Association of Polymorphisms of Metabolism-Related Genes with Psoriasis Vulgaris in Han Chinese

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Aim. Psoriasis is a chronic inflammatory disease with a complex etiology, and psoriasis vulgaris (PsV) is the most common type of psoriasis. Recent studies suggest the relationship between psoriasis and metabolic syndrome in different ethnicities. This study is aimed at evaluating the association of metabolism-related gene variants with the risk of PsV in the Chinese Han population.

Material and Methods. PsV patients (1030) and healthy controls (965) were enrolled in this study. Eighteen single-nucleotide polymorphisms (SNPs) previously reported to be significantly associated with metabolic syndrome were selected. SNPs were detected by next-generation sequencing. Results. Seven SNPs were significantly associated with PsV: rs805303 (P = 0.012, OR = 0.85), rs3177928 (P = 1.37 x 10^-15, OR = 2.51), and rs2247056 (P = 3.73 x 10^-4, OR = 0.67) located in the HLA gene region; rs1047781 (P = 0.012, OR = 1.18), rs281379 (P = 0.014, OR = 1.71), and rs492602 (P = 0.005, OR = 1.86) located in the FUT2 region; and rs2303138 (P = 0.014, OR = 1.18) located in the LNPEP region. After stratified analysis, rs805303 (P = 0.017, OR = 0.74) and rs2303138 (P = 0.041, OR = 1.30) were associated with PsVs when HLA-C*06:02 was positive, and rs805303 (P = 5.62 x 10^-3, OR = 0.68), rs3177928 (P = 0.003, OR = 1.75), rs281379 (P = 0.034, OR = 1.96), and rs492602 (P = 0.025, OR = 2.04) were associated with PsVs when HLA-C*06:02 was negative. Conclusion. PsV and metabolic syndrome may have overlapped susceptible genes in Chinese Han population.

1. Introduction

Psoriasis is a chronic inflammatory disease caused by various factors including genetic factors, with psoriasis vulgaris (PsV) representing the most common type [1]. Recently, it is reported that psoriasis is related to metabolic syndrome. The association of metabolic syndromes such as dyslipidaemia, hypertension, insulin resistance, and abdominal obesity with psoriasis has been investigated. Lu et al. analyzed the top 10 (the top three were in the HLA region) metabolic single-nucleotide polymorphisms (SNPs) associated with psoriasis by genome-wide association study [2]. A meta-analysis of the association of angiotensin-converting enzyme (ACE) gene polymorphisms with psoriasis susceptibility showed that the polymorphisms were associated with the risk of psoriasis in Asians [3]. Angiotensin II type 1 receptor (AT1R) is correlated with hypertension, heart disease, and oxidative stress, and Mohammadi et al. reported that AT1RA1166C (rs5186) polymorphism significantly increased the risk of psoriasis [4]. Cheng et al. found that rs2303138 polymorphism in the LNPEP gene was associated with renin angiotensin and played a key role in cardiovascular disease and diabetes mellitus [5].

However, due to ethnic differences, previous studies reported different results on the association of SNPs with PsV. In particular, very few studies examined the association of metabolic disease-related SNPs with PsV in the Chinese Han population. Therefore, this study is aimed at evaluating the association between metabolic disease-related SNPs and the risk of PsV in the Chinese Han population. We selected 18 SNPs previously reported to be significantly associated with metabolic diseases. In the HLA region, HLA-cw06:02
is the major psoriasis risk gene, which has been validated in different populations worldwide [6]. Therefore, we performed a stratified analysis to evaluate the interaction between HLA-cw06:02 and the selected SNPs.

2. Material and Methods

2.1. Subjects. The study population consisted of 1030 patients with PsV and 965 healthy controls, who visited Affiliated Hospital of Inner Mongolia Medical University from Dec 2011 to May 2018. All subjects recruited were all Chinese Han more than 18 years old, both men and women. PsV patients were diagnosed by at least two clinical dermatologists based on histopathology. Healthy controls visited the hospital for physical examination. All subjects were excluded if they had familial hypertension, primary diabetes type I, or familial hyperlipidemia. The study was approved by the Ethical Committee of Affiliated Hospital of Inner Mongolia Medical University and conducted according to the Declaration of Helsinki principles. All subjects signed informed consent.

2.2. Second-Generation Sequencing. Peripheral venous blood (4 ml) samples were collected from all subjects and stored at 80°C until use. Genomic DNA was extracted from blood samples by using whole-blood DNA extraction kit (AxyPrep, AP-MX-BL-GDNA-25, Suzhou, China). The information of all the SNPs was obtained from PubMed database (https://www.ncbi.nlm.nih.gov/pubmed); then, the primers and probes were designed using Primer3 online (version 0.4.0; http://frodo.wi.mit.edu). The primer sequences for were listed in Table 1.

2.3. Statistical Analysis. Statistical analyses were performed using the PLINK1.07 package (http://pngu.mgh.harvard.edu/purcell/plink/, USA). The frequencies of the alleles of all 19 SNPs were calculated, and the Hardy-Weinberg equilibrium was tested in the cases and controls. Minor allele frequencies (MAF) of each SNP were compared between patients and controls using the Chi-square test. Odds ratio (OR) and the corresponding 95% confidence intervals (95% CI) were calculated. Bonferroni corrected P value threshold of P < 0.05 was set based on multiple tests of 19 genotyped variations.

3. Results

A total of 1030 patients with PsV (532 males and 498 females, mean age: 45.49 ± 17.11 years) and 965 controls (542 males and 423 females, mean age: 45.86 ± 11.59 years) were recruited in this study. There were no significant differences in age and gender between the two groups (P = 0.05). The minor allele frequencies of all 18 SNPs were compared between the two groups. Seven SNPs showed significant difference between the two groups: rs805303 (P = 0.012, OR = 0.85), rs3177928 (P = 1.37 × 10^{-15}, OR = 2.51), and rs2247056 (P = 3.73 × 10^{-4}, OR = 0.67) in HLA; rs1047781 (P = 0.012, OR = 1.18), rs281379 (P = 0.014, OR = 1.71), and rs492602 (P = 5.32 × 10^{-3}, OR = 1.86) in FUT2; and rs2303138 (P = 0.014, OR = 1.18) in LNPPEP. The other 11 SNPs showed no significant difference between the two groups (P > 0.05). The frequencies of rs3177928 A allele, rs1047781 T allele, rs281379 A allele, and rs492602 C allele, and rs2303138 A allele were significantly higher in cases than in controls (P < 0.05). However, the frequencies of rs805303 T allele and rs2247056 T allele were significantly lower in cases than in controls (P < 0.05) (Table 2).

The strongest associations of SNPs and PsV were identified as HLA-C*06:02 (P = 7.82 × 10^{-170}, OR = 7.80), rs3177928 (P = 1.37 × 10^{-15}, OR = 2.51), and rs2247056 (P = 3.73 × 10^{-4}, OR = 0.67), which were all located in the HLA region. In order to identify whether the result was interfered by HLA-cw06:02, we performed stratified analysis. All the subjects were stratified into HLA positive and HLA negative, and there were 694 PsV patients and 175 controls with HLA-cw06:02 (+), 336 PsV patients, and 790 controls with HLA-cw06:02 (-). The results showed that in the positive group rs805303 (P = 0.017, OR = 0.74) and rs2303138 (P = 0.041, OR = 1.299) were associated with PsV, while in the negative group rs805303 (P = 5.62 × 10^{-5}, OR = 0.68), rs3177928 (P = 0.003, OR = 1.75), rs281379 (P = 0.034, OR = 1.95), and rs492602 (P = 0.025, OR = 2.04) were related to PsV (P < 0.05) (Table 3).

4. Discussion

SNPs have been involved in a variety of diseases including PsV [1, 7, 8]. In this study, we investigated 18 polymorphisms reported in previous studies to be associated with metabolic syndrome and examined them in a Chinese Han population. Seven SNPs were found to be significantly associated with PsV patients, including rs805303, rs3177928, and rs2247056 in HLA loci; rs1047781, rs281379, and rs492602 in FUT2 loci; and rs2303138 in LNPPEP loci.

rs492602 in FUT2 loci showed significant association with PsV susceptibility, in agreement with the report by Lu et al. [2]. The FUT2 gene is located at 19q13.33, and it encodes alpha-(1,2)-fucosyltransferase which regulates H antigen (the precursor of the human ABO blood group antigens) on the surface of epithelial cells [9]. FUT2 has relationship with dyslipidemia due to the regulation of glycosphingolipid synthesis. Furthermore, GWAS analysis showed genetic overlap between dyslipidemia and a series of archetypal immune-mediated diseases such as Crohn's disease, ulcerative colitis, rheumatoid arthritis, type 1 diabetes, celiac disease, psoriasis, and sarcoidosis [10]. FUT2 gene polymorphism may be involved in metabolic syndrome and psoriasis through the regulation of dyslipidemia.
Interestingly, all three FUT2 SNPs were associated with psoriasis only in the absence of HLA-C*06:02. We speculate that the role of HLA-C in antigen presentation may interfere with the regulation of H antigen by FUT2, but further studies are needed to confirm this.

We found that the A allele of rs2303138 in LNPEP was associated with PsV, coincident with the results by Cheng et al. [5]. LNPEP (leucyl and cystinyl aminopeptidase) could promote glucose uptake through insulin-stimulated interaction with glucose transporter GLUT4. In addition, LNPEP is
results showed that rs805303 and rs2303138 were related to negative groups and conducted stratified analysis. The region SNP rs805303 was associated with psoriasis independently of the presence of HLA-C*06:02, in contrast to rs3177928, also from the HLA region, which was associated with psoriasis only in the absence of HLA-C*06:02 negatives. Further functional studies are needed to explain the results. Furthermore, rs2247056 was also in the HLA region and it was associated with psoriasis before stratification but lost this association after stratification. Our results are consistent with previous report by Lu et al. who showed that after adjustment for the top psoriasis risk allele HLA-C*06:02, the associations for rs2247056 was mitigated while the association for rs805303 persisted [2]. Because multiple alleles associated with psoriasis risk are identified in HLA loci, it is possible that significant association of rs805303 with psoriasis is due to linkage disequilibrium with other HLA alleles associated with psoriasis risk [18].

In conclusion, we examined 18 previously reported SNPs of metabolic syndrome in a Chinese Han population and found that 7 SNPs located in HLA, FUT2, and LNPEP were associated with PsV in Chinese Han.

### Data Availability
All data are available upon request.

### Conflicts of Interest
The authors declared no conflict of interest.

### Authors’ Contributions
Yu Liu and Xin Li contributed equally to this work.

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Acknowledgments

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References


