

Genetic studies of psoriasis and psoriatic arthritis

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Abstract

Psoriasis and psoriatic arthritis are common chronic immune-mediated diseases of the skin and joints. Psoriasis affects approximately 2-3 % of the Caucasian population and about 30 % of all psoriasis patients develop psoriatic arthritis. Both diseases have a strong genetic component but are also affected by environmental factors and are thus regarded as multifactorial. A major genetic factor contributing to susceptibility to both diseases is believed to reside at the HLA locus on chromosome 6, although different alleles within this locus have been found to associate with the respective diseases. While this is the strongest and most replicated locus, other susceptibility loci have also been identified through genome-wide linkage studies and candidate gene approaches.

The studies in this thesis aimed at refining two susceptibility loci for psoriasis identified with linkage analysis, 3q21 and 5q31-32, with a special emphasis on the PSORS5 region on chromosome 3q21. Another purpose was to investigate whether several autoimmune-associating genes and genomic regions are susceptibility factors for psoriasis/psoriatic arthritis.

Association studies on a psoriatic arthritis case-control material revealed an association with a marker in the TNFB locus within the HLA region. Linkage disequilibrium (LD) between TNFB123 and certain HLA-B antigens was also found. Due to the strong LD within this region, it is difficult to identify the disease-causing allele. No association was found with a microsatellite marker within the CTLA-4 gene, previously associated with rheumatoid arthritis (RA), nor with the eight genotyped markers within the PSORS5 region. This region was identified in a data set of southwestern Swedish families with psoriasis and arthritic symptoms. The lack of association is consonant with the hypothesis of a founder mutation in this region.

The 5q31-32 region was refined with 34 markers in multi-affected psoriasis families. We obtained a peak non-parametric linkage value of 3.1 for marker D5S436 in a subgroup of patients with arthritic symptoms. However, no association was found with 3 SNPs reported to associate with RA and Crohn's disease (CD) and to change the functional activity of 2 cation transporters, SLC22A4 and SLC22A5. These results support the existence of a susceptibility region for psoriasis on chromosome 5q32, probably involved in the arthritic phenotype and not caused by the 3 SNPs within SLC22A4 and SLC22A5.

Analysis of two candidate genes, CSTA and ZNF148, within the linkage region of PSORS5 yielded no significant association. It is therefore unlikely that they harbor the genetic cause of psoriasis at this locus. Fine-mapping of the PSORS5 region revealed both point-wise and haplotype associations that might contribute to psoriasis susceptibility. The only gene within this region was also slightly less expressed in skin biopsies from psoriasis plaque than from control individuals. Further genotyping studies are needed to relate the expression data to the associating genotypes, before a disease susceptibility allele can be identified.

Key words: psoriasis, psoriatic arthritis, complex disease, autoimmune disease, linkage analysis, association analysis, PSORS5, 3q21, 5q31-32, SLC12A8, SLC22A4, SLC22A5, CSTA, ZNF148, expression

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- I. Alenius GM, Friberg C, Nilsson S, Wahlstrom J, Dahlqvist SR, Samuelsson L. Analysis of 6 genetic loci for disease susceptibility in psoriatic arthritis. *J Rheumatol.* 2004 Nov;31(11):2230-5.
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