Am. J. Hum. Genet. 76:164–171, 2005

Report

Mapping of the Major Psoriasis-Susceptibility Locus (*PSORS1*) in a 70-Kb Interval around the Corneodesmosin Gene (*CDSN*)

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Numerous putative susceptibility loci have been described for psoriasis. Among the loci confirmed in the literature, *PSORS1* (the major histocompatibility complex at 6p21.3) has the strongest effect. Recent studies have highlighted a 200-kb candidate region. However, this region has not been well delimited, mainly because of the strong linkage equilibrium among the associated alleles. To finely map *PSORS1*, we set up a study using 17 polymorphic markers in a 525-kb interval around the human leucocyte antigen C locus (*HLA-C*). The results uncovered five loci with alleles strongly associated with psoriasis (Sidak-corrected *P* [P_c] values from 1.8×10^{-7} to .003), all structured in a psoriasis-susceptibility haplotype (PSH). Subsequent analysis of extended haplotypes showed that the PSH was not only present on the traditional psoriasis-susceptibility extended haplotypes (HLA-Cw6-B57, HLA-Cw6-B37, and HLA-Cw6-B13) but also on a haplotype of Sardinian origin (HLA-Cw7-B58) found to be associated with psoriasis ($P_c = .0009$) because of an ancestral recombination with one of the susceptibility haplotypes carrying the *HLA-Cw6* allele. Comparisons of the regions identical by descent among associated and nonassociated haplotypes highlighted a minimum region of 70 kb not recombinant with *PSORS1*, around the corneodesmosin (*CDSN*) gene.

Psoriasis (MIM 177900) is a chronic inflammatory skin disease with a prevalence of 2% in white populations. Skin lesions are characterized by angiogenesis, infiltrates of activated T cells, hyperproliferation of keratinocytes, and altered epidermal differentiation (Barker 1991). Clear evidence for a strong genetic component in susceptibility to psoriasis arises from strong familial clustering and the high concordance rate in MZ twins (Brandrup et al. 1982). Throughout the years, the search for genetic susceptibility factors has been hindered by the multifactorial nature of the disease. Early studies on different ethnic groups have repeatedly highlighted the strong association of the *HLA-Cw6* allele with psoriasis (Tiilikainen et al. 1980; Roitberg-Tambur et al. 1994; Gonzaga et al. 1996). In more recent years, genomewide scans have made it possible to individuate new susceptibility loci and to provide documented evidence of the highly significant linkage for the 6p21.3 region, thus confirming the presence of a major psoriasis-susceptibility gene within the major histocompatibility complex (MHC) (Nair et al. 1997; Trembath et al. 1997; Jenisch et al. 1998). These findings have led to the construction of maps densely filled with genetic markers flanking the human leucocyte antigen C locus (*HLA-C* [MIM 142840]), all focused on the refinement of the localization of *PSORS1* by analysis of linkage disequilibrium (Oka et al. 1999; Nair et al. 2000; Veal et al. 2002).

Although these studies have different conclusions, they highlight a region of 200 kb in which alleles of the *HLA-C* gene, the alpha-helix-coiled-coil-rod homolog gene (*HCR* [MIM 602593]), and the corneodesmosin gene (*CDSN* [MIM 602593]) have been found to be associated with the disease. Overall, these studies confirm the existence, in white populations, of a strong linkage disequilibrium region, between the *HLA-C* and *CDSN* genes, in which it is difficult to distinguish between the susceptibility alleles and the markers in linkage disequilibrium with these alleles. In a recent study of the Sardinian population performed by our group, psoriasis was found to be associated with an allele of the *CDSN* gene encoding the corneodesmosin protein, without any relationship to the *HLA-C* locus. Hypothetically, this decline in linkage disequilibrium may be attributable to

Received July 28, 2004; accepted for publication October 20, 2004; electronically published November 4, 2004.

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0002-9297/2005/7601-0017$15.00

Table 1

Single-Marker Association Study

Locus (Location[a]) and Allele[b]	Frequency in		*P* Value[c]		
	Cases	Controls	*P*	P_c	OR
MIB (0):					
1	.273	.413	.01207	.23453	.54
C1_4_1 (18):					
2	.522	.675	***.00722***	.14737	.53
C1_2_5 (72):					
12	.286	.144	***.00308***	.06554	2.38
SNP 9 (15):					
2	.379	.250	.01798	.32909	1.83
HLA-C (4):					
5	.168	.338	***.00074***	.01620	.40
7	.528	.350	***.00194***	.04178	2.08
C1_4_3 (29):					
4	.130	.325	***5.70×10^{-5}***	***.00125***	.31
8	.422	.269	***.00551***	.11438	1.99
C1_4_4 (5):					
2	.447	.281	***.00295***	.06292	2.07
7	.161	.356	***.00011***	***.00252***	.35
M6S172 (16):					
1	.714	.481	***3.41×10^{-5}***	***.00075***	2.69
4	.311	.538	***6.30×10^{-5}***	***.00139***	.39
C1_2_6 (55):					
2	.447	.694	***1.37×10^{-5}***	***.00030***	.36
OTF-3 (8):					
2	.752	.606	***.00761***	.15473	1.96
C1_3_2 (46):					
1	.596	.363	***.00005***	***.00099***	2.60
CDSN (7):					
TTC	.634	.306	***8.30×10^{-9}***	***1.83×10^{-7}***	3.92
TGT	.385	.563	***.00213***	.04587	.49
C2_4_4 (50):					
2	.745	.538	***.00017***	***.00363***	2.52
C2_4_5 (14):					
4	.646	.400	***1.71×10^{-5}***	***.00038***	2.74
M6S187 (73):					
6	.230	.394	***.00228***	.04907	.46
C4_2_7 (95):					
13	.118	.206	.04617	.64649	.51
C4_4_9 (19):					
5	.683	.725	.48551	1.00000	.82

[a] Distance (in kb) from the preceding locus.

[b] Allele with the largest deviation from the null hypothesis of no association.

[c] *P* is determined by the χ^2 two-tailed test; P_c is the *P* value corrected by the Sidak test for multiple comparisons. All statistically significant values are indicated in bold italics.

ancestral recombination events in this population (Orrù et al. 2002). In an attempt to contribute to the fine mapping of *PSORS1,* we performed a case-control association study combined with a search for identical-by-descent (IBD) haplotypes by the use of 17 genetic markers spaced over a region of 525 kb.

For this study, we recruited 161 unrelated Sardinian patients with psoriasis vulgaris (90 females and 71 males; age at onset 30.4 ± 18.8 years) and 184 individuals belonging to 32 families with multiple cases of psoriasis. Among the families, 68 members were affected. A total of 160 unrelated individuals (84 females and 76 males; mean age 33.0 ± 7.7 years) were used as controls. Diagnosis of psoriasis vulgaris was based on clinical and histological findings. Family trees were used to document the Sardinian background in both patients and controls. After informed consent was obtained, genomic DNA of each individual was isolated from peripheral blood, in accordance with standard methods. This study was approved by the institutional review board and by the local public-health ethics committee.

Genotyping was performed on all individuals by PCR

Table 2

Haplotype Association Study in the Sardinian Population

	Allele at Locus									Cases		Controls		*P* Value[b]			TDT[c]		
Haplotype	*HLA-C*	*C1_4_3*	*C1_4_4*	*M6S172*	*C1_2_6*	*C1_3_2*	*CDSN*	*C2_4_4*	*C2_4_5*	*n*	Frequency[a]	*n*	Frequency[a]	*P*	P_c	OR	T	NT	*P*
A	12	2	***9***	3	7	8	TGT	***9***	***10***	14	.043	11	.034	.69496	.99993	1.28	8	5	.40540
B	12	***6***	1	***5***	–	–	TTT	5	12	4	.012	1	.003	.37296	.97610	4.01	1	0	–
C	4	***7***	1	5	2	***7***	TTT	***8***	3	26	.081	27	.084	.98111	1.00000	.95	15	7	***.00881***
D	5	4	7	4	2	***9***	TGT	***11***	10	14	.043	40	.125	***.00035***	***.00276***	.32	2	19	***.00020***
E	6	***8***	2	1	***8***	1	TTC	2	4	44	.137	17	.053	***.00051***	***.00410***	2.82	12	2	***.00750***
F	7	***9***	***11***	1	5	1	TTC	2	4	55	.171	22	.069	***.00011***	***.00091***	2.79	14	3	***.00760***
G	7	3	***8***	4	2	7	CTC	2	2	13	.040	8	.025	.38266	.97891	1.64	4	9	.16550
H	8	8	2	1	***9***	8	CTC	***10***	11	21	.065	20	.063	.98355	1.00000	1.05	9	10	.81850

Note.—The single alleles found to be associated with psoriasis are underlined. The alleles not always present on all haplotypes are shown in bold italics. "–" indicates ⩾3 variable alleles.

[a] Estimated by the EM method.

[b] *P* is determined by the χ^2 two-tailed test; P_c is the *P* value corrected by the Sidak test for multiple comparisons. All statistically significant values are indicated in bold italics.

[c] T = transmitted; N = not transmitted.

Table 3

Distribution of PSH Haplotypes in Selected Patients with Psoriasis and Controls

Excluded Genotype	Distribution of Haplotype in		*P* Value[a]		
	Cases	Controls	*P*	P_c	OR
HLA-Cw5	87/268	31/212	1.08×10^{-5}	.00012	2.81
C1_4_4*7	86/270	24/206	3.96×10^{-7}	4.76×10^{-6}	3.50
HLA-Cw6	49/222	19/260	6.47×10^{-6}	7.77×10^{-5}	3.59
HLA-Cw7	36/152	12/208	1.73×10^{-6}	2.08×10^{-5}	5.07

[a] *P* is determined by the χ^2 two-tailed test; P_c is the *P* value corrected by the Sidak test for multiple comparisons.

using microsatellite markers *MIB* (Grimaldi et al. 1996); *C1_4_1, C1_2_5, C1_4_3, C_1_4_4, C1_2_6, C1_3_2, C2_4_4, C2_4_5, C4_2_7,* and *C4_4_9* (Oka et al. 1999); and *M6S187* and *M6S172* (Nair et al. 2000). Each PCR reaction mix was loaded onto an automated capillary sequencer (MegaBACE 1000 [Amersham Biosciences]) for electrophoretic separation and registration of electropherograms. The alleles were defined by comparisons with molecular markers, by use of the Genetic Profiler 1.1 software package (Amersham Biosciences) and by direct inspection of the electropherograms. The genotypes of *SNP 9*—located 4 kb centromeric to the *HLA-C* (Veal et al. 2002)—and a polymorphism of the *OTF3* gene (MIM 164177) (Gonzalez et al. 2000) were determined by fluorescent primer extension, with the use of the MegaBACE SnuPe Genotyping Kit (Amersham Biosciences). The genotypes of the *HLA-B, HLA-C,* and *CDSN* loci were obtained as described by Orrù et al. (2002).

The differences in frequencies between patients and controls were evaluated by the two-tailed χ^2 test with 1 df. The odds ratio (OR) was calculated by 2×2 contingency tables. Departures from Hardy-Weinberg equilibrium and the haplotype frequencies were calculated separately in patients and controls, by use of a Markov-chain simulation method and the expectation-maximization (EM) algorithm, respectively, as implemented in ARLEQUIN software (Schneider et al. 2000). To construct the complete haplotypes (17 loci), a maximum of 5–6 loci at a time were analyzed. Moving from the centromeric to the telomeric portion of the haplotype, the analysis was repeated, with the inclusion of one or two new loci each time, until the full haplotypes were generated. To estimate haplotype frequency, a maximum of nine loci at a time, including *HLA-C* and *CDSN,* were assessed. Only haplotypes confirmed in families and with a frequency >0.01 in at least one of the two groups (patients and controls) were considered for subsequent analysis. Less-frequent haplotypes with a variant attributable to the addition or loss of a single repeat, were added to the corresponding more-frequent haplotype. To estimate association between alleles of two different loci, standardized disequilibrium values were calculated: $D' = D/D_{max} = P_{ij} - P_i P_j / P_i(1 - P_j)$, where P_{ij} corresponds to the observed frequency of the *ij* haplotype and P_i and P_j correspond to the frequencies of the *i* and *j* alleles, respectively. Association between haplotypes and psoriasis was also evaluated by the transmission-disequilibrium test (TDT) in 32 families with multiple cases of psoriasis, who were genotyped for all the markers included in the present study. In this study, *P* values were corrected using the Sidak test for multiple comparisons: $P_c = 1 - (1 - P)^k$, where *k* is the number of comparisons. Only P_c values <.01 were considered significant.

Initially, a single-marker case-control association study was performed on 161 cases of psoriasis and 160 controls by the use of 17 genetic markers in an MHC class I region of ~525 kb. Statistical comparisons were made between the genotype frequencies of cases and controls. Those with the strongest deviation from the null hypothesis of no association are shown in table 1. After correction for multiple comparisons, five loci (*M6S172, C1_3_2, CDSN, C2_4_4,* and *C2_4_5*) showed highly significant values for positive association with psoriasis ($P_c < .01$; OR > 2.5). Extremely high significant values were found for the allele *CDSN*TTC* ($P_c = 1.8 \times 10^{-7}$), followed by those for the microsatellites *C2_4_5* ($P_c = .00038$) and *C1_3_2* ($P_c = .0009$); all were located in a region of 70 kb. Four loci centromeric to this region (*C1_2_6, M6S172, C1_4_4,* and *C1_4_5*) shared alleles negatively associated with psoriasis ($P_c < .01$; OR < 0.39). The most centromeric and telomeric markers used in our study had no associated alleles or only revealed a feeble association with psoriasis. At the *HLA-C* locus, the allele *HLA-Cw6* was not associated with psoriasis ($P_c = .233$). No significant deviation from the Hardy-Weinberg equilibrium was observed in the two groups ($P > .05$).

To understand the relationship between the associated loci, we performed a haplotype study, using the maximum-likelihood method calculated by the EM algorithm and the reconstruction of haplotype segregation within families followed by the TDT. Table 2 shows the haplotypes obtained with psoriasis-associated loci plus

MIB	*C1_4_1*	***HLA-B***	*C1_2_5*	*SNP 9*	***HLA-C***	*C1_4_3*	*C1_4_4*	*M6S172*	*C1_2_6*	*OTF3*	*C1_3_2*	***CDSN***	*C2_4_4*	*C2_4_5*	*M6S187*	*C4_2_7*	*C4_4_9*
2	4	**65**	6	1	**8**	8	2	1	*9*	2	*8*	**CTC**	*10*	11	4	9	8
4	4	**13**	17	2	**6**	8	2	1	*9*	2	1	**TTC**	2	4	7	_	_
9	1	**37**	16	2	**6**	8	2	1	*8*	2	1	**TTC**	2	4	4	_	_
8	2	**57**	16	2	**6**	8	2	1	*8*	2	1	**TTC**	2	4	4	_	_
10	5	**58**	12	1	**7**	9	*11*	1	5	2	1	**TTC**	2	4	4	_	7

Figure 1 Haplotypes with IBD regions. Loci and markers are listed across the top, with alleles below. The IBD regions are shown within frames. The alleles not always present on all haplotypes are given in italics, and "–" indicates ⩾3 variable alleles.

HLA-C and shows their distribution in the two groups—patients and controls. The single alleles found to be associated with psoriasis were structured on three different haplotypes, which, in turn, showed significant association with the disease, both in the case-control association study and in the TDT. However, whereas the negatively associated alleles were found on a single haplotype that exclusively carried the *HLA-Cw5* alleles (haplotype D), the positively associated alleles were present on two different haplotypes (haplotypes E and F) that carried the *HLA-Cw6* and *HLA-Cw7* alleles, respectively, and different alleles at the *C1_4_4* and *C1_2_6* loci. The common portion of these haplotypes (*M6S172*1–C1_3_2*1–CDSN*TTC–C2_4_4*2–C_2_4_5*4*) was present in 103 (32%) of the psoriatic chromosomes, compared with 42 (13%) of the control chromosomes ($P_c = 2.5 \times 10^{-7}$; OR = 3.1), and was overtransmitted within families (transmitted = 26; not transmitted = 5; $P = .0002$). This haplotype, which we defined as the "psoriasis-susceptibility haplotype" (PSH), was almost exclusively carried by the E and F haplotypes—since its presence in other haplotypes was rare (four in patients and three in controls)—and, even so, was not correlated to a specific haplotype. As is summarized in table 3, the increased frequency of PSH observed in patients did not depend on a decreased frequency of the D haplotype (HLA-Cw5 and C1_4_4*7 genotypes excluded) or an increased frequency of the E (*HLA-Cw6*) and F (*HLA-Cw7*) haplotypes.

Finally, the construction of the haplotypes, by use of all loci analyzed in the present study (fig. 1), made it possible to search for alleles shared by different haplotypes and to further clarify the nature of the association of PSH with psoriasis. As concerns the two haplotypes with PSH, the E haplotype was found to be the sum of three extended haplotypes (EHs), Cw6-B13 (EH13.1), Cw6-B37 (EH37.1), and Cw6-B57 (EH57.1), whereas the F haplotype corresponded to the extended haplotype HLA-Cw7-B58 (EH58.1).

Thorough examination of the haplotypes from locus *C1_2_5* to locus *C2_4_5* revealed three IBD regions. These regions are represented within frames in figure 1. The largest frame corresponds to the cluster of Cw6 haplotypes and includes the alleles from *C1_2_5* to *C2_4_5* (250 kb). The two allelic variants in the *C1_2_5* and *C1_2_6* loci may be the result of slippage-mispairing mutations. This block of alleles has been reported elsewhere (Nair et al. 2000), and the markers in common that are used in the present study confirm its structure. The smallest frame coincided with *OTF3*2* and included four of the five PSH alleles. However, it is possible that the recombination event did not involve the centromeric end of PSH but that it occurred between the *C1_2_6* and *OTF3* loci as the result of a noncontiguous allele at the *C1_2_6* locus. The HLA-Cw8-B65 (EH65.1) haplotype was included in the table, because it contained a region of 85 kb IBD to the cluster of Cw6 haplotypes. On the basis of the association data found for this haplotype (haplotype H; see table 2), it seemed possible to rule out this region. Hence, the minimum region nonrecombinant with PSH can be restricted to the loci *C1_3_2–C2_4_5*. We conclude that this region has the highest probability of containing *PSORS1*.

Of the 13 microsatellite markers investigated in the present study, 10 corresponded to those studied by Nair et al. (2000). This enabled us to search for PSH alleles (*CDSN* excluded) among the 66 clusters of haplotypes identified by those authors in Northern European white families. The results of our search showed that PSH—or the portion *C1_3_2–C2_4_5*, in which we mapped *PSORS1*—was exclusively present on haplotypes 19–25, corresponding to the cluster of haplotypes HLA-Cw6.

The first important finding emerging from this data is that the genetic background of the Sardinian population, with respect to *PSORS1*, is the same as that of other white populations and that the recently reported lack of association between the *HLA-C* alleles and psoriasis (Orrù et al. 2002) is not the result of the genetic het-

Table 4

Distribution of Genotypes in Selected Individuals

Subject Group and Characteristic	CDSN*TTC	SNP 9*2	HLA-Cw6	HLA-Cw7
CDSN*TTC negative:				
No. of cases with genotype (n = 59)	-	14	3	23
No. of controls with genotype (n = 111)	-	21	11	28
P_c	-	.99998	.99872	.68380
OR	-	1.33	.49	1.89
SNP 9*2 negative:				
No. of cases with genotype (n = 100)	55	-	7	68
No. of controls with genotype (n = 120)	30	-	7	46
P_c	.00012	-	1	.00026
OR	3.67	-	.93	3.42
HLA-Cw6 negative:				
No. of cases with genotype (n = 111)	55	18	-	71
No. of controls with genotype (n = 130)	30	19	-	48
P_c	.00039	1	-	.00059
OR	3.27	1.3	-	3.03
HLA-Cw7 negative:				
No. of cases with genotype (n = 76)	40	44	36	-
No. of controls with genotype (n = 104)	21	30	22	-
P_c	.00014	.00205	.00451	-
OR	4.39	3.39	3.35	-

erogeneity of the population but is, instead, a likely consequence of an ancestral recombination between one of the Cw6 haplotypes and the HLA-Cw7-B58 haplotype. Another important outcome of our study is the definitive exclusion of the loci centromeric to the *M6S172* marker—including the *HLA-C* locus—from the *PSORS1* candidate region.

The *HCR* and *CDSN* genes map inside the *PSORS1* critical region defined in the present study. Both genes have been investigated recently in numerous association studies, because, at a functional level, they are good candidates for psoriasis susceptibility (Simon et al. 1997; Asumalahti et al. 2002; Elomaa et al. 2004). In addition, *SPR1, SEEK1,* and *STG* map to this region, and, although functional data is lacking for these genes, their specific expression in the skin (Holm et al. 2003) has aroused considerable interest. Some polymorphisms of the *CDSN* gene have been found to be associated with psoriasis, but these associations have been attributed to linkage disequilibrium with *HLA-Cw6* (Jenisch et al. 1999; Guerrin et al. 2001; Asumalahti et al. 2002). This can be explained by the block of IBD alleles carried by haplotypes of the Cw6 cluster in an ~250-kb region from the *C1_2_5* marker (19 kb centromeric to *HLA-C*) to the *C2_4_5* marker (60 kb telomeric to *CDSN*), as documented in this and other reports (Nair et al. 2000). In the Sardinian population, an ancestral recombination has confined this block of linkage disequilibrium to the PSH region.

Other studies do not confirm the association of the *CDSN* gene with psoriasis (Gonzalez et al. 2000; Chang et al. 2003), probably because the association of *CDSN* and *HCR* is mostly linked to intragenic haplotypes of SNPs (Jenisch et al. 1999; Asumalahti et al. 2002) and is not always uncovered when the SNPs are considered separately. Our findings support the hypothesis that the *CDSN*TTC* allele is involved in the disease. Major opposition to this hypothesis arises from the fact that this allele was not found to be associated with psoriasis in Thai (Romphruk et al. 2003) and Japanese (Hui et al. 2002) populations. On the basis of the recent identification of a psoriasis-risk haplotype that conserves the *SNP9*2* and *CDSN*TTC* alleles, an equal role for *HLA-C* and *CDSN* in psoriasis susceptibility has been suggested (Capon et al. 2003). Since the *CDSN*TTC* allele had the strongest association in our study, we decided to investigate the effect of *HLA-C* alleles on this association. The results summarized in table 4 show that the influence exerted by these alleles was irrelevant. The strength of association found for the *CDSN*TTC* allele was only slightly decreased in patients and controls negatively selected for the alleles *HLA-Cw6* and *SNP9*2* (OR = 3.3 and 3.7, respectively), compared with the total sampling (OR = 3.9), and was even increased in samples negatively selected for HLA-Cw7 (OR = 4.4). In contrast, *HLA-C* alleles are completely dependent on *CDSN*TTC,* since they lose any tendency whatsoever toward association with psoriasis when this allele is excluded from the sampling.

Although our data demonstrate the independence of the association with the *CDSN*TTC* allele, they do not make it possible to differentiate the effect that this allele has on the rest of the region in which we map *PSORS1*. However, it is likely that minor loci interact with *PSORS1*

in the predisposition to psoriasis. The existence of IBD regions in different HLA psoriasis-susceptibility haplotypes implies that such haplotypes have the same susceptibility allele and therefore confer an identical risk of psoriasis. The data obtained in this study seem to indicate that haplotypes of the HLA-Cw6 cluster confer a higher risk of psoriasis than the HLA-Cw7-B58 haplotype (OR = 5.1 vs. 3.6). The three haplotypes of the Cw6 cluster were elsewhere shown to confer different levels of risk for psoriasis (Jenisch et al. 1998), suggesting that other genetic factors mapping in the MHC region may interact with *PSORS1*. A precious tool to enlighten this aspect will be comparisons among recombinant portions of psoriasis-risk haplotypes. The discovery of the recombinant HLA-Cw7-B58 haplotype should contribute toward unraveling the etiology of psoriasis.

Acknowledgments

The authors wish to thank all the patients with psoriasis whose participation made this project possible. The authors would also like to thank Anna Koopmans for the preparation of the manuscript. This research was supported by grant 1710 from the Sardinian Regional Government.

Electronic-Database Information

The URL for data presented herein is as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for *HLA-C, CDSN, OTF3, HCR,* and psoriasis)

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