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Genetic Associations of Psoriasis in a Pakistani Population

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Abstract

Background—Genetic predisposition to psoriasis, an inflammatory skin disease affecting 0.2 – 4% of world populations, is well established. Thus far, 41 psoriasis susceptibility loci reach genome-wide significance ($p \leq 5 \times 10^{-8}$). Identification of genetic susceptibility loci in diverse populations will help understand the underlying biology of psoriasis susceptibility.

Objectives—The primary objective of this study is to examine psoriasis susceptibility associations previously reported in Chinese and Caucasian populations in a Pakistani cohort.

Methods—Blood samples and phenotype data were collected from psoriasis cases and controls in Islamabad, Pakistan. DNA was isolated and genotypes of selected susceptibility markers were determined. The data were analyzed by chi square tests or logistic regression for psoriasis association.

Results—*HLA-Cw6* showed the strongest association (OR = 2.43, $p = 2.3 \times 10^{-12}$). *HLA-Cw1* showed marginally significant association (OR = 1.66, p = 0.049), suggesting that the *HLA-Cw1-B46* risk haplotype may be present in the Pakistani population. Three other loci (*IL4/IL13*, *NOS2*, *TRAF3IP2*) showed nominally significant association ($p < 0.05$).

Conclusions—*HLA-Cw6* is strongly associated with psoriasis susceptibility in the Pakistani population, as has been found in every other population studied. In addition, *HLA-Cw1* showed marginal association, reflecting the relative geographic proximity and thus likely genetic relatedness to other populations in which *HLA-Cw1–B46* haplotype is known to be associated. A larger cohort and a denser marker set will be required for further analysis of psoriasis associations in the South Asian population.

Introduction

Psoriasis is a chronic inflammatory disease of the skin affecting about 2% of people of European descent. Psoriasis occurs in nearly all other world populations as well, albeit with

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lower prevalence. Early epidemiological studies and anecdotal reports of immune suppressants clearing psoriasis lesions were followed by more systematic investigations of genetic susceptibility and involvement of the immune system in disease pathogenesis[1]. These studies have firmly established the genetic and immunological basis for psoriasis. Currently there are 41 genetic susceptibility loci for psoriasis established at a genome-wide level of significance ($p < 5 \times 10^{-8}$), of which 36 have been identified in European Caucasians and five in the Chinese population (Table 1)[2–12]. Five of the 36 loci identified in Caucasians have also been observed in the Chinese population. In addition to the 41 loci identified by single nucleotide polymorphism (SNP) and insertion/deletion polymorphism analyses, the β-defensin copy number variation (CNV) on chromosome 8 was also found in an initial report to reach genome-wide level of significance in Caucasians[13], but a follow-up analysis of a larger sample found a lower level of significance[14]. The vast majority of the identified susceptibility loci harbor genes active in immune and inflammatory pathways, affirming the interplay between genetic susceptibility and immune responses in psoriasis. Several new biological drugs for psoriasis targeting protein products of genes located in the susceptibility loci are highly efficacious, further supporting the veracity of genome wide association study (GWAS) results.

The markers used to identify genetic loci are surrogates that are not necessarily the causative variation. These markers tag DNA segments, several kilobases to megabases long, containing the true susceptibility variants. Identification of the causative variant(s) will require fine mapping of the loci by additional genotyping and/or by sequencing of the target region in several thousand samples. It is important to define the boundaries of the susceptibility region as accurately as possible before embarking on costly experiments to identify the actual disease predisposing variation(s). Studies of genetic association in ethnically diverse populations will, in addition to identifying susceptibility loci specific to the population studied, help define narrower bounds for further analysis of associated regions that are common to multiple populations by virtue of different mutational profiles and recombination boundaries. Other than several small studies reporting association of psoriasis with MHC genes in Indian populations[15–18], little is known of the genetic basis of psoriasis in South Asia. This study is the first to comprehensively test a population from this region for association with known psoriasis susceptibility loci.

In this study, we report a genetic association analysis of the 24 psoriasis loci known at the time of performing the experiment in a Pakistani cohort of 345 psoriasis cases and 545 controls. This first report of psoriasis association in a large Pakistani sample shows genome-wide significant association ($p < 5 \times 10^{-8}$) of *HLA-Cw6*, nominal significance of *HLA-Cw1* and three other loci, and very low strength of association of *IL12B*, the second most strongly associated locus in Caucasians.

Materials and Methods

Study subjects and DNA samples

For the Pakistani sample, subjects attending regular medical clinics in Islamabad Capital Territory and the Punjab Province were enrolled. Patient recruitment was approved by the Ethics Committee and Interdepartmental Review Board of Pir Mehr Ali Shah Arid Agriculture University Rawalpindi, Pakistan, and adheres to the Declaration of Helsinki Principles. The sample collection consisted of 351 psoriasis cases and 593 controls, all of whom were collected from the same geographic region. Diagnosis of psoriasis was performed as part of routine clinical care by dermatologists, and no attempt was made to classify the study subjects into psoriasis subtypes. Most patients had chronic, nonpruritic lesions showing Auspitz's sign. Eighty percent of the patients had type 1 psoriasis, with an age at onset ≤ 40 years, as defined by Henseler and Christophers[19]. A majority of the cases

were male (59%), 28% had a family history of psoriasis, and 4% had arthritis; mean age at exam was 35.4 years and mean age at onset of disease was 29.6 years (Table S1). Control subjects were adults (58% male, mean age 42.9 years) with no history of psoriasis and unrelated to the cases. After obtaining written informed consent, peripheral blood samples were collected by venipuncture, and DNA was prepared by standard methods.

The Caucasian sample used for comparison of *TNIP1* and *IL12B* associations consisted of 2,602 psoriasis cases and 2,505 unaffected controls collected in the United States following protocols approved by the Institutional Review Board for human subject research of the University of Michigan Medical School. Most of these samples have previously been used in other large-scale association studies of psoriasis[4,7,12].

Markers and genotyping

At the time these experiments were performed, there were 24 known loci of genome wide significance identified in European and Chinese populations (Table 2). The most strongly associated markers at these loci were genotyped. *HLA-Cw6* and *HLA-Cw1* were typed by a combination of eight SNPs, each assayed by a single base extension method (Snapshot assay, Applied Biosystems, Foster City, California), as previously described[20]. The β-defensin CNV was typed by the paralog ratio test (PRT) as previously described[21]. The 32 kb insertion/deletion polymorphism at the epidermal differentiation complex (EDC indel) was typed by a 3-primer fluorescent PCR method followed by size fractionation with capillary electrophoresis as previously described[6]. The remaining markers were genotyped by the Taqman SNP genotyping assay (Applied Biosystems, Foster City, California).

Data analysis

After excluding samples with less than 50% typing success on the panel of 30 markers in this study, data for 345 cases and 545 controls were available for analysis. Mean typing success for both markers and samples of the filtered dataset was 99.0%. For the β-defensin copy number variation (CNV), data were analyzed for association with psoriasis using version 1.43 of CNVtools[22], implementing a strategy of model building and selection described elsewhere[23]. The best fitting model for testing association of the beta-defensin CNV, as assessed by a combination of Bayesian and Akaike information criteria, was a linear trend model of the effects of CNV dosage on odds of disease, with eight copy number components, linear modeling of both means and variances for the multiple peaks of the Gaussian mixture model fitted to the distribution of raw copy number estimates, and a batch parameter to correct for a strong positive bias in copy number peak means of controls vs. cases. All other markers were analyzed with a chi-square test for allelic association. The Breslow-Day test[24] with the adjustment of Tarone[25] was used to assess the homogeneity of odds ratios for the three *IL12B* SNPs in different samples. Fisher's exact test was used to compare risk allele frequencies in Pakistani controls versus samples from the population of locus discovery, and a pooled variance t-test with significance assessed by 100,000 random permutations of case-control status was used to compare beta-defensin copy number in Pakistanis and Europeans. Statistical power for biallelic markers was analyzed with the Genetic Power Calculator [26] under a multiplicative model and an assumed disease prevalence of 0.5%; risk allele frequencies were set to those observed in the unaffected Pakistani controls of this study, and genotype relative risks were estimated using the odds ratio of the largest replication sample for that marker among published psoriasis association studies (discovery samples were avoided because of their upward bias in estimating effect size). Statistical power for the logistic regression test of association of the beta-defensin marker was determined with version 3.12 of G*Power[27]; the odds ratio of association and standard deviation of the copy number distribution for the HSPD21 marker were set to the values observed in the replication sample of Stuart et al.[23].

Results

The results of the genetic association analysis for psoriasis susceptibility for the 24 loci tested are summarized in Table 2. For each locus, one or more of the best known associated markers were tested. For the chromosome 6 *PSORS1* locus, the best known association is with the *HLA-C* gene. This highly polymorphic gene was typed with a set of eight SNPs that could distinguish Cw6 and Cw1, the two known associated alleles, from all other alleles. *HLA-Cw6* showed the strongest association (OR = 2.43, $p = 2.3 \times 10^{-12}$), consistent with previous reports. Interestingly, *HLA-Cw1*, which previously was shown to be associated with psoriasis in Thailand and Japan[20,28–32], showed marginally significant association (OR = 1.66, p = 0.049), suggesting that the *HLA-Cw1-B46* risk haplotype may be present in the Pakistani population. Three other loci (*IL13*, *NOS2*, *TRAF3IP2*) showed nominally significant allelic associations (OR = 1.35, 1.29, 1.70; P = 0.0060, 0.0097, 0.0017).

Not surprisingly, the predicted power of the Pakistani sample to detect association for loci that achieved nominal significance ranges from substantial to excellent (42%, 59%, 60%, 73%, and 100% power for *NOS2*, *TRAF3IP2*, *IL13*, *HLA-Cw1*, and *HLA-Cw6*, respectively, Table 2). It is notable, however, that no significant association was detected for the *TNIP1* marker or for the three *IL12B* SNPs, despite excellent predicted power ranging from 91–99%. Congruously, the *TNIP1* SNP yielded significantly lower strength of association in Pakistanis compared to that observed for our sample of 5,107 Caucasians (OR = 1.13 vs. 1.60, heterogeneity p = 0.042), and even larger differences were seen for all three *IL12B* markers (OR = 0.95–1.05 vs. 1.47–1.54, heterogeneity p = 0.0021–0.00013).

Discussion

This is the first report of a genetic association study of psoriasis in a Pakistani cohort. The most prominent psoriasis susceptibility locus from previous studies in Caucasian and East Asian populations, *HLA-C*, was associated with psoriasis at genome-wide significance levels. *HLA-C* is among the most polymorphic genes in the human genome with over 1,500 alleles. Because it is technically not possible to genotype all of these alleles in a large sample set, we used our previously published limited typing method that can discriminate *HLA-Cw6* and *HLA-Cw1* from all other alleles[20].

In addition to the strong association with *HLA-Cw6*, we also found nominal association with *HLA-Cw1*. Previous reports of psoriasis association with *HLA-Cw1* have come from Thailand and Japan, and in each case, the association was driven by the *HLA-Cw1-B46* haplotype. This haplotype is virtually absent in Caucasian populations, where *HLA-Cw1* is in linkage disequilibrium (LD) with a multitude of other *HLA-B* alleles. In the Thai population, we have previously shown that *HLA-Cw1* haplotypes lacking *HLA-B46* are not associated with psoriasis[20]. The nominal association observed in this study, with only 58 individuals carrying this allele, suggests that the *HLA-Cw1-B46* haplotype is present in Pakistan. Nominal association of psoriasis with *HLA-Cw1* was also found previously in a study from Kuwait with 50 pediatric subjects that had nine subjects carrying this allele[33]. The *HLA-B* alleles carried by these subjects are unknown. Since *HLA-Cw1* is not disease predisposing in non-Asian populations[20], it is possible that *HLA-B46*, or another nearby gene on this haplotype, is the disease predisposing entity in Asian populations. *HLA-B46* is of recent origin in the Asian population, not present in other human populations, and is thought to have arisen from a gene conversion event between *HLA-Cw1* and *HLA-B62*[34].

Since most known psoriasis susceptibility loci were identified in genome scans of thousands of subjects, it is likely that our sample lacks statistical power to detect loci of modest effect. Yet, the nominally significant associations of *IL13/IL4*, *TRAF3IP2* and *NOS2* suggest that

an expanded sample size would detect additional susceptibility loci. In fact, post-hoc power analysis, under the assumption that effect sizes for the analyzed markers are similar in Caucasian Europeans and Pakistanis, indicates that power of the Pakistani sample to detect association exceeds 50% for only six of the 24 tested loci. For most loci, sample sizes on the order of a few to several thousand each of cases and controls are required to achieve 80% power (data not shown). While the most recently published 18 psoriasis susceptibility loci[11,12] were not examined in this study, their strength of association is mostly less than that of the 24 tested markers, so the limited sample size of this study would have little power to detect association for these loci.

Interestingly, the strength of association of *IL12B*, the second most strongly associated gene in Caucasians[4,12] that is also robustly replicated in a Chinese population[5], is significantly lower in our study, despite excellent predicted statistical power of the Pakistani sample to detect association for all three *IL12B* SNPs. A similar albeit less significant result was observed for the *TNIP1* SNP. These findings may be attributable to genetic heterogeneity; i.e., *IL12B* and *TNIP1* are either unassociated with psoriasis in Pakistan, or their association is driven by causative variants different from those in Europeans, which are not well tagged by the markers used in this study. Alternatively, identical causative variants may be driving the association of these two loci in both populations, but the findings reflect differences in historical recombination events that have reduced the level of LD between the tested tag SNPs and the causative variants in Pakistanis relative to Europeans. A comparison of the frequency of the risk allele for each of the markers in the Pakistani controls with its frequency in the population in which the association of the marker with psoriasis was first discovered (Table S2) reveals that 21 of the 30 markers differ significantly in allele frequency using a FDR threshold of 0.1, supporting the notion that haplotype frequencies and LD structure for regions of known psoriasis susceptibility may indeed be quite different in the Pakistani population compared to the European and Chinese populations where these loci were first discovered. Hence both inadequate power and poor tagging of causative variants could be responsible for our failure to detect association for many of the known loci. Analysis of a much denser set of markers in a much larger cohort of Pakistanis is necessary to draw definite conclusions. We are currently conducting a GWAS of psoriasis in 1,000 Indian cases and 1,000 Indian controls, and this study should be useful for answering this and other questions regarding genetic associations with psoriasis in the South Asian population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Bulleted statements

- Psoriasis is an autoimmune disease with 41 known genetic loci of genome wide significance. All of these loci have been identified in European Caucasian or Chinese populations.
- Analysis of this Pakistani cohort showed genome wide significant association for *HLA-Cw6*, and nominal significance for three other loci.
- This study also found nominally significant association with *HLA-Cw1*, an association not previously observed outside of Thailand and Japan.

Table 1

Known psoriasis susceptibility loci of genome wide significance.

No.	Chr.	Position* (Mb)	Nearby Gene(s)	Population	Reference
1	1	8.27	*SLC45A1, TNFRSF9*	Caucasian	12
2	1	24.52	*IL28RA*	Caucasian	9
3	1	25.29	*RUNX3*	Caucasian	12
4	1	67.73	*IL23R*	Caucasian	4
5	1	152.59	*LCE deletion*	Caucasian, Chinese	6, 5
6	2	61.08	*REL*	Caucasian	9
7	2	62.55	*B3GNT2*	Caucasian	12
8	2	163.26	*IFIH1*	Caucasian	9
9	5	15.99	*PTTG1*	Chinese	8
10	5	96.12	*ERAP1*	Caucasian, Chinese	9, 8
11	5	132.00	*IL13/IL4*	Caucasian	4
12	5	150.47	*TNIP1*	Caucasian, Chinese	4, 8
13	5	158.83	*IL12B*	Caucasian, Chinese	45
14	6	0.58	*EXOC2/IRF4*	Caucasian	12
15	6	31.26	*HLA-C*	Caucasian, Chinese	4
16	6	111.91	*TRAF3IP2*	Caucasian	9,10
17	6	138.20	*TNFAIP3*	Caucasian	4
18	6	159.51	*TAGAP*	Caucasian	12
19	7	37.39	*ELMO1*	Caucasian	12
20	8	3.68	*CSMD1*	Chinese	8
21	9	32.52	*DDX58*	Caucasian	12
22	9	110.82	*KLF4*	Caucasian	12
23	10	81.03	*ZMIZ1*	Caucasian	11
24	11	64.14	*PRDX5*	Caucasian	11
25	11	109.96	*ZC3H12C*	Caucasian	12
26	11	128.41	*ETS1*	Caucasian	12
27	12	56.75	*IL23A/STAT2*	Caucasian	4

No.	Chr.	Position* (Mb)	Nearby Gene(s)	Population	Reference
28	13	20.76	*GJB2*	Chinese	8
29	14	35.83	*NFKBIA*	Caucasian	7
30	16	11.37	*SOCS1*	Caucasian	12
31	16	31.00	*FBXL19*	Caucasian	7
32	17	26.12	*NOS2*	Caucasian	7
33	17	40.56	*STAT3, STAT5A/B*	Caucasian	12
34	17	78.18	*CARD14*	Caucasian	12
35	18	61.66	*SERPINB8*	Chinese	8
36	18	51.82	*STARD6, POLI, MBD2*	Caucasian	12
37	19	53.45	*ZNF816A*	Chinese	8
38	19	10.46	*TYK2*	Caucasian	9
39	19	10.82	*ILF3, CARM1*	Caucasian	12
40	20	48.56	*RNF114*	Caucasian	3
41	22	21.98	*UBE2L3*	Caucasian	11

*Positions refer to hg19/GRCh37 (http://genome.ucsc.edu)

Table 2

Association of 30 markers in 24 known psoriasis suspceptibility loci in the Pakistani sample.

Chromosome location	Candidate Gene(s)	Marker[1]	Alleles risk/nonrisk[2]	Risk allele frequency cases/ controls	Odds Ratio for risk allele (95% conf. interval)	*P* value	Predicted power[3]
1p36.11	*IL28RA*	rs4649203	A/G	0.6735/0.6865	0.94 (0.77–1.16)	0.57	0.2089
1p31.3	*IL23R/STAT2*	rs2201841	G/A	0.5407/0.5083	1.14 (0.94–1.38)	0.18	0.2419
1p31.3	*IL23R/STAT2*	rs11209026	G/A	0.9825/0.9789	1.21 (0.60–2.45)	0.59	0.1469
1q21.3	*LCE3B/LCE3B*	LCE3C_LCE3b-del	del/ins[2]	0.6783/0.6430	1.17 (0.96–1.43)	0.13	0.4560
2p16.1	*REL*	rs702873	G/A	0.7926/0.7528	1.26 (1.00–1.58)	0.053	0.1667
2q24.2	*IFIH1*	rs17716942	A/G	0.9250/0.9453	0.71 (0.48–1.05)	0.088	0.1648
5q15	*ERAP1*	rs27524	A/G	0.3912/0.4081	0.93 (0.76–1.14)	0.48	0.2326
5q15	*ERAP1*	rs151823	A/C	0.1541/0.1498	1.03 (0.79–1.35)	0.81	0.1370
5q31.1	*IL13/IL4*	rs20541	G/A	0.7536/0.6934	1.35 (1.09–1.68)	0.0060	0.5965
5q33.1	*TNIP1*	rs17728338	A/G	0.1213/0.1091	1.13 (0.84–1.52)	0.43	0.9096
5q33.3	*IL12B*	rs2082412	G/A	0.6950/0.6865	1.04 (0.85–1.28)	0.71	0.9549
5q33.3	*IL12B*	rs3212227	A/C	0.6948/0.6845	1.05 (0.85–1.29)	0.65	0.9909
5q33.3	*IL12B*	rs4379175	C/A	0.6778/0.6888	0.95 (0.77–1.17)	0.63	0.9365
5q33.3	*PTTG1*	rs2431697	C/T	0.4184/0.4505	0.88 (0.72–1.06)	0.18	0.4329
6p21.33	*HLA-C*	7 SNPs[3]	HLA-Cw6/other	0.2591/0.1260	2.43 (1.88–3.12)	2.3×10^{-12}	1.0000
6p21.33	*HLA-C*	rs1131151	HLA-Cw1/other[4]	0.0473/0.0290	1.66 (1.00–2.77)	0.049	0.7261
6q21	*TRAF3IP2*	rs33980500	T/C	0.1116/0.0689	1.70 (1.22–2.37)	0.0017	0.5865
6q23.3	*TNFAIP3*	rs610604	G/T	0.3217/0.3241	0.99 (0.81–1.21)	0.92	0.4013
8p23.1	*DEFB4/DEFB103*	HSPD21[5]	+cn/−cn[6]	4.4099/4.3322[7]	1.06 (0.94–1.19)	0.34	0.1681
8p23.2	*CSMD1*	rs7007032	C/T	0.3953/0.3906	1.02 (0.84–1.24)	0.84	0.2095
8p23.2	*CSMD1*	rs10088247	C/T	0.3401/0.3230	1.05 (0.86–1.28)	0.66	0.2244
12q13.3	*IL23A*	rs2066807	C/G	0.9752/0.9696	1.24 (0.68–2.23)	0.48	0.1953
13q12.11	*GJB2*	rs3751385	T/C	0.1210/0.1322	0.90 (0.68–1.21)	0.49	0.1714
14q13.2	*NFKBIA*	rs12586317	T/C	0.7791/0.7787	1.00 (0.80–1.26)	0.99	0.2145
16p11.2	*FBXL19*	rs10782001	G/A	0.6327/0.6204	1.16 (0.86–1.28)	0.60	0.3104
17q11.2	*NOS2*	rs4795067	G/A	0.4491/0.3870	1.29 (1.06–1.57)	0.0097	0.4222
18q22.1	*SERPINB8*	rs514315	T/C	0.6739/0.6409	1.16 (0.95–1.42)	0.15	0.1989
19p13.2	*TYK2*	rs12720356	A/C	0.9913/0.9898	1.17 (0.43–3.17)	0.76	0.0963

Chromosome location	Candidate Gene(s)	Marker[1]	Alleles risk/nonrisk[2]	Risk allele frequency cases/ controls	Odds Ratio for risk allele (95% conf. interval)	*P* value	Predicted power[3]
19q13.41	*ZNF816A*	rs11084211	G/A	0.6258/0.5975	1.13 (0.92–1.38)	0.24	0.2007
20q13.13	*RNF114*	rs495337	C/T	0.4399/0.4490	0.96 (0.79–1.17)	0.71	0.4979

[1] In addition to SNPs that are denoted by their dbSNP rsid, other markers listed include LCE3C_LCE3B-del, which is a deletion-insertion of 32.2-kb segment encompassing *LCE3C* and *LCE3B* genes; *HLA-Cw6*, which is assayed by seven SNPs in exons 2 and 3 of *HLA-C* (rs28732105, rs1050409, rs1131123, rs1131118, rs1050384, rs17839985, and rs41547419); *HLA-Cw1*, which is uniquely tagged by the A allele of SNP rs1131151 in exon 2 of *HLA-C*; and HSPD21, which is the PRT assay for the beta-defensin CNV described by Aldhous et al. (2010).

[2] Determination of risk allele based on published reports, except for rs4379175, where the positively associated allele in the large Michigan case-control cohort is designated as risk. For HSPD21, an increase in copy number (+cn) is associated with increased risk of psoriasis, and mean copy numbers of the beta-defensin CNV are shown instead of allele frequencies (mean computed after fitting of bias-corrected Gaussian mixed model to the distribution of raw copy number estimates).

[3] Predicted power of the Pakistani sample to detect association for the marker at a nominal level of significance (α=0.05), assuming an effect size equal to that observed in Caucasians, a multiplicative model, a disease prevalence of 0.5%, and a risk allele frequency estimated from the unaffected Pakistani controls.