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ORIGINAL PAPER

HLA-A*01:01 in MHC is associated with psoriatic arthritis in Chinese Han population

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Abstract

To verify whether PsA-associated HLA alleles proposed in other populations are also related to PsA in Chinese Han population, a study of PsA susceptible alleles in the HLA-A, HLA-B, HLA-C and HLA-DRB1 alleles was presented for Chinese Han population. Genotyping was performed by Illumina Miseq platform (Illumina, USA). 50 subtypes and 77 subtypes of HLA-A, HLA-B, HLA-C and HLA-DRB1 with minor allele frequency (MAF) > 1% were genotyped from two-digit and four-digit resolution analysis in 111 PsA and 207 HCs (healthy controls) collected from Chinese Han population, respectively. Data handling, quality control and association analysis were performed using SPSS 25.0 software. In risk estimate, by mean of Bonferroni correction, a newfound four-digit allele HLA-A*01:01 [$P = 5.5 \times 10^{-4}$, OR 3.35 (1.69–6.66)], four-digit allele HLA-C*06:02 [$P = 8.5 \times 10^{-7}$, OR 3.80 (2.23–6.47)] and six two-digit alleles HLA-A*01 [$P = 5.2 \times 10^{-5}$, OR 3.43 (1.89–6.23)], HLA-B*13 [$P = 4.0 \times 10^{-6}$, OR 2.65 (1.76–4.01)], HLA-B*27 [$P = 7.5 \times 10^{-4}$, OR 5.84 (2.09–16.29)], HLA-B*57 [$P = 5.8 \times 10^{-5}$, OR 20.10 (4.65–86.83)], HLA-C*03 [$P = 2.1 \times 10^{-4}$, OR 0.40 (0.25–0.65)], HLA-C*06 [$P = 1.9 \times 10^{-12}$, OR 4.48 (2.95–6.81)] showed statistical significance by the univariate binary logistic regression analysis. Besides, in the binary logistic regression analysis with multiple variables, when the two alleles HLA-A*01:01 and HLA-C*06:02 were considered as covariates, HLA-A*01:01 [$P = 2.7 \times 10^{-3}$,OR 2.95 (1.46–5.98)] also showed significant association for PsA as risk factor, but may be not the main risk factor [HLA-C*06:02, $P = 3.0 \times 10^{-6}$, OR 3.68 (2.13–6.37)]. When all the above two-digit alleles were included as covariates, HLA-A*01 [$P = 4.8 \times 10^{-2}$, OR 2.00 (1.01–3.94)], HLA-B*13 [$P = 4.2 \times 10^{-5}$, OR 2.62 (1.65–4.16)], HLA-B*27 [$P = 1.7 \times 10^{-4}$, OR 7.62 (2.64–21.96)], HLA-B*57 [$P = 2.97 \times 10^{-4}$, OR 15.90 (3.55–71.18)], HLA-C*06 [$P = 6.1 \times 10^{-5}$, OR 2.70 (1.66–4.40)] showed significant for PsA as risk factors, HLA-C*03 [OR 0.65 (0.39–1.09), $P = 0.10$] showed no association with PsA. In conclusion, we assessed HLA-A, HLA-B, HLA-C and HLA-DRB1 alleles in PsA cohort of Chinese Han population, found HLA-A*01:01 and HLA-A*01 may be the susceptible genes associated with PsA, and also confirmed the association of four loci with PsA in Chinese Han population. These findings may extend the susceptibility HLA alleles of PsA and help in developing possible genetic markers to predict PsA.

Keywords Psoriatic arthritis · HLA-A*01:01 allele · Chinese Han population · Human leucocyte antigen · Genetics

Abbreviations

PsA	Psoriatic arthritis
PsC	Cutaneous psoriasis
PsV	Psoriasis vulgaris
GWAS	Genome-wide association studies
HLA	Human leucocyte antigen
MHC	Major histocompatibility complex
HC	Healthy control

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Introduction

Psoriatic arthritis (PsA) is a chronic autoimmune disease. Patients with PsA usually have psoriatic skin, which is caused by the attacking of keratinocytes by immune cells and includes epidermal hyperplasia, hyperkeratosis,

parakeratosis, Munro's microabscesses and mixed dermal infiltrates, and arthritis damage presenting peripheral arthritis, finger pain, cystitis and axial disease. In the world population, about 30% patients with psoriasis have PsA, the prevalence of PsA may close to 1% [10]. Patients with PsA are more likely to have a higher risk to suffer from cardiovascular events, depression and anxiety [16]. The pathogenesis of PsA is complex and still unclear, it is usually believed that both genetic and environmental factors contribute to the onset of PsA.

PsA has been studied recently and a number of associated variants within human leucocyte antigen (HLA) have been discovered. The genome-wide association studies (GWAS) was the usually method to study the genovariation of PsA patients, and some susceptibility loci had been identified associated with PsA (e.g. IL23R, TNFAIP3 [24], TRAF3IP2 [13] and Rel [9]). And the biological function of these genes correlation with some signaling pathways related to disease pathology of PsA. For instance, TNFAIP3 encodes a zinc finger protein, a negative regulator of inflammatory response in NFκB pathway [18]. However, the GWAS studies are mainly focus on non-MHC (major histocompatibility complex). In research of the rare mutations in MHC, sequence analysis and HLA fine-mapping analysis were more useful methods.

The MHC plays an important role in the immune-related diseases at 6p21.3, and confers a strong genetic risk of PsA. Genetic studies for MHC had revealed a number of PsA-associated HLA alleles. Among these alleles, some played as protective role and some conferred susceptible risk in pathological process of PsA. For example, HLA-B*38, HLA-B*13, HLA-B*37, HLA-B*27, HLA-B*17 and HLA-Bw*16 were extremely strong or strong susceptibility-associated alleles for PsA, and HLA-B*12 and HLA-Bw*35 were extremely strong or strong protective alleles for PsA in white population [27]. HLA-B*38 and HLA-Cw6 alleles were positively associated with PsA, HLA-A*11 and HLA-B*7 were negatively associated with PsA in Argentine population [20].

PsA and PsC (cutaneous psoriasis) are the subphenotypes of PsV (psoriasis vulgaris), and both PsA and PsC were associated MHC. Compared to PsC, there were some potential specific genetic markers for PsA. For instances, HLA-B*27, HLA-B*38, HLA-B*39 and HLA-C*12 were confirmed as PsA-specific risk alleles in a family based association study [8]. The frequency of HLA-B*27 and HLA-Cw*12 were significant higher in PsA patients in Chinese population comparing to psoriasis [14]. Notably, HLA-B was the primary risk heterogeneity between PsA and PsC, HLA-B amino acid position 45 was the driving MHC position to modulate differential risk of PsA and PsC [17], and amino acid at position 97 of HLA-B that increased PsA risk was the most significant associated with PsA [3].

However, most of these studies on PsA were performed in European groups (e.g., UK [12], Irish [25], Spanish [19], Polish [23]), and the study on Chinese population is few [14]. Thus, in this study, we aimed to investigate the association of HLA alleles with PsA in Chinese Han population.

Materials and methods

Study population

In this population-based case–control study, we included 111 adult psoriasis patients with PsA (72 male, 39 female; mean ± SD age 45.10 ± 13.50 years, range 14–80) and 207 ethnically and geographically matched healthy controls (HCs) (131 male, 76 female; mean ± SD age 45.81 ± 13.51 years, range 14–80). In addition, there was no significant difference in gender between case group and healthy control (HC) group ($P > 0.05$, $\alpha = 0.05$) by Chi-square test.

All participants were Chinese Han population from mainland of China, and all affected patients were recruited from multiple hospitals in the area of China. All adult psoriasis patients with PsA were diagnosed and confirmed by at least two experienced dermatologists according to the standard of diagnosis of CASPAR (ClASsification criteria for Psoriatic ARthritis). The demographic and clinical characteristics of the study population information through a full clinical checkup were collected by well-designed questionnaire surveys. All the controls used were individuals recruited from the same area without psoriasis, any autoimmune disorders systemic disorders and any family history of psoriasis (including first-, second- and third-degree relatives). Informed consent was obtained from all individual participants included in the study. This study was approved by the Ethics Committee of Anhui Medical University, and conducted according to Declaration of Helsinki principles.

Blood sampling and DNA extraction

EDTA-anticoagulated venous blood samples were collected from all participants. Genomic DNA was extracted from peripheral blood lymphocytes by standard procedures using Flexi Gene DNA kits (Qiagen, Hilden, Germany). The concentration and purity of DNA measured by Nanodrop 2000 (Thermo Fisher Scientific, USA) were ≥ 10 ng/μL, OD260/OD280 = 1.8–2.2. And the DNA integrity was tested by agarose gel electrophoresis. Extracted genomic DNA was amplified by PCR using locus-specific primers for each of the HLA-A, HLA-B, HLA-C and HLA-DRB1 loci based on the association between HLA and PsA demonstrated in different populations.

HLA-A, HLA-B, HLA-C and HLA-DRB1 genotyping

Depending on the FastTarget™ multi-purpose region enrichment sequencing technology, two-way sequence-based typing was performed for HLA genotyping. The primers of 11 enrichment and amplification segments and 3 enrichment systems had been designed to amplify exon 2 and exon 3 of HLA-A, HLA-B, HLA-C and HLA-DRB1 region and build multiplex PCR amplification systems of the target regions. PCR (ABI 7300 Real-Time PCR System, Thermo Fisher Scientific, USA) amplification had been performed through bidirectional sequencing using Illumina Miseq system (Illumina, USA) in 2 × 250 bp sequencing mode. Bioinformatics reading, quality check for the PCR amplification products that the sequencing quality value Q30 for all samples was not less than 92%. Filter incompatible reads, compared the products to primers and HLA database (IPD-IMGT/HLA 3.21.0, http://hla.alleles.org/alleles/index.html), then deep sequencing of overall sequencing of each sample had been performed using software Blast+ (https://blast.ncbi.nlm.nih.gov/Blast.cgi). Through aligned to HLA reference sequences and compared with HLA database, then the four-digit allele of each sample was typed using software HLAminer v.1.3.1.

Statistical analysis

Univariate logistic regression analysis

In this study, SPSS 25.0 software was used for all statistical analysis. The frequencies of HLA-A, HLA-B, HLA-C and HLA-DRB1 alleles were calculated by direct counting of HLA genotypes, and compared between patients with PsA and HCs. For each HLA allele with frequencies greater than 0.01, we assessed variant risk in a univariate logistic regression model. In total, 50 subtypes of HLA-A, HLA-B, HLA-C and HLA-DRB1 with minor allele frequency (MAF) > 1% were genotyped from the two-digit resolution analysis, 77 subtypes of HLA-A, HLA-B, HLA-C and HLA-DRB1 with minor allele frequency (MAF) > 1% were genotyped from the four-digit resolution analysis in 111 PsA and 207 HCs. P values were regarded as significant if they were less than 0.05 in one hypothesis test, with the consideration of multiple tests and based on formal Bonferroni correction, the threshold for statistical significance of HLA-A, HLA-B, HLA-C and HLA-DRB1 alleles were $P < 1 \times 10^{-3}$ (P0/n, P0 = 0.05, $n = 50$ HLA subtypes) and $P < 6.5 \times 10^{-4}$ (P0/n, P0 = 0.05, $n = 77$ HLA subtypes) for two-digit and four-digit resolution analysis, respectively [1]. The risk contributed by the alleles was evaluated by calculating the odds ratio (OR) with 95% CI.

Multivariate logistic regression analysis

Logistic regression analysis with multiple variables is an effective method to analysis whether the gene had an independent participation in the pathological process of PsA and finds the possible interaction of gene–gene. It is recognized that the HLA alleles are highly polymorphic, and there is a linkage disequilibrium between some HLA genes. To identify the independent contribution of HLA alleles, we tested a binary regression model by including the HLA-C, HLA-B, HLA-A, and HLA-DRB1 risk variants identified by the stepwise regression analysis as covariates. We considered all results significant at the $\alpha = 0.05$ level, and the risk contributed by the alleles was evaluated by calculating the odds ratio (OR) with 95% CI.

Results

For the univariate logistic regression analysis, six HLA alleles and two HLA alleles were showed significant association with PsA in the two-digit resolution and four-digit resolution analysis, respectively. These significant two-digit HLA alleles were HLA-A*01 [$P = 5.2 \times 10^{-5}$, OR 3.43 (1.89–6.23)], HLA-B*13 [$P = 4.0 \times 10^{-6}$, OR 2.65 (1.76–4.01)], HLA-B*27 [$P = 7.5 \times 10^{-4}$, OR 5.84 (2.09–16.29)], HLA-B*57 [$P = 5.8 \times 10^{-5}$, OR 20.10 (4.65–86.83)], HLA-C*03 [$P = 2.1 \times 10^{-4}$, OR 0.40 (0.25–0.65)] and HLA-C*06 [$P = 1.9 \times 10^{-12}$, OR 4.48 (2.95–6.81)] (Table 1; Fig. 1), where HLA-C*03 was a protective allele for PsA in Chinese Han population, the rest of alleles were risk alleles. And the significant four-digit HLA alleles were HLA-A*01:01 [$P = 5.5 \times 10^{-4}$, OR 3.35 (1.69–6.66)] and HLA-C*06:02 [$P = 8.5 \times 10^{-7}$, OR 3.80 (2.23–6.47)] (Table 2; Fig. 2), they were both risk alleles.

Binary logistic regression with multiple variables was applied to all genotyped HLA passed quality control. For the two-digit associated HLA alleles, including the HLA-A*01, HLA-B*13, HLA-B*27, HLA-B*57, HLA-C*03 and HLA-C*06 alleles as covariates, the results in the multivariate logistic regression analysis showed that, except HLA-C*03 [$P = 0.99$, OR 0.65 (0.39–1.09)], the rest of alleles [HLA-A*01, $P = 4.8 \times 10^{-2}$, OR 2.00 (1.01–3.94); HLA-B*13, $P = 4.2 \times 10^{-5}$, OR 2.62 (1.65–4.16); HLA-B*27, $P = 1.7 \times 10^{-4}$, OR 7.62 (2.64–21.96); HLA-B*57, $P = 2.97 \times 10^{-4}$, OR 15.90 (3.55–71.18); HLA-C*06, $P = 6.1 \times 10^{-5}$, OR 2.70 (1.66–4.40)] had statistical significance as risk factor, see Table 3. For the four-digit associated HLA alleles, that is the HLA-A*01:01 and HLA-C*06:02 alleles as covariates, in the multivariate logistic regression analysis, HLA-A*01:01 [$P = 2.7 \times 10^{-3}$, OR 2.95 (1.46–5.98)] still showed significant association for PsA as risk factor, see Table 4. HLA-A*01:01 may be as a risk

Table 1 The two-digit resolution analysis: distribution of HLA-A, HLA-B, HLA-C and DRB1 alleles in 111 PsA and 207 healthy controls ($n=50$ subtypes)

Number	Allele	Groups		OR	95% CI	*P*	S/NS*
		PsA ($n=111$)	HC ($n=207$)				
1	HLA-A*01	31 (14.35%)	19 (4.66%)	3.43	1.89–6.23	5.2×10^{-5}	S
2	HLA-A*02	84 (38.89%)	160 (39.22%)	0.99	0.70–1.38	0.94	NS
3	HLA-A*03	4 (1.85%)	16 (3.92%)	0.46	0.15–1.40	0.17	NS
4	HLA-A*11	39 (18.06%)	84 (20.59%)	0.85	0.56–1.30	0.45	NS
5	HLA-A*24	31 (14.35%)	56 (13.73%)	1.05	0.66–1.69	0.83	NS
6	HLA-A*26	5 (2.31%)	6 (1.47%)	1.59	0.48–5.26	0.45	NS
7	HLA-A*30	9 (04.17%)	11 (2.70%)	1.57	0.64–3.85	0.32	NS
8	HLA-A*31	2 (0.93%)	14 (3.43%)	0.26	0.06–1.17	0.08	NS
9	HLA-A*33	5 (02.31%)	31 (7.60%)	0.29	0.11–0.75	0.01	NS
10	HLA-B*07	7 (3.15%)	14 (3.43%)	0.92	0.36–2.30	0.85	NS
11	HLA-B*13	62 (27.93%)	52 (12.75%)	2.65	1.76–4.01	4.0×10^{-6}	S
12	HLA-B*15	18 (8.11%)	66 (16.18%)	0.46	0.26–0.79	0.005	NS
13	HLA-B*27	15 (6.76%)	5 (1.23%)	5.84	2.09–16.29	7.5×10^{-4}	NS
14	HLA-B*35	9 (4.05%)	49 (12.01%)	0.31	0.15–0.64	0.002	NS
15	HLA-B*37	11 (4.95%)	2 (0.49%)	10.58	2.32–48.19	0.002	NS
16	HLA-B*38	7 (3.15%)	1 (0.25%)	13.25	1.62-108.41	0.02	NS
17	HLA-B*39	5 (2.25%)	4 (0.98%)	2.33	0.62–8.76	0.21	NS
18	HLA-B*40	22 (9.91%)	46 (11.27%)	0.87	0.51–1.48	0.60	NS
19	HLA-B*44	3 (1.35%)	14 (3.43%)	0.39	0.11–1.36	0.14	NS
20	HLA-B*46	10 (4.50%)	29 (7.11%)	0.62	0.29–1.29	0.20	NS
21	HLA-B*48	4 (1.80%)	17 (4.17%)	0.42	0.14–1.27	0.13	NS
22	HLA-B*51	9 (4.05%)	39 (9.56%)	0.40	0.19–0.84	0.016	NS
23	HLA-B*52	4 (1.80%)	12 (2.94%)	0.61	0.19–1.90	0.39	NS
24	HLA-B*55	1 (00.45%)	6 (1.47%)	0.30	0.04–2.53	0.27	NS
25	HLA-B*56	2 (00.90%)	6 (1.47%)	0.61	0.12–3.04	0.55	NS
26	HLA-B*57	20 (9.01%)	2 (0.49%)	20.10	4.65–86.83	5.8×10^{-5}	S
27	HLA-B*58	4 (1.80%)	15 (3.68%)	0.48	0.16–1.47	0.20	NS
28	HLA-B*67	3 (1.35%)	4 (0.98%)	1.38	0.31–6.24	0.67	NS
29	HLA-C*01	34 (15.38%)	76 (18.40%)	0.81	0.52–1.25	0.34	NS
30	HLA-C*02	6 (2.71%)	6 (1.45%)	1.89	0.60–5.94	0.27	NS
31	HLA-C*03	24 (10.86%)	96 (23.24%)	0.40	0.25–0.65	2.1×10^{-4}	S
32	HLA-C*04	10 (4.52%)	32 (7.75%)	0.56	0.27–1.17	0.12	NS
33	HLA-C*06	77 (34.84%)	44 (10.65%)	4.48	2.95–6.81	1.9×10^{-12}	S
34	HLA-C*07	30 (13.57%)	52 (12.59%)	1.09	0.67–1.77	0.73	NS
35	HLA-C*08	16 (7.24%)	39 (9.44%)	0.75	0.41–1.37	0.35	NS
36	HLA-C*12	12 (5.43%)	12 (2.91%)	1.92	0.85–4.35	0.12	NS
37	HLA-C*14	4 (1.81%)	22 (5.33%)	0.33	0.11–0.96	0.04	NS
38	HLA-C*15	7 (3.17%)	25 (6.05%)	0.51	0.22–1.19	0.12	NS
39	HLA-DRB1*03	4 (1.95%)	15 (4.07%)	0.47	0.15–1.43	0.19	NS
40	HLA-DRB1*04	41 (20.00%)	59 (15.99%)	1.31	0.84–2.04	0.23	NS
41	HLA-DRB1*07	39 (19.02%)	42 (11.38%)	1.83	1.14–2.94	0.013	NS
42	HLA-DRB1*08	1 (0.49%)	17 (4.61%)	0.10	0.01–0.77	0.03	NS
43	HLA-DRB1*09	15 (7.32%)	39 (10.57%)	0.67	0.36–1.24	0.20	NS
44	HLA-DRB1*10	4 (1.95%)	3 (0.81%)	2.43	0.54–10.96	0.25	NS
45	HLA-DRB1*11	16 (7.80%)	33 (8.94%)	0.86	0.46–1.61	0.64	NS
46	HLA-DRB1*12	33 (16.10%)	45 (12.20%)	1.38	0.85–2.25	0.19	NS
47	HLA-DRB1*13	4 (1.95%)	25 (6.78%)	0.27	0.09–0.80	0.02	NS
48	HLA-DRB1*14	14 (6.83%)	24 (6.50%)	1.05	0.53–2.08	0.88	NS
49	HLA-DRB1*15	10 (4.88%)	23 (6.23%)	0.77	0.36–1.65	0.51	NS
50	HLA-DRB1*16	24 (11.71%)	42 (11.38%)	1.03	0.61–1.76	0.91	NS

HC healthy control, *HLA* human leucocyte antigen, *PsA* psoriatic arthritis, *CI* confidence interval, *OR* odds ratio, *S* significant difference, *NS* nonsignificant difference

*Correct *P* value by Bonferroni correction for multiple testing. The effective number of chromosomes actually genotyped for HLA-A, B, C and DRB1 are 216, 222, 221 and 205 for PsA with 408, 408, 413 and 369 for healthy controls

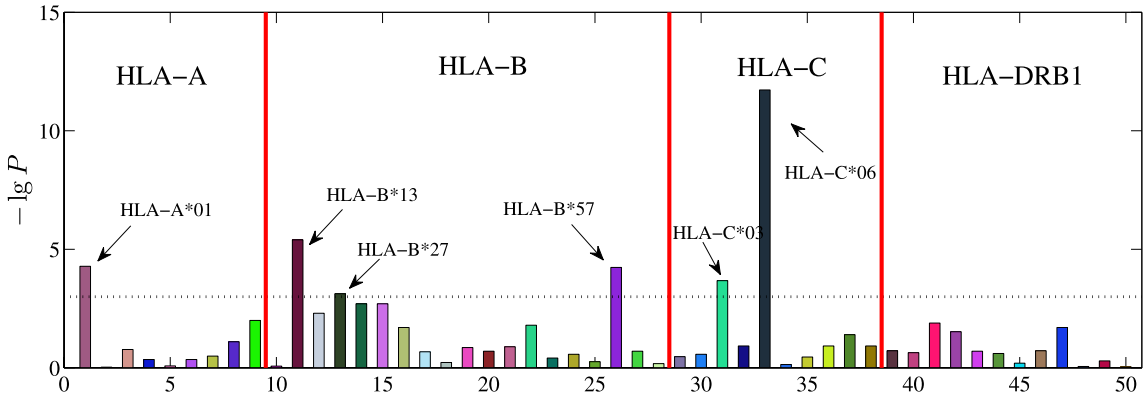

Fig. 1 The two-digit resolution analysis: distribution of HLA-A, HLA-B, HLA-C and DRB1 alleles in patients with psoriatic arthritis ($n=111$) and healthy controls ($n=207$) ($n=50$ HLA subtypes, Crude $P<1\times10^{-3}$ regarded as significant by Bonferroni correction for multiple testing)

factor for PsA independent from other HLA alleles (e.g., HLA-C*06:02) is a new result in Chinese Han population and did not reported in previous literatures, but may be not the main risk factor [HLA-C*06:02, $P=3.0\times10^{-6}$, OR 3.68 (2.13–6.37)].

Discussion

PsA is a normal chronic autoimmune disease affected skin and musculoskeletal system cells. The exact reason of PsA pathogenesis is not clear, but a number of genetic variations of PsA have been revealed in several GWAS studies and sequence confirming studies. Accumulating evidences indicate that MHC is closely association with PsA. People with certain HLA alleles may be more likely to develop PsA, for example, people with HLA-B*27, HLA-B*38, HLA-B*39 and HLA-C*12 alleles can increase the susceptibility to PsA [8].

In the current study, we found that the allele frequency of HLA-A*01:01 was significantly increased among Chinese Han PsA patients, indicating that HLA-A*01:01 maybe a risk factor for PsA patients. Notably, HLA-A*01:01 had not being reported as an independent risk factor for PsA in the literatures up to now. The associations between HLA-A*01, HLA-B*13, HLA-B*27, HLA-B*57, HLA-C*06, HLA-C*06:02 and PsA were also confirmed, which is in accordance with the past researches.

It is known that numerous HLA alleles play an important role in the autoimmune system diseases, HLAs serve as a link between the immune system and what happens inside cells, any alteration on the part of HLA might confuse the immune system when the infections occurs, thus people in that case may increase susceptibility or decrease susceptibility to certain disease [6]. In a large European sample, HLA-A*01:01 was not an independent susceptible gene for PsA and PsC [17]. Maybe different in the race, the HLA alleles also have different structure. In our study, we found that HLA-A*01:01 was a risk factor for PsA in Chinese Han population in binary logistic regression analysis at both univariate and multivariate model. Similarly, the allele HLA-A*01:01 also conferred a strikingly increased risk of EBV-related Hodgkin lymphoma [11]. By contrast, HLA-A*01:01 played as a protective factor in virus infectious diseases [15] and had a striking decrease in the frequency in leprosy patients compare to controls [21, 22].

In this study, HLA-A*01 showed weakly associated with psoriasis patients with PsA in Chinese Han population. In accordance with a means of meta-analysis study [26], HLA-A*01 was found to be a weak risk factor PsA in Caucasian cases. Additionally, HLA-B*27 and HLA-C*06 showed strongly significant associated with PsA suggesting that psoriasis patients with the HLA-B*27 and/or HLA-C*06 may have higher risk of developing PsA [7, 8, 14, 27]. In accordance with these population-based studies, HLA-B*27 and HLA-C*06 also showed significant associated with psoriasis patients with PsA in Chinese Han population. Furthermore, HLA-B*13 and HLA-B*57 also showed significant associated with psoriasis patients with PsA in the previously studies in Caucasians [5].

In our study, based on the Chinese Han population, HLA-C*06:02 showed strongly associated with psoriasis patients with PsA. HLA-C*06:02 and HLA-B*27 are associated with both PsA and psoriasis. Several population-based studies had showed that HLA-C*0602 only present in 20% of PsA patients and conferred strongest genetic marker for psoriasis [2, 4, 12]. For the purpose of distinguish HLA association between PsA and PsC and find PsA-specific associated HLA alleles, further studies had been performed among different European populations. Interestingly, the HLA-C*06:02 as a risk factor for PsA compared to controls in Caucasians from the Greater Toronto Area [7] and UK [12], HLA-C*06:02 was played as a protective role for PsA within psoriasis in

Table 2 The four-digit resolution analysis: distribution of HLA-A, HLA-B, HLA-C and DRB1 alleles in 111 PsA and 207 healthy controls ($n = 77$ subtypes)

Number	Allele	Group		OR	95% CI	Crude *P* value	S/NS*
		PsA ($n = 111$)	HCs ($n = 207$)				
1	HLA-A*01:01	23 (10.65%)	14 (3.43%)	3.35	1.69–6.66	5.5×10^{-4}	S
2	HLA-A*02:01	32 (14.81%)	63 (15.44%)	0.95	0.60–1.51	0.84	NS
3	HLA-A*02:06	14 (6.48%)	33 (8.09)	0.79	0.41–1.51	0.47	NS
4	HLA-A*02:07	12 (5.56%)	18 (4.41%)	1.28	0.60–2.70	0.53	NS
5	HLA-A*02:24	5 (2.31%)	4 (0.98%)	2.39	0.64–9.01	0.20	NS
6	HLA-A*02:549	2 (0.93%)	7 (1.72%)	0.54	0.11–2.60	0.44	NS
7	HLA-A*02:57	1 (0.46%)	6 (1.47%)	0.31	0.04–2.61	0.28	NS
8	HLA-A*02:65	6 (2.78%)	5 (1.23%)	2.30	0.69–7.63	0.17	NS
9	HLA-A*03:01	3 (1.39%)	12 (2.94%)	0.47	0.13–1.67	0.24	NS
10	HLA-A*11:01	25 (11.57%)	44 (10.78%)	1.08	0.64–1.82	0.77	NS
11	HLA-A*11:02	8 (3.70%)	11 (2.70%)	1.39	0.55–3.50	0.49	NS
12	HLA-A*11:05	4 (1.85%)	14 (3.43%)	0.53	0.17–1.63	0.27	NS
13	HLA-A*24:02	20 (9.26%)	38 (9.31%)	0.99	0.56–1.75	0.98	NS
14	HLA-A*24:03	4 (1.85%)	6 (1.47%)	1.26	0.35–4.53	0.72	NS
15	HLA-A*26:01	3 (1.39%)	6 (1.47%)	0.94	0.23–3.81	0.94	NS
16	HLA-A*30:01	7 (3.24%)	5 (1.23%)	2.70	0.85–8.61	0.09	NS
17	HLA-A*31:01	2 (0.93%)	13 (3.19%)	0.28	0.06.35–1.27	0.10	NS
18	HLA-A*33:03	4 (1.85%)	27 (6.62%)	0.27	0.09–0.77	0.02	NS
19	HLA-B*07:02	3 (1.35%)	7 (1.72%)	0.78	0.20–3.07	0.73	NS
20	HLA-B*13:01	11 (4.95%)	17 (4.17%)	1.20	0.55–2.61	0.65	NS
21	HLA-B*13:02	23 (10.36%)	21 (5.15%)	2.13	1.15–3.94	0.02	NS
22	HLA-B*13:08	15 (6.76%)	8 (1.96%)	3.62	1.51–8.69	0.004	NS
23	HLA-B*13:15	13 (5.86%)	6 (1.47%)	4.17	1.56–11.12	0.004	NS
24	HLA-B*15:01	6 (2.70%)	17 (4.17%)	0.64	0.25–1.64	0.35	NS
25	HLA-B*15:18	2 (0.90%)	5 (1.23%)	0.73	0.14–3.81	0.71	NS
26	HLA-B*27:04	14 (6.31%)	1 (0.25%)	27.39	3.58-209.76	0.001	NS
27	HLA-B*35:01	1 (0.45%)	12 (2.94%)	0.15	0.02–1.16	0.07	NS
28	HLA-B*35:43	2 (0.90%)	26 (6.37%)	0.13	0.03–0.57	0.006	NS
29	HLA-B*37:01	11 (4.95%)	2 (0.49%)	10.58	2.32–48.19	0.002	NS
30	HLA-B*38:02	6 (2.70%)	1 (0.25%)	11.31	1.35–94.51	0.03	NS
31	HLA-B*40:01	7 (3.15%)	19 (4.6%)	0.67	0.28–1.61	0.37	NS
32	HLA-B*40:02	1 (0.45%)	6 (1.47%)	0.30	0.04–2.53	0.27	NS
33	HLA-B*40:285	1 (0.45%)	8 (1.96%)	0.23	0.03–1.82	0.16	NS
34	HLA-B*44:02	2 (0.90%)	6 (1.47%)	0.61	0.12–3.04	0.55	NS
35	HLA-B*46:01	10 (4.50%)	29 (7.11%)	0.62	0.29–1.29	0.20	NS
36	HLA-B*48:01	3 (1.35%)	13 (3.19%)	0.42	0.12–1.48	0.18	NS
37	HLA-B*51:01	6 (2.70%)	18 (4.41%)	0.60	0.24–1.54	0.29	NS
38	HLA-B*51:02	1 (0.45%)	8 (1.96%)	0.23	0.03–1.82	0.16	NS
39	HLA-B*52:01	3 (1.35%)	10 (2.45%)	0.55	0.15-2.00	0.36	NS
40	HLA-B*57:01	13 (5.86%)	2 (0.49%)	12.63	2.82–56.48	0.0009	NS
41	HLA-B*58:01	2 (0.90%)	8 (1.96%)	0.45	0.10–2.16	0.32	NS
42	HLA-B*67:01	3 (1.35%)	4 (0.98%)	1.38	0.31–6.24	0.67	NS
43	HLA-C*01:02	22 (9.95%)	44 (10.65%)	0.93	0.54–1.59	0.78	NS
44	HLA-C*01:03	7 (3.17%)	17 (4.12%)	0.76	0.31–1.87	0.55	NS
45	HLA-C*01:67	2 (0.90%)	8 (1.94%)	0.46	0.10–2.20	0.33	NS
46	HLA-C*03:02	5 (2.26%)	13 (3.15%)	0.71	0.25–2.02	0.52	NS
47	HLA-C*03:03	5 (2.26%)	28 (6.78%)	0.32	0.12–0.84	0.02	NS

Table 2 (continued)

Number	Allele	Group		OR	95% CI	Crude *P* value	S/NS*
		PsA ($n=111$)	HCs ($n=207$)				
48	HLA-C*03:04	7 (3.17%)	37 (8.96%)	0.33	0.15–0.76	0.009	NS
49	HLA-C*04:01	7 (3.18%)	21 (5.08%)	0.61	0.26–1.46	0.27	NS
50	HLA-C*06:02	42 (19.00%)	24 (5.81%)	3.80	2.23–6.47	8.5×10^{-7}	S
51	HLA-C*06:04	13 (5.89%)	11 (2.67%)	2.28	1.01–5.19	0.05	NS
52	HLA-C*06:102	14 (6.33%)	4 (0.97%)	6.92	2.25–21.27	0.0007	NS
53	HLA-C*06:127	4 (1.81%)	3 (0.73%)	2.52	0.56–11.36	0.23	NS
54	HLA-C*07:02	22 (9.95%)	34 (8.23%)	1.23	0.70–2.16	0.47	NS
55	HLA-C*08:01	11 (4.98%)	22 (5.33%)	0.93	0.44–1.96	0.85	NS
56	HLA-C*08:03	2 (0.90%)	7 (1.69%)	0.53	0.11–2.57	0.43	NS
57	HLA-C*08:72	3 (1.36%)	5 (1.21%)	1.12	0.27–4.74	0.88	NS
58	HLA-C*12:02	9 (4.07%)	6 (1.45%)	2.88	1.01–8.20	0.05	NS
59	HLA-C*14:02	4 (1.81%)	12 (2.91%)	0.62	0.20–1.93	0.41	NS
60	HLA-C*15:02	5 (2.26%)	8 (1.94%)	1.17	0.38–3.63	0.78	NS
61	HLA-DRB1*03:01	4 (1.95%)	15 (4.07%)	0.47	0.15–1.43	0.19	NS
62	HLA-DRB1*04:03	25 (12.20%)	43 (11.65%)	1.05	0.62–1.78	0.85	NS
63	HLA-DRB1*04:07	13 (6.34%)	14 (3.79%)	1.72	0.79–3.73	0.17	NS
64	HLA-DRB1*07:01	39 (19.02%)	42 (11.38%)	1.83	1.14–2.94	0.01	NS
65	HLA-DRB1*08:03	1 (0.49%)	17 (4.61%)	0.10	0.01–0.77	0.03	NS
66	HLA-DRB1*09:01	15 (7.32%)	39 (10.57%)	0.67	0.36–1.24	0.20	NS
67	HLA-DRB1*10:01	4 (1.95%)	3 (0.81%)	2.43	0.54–10.96	0.25	NS
68	HLA-DRB1*11:01	11 (5.37%)	22 (5.96%)	0.89	0.42–1.88	0.77	NS
69	HLA-DRB1*11:03	4 (1.95%)	8 (2.17%)	0.90	0.27–3.02	0.86	NS
70	HLA-DRB1*12:01	33 (16.10%)	45 (12.20%)	1.38	0.85–2.25	0.19	NS
71	HLA-DRB1*13:01	4 (1.95%)	18 (4.88%)	0.39	0.13–1.16	0.09	NS
72	HLA-DRB1*14:01	8 (3.90%)	11 (2.98%)	1.32	0.52–3.34	0.56	NS
73	HLA-DRB1*14:05	5 (2.44%)	10 (2.71%)	0.90	0.30–2.67	0.85	NS
74	HLA-DRB1*15:01	6 (2.93%)	7 (1.90%)	1.56	0.52–4.70	0.43	NS
75	HLA-DRB1*15:03	3 (1.46%)	11 (2.98%)	0.48	0.13–1.75	0.27	NS
76	HLA-DRB1*16:01	10 (4.88%)	21 (5.69%)	0.85	0.39–1.84	0.68	NS
77	HLA-DRB1*16:02	14 (6.83%)	21 (5.69%)	1.21	0.60–2.44	0.59	NS

HC healthy control, *HLA* human leucocyte antigen, *PsA* psoriatic arthritis, *CI* confidence interval, *OR* odds ratio, *S* significant difference, *NS* nonsignificant difference

*Correct *P* value by Bonferroni correction for multiple testing. The effective number of chromosomes actually genotyped for HLA-A, B, C and DRB1 are 216, 222, 221 and 205 for PsA with 408, 408, 413 and 369 for healthy controls

Irish population [25], and also there was no association between PsA and HLA-C*06:02 when controlled for the age of psoriasis onset in Caucasians from UK, Ireland and Australia populations [3].

In conclusion, we investigated the association of 28 candidate HLA alleles with PsA in Chinese Han population with the genotyping data of 111 adult psoriasis patients with PsA and 207 HCs. To our best knowledge, our study was the first one to relatively comprehensively explore the association between the genetic polymorphisms of HLA loci and PsA in Chinese Han population using binary logistic regression analysis with univariate and multivariate model through both two-digit and four-digit resolution. We found HLA-A*01:01 maybe as a new independent, but not the strongest associated allele for PsA in Chinese Han population, which had not been presented as an independent risk factor in the literature. The HLA-A*01:01 allele may be a risk factor in PsA, which suggests the participation of autoimmunity in the pathogenesis of PsA. Additionally, we verified that HLA-A*01, HLA-B*13, HLA-B*27, HLA-B*57, HLA-C*06 and HLA-C*06:02 were as risk alleles for PsA in Chinese Han population which were basically consistent with the previous studies in other populations. The results extend the susceptibility HLA alleles of PsA in Chinese Han population. However, due to the insufficient numbers of research objective, our study is only a rough selection of

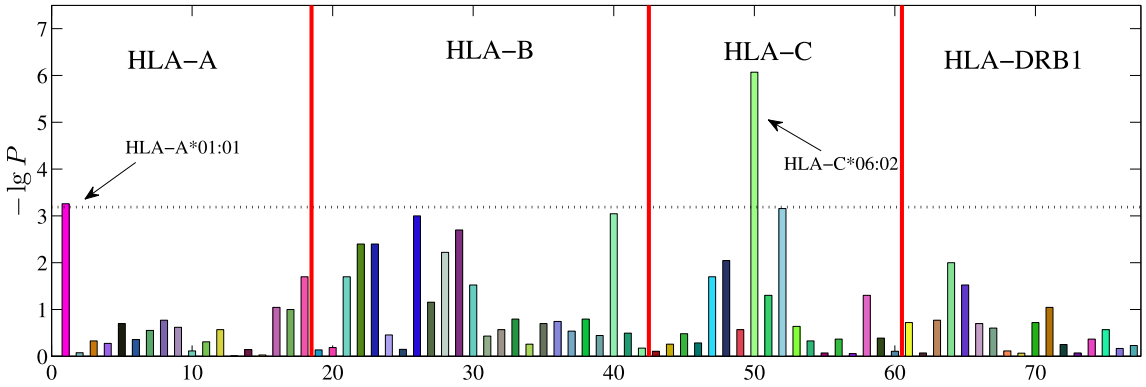

Fig. 2 The four-digit resolution analysis: distribution of HLA-A, HLA-B, HLA-C and DRB1 alleles in patients with psoriatic arthritis ($n=111$) and healthy controls ($n=207$) ($n=77$ HLA subtypes, Crude $P<6.5\times10^{-4}$ regarded as significant by Bonferroni correction for multiple testing)

Table 3 Summary of two-digit HLA alleles for PsA by multivariate logistic regression analysis

Allele	β	*P* value	OR	95% CI
HLA-A*01	0.69	4.8×10^{-2}	2.00	1.01–3.94
HLA-B*13	0.96	4.2×10^{-5}	2.62	1.65–4.16
HLA-B*27	2.03	1.7×10^{-4}	7.62	2.64–21.96
HLA-B*57	2.77	2.97×10^{-4}	15.90	3.55–71.18
HLA-C*03	− 0.43	0.99	0.65	0.39–1.09
HLA-C*06	0.99	6.1×10^{-5}	2.70	1.66–4.40
Constant	− 1.17	8.97×10^{-20}	0.31	–

HLA human leucocyte antigen, *PsA* psoriatic arthritis, *CI* confidence interval, *OR* odds ratio, β regression coefficients

Table 4 Summary of four-digit HLA alleles for PsA by multivariate logistic regression analysis

Allele	β	*P* value	OR	95% CI
HLA-A*01:01	1.08	2.7×10^{-3}	2.95	1.46–5.98
HLA-C*06:02	1.30	3.0×10^{-6}	3.68	2.13–6.37
Constant	− 0.85	1.76×10^{-19}	0.43	–

HLA human leucocyte antigen, *PsA* psoriatic arthritis, *CI* confidence interval, *OR* odds ratio, β regression coefficients

possible susceptibility genes for PsA, further study of larger samples and many questions concerning the role of HLA genes in PsA that still need to be addressed.

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Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to declare.

Ethical approval This study was approved by the Ethics Committee of AnHui Medical University, and conducted according to Declaration of Helsinki principles.

Informed consent The participants provided written informed consent.

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