The Major Psoriasis Susceptibility Locus PSORS1 Is not a Risk Factor for Late-Onset Psoriasis

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PSORS1 is the major susceptibility locus for psoriasis vulgaris (PV) and lies within an approximately 200 kb segment of the major histocompatibility complex on chromosome 6p21.3. Alleles of candidate genes in this region including human leukocyte antigen (HLA)-C, α-helical coiled coil rod (HCR), and corneodesmosin (CDSN) show association with early-onset PV. Late-onset psoriasis (LOP) is defined as a disease with onset after 40 y of age and is typically sporadic. We assessed the role of PSORS1 in genetic susceptibility to LOP. Genotyping for HLA-C alleles and seven single nucleotide polymorphisms (SNP) within the genes HCR and CDSN was performed in LOP (n = 145) and normal controls (n = 309). Statistical analysis of allelic frequencies included calculation of odds ratio and χ^2 comparisons. LOP demonstrated only a weak association to PSORS1 alleles HLA-Cw*6 (p = 0.037), CDSN*5 (p = 0.041), HCR*WC (p = 0.013), and HCR SNP +325 (p = 0.038). Patients with age of onset for psoriasis of 50 y or above provided no evidence of association with any of these alleles. These data suggest that the study cohort may include a number of subjects who harbor PSORS1 predisposition to early-onset psoriasis and yet do not present with disease by the age of 40 y. Thus this study demonstrates that PSORS1 is not a major inherited risk factor in the pathogenesis of LOP. These data suggest that the exclusion of LOP subjects from case–control studies will aid further delineation of the PSORS1 locus. Future genome-wide studies will be required to identify loci conferring risk for late-onset disease.

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Psoriasis is a chronic, debilitating inflammatory skin disease affecting diverse ethnic groups with a population incidence of 2%–3% in populations of European origin (Christophers, 2001). Genome-wide scans performed using families with early-onset psoriasis have identified at least nine putative psoriasis susceptibility loci (Capon et al, 2002). The major susceptibility locus for psoriasis (PSORS1) is within the major histocompatibility complex (MHC) on chromosome 6p21.3 (Nair et al, 1997; Trembath et al, 1997), and accounts for approximately 35%–50% of the genetic risk for psoriasis. An approximately 200 kb consensus region for PSORS1 lies within the MHC class I region (Balendran et al, 1999; Oka et al, 1999; Nair et al, 2000) and contains potential candidate genes for psoriasis susceptibility including human leukocyte antigen (HLA)-C, α-helical coiled coil rod (HCR), and corneodesmosin (CDSN). Specific alleles of these genes, HLA-Cw*0602, HCR*WWCC, and CDSN*5, have consistently demonstrated significant association with familial psoriasis vulgaris (PV) with each found in strong linkage disequilibrium with each other. We recently demonstrated differing patterns of genetic association in two clinically distinct subsets of psoriasis. In guttate psoriasis, evidence of allelic association for PSORS1 appears at least as prominent as that seen in PV. In contrast, palmoplantar pustular psoriasis (PPP) shows no evidence of PSORS1 association (Asumalahti et al, 2003).

PV has been subclassified according to age of onset. Early-onset psoriasis (also referred to as type 1) has onset before the age of 40 y, with peak onset at 16–22 y of age and comprises 70% of all psoriatics. Late-onset psoriasis (LOP), also termed type II psoriasis, shows onset at or after age 40 y with a peak age of onset between 57 and 60 y (Henseler and Christophers, 1985). Although these forms of psoriasis cannot be distinguished on clinical or histopathological grounds, however, a distinct pattern of HLA association has been reported. Hence, with early-onset psoriasis, which also displays a strong family history, strong association with Class 1 HLA alleles and specifically HLA-Cw6 is observed. In contrast, LOP is rarely familial and typically demonstrates an increased frequency of HLA-Cw2 and HLA-B27 (Henseler, 1997). Clinically, early-onset psoriasis is found to be more extensive, is frequently recurrent, and more frequently associated with involvement of nail.

A single nucleotide polymorphism (SNP) at position +1243 of the CDSN gene showed the strongest evidence of association in patients with a very early age of onset (0–20 y). The strength of association decreased in patients with an increased age of onset (21–39 y) and in late-onset patients (i.e., >40 y) the association between CDSN and

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psoriasis was barely significant (Tazi *et al*, 1999). The same study also showed a diminished, although still a highly significant association with HLA-Cw6, across all three of these age of onset groups.

In this work, we have investigated the role of specific PSORS1 susceptibility alleles in LOP. We genotyped patients and controls for the markers described in previous mapping studies, in order to provide a comprehensive assessment of PSORS1 candidate genes in psoriasis susceptibility and to further our understanding of the etiology of the disease in LOP.

Results

A comparison of allele frequencies between all late onset subjects with chronic plaque psoriasis and controls revealed a statistically significant increase in allele frequency for HLA-Cw*0602 (p = 0.037), CDSN*5 (p = 0.041), HCR*WC (p = 0.013), and HCR SNP + 325T (p = 0.038) in the total late-onset patient group (Table S1). Carriage frequencies (Table S2), in which the presence or absence of an allele is scored per individual, demonstrated that all alleles previously identified to be associated with type I psoriasis are increased in the late-onset patient group compared with controls; however, only HLA-C and HCR alleles were significantly increased. Thus, of the late-onset group (age of onset ⩾40 y old), 30.3% (n = 44) carried the HLA-Cw*0602 allele compared with 15.5% (n = 47) in the controls (p = 2 × 10^{-4}) (Table S2). HCR*WC showed a significant increase (p = 0.016) in carrier frequency of 52% in the late-onset subjects compared with 39.1% in controls (Table S2). Also, HCR SNP + 2327G showed a significant increase in carrier frequency, with 54.8% in controls compared with 66% in patients (p = 0.027).

To further examine the role of age of onset, the patient group was stratified for subjects presenting at or after the age of 50 y old. In this stratified group, no significant differences were observed for allele frequencies between cases and controls for any of the genes studied (Table S1). In an analysis of allele carriage frequencies, comparing cases and controls only the haplotype of the HCR SNP, i.e., HCR*WC, produced a significant change. Thus HCR*WC was increased (54.5%, p = 0.034) in the ⩾50 y age group, compared with a carriage frequency of 39.1% in the control group (Table S2); however, with correction for multiple testing this was also not significant.

Discussion

Psoriasis linkage and association studies have identified a major psoriasis susceptibility locus for psoriasis on chromosome 6p21.3 (PSORS1) within the MHC (Nair *et al*, 1997; Trembath *et al*, 1997). Within this locus, there are three main candidate genes for psoriasis susceptibility, HLA-C, CDSN, and HCR. One hundred and forty-five patients with psoriasis presenting in later life and 309 normal control individuals were genotyped for 22 HLA-C alleles and a total of 7 SNPs from CDSN and HCR genes. These markers have previously demonstrated a significant association with psoriasis (Ca-

pon *et al*, 2002). Our analysis reveals evidence of only a weak association for HLA-Cw*6, CDSN*5, HCR*WC, and HCR SNP + 325T in the late-onset group taken as a whole. Carriage frequencies for these alleles were also increased in the patient group compared with controls and although these results reach statistical significance, odds ratios suggest that this association is several orders of magnitude less than observed in classical early-onset disease. The age ranges for late- and early-onset psoriasis represent two overlapping normal distributions (Christophers and Henseler, 1989). Thus, it is possible that the weak association observed for PSORS1 alleles in this cohort of late-onset patients may result from a number of type I psoriasis patients within the area of overlap of the two normal distributions. To examine this, we analyzed data for patients with an increased age of onset for psoriasis, namely 50 y and above. With this stratification, no evidence was found, based on examination of allele frequencies, for allelic association with the alleles at the PSORS1 locus. Analysis of allele carrier frequencies followed a similar pattern; however, a small non-significant increase was observed for HCR*WC. Thus, these findings suggest diminished association with PSORS1 alleles with increasing age of onset for psoriasis. The patient group was also stratified based on family history of psoriasis (data not shown); however, association with HLA-C was observed in both those with and without a family history of psoriasis. This suggests separation on the basis of family history of psoriasis is not an effective means of screening out individuals from the region overlapping with the normal distribution of early-onset psoriasis. Thus preliminary analysis suggests stratification by age of onset appears to be a more effective means of identifying patients with PSORS1-associated psoriasis who develop disease after the age of 40 y.

These results may help to further define the role of PSORS1 in psoriasis susceptibility and in turn assist in categorizing the various subtypes of the disease. For example guttate psoriasis, which typically has an age of onset in adolescence or young adulthood, shows strong association with PSORS1, identical to that observed in familial psoriasis. In contrast, PPP, like LOP, shows no association with PSORS1 (Asumalahti *et al*, 2003).

Classically, age of onset before or after 40 y of age has been used as a convenient means of classification of early-onset psoriasis and LOP (Christophers and Henseler, 1989). Our findings provide compelling evidence that early-onset psoriasis and LOP do not show the same association with PSORS1 and therefore are genetically distinct subsets of the disorder. Furthermore, these discussions confirm the earlier finding in type I and II psoriasis (Henseler and Christophers, 1985) of an overlap in the age of onset of psoriasis, between age of onset at 40 y and age of onset at 50 y of age.

A more instructive way to discriminate type I and II psoriasis may be to separate them according to their association with PSORS1. Such distinction may inform future genetic studies of psoriasis subtypes. This might prove informative in assessing future patient treatment, in the design of clinical trials, and as an exclusion criterion in future studies of the etiology of LOP. No studies of other psoriasis susceptibility loci (PSORS 2–9) have yet been

undertaken in relation to LOP. Thus, it is possible that a genetic contribution from one or more of these loci may be relevant in LOP and hence future studies of these regions may prove helpful in characterizing any genetic component of LOP.

Materials and Methods

Patients and controls Ethical approval was given by the medical ethics committee of St Thomas's Hospital and informed written consent was obtained from all participating subjects. All studies were performed in accordance with the requirements of the Helsinki Declaration. All patients had a diagnosis of chronic plaque psoriasis, confirmed by a trained dermatologist, using standard clinical criteria (Camp, 1998). Patients were categorized as having LOP if the disease occurred at age 40 y old or older (Table I). Recruitment was via dermatology clinics at three UK regional centers namely London ($n = 61$), Glasgow ($n = 48$), and Manchester ($n = 36$) (total $n = 145$). All patients were of Northern European origin. DNA was extracted from peripheral venous blood samples by standard methods (Young *et al*, 2003). In addition, DNA samples ($n = 309$) from ethnically matched controls were obtained from two UK populations, namely volunteers recruited from hospital staff of Guys and St Thomas' Hospitals, London UK ($n = 165$) and DNA samples from individuals contributing to the DNA bank of the Tissue Typing laboratory, Guys Hospital, UK ($n = 144$). The same group of normal control individuals was used previously to demonstrate positive association in an early-onset psoriasis patient cohort (Asumalahti *et al*, 2003).

Genotyping The patient and control cohorts were genotyped by a polymerase chain reaction sequence-specific primer (PCR-SSP) method for 22 common HLA-C alleles (Bunce *et al*, 1995). Individuals were also genotyped for CDSN SNPs at +619, +1240, and +1243 using a PCR-SSP-based assay, which identified eight distinct alleles of CDSN based on in *cis* genotyping at these three positions (Allen *et al*, 1999). In addition, CDSN SNPs +1215 and +1236 were assayed by the "Taqman"-Sequence Detection System (PE Applied Biosystems, Warrington, UK). Genotyping for HCR SNPs +325 (+269) and +2327 (+2271) was performed using a radioactive oligonucleotide hybridization assay (Jeffreys *et al*, 2000). The high-risk psoriasis HCR allele for psoriasis susceptibility, HCR*WWCC, is defined by four SNPs +307T, +325T, +1723T, and +2327G (Asumalahti *et al*, 2002). We genotyped two of these SNPs (+325 and +2327), which identify the majority of HCR*WWCC alleles (Veal *et al*, 2002).

Statistical analysis A case–control comparison was made of allele frequencies and allele carriage frequencies for each SNP.

Table I. Demographics for late-onset psoriasis patients

	All cases, n = 145	Age of onset ⩾50 y, n = 66
Sex		
Male	74	30
Female	71	36
Age of onset		
Mean	52.5	62
Range	40–81	50–81
Nail involvement	(n = 101)	(n = 53)
	69 (68%)	37 (70%)
Family history	(n = 84)	(n = 44)
	37 (44%)	16 (36%)

Statistical comparison of all patients and control individuals was made using the χ^2 test and by calculation of odds ratios derived from allele carriage frequencies. Patients with age of onset for psoriasis of ⩾50 y of age were also analyzed as a subset, as above.

Supplementary Material

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