

Molecular Genetics of Psoriasis

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Abstract

Psoriasis is a chronic inflammatory skin disease. Based on family studies, a strong genetic component exists in the etiology of psoriasis, but environmental factors are also needed to trigger the disease onset. Both linkage and association analyses have assigned the major locus for psoriasis susceptibility, PSORS1, to 6p21.3 in all populations studied. The PSORS1 locus has been narrowed down to an approximately 200 kb region in the centromeric part of the MHC class I region.

In this study, a novel candidate gene at the PSORS1 locus, HCR (Pg8), was cloned and found to be highly polymorphic. In a large trio family material from seven different populations, a specific allele of the HCR gene, HCR*WWCC, was shown to be strongly associated with chronic plaque psoriasis (PV). However, two previously identified susceptibility alleles of the locus, HLA-Cw*6 and CDSN*5, showed a similar association. These three

susceptibility alleles were found to belong to the same extended susceptibility haplotype and their separation was not possible even with a sample size of almost 1700 chromosomes.

The three PSORS1 susceptibility alleles were also studied in two clinical variants of psoriasis, guttate psoriasis (GP) and palmoplantar pustulosis (PPP), to see whether the locus was involved in the pathogenesis of subtypes and whether

these could be used to differentiate the three alleles. GP was shown to have a similar but even stronger association with PSORS1 susceptibility alleles than PV, however, it did not help in separating the three genes. PPP was not associated with any of the PSORS1 alleles, suggesting a different etiology or molecular mechanism than for PV or GP.

Functional evidence for HCR as a potential psoriasis gene was also gained. Expression of the HCR mRNA



Kati Asumalahti defended her thesis on April 3, 2003 in Helsinki Medical Faculty. Faculty Opponent was James T. Elder, MD, PhD, Professor of Dermatology, Department of Dermatology, University of Michigan, Michigan, USA and Supervisor has been Professor, Juha Kere, MD, PhD, Department of Biosciences at Novum and Clinical Research Center, Karolinska Institute, Sweden and Department of Medical Genetics, University of Helsinki

and protein was altered in the keratinocytes of lesional psoriatic skin compared with non-lesional psoriatic and normal skin. In addition, the HCR*WWCC allele was predicted to adopt an altered secondary structure compared with the wild-type allele, which could affect the antigenic properties of the protein.

The PSORS1 locus is estimated to account for 30-50% of familial psoriasis, thus other susceptibility loci likely exist. In genome-wide linkage analyses, several minor putative psoriasis susceptibility loci have been identified (PSORS2-7), but similar to other complex diseases, most of them have not been replicated in subsequent studies in

different populations. In this study, a genome-wide scan in Finnish psoriasis families not associated with PSORS1 was performed to find other susceptibility loci. A minor susceptibility locus for psoriasis was mapped to 18p. The 18p locus has previously been suggested as a susceptibility locus for psoriasis in a British population. Taken together, these two mapping results yield sufficient evidence to name 18p as a new candidate locus for psoriasis.

List of original publications

This thesis is based on the following original publications.

- I Asumalahti K, Laitinen T, Itkonen-Vatjus R, Lokki M-L, Suomela S, Snellman E, et al. A candidate gene

for psoriasis near HLA-C, HCR (Pg8), is highly polymorphic with a disease-associated susceptibility allele. *Human Mol Gen* 2000; 9: 1533-1542.

- II Asumalahti K, Veal C, Laitinen T, Suomela S, Allen M, Elomaa O, et al. Coding haplotype analysis supports HCR as the putative susceptibility gene for psoriasis at the MHC PSORS1 locus. *Human Mol Gen* 2002; 11: 589-597.
- III Asumalahti K, Ameen M, Suomela S, Hagforsen E, Michaëlsson G, Evans J, et al. Genetic analysis of PSORS1 distinguishes guttate psoriasis and palmoplantar pustulosis. *J Invest Dermatol* (in press).
- IV Asumalahti K, Laitinen T, Lahermo P, Suomela S, Itkonen-Vatjus R, Jansen C, et al. Psoriasis susceptibility locus on 18p revealed by genome scan in Finnish families not associated to PSORS1. (Submitted).