# Analysis of 6 Genetic Loci for Disease Susceptibility in Psoriatic Arthritis

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*ABSTRACT.* ***Objective.*** To analyze the association of several autoimmune disease susceptibility loci in a population of patients with psoriasis and defined joint disease from northern Sweden.

***Method.*** One hundred twenty patients with psoriasis and defined joint disease were examined clinically, radiologically, and with laboratory-based analyses. Disease classification was based on peripheral and/or axial engagement. The tumor necrosis factor (TNF) locus, 1q21 (PSORS4), 3q21 (PSORS5), 8q24, 16q21, and the CTLA4 gene were analyzed using a total of 38 microsatellite markers and 2 single nucleotide polymorphisms (SNP). Ninety-four controls with the same ethnic background as the patients were randomly selected from the same region of Sweden.

***Results.*** An association was found with one of the markers in the TNFB locus within the HLA region ($p = 0.012$, $p_c = 0.024$). Three markers at the PSORS4 locus on chromosome 1q21 and 2 markers at the 8q24 locus showed nominal p values of $< 0.05$. After applying the Bonferroni correction for multiple analyses these markers did not reach significance. No other marker showed significant association. In a subgroup of the patients, possible linkage disequilibrium between the TNFB123 and HLA-B antigens, B17, B27, B37, B44, and B62 was analyzed. A significant linkage ($p = 0.0001$) was found.

***Conclusion.*** We identified an association between psoriatic arthritis and one of the microsatellite markers within the TNFB locus at the HLA region on chromosome 6. Linkage disequilibrium between TNFB123 and certain HLA-B antigens was found. (J Rheumatol 2004;31:2230–5)

*Key Indexing Terms:*
PSORIATIC ARTHRITIS GENETIC LOCI ASSOCIATION TNFB MHC

Psoriatic arthritis (PsA), an inflammatory joint disease associated with psoriasis, is a heterogeneous disease with various patterns such as mild mono-oligoarthritis or very severe, erosive and destructive polyarthritis indistinguishable from rheumatoid arthritis (RA), or spondyloarthropathy with axial engagement[1]. The reported prevalence of PsA among patients with psoriasis varies between 7% and 40% in different studies[2-4]. In PsA, psoriasis in the skin usually precedes the onset of arthritis.

Genetic factors are believed to be of importance in the pathogenesis of autoimmune diseases such as PsA[5,6]. Genetic studies aimed at identifying disease susceptibility genes in PsA are relatively few, but there is a recent report from a genome scan linkage analysis[7]. In adjacent inflammatory diseases, i.e., psoriasis, RA, and ankylosing spondylitis (AS), linkage and association studies have been undertaken to identify potential susceptibility genes[8-11]. Based on these studies several disease susceptibility loci on different chromosomes have been proposed.

A region of interest that has been the major focus of most research in autoimmune diseases is the HLA region on chromosome 6[12]. In psoriasis, association with the Cw6 allele at the HLA-C locus[13] is the strongest and most reproducible association and is referred to as PSORS1 (MIM#177900)[14]. This association was confined to psoriasis with an early onset[15]. The situation in PsA is considerably more complex and genetic studies have shown associations with several HLA antigens including HLA-B13, B17, B27, B38, B39, Cw6, DR4, DR7, and DQ3[16-20]. Association with PsA has also been found with the MICA-A9 triplet repeat polymorphism and with polymorphisms in

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the tumor necrosis factor alpha (TNFA) region, which are located within the MHC region[21,22]. Disease association with the TNF region of chromosome 6 has been established for RA[9,23-25] and AS[26-28].

T lymphocytes are believed to play an important role in the pathogenesis of PsA and have been located in psoriatic skin lesions as well as in the synovium of patients with PsA[29,30]. The cytotoxic T lymphocyte antigen 4 (CTLA4) is expressed on the surface of activated T lymphocytes and is important in the downregulation of the T lymphocyte response and T lymphocyte homeostasis, and in maintenance of peripheral tolerance. The CTLA4 gene region on chromosome 2q33 contains several polymorphisms. Associations between 2 of these, one SNP in position +49 and a dinucleotide (AT)n repeat in the 3' untranslated region (3'UTR), and susceptibility to RA have been found[31].

Another psoriasis susceptibility locus, PSORS5 (MIM#604316) on chromosome 3q21, was identified by Enlund, *et al*[32] in linkage and association analyses of families originating from southwest Sweden. In a genome scan, with stratification of families according to self-reported joint complaints, families with joint complaints showed linkage to 3q21 ($p = 0.004$)[33]. This locus has been further narrowed down to a 250 kb interval where an association with psoriasis was restricted to 5 SNP[34]. Additionally, this chromosomal region has been identified, by a genome scan, as a susceptibility locus for RA[9]. As a result of genome-wide linkage analysis, chromosome 1q21 (PSORS4)[35] and 8q24[14] have been suggested as susceptibility regions for psoriasis. The recent results from a genome scan show evidence for linkage between PsA and a marker on chromosome 16q21, with a LOD score of 4.19 in individuals with paternal transmission[7].

Based on the results of these studies on psoriasis, PsA, RA, and AS, we investigated association between several potential PsA susceptibility loci in a cohort of psoriatic patients with defined joint disease from northern Sweden. We performed our study with particular focus on analyzing the TNF locus, 3q21 (PSORS5), 1q21 (PSORS4), 8q24, 16q21, and the CTLA4 gene for microsatellite markers and SNP.

## MATERIALS AND METHODS

*Patients.* One hundred twenty patients with inflammatory joint disease and psoriasis, or a history of psoriasis, were included in this study based at the outpatient clinic of the Department of Rheumatology, University Hospital, Umeå. All patients were diagnosed by a dermatologist as having psoriasis of the skin, one of whom had pustulosis palmoplantaris. Peripheral arthritis was diagnosed when a swollen and tender joint with symptom duration of more than 6 weeks, located outside the spinal column and/or sacroiliac joints, was present. In 90 patients with peripheral arthritis, radiological examinations of the joints were performed and evaluated for erosions (≥ grade 2) according to the Larsen grading system[36]. The diagnosis of axial disease was based on radiological findings in the sacroiliac joints according to the New York criteria (≥ 2)[37] and/or syndesmophytes, ligamentous ossification, vertebral squaring, and shining corners of the spine[38]. The classification of the disease pattern was based on actual and/or previous findings of peripheral/axial engagement diagnosed by a rheumatologist and as reported in the hospital records. Twelve of the patients had a rheumatoid factor and 5 of them fulfilled the criteria for RA[39] as well. However, 2 of them had arthritis in the distal interphalangeal (DIP) joints and another 2 had enthesitis. Demographic data of the patients are presented in Table 1.

Ninety-four controls were randomly selected from a population register from the same part of Sweden and with the same ethnic background as the patients. The Regional Research Ethics Committee of Umeå University approved this study.

*DNA extraction.* Genomic DNA was extracted from the peripheral lymphocytes in 10 ml venous blood samples, anticoagulated with EDTA, using phenol-chloroform[40] or a modified salt-out method[41].

*Genotyping.* A total of 40 markers were analyzed. Information on these markers is given in Table 2. Eight markers were genotyped within the PSORS5 area on chromosome 3q21[32] (2 SNP and 6 microsatellite markers), 13 microsatellite markers within the PSORS4 locus on chromosome 1q21[35] over a distance of 9.91 Mb, 10 microsatellite markers within the psoriasis susceptibility locus on chromosome 8q24[14] over a distance of 5.6 Mb, and 6 microsatellite markers on chromosome 16q21 over a distance of 5.24 Mb. Within the HLA locus on chromosome 6, 2 microsatellite markers were genotyped, one within intron 1 of the TNFB gene (lymphotoxin alpha) and another located upstream to the TNFB gene. Finally, one microsatellite marker within the gene CTLA4 was genotyped[31].

All SNP were genotyped by Taqman fluorogenic 5' nuclease assays (Applied Biosystems, Foster City, CA, USA). Taqman primers and probes were designed using Primer Express software (Applied Biosystems). Taqman assays were performed according to the manufacturer's guidelines. The microsatellite markers were amplified by polymerase chain reaction (PCR) with optimized annealing temperature. PCR products were separated by electrophoresis on an ABI Prism 3100 Genetic Analyzer (Applied Biosystems) and on an ABI 377 (Applied Biosystems) according to ABI protocols. Genotyping was performed using Genescan Analysis 3.7/2.1 and Genotyper 3.7/2.0.

*Statistics.* The chi-square test was used for comparing allele frequencies between cases and controls. When the tables were sparse, the p values were estimated by simulation. For each of the regions the nominal p values achieved were subjected to Bonferroni correction using the number of markers tested for in that region. In regions where multiple markers were genotyped we tested for association to constructed haplotypes rather than single markers using the EHplus software[42]. EHplus was also used when testing for linkage disequilibrium and forming haplotypes in the HLA region. For the (AT)n repeat of CTLA4, the alleles were first dichotomized into repeat lengths ≤ 82 bp and > 82 bp in accord with the hypotheses of the existence of a functional cutoff value for short and long alleles[43].

## RESULTS

Results from the association study of 5 different loci and

*Table 1.* Demographic data for patients with PsA.

| | N = 120 |
|---|---|
| Mean age at inclusion, yrs ± SD | 47.3 ± 12.7 |
| Mean age at onset of skin disease, yrs ± SD | 26.2 ± 13.5 |
| Duration of skin disease, yrs ± SD | 21.8 ± 14.0 |
| Mean age at onset of joint/axial disease, yrs ± SD | 34.0 ± 12.6 |
| Duration of joint/axial disease, yrs ± SD | 13.8 ± 10.4 |
| Family history of skin disease, n (%) | 64 (53.3) |
| Peripheral arthritis, n (%) | 91 (75.8) |
| Axial disease, n (%) | 7 (5.8) |
| Peripheral and axial disease, n (%) | 22 (18.3) |

*Table 2.* Microsatellite markers and SNP on chromosome 3q21, 1q21, 8q24, TNFB region, 16q21, and the CTLA4 gene presented with location, Mbp, p, and corrected p ($p_c$).

| Marker | Location | Mbp | p ($p_c$) |
|---|---|---|---|
| B1551S3 (rs1554241) | PSORS5 (MIM#604316) | 125.41 | 0.53 |
| B1551S4 (rs702045) | PSORS5 | 125.42 | 0.52 |
| D3S1267 | PSORS5 | 119.77 | 0.24 |
| D3S1551[a] | PSORS5 | 125.42 | 0.63 |
| D3S1587 | PSORS5 | 127.71 | 0.77 |
| D3S1765[a] | PSORS5 | 130.41 | 0.59 |
| D3S3552[a] | PSORS5 | 131.23 | 0.61 |
| D3S1269[a] | PSORS5 | 131.57 | 0.93 |
| D1S2696 | PSORS4 (MIM#603935) | 147.41 | 0.63 |
| D1S2612 | PSORS4 | 149.70 | 0.97 |
| D1S2222 | PSORS4 | 150.09 | 0.12 |
| D1S498 | PSORS4 | 151.88 | 0.63 |
| D1S2347 | PSORS4 | 151.90 | 0.43 |
| D1S2343 | PSORS4 | 152.40 | 0.86 |
| D1S2858 | PSORS4 | 154.71 | 0.28 |
| D1S305[b] | PSORS4 | 154.95 | 0.03 (0.44) |
| D1S2140 | PSORS4 | 156.08 | 0.26 |
| D1S303 | PSORS4 | 156.13 | 0.04 (0.56) |
| D1S2624 | PSORS4 | 156.32 | 0.78 |
| D1S394 | PSORS4 | 157.00 | 0.05 (0.59) |
| D1S2777 | PSORS4 | 157.32 | 0.14 |
| D8S1813 | 8q24 | 128.4 | 0.02 (0.23) |
| D8S1801 | 8q24 | 131.0 | 0.23 |
| D8S1782 | 8q24 | 131.1 | 0.50 |
| D8S1732 | 8q24 | 131.3 | 0.03 (0.30) |
| D8S1701 | 8q24 | 131.5 | 0.76 |
| D8S1712 | 8q24 | 132.2 | 0.72 |
| D8S284[c] | 8q24 | 132.5 | 0.42 |
| D8S1765 | 8q24 | 132.7 | 0.09 |
| D8S557 | 8q24 | 133.7 | 0.70 |
| D8S558 | 8q24 | 134.0 | 0.54 |
| TNF (Accession ID: GDB: 185040) | PSORS1 #177900 | | 0.06 |
| TNFB (Accession ID: GDB: 182382) | PSORS1 | | 0.012 (0.024) |
| D16S267[d] | 16q21 | 63.23 | 0.17 |
| D16S3038 | 16q21 | 58.50 | 0.18 |
| D16S3089 | 16q21 | 60.60 | 0.09 |
| D16S3094 | 16q21 | 59.71 | 0.42 |
| D16S503 | 16q21 | 63.74 | 0.20 |
| D16S526 | 16q21 | 59.12 | 0.29 |
| CTLA4 (AT)n | CTLA4-gene (2q33) | | 0.32 |

[a] Associates in the original psoriasis study of families from Southwest Sweden[32]. [b] Gave the highest NPL value in the original psoriasis genome scan[35]. [c] Gave the highest NPL value in the original psoriasis genome scan[14]. [d] Gave the highest LOD score with paternal transmission in the study of chromosome 16q[7].

one candidate gene are presented in Table 2. Selection of these genetic loci was based on previously published susceptibility loci in psoriasis, PsA, and/or RA. At the HLA region, one of the 2 markers tested for, TNFB, showed an association with PsA (p = 0.012, $p_c$ = 0.024). The distribution of the TNFB alleles in patients and controls is presented in Table 3. When patients with PsA were stratified for TNFB alleles the association was confined to carrier of allele 123 (odds ratio, OR = 2.03, 95% confidence interval, 95% CI = 1.1–3.75).

Three markers at the PSORS4 locus on chromosome 1q21 within a region of 2.05 Mb, and 2 markers at the 8q24 locus within a region of 2.9 Mb, showed p values < 0.05. However, when corrections for multiple analyses were applied, these markers did not reach significance. No other marker showed any significant association regardless of single marker analysis or as part of constructed haplotypes for regions where multiple markers were genotyped (data not shown).

In a subgroup (n = 83) of the patients, previously HLA typed[44], we analyzed a possible linkage disequilibrium with the TNFB allele 123 and HLA-B antigens that we found increased in patients with PsA in that study: namely, HLA-B17, B37, B44, and B62[44]. HLA-B27 and Cw*0602 appar-

*Table 3*. The distribution of alleles of marker TNFB in patients and controls.

| Allele Size | 117 | 119 | 121 | 122 | 123 | 125 | Total |
|---|---|---|---|---|---|---|---|
| Patient | 0 | 16 | 26 | 90 | 101 | 3 | 236 |
| Control | 1 | 25 | 24 | 76 | 56 | 0 | 182 |

ently associated with PsA[16] were also analyzed for linkage disequilibrium. There was an overall significant linkage disequilibrium (p = 0.0001) between TNFB123 and HLA-B antigens B17 (D' = 1), B27 (D' = 0.45), B37 (D' = –0.10), B44 (D' = 0.46), and B62 (D' = 0.57). Between Cw*0602 and TNFB123 there was, however, no significant linkage disequilibrium (D' = 0.21; p = 0.35).

Haplotypes were estimated from this subgroup for the 3 genes HLA-C, HLA-B, and TNFB (Table 4).

## DISCUSSION

We analyzed genetic disease susceptibility loci in patients with psoriasis and defined joint inflammation. We investigated 6 different candidate susceptibility regions — the HLA region on chromosome 6p (PSORS1), 1p21 (PSORS4), 3q21 (PSORS5), 8q24, 16q21, and the CTLA4 gene on chromosome 2q33 — in patients with PsA. The candidate regions were chosen to test associations based on previously reported association or linkage studies in psoriasis, PsA, RA, and/or AS. We found an association with the HLA region with one of the 2 microsatellite markers analyzed within the TNFB region. The microsatellite marker detected 6 alleles (Table 3) and the association with PsA was confined to allele 123. Studies on PsA have shown association with TNFA[21,22]. Two studies, however, report an association between TNFB and psoriasis[45,46] in addition to an association study of TNFB with RA[23]. In order to explore the primary disease association of TNFB with psoriasis or PsA, separate patient groups representing each disease should be investigated.

The HLA region is characterized by high diversity and strong linkage disequilibrium. This could explain why different studies report association between PsA and different HLA antigens and/or loci. Alternatively, each genetic contribution of the HLA region in PsA is of minor importance compared with other autoimmune diseases. We examined a homogeneous population comprising patients and controls from northern Sweden with the same ethnic background. This population is very well suited for genetic association studies since it derives from a founder population and has been fairly isolated throughout history. Populations such as this probably have a linkage disequilibrium that stretches over a longer distance than in mixed populations. The association within the HLA region that we found is consistent with findings in other autoimmune diseases such as RA[9,23-25] and AS[26-28]. Although the association with the HLA region was not strong, it is in line with our previous findings among patients with psoriasis and defined joint disease[44]. In that study we were unable to verify the strong association with the HLA region (B and C antigens) described by others[16,47]. However, there were convincing linkage disequilibriums between TNFB123 and HLA antigens B17, B27, B37, B44, and B62, previously shown to be associated with PsA[16,44]. All patients carrying B17-TNFB123 or B37-TNFB123 also carry Cw6; these haplotypes constitute 7% of the patient haplotypes. However, none of the haplotypes with TNFB123 and B27, B44, or B62 carried Cw6. This latter group of haplotypes constitute up to 26% of the patients studied. Since TNFB123 showed linkage disequilibrium to at least 4 different B antigens we suggest TNFB123 is a more reliable marker for disease susceptibility or disease association in PsA than any of the HLA-B antigens.

*Table 4*. Estimated haplotype frequencies in patients for HLA-C, HLA-B, and TNFB.

| Cw | B | TNFB | Frequency, % |
|---|---|---|---|
| Any | Any | Non 123 | 54.7 |
| Non Cw6 | B27 | 123 | 10.5 |
| Non Cw6 | x | 123 | 8.6 |
| Non Cw6 | B62 | 123 | 8.0 |
| Non Cw6 | B44 | 123 | 7.4 |
| Cw6 | B17 | 123 | 5.4 |
| Cw6 | x | 123 | 3.4 |
| Cw6 | B37 | 123 | 1.9 |

x: Any allele but B17, B27, B37, B44, or B62.

PSORS5, on chromosome 3q21, is a psoriasis susceptibility locus described by members of our group based in Gothenburg[32], and a linkage with the region was noted in families with joint complaints in a linkage study[33]. We could not confirm those earlier findings in this study of patients with defined arthritis from northern Sweden. The lack of association is consonant with the hypothesis that PSORS5 is a psoriasis locus in patients originating from southwest Sweden[32].

Karason and coworkers have recently reported evidence for a PsA susceptibility locus on chromosome 16q, especially when associated with paternal transmission to affected individuals[7]. In our study we found no association between PsA and any of the examined markers on the chromosome 16q region, nor are we able to make definitive statements about any possible evidence for paternal transmission.

CTLA4 is an important surface molecule involved in the regulation of the T lymphocyte subset proposed to be involved in the pathogenesis of PsA. Several SNP markers have been reported to be associated with autoimmune diseases[31,48-50]. Recently, a SNP with a potential functional role in Graves' disease was identified[51]. In our study, we analyzed a dinucleotide repeat marker in the 3' untranslated

region of CTLA4 following the reported association of this marker with RA[31]. However, we found no such association indicating that CTLA4 is not involved in PsA susceptibility. In light of the recent findings for Graves' disease, the negative result in our study should be interpreted as an indication that no strong effect was found in the population examined. Further, before CTLA4 can be completely excluded from involvement in PsA, extended association analyses need to be performed on several patient cohorts from different populations.

Analysis of 2 other susceptibility loci described as being associated with psoriasis, i.e., PSORS4 (1q21)[35] and the 8q24 region[14], did not reveal any significant associations, indicating that these loci may be of less importance in PsA compared with psoriasis.

There has been considerable discussion as to whether PsA is a single clinical entity or a coincidental condition involving psoriasis and RA or AS. In some patients, especially those with symmetrical polyarthritis, PsA has a pattern similar to RA, while others have a disease pattern with dactylitis, DIP joint engagement, enthesitis, oligoarthritis, or axial involvement similar to seronegative spondyloarthropathies. It would have been interesting to stratify our patients for the heterogeneous disease pattern in our analyses. However, we were unable to subgroup the patients because such stratification would result in small sample sizes. Given that psoriasis and RA, or other autoimmune diseases, share a degree of clinical overlap with PsA, the existence of a common mutation or common genes with disease-specific mutations is an interesting hypothesis. Other genetic and/or environmental factors would then determine the disease-specific phenotypes. In this study we identified a weak association between PsA and the TNFB locus within the HLA region on chromosome 6, but no association with any of the other candidate loci analyzed. Since we have not investigated associations between TNFB and patient cohorts with psoriasis, AS, or RA, we are unable to conclude that this finding is unique for patients with PsA. However, our findings could be an indication that PsA differs from the other autoimmune diseases and is an entity in its own right.

In conclusion, we tested 6 chromosomal regions for association with PsA, 4 of which had not previously been analyzed in patients with defined PsA. We found an association with one microsatellite marker at the locus located within the HLA region on chromosome 6. Analyses of the other chromosome regions, i.e., PSORS4 (1q21), PSORS5 (3q21), 8q24, 16q21, and the candidate gene CTLA4 on chromosome 2q33, did not show association with PsA in our patients originating from northern Sweden. Autoimmune diseases are complex, with a substantial degree of heterogeneity. We can therefore expect that some disease loci are common to several autoimmune diseases, while other loci are disease-specific. The HLA region has been shown to be associated in a number of studies with autoimmune diseases. Our study has confirmed the involvement of a gene(s) in the HLA region for PsA also. The other loci investigated in this study could be disease-specific, thereby explaining the lack of association with PsA.

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