

The Genetics of Psoriasis – Selected Novelties in 2008

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SUMMARY The genetic background of psoriasis is clearly demonstrated by the familial occurrence, data from epidemiological studies, twin studies, and results of genome-wide scan investigations. In the last years, molecular genetics analyses have permitted new insights into psoriasis. A number of studies indicate the likely genomic location of psoriasis susceptibility genes and suggest their possible identity and function. According to current concepts, psoriasis is caused by the interplay of multiple genes and different trigger factors, and the disease is classified in the group of genetically “complex” diseases. The first associated locus (PSORS1) resides within the HLA region (6p21.3). Strong association of HLA-Cw6 allele at this locus was first reported in Finnish population over 26 years ago. However, the exact location of PSORS1 gene remains controversial due to extensive linkage disequilibrium across the region. Two genes lying within this interval have been intensively studied with respect to their role in psoriasis susceptibility: HCR and corneodesmosin (CDSN). The precise location of PSORS 1 is under intense screening. Other candidate loci identified by genetic linkage research include PSORS 2 (17q25), PSORS 3 (4q34), PSORS 4 (1q21), PSORS 5 (3q21), PSORS 6 (19p13), PSORS 7 (1p32), PSORS 8 (16q) and PSORS 9 (4q31). Despite a large body of new data, the extent of genetic heterogeneity and the role of environmental triggers and modifier genes have not yet been clarified. The isolation of novel susceptibility genes will provide an insight into the precise pathways that control the disease. Such pathways will also reveal additional candidate genes that can be tested for molecular alterations resulting in the disease.

KEY WORDS: psoriasis, genetics

Psoriasis is a chronic inflammatory skin disease affecting about 2% of white European and North American population. The disease is clinically and histologically characterized by hyperproliferation and abnormal differentiation. The disorder is mediated by T cells, dendritic cells and inflammatory

cytokines (1). The existence of genetic contribution in psoriasis is well accepted. Previous twin studies in psoriasis report that concordance of the disease in monozygotic twins is much higher than in dizygotic twins, being approximately 72% and 15%-23%, respectively, for northern European in-

dividuals. These results indicate that genetic components play a role in predisposition to psoriasis and it is estimated that the heritability is between 60% and 90% (2). During the past twelve years, several genetic scans of the genome have been carried out with DNA samples from families with psoriasis, to localize genes that confer susceptibility to psoriasis (3). This has led to identification of at least 19 different psoriasis-susceptibility loci. But, few of the genes within these loci have been identified and their association with psoriasis has not been always replicated in studies of other populations. A clear inheritance model is not known. Geneticists classify psoriasis in the group of genetically 'complex' diseases, together with diabetes mellitus, rheumatoid arthritis, etc. The first associated locus (PSORS1) on chromosome 6p21.3 is the only locus that has consistently been identified in genetic investigations of families with psoriasis in several populations (4-8). On the basis of a decade of genome-wide linkage scans, PSORS1 is the strongest susceptibility locus detectable by family-based linkage studies, accounting for one-third to one-half of the genetic liability to psoriasis (9). The strong association of HLA-Cw6 and psoriasis that was initially reported in Finnish population patients with psoriasis (10) is now thought to be due to linkage disequilibrium with the nearby variant. Linkage disequilibrium describes the tendency for particular alleles at two or more loci to be inherited together more often than would be predicted by chance. The exact location of PSORS1 is not established. Elder *et al.* (11) identified over 60 ancestral haplotypes across the MHC and then found the shortest region common to different risk haplotypes. This region is extending for 300-kb telomerically from (but not including) HLA-B, including HLA-C, HCG27, PSORS1C3, OTF3, TCF19, SPR1, SEEK1, HCR, CDSN, STG and HCG22 genes. According to data from German and US population with psoriasis, PSORS1 lies within a 60-kb region which is telomeric to the HLA-C region that is known as risk haplotype 1 (RH1) (12), and in a gene encoding endogenous retrovirus (RVK). Although PSORS1 has been the only locus for psoriasis in all genetic studies to date, its estimated penetrance is less than 15%, indicating that other genetic/environmental factors may also contribute to the liability to the disease. According to current concepts, psoriasis is caused by the interplay and epistasis of multiple genes and different trigger factors (13). The identification of these factors will be important to understand the full contribution of PSORS1 to the susceptibility to psoriasis. PSORS2 on chromosome 17q25

was the first identified non-MHC locus that confers susceptibility to psoriasis. Tomfohrde *et al.* were the first to identify this locus (14). Evidence from other linkage studies on a single large pedigree in Taiwan and Israeli Jewish Moroccan families replicated those linkage findings, mapping this psoriasis susceptibility locus to the distal end of chromosome 17q (15,16). Chromosome 17q25 is likely to carry at least three psoriasis susceptibility variants: two low-penetrance loci (*SLC9A3R1* and *NAT9*) and one high-penetrance locus (*RAPTOR*) (1). Epidermal differentiation complex (EDC) on chromosome 1q21 (*PSORS4*) spans more than 2 Mb and contains several genes involved in epidermal differentiation. Association of chromosome 1q21 with psoriasis was first described in a set of Italian families (17) and also in several families from the United States (18). Chromosome 3q21 (*PSORS5*) was first investigated in Swedish population. *SLC12A8* gene within *PSORS5* locus was the first gene that was proposed to be associated with psoriasis and it was identified in patients with psoriasis in Swedish population (19). Chromosome 4q28-q31 has continued to be of interest with respect to psoriasis. Although the effects of this locus are relatively weak, it is detected consistently in many genome-wide scans of families from both Europe and Han Chinese population (20).

OVERLAP OF PSORIASIS LOCI WITH OTHER INFLAMMATORY AND AUTOIMMUNE DISEASES

Psoriasis is an inflammatory disease that strongly depends on the cellular immune system activation (13). It is not clear whether it is an autoimmune disease with reactivity to self-antigens. There is an overlap with a number of other autoimmune diseases like Crohn's disease, inflammatory bowel diseases, diabetes and multiple sclerosis. This overlap is seen at the level of altered biochemical pathways and with respect to the locations of putative loci (13).

Genes that have been shown to be shared nearly always encode products that regulate immune system and include *PTPN22*, *SUMO4*, *TNF- α* , and *IL-12B/IL-23 R*. The *PTPN22* gene encodes the protein lymphoid tyrosine phosphatase (Lyp), which has an N-terminal phosphatase domain and a long C-terminus with many proline-rich motifs. The R620W polymorphism in *PTPN22* is associated with several immune-mediated diseases including rheumatoid arthritis (21).

GENETICS OF PSORIASIS IN THE LAST YEAR: WHAT'S NEW?

Searching the Medline database 2008 for the topic of 'genetic aspect of psoriasis' resulted in a number of bibliographic items.

Alteration of the p16INK4a gene by epigenetic changes has been described in some hyperproliferative diseases. Its importance in psoriasis has not been established. Chan *et al.* (22) investigated the methylation status of the p16INK4a gene in psoriatic epidermis, its clinical significance and possible epigenetic mechanisms of psoriasis. The authors conclude that methylation of the p16INK4a gene promoter is found in psoriatic epidermis, which is associated with the mRNA level of p16INK4a expression and activity of the disease. The data obtained indicate that methylation of p16INK4a promoter may play a potential role in the pathogenesis of psoriasis.

It is known that psoriatic patients with the early onset disease (type I) usually have a strong genetic component to the disease. Smith *et al.* (23) investigated the role of the protein tyrosine phosphatase nonreceptor type 22 (PTPN22) gene region for susceptibility to type I psoriasis. Thirteen single nucleotide polymorphisms (SNPs) mapping to PTPN22 region were genotyped in 647 patients with psoriasis type I and 566 normal controls. This study demonstrated association of two SNPs (rs1217414 and rs3789604) in the PTPN22 region with type I psoriasis, providing evidence for a role of this gene in type I psoriasis. A group of authors from Bangkok, Thailand (24) investigated association of the interleukin-10 distal promoter (-2763A/C) polymorphism in patients with late onset psoriasis. There were no significant differences in the allele frequencies of any of the four SNPs between patients with psoriasis. However, the frequency of the -2763A allele was increased in patients with late onset psoriasis compared with controls and patients with early onset psoriasis. The authors conclude that the -2763A allele and extended AAGC haplotype can be used as genetic markers for susceptibility to late onset psoriasis in Thai population.

Very interesting is the article by Capon *et al.* (25). They carried out a genome-wide association scan and analyzed more than 408,000 SNPs in an initial sample of 318 cases and 288 controls. Outside of MHC, they observed a single cluster of disease-associated markers spanning 47 kb on chromosome 20q13. They identified ZNF313/RNF114 as a novel psoriasis susceptibility gene

with a putative role in the regulation of immune response. Real-time polymerase chain reaction (PCR) experiments showed ZNF313 to be abundantly expressed in the skin, T-lymphocytes and dendritic cells.

Chang *et al.* (26) investigated association between P478S polymorphism of the filaggrin gene and risk of psoriasis in a Chinese population in Taiwan. Filaggrin (*FLG*) is a key protein that facilitates terminal differentiation of the epidermis. The results of this study suggest that *FLG* P478S polymorphism may confer susceptibility to the development of psoriasis in the Chinese population in Taiwan.

Baran *et al.* (27) from Poland investigated association between IL-6 and IL-10 SNPs and susceptibility to psoriasis vulgaris. No significant differences were found in the polymorphisms of IL-6 and IL-10 promoter genes between patients with psoriasis and healthy controls.

Yang *et al.* (28) mapped a psoriasis-susceptibility gene to a 3.8 Mb of the 17q terminus in five generations of a Chinese family with autosomal-dominant psoriasis. To identify the mutations responsible for psoriasis in this family, the authors sequenced 78 genes in this region and found four gene variants co-segregating with psoriasis. This report suggests that ZNF750 mutations could contribute to psoriasis susceptibility.

A very interesting investigation of the polymorphisms of IL12B and IL23R genes comes from Nair *et al.* (29). Several lines of evidence have recently converged to suggest that IL-23 might play a particularly important role in the immunopathogenesis of not only psoriasis but also of Crohn's disease and other inflammatory diseases. Nair *et al.* (29) examined four SNPs for association with psoriasis in two groups of North American and German Caucasians: 1810 cases, 2522 controls and 509 pedigrees. Both IL12B markers showed highly significant association with psoriasis in the case-control and family based analysis. The IL23R SNPs also showed significant association in both cases and controls. For both genes common risk haplotypes were identified whose statistical significance approached (IL23R) or exceeded (IL12B) genome-wide criteria. These results confirm association between IL12B and IL23R and psoriasis in Caucasian population and provide a genetic basis for clinical association between psoriasis and Crohn's disease.

Garcia *et al.* (30) also examined IL-23R. The aim of this study was to better characterize the

IL23R psoriasis association. They used a fine mapping strategy to identify 59 additional IL23R linked SNPs which were genotyped in their three independent, white North American sample sets (2800 individuals). A sliding window of haplotype association demonstrates colocalization of psoriasis susceptibility effects within the boundaries of IL23R across all sample sets, and decreasing the likelihood that neighboring genes, particularly IL12RB2, are driving the association of this region. Additional work on haplotypes identified two 5-SNP haplotypes with a strong protective effect. Furthermore, this work is essential for the role of IL23R genetics in response to pharmacotherapy.

Baran *et al.* (31) investigated association between interferon gamma (IFN- γ) promoter gene SNP in position 874 and susceptibility for psoriasis vulgaris in a group of 76 patients. Control group consisted of 76 healthy volunteers. According to the results of this study, IFN- γ polymorphism is associated with psoriasis vulgaris.

Sun *et al.* from China (32) investigated three suggested psoriasis susceptibility loci at 2p22.3-11.2, 13q21-32 and 17.q22-25.3 in a Chinese population. This study indicates that 2p22.3-11.2 is a novel psoriasis susceptibility locus in Chinese Han population and confirms that psoriasis is a genetically heterogeneous disease.

Wang *et al.* from China (33) investigated MCP-1 as an important CC-type chemokine responsible for monocyte and T-lymphocyte recruitment in psoriasis. A SNP of the MCP-1 gene in the gene regulatory region was found to be related to the expression of MCP-1, and the associations of this polymorphism with many inflammatory diseases were confirmed in this study. The authors examined this polymorphism in 597 patients with plaque psoriasis and 530 healthy controls using the PCR restriction length polymorphism method. They also tested serum MPC-1 level. Results of this study showed the -2518 MPC-1 polymorphism to be related to susceptibility to plaque type psoriasis. Individuals with GG or AG genotypes were at a higher risk of psoriasis than those with AA genotype.

Hollox *et al.* (34) analyzed the genomic copy number polymorphism of the beta-defensin region on chromosome 8 in 179 Dutch psoriasis patients and 272 controls, and in 319 German psoriasis patients and 315 controls. Comparisons in both cohorts showed significant associations between a higher genomic copy number of beta-defensin gene and the risk of psoriasis. The antimicrobial and proinflammatory nature of beta-defensins

suggest that quantitative variation in gene dosage might contribute to susceptibility to infectious and inflammatory diseases.

Very interesting is a new hypothesis of French authors (35) on the genetics of psoriasis and other "complex" diseases. According to this hypothesis, the occurrence of psoriasis could be linked to an abnormal activation of one or more endogenous retroviral element copies due to their location and/or modification of their sequence.

After this presentation of new data in the field of the genetics of psoriasis, we can presume that future research will focus on elucidating the crucial pathogenetic relationship between psoriasis susceptibility genes, the gene transcripts that are expressed and cellular lines which initiate and perpetuate psoriasis.

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