original article

Associations between human leukocyte antigen C locus polymorphism and psoriatic arthritis in populations of European and Middle Eastern descent: a meta-analysis

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BACKGROUND: Gene-disease association between human leukocyte antigen (HLA)-C locus polymorphism and psoriatic arthritis (PsA) remains controversial.

OBJECTIVE: Evaluate the relationship between HLA-C locus polymorphism and PsA in populations of European and Middle Eastern descent.

SEARCH METHODS: PubMed, PMC, Elsevier and Google Scholar databases from 1980 to January 2020. The search was limited to articles in English.

SELECTION CRITERIA: Case-control studies (with unrelated participants) that had allele/genotype data on the association between HLA-C locus polymorphism and PsA susceptibility.

DATA COLLECTION AND ANALYSIS: Two investigators searched independently in searching the literature. Disagreements were resolved by discussion and consultation with a third researcher. The Q-Genie tool was used to assess the quality of articles.

RESULTS: Twenty-five studies met the inclusion criteria. At the allelic level, three alleles were associated with an increased risk of PsA and five were associated with a reduced risk. At the phenotypic level, four alleles were associated with increased risk of PsA and three were associated with a reduced risk. At both the allelic and phenotypic levels, the results revealed that HLA-C*04 played a protective role in PsA (The pooled odds ratio [OR] is 0.66 for allelic level and 0.63 for phenotypic level), while HLA-C*02, *06 and *12 increased the risk of suffering from PsA (The pooled ORs of C*02, *06 and *12 are 2.21, 2.63 and 1.49 for allelic level, and 1.79, 2.96 and 2.25 for phenotypic level, respectively).

CONCLUSION: The pooled results showed a significant association between PsA and the HLA-C gene in populations of European and Middle Eastern descent. At both the allelic and phenotypic levels, the HLA-C*02, *06 and *12 may contribute to susceptibility to PsA, while HLA-C*04 may confer a protective role against PsA.

REGISTRATION: Not registered.

CONFLICT OF INTEREST: None.

Psoriatic arthritis (PsA) is a chronic inflammatory arthropathy characterized by arthritis, enthesitis and spondylitis.[1] The estimated global prevalence of PsA is 133 per 100 000 subjects;[2] and 0.19% in Europe and 0.01% in the Middle East.[3] In addition, PsA occurs in up to 30% of patients with psoriasis.[4] Thus, it can be considered a "disease within a disease". PsA is significantly associated with mortality and the estimated cost to healthcare systems is equivalent to that of rheumatoid arthritis.[5] The precise etiology of PsA is unclear, but accumulating evidence suggests a key role for genetic factors in PsA with respect to disease susceptibility and expression.[6]

The human leukocyte antigen (HLA) is a polymorphic genetic system encoding the genes involved in the immune response. HLA variation plays a major role in susceptibility to infectious and autoimmune diseases. Various studies have demonstrated a relationship between HLA-C polymorphism and susceptibility to PsA. Reports of an association between the presence of the HLA-C*06 allele and PsA are consistent;[7-10] for example, Chandran et al showed that the frequency of HLA-C*06 was significantly increased (P<.0001) in PsA patients compared with controls, with an odds ratio (OR) of 1.72.5 In contrast, studies from some populations indicate no association between HLA-C*06 and PsA;[11-14] for example, Grubić et al demonstrated that the difference in distribution of HLA-C*06 in both PsA patients and controls was not significant.[14] Therefore, the association between HLA-C locus polymorphism and PsA remains controversial. We conducted this meta-analysis to estimate the precise association between HLA-C locus polymorphism and PsA in Caucasian populations.

METHODS

Study search strategy

We conducted a systematic search of studies on the association between HLA-C polymorphism and PsA susceptibility using the PubMed, PMC, Elsevier and Google Scholar databases from 1980 to January 2020, using the search term "((((psoriatic arthritis[MeSH Terms]) OR psoriatic arthritis[Title/Abstract]) OR PsA[Title/Abstract])) AND (((HLA-Cw[Title/Abstract]) OR HLA-C[MeSH Terms]) OR HLA-C[Title/Abstract])". Search results were limited to studies in English.

Inclusion criteria were defined as follows: case-control studies (with unrelated participants) that had allele/genotype data that evaluated the association between HLA-C locus polymorphism and PsA susceptibility. Moreover, studies reporting the results of different subpopulations were treated as separate studies with respective OR and 95% CI values assessed independently.

Studies were excluded if they evaluated subjects not of European and Middle Eastern descent, the study was based on family or sibling pairs, the allele/genotype frequencies or numbers were not given, or review articles, abstracts and books. When the same patient population was reported in numerous publications, only the most complete or recent study was used.

Data extraction

Using the criteria described above, each manuscript was screened, assessed for quality and data were extracted by two investigators independently with cross-checking. Disagreements were resolved by discussion and consultation with a third researcher. The following data were extracted: first author, year of publication, ethnicity, detection method and the numbers of cases and controls. Eligibility of studies was determined using the Q-Genie tool.[15] Studies with scores ≤35 were of low-quality, those scoring between 36 and 45 were of moderate quality and those >45 were high-quality. Genetic data were classified as either allelic or phenotypic.

Statistical analysis

Data extracted from eligible studies were processed prior to conducting the meta-analysis. Frequency data were translated into numerical values by multiplying the number of samples with values, and numerical data were extracted directly. An I^2 test was used to evaluate heterogeneity among studies.[16] A fixed-effects model was used if I^2<50%, otherwise, a random-effects model was used.[17] P values of less than .05 were considered statistically significant. Random-effects model-based subgroup analysis stratified by quality was performed to determine the source of heterogeneity. If quality was not able to explain heterogeneity, univariate random-effects meta-regression was used to explore the heterogeneity, such as publication year, number of cases and case/control ratio. Potential publication bias was intuitively evaluated using funnel plots. Meanwhile, bias was estimated using an Egger's test.[18] Meta-analysis was conducted using STATA 12.0 software.

RESULTS

Included studies

A total of 153 studies were identified after initial review using the search strategies previously described, and 24 articles were retained for meta-analysis (**Figure 1**).[7-10,19-38] After accessing the full-text of the eligible stud-

ies, one study[19] was split into two studies because it contained data for two different subpopulations. Thus, 25 studies were included (**Table 1**).

Results of meta-analysis

The meta-analyses of OR, 95% CI and I^2-statistics between HLA-C polymorphism and PsA are presented in **Table 2**. At the allelic level, eight alleles had a significant association with PsA. HLA-C*02, *06 and *12 were associated with an increased risk of PsA, while HLA-C*03, *04, *05, *07 and *16 had a decreased risk of PsA. At the phenotypic level, seven phenotypes had a significant association with PsA. Positive associations were observed for HLA-C*01, *02, *06 and *12. Negative associations were observed for HLA-C*04, *14 and *15. At both the allelic and phenotypic levels, the results showed that HLA-C*04 played a protective role in PsA while HLA-C*02, *06 and *12 increased the risk for PsA (**Figures 2 and 3**).

Subgroup analysis and heterogeneity

When more than four studies had been published, a subgroup analysis of quality was performed (**Table 2**). Sufficient numbers of high- and moderate-quality studies were included and thus, subgroup analysis of low-quality studies is not shown. HLA-C*02 and *06 at allelic level and HLA-C*06 at the phenotypic level were associated with an increased risk of PsA in both high- and moderate-quality subgroups. HLA-C*03, *04 and *07 at the allelic level and HLA-*04 and *07 at the phenotypic level were associated with a decreased risk of PsA in both subgroups. Moreover, the quality explained the heterogeneity observed in HLA-C*07 at the allelic and phenotypic levels because heterogeneity of the subgroups was reduced to zero. Except for the heterogeneity of HLA-C*07 at the allelic level, sources of heterogeneity for the other studies were explored using univariate meta-regression. However, year of publication, size of case and case/control ratio were not statistically correlated with heterogeneity (P>.05).

Publication bias

The funnel plots showed no evidence of obvious asymmetry. When assessed by the Egger's test, no publication bias was found (P>.05).

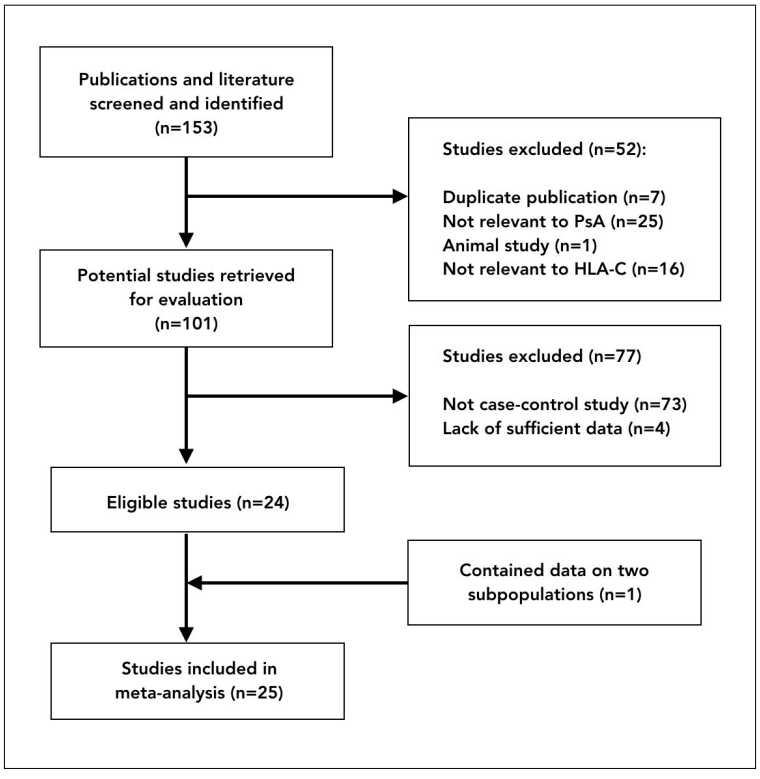

Figure 1. Study selection diagram. HLA: human leukocyte antigen, PsA: psoriatic arthritis.

DISCUSSION

PsA is a chronic immune-mediated inflammatory disorder whereby environmental factors trigger disease in genetically susceptible individuals, with multiple genetic factors contributing to disease susceptibility. PsA is associated with the presence of psoriasis and has a serious impact on the quality of life of patients, an impact that has been demonstrated as lower than that of patients with psoriasis alone.[1] Several articles demonstrated a correlation between HLA-C and PsA. The most intriguing allele, HLA-C*06, has already been described in a number of populations with susceptibility to PsA, such as native populations of the Czech Republic,[20] Spain,[21-22] Great Britain,[9] Poland,[23] Romania,[24] Sweden[25] and Newfoundland.[19] Furthermore, genome-wide association studies have confirmed that the HLA-C region is involved in susceptibility to PsA in populations of European and Middle Eastern descent.[1,39,40] The pathogenesis of PsA embraces both innate immunity and a major histocompatibility complex class I (MHC class I) T-cell related cytotoxic response. Additionally, PsA could be viewed as a ''MHC-I-opathy'' due to interactions between MHC class I alleles modifying expression and tissue specific factors.[41] Nevertheless, no association was found between HLA-C*06 and PsA in the Croatian population14 or in Canadians from Ontario.19 It is noteworthy that HLA-C*06 has been shown to be related to PsA in patients with Type I psoriasis in young-onset disease (≤40 years), but not with Type II psoriasis with onset older than 40 years.9 Recent studies have

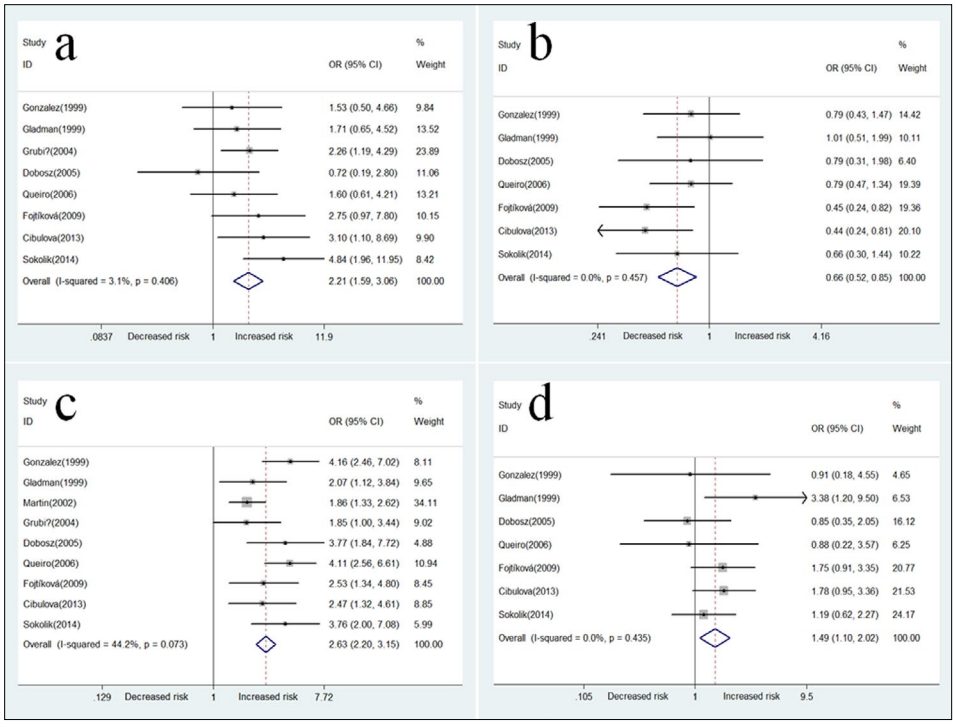

Figure 2. Forest plots of the association between HLA-C allele frequencies and psoriatic arthritis (Study a: HLA-C*02; Study b: HLA-C*04; Study c: HLA-C*06; Study d: HLA-C*12).

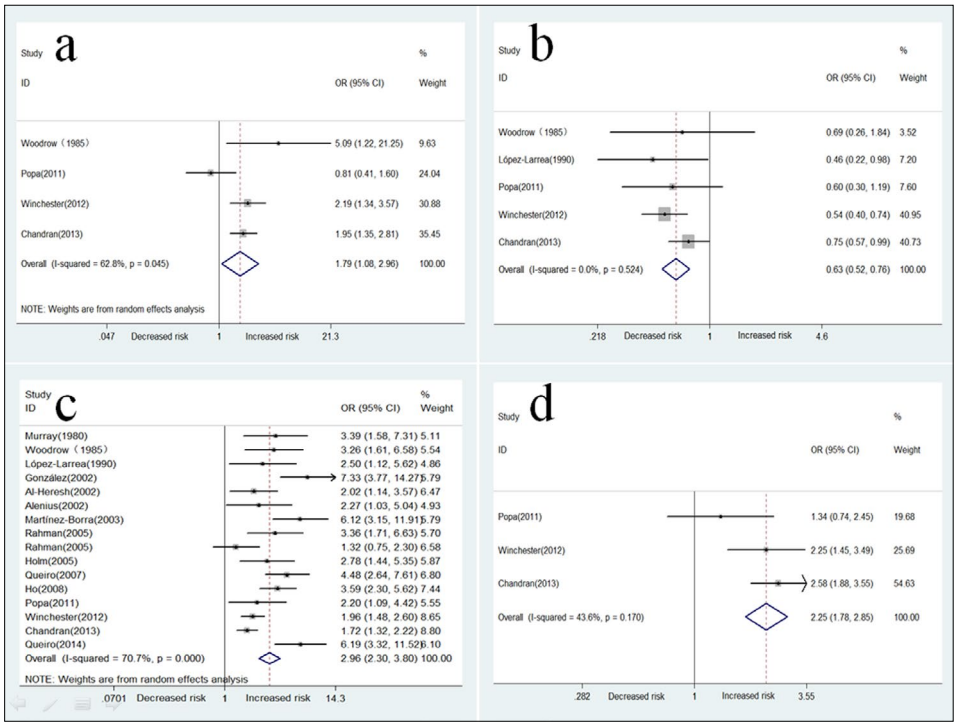

Figure 3. Forest plots of the association between HLA-C phenotype frequencies and psoriatic arthritis (Study a: HLA-C*02; Study b: HLA-C*04; Study c: HLA-C*06; Study d: HLA-C*12).

Table 1. Characteristics of the 25 studies included in the meta-analysis.

First author	Year	Sample size		Typing method	HLA-C/Cw	Data form	Q-Genie
		Cases	Controls				
Murray	1980	52	126	Serology	6	P	M
Woodrow	1985	50	115	Serology	1, 2, 3, 4,5, 6, 7	P	M
López-Larrea	1990	104	109	Serology	4, 5, 6	P	M
Gonzalez	1999	65	177	SSOP	01, 02, 03, 04, 05, 06, 07, 08, 12, 14, 15, 16	A	M
Gladman	1999	94	100	SSP	01, 02, 03, 04, 05, 06, 07, 08, 12, 14, 15, 16, 17	A	M
Martin	2002	355	295	SSOP	06	A	M
González	2002	81	110	SSP	06	P	M
Al-Heresh	2002	124	101	SSP	06	P	L
Alenius	2002	84	70	SSP	03, 06	P	M
Martínez-Borra	2003	74	104	SSP	06	P	M
Grubić	2004	58	157	SSP	02, 06, 07	A	L
Dobosz	2005	41	80	SSP	01, 02, 03, 04, 05, 06, 07, 08, 12, 14, 15, 16, 17, 18	A	H
Rahman	2005	103	105	SSOP	06	P	M
Rahman	2005	202	100	SSOP	06	P	M
Holm	2005	65	371	-	06	P	L
Queiro	2006	100	177	SSOP	01, 02, 03, 04, 05, 06, 07, 08, 12, 14, 15, 16	A	M
Ho	2008	453	166	SSOP	06	P	M
Queiro	2008	120	170	SSOP	06	P	M
Fojtíková	2009	100	94	SSP	01, 02, 03, 04, 05, 06, 07, 08, 12, 14, 15, 16, 17	A	H
Popa	2011	81	124	SSP	01, 02, 03, 04, 05, 06, 07, 08, 12, 14, 15, 16, 17	P	M
Winchester	2012	359	1000	SBT	01, 02, 04, 05, 06, 07, 12	P	L
Cibulova	2013	101	99	SSP	01, 02, 03, 04, 05, 06, 07, 08, 12, 14, 15, 16, 17	A	M
Chandran	2013	678	688	SSOP	01, 02, 03, 04, 05, 06, 07, 08, 12, 14, 15, 16, 17, 18	P	H
Sokolik	2014	50	123	SSP	01, 02, 03, 04, 05, 06, 07, 08, 12, 14, 15, 16, 17, 18	A	H
Queiro	2014	110	110	SSP	06	P	M

SSOP: sequence-specific oligonucleotide probes, SSP: sequence-specific primers, SBT: Sequence-based typing, A: allele counts or frequencies, P: phenotype counts or frequencies, Q-Genie: quality of genetic studies, L: low-quality study, M: moderate-quality study, H: high-quality study. C/Cw: serology/molecular nomenclature.

Table 2. Associations between HLA-C polymorphism and psoriatic arthritis and subgroup analyses based on quality at allelic and phenotypic levels.

HLA-C/Cw		Eligible studies	Heterogeneity		Association		Egger's Test	
			P	I^2 (%)	*P*	OR	95% CI	t
01	Allele	7	0.965	0.0	0.533	1.119	0.785-1.596	-0.77
02	Allele	8	0.406	3.1	<0.001	2.208	1.594-3.060	-1.06
03	Allele	7	0.952	0.0	0.004	0.673	0.512-0.884	-0.79
04	Allele	7	0.457	0.0	0.001	0.663	0.519-0.846	0.35
05	Allele	7	0.954	0.0	0.006	0.609	0.428-0.866	0.99
06	Allele	9	0.073	44.2	<0.001	2.631	2.200-3.146	1.07
07	Allele	8	0.054	49.3	<0.001	0.710	0.597-0.843	0.39
08	Allele	7	0.048	52.7	0.956	0.978	0.436-2.190	-0.97
12	Allele	7	0.435	0.0	0.010	1.490	1.102-2.015	-0.55
14	Allele	7	0.988	0.0	0.945	0.979	0.529-1.809	1.22
15	Allele	7	0.987	0.0	0.515	0.828	0.469-1.462	0.81
16	Allele	7	0.558	0.0	0.010	0.503	0.299-0.846	-1.06
17	Allele	5	0.848	0.0	0.058	0.376	0.142-0.993	-2.24
18	Allele	2	0.188	42.2	0.707	1.404	0.239-8.229	-
01/1	Phenotype	4	0.842	0.0	<0.001	1.952	1.489-2.560	-1.50
02/2	Phenotype	4	0.045	62.8	0.023	1.791	1.084-2.959	0.09
03/3	Phenotype	4	0.023	68.5	0.673	0.872	0.462-1.645	0.93
04/4	Phenotype	5	0.524	0.0	<0.001	0.630	0.523-0.760	-0.63
05/5	Phenotype	5	0.006	72.6	0.115	0.653	0.384-1.109	-1.27
06/6	Phenotype	16	<0.001	70.7	<0.001	2.956	2.298-3.804	2.62
07/7	Phenotype	4	<0.001	85.9	0.330	0.789	0.489-1.272	-0.25
08	Phenotype	2	0.855	0.0	0.428	0.861	0.596-1.246	-
12	Phenotype	3	0.170	43.6	<0.001	2.253	1.781-2.852	-3.46
14	Phenotype	2	0.482	0.0	0.046	0.492	0.245-0.986	-
15	Phenotype	2	0.981	0.0	0.005	0.491	0.299-0.806	-
16	Phenotype	2	0.411	0.0	0.065	0.685	0.458-1.023	-
17	Phenotype	2	0.920	0.0	0.470	1.341	0.604-2.976	-
18	Phenotype	1	-	-	0.194	7.135	0.368-138.388	-

HLA: human leucocyte antigen, OR: pooled odds ratio, CI, confidence interval, -: not available.

shown that HLA-C*06 causes early-onset skin disease in both PsA and psoriasis and is not linked to nail or joint diseases.[41,42] Therefore, the conflicting results described above may be explained by the bias of age at psoriasis onset or small sample size. Several investigators focused only on the role of HLA-C*06 with PsA susceptibility and then only presented the results of HLA-C*06, ignoring other alleles. The meta-analysis in the present study indicated that besides HLA-C*06, HLA-C*02 and *12 were also factors causing susceptibility to PsA, while HLA-C*04 was a protective factor for PsA at both allelic and phenotypic levels in all studies of the entire population. The effects of HLA-C*02 and *12 may be due to linkage disequilibrium with locus B (B27, B38, B39, B8), and more specifically to the asparagine residue at position 97 (common to B27,

Table 2 (cont.). Associations between HLA-C polymorphism and psoriatic arthritis and subgroup analyses based on quality at allelic and phenotypic levels.

HLA-C/Cw		High quality				Moderate quality				
		P	I^2 (%)	OR	95% CI	*P*	I^2 (%)	OR	95% CI	*P*
01	Allele	0.474	0.0	1.123	0.603-2.094	0.714	0.0	1.117	0.726-1.720	0.614
02	Allele	0.330	62.1	2.589	1.449-4.627	0.001	0.0	1.937	1.175-3.193	0.010
03	Allele	0.464	0.0	0.605	0.376-0.972	0.038	0.0	0.711	0.509-0.992	0.045
04	Allele	0.744	0.0	0.569	0.371-0.872	0.010	19.2	0.715	0.531-0.964	0.028
05	Allele	0.368	0.0	0.777	0.394-1.532	0.466	0.0	0.558	0.369-0.844	0.006
06	Allele	0.321	0.0	3.226	2.198-4.735	<0.001	63.4	2.568	2.073-3.182	<0.001
07	Allele	0.709	0.0	0.726	0.534-0.988	0.042	0.0	0.601	0.478-0.755	<0.001
08	Allele	0.378	36.2	1.145	0.441-2.972	0.781	68.1	0.945	0.566-1.577	0.827
12	Allele	0.603	0.0	1.291	0.865-1.924	0.211	4.1	1.803	1.132-2.872	0.013
14	Allele	0.276	0.0	0.865	0.207-3.617	0.843	0.0	1.006	0.510-1.986	0.985
15	Allele	0.456	0.0	1.248	0.400-3.890	0.703	0.0	0.728	0.376-1.410	0.346
16	Allele	0.338	21.8	0.505	0.195-1.304	0.158	0.0	0.503	0.270-0.936	0.030
17	Allele	0.111	0.0	0.269	0.068-1.058	0.060	0.0	0.611	0.146-2.565	0.501
18	Allele	-	-	-	-	-	-	-	-	-
01/1	Phenotype	0.273	-	1.925	1.288-2.877	0.001	0.0	1.579	0.838-2.978	0.158
02/2	Phenotype	0.937	-	1.945	1.348-2.807	<0.001	80.7	1.149	0.633-2.086	0.647
03/3	Phenotype	0.451	-	0.627	0.477-0.824	0.001	69.6	1.040	0.635-1.704	0.877
04/4	Phenotype	0.575	-	0.751	0.570-0.990	0.042	0.0	0.564	0.359-0.885	0.013
05/5	Phenotype	0.294	-	1.103	0.819-1.484	0.520	61.9	0.403	0.210-0.773	0.006
06/6	Phenotype	0.061	-	1.715	1.324-2.222	<0.001	59.1	3.468	2.892-4.159	<0.001
07/7	Phenotype	0.825	-	0.640	0.517-0.792	<0.001	0.0	0.632	0.404-0.988	0.044
08	Phenotype	-	-	-	-	-	-	-	-	-
12	Phenotype	0.179	-	-	-	-	-	-	-	-
14	Phenotype	-	-	-	-	-	-	-	-	-
15	Phenotype	-	-	-	-	-	-	-	-	-
16	Phenotype	-	-	-	-	-	-	-	-	-
17	Phenotype	-	-	-	-	-	-	-	-	-
18	Phenotype	-	-	-	-	-	-	-	-	-

HLA: human leucocyte antigen, OR: pooled odds ratio, CI, confidence interval, -: not available.

B38, B8), as the principal risk element for PsA.[1] We also found that a number of genes were significantly correlated with PsA at the allelic/phenotypic level but not at the phenotypic/allelic level in whole population studies, such as HLA-C*07/*01. The discrepancy is presumably because of the multifactorial nature of PsA and the limitations of the research.

Intra-study heterogeneity is important in meta-analysis. Heterogeneity can be effectively removed when stratified by quality for HLA-C*07. Moreover, sources of heterogeneity for other factors were explored using univariate meta-regression based on year of publication, size of cohort and case/control ratio. Nevertheless, they were not statistically correlated with heterogene-

ity. Heterogeneity may arise from the different genetic backgrounds, environmental exposure, bias for cases and controls through selection or unknown variables.

Meta-analysis is a useful strategy to improve analysis and statistical evidence by enlarging the effective sample size. To our knowledge, this is the first meta-analysis that has combined previously-published case-control studies to precisely analyze the association between HLA-C polymorphism and risk of PsA in Caucasian populations. Nevertheless, several inherent limitations of this meta-analysis should be addressed. First, we only considered reports published in English so language bias is inevitable. Studies with negative data may not have been represented because they are more difficult to publish than studies with positive data. Second, the populations studied here were only populations of European and Middle Eastern descent. Thus, the conclusions of this study should be interpreted with caution for individuals of other ethnicities. Multi-ethnic populations should be incorporated into future studies. Finally, we were unable to explore the possibility that results would vary in subjects of different ages, duration of disease and discrepancies in clinical characteristics.

In conclusion, the pooled results suggest a significant association between PsA and HLA-C polymorphism in populations of European and Middle Eastern descent. At the allelic level, HLA-C*02, *06 and *12 were associated with increased risk of PsA, while HLA-C*03, *04, *05, *07 and *16 had a decreased association of risk of PsA. At the phenotypic level, seven phenotypes had significant association with PsA. Positive associations were observed for HLA-C*01, *02, *06 and *12. Negative associations were observed for HLA-C*04, *14 and *15. At both allelic and phenotypic levels, HLA-C*02, *06 and *12 may contribute to susceptibility to PsA, while HLA-C*04 may confer a protective role against PsA. To further establish these relationships, future studies with larger sample sizes, and more accurate disease subgroup stratification with multi-ethnic sample groups are required.

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