

The MHC Genes in Psoriasis

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Abstract: Psoriasis is a common, immunologically-mediated, inflammatory and hyperproliferative disease of the skin and joints. Available evidence indicates that a major psoriasis gene (PSORS1) resides in the major histocompatibility complex (MHC), and that several additional psoriasis susceptibility genes reside elsewhere. Identification of the PSORS1 gene has been hampered by the existence of strong linkage disequilibrium (LD) in the MHC. Because it is not possible to rely on p-values associated with single alleles or short haplotypes, we and others have addressed this problem by assessing the risk associated with long “ancestral haplotypes” vs. their recombinant descendant haplotypes (recombinant ancestral haplotype mapping). Utilizing this technique, two different groups have identified a haplotype containing HLA-Cw6, “allele 5” of corneodesmosin (CDSN), and specific alleles at six intervening genes as the most likely location for PSORS1. Recently, a multicenter collaboration has been formed to identify which of the genes (or regulatory elements) on this haplotype is the “true” susceptibility allele. This collaboration is essential, as the number of informative recombinants is small due to the proximity of the genes in question. It will also be important to entertain the possibilities that multiple genes on the same haplotype influence risk, and that multiple distinct MHC alleles/haplotypes can influence risk (allelic heterogeneity). A collaborative approach involving very large numbers of families and/or cases and controls is the best way to address both of these critical questions.

Key Words: HLA antigens, major histocompatibility complex, linkage, association.

INTRODUCTION

Psoriasis is characterized by complex alterations in epidermal growth and differentiation, multiple biochemical, immunological, inflammatory, and vascular abnormalities, and a poorly-understood relationship to nervous system function [1]. Many observations suggest that psoriasis is a T-cell-mediated disease with a T1-dominated cytokine profile, driven by a positive feedback loop from activated T-cells to antigen-presenting cells that is mediated by interferon- (IFN-) and tumor necrosis factor- (TNF-). The cause of psoriasis remains unknown.

The rationale for considering psoriasis to be a genodermatosis has been reviewed in detail [2]. Substantial genetic epidemiologic data [3] and multiple genome-wide linkage scans [4-11] strongly support an oligogenic model of inheritance, with a major susceptibility locus (PSORS1, psoriasis susceptibility 1 [12]) residing within the major histocompatibility complex (MHC). However, whole-genome screens in psoriasis and other common human diseases have produced inconsistent results [13]. An oligogenic model provides a plausible explanation for this inconsistency. If alleles at multiple loci are required to develop disease in any given individual, then the frequency of each disease allele is likely to be substantial in order to yield an overall prevalence of up to 2%. Indeed, there are now several multifactorial

disorders in which the prevalence of a disease allele is quite high (20-80% range) [14-16]. These common disease alleles probably arose early in the history of modern humans [17]. This is widely known as the “common variant-common disease” hypothesis [18]. Low penetrance and high frequency of disease alleles are considered to be the two main reasons why “old” disease alleles have been difficult to identify by linkage [19]. On the other hand, tests of association are more powerful than tests of linkage, when the genes being sought are relatively common and of relatively low effect [20]. As the common variant-common disease hypothesis fits well with available HLA association data in psoriasis, it is not surprising that some of the most rewarding attempts to fine-map PSORS1 have made use of association, rather than linkage (see below).

The MHC is the home of the genes encoding human leukocyte antigens (HLA). HLA associations in psoriasis have been recognized for over 35 years [21]. The strongest HLA associations that we identified in early-onset, familial psoriasis were HLA-Cw6, -B57, and -DQ9 [22], all of which belong to the extended MHC haplotype EH57.1 [23]. Psoriatic arthritis (PsA) is also associated with HLA-Cw6, particularly in those with early-onset disease [24, 25]. The association of psoriasis with the EH57.1 extended haplotype is consistent with the presence of one or more disease alleles on a chromosome carried in the founders of the modern-day European population ~ 40,000 years ago [26]. Earlier studies localized the disease determinant to the Class I end of this haplotype [22, 27]. However, there are many genes in the MHC Class I region, and they exist in tight linkage disequi-

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librium (LD) with each other. Proving which of them is the true disease allele has been a challenge. To address this problem, we and others have performed recombinant ancestral haplotype mapping in the MHC (see below).

Several studies have documented a strong association between psoriasis and an MHC Class I haplotype that is common in Japan and Thailand (HLA-A*0207, -B*4601, -Cw*01) [28-32]. This haplotype, which is rare in Caucasians, was associated with psoriasis when found in *cis* to any of three HLA Class II haplotypes [29]. These findings suggest that the psoriasis determinant also resides on the Class I end of these chromosomes. Choonhakarn *et al.* found that the distribution of HLA risk haplotypes differed between early- and late-onset psoriatics, with the latter group being characterized by a greater proportion of Cw1-B46 haplotypes [29]. In 95 patients with age of onset < 40 years, 41% of MHC risk haplotypes carried HLA-Cw6, and 59% carried Cw1-B46. In 45 patients with age of onset ≥ 40, only 25% of risk haplotypes carried HLA-Cw6, and 75% carried Cw1-B46. HLA-Cw1 has not been consistently associated with cutaneous psoriasis when found in *cis* with other HLA-B alleles (e.g., HLA-B27). Together, these observations suggest that HLA-B46 might be the causative allele on this haplotype, and that HLA-B46 might confer a different age-at-onset distribution. This data indicates that we must be prepared to accept the existence of genetic heterogeneity at PSORS1.

The transmission disequilibrium test (TDT) [33] has been a preferred method for assessment of LD because it controls for population stratification (an artifact in which cases and controls are inadvertently drawn from different populations). While it is well-recognized that case-control analysis can be confounded by population stratification [34], others argue that this is a problem only under rare circumstances [35]. Moreover, methods have been developed such that sets of markers distributed across the chromosomes can be used to determine whether stratification is present, and, if necessary, to control for it [36, 37]. In the TDT, two parents need to be ascertained for each proband, whereas only one or fewer controls need be ascertained per case in case-control studies. It is therefore easier and less expensive to conduct a case-control study.

Haplotype mapping is of great value in association studies. Haplotypes produce “signatures” that come closest to matching the history of the disease chromosome, and therefore have the most power to detect the disease allele. Moreover, we have shown that fine mapping of disease genes in regions of strong LD (such as the MHC) may be

critically dependent upon the identification of informative recombinant ancestral haplotypes arising after the formation of the disease allele ([38], and see below). However, a critical question is how well haplotypes can be estimated from case-control populations, because any inaccuracies in haplotype assignment may lead to errors in the correct inference of recombinant ancestral haplotypes. Recently, methods have been developed whereby haplotypes can be estimated with high accuracy, especially when marker density is high and the study population is large [39]. Therefore, it would appear that case-control sampling will be a preferred method not only for additional fine mapping of the MHC, but also for non-MHC loci.

FINE MAPPING OF PSORS1

To fine-map PSORS1 in early-onset PsV, we performed an association analysis on 339 families using 62 physically mapped microsatellite markers spanning the MHC [38]. Using the TDT to analyze individual markers, significant LD was observed across most of the MHC. However, the strongest evidence of association was found in a ~300 kb region extending from MICA to corneodesmosin (CDSN). Haplotypes composed of 34 microsatellite markers spanning 1.2 Mb of the central MHC were clustered using a hierarchical method implemented in SYSTAT. Clusters were then tested for risk using the TDT. This analysis identified six risk clusters for which T (# transmissions) + NT (# non-transmissions) = 10 and % T = 60%. These risk clusters shared a haplotype of 8 markers, corresponding to a 60 kb fragment of ancestral haplotype 57.1. We named this risk haplotype 1 (RH1). The location of this haplotype with respect to known genes in the region is shown in Fig. 1. Sixty-one % of the affected individuals in our sample carried RH1, and therefore in all probability carry the same disease allele at PSORS1.

We recently performed linkage analyses across the MHC that were weighted by the presence or absence of RH1 (Fig. 2). Using either of two weighting schemes, the results indicated that essentially all the linkage information was contained in the RH1-positive individuals. This argues against marked allelic heterogeneity at PSORS1 in our sample.

One of the RH1-positive risk haplotypes, denoted “cluster 17”, did not carry HLA-Cw6. It also differed from the remaining risk chromosomes across much of the interval labelled “RH2” in Fig. 1. Therefore, cluster 17 played an important role in defining the shortest haplotype that appeared to carry risk. However, the TDT p value for cluster 17 was only of borderline significance (T:NT = 21:10, TDT

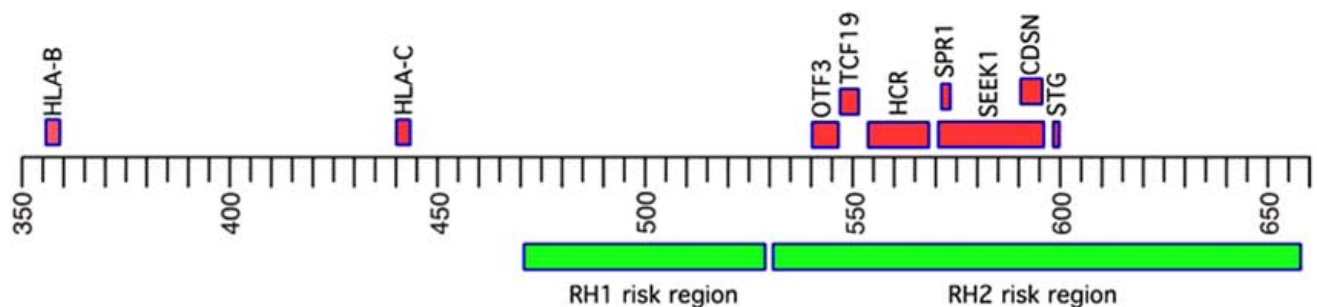


Fig. (1). Map of the RH1 and RH2 regions with respect to known genes. Map coordinates are zeroed on the microsatellite marker D6S273.

p value = 0.048). In order to better assess the significance of this result, we have performed a multicenter collaboration to type a single marker (M6S161) for which one allele (249 nt) was unique to cluster 17. Each center performed its own genotyping. Our original study was based on 509 families yielding 2,182 founder chromosomes. The collaboration typed 1,242 additional families, yielding 5,091 founder chromosomes. The data were analyzed using the pedigree disequilibrium test (PDT). Our analysis indicates that whereas our original sample yielded 60.9 % transmission, $p = 0.041$, the replication sample yielded only 49.2 % transmission, $p = 0.99$, and the combined sample yielded 54.6% transmission, $p = 0.18$ (J. Invest. Dermatol. Manuscript in press). Based on these results, we believe that cluster 17 is unlikely to be a risk chromosome. This is an important result, because it puts HLA-Cw6 back on the list of candidate genes for PSORS1.

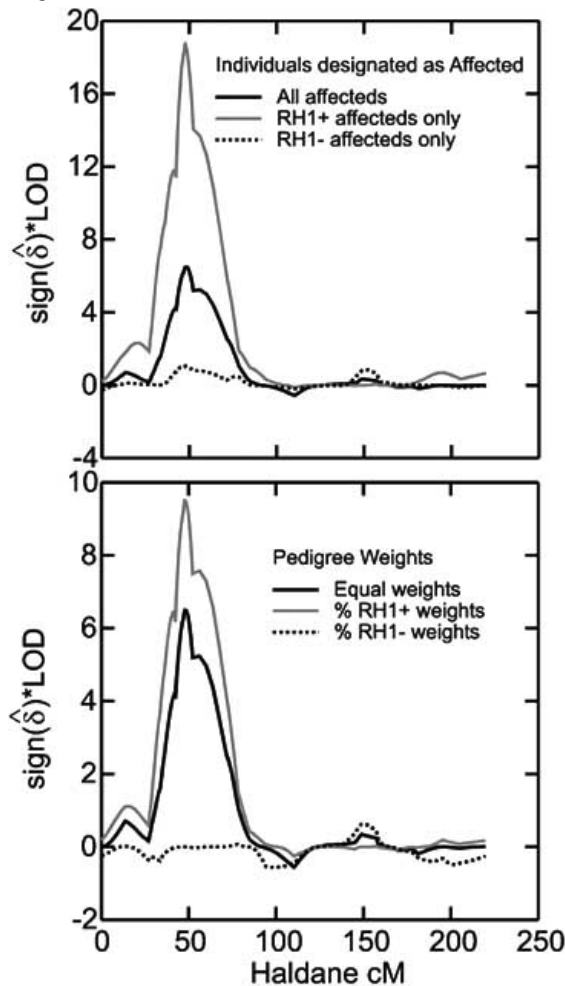


Fig. (2). PSORS1 linkage as a function of RH1. In the top panel, either only RH1(+) or RH1(-) individuals were designated as affected, and other affecteds were designated as unknown. In the bottom panel, pedigrees were weighted by the percentage of RH1(+) or RH1(-) psoriatics in the pedigree.

Making use of a fosmid cloning vector and shotgun sequencing of fosmid clones, we have determined the complete DNA sequence of a region of an approximately 350 kb region containing HLA-C and seven other genes (OTF3,

TCF19, HCR, SPR1, SEEK1, STG and CDSN) on 10 chromosomes representing two unique risk and five unique non-risk haplotypes, risk having been determined previously by cluster analysis [38]. Our preliminary analysis of these data has focused on the expressed regions of these genes. This analysis indicates that HLA-C and CDSN are the only genes that have predicted protein alleles unique to psoriasis risk haplotypes. Two missense SNPs and one silent SNP in exon 2 of HLA-C are unique to risk among the 10 sequenced haplotypes. CDSN has five different combinations of missense SNPs, one of which is the previously reported "allele 5" or "TTC allele" [40-42]. As previously reported [43], our data do not support a role for HCR as the PSORS1 disease gene, as the "WWCC" putative risk allele is present on a major non-risk chromosome (cluster 26, marked by the presence of HLA-Cw7 and -B8).

The vast majority of individuals who carry HLA-Cw6 also carry the TTC allele at CDSN due to linkage disequilibrium, markedly complicating the task of determining which of these two genes is the PSORS1 gene. It is even possible that both genes play a role, as we and others (see below) have observed a rare haplotype in which HLA-Cw6 and the CDSN TTC allele are both present, but much of the intervening sequence does not match the sequence of the risk haplotype. At this stage, the numbers of individuals carrying this haplotype is too small to make a convincing determination of risk status. To address this problem, the world's major psoriasis genetic laboratories have formed a consortium, supported by the National Psoriasis Foundation, whose objective is to type a large number of individuals for HLA Class I SNPs, to construct haplotypes from these SNPs, and to search for additional examples of informative recombinant haplotypes, including the double recombinant just mentioned. This project will benefit by collaboration with two major genome centers (one housed at MIT/Whitehead Institute and the other at the Karolinska Institute) for low-cost, high-throughput SNP genotyping. By means of this collaboration, there is optimism that the problem of determining whether HLA-Cw6, the CDSN TTC allele, or a combination of the two constitutes the disease determinant at PSORS1.

The other major study utilizing recombinant ancestral haplotype analysis for fine mapping of PSORS1 was by Trembath and co-workers [44]. Utilizing 59 SNPs identified by resequencing the MHC Class I region, they genotyped 171 parent-offspring trios and analyzed them as single markers and haplotypes using the TDT. Their analysis revealed 2 SNPs mapping just centromeric to HLA-C that yielded highly significant evidence for disease association. Comparison with our DNA sequence data reveals a possible explanation for the high significance of these SNPs in that study. Of the SNPs tested by Veal *et al*, only these two SNPs (n.7 and n.9) proved to reside in a region of sequence divergence between cluster 25 (HLA-Cw6-B57), which is a major risk haplotype, and cluster 26 (HLA-Cw7-B8), which is a major non-risk haplotype found with a haplotype frequency of approximately 10% in Caucasians. Therefore, we believe that the higher risk associated with these two SNPs reflects a "dilution" of risk for the other SNPs caused by the coincidental similarity of Clusters 25 and 26 across much of the risk region. Indeed, it is cluster 26 that also

carries the WWCC risk allele at HCR, thus greatly diminishing the chance that it could be the susceptibility allele. Overall, however, our sequence data are in excellent agreement with the SNP haplotypes determined by Veal *et al.* This agreement gives us encouragement that by collaborating with other laboratories to increase our sample size, we should be able to identify enough individuals carrying informative recombinant ancestral haplotypes to solve the riddle of PSORS1.

A third important study was carried out by Inoko and coworkers [45]. Utilizing case-control association analysis, this study of 76 cases and 132 healthy controls identified a 111 kDa interval telomeric to HLA-C that yielded highly significant associations with psoriasis. However, this study did not attempt to define recombinant ancestral haplotypes. Moreover, only 8 of 76 cases were positive for HLA-Cw6 (10.5%), as opposed to 60-70% in the two studies described above. Given the high prevalence of the HLA-Cw1-B46 haplotype in the Japanese population, it seems possible that a substantial number of the affected individuals may carry a different risk allele than the one marked by HLA-Cw6, thereby complicating analysis of these data.

There have been a large number of individual studies focusing on individual candidate genes in the interval defined in Fig. 1. We have not attempted to review these studies here, as we believe that only an analysis of informative haplotypes can provide meaningful information for localization of the disease gene. At the same time, it is important to acknowledge the possibility that additional modifier genes may exist on one or more of risk haplotypes we have discussed here, serving either to increase or decrease risk. For instance, the -238A allele at the TNFA locus is known to encode a high-expression allele, and among risk haplotypes, is found only on the HLA-Cw6-B57 extended haplotype. Indeed, even the HLA-DR7 or -DQ9 alleles found on this haplotype may make their own contribution to risk. Again, collaborative genotyping of flanking markers on large numbers of individuals will be required to address this possibility. At this time, however, we believe that the first priority should be to distinguish between the HLA-Cw6 and CDSN alleles in the MHC Class I region. Identification of the "true" PSORS1 gene will undoubtedly aid immunologists and skin biologists in formulating appropriate testable hypotheses for elucidating the functional role played by the PSORS1 gene product in this still-enigmatic disease.

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