Ann Dermatol Vol. 33, No. 1, 2021
pISSN 1013-9087 · eISSN 2005-3894
https://doi.org/10.5021/ad.2021.33.1.61

ORIGINAL ARTICLE

A Large-Scale, Stratified Genetic Analysis of the Major Histocompatibility Complex Region in Early- and Late-Onset Psoriasis in China

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Background: Psoriasis vulgaris is a chronic inflammatory skin disease which occur at any age. It can be clinically classified into two age-onset subtypes: early-onset psoriasis (EOP; <40 years) and late-onset psoriasis (LOP; ≥ 40 years). More evidence showed EOP and LOP have different genetic architecture, notably the risk allele human leukocyte antigen (HLA)-C*06:02 located within the major histocompatibility complex (MHC) region, which was reported to be the outstanding variant associated with EOP. However, genetic structure of EOP and LOP have not been fully elucidated. **Objective:** To investigated HLA genetic heterogeneity between EOP and LOP in China. **Methods:** We first calculated the MHC-based heritability of EOP and LOP respectively. Then, we conducted a large-scale, stratified analysis including 7,097 EOP, 1,337 LOP patients, and 9,906 healthy controls by using MHC target sequencing data from a previous study. **Results:** We observed that HLA alleles collectively explained a larger heritability of EOP (27.4%) than LOP (11.3%). Further association analysis identified three independent loci (HLA-C*01:02, $p=6.70\times10^{-8}$; HLA-A amino acid position 9, $p=3.27\times10^{-17}$; and HLA-A amino acid position 161, $p=5.75\times10^{-10}$) that confer specific susceptibility to EOP. Our data also confirmed HLA-C*06:02 as an independent psoriasis-associated variant, contributing a higher degree of risk to EOP than LOP. Moreover, case-case analysis confirmed that HLA-C*06:02-positive psoriasis patients have earlier onset. **Conclusion:** Our analysis indicating that different genetic background underlie the EOP and LOP. We believe these findings will serve to predict psoriasis risk in the future and facilitate clinical decision. **(Ann Dermatol 33(1) 61~67, 2021)**

-Keywords-
Genetic heterogeneity, Genetic susceptibility, Genotype-phenotype association, Major histocompatibility complex, Psoriasis

INTRODUCTION

Psoriasis vulgaris is a chronic inflammatory skin disease characterized by erythematous, squamous, and thickened plaques. It is a worldwide disease, with prevalence ranging from 0.09% to 11.8%. It affects most races and can manifest at any age of life. Age-onset analyses in psoriasis patients have shown that heredity and clinical course are associated with the age at which the first symptoms of psoriasis are shown. Therefore, psoriasis can be divided into the clinical subtypes, early-onset psoriasis (EOP) and late-onset psoriasis (LOP), with a dividing age of onset of

Received April 8, 2020, Revised August 11, 2020, Accepted for publication August 18, 2020

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40 years[1]. Compared to LOP, EOP has distinct clinical, evolutionary, and genetic features. EOP comprises the majority of psoriasis patients, is more likely to be familial, and has a severe clinical course[1]. For instance, an epidemiologic study of psoriasis reported that EOP patients account for 86.19% of all patients with psoriasis in Han Chinese and EOP patients were more likely to have affected first-degree relatives[2]. On the other hand, LOP patients have a higher likelihood of having psoriasis comorbidities, such as type 2 diabetes and autoimmune thyroiditis. LOP patients are also more likely to be anxious compared with EOP patients[3].

The major histocompatibility complex (MHC) region, also known as human leukocyte antigen (HLA) was first associated with psoriasis in 1972[4]. HLA-C*06:02 in the class I HLA region has been proven to be the most significant risk allele for psoriasis in both European[5] and Chinese populations[6-8]. In a previous study, our group sequenced the entire 5-Mb MHC region in 10,689 healthy controls and 9,946 psoriasis patients of Han Chinese ancestry. We constructed a Han-MHC database and identified eight independent susceptibility loci associated with psoriasis, including HLA-C*06:02, amino acids at positions 9 and 67 in HLA-B, HLA-C*07:04, rs118179173, amino acid at position 116 in HLA-B, DPB1*05:01, and amino acid at position 281 in BTNL2[9]. Moreover, by analyzing genetic associations between psoriasis subphenotypes divided by age of onset and shared control subjects, our group found that the number of susceptible variants decreased as the onset age of psoriasis increased[10]. In addition, several other genetic studies have reported that HLA-C*06 is more strongly associated with EOP in various races[11].

Considerable evidence therefore indicates that genetics could play an important role in age of psoriasis onset. However, previous work has been marred by inconsistent results due to low sample sizes, technical variability, and racial stratification. Therefore, we performed a comprehensive, stratified analysis using direct, targeted sequencing data of the MHC to evaluate genetic susceptibility of EOP and LOP patients in a large Han Chinese population.

MATERIALS AND METHODS

Samples

After verification of clinical data, a total of 8,434 patients suffering from psoriasis were enrolled in the study and divided into two groups according to age of onset, including 7,097 EOP (age of onset defined as under 40 years) and 1,337 LOP cases (age of onset defined as 40 years or older), patients with psoriatic arthritis were not included. We also included 9,906 healthy Han Chinese subjects as controls. All participants provided written informed consent and were recruited according to protocols approved by the institutional ethics committee (No.20131349).

Genotyping and quality control

The HLA sequences were generated, and stringent quality control was conducted, in our previous MHC-targeted sequencing study[9]. In addition, we excluded variants with minor allele frequency (MAF) $<1\%$, Hardy-Weinberg equilibrium with $p<10^{-4}$, or a call rate $<99\%$. Finally, we obtained a total of 26,775 markers including single-nucleotide polymorphisms (SNPs), classic alleles, and amino acid residues. We analyzed SNPs, HLA classic alleles, and HLA amino acid across the MHC region for association with subtypes of psoriasis using a p-value threshold of 1.87×10^{-6} (Bonferroni correction, $0.05/26{,}775=1.87\times10^{-6}$) as the cutoff for statistical significance.

Heritability of psoriasis conferred by the MHC locus

After quality control, All SNPs in the MHC region (MAF $\geq$ 1%, hardy-Weinberg equilibrium with $p>10^{-4}$, and a call rate $>99\%$) were included for calculating MHC-based heritability. This was performed by using a variance component model with a genetic relationship matrix implemented in genome-wide complex trait analysis (GCTA)[12]. The disease prevalence was set to 0.47% as previously reported[13].

Statistical analyses

We used a logistic regression model applied in PLINK v.1.9 (Center for Human Genetic Research, Massachusetts General Hospital, Boston, MA, USA)[14] to analyze the associations of all variants with psoriasis susceptibility in each subgroup. The following were analyzed: 1) associations between HLA alleles and EOP susceptibility; 2) associations between HLA alleles and LOP susceptibility; 3) a direct comparison of EOP with LOP. To control for population stratification, we included sex and region as covariates. For stepwise analysis, we included the identified markers as covariants in the logistic regression analysis to condition on them and to further find additional independent variants. This was repeated in a forward stepwise approach until no variation exceeded the predefined significance threshold after Bonferroni correction ($p<1.87\times10^{-6}$). Pearson correlation between variants was calculated by using R version 3.63 (R Foundation for Statistical Computing, Vienna, Austria) and the square of correlation coefficient (r^2) was used to measure the correlation level.

Three-dimensional ribbon models for HLA-A

To determine if HLA-A amino acid positions that associated with EOP were located in the binding groove of the

HLA molecule, we used VMD v. 1.92 (Visual Molecular Dynamics; University of Illinois at Urbana-Champaign, Urbana, IL, USA)[15] to prepare HLA-A structures based on Protein Data Bank entry $1\times7q$[16].

Statistical power calculation

Statistical power of our study was evaluated by Power and Sample Size Software v.3.1.2 (Vanderbilt University School of Medicine, Nashville, TN, USA). The type I error was set to 1.87×10^{-6}.

RESULTS

HLA contributes a greater proportion of the heritability of EOP than LOP

Using GCTA, we calculated that HLA alleles collectively explained more phenotypic variance of EOP (27.4%, standard error [SE]=0.010) than LOP (11.3%, SE=0.015), implying that EOP has a much stronger genetic component than LOP. To further investigate this result, we performed a comprehensive, stratified analysis to search for psoriasis age-of-onset-specific risk alleles.

EOP versus control

The results of our association analysis of the MHC region with EOP susceptibility are shown in Table 1. As previously reported[1,17], the strongest association observed was between the HLA-C*06:02 allele and EOP ($p=1.00\times10^{-1,027}$), followed by HLA-C*07:04 ($p=2.43\times10^{-38}$). In addition, the allele HLA-C*01:02 also showed a significant association ($p=6.70\times10^{-8}$), which has not been reported previously. After conditioning on HLA-C, rs118179173 ($p=9.20\times10^{-67}$) was the top signal. Further conditional analysis identified two new amino acids in the HLA-A gene (position 9, $p=3.27\times10^{-17}$; and position 161, $p=5.75\times10^{-10}$). When we conditioned on HLA-C, rs118179173, and HLA-A, a significant independently associated signal for HLA-DPB1*05:01 ($p=2.00\times10^{-15}$) was observed. We also showed independent associations at three amino acids in the HLA-B gene (position 9, $p=1.10\times10^{-14}$; position 67, $p=8.26\times10^{-17}$, and position 116; $p=1.20\times10^{-6}$), which were reported to be associated with psoriasis as a whole in our previous study. In addition, we verified an association signal on BTNL2:M295V ($p=2.57\times10^{-7}$), which was strongly correlated with a previously reported variant for BTNL2:R281K ($r^2=0.953$, $p<2.2\times10^{-16}$) in our dataset[9]. When conditioning on all the above loci, no association reached the predefined significance threshold (Supplementary Fig. 1).

Table 1. Association of HLA variants with EOP and LOP in China

HLA variant	EOP vs. Control				LOP vs. Control				EOP vs. LOP			
	Frequency		OR (95% CI)	*p*-value*	Frequency		OR (95% CI)	*p*-value*	Frequency		OR (95% CI)	*p*-value*
	Freq_ EOP	Freq_ Control			Freq_ LOP	Freq_ Control			Freq_ EOP	Freq_ LOP		
HLA-C alleles												
C*06:02	0.4522	0.1104	16.48	1.00×10^{-1072}	0.3624	0.1104	5.982	2.37×10^{-222}	0.4522	0.3624	2.101	1.71×10^{-32}
C*07:04	0.01529	0.0102	4.418	2.43×10^{-38}	0.01907	0.0102	3.483	1.81×10^{-13}	-	-	-	-
C*01:02	0.1031	0.1387	1.271	6.70×10^{-08}	-	-	-	-	-	-	-	-
rs118179173	0.04516	0.0317	3.994	9.20×10^{-67}	-	-	-	-	-	-	-	-
HLA-A alleles												
A-F9	0.371	0.3288	1.289	3.27×10^{-17}	-	-	-	-	-	-	-	-
A-D161E	0.026	0.03765	0.5781	5.75×10^{-10}	-	-	-	-	-	-	-	-
HLA-DPB1 alleles												
DPB1*05:01	0.3597	0.3643	1.277	2.00×10^{-15}	-	-	-	-	-	-	-	-
HLA-B alleles												
B-Y9	0.1668	0.2165	0.7458	1.10×10^{-14}	-	-	-	-	-	-	-	-
B-A41T	-	-	-	-	0.3728	0.3231	0.6912	6.71×10^{-12}	-	-	-	-
B-Y67C	0.09053	0.08742	1.733	8.26×10^{-17}	0.1043	0.08742	1.568	1.81×10^{-8}	-	-	-	-
B-Y116S	0.3137	0.3262	1.188	1.20×10^{-06}	-	-	-	-	-	-	-	-
BTNL2 alleles												
BTNL2: M295V	0.05693	0.06405	1.373	2.57×10^{-07}	-	-	-	-	-	-	-	-

HLA: human leukocyte antigen, EOP: early-onset psoriasis, LOP: late-onset psoriasis, OR: odds ratio, CI: confidence interval, -: not available. **p*-value from stepwise regression analysis.

LOP versus control

The results of association analysis of the MHC region with LOP susceptibility are shown in Table 1. We identified HLA-C*06:02 ($p=2.37\times10^{-222}$) and HLA-C*07:04 ($p=1.81\times10^{-13}$) associated with LOP. When we conditioned on HLA-C*06:02 and HLA-C*07:04, we observed that HLA-B amino acid position 41 ($p=6.71\times10^{-12}$) and amino acid position 67 ($p=1.81\times10^{-8}$) remained independently associated with LOP (Supplementary Fig. 2).

EOP versus LOP

In order to further reveal the HLA genetic heterogeneity between psoriasis subtypes, we carried out case-only analysis by making direct comparisons between the EOP and LOP groups. HLA-C*06:02 ($p=1.71\times10^{-32}$) reached our predefined significance threshold (Table 1). After we conditioned on HLA-C*06:02, no new loci or genes were observed (Fig. 1).

DISCUSSION

In this study, we first calculated the MHC-derived heritability of EOP and LOP individually, observing that HLA alleles collectively explained a larger proportion of the phenotypic variance of EOP (27.4%) than LOP (11.3%). Next, we fine-mapped HLA associations in EOP and LOP. As previously reported, HLA-C*06:02 was the most significant association with EOP[1,17], and HLA-C*06:02-positive psoriasis patients had earlier onset[11]. We also detected a significant association between HLA-C*06:02 and LOP. HLA-C*06:02, HLA-C*07:04, and amino acid position 67 in HLA-B have been confirmed both in EOP-control and LOP-control studies in the Han Chinese population. This suggests that these three loci are strongly associated with psoriasis in the Han Chinese population, while other loci showed onset-specific associations with psoriasis. Further study of LOP vs. EOP confirmed HLA-C*06:02 as a risk factor in psoriasis, contributing more risk to EOP ($p=1.71\times10^{-32}$). Therefore, we have conducted a systematic, stratified analysis of psoriasis associations in the MHC, and defined genetic heterogeneity between EOP and LOP subtypes.

In our MHC-region association analysis comparing EOP patients and controls, we found eleven independent susceptibility loci (Table 1). Seven of them (HLA-C*06:02, HLA-C*07:04, rs118179173, HLA-DPB1*05:01, and amino acids at positions 9, 67, and 116 in HLA-B) have previously reported associations with psoriasis in the Han Chinese population. One (BTNL2:M295V) is in strong linkage disequilibrium with BTNL2:R281K ($r^2=0.953$, $p<2.2\times10^{-16}$), which has also been reported to be associated with psoriasis[9]. Hence, we have confirmed all eight psoriasis-risk HLA loci from our previous psoriasis-control ana-

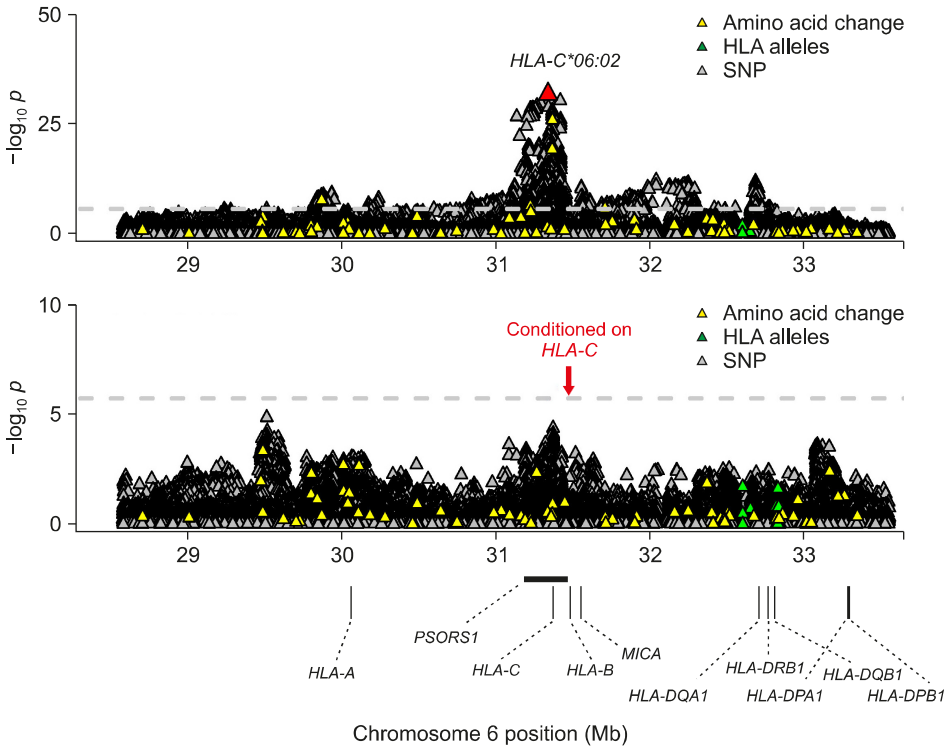

Fig. 1. Stepwise Conditional Association Analysis between early-onset psoriasis (EOP) and late-onset psoriasis (LOP). Association analysis of human leukocyte antigen (HLA)-C in EOP versus LOP. The horizontal axis shows genomic position and the vertical axis shows negative $\log_{10}$-transformed *p*-values of associations. The dashed horizontal line corresponds to the significance threshold of $p=1.87\times10^{-6}$. The red triangles represent the most associated variants. The yellow triangles represent amino acid positions. The green triangles represent HLA alleles and the grey triangles represent single-nucleotide polymorphisms (SNPs).

lysis. Moreover, we identified three novel loci (HLA-C*01:02, and amino acids 9, and 161 in HLA-A) associated with EOP, but not with psoriasis. Notably, HLA-C*01:02 has been reported to be associated with psoriasis in the southern Chinese population[18]. HLA-A amino acids 9 and 161 are located at functional pockets of HLA-A molecules, suggesting potential biological significance (Fig. 2). These findings suggest that HLA-C*01:02, and amino acids 9 and 161 of HLA-A may serve as EOP-specific susceptibility loci.

Previous small case-control studies have not found associations between HLA-C alleles and LOP[19-21]. However, we observed four independent loci (HLA-C*06:02, HLA-C*07:04, and HLA-B amino acids 41 and 67) (Table 1) associated with LOP. In contrast to previous studies[19,20], HLA-C*06:02 had the strongest association with LOP in our data. Also of note, HLA-B amino acid 41 was independently associated with LOP, and not with EOP, while HLA-B amino acids 9 and 116 were independently associated with EOP, and not with LOP. In order to confirm whether HLA-B amino acid 41 is an LOP-specific risk loci, we conducted a linkage analysis of three amino acid loci in HLA-B (amino acids 9, 41, and 116). We found that HLA-B amino acid 9 is in weak linkage with HLA-B amino acid 41 ($r^2=0.113$, $p<2.2\times10^{-16}$) and HLA-B amino acid 116 ($r^2=0.096$, $p<2.2\times10^{-16}$). In EOP-control analysis, when we conditioned on HLA-B amino acids 41 and 116/9, 116/9 still reached our significance threshold ($p=1.47\times10^{-11}$ and $p=1.18\times10^{-6}$ respectively). However, when conditioned on amino acids 116 and 9 in our LOP-control cohort, HLA-B amino acid 41 did not meet the significance threshold in LOP-control analysis ($p=0.0012$). This means that the LOP-associated variant HLA-B amino acid 41 was not independent of EOP-associated HLA-B variants. Further, HLA-B amino acid position 41 was not located at antigenic peptide binding pockets in three-dimensional ribbon models. We therefore speculate that HLA-B amino acid 41 is not an independent LOP-specific susceptibility locus.

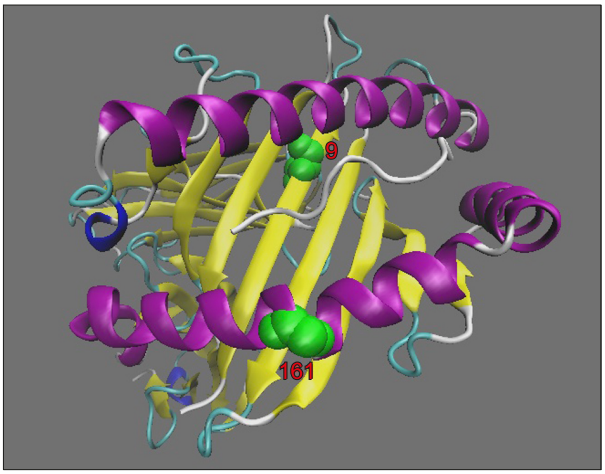

Fig. 2. Three-dimensional ribbon models for human leukocyte antigen (HLA)-A. The protein structures of HLA-A are based on Protein Data Bank entries 1×7q and prepared using VMD (version 1.92). The green spheres represent amino acid residues at HLA amino acid position 9 and 161 respectively. Number 9 represent HLA amino acid position 9. Number 161 represent HLA amino acid position 161.

We further directly compared EOP with LOP and confirmed that HLA-C*06:02 contributes more risk to EOP. Comparing the results from EOP-control and LOP-control studies, we have identified eight susceptibility loci (HLA-C*01:02, rs118179173, HLA-DPB1*05:01, HLA-A amino acids 9 and 161, HLA-B amino acids 9 and 116, and BTNL2) associated with EOP. However, we didn't verify these loci in EOP vs. LOP analysis. It is possible that this is due to our smaller LOP sample size, which could influence the detection of susceptibility loci in LOP vs. control and EOP vs. LOP. We calculated the power of LOP-control analysis for detecting HLA-C*01:02, rs118179173, HLA-A amino acids 9, and 161, HLA-B amino acids 9 and 116, DPB1*05:01, and BTNL2:M295V were 5.5%, 100%, 30.2%, 1.1%, 16.0%, 2.9%, 26.9%, and 5.6%, respectively, most of which were below 80%. There is a possibility that some of the EOP-associated variants were also conferring risk for LOP, but we did not have sufficient power to detect them. Also, the smaller sample size of our EOP-LOP analysis suggests that the case-case analysis had lower power, which may have caused EOP-specific variants to go undetected. However, it is noteworthy that our previous psoriasis-control study had a larger sample size than the EOP-control analysis in this study, while the results of our EOP association analysis validated all previously identified psoriasis-risk variants. Further, of the three novel EOP susceptibility HLA loci: HLA-C*01:02, and HLA-A amino acids 9 and 161, the first one was reported to be associated with schizophrenia in Europeans[22] and the latter two variants (HLA-A amino acids 9 and 161) were reside in peptide-binding grooves of HLA (Fig. 2). Hence, we have good reason to believe that the three novel independent loci are susceptibility factors specific to EOP, at least in the Han Chinese population. However, the functional mechanisms of these variants in EOP are unknown. It is possible that they constitute or contain specific peptide-binding grooves in HLA-A/HLA-C molecules[23], presenting restricted auto-antigens and further modulating adaptive immune responses. For example, an unbiased analysis indicated that $CD8^+$ T recognizes an HLA*06:02-restricted melanocytic ADAMTSL5 in psoriasis[24]. Further studies on the mechanisms under-

lying searches for allele-restricted auto-antigens are needed. We also compared our new results with those from previously published psoriasis association analyses of the MHC region in other populations. One study identified an association between HLA-C*12:02 and LOP in a Japanese cohort[21]. However, in a Brazilian study[25] and a UK Caucasian population[17], no association was detected between HLA-C*12:02 and LOP. In our dataset, HLA-C*12:02 did not meet the significance threshold.

In conclusion, we have conducted a comprehensive, stratified analysis of genetic variation in the MHC region in relation to psoriasis. We found that EOP has a stronger genetic background than LOP and we identified three novel independent loci (HLA-C*01:02, and HLA-A amino acids 9 and 161) that showed onset-specific association with EOP in the Han Chinese population. Moreover, case-case analysis confirmed that HLA-C*06:02-positive psoriasis patients have earlier onset. We believe these findings will serve to predict psoriasis risk in the future and facilitate clinical decision.

ACKNOWLEDGMENT

We are grateful to all participants, their families and healthy controls who donated blood samples in this study.

SUPPLEMENTARY MATERIALS

Supplementary data can be found via http://anndermatol.org/\src/sm/ad-33-061-s001.pdf.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

FUNDING SOURCE

This work was supported by the National Natural Science Foundation of China (81872527, 81803117) and the study sponsors took part in study design, review and decision to submit the manuscript for publication.

DATA SHARING STATEMENT

The raw sequencing data from samples evaluated in the Han-MHC project have been deposited in the Sequence Read Archive (SRA) under the accession SRA205317.

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