GENETICS

Genetic associations of psoriasis in a Pakistani population

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Summary

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Conflicts of interest

None declared.

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Background Genetic predisposition to psoriasis, an inflammatory skin disease affecting 0·2–4% of the world population, is well established. Thus far, 41 psoriasis susceptibility loci reach genome-wide significance ($P \le 5 \times 10^{-8}$). Identification of genetic susceptibility loci in diverse populations will help understand the underlying biology of psoriasis susceptibility.

Objectives The primary objective of this study was 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 analysed using χ^2 tests or logistic regression for psoriasis association.

Results HLA-Cw6 showed the strongest association [odds ratio (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 geographical proximity and thus likely genetic relatedness to other populations in which the 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.

What's already known about this topic?

• 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.

What does this study add?

- 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 Thailand and Japan.

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 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 a 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 harbour 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 in length, 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 boundaries 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 the association of psoriasis with major histocompatibility complex genes in Indian populations,^{15–18} little is known of the genetic basis of psoriasis in South Asia. This study is the first to test comprehensively 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 geographical 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 per cent of the patients had type one psoriasis, with an age at onset \leq 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 examination was 35.4 years and mean age at onset of disease was 29.6 years (Table S1.). The 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 2602 psoriasis cases and 2505 unaffected controls collected in the U.S.A. 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 using a combination of eight SNPs, each assayed by a single base extension method (Snapshot assay; Applied Biosystems, Foster City, CA, U.S.A.), as previously described.²⁰ The β -defensin CNV was typed by the paralogue ratio test as previously described.²¹ The 32-kb insertion/deletion polymorphism at the epidermal differentiation complex was typed by a 3-primer fluorescent polymerase chain reaction 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).

Data analysis

After excluding samples with < 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

Table 1	Known	psoriasis	susceptibility	v loci of	genome-wide	significance
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No.	Chr.	Position ^a (Mb)	Nearby gene(s)	Population	Referen
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	ERAP 1	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	4 5
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
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

both markers and samples of the filtered dataset was 99.0%. For the β -defensin CNV, data were analysed for association with psoriasis using version 1.43 of CNVtools,²² implementing a strategy of model building and selection described elsewhere.¹⁴ The best-fitting model for testing association of the β -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 modelling 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 analysed with a χ^2 test for allelic association. The

Breslow–Day test²³ with the adjustment of Tarone²⁴ was used to assess the homogeneity of odds ratios (ORs) for the three IL12B SNPs in different samples. Fisher's exact test was used to compare risk allele frequencies in Pakistani controls vs. 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 β -defensin copy number in Pakistanis and Europeans. Statistical power for biallelic markers was analysed with the Genetic Power Calculator²⁵ 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 OR of the largest replication sample for that marker

$ \begin{array}{llllllllllllllllllllllllllllllllllll$			Candidate gene(s)	Marker ^a	Alleles, risk/nonrisk ^b	Risk allele frequency, cases/controls	Odds ratio for risk allele (95% CI)	P value	Predicted power ^c
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$			rs4649203	A/G	0.6735/0.6865	$0.94 \ (0.77 - 1.16)$	0.57	0.2089
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	31.11 L13K/KTR1 N11000.6 (Λ_{Λ}) 0923(0,63) 014 013 013 0143 013 0143 013 0143 013 0143 013 0143 013 0143 013 0143 013 0143 013 0143 013 0143 013 0143 013 0143 0133 0143 0133 0143 0133 0143 0133 0143 0133 0143 0133 0143 0133 0143 0133 0143 0133 0143 0133 0143 0133 0143 0133 0143 0133		STAT2	rs2201841	G/A	0.5407/0.5083	$1 \cdot 14 \ (0.94 - 1.38)$	0.18	0.2419
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	qt13 ICEB/MCF3IB ICHS/LICEB-Med de/ins 0653/06430 117 0451 0453 0453 qt13 ERI rs77363 G/A 07326/0733 0731 0454 0453 0453 qt23 ITHI rs1716942 G/A 07326/0733 0731 0454 0453 qt33 ERM1 rs17364 G/A 0731/04403 1333 0433 0433 qt31 ILLB rs173163 G/A 0731/04403 1333 0433 0433 qt33 ILLB rs13173 A/C 0436/06885 1046 0435 0433 qt33 ILLB rs13173 A/C 0438/06885 1046 0437 0433 qt33 ILLB rs131131 ILLA rs131131 ILLB rs13113 ILLA rs13113 ILLA rs13113 ILLB rs13113 ILLB rs13113 ILLB rs13113 ILLB rs13113 ILLB rs1311313 ILLB rs13113 <		STAT2	rs11209026	G/A	0.9825/0.9789	$1.21 \ (0.60-2.45)$	0.59	0.1469
RL $rs702873$ G/A $0.7926/0.7528$ 1.26 (100-1:58) FHH1 $rs17716942$ A/G $0.3912/0.49813$ 0.771 ($0.48-1.05$) EMP1 $rs27524$ A/G $0.3912/0.4981$ 0.93 ($0.76-1.14$) EMP1 $rs151823$ A/C $0.1541/0.4983$ 0.771 ($0.48-1.05$) EMP1 $rs151823$ A/C $0.1541/0.4983$ $0.797-0.1351$ IIJ/IH $rs151823$ A/C $0.1213/0.1091$ 1.03 ($0.79-1.68$) IIJ/IB $rs1728338$ A/G $0.7113/0.1091$ 1.13 ($0.84-1.52$) III2B $rs2082412$ G/A $0.7713/0.1091$ 1.13 ($0.84-1.52$) III2B $rs2312227$ A/C $0.6948/0.6885$ 0.95 ($0.77-1.07$) III2B $rs321327$ A/C $0.6771/0.6685$ 1.04 ($0.85-1.28$) III2B $rs321327$ A/C $0.6771/0.6685$ 1.06 ($0.77-1.17$) III2B $rs321327$ A/C $0.6770/0.6885$ 0.95 ($0.77-1.07$) III2B $rs337300500$ $0.773/$	p(k) RL p(3)2(3) G/A p(3)2(4) P(4) P(3)2(4) P(3)2(4) </td <td></td> <td>LCE 3B</td> <td>LCE3C_LCE3b-del</td> <td>del/ins</td> <td>0.6783/0.6430</td> <td></td> <td>0.13</td> <td>0.4560</td>		LCE 3B	LCE3C_LCE3b-del	del/ins	0.6783/0.6430		0.13	0.4560
IFH1 $s_17716942$ Λ/G $0.9250/0.9453$ 0.71 $(0.48-1.05)$ EMP1 s_27524 Λ/G $0.3312/0.4081$ 0.33 0.71 $(0.48-1.05)$ EMP1 s_527524 Λ/G $0.3312/0.4081$ 0.33 $0.75-1.14$ EMP1 s_52754 Λ/G $0.1541/0.1498$ 1.03 $(0.9-1.69)$ IL13/IL4 s_520541 G/A $0.7356/0.6934$ 1.33 $(1.09-1.69)$ IL12B $s_52082412$ G/A $0.7536/0.66855$ $1.048-1.52$ 1.33 IL12B $s_52082412$ G/A $0.6593/0.68655$ 1.04 $0.84-1.52$ IL12B $s_5312227$ Λ/C $0.6434/0.68655$ 1.04 $0.85-1.29$ IL12B $s_5308247$ C/T $0.4184/0.4505$ 0.95 $(0.77-1.17)$ PHA-C $7.8W8$ $1.1A-Cw6/other 0.2591/0.2500 1.66 (0.77-1.06) HIA-C 7.8W8 1.16/0.0688 1.06 (0.77-1.17) TAA-C 7.87$	q4.1 IIII Is171(6)4.2 A/G 0.930(0.943) 0.71 0.048 0.163 q15 B&PI s177(6)4.1 s177(6)4.2 A/G 0.3312(0.4943) 0.031 0.733 0.23			rs702873	G/A	0.7926/0.7528	1.26 (1.00–1.58)	0.053	0.1667
EMP1 $r_{3}27524$ Å/G $0.3912/0.4081$ 0.93 $(7.6-1.14)$ ERAP1 $r_{3}51823$ Å/C $0.1541/0.1498$ 1.03 $(7.9-1.35)$ IL13/IL4 $r_{3}51823$ Å/C $0.7536/0.6934$ 1.03 $(0.79-1.35)$ TMP1 $r_{3}1723338$ Å/G $0.7536/0.6934$ 1.33 $(0.79-1.68)$ TMP1 $r_{3}17723338$ Å/G $0.7536/0.6934$ 1.33 $(0.79-1.68)$ TMP1 $r_{3}17723338$ Å/G $0.1213/0.1091$ 1.13 $(0.84-1.52)$ IL12B $r_{3}2312227$ Å/C $0.6958/0.6865$ 1.04 $(0.87-1.29)$ IL12B $r_{3}3121227$ Å/C $0.6948/0.6865$ 1.04 $(0.87-1.2)$ IL12B $r_{3}3121227$ Å/C $0.6948/0.6888$ 0.95 $(0.77-1.17)$ PIA-C 7 SNPs PIA-C 7 SNPs $1.4A-C$ 7 SNPs 1.76 $(0.72-1.23)$ TAF31P2 $r_{3}33980500$ $7/C$ $0.4134/0.4505$ 0.73 $(0.72-1.66)$	(15) ER(P1 5.275;4 \ld{C} (0.311/\)-401 (0.331/\)-401 (0.331/\)-401 (0.331/\)-401 (0.331/\)-401 (0.341/\)-101 (0.44) (0.231/\)-001 (31) 1111/l rs1773338 \ld{C} 0.1541/\0.101 1.131 (0.44) 0.933 0.933 (313) 11128 rs1773338 \ld{C} 0.1541/\0.101 1.131 (0.44) 0.933 (313) 11128 rs1773338 \ld{C} 0.1541/\0.101 1.131 (0.44) 0.933 (313) 11128 rs21731/3 A/G 0.433/\0.026 1.131 (0.44) 0.933 (313) 11128 rs21731/3 A/G 0.433/\0.026 0.1131 0.933 (311) 11128 rs2131/3 HLA-C 718 0.433/\0.026 0.721 0.933 0.933 (311) 11128 rs2131/3 HLA-C 711 0.943 0.943 0.933 0.933 0.933 0.933 0.933 0.933 0.933 0.933 0.933			rs17716942	A/G	0.9250/0.9453		0.088	0.1648
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$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	q3.1 NUI1 ss173338 N/G 0.111/0.101 (1.12)<		4	rs20541	G/A	0.7536/0.6934		0.0060	0.5965
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	q333 III2B s2082412 G/A $0.9530^{\circ}.6865$ 104 $0.851^{\circ}.123$ 0.71 0.954 q333 III2B s3371227 A/C $0.6480^{\circ}.6865$ 104 $0.655^{\circ}.0390$ 0.936 q333 III2B s3371257 A/C $0.6480^{\circ}.6865$ $0.956^{\circ}.057-117$ $0.655^{\circ}.0390$ $0.936^{\circ}.0390^{\circ}$ q313 HA-C 7 SNB HIA-C $7.5N^{\circ}$ $0.4134^{\circ}.0450^{\circ}.0390^{\circ}$ $0.88^{\circ}.072-106^{\circ}.0381^{\circ}$ $0.936^{\circ}.0726^{\circ}.0390^{\circ}$ 20133 TMAJFD s3131151 HIA-C $7.5N^{\circ}$ $0.4134^{\circ}.0230^{\circ}.0290^{\circ}$ $0.756^{\circ}.0490^{\circ}$ $0.726^{\circ}.0730^{\circ}.0750^{\circ}$ 20131 TMAJFD s3030000 T/C $0.311/0.32341^{\circ}.0200^{\circ}$ $0.726^{\circ}.0401^{\circ}.0750^{\circ}.0401^{\circ}$ $0.726^{\circ}.0401^{\circ}.0750^{\circ}.0401^{\circ}$ $0.726^{\circ}.0401^{\circ}.0750^{\circ}.0401^{\circ}$ $0.726^{\circ}.0401^{\circ}.0750^{\circ}.0401^{\circ}$ $0.726^{\circ}.0401^{\circ}.0750^{\circ}.0401^{\circ}.0750^{\circ}.0401^{\circ}.0750^{\circ}.0401^{\circ}.0750^{\circ}.0401^{\circ}.0750^{\circ}.0401^{\circ}.0750^{\circ}.0401^{\circ}.0750^{\circ}.0401^{\circ}.0750^{\circ}.0401^{\circ}.0750^{\circ}.0401^{\circ}.0750^{\circ}.0401^{\circ}.0750^{\circ}.0401^{\circ}.0750^{\circ}.0401^{\circ}.0750^{\circ}.0401^{\circ}.0750^{\circ}.0401^{\circ}.0750^{\circ}.0401^{\circ}.0750^{\circ}.0401^{\circ}.0750^{\circ}.0401^{\circ}.0750^{\circ}.0750^{\circ}.0401^{\circ}.0750^{\circ}.0$			rs17728338	A/G	0.1213/0.1091		0.43	0.9096
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	q3.3 III.1b $rs32112.17$ MC 0.6934 /0.6845 105 085 0.930 q3.3 PTIG $rs439175$ C/T 0.6734 /0.688 0.935 0.712 0.933 0.935 $p2133$ PTIG $rs2341697$ C/T 0.6734 /0.688 0.935 0.72 0.935 $p2133$ PLA-C $rs131151$ HLA-C 7.878 0.635 0.935 0.725 $p2133$ TMARID $rs2390500$ 7.7 0.0417 0.235 0.725 $p2131$ TMARID $rs3990500$ 7.7 0.0473 0.0439 0.725 $p231$ TMARID $rs700031$ 7.7 $0.3116/0.324$ 0.712 0.0491 0.735 $p231$ TXA 0.736 $0.9353/0.3296$ 1.76 $0.931/0.3296$ 0.72 0.949 0.736 $p312.11$ ORD $rs7007312$ 0.71 $0.931/0.9230$ 1.76 $0.931/0.923$ 0.716 $p312.11$ <			rs2082412	G/A	0.6950/0.6865		0.71	0.9549
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	q3.3 III.1B rs43791/5 C/A $0.6778/0.6888$ 0.95 $0.77-1.17$ 0.63 0.93 q3.3.3 HLAC rs131151 HLA-Cw/oher $0.235/0.1260$ 0.48 0.726 0.433 p1.3.3 HLAC rs1131151 HLA-Cw/oher $0.235/0.0290$ 1.66 $(-0.2-27)$ 0.049 0.726 q21 TRAFID rs131151 HLA-Cw/oher $0.331/0.0290$ 1.66 $(-0.2-27)$ 0.049 0.726 q21 TRAFID rs131151 HLA-Cw/oher $0.331/0.0290$ 1.66 $(-0.2-27)$ 0.049 0.726 q21 DEFMORENDI rs700041 $0.711/0.0289$ 1.70 $0.231/0.231$ 0.93 0.93 q21 DEFMORENDI rs700031 CT $0.331/0.233$ 0.712 0.93 0.93 0.93 0.726 q21 DEFMORENDIR rs700031 CT $0.331/0.233$ 0.936 0.214 $0.237/0.236$ 0.93 $0.234/0.230$ 0.2124			rs3212227	A/C	0.6948/0.6845	$1.05 \ (0.85 - 1.29)$	0.65	0.9909
PTTG1 rs2431697 C/T $0.4184/0.4505$ 0.88 $(0.72-1.06)$ $(0.4184/0.4505)$ (0.88) $(0.72-1.06)$ $(0.4184/0.4505)$ (0.88) $(0.72-1.06)$ $(0.4184/0.4505)$ (0.88) $(0.72-1.06)$ $(0.72$	q333 PTG1 ss2431697 C/T $0.4184/0.4605$ 0.88 $0.72-106$ 0.13 0.0127 0.33 0.013 p1133 HLAC 7.87ks HLA-Cw/okner $0.2591/0.1260$ 2.431 $(88-112)$ 2.33 10^{-12} 10^{-012} p2133 Taki Th s1331050 T/C $0.1116/0.0689$ $1.701(1.22.37)$ 0.099 0.726 p233 Taki Th s13306100 T/C $0.1117/0.0689$ $1.701(1.22.37)$ 0.0917 0.726 p233 Taki Th s13306100 T/C $0.3117/0.3241$ $0.939(481-12)$ 0.0917 0.939 0.716 p233 CSMD1 s1088247 C/T $0.3317/0.3230$ 10.606 0.234 0.203 p233 TI23A rs2066807 C/G $0.3317/0.3230$ 10.606 0.234 0.203 p31.1 TI23A rs2066807 C/G $0.3417/0.3230$ $0.090(0.88-1.21)$ 0.949 0.213 p31.2 TI23A			rs4379175	C/A	0.6778/0.6888	0.95 (0.77–1.17)	0.63	0.9365
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$			rs2431697	C/T	0.4184/0.4505	0.88 (0.72–1.06)	0.18	0.4329
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	p_{2133} HLA-C rsl 11151 HLA-Cwl/other $0.473/0.0290$ $1.66 (1.00-2.77)$ 0.499 0.726 q_{211} TRARIIP2 rs33980500 T/C $0.1116/0.0689$ $1.70 (1.22-2.37)$ 0.017 0.536 q_{221} DEFPM/DEFBI03 HSPD21 $-en/-en$ $-0.116/0.0689$ $1.70 (1.22-2.37)$ 0.017 0.533 q_{221} DEFPM/DEFBI03 HSPD21 $-en/-en$ $-0.909/4.3322$ $1.06 (0.94-1.19)$ 0.941 0.163 p_{232} CSMD1 rs10088247 C/T $0.3395/0.3306$ $10.7 (0.02, 17)$ 0.949 0.214 p_{232} CSMD1 rs10088247 C/T $0.3401/0.32306$ $10.7 (0.08-1.28)$ 0.166 0.224 q_{113} II233 rs2066807 C/C $0.3401/0.33206$ $10.7 (0.08-1.26)$ 0.949 0.171 q_{112} rs1238317 T/C $0.1210/0.1322$ $0.900 (0.86-1.28)$ 0.76 0.917 q_{112} rs12358317 T/C $0.1239/0.5409$ <td< td=""><td>3</td><td></td><td>7 SNPs</td><td>HLA-Cw6/other</td><td>0.2591/0.1260</td><td>2.43 (1.88–3.12)</td><td>2.3×10^{-12}</td><td>1.0000</td></td<>	3		7 SNPs	HLA-Cw6/other	0.2591/0.1260	2.43 (1.88–3.12)	2.3×10^{-12}	1.0000
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	q1 TtA/f3IP2 rs33980500 T/C 0-116 0-0617 0-586 q2.3 TNFAIP3 rs610604 G/T 0-3117/0-3241 0-99 0-401 0-92 0-401 p3.3.1 DFPM/DEFB103 HSPD21 $+\pi m/-m$ 0-3117/0-3241 0-99 0-811-21 0-92 0-401 p3.3.1 DFPM/DEFB103 HSPD21 $+\pi m/-m$ 0-3117/0-3230 1-06 0-314 0-30 p3.3.2 CSMD1 rs7066807 C/T 0-3357/0-3306 1-06 0-316 0-214 p3.1.1 GP2 rs71787 1-10 0-350 0-46 0-213 q1.1.2 GP2 rs71385 T/C 0-711/0-7323 0-90 0-66 0-214 q1.2.2 NFRBIA rs1058201 T/C 0-710/0-1322 0-90 0-66 0-214 q1.2.2 NFRBIA rs1058201 T/C 0-710/0-1322 0-90 0-66 0-214 q1.2.2 NFRBIA rs10582017 T/C 0-710/0-7387<			rs1131151	HLA-Cw1/other	0.0473/0.0290	1.66(1.00-2.77)	0.049	0.7261
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	q23.3 TNFAIP3 rs610604 G/T 0.3217/0-3241 0.99 (0.81-1.21) 0.92 0.401 p33.1 DFFD#/DFFB103 HSPD21 +tan/-cn 4.4099/4.3322 1:06 (0.94-1:19) 0.34 0.168 p33.2 CSMD1 rs7007032 C/T 0.335/0.3906 1:02 (0.84-1:24) 0.34 0.202 p33.2 CSMD1 rs7007032 C/T 0.3410/0.3230 1:06 (0.84-1:24) 0.34 0.202 p33.2 CSMD1 rs1088247 C/T 0.3410/0.3230 1:05 (0.84-1:23) 0.46 0.203 3q12.1 MFBIA rs1088247 C/T 0.3410/0.3230 1:06 (0.84-1:23) 0.46 0.213 4q13.2 MFBIA rs1038247 T/C 0.1210/0.1332 0.90 (0.86-1:28) 0.49 0.214 4q13.1 NFBIA rs1038247 T/C 0.1210/0.1332 0.90 (0.86-1:28) 0.49 0.112 4q13.2 MFBIA rs10782001 G/A		P2	rs33980500	T/C	0.1116/0.0689	1.70 (1.22–2.37)	0.0017	0.5865
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	p23.1 DEFb4/DEFB103 HSPD21 $+cn/-cn$ $4+099/4.3322$ $1-6(0.94+1.19)$ 0.34 0.168 p23.2 CSMD1 $rs7007032$ C/T $0.33953/0.3306$ $11-06(0.94+1.24)$ 0.84 0.203 p23.2 CSMD1 $rs7007032$ C/T $0.3353/0.3306$ $10-06(0.84-1.28)$ 0.66 0.233 p23.2 CSMD1 $rs10888.47$ C/T $0.3751/0.9696$ $1-212(0-0.1322)$ $0.96(0.84-1.28)$ 0.66 0.233 2q13.1 T/C $0.7791/0.7787$ $1-124(0.68-1.23)$ 0.49 0.173 q13.2 FBXL19 $rs1078001$ G/A $0.4491/0.3870$ $0.719/0.7787$ $0.090(0.640)$ 0.710 $0.990(0.640)$ 0.710 $0.990(0.640)$ 0.710 $0.990(0.640)$ 0.710 $0.990(0.640)$ 0.710 $0.990(0.640)$ 0.710 $0.990(0.640)$ 0.710 $0.990(0.640)$ 0.710 $0.990(0.640)$ $0.710(0.98-1.26)$ $0.910(0.98-1.26)$ $0.910(0.96-1.26)$ $0.910(0.96-1.26)$ $0.910(0.910(0.912)$ $0.710(0.98-1.26)$		3	rs610604	G/T	0.3217/0.3241	$0.99 \ (0.81 - 1.21)$	0.92	0.4013
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	p23.2 CSMD1 rs/007032 C/T $0.3953/0.3906$ 1.02 $(0.84-1.24)$ 0.84 0.203 p23.2 CSMD1 rs/0008247 C/T $0.3401/0.3230$ 1.05 $(0.84-1.28)$ 0.666 0.223 p13.2 CSMD1 rs/1008247 C/T $0.3401/0.3230$ 1.055 $(0.8-1.28)$ 0.666 0.223 3q1.2.11 GB2 rs/3751385 T/C $0.1210/0.1322$ 0.900 $0.68-1.21$ 0.648 0.213 4q13.2 NKBIA rs/1286317 T/C $0.7791/0.7787$ 1.126 $0.8-1.26$ 0.971 0.717 4q13.2 FRX1A rs/1278001 G/A $0.5327/0.6204$ 1.16 $0.8-1.26$ 0.919 0.216 6p11.2 FRX1A rs/172031 G/A $0.4491/0.3870$ 0.660 0.75 0.999 0.116 6p11.2 FRX1B rs/1431/0.3870 G/A $0.4491/0.3870$ 1.126 $0.96-1.26$ 0.76 0.995 6p13.1		DEFB103	HSPD 2 1	+cn/-cn	4.4099/4.3322	$1.06 \ (0.94 - 1.19)$	0.34	0.1681
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	p23.2 CSMD1 rs1008847 C/T $0.3401/0.3230$ 1.05 ($0.86-1.28$) 0.66 0.224 2q13.3 IL23A rs2066807 C/G $0.9752/0.9696$ $1:24$ ($0.68-2.23$) 0.48 0.195 3q12.11 GJB2 rs3751385 T/C $0.1210/0.1322$ 0.90 ($0.68-1.21$) 0.49 0.171 4q13.2 NFKBIA rs12386317 T/C $0.7791/0.7787$ 1.00 ($0.80-1.26$) 0.99 0.917 6p11.2 FBXLI9 rs10782001 G/A $0.537/0.6204$ 1.16 ($0.86-1.27$) 0.99 0.912 7q11.2 NOS2 rs4795067 G/A $0.5327/0.6204$ 1.16 ($0.86-1.27$) 0.99 0.912 7q11.2 NOS2 rs4795067 G/A $0.6337/0.6204$ 1.16 ($0.95-1.42$) 0.097 0.913 7q11.2 NOS2 rs1078201 G/A $0.6539/0.6409$ 1.16 ($0.95-1.42$) 0.007 0.913 9p13.2 TYC $0.913/0.9864$ 1.16 ($0.95-1.42$) 0.005 0.916 </td <td></td> <td></td> <td>rs7007032</td> <td>C/T</td> <td>0.3953/0.3906</td> <td>$1.02 \ (0.84 - 1.24)$</td> <td>0.84</td> <td>0.2095</td>			rs7007032	C/T	0.3953/0.3906	$1.02 \ (0.84 - 1.24)$	0.84	0.2095
II23A rs2066807 C/G 0.9752/0.9696 1.24 (0.68-2.23) GB2 rs3751385 T/C 0.1210/0.1322 0.90 (0.68-1.21) NERMA	2q13.3 IL23A rs2066807 C/G 0.9752/0.9696 1:24 (0.68-2.23) 0.48 0.195 3q12.11 GJB2 rs3751385 T/C 0.1210/0:1322 0.90 (0.68-1:21) 0.49 0.171 4q13.2 NFKBIA rs12586317 T/C 0.1210/0:1322 0.90 (0.68-1:21) 0.49 0.171 6p11.2 FBXL19 rs12586317 T/C 0.7791/0.7787 1:00 (0.80-1:26) 0.99 0.214 6p11.2 FBXL19 rs10782001 G/A 0.4491/0.3870 1:16 (0.86-1:28) 0.600 0.912 0.492 0.125 7q11.2 NOZ2 rs4795067 G/A 0.4491/0.3870 1:20 (1.06-1:57) 0.0997 0.195 0.919 9p13.2 TYR2 rs110742115 T/C 0.913/0.9898 1:17 (0.43-3.17) 0.766 0.9097 0.249 9p13.2 TYR1 rs11084211 G/A 0.913/0.9898 1:16 (0.95-1.42) 0.766 0.906 0.919 0.916 0.919 0.918 0.919 0.919 0.910 0.910 0.919 0.910 0.910 0.910 0.910 0.9			rs10088247	C/T	0.3401/0.3230	$1.05 \ (0.86 - 1.28)$	0.66	0.2244
GJB2 rs3751385 T/C 0.1210/0.1322 0.90 (0.68–1.21) NERRIA **1784317 T/C 0.7701/0.7787 1.00 (0.80-1.26)	3q12.11GJB2rs3751385T/C $0.1210/0.1322$ 0.90 $(0.68-1.21)$ 0.49 0.171 4q13.2NFKBIArs12586317T/C $0.7791/0.7787$ 1.00 $(0.80-1.26)$ 0.99 0.214 6p11.2FBXL19rs10782001G/A $0.6327/0.6204$ 1.16 $(0.86-1.28)$ 0.600 0.310 7q11.2NOS2rs4795067G/A $0.4491/0.3870$ 1.29 $(1.6-1.57)$ 0.0097 0.422 8q22.1SERPINB8rs514315T/C $0.6739/0.6409$ 1.120 $(1.29)(1.06-1.57)$ 0.0097 0.749 8q22.1SERPINB8rs514315T/C $0.6739/0.6409$ 1.16 $(0.95-1.42)$ 0.0097 0.740 9p13.2TYK2rs11084211G/A $0.6739/0.64499$ 1.16 $(0.79-1.42)$ 0.76 0.906 9p13.1.3TYK2rs11084211G/A $0.6739/0.64499$ 1.17 $(0.43-3.17)$ 0.76 0.906 9p13.2.2TYK2rs11084211G/A $0.6138/0.5975$ 1.17 $(0.43-3.17)$ 0.74 0.74 9p13.1.3RNF114rs495337C/T $0.4399/0.4490$ 0.66 $0.791.138$ 0.74 0.76 0.96 9p13.1.3RNF114rs495337C/T $0.4399/0.4490$ 0.66 $0.791.138$ 0.74 0.76 0.96 9p13.1.3RNF114rs495337C/T $0.4399/0.4490$ 0.66 $0.791.138$ 0.74 0.76 0.96 9p13.1.3RNF114rs495337 </td <td></td> <td></td> <td>rs2066807</td> <td>C/G</td> <td>0.9752/0.9696</td> <td>$1.24 \ (0.68 - 2.23)$</td> <td>0.48</td> <td>0.1953</td>			rs2066807	C/G	0.9752/0.9696	$1.24 \ (0.68 - 2.23)$	0.48	0.1953
NERBLA ***13586317 T/C 0.7791/0.7787 1.00 (0.80-1.36)	4q13.2NFRBIArs12586317T/C $0.7791/0.7787$ 1.00 $(0.80-1.26)$ 0.99 0.214 6p11.2FBXL19rs10782001G/A $0.6327/0.6204$ 1.16 $(0.86-1.28)$ 0.60 0.310 7q11.2NOS2rs4795067G/A $0.4491/0.3870$ 1.29 $(1.06-1.57)$ 0.0097 0.422 8q22.1SERPINB8rs514315T/C $0.6739/0.6409$ 1.16 $(0.95-1.42)$ 0.0097 0.949 9p13.2TYK2rs11084211G/A $0.6739/0.6409$ 1.17 $(0.43-3.17)$ 0.076 0.996 9p13.2TYK2rs11084211G/A $0.6439/0.6409$ 1.17 $(0.43-3.17)$ 0.76 0.996 9p13.2TYK2rs11084211G/A $0.6439/0.64499$ 1.17 $(0.43-3.17)$ 0.76 0.996 9p13.13TYK2rs11084211G/A $0.6258/0.5575$ 1.17 $(0.42-1.38)$ 0.76 0.906 9q13.13RNF114rs495337C/T $0.4339/0.4490$ 0.96 $(0.79-1.17)$ 0.74 0.20 9q13.13RNF116rs495337C/T $0.4339/0.4490$ 0.96 $(0.79-1.17)$ 0.74 0.24 0.201 913.13RNF114rs495337C/T $0.4339/0.4490$ 0.96 $(0.79-1.17)$ 0.74 0.24 0.201 913.13RNF114rs495337C/T $0.4399/0.4490$ 0.96 $(0.79-1.17)$ 0.74 0.24 0.24 913.14RNF114rs495337C/T </td <td></td> <td></td> <td>rs3751385</td> <td>T/C</td> <td>0.1210/0.1322</td> <td>$0.90 \ (0.68 - 1.21)$</td> <td>0.49</td> <td>0.1714</td>			rs3751385	T/C	0.1210/0.1322	$0.90 \ (0.68 - 1.21)$	0.49	0.1714
	6p11.2FBXL19rs10782001 G/A $0.6327/0.6204$ 1.16 $(0.86-1.28)$ 0.60 0.310 7q11.2NOS2rs4795067 G/A $0.4491/0.3870$ 1.29 $(1.06-1.57)$ 0.0097 0.422 8q22.1SERPINB8rs514315 T/C $0.6739/0.6409$ 1.16 $(0.95-1.42)$ 0.0097 0.76 9p13.2TYK2rs12720356 A/C $0.9913/0.9898$ 1.17 $(0.43-3.17)$ 0.76 0.906 9p13.2TYK2rs11084211 G/A $0.6258/0.5975$ 1.13 $(0.92-1.38)$ 0.76 0.200 9q13.41ZNF816Ars11084211 G/A $0.6439/0.4490$ 0.606 $0.79-1.17$ 0.74 0.200 9q13.13RNF114rs495337 C/T $0.4339/0.4490$ 0.96 $(0.79-1.17)$ 0.71 0.74 1. confidence interval. *In addition to single nucleotide polymorphisms (SNPs) that are denoted by their SNP database refSNP cluster ID numbers, other markers listed include ICE3C_ICE3B-del, wh1. confidence interval. *In addition to single nucleotide polymorphisms (SNPs) that are denoted by their SNP database refSNP cluster ID numbers, other markers listed include ICE3C_ICE3B-del, wh1. confidence interval. *In addition to single nucleotide polymorphisms (SNPs) that are denoted by their SNP database refSNP cluster ID numbers, other markers listed include ICE3C_ICE3B-del, wh1. confidence interval. *In addition to single nucleotide polymorphisms (SNPs) that are denoted by their SNP database refSNP cluster ID numbers, other markers listed include ICE3C_ICE3B-del, wh1.11118, rs1050384, rs17839985 and rs41547			rs12586317	T/C	0.7791/0.7787	$1 \cdot 00 \ (0 \cdot 80 - 1 \cdot 26)$	0.99	0.2145
FBXL19 rs10782001 G/A 0.6327/0.6204 1.16 (0.86–1.28)	7q11.2NOS2rs4795067 G/A $0.4491/0.3870$ 1.29 $(1.06-1.57)$ 0.0097 0.422 8q22.1SERPINB8rs514315 T/C $0.6739/0.6409$ 1.16 $(0.95-1.42)$ 0.015 0.198 9p13.2TYK2rs12720356 A/C $0.9913/0.9898$ 1.17 $(0.43-3.17)$ 0.76 0.906 9p13.1TYK2rs11084211 G/A $0.6258/0.5975$ 1.13 $(0.92-1.38)$ 0.76 0.096 9q13.41ZNF816Ars11084211 G/A $0.4399/0.4490$ 0.6456 0.996 $0.79-1.17$ 0.74 0.200 9q13.13RNF114rs495337 C/T $0.4399/0.4490$ 0.96 $(0.79-1.17)$ 0.71 0.74 0.201 1. confidence interval. *In addition to single nucleotide polymorphisms (SNPs) that are denoted by their SNP database refSNP duster ID numbers, other markers listed include ICE3C_ICE3B-del, wha deletion-insertion of 32.2-bk segment encompassing the LCE3C and LCE3B genes; HLA-C66, which is assayed by seven SNPs in exons two and three of HLA-C (rs28732105, rs1050490, rs1131121.131118, rs1050384, rs17839985 and rs41547419); HLA-Cw1, which is uniquely tagged by the A allele of SNP rs1131151 in exon two of HLA-C; and HSD21, which is the paralogue ratio test as			rs10782001	G/A	0.6327/0.6204	$1 \cdot 16 \ (0 \cdot 86 - 1 \cdot 28)$	0.60	0.3104
NOS2 rs4795067 G/A 0-4491/0-3870 1-29 (1-06-1-57)	8q22.1 SRPINB8 rs514315 T/C 0.6739/0.6409 1.16 (0.95-1-42) 0.15 0.198 9p13.2 TYK2 rs12720356 A/C 0.9913/0.9898 1.17 (0.43-3.17) 0.76 0.096 9p13.2 TYK2 rs11084211 G/A 0.6258/0.5975 1.13 (0.92-1.38) 0.24 0.200 9q13.41 ZNF816A rs11084211 G/A 0.4339/0.4490 0.4309/0.4490 0.96 (0.79-1.17) 0.74 0.24 0.200 0q13.13 RNF114 rs495337 C/T 0.4339/0.4490 0.96 (0.79-1.17) 0.71 0.497 1, confidence interval. *In addition to single nucleotide polymorphisms (SNPs) that are denoted by their SNP database refSNP cluster ID numbers, other markers listed include ICE3C_ICE3B-del, wh 1, confidence interval. *In addition to single nucleotide polymorphisms (SNPs) that are denoted by their SNP database refSNP cluster ID numbers, other markers listed include ICE3C_ICE3B-del, wh 1, a deletion-insertion of 32.2-2-kb segment encompassing the ICE3C and ICE3B genes; HIA-C66, which is assayed by seven SNPs in exons two and three of HIA-C (rs28732105, rs1050490, rs113112 1,11118, rs1050384, rs17839985 and rs41547419); HIA-Cw1, which is uniquely tagged by the A allele of SNP rs1131151 in exon two of HIA-C; and HSPD21, which is the par			rs4795067	G/A	0.4491/0.3870	1.29 (1.06 - 1.57)	0.0097	0.4222
SERPINB8 rs514315 T/C 0·6739/0·6409 1·16 (0·95–1·42)	9p13.2 TYK2 rs12720356 A/C 0.9913/0.9898 1.17 (0.43-3.17) 0.76 0.906 9q13.41 ZNF816A rs11084211 G/A 0.6258/0.5975 1.13 (0.92-1.38) 0.24 0.200 9q13.13 RNF114 rs495337 C/T 0.4399/0.4490 0.96 (0.79-1.17) 0.71 0.497 1, confidence interval. *In addition to single nucleotide polymorphisms (SNPs) that are denoted by their SNP database refSNP cluster ID numbers, other markers listed include ICE3C_ICE3B-del, wh a deletion-insertion of 32.2-kb segment encompassing the ICE3C and ICE3B genes; HIA-C66, which is assayed by seven SNPs in exons two and three of HIA-C (rs28732105, rs1050490, rs113112 st1181118, rs1050384, rs17839985 and rs41547419); HIA-Cw1, which is uniquely tagged by the A allele of SNP rs1131151 in exon two of HIA-C; and HSPD21, which is the paralogue ratio test as		38	rs514315	T/C	0.6739/0.6409	$1 \cdot 16 \ (0.95 - 1.42)$	0.15	0.1989
TYK2 rs12720356 A/C 0.9913/0.9898 1.17 (0.43–3.17)	9q13.41 ZNF816A rs11084211 G/A 0.6258/0.5975 1.13 (0.92–1.38) 0.24 0.200 0q13.13 RNF114 rs495337 C/T 0.4399/0.4490 0.96 (0.79–1.17) 0.71 0.497 1, confidence interval. *In addition to single nucleotide polymorphisms (SNPs) that are denoted by their SNP database refSNP cluster ID numbers, other markers listed include ICE3C_ICE3B-del, wh 1, confidence interval. *In addition to single nucleotide polymorphisms (SNPs) that are denoted by their SNP database refSNP cluster ID numbers, other markers listed include ICE3C_ICE3B-del, wh 1, a deletion-insertion of 32.2-2b segment encompassing the ICE3C and ICE3B genes; HIA-C66, which is assayed by seven SNPs in exons two and three of HIA-C (rs28732105, rs1050409, rs113112 131118, rs1050384, rs17839985 and rs41547419); HIA-Cw1, which is uniquely tagged by the A allele of SNP rs1131151 in exon two of HIA-C; and HSPD21, which is the paralogue ratio test as			rs12720356	A/C	0.9913/0.9898	$1 \cdot 17 \ (0.43 - 3 \cdot 17)$	0.76	0.0963
ZNF816A rs11084211 G/A 0.6258/0.5975 1.13 (0.92–1.38)	0q13.13 RNF114 rs495337 C/T 0.4399/0.4490 0.96 (0.79-1.17) 0.71 0.497 I, confidence interval. *In addition to single nucleotide polymorphisms (SNPs) that are denoted by their SNP database refSNP cluster ID numbers, other markers listed include ICE3C_ICE3B-del, wh s a deletion-insertion of 32.2-kb segment encompassing the LCE3C and ICE3B genes; HIA-C66, which is assayed by seven SNPs in exons two and three of HIA-C (rs28732105, rs1050490, rs113112 s111118, rs1050384, rs17839985 and rs41547419); HIA-Cw1, which is uniquely tagged by the A allele of SNP rs1131151 in exon two of HIA-C; and HSPD21, which is the paralogue ratio test as		V.	rs11084211	G/A	0.6258/0.5975		0.24	0.2007
RNF114 rs495337 C/T 0-4399/0-4490 0.96 (0-79–1-17)	I, confidence interval. ^a In addition to single nucleotide polymorphisms (SNPs) that are denoted by their SNP database refSNP cluster ID numbers, other markers listed include LCE3C_LCE3B-del, wh s a deletion-insertion of 32.2-kb segment encompassing the LCE3C and LCE3B genes; HLA-CW6, which is assayed by seven SNPs in exons two and three of HLA-C (rs28732105, rs1050409, rs113112 s1131118, rs1050384, rs17839985 and rs41547419); HLA-CW1, which is uniquely tagged by the A allele of SNP rs1131151 in exon two of HLA-C; and HSPD21, which is the paralogue ratio test a	[rs495337	C/T	0.4399/0.4490	0.96 (0.79–1.17)	0.71	0.4979
or the β -defension copy number variation (CNV) described by Aldhous et al. ²¹ ^b Determination of risk allele based on published reports, except for rs4379175, where the positively associated as the second		e large Michigan case-control c	cohort is design	ated as risk. For HSP	D21, an increase in copy	number (+cn) is associated with increa	sed risk of psoriasis, and mean copy nu	imbers of the β -d	efensin
for the β -defension copy number variation (CNV) described by Aldhous et al. ^{21 b} 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 β -defension	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 β-defension	JV are shown instead of allele f	frequencies (me	an computed after fi	tting of bias-corrected G	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). ^c Predicted power of the Pakistani	of raw copy number estimates). ^c Predi	cted power of the	Pakistan

 $0{\cdot}5\%,$ and a risk allele frequency estimated from the unaffected Pakistani controls.

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 β -defensin marker was determined using version 3.12 of G*Power;²⁶ the OR 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.*¹⁴

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,^{20,27–31} 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 = 0.006, 0.0097, 0.0017, respectively).

Not surprisingly, the predicted power of the Pakistani sample to detect an 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% to 99%. Congruously, the TNIP1 SNP yielded significantly lower strength of association in Pakistanis compared with that observed for our sample of 5107 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 1500 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, which can discriminate between HLA-Cw6 and HLA-Cw1 and all other alleles.²⁰

In addition to the strong association with HLA-Cw6, we also found a 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 paediatric subjects in which nine subjects carried this allele.³² The HLA-B alleles carried by these subjects are unknown. As 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-B62.33

As 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 analysed markers are similar in caucasian Europeans and Pakistanis, indicates that the power of the Pakistani sample to detect an association exceeds 50% for only six of the 24 tested loci. For most loci, sample sizes in 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 loci, 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 false discovery rate threshold of 0.1; this supports the notion that haplotype frequencies and LD structure for regions of known psoriasis susceptibility may indeed be quite different in the Pakistani population compared with 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 1000 Indian cases and 1000 Indian controls, and this study should be useful for answering this and other questions regarding genetic associations with psoriasis in the South Asian population.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website.

Table S1. Clinical characteristics of the Pakistani psoriasis cases.

Table S2. Comparison of risk allele frequencies in Pakistan vs. population of disease locus discovery for 30 markers in 24 known psoriasis susceptibility loci.