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ORIGINAL RESEARCH ARTICLE

HLA Correlations with Clinical Phenotypes and Risk of Metabolic Comorbidities in Singapore Chinese Psoriasis Patients

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Abstract

Introduction Psoriasis is a systemic, chronic inflammatory disease that not only afflicts the skin but is also associated with cardiovascular disease and metabolic syndrome. The strongest susceptibility loci for the disease is within the human leukocyte antigen (HLA) complex, though specific HLA allelic associations vary between populations.

Objective Our objective was to investigate HLA associations with clinical phenotypes of psoriasis and metabolic syndrome in Chinese psoriasis cases.

Methods We conducted an observational case–control study in Singapore with a cohort of psoriasis cases consecutively recruited from an outpatient specialist dermatological center ($n = 120$) compared with 130 healthy controls.

Results Significant HLA associations with psoriasis were observed with HLA-A*02:07, B*46:01, C*01:02, and C*06:02. The three-locus haplotype of A*02:07-C*01:02-B*46:01 was also significant (odds ratio [OR] 3.07; $p = 9.47 \times 10^{-5}$). We also observed an association between nail psoriasis and HLA-A*02:07 carriers (OR 4.50; $p = 0.002$), whereas C*06:02 carriers were less prone to have nail involvement (OR 0.16; $p = 0.004$). HLA-A*02:07 was also identified as a possible risk allele for hypertension (OR 2.90; $p < 0.05$), and C*01:02 was a possible risk allele for dyslipidemia (OR 3.36; $p < 0.05$), both known to be common comorbidities in patients with psoriasis.

Conclusion Our results demonstrate the growing importance of discerning population-specific clinical phenotypes and their association with certain HLA alleles in psoriasis.

1 Introduction

Psoriasis is a chronic, inflammatory disorder characterized by keratinocyte hyperproliferation and lymphocytic infiltration of the lesion [1, 2]. Although the occurrence of psoriasis is not limited to a single geographic region or ethnic group, its prevalence varies, occurring in nearly 0.73–2.9% of Europeans and < 0.5% of Chinese and other Asian populations

Key Points

Different clinical phenotypes of psoriasis exhibit an association with certain human leukocyte antigen (HLA) alleles, and these alleles are specific to each population.

Comorbidities in psoriasis, including hypertension and dyslipidemia, were associated with carriage of HLA-A*02:07 and HLA-C*01:02, respectively.

The identification of population-specific phenotypes can aid clinicians in the diagnosis and clinical management of psoriasis.

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[3]. The association between psoriasis and human leukocyte antigen (HLA), specifically with HLA-Cw*06, was first reported in the 1980s [4] and has been confirmed in subsequent studies [5–7]. The disease prevalence is closely correlated with the frequency of the HLA-Cw*06 allele in these populations [8], and environmental factors have been suggested to contribute a role [3]. Psoriasis patients carrying the HLA-Cw*06 allele appear to have a distinct clinical phenotype compared with non-Cw*06 carriers, such as association with an earlier age of psoriasis onset [9, 10], more severe disease course, higher incidence of guttate psoriasis [11, 12], increased observations of Koebner's phenomenon [6], and remission of psoriasis symptoms during pregnancy [10].

HLA-Cw*01 and HLA-B*46 alleles have been associated with psoriasis in Asian populations, including Japanese [13], Thai [14], and Chinese [15]. The limited number of studies investigating the correlations between clinical presentation of psoriasis and the B*46-Cw*01 haplotype have suggested that the clinical form of psoriasis from these carriers might be distinct from that in HLA-Cw*06 carriers [14, 15]. Specifically, this haplotype was associated with late-onset of psoriasis (at > 40 years) [14] and Psoriasis Area and Severity Index (PASI) scores > 10 [15]. However, these clinical associations were elicited from different ethnic groups and with lower-resolution HLA-genotyping methods. Hence, in this study, we evaluated these parameters in a single population using sequence-based typing (SBT) to achieve a better resolution.

Metabolic syndrome is a common problem encountered in the clinical management of patients with psoriasis. Metabolic syndrome is defined as the presence of three or more criteria of the NCEP-ATP III (US National Cholesterol Education Programme Adult Treatment Panel III) in an individual: abdominal obesity, hypertriglyceridemia, low level of high-density lipoprotein (HDL) cholesterol, high blood pressure, and raised fasting blood glucose. In a meta-analysis of 35 observational studies across 20 countries, the odds of metabolic syndrome were increased more than twofold among patients with psoriasis when compared with non-psoriasis controls [16]. Importantly, most studies also reported a high overall prevalence of metabolic syndrome among patients with psoriasis, ranging from 14 to 40%. There also appears to be a dose–response relationship between severity of psoriasis and prevalence of metabolic syndrome [17]. Furthermore, psoriasis has been shown in a meta-analysis to be associated with an up to threefold increase in the risk of myocardial infarction and a 1.6-times higher risk of stroke [18]. Taken together, these findings reinforce the universal importance of regular screening for cardiometabolic risk factors and appropriate lifestyle modifications in patients with psoriasis [19].

With the increasing prevalence of obesity and diabetes among the general population, metabolic syndrome will likely become an even more common problem in the coming decade. Thus, identifying potential genetic and biomarkers for metabolic syndrome associated with psoriasis can help minimize or prevent potential cardiovascular and cerebrovascular morbidity and mortality via early detection and intervention. To the best of our knowledge, this is the first study that attempts to correlate associations between HLA genotypes, psoriasis, and components of metabolic syndrome in a single cohort.

2 Materials and Methods

2.1 Patient Collection

A total of 120 unrelated Chinese psoriasis patients were recruited from the National Skin Centre in Singapore between 2015 and 2018. At the time of recruitment, venous blood was collected in K3 EDTA tubes (Griener Bio-One, GmbH, Kremsmünster, Austria), and patients were assessed for a family history of psoriasis and other comorbidities. This study was approved under institutional review board number 2014/01132 "Genetic susceptibility in psoriasis with psoriatic arthritis and metabolic syndrome" and conducted according to the principles of the Declaration of Helsinki. Patients were aged ≥ 21 years with a clinical diagnosis of psoriasis confirmed by a dermatologist and were recruited from the Psoriasis and Photodermatology Clinics, which see moderate-to-severe cases of psoriasis. Venous plasma glucose was measured via the glucose oxidase method, and serum cholesterol and triglycerides were measured via enzymatic procedures. A questionnaire was used to collect data on ethnicity, age, psoriasis duration, and self-reported diagnosis of diabetes (fasting blood glucose ≥ 7.0 mmol/L or random blood glucose ≥ 11.1 mmol/L), hypertension (systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg), dyslipidemia (HDL < 1.0 mmol/L and/or low-density lipoprotein [LDL] > 3.4 mmol/L and/or triglycerides > 1.7 mmol/L) and ischemic heart disease. Controls were 130 healthy Singapore Chinese donors from an anonymized database [20].

2.2 DNA extraction and Genotyping Analysis

DNA was extracted from whole blood using the Gentra Puregene Blood and Tissue Kit (Qiagen GmbH, Hilden, Germany) according to manufacturer's instructions. Briefly, red blood cell (RBC) lysis buffer was added to whole blood to lyse RBCs. After RBC lysis, tubes were centrifuged to pellet the peripheral blood mononuclear cells (PBMCs). PBMCs were subsequently lysed with cell lysis buffer and

vortexed to completely lyse cells. Protein precipitation solution was added and vortexed to precipitate the protein. This was followed by another round of centrifugation, after which the supernatant was decanted into isopropanol to precipitate the DNA. The DNA pellet was then washed with 70% ethanol, and DNA hydration solution was used to dissolve the DNA pellet.

Polymerase chain reaction (PCR) was carried out to amplify the HLA loci of interest, namely HLA-A, -B, -C, and -DRB1 on the ProFlex PCR System (Applied Biosystems, Carlsbad, CA, USA) using previously described primers and protocols [21, 22]. Amplicons were purified using an illustra GFx PCR purification kit (GE Healthcare, Pittsburgh, PA, USA) or ExoSAP-IT (Applied Biosystems) for major histocompatibility complex (MHC) class I loci and HLA-DRB1, respectively. Cycle sequencing was carried out using Big Dye version 1.1 (Applied Biosystems), and HLA alleles were assigned using SBTengine version 3.19 (GenDX, Yalelaan, Utrecht, The Netherlands).

2.3 Statistical Analyses

Statistical analysis was performed using R (version 3.5.1). Allele frequencies (number of alleles divided by total number of alleles) and genotype frequencies (number of people homozygous or heterozygous for an allele divided by total number of people in that category) were obtained by direct counting. The presence of linkage disequilibrium was determined by Fisher's exact test (two-tailed), and the resultant p values were adjusted using the Bonferroni correction for the number of allele subtypes observed at each locus. The same process was used to determine correlations with combinations of alleles. Alleles that exhibited significant (corrected $p < 0.05$) correlations with psoriasis were tested for correlations with clinical symptoms within the psoriasis population. The clinical symptom correlations were determined by Fisher's exact test (two-tailed) and were adjusted using the Bonferroni correction of the number of tests performed for each allele.

3 Results

3.1 Study Population

In this study, 120 Chinese psoriasis patients were recruited from a single clinical center between 2015 and 2018. The age of patients ranged from 21 to 83 years, with 75% of cases diagnosed before they reached 40 years of age (defined as early-onset psoriasis) (Table 1). The psoriatic population was predominantly male (77.5%), duration of the psoriasis was 16.4 ± 11.5 years, and 24% of cases reported a family history of the disease, where the disease was more commonly inherited via the paternal (16%) than the maternal lineage (4%) (Table 1).

In this cohort, 72% of subjects reported issues with their joints and nails. Early psoriatic arthritis, defined as the presence of joint-related symptoms such as early morning stiffness and inflammatory joint pain in the absence of physical signs of joint tenderness and/or swelling, was reported in 5% of the subjects; psoriatic arthritis with clinical synovitis was diagnosed in 18%. Nail psoriasis, defined as the presence of one or more clinical features of nail pitting, onycholysis, subungual hyperkeratosis, oil drop sign, and splinter hemorrhages, was observed in 68%. Both psoriatic arthritis and nail psoriasis were more frequent in males, but this difference was not statistically significant (Table 1).

Table 1 Demographic characteristics of psoriasis cohort

Characteristics	Total ($n = 120$)	Male ($n = 93$)	Female ($n = 27$)
Age (years)			
21–39	36 (30.0)	26 (28.0)	10 (37.0)
40–59	60 (50.0)	47 (50.5)	13 (48.1)
≥ 60	24 (20.0)	20 (21.5)	4 (14.8)
Age of onset (years)			
< 20	24 (20.0)	17 (18.3)	7 (25.9)
20–39	66 (55.0)	50 (53.8)	16 (59.3)
40–59	26 (21.7)	22 (23.7)	4 (14.8)
≥ 60	4 (3.3)	4 (4.3)	0 (0)
Duration of psoriasis (years)			
< 5	15 (12.5)	12 (12.9)	3 (11.1)
5–9	22 (18.3)	20 (21.5)	2 (7.4)
10–19	38 (31.7)	28 (30.1)	10 (37.0)
20–29	29 (24.2)	21 (22.6)	8 (29.6)
30–39	10 (8.3)	7 (7.5)	3 (11.1)
≥ 40	6 (5.0)	5 (5.4)	1 (3.7)
Family history	29 (24.2)	20 (21.5)	9 (33.3)
Paternal affected	19 (15.8)	12 (12.9)	7 (25.9)
Maternal affected	5 (4.2)	4 (4.3)	1 (3.7)
Siblings affected	17 (14.2)	11 (11.8)	6 (22.2)
Nail/joint complaints			
Early psoriatic arthritis	6 (5.0)	4 (4.3)	2 (7.4)
Psoriatic arthritis	22 (18.3)	19 (20.4)	3 (11.1)
Nail psoriasis	82 (68.3)	66 (71.0)	16 (59.3)
Metabolic comorbidities			
Hypertension	39 (32.5)	33 (35.5)	6 (22.2)
Diabetes mellitus	16 (13.3)	13 (14.0)	3 (11.1)
Dyslipidemia	37 (30.8)	26 (28.0)	11 (40.7)
Obesity	92 (76.7)	68 (73.1)	24 (88.9)
Metabolic syndrome	53 (44.2)	38 (40.9)	15 (55.6)

Data are presented as n (%)

Obesity (77%), measured with the Asian body mass index criteria (≥ 27.5 kg/m^2), was the most frequent comorbidity in this cohort, followed by hypertension (33%), dyslipidemia (31%), and diabetes mellitus (13%). Dyslipidemia was more common and disproportionately higher in women (41%) than in men (28%), whereas hypertension was more common in men (36 vs. 22%) (*p* values were not statistically significant) (Table 1).

3.2 HLA Allele and Haplotype Associations with Psoriasis

Four subjects who could not be genotyped at the HLA-DRB1 locus were excluded from analysis, and 116 psoriasis patients remained for HLA association testing. Elevated allele frequencies of HLA-A*02:07, B*46:01, C*01:02, and C*06:02 were observed in psoriasis cases (Table 2), with carriage of C*06:02 and A*02:07 conferring the highest odds of psoriasis (9.56 and 3.34, respectively). In contrast, the allele frequency of A*33:03 was significantly lower in patients with psoriasis than in controls (Table 2). When genotype frequencies were considered, the association between psoriasis and the same alleles (A*02:07, B*46:01, C*01:02, C*06:02) remained (Table 3), additionally, B*13:02 was present at significantly higher frequencies in patients with psoriasis (10%) than in controls (0.8%). Despite previous reports of MHC class II association with psoriasis [13, 23–25], we did not observe any significant associations with the HLA-DRB1 locus in this cohort (Tables S1 and S2 in the Electronic Supplementary Material [ESM]).

Due to extensive linkage disequilibrium within the MHC, certain HLA haplotypes are passed down from parent to offspring as an extended haplotype. HLA-C*06:02 is in linkage with two distinct HLA-B alleles, B*13 and B*57 [10]. These C*06 haplotypes, B*13:02-C*06:02 ($n = 12$) and B*57:01-C*06:02 ($n = 3$), were observed in Singapore Chinese, but neither haplotype was significantly associated with psoriasis in this study. When the other two-locus haplotypes were considered, only two haplotypes were statistically significant after correction for multiple testing: A*02:07- B*46:01 and A*02:07-C*01:02 (Table 4). Although A*02:07-C*01:02-B*46:01 and A*02:07-C*01:02-B*46:01-DRB1*09:01 haplotypes were significantly elevated in psoriasis patients, these haplotypes did not remain significant after Bonferroni correction (Table S3 in the ESM).

We also investigated possible associations between clinical symptoms of psoriasis patients and HLA alleles (A*02:07, B*46:01, C*01:02, C*06:02) that were significantly associated with psoriasis. Although A*02:07, B*46:01, and C*01:02 were identified as risk alleles for psoriasis, none were associated with an earlier age of disease onset (Table S4 in the ESM). Homozygosity for these risk alleles also had no apparent additional risk in development of psoriasis (Table S5 in the ESM).

3.3 HLA Association with Clinical Features of Psoriasis and Metabolic Syndrome

Here, we report that the B*46:01 allele conferred an increased risk of psoriatic arthritis among psoriasis patients (Table 5). Additionally, A*02:07 carriers had the highest odds of reporting nail psoriasis; in contrast, the C*06:02 allele was negatively associated with nail psoriasis (Table 5).

Table 2 Allele frequencies of major histocompatibility complex class I specificities in patients with psoriasis and control subjects

Allele	Allele frequency		OR (95% CI)	*p* value[a]
	Psoriasis ($2n = 232$)	Controls ($2n = 260$)		
HLA-A				
A*02:07	74 (31.9)	32 (12.3)	3.34 (2.10–5.29)	< 0.0001
A*33:03	14 (6.0)	40 (15.4)	0.35 (0.19–0.67)	< 0.05
HLA-B				
B*13:02	12 (5.2)	2 (0.8)	7.04 (1.56–31.8)	ns
B*46:01	68 (29.3)	40 (15.4)	2.28 (1.47–3.54)	< 0.01
B*58:01	13 (5.6)	27 (10.4)	0.51 (0.26–1.02)	ns
HLA-C				
C*01:02	77 (33.2)	48 (18.5)	2.19 (1.45–3.33)	< 0.01
C*06:02	16 (6.9)	2 (0.8)	9.56 (2.17–42.0)	< 0.01

Data are presented as *n* (%) unless otherwise indicated

CI confidence interval, *HLA* human leukocyte antigen, *ns* not significant, *OR* odds ratio

[a] *p* values were corrected for multiple testing

Table 3 Genotype frequencies of major histocompatibility complex class I specificities in patients with psoriasis and control subjects

Allele	Genotype frequency		OR (95% CI)	*p* value[a]
	Psoriasis ($n=116$)	Controls ($n=130$)		
HLA-A				
A*02:07	66 (56.9)	28 (21.5)	4.81 (2.76–8.39)	< 0.0001
A*33:03	14 (12.1)	38 (29.2)	0.33 (0.17–0.65)	< 0.05
HLA-B				
B*13:02	12 (10.3)	1 (0.8)	14.88 (1.90–116.4)	< 0.05
B*46:01	59 (50.9)	35 (26.9)	2.81 (1.65–4.78)	< 0.01
HLA-C				
C*01:02	67 (57.8)	41 (31.5)	2.97 (1.76–5.00)	< 0.001
C*06:02	16 (13.8)	1 (0.8)	20.64 (2.69–158.3)	< 0.001

Data are presented as n (%) unless otherwise indicated

CI confidence interval, *HLA* human leukocyte antigen, *ns* not significant, *OR* odds ratio

[a] *p* values were corrected for multiple testing

Table 4 Two-locus haplotype analysis of psoriasis patients and control subjects

Two-locus HLA		Haplotype frequency (%)		OR (95% CI)	*p* value[a]
		Psoriasis ($2n=232$)	Controls ($2n=260$)		
A*02:07	B*40:01	11.2	2.3	5.34 (1.48–19.26)	ns
A*02:07	B*46:01	44.0	19.2	3.30 (1.86–5.83)	< 0.05
A*11:01	B*46:01	19.8	9.2	2.43 (1.15–5.14)	ns
A*30:01	B*13:02	8.6	0.8	12.17 (1.53–96.60)	ns
A*33:03	B*40:01	0.9	7.7	0.10 (0.01–0.83)	ns
A*02:07	C*01:02	46.6	19.2	3.66 (2.07–6.46)	< 0.01
A*02:07	C*07:02	14.7	2.3	7.27 (2.07–25.51)	ns
A*30:01	C*06:02	8.6	0.8	12.17 (1.53–96.60)	ns
A*33:03	C*03:04	1.7	8.5	0.19 (0.04–0.88)	ns
A*02:07	DRB1*09:01	30.2	11.5	3.31 (1.70–6.46)	ns
A*33:03	DRB1*15:01	0.9	6.9	0.12 (0.01–0.94)	ns
B*13:02	C*06:02	10.3	0.8	14.88 (1.90–116.36)	ns
B*46:01	C*01:02	48.3	26.9	2.53 (1.49–4.31)	ns
B*46:01	C*07:02	9.5	2.3	4.43 (1.21–16.31)	ns
B*38:02	DRB1*16:02	9.5	1.5	6.70 (1.45–30.92)	ns
B*46:01	DRB1*09:01	30.2	15.4	2.38 (1.28–4.42)	ns
B*46:01	DRB1*11:01	6.9	0.8	9.56 (1.18–77.61)	ns
C*01:02	DRB1*04:06	6.9	0.8	9.56 (1.18–77.61)	ns
C*01:02	DRB1*09:01	32.8	16.2	2.53 (1.38–4.64)	ns
C*01:02	DRB1*11:01	7.8	1.5	5.38 (1.14–25.45)	ns

CI confidence interval, *HLA* human leukocyte antigen, *ns* not significant, *OR* odds ratio

[a] *p* values were corrected for multiple testing

Nail psoriasis was present in all patients with psoriatic arthritis, but not all patients with nail psoriasis had psoriatic arthritis (Table S6 in the ESM).

Metabolic comorbidities manifested by patients included hypertension, diabetes mellitus, dyslipidemia, and obesity. In this cohort, carriage of A*02:07 conferred a higher risk of hypertension, and carriage of C*01:02 conferred a higher risk of dyslipidemia (Table 6). However, none of the remaining psoriasis risk alleles conferred such an added risk to any of the comorbidities investigated. Diabetes and obesity also

showed no association with A*02:07, B*46:01, C*01:02, C*06:02, or A*33:03.

Although the frequency of the A*02:07-C*01:02-B*46:01 haplotype was not significantly elevated when comparing patients with psoriasis and healthy controls, when we investigated this three-locus haplotype to see whether it correlated with any other clinical feature within the psoriasis population, this haplotype combination conferred a higher risk of hypertension (OR 2.69; uncorrected $p = 0.02$) and nail psoriasis (OR 3.19; uncorrected $p = 0.009$).

In combination, our data suggest that specific clinical features associated with psoriasis, such as nail psoriasis, are significantly enhanced among Asian patients because of the high frequency of A*02:07 carriers in contrast to the low frequency of occurrences of C*06:02.

4 Discussion

The MHC region has been consistently identified as a psoriasis susceptibility locus [4, 6, 26, 27], and HLA associations have been previously reported across different ethnic groups [3]. In this study, we demonstrated that the frequencies of A*02:07, B*13:02, B*46:01, C*01:02, and C*06:02 were significantly elevated in Singaporean Chinese psoriasis patients. Although reports have shown associations between additional HLA alleles and psoriasis, the risk conferred by C*06:02 remained the highest across these studies [14, 15, 28].

Caucasian C*06:02 carriers have an earlier age of psoriasis onset but are less likely to have nail lesions [10]; the same finding has also been reported in Chinese psoriasis cases [29]. However, C*06:02 carriers in our study ($n = 16$) did not have an earlier age of onset, although this lack of association might be due to the low population frequency of C*06:02 in Asia. Nonetheless, C*06:02-positive psoriasis patients in this study were also less likely to report psoriatic arthritis or nail psoriasis, which corroborates previous reports [10, 29]. Conversely, the HLA-A*02:07 allele was positively associated with psoriatic arthritis and nail psoriasis, thus confirming reports of the association in Japanese [25], Thai [14], and Taiwan Chinese [15] populations, affirming that A*02:07-positive psoriasis might be a clinical group distinct from C*06:02 psoriasis.

In addition to being associated with certain subtypes of psoriasis, the presence of specific HLA alleles can also be a predictor of response to psoriasis treatment. In a recent study, the authors reported that the presence of HLA-A-Bw4-80I was more commonly found in psoriasis patients who required two or more biologics, meaning that this group demonstrated a poor response to biologics [30]. HLA-A-Bw4-80I alleles include HLA-A*24 and HLA-A*32, and these HLA can be recognized by inhibitory KIR3DL1 and activating KIR3DS1 expressed on natural killer (NK) cells

Table 5 Correlations between human leukocyte antigen genotype frequencies and nail/joint complaints

Nail/joint complaints	Allele[a]	Genotype frequency (%) of allele		OR (95% CI)	*p* value[b]
		Joint complaint present	Joint complaint absent		
Early psoriatic arthritis	A*02:07	50.0	57.3	0.75 (0.14–3.86)	ns
	A*33:03	16.7	11.8	1.49 (0.16–13.79)	ns
	B*46:01	33.3	51.8	0.46 (0.08–2.64)	ns
	C*01:02	33.3	59.1	0.35 (0.06–1.97)	ns
	C*06:02	16.7	13.6	1.27 (0.14–11.61)	ns
Psoriatic arthritis	A*02:07	80.0	52.1	3.68 (1.15–11.82)	ns
	A*33:03	15.0	11.5	1.36 (0.34–5.41)	ns
	B*46:01	85.0	43.8	7.29 (2.00–26.52)	< 0.01
	C*01:02	80.0	53.1	3.53 (1.10–11.33)	ns
	C*06:02	5.0	15.6	0.28 (0.04–2.29)	ns
Nail psoriasis	A*02:07	68.4	32.4	4.50 (1.95–10.38)	<0.01
	A*33:03	10.1	16.2	0.58 (0.19–1.82)	ns
	B*46:01	59.5	32.4	3.06 (1.35–6.96)	< 0.05
	C*01:02	67.1	37.8	3.35 (1.48–7.55)	< 0.05
	C*06:02	6.3	29.7	0.16 (0.05–0.50)	< 0.01

CI confidence interval, *ns* not significant, *OR* odds ratio

[a]The total number of individuals bearing the respective alleles were as follows: A*02:07 ($n = 66$), A*33:03 ($n = 14$), B*46:01 ($n = 59$), C*01:02 ($n = 67$), C*06:02 ($n = 16$)

[b]*p* values were corrected for multiple testing

Table 6 Correlations between human leukocyte antigen genotype frequencies and metabolic comorbidities

Comorbidity	Allele[a]	Genotype frequency (%) of allele		OR (95% CI)	*p* value[b]
		Comorbidity present	Comorbidity absent		
Hypertension	A*02:07	67.1	41.3	2.90 (1.34–6.27)	< 0.05
	A*33:03	10.0	15.2	0.62 (0.20–1.90)	ns
	B*46:01	58.6	39.1	2.20 (1.03–4.70)	ns
	C*01:02	65.7	45.7	2.28 (1.07–4.89)	ns
	C*06:02	10.0	19.6	0.46 (0.16–1.33)	ns
Diabetes	A*02:07	65.0	47.5	2.06 (0.72–5.88)	ns
	A*33:03	5.0	15.3	0.29 (0.03–2.47)	ns
	B*46:01	55.0	40.7	1.78 (0.64–4.96)	ns
	C*01:02	60.0	45.8	1.78 (0.63–4.98)	ns
	C*06:02	5.0	16.9	0.26 (0.03–2.15)	ns
Dyslipidemia	A*02:07	60.9	43.2	2.05 (0.90–4.66)	ns
	A*33:03	9.4	18.9	0.44 (0.14–1.44)	ns
	B*46:01	57.8	32.4	2.85 (1.22–6.67)	ns
	C*01:02	67.2	37.8	3.36 (1.45–7.83)	< 0.05
	C*06:02	12.5	18.9	0.61 (0.20–1.85)	ns
Obesity	A*02:07	65.0	55.2	1.51 (0.55–4.11)	ns
	A*33:03	10.0	12.5	0.78 (0.16–3.78)	ns
	B*46:01	50.0	51.0	0.96 (0.37–2.51)	ns
	C*01:02	60.0	57.3	1.12 (0.42–2.98)	ns
	C*06:02	0.0	16.7	na	ns
Metabolic syndrome	A*02:07	60.4	50.0	1.52 (0.69–3.39)	ns
	A*33:03	11.3	15.2	0.71 (0.22–2.29)	ns
	B*46:01	56.6	39.1	2.03 (0.91–4.53)	ns
	C*01:02	67.9	43.5	2.75 (1.21–6.25)	ns
	C*06:02	15.1	15.2	0.99 (0.33–2.98)	ns

CI confidence interval, *na* not applicable, *ns* not significant, *OR* odds ratio

[a]The total number of individuals bearing the respective alleles were as follows: A*02:07 ($n=66$), A*33:03 ($n=14$), B*46:01 ($n=59$), C*01:02 ($n=67$), C*06:02 ($n=16$)

[b]*p* values were corrected for multiple testing

[31, 32]. Hence, the authors suggested that the presence of these alleles might influence NK cell response and weaken the effectiveness of biologic therapy.

HLA-B*46 arose from recombination between HLA-C*01:02 and HLA-B*15:01 [33, 34] and is in linkage disequilibrium with C*01:02, forming a haplotype with a very limited geographic distribution within Southeast Asia [35, 36]. An association between the B*46:01 and Cw*01 alleles and psoriasis has been previously reported in northeastern Thai, Japanese, and Taiwan Chinese populations [8, 13–15]. Furthermore, a study in a Thai population ($n=140$) reported a later age of psoriasis onset in B*46:01/Cw*01 carriers [14], but such an association was not observed in this study, even though we had a similar sample size. Such an observation might be due to the different ethnicities, socioeconomic factors, or access to healthcare, so more studies should be conducted to verify the association between B*46:01/Cw*01 alleles and age of psoriasis onset.

The B*46:01-Cw*01 haplotype was observed at elevated frequencies among psoriatics in the current study, although it did not reach statistical significance after correction for multiple testing. Instead, the A*02:07-B*46:01 and A*02:07-C*01:02 haplotypes remained significant after correction. This suggests that the psoriasis susceptibility locus might lie nearer to the telomeric A*02:07 locus instead of B*46:01 being a susceptibility locus, as proposed in the Taiwanese study [15]. Moreover, A*02:07 has a valine residue at position 95, which was associated with increased risk of psoriasis in psoriasis patients of European ancestry, whereas the risk amino acids for HLA-B were not similar [37]. This supports the associated risk allele for psoriasis to be closer to the HLA-A locus than to HLA-B. Further evidence for the susceptibility locus to be A*02:07 is bolstered

by a transethnic genome-wide meta-analysis (GWMA) that highlighted A*02:07 as a susceptibility allele in Chinese psoriasis cases [38].

In addition to reporting HLA alleles that increase the risk of psoriasis, we observed that A*33:03 was associated with a reduced risk of this disease. This protective effect has been reported in Thai [14] and Korean [39] populations, but this is the first study to report it in Han Chinese. This allele is part of a conserved extended MHC haplotype, A*33:03-C*03:02-B*58:01-DRB1*03:01, that spans nearly the entire MHC region [40]. Even so, it is interesting that only the HLA-A locus, but not the haplotype, demonstrated a significant protective effect against psoriasis. HLA-A*33:03 has been reported to be a risk factor for ticlopidine-induced liver injury [41] and is also associated with susceptibility to enterovirus 71 infection [42] and development of nasopharyngeal carcinoma [43], but how this allele confers its protective effect remains to be investigated.

Dyslipidemia is a common comorbidity in psoriasis patients with metabolic syndrome [44, 45] and is an established risk factor for cardiovascular disease. To elucidate this link, emerging evidence indicates that dyslipidemia may be associated with altered lipoprotein function and accelerated atherosclerosis in psoriasis [46]. It has also been shown recently that patients with psoriasis have higher levels of oxidized LDL and high-sensitivity C-reactive protein, which are atherogenic risk markers, than do healthy controls [47].

Interestingly, an association between C*01:02 and dyslipidemia was observed in this study. Genome-wide association studies on dyslipidemia in Caucasians showed that risk loci for dyslipidemia are not found within the MHC [48, 49], but a study in a Japanese cohort found that BTN2A1 (rs6929846), a gene within the MHC class I region, was associated with increased risk of dyslipidemia [50]. Hence, it will be interesting to see whether this association between HLA-C*01:02 and dyslipidemia can be replicated in larger cohorts.

One limitation is that PASI scores were not available for recruited subjects in this study, and it would have been interesting to know whether certain HLA alleles were associated with higher PASI scores. Although some of the patients may have had PASI scores recorded as part of their clinical care, a "spot" PASI score taken at recruitment might not have been suitable to assess the severity of psoriasis, as patients might have quiescent, mild, or well-controlled disease as a result of ongoing treatment.

The small size of our patient population is another limitation of this study; a larger replication study should be performed to establish genotype–phenotype correlations and predict the risk of developing comorbidities in psoriasis, so that high-risk patients may be stratified for early intervention.

In conclusion, we have demonstrated a high prevalence of metabolic comorbidities in our Singapore Chinese psoriasis cohort, particularly obesity, hypertension, and dyslipidemia. HLA-A*02:07 was associated with hypertension and C*01:02 was associated with dyslipidemia in psoriasis. Nail psoriasis was positively associated with HLA-A*02:07 and less likely to be present in HLA-C*06:02 carriers. B*46:01 psoriatics were also more likely to report psoriatic arthritis. This is a significant addition to our understanding of psoriasis, as the population-specific genetic background manifests itself in the enhanced occurrence of subsets of clinical features within psoriasis.

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Compliance with Ethical Standards

Conflict of interest MS, SWDL, EST, HHO, and ECR have no conflicts of interest that are directly relevant to the content of this article.

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