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Association of *ERAP1* gene polymorphisms with the susceptibility to psoriasis vulgaris

A case–control study

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Abstract

Psoriasis vulgaris (PsV), also known as plaque psoriasis, is a life-threatening autoimmune skin disease. Inflammatory factors may contribute to the development of PsV. Present study aimed to explore the association of endoplasmic reticulum aminopeptidase 1 (*ERAP1*) gene polymorphisms (rs26653 and rs27524) with PsV susceptibility in a Chinese Han population. Subgroup analysis was also performed based on the onset of PsV.

Present case–control study included 143 patients with PsV and 149 healthy controls. Direct sequencing method was used for genotyping *ERAP1* polymorphisms. Chi-squared test was used to estimate the association between *ERAP1* polymorphisms and PsV susceptibility. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to assess association strength.

The polymorphism rs26653 was positively correlated with PsV susceptibility (CC vs GG, $P = .047$, OR = 1.964, 95% CI = 1.006–3.834; C vs G, $P = .042$, OR = 1.403, 95% CI = 1.011–1.946). Meanwhile, its CC genotype and C allele were positively associated with the early onset of PsV ($P = .036$, OR = 2.080, 95% CI = 1.044–4.145; $P = .034$, OR = 1.443, 95% CI = 1.028–2.024) and increased PsV risk in the subgroup with family history ($P = .029$, OR = 2.149, 95% CI = 1.075–4.296; $P = .027$, OR = 1.466, 95% CI = 1.044–2.059).

ERAP1 gene rs26653 polymorphism may increase the risk of PsV in Chinese Han population.

Abbreviations: CHB = Chinese Han in Beijing, CIs = confidence intervals, EO-PsV = early onset psoriasis vulgaris, ERAP1 = endoplasmic reticulum amino peptidase 1, GWAS = genome wide association study, HLA = human leukocyte antigen, HWE = Hardy–Weinberg equilibrium, INF = interferon, LO-PsV = late onset psoriasis vulgaris, MHC = major histocompatibility complex, NF-κB = nuclear factor kappa B, ORs = odds ratios, PsV = psoriasis vulgaris, SNPs = single-nucleotide polymorphisms.

Keywords: *ERAP1*, polymorphisms, psoriasis vulgaris, subgroup analysis

1. Introduction

Psoriasis vulgaris (PsV) is one of the most common long lasting inflammatory skin diseases.[1] PsV usually affects back, scalp, elbows, and knees,[2] and is characterized by erythema and plaques. PsV may attack people of all ages, but mainly in young adults. According to onset age, PsV could be divided into early onset PsV (EO-PsV) and late onset PsV (LO-PsV).[3] PsV, a life-threatening disease, is intractable and tends to relapse. Even worse, PsV may cause different complications.[4] PsV decreases the life quality of its patients, and imposes heavy mental pressure and economic burden on family member.[5] Epidemiology study has suggested that PsV exhibits high prevalence globally.[6] The pathogenesis of PsV is not fully understood, but it is well known that vascular remodeling, epidermal hyper-proliferation and inflammation are major histopathology for PsV. PsV is universally considered to be a genetic disease which is affected by ethnicity, region, and environment factors.[7,8] T-cells mediate the proliferation of cutaneous cells in patients with PsV.[9] Many elements in immune system may contribute to the development of PsV.[10]

Endoplasmic reticulum amino peptidase 1 (ERAP1), an aminopeptidase induced by γ-interferon (INF), belongs to the zinc finger metal matrix peptidase M1 family.[11] As a cytokine receptors on cell surface, ERAP1 may act as an antigen-processing machinery involved in proteins' process and transport.[12,13] Additionally, ERAP1 also participates in the trimming of HLA class-I-binding precursors,[14,15] and regulates the function of natural killer cells.[16] Besides, ERAP1 has been reported to take part in psoriasis.[17]*ERAP1* gene is located at chromosome 5q15. Many polymorphisms in *ERAP1* gene have been identified to be possibly able to alter proteins' conformational structure, specificity, and activity.[18] Nonsynonymous single-nucleotide polymorphisms (SNPs), rs26653 (Arg127Pro), rs30187 (Lys528Arg), and rs27044 (Gln730Glu) have been found in different exons in *ERAP1* gene. Genome-wide association study (GWAS) found that rs27524 is an additional

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Table 1

Primer sequences of *ERAP1* gene polymorphisms.

rs ID	Region	Allele	Variation	Primer sequence	Annealing (°C)
rs26653	Exon2	C/G	Arg127Pro	F: 5′-GAGGCAAATTGCTAGATCGGA-3′ R: 5′-GCTGGTCGGCTTTGGTGA-3′	55
rs27524	3′UTR	A/G	None	F: 5′-GGAGAGAGGCTATCGGAAGAACCC-3′ R: 5′-CCGAAAGATTGCCAGCATAGTGAA-3′	60

psoriasis-associated variant.[19] And some polymorphisms are significantly associated with human leukocyte antigen (HLA)-C*06 in patients with psoriasis.[20,21] All the evidences suggested that *ERAP1* gene polymorphisms played a crucial role in inflammatory response in PsV.

Polymorphism distributions are usually different between regions. In current study, we selected 2 SNPs not widely studied in China, rs26653 and rs27524, to detect their association with PsV susceptibility in a Chinese Han population.

2. Materials and methods

2.1. Study subjects

A total of 143 patients with PsV were recruited from Linyi People's Hospital. Healthy individuals without systemic autoimmune disorders and skin lesions were enrolled as control group. Healthy controls were matched with the cases in both age and gender. These participants were Chinese Han people. The current study was approved by the Ethic committee of Linyi People's Hospital. Informed consent was signed by each participant. Demographic and clinical characteristics were recorded through questionnaire.

2.2. Genotyping

Blood samples were collected from each subject and processed with EDTA. Then genomic DNA was extracted using DNA extraction kit (TIANGEN, Beijing, China) according to the manufacturer's specification.

The PCR primers for *ERAP1* gene rs26653 and rs27524 polymorphisms were designed using Primer Premier 5.0 (Table 1). *ERAP1* gene polymorphisms were amplified through PCR and sequenced adopting direct sequencing method.

2.3. Statistical analysis

The conformity to Hardy–Weinberg equilibrium (HWE) was examined to detect the representativeness of the subjects. Genotype and allele frequencies were calculated through direct counting. Correlation between *ERAP1* gene polymorphisms and PsV susceptibility was assessed using odds ratios (ORs) with corresponding 95% confidence intervals (CIs). All of the calculations were performed with PASW 18.0. All the tests were 2-tailed, and *P*-values $<.05$ were considered as statistical significance.

3. Results

3.1. Characteristics of subjects

Age and gender showed no significant difference between case and control groups. As for the age of onset, it was below 40 years in 125 (87.41%) patients (EO-PsV) and over 40 in 18 (12.59%) cases (LO-PsV). Among the patients, the onset age and disease duration were 30.52 ± 9.14 and 11.32 ± 6.19 years, respectively. Only 19 patients had the family history of PsV, while none of the controls had the family history (Table 2).

3.2. Association of ERAP1 gene SNPs with the susceptibility to PsV

Genotype distributions of *ERAP1* gene rs26653 and rs27524 SNPs did not deviate from HWE in control group (Table 3, $P > .05$), revealing that the controls were representative for general population.

The frequencies of the GG, GC, and CC genotypes of rs26653 SNP were 25.17%, 51.05%, 23.78% in patients with PsV, and 34.90%, 48.32%, 16.78% in healthy controls. Besides, the CC genotype and C allele were significantly more frequent in patients with PsV than in healthy controls, indicating that they could significantly increase PsV susceptibility ($P = .047$, OR = 1.964, 95% CI = 1.006–3.834; $P = .042$, OR = 1.403, 95% CI = 1.011–1.946). As for rs27524 SNP, its AA genotype and A allele exhibited higher frequencies in patients with PsV than in the controls, but the difference was not significant (20.98 vs 14.09, $P = .076$). While the frequencies of the GG and GA genotypes and the G allele were similar between case and control groups ($P > .05$ for all). So rs27524 SNP might had no significant association with PsV risk (Table 3).

3.3. Subgroup analysis on the association between ERAP1 SNPs and PsV risk

The CC genotype and C allele of rs26653 SNP were significantly correlated with increased risk of EO-PsV (Table 4, $P = .036$, OR = 2.080, 95% CI = 1.044–4.145; $P = .034$, OR = 1.443, 95% CI = 1.028–2.024). No association was observed between rs26653 SNP and LO-PsV; nor was between rs27524 SNP and either EO-PsV or LO-PsV. However, the AA genotype and A

Table 2

Characteristics of subjects.

Characteristic	Case n = 143 (%)	Control n = 149 (%)	*P*
Age	42.39 ± 12.12	41.28 ± 11.59	.790
Gender			.884
Male	78 (54.55)	80 (53.69)	
Female	65 (45.45)	69 (46.31)	
Duration of PsV	11.32 ± 6.19		
Onset age	30.52 ± 9.14		
Family history	19	0	
PsV types			
EO-PsV	125 (87.41)		
LO-PsV	18 (12.59)		

EO-PsV = early onset PsV, LO-PsV = late onset PsV, PsV = psoriasis vulgaris.

Table 3

Association of *ERAP1* gene single-nucleotide polymorphisms with the susceptibility of PsV.

Genotype/allele	Case n = 143 (%)	Control n = 149 (%)	*P*	OR (95% CI)
rs26653				
GG	36 (25.17)	52 (34.90)	–	–
GC	73 (51.05)	72 (48.32)	.162	1.465 (0.857–2.501)
CC	34 (23.78)	25 (16.78)	.047	1.964 (1.006–3.834)
G	145 (50.70)	176 (59.06)	–	–
C	141 (49.30)	122 (40.94)	.042	1.403 (1.011–1.946)
P_{HWE}		0.993		
rs27524				
GG	44 (30.77)	57 (38.26)	–	–
GA	69 (48.25)	71 (47.65)	.380	1.259 (0.753–2.106)
AA	30 (20.98)	21 (14.09)	.076	1.851 (0.935–3.662)
G	157 (54.90)	185 (62.08)	–	–
A	129 (45.10)	113 (37.92)	.078	1.345 (0.967–1.871)
P_{HWE}		.883		

95% CI = 95% confidence interval, OR = odds ratio, P_{HWE} = *P*-value for Hardy–Weinberg equilibrium, PsV = psoriasis vulgaris.

allele of rs27524 SNP showed a tendency toward being related to EO-PsV, which might become significant in a larger sample size.

Subgroup analysis based on gender revealed no significant association of rs26653 and rs27524 SNPs with PsV susceptibility, either in males or in females (Table 5, $P > .05$).

Subgroup analysis based on family history showed that rs26653 CC genotype was distinctly correlated with enhanced PsV risk in the patients with family history (Table 6, $P = .029$, OR = 2.149, 95% CI = 1.075–4.296). Such association was also observed for rs26653C allele ($P = .027$, OR = 1.466, 95% CI = 1.044–2.059). No obvious association was detected between rs26653 SNP and PsV risk in patients without family history. While rs27524 SNP had no significant association with PsV risk in either of the subgroups with and without family history ($P > .05$).

4. Discussion

Disorders in immune system in regard to skin cells (especially the excessive and rapid growth of epidermal layer during wound repair) may lead to skin diseases, including PsV.[22] Presently, PsV has been regarded as a complex and multifactorial disease, and its pathogenesis is reportedly associated with hereditary factors, immune or inflammatory factors, life style, and other environmental factors.[23–26] Hyper-proliferative and infiltrating keratinocytes interact with activated immune cells and thus result in PsV onset.[27] A variety of immune cells play important roles in PsV pathogenesis. These immune cells, moving from dermis to epidermis, secrete cytokines, and participate in different immune pathways.[10] Various immune pathways have been proved to be involved in PsV, including TH17 pathway, passive immunity pathway, and nuclear factor kappa B (NF-κB) subunit 1 and interferon signaling pathways.[3,28–31] Immune or inflammatory genes involved in these pathways may be associated with the occurrence of PsV.

The ERAP1 could regulate the link between peptides and major histocompatibility complex (MHC) class I molecules, such as HLA-C.[32] It has been reported that mutations in *ERAP1* gene are correlated with PsV susceptibility only in people harboring certain alleles of the HLA-C.[21] GWAS and meta-analysis found that mutations in *ERAP1* gene were distinctly related to the development of PsV.[21,23] In addition, *ERAP*1 gene rs26653 SNP was positively associated with different inflammatory diseases, such as ankylosing spondylitis and inflammatory bowel disease.[33] Therefore, it is reasonable to speculate that *ERAP*1 gene SNPs might be correlated with PsV susceptibility in Chinese

Table 4

Subgroup analysis of association between *ERAP1* single-nucleotide polymorphisms and PsV susceptibility based on onset of PsV.

				EO-PsV vs control		LO-PsV vs control	
Genotype/allele	EO-PsV n = 125 (%)	LO-PsV n = 18 (%)	Control n = 149 (%)	*P*	OR (95% CI)	*P*	OR (95% CI)
rs26653							
GG	31 (24.80)	5 (27.78)	52 (34.90)	–	–	–	–
GC	63 (50.40)	10 (55.56)	72 (48.32)	.177	1.468 (0.839–2.566)	.522	1.444 (0.466–4.477)
CC	31 (24.80)	3 (16.67)	25 (16.78)	.036	2.080 (1.044–4.145)	.773	1.248 (0.276–5.642)
G	125 (50.00)	20 (55.56)	176 (59.06)	–	–	–	–
C	125 (50.00)	16 (44.44)	122 (40.94)	.034	1.443 (1.028–2.024)	.687	1.154 (0.575–2.317)
rs27524							
GG	38 (30.40)	6 (33.33)	57 (38.26)	–	–	–	–
GA	60 (48.00)	9 (50.00)	71 (47.65)	.385	1.268 (0.742–2.165)	.738	1.204 (0.405–3.582)
AA	27 (21.60)	3 (16.67)	21 (14.09)	.065	1.929 (0.955–3.894)	.702	1.357 (0.311–5.923)
G	136 (54.40)	21 (58.33)	185 (62.08)	–	–	–	–
A	114 (45.60)	15 (41.67)	113 (37.92)	.069	1.372 (0.975–1.931)	.662	1.169 (0.579–2.361)

95% CI = 95% confidence interval, EO-PsV = early onset PsV, LO-PsV = late onset PsV, OR = odds ratio, PsV = psoriasis vulgaris.

Table 5

Subgroup analysis of association between *ERAP1* single-nucleotide polymorphisms and PsV susceptibility based on gender.

	Male		Female		Male		Female	
Genotype/allele	Case n = 78 (%)	Control n = 80 (%)	Case n = 65 (%)	Control n = 69 (%)	*P*	OR (95% CI)	*P*	OR (95% CI)
rs26653								
GG	19 (24.36)	29 (36.25)	17 (26.15)	23 (33.33)	–	–	–	–
GC	40 (51.28)	39 (48.75)	33 (50.77)	33 (47.83)	.226	1.565 (0.756–3.240)	.453	1.353 (0.613–2.984)
CC	19 (24.36)	12 (15.00)	15 (23.08)	13 (18.84)	.059	2.417 (0.958–6.099)	.368	1.561 (0.591–4.126)
G	78 (50.00)	97 (60.63)	67 (51.54)	79 (57.25)	–	–	–	–
C	78 (50.00)	63 (39.37)	63 (48.46)	59 (18.84)	.057	1.540 (0.986–2.405)	.348	1.259 (0.778–2.038)
rs27524								
GG	23 (29.49)	31 (38.75)	21 (32.31)	26 (37.68)	–	–	–	–
GA	38 (48.72)	38 (47.50)	31 (47.69)	33 (47.83)	.404	1.348 (0.668–2.720)	.695	1.163 (0.546–2.476)
AA	17 (21.79)	11 (13.75)	13 (20.00)	10 (14.49)	.120	2.083 (0.821–5.283)	.352	1.610 (0.589–4.398)
G	84 (53.85)	100 (62.50)	73 (56.15)	85 (61.59)	–	–	–	–
A	72 (46.15)	60 (37.50)	57 (43.85)	53 (38.41)	.119	1.429 (0.912–2.238)	.366	1.252 (0.769–2.039)

Table 6

Subgroup analysis of association between *ERAP1* single-nucleotide polymorphisms and PsV susceptibility based on family history.

	Family history			With family history		Without family history	
Genotype/allele	No n = 124 (%)	Yes n = 19 (%)	Control	*P*	OR (95% CI)	*P*	OR (95% CI)
rs26653							
GG	30 (24.19)	6 (31.58)	52 (34.90)	–	–	–	–
GC	63 (50.81)	10 (52.63)	72 (48.32)	.146	1.517 (0.864–2.661)	.735	1.204 (0.412–3.520)
CC	31 (25.00)	3 (15.79)	25 (16.78)	.029	2.149 (1.075–4.296)	.958	1.040 (0.240–4.504)
G	123 (49.60)	22 (57.89)	176 (59.06)	–	–	–	–
C	125 (50.40)	16 (42.11)	122 (40.94)	.027	1.466 (1.044–2.059)	.891	1.049 (0.529–2.079)
rs27524							
GG	37 (29.84)	7 (36.84)	57 (38.26)	–	–	–	–
GA	61 (49.19)	8 (42.11)	71 (47.65)	.306	1.324 (0.774–2.264)	.875	0.918 (0.314–2.682)
AA	26 (20.97)	4 (21.05)	21 (14.09)	.072	1.907 (0.939–3.873)	.514	1.551 (0.412–5.844)
G	135 (54.44)	22 (57.89)	185 (62.08)	–	–	–	–
A	113 (45.56)	16 (42.11)	113 (37.92)	.071	1.370 (0.973–1.930)	.617	1.191 (0.600–2.362)

Han population. In the present study, we selected 2 SNPs with the minor allele frequencies >.05 in CHB (Chinese Han in Beijing) to verify the hypothesis.

We found that the CC genotype of rs26653 SNP increased PsV susceptibility by 1.964 times. At the same time, the degree of increase in disease risk by its C allele was up to 1.403 times. These findings partly accorded with those from a previous study by Lysell et al which found that rs26653 was strongly correlated with psoriasis susceptibility in their studied population.[34] Our subgroup analysis found significantly enhanced disease risk related to rs26653 CC genotype for EO-PsV, and its C allele elevated the disease susceptibility by 1.443 folds for EO-PsV. However, no significant association was observed for LO-PsV. We failed to find any significant association for *ERAP1* SNPs with PsV risk, in either male or female subgroup. While the CC genotype and C allele of rs26653 SNP increased PsV risk in patients with the family history by 2.149 and 1.466 times, respectively. Besides, rs26653 was obviously associated with the response to ustekinumab therapy among patients with psoriasis.[35]

Minor allele of rs27524 SNP had higher frequency in patients with PsV than in healthy controls. There was a tendency for the relationship of *ERAP1* gene rs27524 SNP with increased PsV risk, though without statistical significance. No significant association was discovered of rs27524 SNP with PsV types, genders, or with or without family history. Our findings accorded with those from a previous study by Lysell and colleagues in a Sweden population.[34] But divergence still exists. For instance, Yang et al suggested that rs27524 SNP was distinctly associated with PsV risk.[36] In addition, GWAS demonstrated that rs27524 A allele was significantly associated with classical Hodgkin lymphoma, another inflammatory disease.[19]

In summary, rs26653 SNP may be positively correlated with PsV susceptibility in Chinese Han population. Several limitations in present study should be stated. First of all, sample size was not large enough that might reduce analysis power. Secondly, only 1 ethnic group was included in our study, and this situation might limit the application range of our results. Thirdly, the results were not adjusted for potentially confounding factors. Additionally, gene–environment interactions were not taken into account in the current study. Therefore, well designed studies with enlarged sample size and ethnicity number are needed to further verify our findings in the future.

Author contributions

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