animal models, systemic delivery of TGF-β1 or intramuscular injection of TGF-β1 plasmid inhibits acute and chronic arthritis [18]. We have...
investigated the effect of the positional and functional candidate gene *TGFB1* on susceptibility to and severity of AS in an English and a Finnish population.

**Patients and methods**

**Families with AS**

One thousand three hundred and thirty-three individuals from 212 parent–case trio families and 184 AS affected-sibling pair families were recruited from the UK. AS patients were identified from several sources: the Royal National Hospital for Rheumatic Diseases AS database; patients attending the Nuffield Orthopaedic Centre, Oxford; in response to public appeals; and by referral from British rheumatologists. Among the parent–case trios there were 31 parent–case affected pairs; other families were simplex, i.e. there was one affected subject in the family. There were 437 individuals in the 170 Finnish families recruited from the Rheumatism Foundation Hospital in Heinola, Finland. These included 12 affected sibling pairs, 11 parent–case affected pairs and 147 simplex families. Both the English and Finnish patients and families had been included in previous studies [6, 19, 20]. Patients who showed clinical evidence of primary AS and fulfilled the modified New York diagnostic criteria [21] were selected for the study. Sacroilitis was confirmed by a qualified radiologist and the diagnosis of AS was confirmed by a qualified rheumatologist. All the patients were >16yr old. Genomic DNA was prepared from peripheral venous blood by standard methods. A structured questionnaire was used to assess the presence of acute anterior uveitis (AAU), IBD, psoriasis and peripheral arthritis, age of symptom onset, age at diagnosis, disease duration and disease severity scores, including the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [22] and the Bath Ankylosing Spondylitis Functional Index (BASFI) [23]. The study protocol reported here was approved by research ethics committee boards in both England and Finland. All participants gave informed consent prior to enrolment.

**HLA B27, TGFB1 SNP and microsatellite genotyping**

We genotyped five polymorphisms located in the promoter and coding region of the *TGFB1* gene and three microsatellite markers flanking the *TGFB1* locus in families with AS. One thousand and seven individuals from 212 English and 170 Finnish families with AS were genotyped for all the five SNPs. Seven hundred and sixty-two individuals from 184 multiplex families with AS were typed for the two polymorphisms in the promoter region of the *TGFB1* gene and three microsatellite markers. SNP genotyping was performed using the polymerase chain reaction–sequence specific primer (PCR-SSP) method [24] (~800 G/A, −509 C/T, +869 T/C, +915 G/C and +1632 C/T). Positive and negative controls were included in all the reactions. The same positive controls were used in both the Finnish and the English data set and all ambiguous samples were repeated. HLA B27 was detected by the method described by Bunce et al. [25]. Families with an HLA B27-positive proband were included in the analysis.

Three microsatellites spanning 6.4 centimorgans (cM) around the *TGFB1* locus were genotyped: d19s421, d19s223 and d19s217. The microsatellites were amplified under optimized PCR conditions, and the PCR products were separated and detected by capillary electrophoresis using an ABI Prism 3700 genotyper (Applied Biosystem, Warrington, UK). Products were then sized and manual inheritance checks performed using Genotyper version 1.1 (PE Biosystem, Foster City, CA, USA) and Genescan version 2.1 (PE Biosystems).

**Statistical analysis**

Mendelian inheritance of markers was checked using the program GAS (version 2.0) [unpublished, A. Young]. The \( \chi^2 \) test for a 3 × 2 contingency table was used to examine whether the genotype frequencies were in Hardy–Weinberg equilibrium. \( P > 0.05 \) was accepted as indicating non-significant deviation from Hardy–Weinberg equilibrium. Association between *TGFB1* polymorphisms and disease susceptibility was studied with the transmission disequilibrium test (TDT) using the program Transmit (version 2.5) [26]. \( P \) values were obtained by statistical simulation using 1000 replicates, using the robust variance option to assess association independent of linkage. Non-parametric linkage analysis was performed using the program Genehunter-Plus for qualitative data [27] and Merlin-Regress for quantitative data [28]. Association was evaluated in a subset of families which showed a positive non-parametric linkage score. Association between *TGFB1* polymorphisms and the age of symptom onset, BASDAI and BASFI was assessed using the Quantitative Transmission Disequilibrium Test (QTDT) [29]. Population stratification and total evidence of association were assessed using QTDT. *TGFB1* haplotypes were constructed using the Phase program [30]. Mendelian inheritance of haplotypes was checked manually and only haplotypes which were constructed with >90% certainty were accepted for further analysis. These haplotypes were used as input for QTDT to assess the association between *TGFB1* haplotypes and the age of symptom onset, BASDAI and BASFI.

BASFI and BASDAI were correlated with disease duration and gender in this data set and were treated as covariates in the analysis. The association between the polymorphisms and the presence of AAU, peripheral arthritis or IBD was studied using the \( \chi^2 \) test. For the inter-ethnic comparison, the haplotypes were constructed using the program Transmit [26]. The pairwise linkage disequilibrium (LD) between the SNPs was calculated using Lewontin’s standardized disequilibrium coefficient \( D’ \) [31], calculated using the program HaploXT [32]. The program Entropy was used to identify the subset of SNPs that best approximates the haplotypic diversity in the population [www.well.ox.ac.uk/~rmott/SNPS]. The power of the study to detect association with susceptibility to AS was determined using TDT Power Calculator [33]. This program does not allow for missing parents in the data, and thus in our study gave an overestimate of the actual power.

**Results**

**Clinical description of the families**

The clinical characteristics of the AS patients are described in Table 1.

**Disease susceptibility**

Transmitted and untransmitted marker and SNP haplotype frequencies estimated using Transmit are given in Tables 2 and 3.

**TABLE 1. Clinical description of the AS patients**

<table>
<thead>
<tr>
<th></th>
<th>English AS</th>
<th>Finnish AS</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASFI</td>
<td>3.6 ± 2.7</td>
<td>3.7 ± 2.2</td>
</tr>
<tr>
<td>BASDAI</td>
<td>3.9 ± 2.1</td>
<td>5.2 ± 1.8</td>
</tr>
<tr>
<td>Age at symptom onset (yr)</td>
<td>22.4 ± 7.6</td>
<td>26.1 ± 8.0</td>
</tr>
<tr>
<td>Disease duration (yr)</td>
<td>22.0 ± 13</td>
<td>20.0 ± 10</td>
</tr>
<tr>
<td>Males, females (%)</td>
<td>381 (63), 224 (37)</td>
<td>122 (64), 70 (36)</td>
</tr>
<tr>
<td>AAU (%)</td>
<td>222 (37)</td>
<td>79 (52)</td>
</tr>
<tr>
<td>IBD (%)</td>
<td>38 (6.3)</td>
<td>10 (6.5)</td>
</tr>
<tr>
<td>Peripheral arthritis (%)</td>
<td>Not available</td>
<td>119 (76)</td>
</tr>
</tbody>
</table>

Data are mean (S.D.) or \( n \) (%).
By within-family analysis, a marginal association was noted between the rare TGFB1 +1632 T allele and AS in a Finnish population (4.2 vs 5.3\% , \( P = 0.04 \)) and in the combined data set (2.8 vs 3.7\% , \( P = 0.03 \)), but not in the English data set alone (1.7 vs 1.9\% , \( P = 0.79 \)). No association was noted between any other SNP or marker haplotype and AS.

Non-parametric linkage analysis and evaluation of association among the families showing linkage to the TGFB1 locus

The multipoint non-parametric linkage analysis using Genehunter Plus showed weak evidence of linkage centromeric to the TGFB1 locus. The highest LOD score was obtained 2 cM centromeric from the TGFB1 gene between the markers d19s421 and d19s223, the peak LOD score being 1.3 (\( P = 0.02 \)) at 63 cM from the p-telomere.

Ninety-six families showed a positive non-parametric linkage (NPL) score, but no association was detected between AS and TGFB1/C0800 or/C0509 polymorphisms among these families. TGFB1 +1632 C/T polymorphism, which showed a weak association, was not genotyped in the subgroup of families with a positive NPL score, because of the LD between this SNP and the promoter polymorphisms.

Disease severity results

Association was noted between age at symptom onset and TGFB1 polymorphisms in different populations, but this was not consistently observed in the three family collections. In the English parent-case trio families, association with age at onset was
noted for \( TGFB1 -509 \) (allele 2 associated with age of onset greater by 2.1 yr, \( P = 0.007 \)) and +1632 (allele 2 associated with age of onset greater by 4.2 yr, \( P = 0.05 \)), haplotypes of the promoter region variants –800/–509 (haplotype 1/1 associated with age of onset lower by 1.8 yr, \( P = 0.02 \); haplotype 1/2 associated with age of onset greater by 2.1 yr, 0.007), and haplotypes of the coding region variants +869/+915/+1632 (haplotype 1/1/1 associated with age of onset lower by 1.7 yr, \( P = 0.01 \); haplotype 2/1/1 associated with age of onset greater by 1.8 yr, \( P = 0.03 \); haplotype 2/1/2 associated with age of onset greater by 4.9 yr, \( P = 0.03 \)). The promoter region associations were not replicated in the English affected sibling pair families, and when all English families were analysed together no significant association was noted for \( TGFB1 -800 \) or –509 or their haplotypes. When we pooled English and Finnish families genotyped for the coding region polymorphisms, weak association was noted for \( TGFB1 +915 \) (allele 1 associated with age of onset greater by 2.5 yr, \( P = 0.01 \)) and +1632 (allele 2 associated with age of onset greater by 3.2 yr, \( P = 0.02 \)) variants, and haplotypes of coding region polymorphisms +869/+915/+1632 (haplotype 2/2/1 associated with age of onset lower by 2.3 yr, \( P = 0.05 \); haplotype 2/1/1 associated with age of onset greater by 4.2 yr, \( P = 0.006 \)). No significant association was observed with age of symptom onset in the Finnish families, although the data set was too small to provide adequate power to exclude a significant association, particularly of haplotypes.

No effect of population stratification on these associations was noted in the data set. No other associations were noted between quantitative traits and any of the polymorphisms. No linkage was noted in the data set. No other associations were noted between haplotypes.

**Table 4. Localization of SNPs and identification of haplotypes of the \( TGFB1 \) gene**

<table>
<thead>
<tr>
<th>Nucleotide</th>
<th>Alleles</th>
<th>Haplotype</th>
<th>–800</th>
<th>–509</th>
<th>+869</th>
<th>+915</th>
<th>+1632</th>
<th>Frequency n (%)</th>
<th>Frequency n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>G/A</td>
<td>C/T</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>English</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Finnish</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>G</td>
<td>C</td>
<td>T</td>
<td>G</td>
<td>C</td>
<td>1351 (0.52)</td>
<td>532 (0.62)</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>G</td>
<td>T</td>
<td>C</td>
<td>G</td>
<td>C</td>
<td>650 (0.25)</td>
<td>154 (0.18)</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td>A</td>
<td>C</td>
<td>T</td>
<td>G</td>
<td>C</td>
<td>208 (0.08)</td>
<td>51 (0.06)</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td>G</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>182 (0.07)</td>
<td>26 (0.03)</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td>G</td>
<td>C</td>
<td>C</td>
<td>G</td>
<td>C</td>
<td>52 (0.02)</td>
<td>5 (0.006)</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td>G</td>
<td>T</td>
<td>T</td>
<td>G</td>
<td>C</td>
<td>26 (0.01)</td>
<td>34 (0.04)</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td>G</td>
<td>T</td>
<td>C</td>
<td>G</td>
<td>T</td>
<td>52 (0.02)</td>
<td>26 (0.03)</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td>G</td>
<td>C</td>
<td>T</td>
<td>C</td>
<td>C</td>
<td>26 (0.01)</td>
<td>9 (0.01)</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td>G</td>
<td>T</td>
<td>T</td>
<td>G</td>
<td>T</td>
<td>0</td>
<td>9 (0.01)</td>
</tr>
</tbody>
</table>

Haplotypes with frequency greater than 1% are shown. There were 2598 haplotypes in the English cohort and 858 haplotypes in the Finnish cohort.

**Table 5. LD values between the SNPs for the combined data set**

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Ethnic group</th>
<th>–509 C/T</th>
<th>+869 T/C</th>
<th>+915 G/C</th>
<th>+1632 C/T</th>
</tr>
</thead>
<tbody>
<tr>
<td>–800 G/A</td>
<td>Finnish</td>
<td>0.88 (0.002)</td>
<td>0.88 (0.002)</td>
<td>0.41 (0.6)</td>
<td>0.39 (0.6)</td>
</tr>
<tr>
<td></td>
<td>English</td>
<td>0.79 (0)</td>
<td>0.87 (0)</td>
<td>1 (0.007)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>–509 C/T</td>
<td>Finnish</td>
<td>0.64 (0.02)</td>
<td>0.74 (0.02)</td>
<td>0.76 (0)</td>
<td>0.76 (0)</td>
</tr>
<tr>
<td></td>
<td>English</td>
<td>0.77 (0)</td>
<td>0.63 (0.008)</td>
<td>0.73 (0)</td>
<td>0.73 (0)</td>
</tr>
<tr>
<td>+869 T/C</td>
<td>Finnish</td>
<td>0.58 (0)</td>
<td>0.58 (0)</td>
<td>0.46 (0)</td>
<td>0.46 (0)</td>
</tr>
<tr>
<td></td>
<td>English</td>
<td>0.64 (0)</td>
<td>0.64 (0)</td>
<td>0.69 (0.0002)</td>
<td>0.69 (0.0002)</td>
</tr>
<tr>
<td>+915 G/C</td>
<td>Finnish</td>
<td>0.32 (0.7)</td>
<td>0.32 (0.7)</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td></td>
<td>English</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The table shows Lewontin’s standardized disequilibrium coefficient \( D' \) (\( P \) value). All calculations are based on 1 degree of freedom.
between the systemic sclerosis [39] and osteoporosis [40, 41]. An association of musculoskeletal diseases, including rheumatoid arthritis [38], and these diseases may share common underlying predisposing pathology as subclinical ileitis is found in 49% of patients with AS [37] and these diseases may share common underlying predisposing genes. Our study noted a weak association between the rare TGFB1 +1632 T allele and susceptibility to AS and age of symptom onset. However, the lack of association of TGFB1 promoter polymorphisms, which are in tight LD with the TGFB1 +1632 alleles, with AS in families with positive NPL scores at the locus indicates that these polymorphisms do not explain the observed linkage of chromosome 19 with disease susceptibility. It should be noted that the P values reported here are not corrected for the multiple comparisons involved, as the number of independent comparisons would be difficult to determine. However, the positive P values reported are unlikely to be significant if such correction is employed, and these findings will require further confirmation.

Polymorphisms of TGFB1 have been implicated in a variety of musculoskeletal diseases, including rheumatoid arthritis [38], systemic sclerosis [39] and osteoporosis [40, 41]. An association between the TGFB1 +869 CC genotype and both ossification of the posterior longitudinal ligament in the cervical spine and spinal osteophytosis has been reported in Japanese patients [42, 43]. No association between IBD or Crohn’s disease and osteophytosis has been reported in Japanese patients [42, 43]. However, LD varies drastically across the genome and these studies were limited to two chromosomal regions in the genome. To our knowledge, no studies investigating the disequilibrium between a Finnish and an English population at the TGFB1 locus have been conducted previously. Additionally, small LD differences, such as those observed in our study, especially within genes, may be relevant in the location of the causative disease-associated variants.

The TGFB1 gene consists of seven exons encompassing 23.5 kb on chromosome 19q13.1. Three SNPs in the promoter region, one insertion/deletion in the 5’ untranslated region, two SNPs in the signal peptide sequence, one SNP in intron 4 and one SNP in exon 5 have been identified previously [41, 50]. Polymorphism at positions +869 T/C and +915 G/C in the signal protein sequence of the TGFB1 gene change codon 10 (Leu[54-Pro]) and codon 25 (Arg[56-Pro]) respectively, and polymorphism in exon 5 at position +1632 C/T changes codon 263 (Thr[62-Ile]). We typed all the known polymorphisms in the TGFB1 gene except the −988 C/A, +72 insertion and 713–8delC [41]. The TGFB1 +72 insertion was not included in the study as it exhibits almost complete LD with the TGFB1 +915 polymorphisms [50]. TGFB1 −988 C/A and 713–8delC were excluded because their low frequency would make our current sample size inadequate to achieve required power [33].

Haplotypic analysis is usually more powerful than studying individual polymorphisms in LD mapping, and haplotype-based methods have recently contributed to the identification of genes for complex diseases [51–53]. During recent decades, haplotype-based analyses have commonly been used successfully in HLA genetics [54, 55]. We aimed to capture all the common variation within the TGFB1 locus and hence constructed haplotypes within this region. Two major haplotypes accounted for 79% of the total number of haplotypes in our data set. This conservation of haplotypes may be attributable to the fact that all the individuals in our study were of Caucasian origin, or it may suggest that selective pressure acts on this functionally important locus. We attempted to assess the diversity of this locus using the program Entropy. The promoter polymorphisms and the TGFB1 +869 T/C variant account for most of diversity at this locus and a relatively small increase in diversity is attributable to the rare variants TGFB1 +915 G/C and +1632 C/T. This observation enables targeted SNP selection in association studies of common complex diseases, where underlying disease causing variants are likely to be of relatively high frequency.

In vivo, TGF-β1 acts in combination with other peptide growth regulators, such as epidermal growth factor and its homologue TGF-α, platelet-derived growth factor and basic fibroblast growth factor. The synthesis, secretion, activation and tissue-specific expression of TGF-β1 are tightly regulated processes. Understanding of the true role of TGF-β1 in disease pathogenesis would require dissection of these interactions and the regulation of TGFB1. Other TGF-β isoforms, such as TGF-β2 and TGF-β3, and other related molecules, such as TGF-β receptors, latent TGF-β binding proteins and other regulatory molecules, may play a role in...
the pathology of AS. The latent TGF-\(\beta\) binding protein 4 gene and the fibroblast growth factor 22 precursor gene are located on chromosome 19 (19q13.2 and 19p13.3, respectively) and they are potentially interesting positional candidate genes in AS. Several polymorphisms have been found in the TGF-\(\beta\) III receptor gene [56], which could potentially affect TGF-\(\beta\) signalling. TGF-\(\beta\)2 mRNA has been detected in biopsy specimens from the sacroiliac joints of patients with AS, suggesting that TGF-\(\beta\)2 may play an active role in spondylitis [57]. TGF-\(\beta\)2 is abundantly present in the anterior chamber of the eye and could potentially be involved in the pathogenesis of AAA [58]. It is also likely that yet unknown gene–gene interactions or gene–environment interactions play a significant role in AS pathology. To study these issues would require a completely different study design.

It has been demonstrated that the plasma concentration of active and acid-activatable latent TGF-\(\beta\)1 is predominantly under genetic control (heritability estimate 0.54). The \(-509\) C/T promoter polymorphism in the \(TGFB1\) gene has been shown to be significantly associated with higher concentrations of TGF-\(\beta\)1, explaining 8.2% of the additive genetic variance in TGF-\(\beta\)/C12 concentration [59]. Furthermore, the polymorphisms at positions +869 T/C and +915 G/C in the signal protein sequence of the \(TGFB1\) gene, which change codon 10 (Leu\(^{10}\)-Pro) and codon 25 (Arg\(^{25}\)-Pro) respectively, have been reported to be related to variations in the production of TGF-\(\beta\)1 [35, 40]. However, it remains to be determined whether differences in the circulating concentration of TGF-\(\beta\)1 among individuals with different \(TGFB1\) genotypes affect the concentrations of the cytokine in the sacroiliac joints and entheses. The local effects of TGF-\(\beta\)1 in AS require further elucidation. TGF-\(\beta\)1 may have a promising therapeutic potential for AS, and our findings do not exclude a key role of TGF-\(\beta\)1 protein in the pathogenesis of AS. Our study suggests that \(TGFB1\) polymorphisms play a minor role in AS and do not explain the linkage of chromosome 19 to AS susceptibility.

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Conflict of interest

The authors have declared no conflicts of interest.

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