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Original Research

HLA-DQA1 and *DQB1* Alleles are Associated with Acitretin Response in Patients with Psoriasis

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Abstract

Background: Psoriasis vulgaris is an immune-mediated inflammatory skin disease. Although the pathogenesis of psoriasis is unclear, genetic susceptibility, such as *HLA-C*06:02*, is believed to be a major risk factor. However, there is a paucity of knowledge regarding the relationship between genetics and the response to systemic treatment of psoriasis. We hypothesized that genetic variations in human leukocyte antigen (*HLA*) genes may act as predictors of acitretin treatment in psoriasis. The aim of our study was to explore the presence of *HLA* gene variants in patients with moderate-to-severe psoriasis receiving acitretin treatment. **Methods**: A total of 100 Han Chinese patients with psoriasis completed the study. 24 patients including 16 responders and 8 non-responders underwent deep sequencing by MHC targeted region capture and 76 samples were genotyped by Sanger sequencing (SBT) based *HLA* typing for validation. **Results**: Regressions with adjustment for age, sex, body mass index (BMI), and baseline psoriasis area and severity index (PASI) revealed that two *HLA* alleles (*HLA-DQA1*:02:01*, *DQB*:02:02*) were associated with the response to acitretin. The *DQA1*0201*-positive patients showed a better response to acitretin compared to the *DQA1*0201*-negative patients (relative risk (RR) = 10.34, 95% confidence interval (CI): 2.62–40.77, p = 0.001), and the *DQB1*0202*-positive patients manifested a better response to acitretin when compared to the *DQB1*0202*-negative patients (RR = 21.01, 95% CI: 2.53–174.27, p = 0.005). **Conclusions**: Our observations support the potential role of *HLA-DQA1*:02:01* and *DQB*:02:02* as pharmacogenetic markers of the acitretin response in patients with psoriasis.

Keywords: psoriasis; acitretin; human leukocyte antigen; pharmacogenetics; response

1. Introduction

Psoriasis vulgaris is a chronic, immune-mediated inflammatory disease that affects approximately 2–3% of the general population [1–3]. It is characterized by increased proliferation of keratinocytes and abnormal activation of T-cells [4–6]. However, the pathogenesis of psoriasis remains poorly understood and may include genetic and immunological factors and abnormal metabolism [3,7,8]. The severity of psoriasis vulgaris is defined using the psoriasis area and severity index (PASI) or body surface area (BSA), which can be categorized into three stages: mild, moderate, and severe. For moderate and severe psoriasis vulgaris, systemic therapies or phototherapies such as methotrexate, cyclosporin, retinoids, and etanercept are used either as single agents or in combination [9,10].

Acitretin is a second-generation retinoid that is usually used as a first-line medication for treating moderate-severe psoriasis in China. Mechanistically, acitretin inhibits the proliferation and differentiation of keratinocytes in the skin and induces the differentiation of regulatory T cells [11]. However, only 50–60% of patients respond well to acitretin, and the factors involved in drug response prediction are unclear [12]. Our previous research showed that the *rs1802073G > T* polymorphism in *SFRP4* is significantly associated with the response to acitretin in patients with psoriasis [13]. Another study revealed that the frequency of the *-460TT* genotype of the *VEGF* gene was significantly higher in patients who did not respond to acitretin than in those who did, although the number of patients was small [14]. To date, few studies have revealed the pharmacogenomic profile of acitretin; therefore, little is known about possible inter-individual genetic predicting factors involved in the response to acitretin. Careful pharmacogenomic studies and state-of-the-art technologies are needed to better answer this question.

In the past 50 years, studies have found that genes within the human major histocompatibility complex (MHC) region at 6p21.3 are associated with the pathogenesis of psoriasis [15–18]. In the past, Zhang *et al.* [15] found multiple new susceptibility loci for psoriasis in the *HLA* genes, such as *HLA-C*, *HLA-B*, and *HLA-DPB1*, through deep sequencing of the MHC region in controls and psoriasis cases. The underlying mechanism could be explained by a malfunction in *HLA* gene alleles that regulate the expression of T cell function-related key proteins, which could disrupt the balance between T-helper cells, mainly Th1/Th17, and

cause the progression of psoriasis [19,20]. The induction of regulatory T cell differentiation is a major pharmacological mechanism of acitretin. Therefore, it is rational to hypothesize that *HLA* gene alleles could influence acitretin efficacy by altering T cell function in patients with psoriasis.

In this study, MiSeq high-throughput sequencing was used to analyze *HLA* typing in 100 patients with psoriasis who were treated with acitretin for at least 8 weeks. We also sought to identify the relationship between several *HLA* alleles and acitretin efficacy.

2. Materials and Methods

2.1 Patients

A group of 100 Han Chinese patients diagnosed with moderate-to-severe psoriasis vulgariswas recruited through the Department of Dermatology, Xiang Ya Hospital, Central South University. The psoriasis patients who enrolled in this research with the inclusion criteria as follows: (i) patients fulfilled the diagnostic criteria for psoriasis vulgaris, and the PASI score $\geq$5; (ii) patients were at least 18 years old; (iii) no medicines were received in the last four weeks before enrollment. The exclusion criteria were as follows: (i) patients who had other dermatological problems or any other diseases, and required pharmacological treatment; (ii) patients who failed to accomplish 8 weeks' treatment. In addition to the above criteria, the patients who with significant efficacy (achieved 90% PASI improvement) and significantly ineffective (failed to achieve 10% PASI improvement) were enrolled in discovery phases. All patients were systematically treated with acitretin (Huapont Pharm, 30 mg/day) for eight weeks (Fig. 1). Responders were defined as those who achieved 75% PASI improvement (PASI75) at eight weeks, and non-responders were those who failed to achieve PASI75. Data on basic patient characteristics were collected. PASI values were recorded at baseline and at week 8 after acitretin treatment.

2.2 MHC Target Region Sequencing

Twenty-four samples (16 responders and 8 non-responders) in the discovery phase were sequenced using the MHC targeted region capture method described previously [15,21]. DNA was extracted by a commercial DNA extraction kit (QIAamp, QIAGEN GmbH) from the PBMCs (Peripheral Blood Monouclear Cells), the shotgun libraries were constructed using 3 μg of genomic DNA, which was sheared into approximately 500 bp fragments in Tris-ethylene diamine tetra acetic acid (EDTA) buffer. DNA overhangs were converted into blunt ends using T4 polynucleotide kinase. T4 DNA polymerase and Klenow polymerase, and then the blunt ends fragments were subsequently A-tailed. Illumina sequencing adaptors with an overhang of a single T base were ligated to the A-tailed products by T4 DNA ligase. Further, the ligated fragments were amplified via PCR with four cycles. Finally, 1 μg of each prepared shotgun library was subsequently hybridized

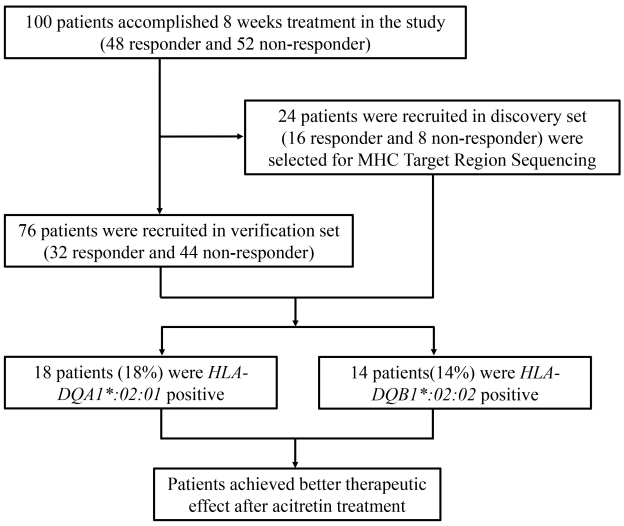

Fig. 1. Flow diagram: acitretin was prescribed and provided for all subjects at the time of enrolment. All subjects were followed for at least 8 weeks with an onsite interview at 4 weeks interval; 24 subjects were recruited in discovery phases, including 16 responders (achieved 90% PASI improvement) and 8 non-responders (failed to achieve 10% PASI improvement).

with capture probes by incubation at 65 °C for 70 h according to the manufacturer's instructions (Roche NimbleGen). The enriched targeted fragments were washed both at 47 °C and at room temperature and then amplified using Platinum Pfx DNA polymerase (Invitrogen) using the following protocol: incubation at 94 °C for 2 min followed by 15 cycles of 94 °C for 15 s, 58 °C for 30 s and 72 °C for 50 s and a final extension step at 72 °C for 5 min. PCR products were sequenced using an Illumina HiSeq 2000 sequencer.

2.3 Variant Calling and HLA Typing

The sequences of sequenced samples were mapped to the NCBI human genome reference assembly (Hg18) using BWA48. The average depth of the sequencing was 80x for the MHC region. BAM files were realigned around known indels using GATK v 1.6 (Genome Analysis Toolkit 49). All aligned reads were subjected to CountCovariates (GATK) on the basis of known single-nucleotide variants (SNVs) (dbSNP135), and the base quality was then recalibrated. A high quality single-nucleotide variant (SNV) genotype quality of $\geq$20$\times$ and sequencing depth of allele $\geq$5$\times$ were selected as the candidate variants required, The variants with low genotype call rates ($<$90%) and low mean depth ($<$6$\times$) were removed. A local de novo assembly method was used to obtain accurate typing results for each sample.

2.4 HLA-Sanger Sequencing (SBT) High Resolution Typing

SBT-based HLA typing was used to validate the 76 samples. For samples identified as homozygous, PCR-

Table 1. Characteristics of patients with psoriasis in each set.

Characteristics	Discovery set (n = 24)		p	Verification set (n = 76)		p	Total (n = 100)		p
	Responder (n = 16)	Non-responder (n = 8)		Responder (n = 32)	Non-responder (n = 44)		Responder (n = 48)	Non-responder (n = 52)	
Age (mean ± SD)[1]	34.7 ± 12.5	44.6 ± 13.5	0.088	36.5 ± 11.7	41.1 ± 12.4	0.102	35.9 ± 11.8	41.6 ± 12.5	0.020
PASI at baseline (mean ± SD)	13.8 ± 4.2	14.1 ± 6.7	0.881	13.4 ± 6.6	13.0 ± 6.9	0.792	13.5 ± 5.8	13.1 ± 6.8	0.773
BMI (mean ± SD)	23.3 ± 4.0	25.7 ± 4.2	0.187	22.1 ± 3.2	22.9 ± 3.7	0.294	22.5 ± 3.5	23.4 ± 3.9	0.235
Male, n (%)	12 (75)	3 (37.5)	0.180	27 (84.4)	30 (68.2)	0.107	39 (81.2)	33 (63.5)	0.048
Female, n (%)	4 (25)	5 (62.5)		5 (15.6)	14 (31.8)		9 (18.8)	19 (36.5)	

[1] mean ± SD (range), years. PASI, psoriasis area and severity index; BMI, body mass index; SD, standard deviation.

sequence-specific primer (SSP) was used for further validation. The PCR reaction conditions were described in 2.2.

2.5 Statistical Analysis

All analyses were performed using the SPSS 23.0 statistical package (IBM SPSS, Chicago, IL, USA). Fisher's exact test was used when data were sparse. Comparisons of continuous variables between the different genotype groups were performed using independent-sample *t*-tests. The chi-square test was used to examine the association between *HLA* types and acitretin response, when one or two of the cells have expected count less than 5, an alternative approach with 2 × 2 contingency tables is to use the continuity correction of chi-square test or Fisher's exact test. Relative risk (RR) has been reported to indicate the odds of drug sensitivity or resistance in patients who carry certain *HLA* alleles. A binary logistic regression model was used to estimate the RR, adjusted for age, sex, BMI, and baseline PASI. The significance level was set at $p < 0.05$.

3. Results

3.1 Basic Patient Characteristics

In total, 100 patients (28 women and 72 men) completed the study and their samples were sequenced for the presence of *DQA1* and *DQB1* alleles. Interestingly, the ages of non-responders were significantly older than those of the responders (41.6 ± 12.5 vs. 35.9 ± 11.8, $p = 0.020$). However, among the discovery (24 patients) and verification (76 patients) sets, there were no significant differences in age, PASI at baseline, BMI, and sex (Table 1).

3.2 MHC Target Region Sequencing Analysis

Twenty four patient samples were selected for MHC target region sequencing analysis. After identification of all the *HLA* alleles, chi-square test analyses were used to identify the allele distribution between the responder and non-responder groups of acitretin. We obtained 11 positive *HLA* alleles in this study. As shown in Table 2, we found that *HLA-A*:30:01, B*:13:02, C*:01:02, DQB1*:02:02, DQB1*:03:03, DQB1*:05:01, G*:01:05N, DMB*:01:01, DMB*:01:03, MICA*:008:01*, and *MICA*:010:01* were significantly associated with acitretin response.

3.3 HLA Typing Analysis

We analyzed the relationship between *HLA-DQA1* and *DQB1* gene polymorphisms and the response to acitretin in the verification set and found an increased RR to acitretin in patients who were *DQA1*0201*-positive (POS) and *DQB1*0202* POS. The combination of data from the discovery and verification sets supported this finding. The adjusted RRs were consistent with the crude estimates.

*DQA1*0201* was significantly more frequent in responders than in non-responders (18/30 vs 3/49, $p = 0.0001$), and *DQA1*0201* POS was associated with a better response to acitretin compared to *DQA1*0201*-negative (NEG) (RR = 10.34, 95% confidence interval (CI): 2.62–40.77, $p = 0.001$).

*DQB1*0202* was significantly more frequent in responders than in non-responders (14/34 vs 1/51, $p = 0.00014$), and *DQB1*0202* POS was associated with a better response to acitretin compared to *DQB1*0202* NEG (RR = 21.01, 95% CI: 2.53–174.27, $p = 0.005$) (Table 3).

As presented in Table 4, we observed an obvious increase in the response rate to acitretin in patients with *DQA1*0201* and *DQB1*0202*. At week 8, PASI75 was achieved in 93.3% (14 of 15) of patients with *DQA1*0201–DQB1*0202*, compared to 38.0% (30 of 79) of patients without *DQA1*0201–DQB1*0202* (RR = 24.69, $p = 0.003$, 95% CI: 2.92–208.91). Additionally, 85.7% (18 of 21) of patients with *DQA1*0201* reached PASI75, compared to patients without *DQA1*0201– DQB1*0202* (RR = 10.34, $p = 0.001$, 95% CI: 2.62–40.77).

4. Discussion

According to a previous report, *HLA-DQA1*0201* and *DQB1*0202* are susceptible genes for psoriasis, and 21% of patients with psoriasis were *DQA1*0201* POS [22]. Although the frequency of *DQA1*0201* positivity in patients with psoriasis in our study was slightly lower (18%) than that reported in Zhang's study (24%) [15], the allele frequency of both variants was much higher in patients with psoriasis than in healthy controls (8%) [22].

In the present study, we found an association between the presence of *DQA1*02:01* and *DQB1*02:02* alleles and a good clinical response to acitretin in the Han

Table 2. HLA types associated with acitretin response in the discovery set.

HLA alleles	Responder (n = 16)		Non-responder (n = 8)		p [1]
	32 alleles (%)		16 alleles (%)		
	positive	negative	positive	negative	
A:30:01*	9 (28.1)	23 (71.9)	0 (0)	16 (100)	0.05[1]
B:13:02*	10 (31.3)	22 (68.7)	0 (0)	16 (100)	0.033[1]
C:01:02*	3 (9.4)	29 (90.6)	6 (37.5)	10 (62.5)	0.05[1]
DQB1:02:02*	9 (28.1)	23 (71.9)	0 (0)	16 (100)	0.05[1]
DQB1:03:03*	3 (9.4)	29 (90.6)	6 (37.5)	10 (62.5)	0.05[1]
DQB1:05:01*	1 (3.1)	31 (96.9)	5 (31.2)	11 (68.8)	0.012[2]
G:01:05N*	9 (28.1)	23 (71.9)	0 (0)	16 (100)	0.05[1]
DMB:01:01*	23 (71.9)	9 (28.1)	5 (31.2)	11 (68.8)	0.007
DMB:01:03*	9 (28.1)	23 (71.9)	10 (62.5)	6 (37.5)	0.022
MICA:008:01*	17 (53.1)	15 (46.9)	3 (18.8)	13 (81.2)	0.023
MICA:010:01*	3 (9.4)	29 (90.6)	6 (37.5)	10 (62.5)	0.05[1]

[1]Number of alleles used for Fisher's exact test, because two cells (50.0%) have expected count less than 5. [2]Number of *DQB1*:05:01* used for continuity correction of chi-square test, because one cell (25.0%) have expected count less than 5.

Table 3. The association of *HLA-DQA1* and *DQB1* alleles with acitretin response in patients with psoriasis.

Phase	HLA alleles	Responder (n, %)		Non-responder (n, %)		p [1]	p [d 2]	Adjusted RR [2] [95% CI]
		positive	negative	positive	negative			
Verification set	*DQA1*:02:01*	9 (29.0)	22 (71.0)	2 (4.4)	43 (95.6)	0.008	0.015	8.41 (1.52–46.60)
	DQB1:02:02*	6 (19.4)	25 (80.6)	1 (2.2)	44 (97.8)	0.016	0.03	12.87 (1.27–130.10)
Discovery + Verification Set	*DQA1*:02:01*	18 (37.5)	30 (62.5)	3 (5.8)	49 (94.2)	0.0001	0.001	10.34 (2.62–40.77)
	DQB1:02:02*	14 (29.2)	34 (70.8)	1 (1.9)	51 (98.1)	0.00014	0.005	21.01 (2.53–174.27)

[1] Number of alleles used for chi-square tests is presented in this table; [2] Adjusted by age, sex, PASI at baseline and BMI through a binary logistic regression model, RR >1 means response to acitretin, RR <1 means non-response to acitretin. RR, relative risk; CI, confidence interval; BMI, body mass index.

Chinese population. Patients carrying the *DQA1*02:01* or *DQB1*02:02* loci had a better response than non-carriers to acitretin treatment, which suggests that the *DQA1*02:01* or *DQB1*02:02* loci may act as genetic predictors of the response to acitretin, although we cannot exclude the possibility of linkage disequilibrium between *DQA1*02:01* and *DQB1*02:02* and other genetic features of psoriasis. Additionally, compared to the patients who were *DQA1*0201* NEG–*DQB1*0202* NEG, the patients with *DQA1*:02:01* POS had a good response to acitretin (RR = 10.34, p = 0.001), and patients with *DQA1*0201* POS–*DQB1*0202* POS were associated with a better response (RR = 24.69, p = 0.003). Therefore, *DQB1*0202* is an important allele for the response to acitretin in psoriasis (Table 4).

Acitretin belongs to the family of retinoid and is also known as a member of the retinoic acid receptors (RARs) agonist family. RARs are highly expressed in the keratinocytes, and the expression levels of RARα in psoriatic lesional skin were significantly reduced compared to normal skin [23,24]. Acitretin can activate multiple RARs and regulates transcription factors, such as dimers of RAR/RXR (retinoid X receptor), signal transducer and activator of transcription 1, NF-κB [25–27]. Therefore, acitretin plays key roles in regulating keratinocyte proliferation and differentiation.

Acitretin has anti-inflammatory effects. It decreases the populations of T-cells, Th1 cells, and Th17 cells in psoriasis lesions, which are essential for the genesis of psoriatic plaques, further leading to the inhibition of intra-epidermal inflammation [11,28]. *DQA1* and *DQB1* encode the α chain of the T-cell receptor. One possible explanation for our finding is that *DQA1*02:01* and *DQB1*02:02* may alter the expression of T-cell receptors, increasing the sensitivity of T cells to acitretin, thereby leading to a further decrease in Th1 and Th17 cell populations in psoriasis lesions.

DQA1 and *DQB1* belong to *HLA* Class II alpha and beta paralogues respectively, which consist of an alpha (DQA) and a beta chain (DQB). The two chains anchored in the membrane form a functional protein complex, known as the antigen-binding DQ$\alpha\beta$ heterodimer. Within the DQ molecule, 76 polymorphisms have been identified on DQA and 978 have been found on DQB, which allows for a wide range of peptide-binding specificities. Nevertheless, gene mutations causing malfunction of *DQA1* and

Table 4. The association of *HLA-DQA1*:02:01–DQB1*:02:02* alleles with acitretin response in patients with psoriasis.

HLA alleles	Responder (n, %)	Non-responder (n, %)	*p*	*p* [d 2]	Adjusted RR [2] [95% CI]
DQA1:02:01POS DQB1*:02:02POS* VS *DQA1*:02:01NEG DQB1*:02:02NEG*	14 (93.3) / 30 (38.0)	1 (6.7) / 49 (62.0)	0.00008	0.003	24.69 (2.92–208.91)
DQA1:02:01POS* [1] VS *DQA1*:02:01NEG DQB1*:02:02NEG*	18 (85.7) / 30 (38.0)	3 (14.3) / 49 (62.0)	0.0001	0.001	10.34 (2.62–40.77)

[1] Patients with *DQA1*:02:01* POS include those with *DQA1*:02:01* POS–*DQB1*:02:02* POS and *DQA1*:02:01* POS–*DQB1*:02:02* NEG; [2] Adjusted by age, sex, PASI at baseline and BMI through a binary logistic regression model. RR, relative risk; CI, confidence interval.

DQB1 were found to be associated with autoimmune disorders such as rheumatoid arthritis [29,30], multiple sclerosis [31,32], and even cancer [33]. In addition, *DQA1* and *DQB1* gene mutations have also been found to be associated with adverse drug reactions and drug efficacy. For instance, two independent loci in the *HLA-DQB1* (126Q) and *HLA-B* regions are associated with a rare but fatal adverse drug event: clozapine-induced agranulocytosis [34], and the *HLA-DQA1*05* allele is associated with a high rate of immunogenicity in biotherapy [35]. A 14 bp-insertion/deletion (INS/DEL) polymorphism in exon 8 of *HLA-G* was associated with an increased acitretin response (Odds ratio (OR) = 7.74, p = 0.008) [36]. In the discovery set samples of our study, we also identified a different *HLA-G* gene variant (G*:01:05N) that was associated with an increased acitretin response (p = 0.05) (Table 2). Although we determined that *HLA-DQA1*02:01* and *HLA-DQB1*02:02* were associated with acitretin response for the first time, several limitations should be noted: First, the sample size was considered not large enough, and the coverage of MHC sequencing was insufficient, these may leads to false-positive SNPs presented in the result. Second, the high level of polymorphism in the MHC region means HLA genotyping is a complex work, which hinders subsequent confirmation and functional exploration.

5. Conclusions

In summary, patients with moderate-to-severe psoriasis require an individualized approach during treatment with acitretin, and an understanding of the clinical relevance of *HLA* gene polymorphisms in relation to acitretin treatment for psoriasis is needed. Our data suggest that *DQA1*02:01* and *DQB1*02:02* alleles as the pharmacogenetic markers of the response to acitretin may provide a useful reference in psoriasis for targeted therapies.

Author Contributions

XZ performed the experiments, analyzed data and wrote the manuscript; WZ and YK collected biological sample; XZ and YH analyzed the data; WZ and WC designed the experiments, carried out and summarized data analysis, contributed to the text of the manuscript.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the Declaration of Helsinki, and approved by Ethics Committee of Xiangya Hospital (protocol code: 201512526).

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Conflict of Interest

The authors declare no conflict of interest.

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