Human leukocyte antigen and demographic characteristics in Chinese patients with active peripheral type psoriatic arthritis who had inadequate response to conventional disease-modifying antirheumatic drugs in a single dermatologic clinic

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Abstract

Background
Correlation between severity of psoriasis and psoriatic arthritis (PsA) is inconsistent. Also, human leukocyte antigen (HLA)-Cw6 was found to be underrepresented in severe psoriasis who failed conventional systemic therapies, but the effect of HLA polymorphism on PsA severity needs to be confirmed.

Objectives
To describe the severity of psoriasis, demographic features and HLA polymorphism among Chinese patients with active peripheral type PsA who had inadequate response to conventional disease-modifying antirheumatic drugs.

Methods
We included all patients with PsA who had at least 3 tender and swollen peripheral joints despite at least two conventional non-biologic treatments in our clinic. Demographic results were compared with global pivotal studies of biologics for PsA. HLA-Cw and HLA-DRB1 genotyping was also analyzed.

Results
We identified 60 patients who met our inclusion criteria. The male to female ratio was 1.31:1. The majority of patients presented with psoriasis first (81.7%). The mean interval between psoriasis and PsA was 7.2 ± 8.1 years (mean ± SD). The baseline number of
tender and swollen joints was $14.9 \pm 10.7$ and $11.3 \pm 10.2$, respectively. In total, 41.7% subjects had more than 3% body surface area involvement of psoriasis. Genotyping of HLA-Cw and HLA-DRB1 was performed in 47 subjects. HLA-Cw*0702 was the most frequent allele (29.8%), followed by HLA-Cw*01 (26.6%). The frequency of HLA-Cw*0602 allele was similar to normal population. The most frequent HLA-DRB1 allele was HLA-DRB1*04 (20.2%), followed by HLA-DRB1*08 (16.0%). No cases carrying HLA-DRB1*13 were detected.

Conclusions

Compared with Western population, our patients had less psoriasis and PsA burden. The frequencies of HLA-Cw*06, HLA-Cw*12, and HLA-DRB1*07 were not increased. In contrast, HLA-Cw*0702 and HLA-DRB1*08 allele frequencies were increased compared with psoriasis patients and normal population in Taiwan. Future studies are still needed to characterize the demographic and genetic features of high need PsA patients.

Introduction

Psoriatic arthritis (PsA) is a chronic immune-mediated inflammatory disease often associated with psoriasis. PsA can be further classified into peripheral arthritis, spondyloarthropathy, enthesitis, and/or dactylitis. The annual incidence of PsA varied significantly among studies (median 6.4, range 0.1–23.1 cases per $10^5$ inhabitants), which was extremely low in Japanese population and higher in the Western population[1]. The reported prevalence of PsA from cross-sectional surveys also shows discordancy, ranging from 6% to 42% among patients with psoriasis[1]. Compared with Caucasians, the prevalence of PsA in Asians patients with psoriasis was lower, about 14.3% in Japanese[2], 11.2% in Korean[3], 5.3% in Han Chinese[4], and 8.5% in Indian population[5]. But under-diagnosis may be common and might account for the lower incidence and prevalence in some studies.

The pathogenesis of PsA remained uncertain but both genetic and environmental factors might play important roles. Because PsA is usually associated with psoriasis, it is conceivable that lower PsA prevalence is linked to lower psoriasis prevalence. Human leucocyte antigen (HLA)-Cw*06 allele is the most important psoriasis susceptibility gene. The lower prevalence of psoriasis in Asia-Pacific countries may be in part due to the lower prevalence of HLA-Cw*06 positivity within the population [6–8]. However, the association between PsA and HLA-Cw*06 is more ambiguous. Some studies showed that HLA-Cw*06 positivity is higher in patients with PsA [9–11], but HLA-Cw*06 together with HLA-DRB1*07 positivity has also been demonstrated to be a negative predictor for PsA severity in Western countries [12].

Over more than a decade, biologics have been increasingly used in the treatment of PsA, and also of psoriasis (but to a lesser extent)[13]. Previously, HLA-Cw6 was found to be under-represented in severe psoriasis who failed conventional treatment and were candidates for biologics[14], but the same effect of HLA polymorphism on PsA has not been assessed.

In phase 3 pivotal trials of biologics for psoriasis, 21.3–33.1% of patients had PsA. In similar studies performed in Asia, only 8.8–25.6% had PsA [15]. However, the correlation between severity of psoriasis and PsA has been a matter of dispute[16]. In addition, most pivotal trials of biologics for psoriatic disease were conducted in Western countries with limited non-white subjects, especially in PsA trials (Table 1). Up to now, no phase 3 clinical trials of biologics have been conducted only in Asia for PsA.
Table 1. Demographic features of our study and PsA pivotal studies\(^a\).

|                | Mease et al.\(^{20}\), n = 60 | Antoni et al.\(^{25}\), 2005, n = 200 | Mease et al.\(^{21}\), 2005, n = 313 | Kavanaugh et al.\(^{22}\), 2012, n = 405 | Mease et al.\(^{16}\), 2014, n = 409 | Ritchlin et al.\(^{23,8}\), 2014, n = 312 | Mease et al.\(^{27}\), 2014, n = 168 | Mease et al.\(^{26}\), 2015, n = 606 | Edwards et al.\(^{24}\), 2016, n = 505 | Mease et al.\(^{28}\), 2017, n = 424 | Nash et al.\(^{30}\), 2017, n = 363 | Mease et al.\(^{29}\), 2017, n = 422 | Our study, n = 60 |
|----------------|--------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|
| **Biologics**  | ETN                            | INX                                 | ADA                                 | GOL                                 | CZP                                 | UST                                 | BRO                                 | SEC                                 | APR                                 | ABT                                 | IXE                                 | TOF                                 | ETN                                 |
| **Asian Countries** | Nil                            | Nil                                 | Nil                                 | Nil                                 | Nil                                 | Russian                             | Nil                                 | Australia, Philippines, Russian, Singapore, Thailand | Australia, Russia, Republic of Korea | Nil                                 | Australia, Taiwan                   | Australia, Russia, Taiwan            | Taiwan                             |
| M/F (M%)       | 56.7                           | 61                                  | 55.6                                | 60.2                                | 44.7                                | 47.4                                | 36                                  | 45.5                                | 46.7                                | 45                                  | 46.6                               | 46.7                               | 56.7                               |
| Ethnicity (Asian %) | -                              | -                                  | -                                  | -                                  | 1.7                                 | -                                  | 1.8                                 | 19                                  | 3                                   | 0.2                                 | 6                                  | -                                  | 100                                |
| Mean age (years) | 44.8                           | 46.8                                | 48.9                                | 47                                  | 47.5                                | 48.3                                | 52.3                                | 49                                  | 49.7                                | 50.4                                | 51.9                               | 47.9                               | 44.5                               |
| BW (kg)        | 86                             | 85.7                                | 85.2                                | 84.4                                | 84.4                                | 90.7                                | 82.9                                | 84.9                                | 88.7                                | -                                   | 72.2                               | 72.2                               |                                                  |
| Duration of PsA (years) | 9.3                            | 8                                   | 9.5                                 | 7.5                                 | 8.5                                 | 5.1                                 | 8.7                                 | -                                   | 7.3                                 | 8.5                                 | 10                                  | 6.1                                 | 6.3                                 |
| Duration of PsO (years) | 18.3                           | -                                   | 17.1                                | 18.3                                | -                                   | 12                                  | -                                   | 17.7                                | -                                   | 15.8                                | -                                   | 13.5                               |                                                  |
| BSA > 3%       | 63.30%                         | 85.00%                              | 44.70%                              | 73.10%                              | 61.60%                              | 77.20%                              | 62.50%                              | 53.60%                              | 55.20%                              | 69.30%                              | 55.90%                             | 73.90%                             | 41.70%                             |
| PASI \(^c\)    | 8.1                            | 10.8                                | 7.9                                 | 9.9                                 | 7.4                                 | 8.4                                 | -                                   | 13.8                                | 7.7                                 | 7.3                                 | 5.9\(^d\)                          | 6.7                                 | 11                                 |
| BSA \(^c\)     | -                              | -                                   | -                                  | 16.3                                | -                                   | -                                   | -                                   | -                                   | 11.4\(^d\)                         | -                                   | 15.7                               |                                                  |
| Tender joint count | 20.8                           | 24.9                                | 24.9                                | 22.9                                | 20.3                                | 21.7                                | 24.3                                | 24.1                                | 20                                  | 20.2                                | 22.5                               | 19.6                               | 14.9                               |
| Swollen joint count | 14.4                           | 14.2                                | 14.3                                | 13.1                                | 10.6                                | 11.3                                | 12.6                                | 13.4                                | 11.4                                | 11.6                                | 12.3                               | 11.5                               | 11.3                               |
| MTX use at baseline (%) | 46.7                           | 46                                  | 32.3                                | 47.9                                | 63.6                                | 49.7                                | 50                                  | 60.7                                | 51.9                                | 60.4                                | 41                                 | 83.9                               | 33.3                               |
| Systemic corticosteroid use at baseline (%) | 30                             | 12.5                                | 14.4                                | 16                                  | -                                   | 16                                  | 18.5                                | 15.7                                | 14.5                                | 25.2                                | 14.6                               | 19.2                               | 1.7                                 |

\(^a\) indicates no data available

\(^b\) Data are reported as median.

\(^c\) Assessed in patients with psoriasis on at least 3% of their body surface area.

\(^d\) Assessed all patients.

Abbreviations for biologics: abatacept (ABT), adalimumab (ADA), apremilast (APR), brodalumab (BRO), certolizumab (CZP), etanercept (ETN), golimumab (GOL), infliximab (IFX), ixekizumab (IXE), secukinumab (SEC), tofacitinib (TOF), ustekinumab (UST).

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Psoriatic arthritis, psoriasis, and HLA in Asian
The purpose of this study was to describe the demographic features and HLA distribution of Chinese PsA patients who had inadequate response to conventional disease-modifying anti-rheumatic drugs and to compare these features with the Western subjects.

Materials and methods

Study design

This is a retrospective review of all patients with plaque psoriasis who also fulfilled the reimbursement criteria of biologics use for PsA in our clinic from January 2010 to July 2017. Demographic data includes patient age, gender, age of onset of psoriasis and PsA, total tender/swollen joint counts, previous and current biologics use, body surface area (BSA) of psoriasis, and psoriasis area and severity index (PASI). The study was approved by the local investigational research bureau of National Taiwan University Hospital. IRB/REC number: 201707057RINA All patient records and information were anonymized and de-identified before the analysis.

Patients

We included all consecutive patients who had chronic plaque psoriasis and met reimbursement criteria for biologics, i.e. who had at least 3 tender peripheral joints out of 78 and swollen peripheral joints out of 76, despite previous methotrexate (or sulfasalazine or cyclosporine) and leflunomide, each for at least 3 months in addition to oral nonsteroidal anti-inflammatory drugs (NSAIDs). Patients with only psoriatic spondyloarthritis were excluded from this study. All patients were first evaluated by both rheumatologists and dermatologists for confirmative diagnosis and the PsA severity was reconfirmed by independent joint assessors by clinical pictures (with or without image studies and serology data) per reimbursement requirement. None of the patients were relatives.

Statistical analysis

Data were analyzed with the Statistical Package for Social Scientists (SPSS) version 11.5. Demographic data and clinical characteristics were summarized as the mean ± standard deviation for continuous variables. For categorical variables, proportions were described as percentages. Comparisons of two groups were made using the Pearson’s χ² test for non-continuous variables. The Fisher’s exact test was used when the expected count was < 5. Mann–Whitney U tests were used for comparing continuous variables. Statistical significance was set at P < 0.05.

Results

We identified 60 patients (56.7% male) who met inclusion criteria in the study. The demographic features of our study and previous PsA pivotal studies are shown in Table 1. There is a slight male predilection (male to female ratio of 1.31:1). All the patients had chronic plaque type psoriasis. The majority of patients presented with psoriasis first (81.7%) followed by concurrent psoriasis and PsA during the same calendar year (15.0%). The mean age at presentation of psoriasis was 31.0 ± 13.1 years (mean ± SD) and the mean interval between psoriasis and PsA was 7.2 ± 8.1 years. Most subjects had type I psoriasis (age of onset < 40 years old, 73.3%). Compared with type II psoriasis, the former showed a significantly longer psoriasis-arthritis latency period (p = 0.001) and a trend to have more tender and swollen joints counts (not statistically significant, Table 2). The mean age when biologic was first initiated was 44.5 ± 10.6 years and the disease duration of PsA to initiate biologics was 6.3 ± 6.3 years. The
baseline number of tender and swollen joints was 14.9 ± 10.7 and 11.3 ± 10.2, respectively. In total, 41.7% subjects had more than 3% BSA involvement. In those patients, the baseline psoriasis area severity index (PASI) was 11.0 ± 6.5 and the baseline BSA was 15.7 ± 15.9. Compared with patients who had less than 3% BSA involvement, patients with more extensive psoriasis had significantly greater body weight (p = 0.004), and positive trends of more swollen joint counts, tender joint counts, and longer duration of psoriasis (Table 3). Twenty-five patients (36.7%) had been treated with more than one biologic agent and the most frequently prescribed biologic agent was etanercept (60.0%), followed by golimumab (43.3%), adalimumab (35.0%), and ustekinumab (6.7%). Genotyping of HLA-Cw and HLA-DRB1 was performed on DNA samples of 47 subjects (Table 4). Among them, HLA-Cw*0702 was the most frequent allele (29.8%) followed by HLA-Cw*01 (26.6%). The frequency of HLA-Cw*0602 was similar to normal population. The most common HLA-DRB1 allele was HLA-DRB1*04 (20.2%), followed by HLA-DRB1*08 (16.0%). Interestingly, there was no patient had HLA-DRB1*13 allele. There was no significant HLA-Cw and HLA-DRB1 allele difference between type I and type II psoriasis. There were 10 patients (16.7%) who had dactylitis in our study group and HLA data were available in 8 patients who had dactylitis and 39 patients who had no dactylitis. When comparing the two groups, no apparent statistical significance was noted (S1 Table). Besides, when comparing the demographic and clinical characteristics between patients with HLA data and patients without HLA data, there was no significant difference between the two groups, except for the duration of PsA (S2 Table).

### Discussion

Frequency of PsA is lower in most Asian studies. Although there are several systemic review articles, retrospective and cross-sectional epidemiologic studies of PsA in Asian countries [1–5, 17], no Asian subgroup analysis or Asia only studies exists for phase 3 pivotal trials for biologics of PsA which included patients with at least 3 tender and swollen joints. In contrast, several phase 3 pivotal studies and subgroup analysis of global pivotal studies of biologics for psoriasis exist for Asian subjects. In the psoriasis trials, Asian subjects were generally 15–20

| Number of patients (%) | Gender M (%) | PsO onset age | PsA onset age | Baseline BSA | Baseline PASI | Latency | TJC | SJC | BW (kg) | Age at bDMARD |
|------------------------|--------------|---------------|---------------|--------------|----------------|--------|-----|-----|--------|----------------|
| BSA<3%                 | 35 (58.3)    | 51.4          | 32.2          | 37.7         | 0.9            | 3.0    | 14.3| 9.8 | 68.5   | 44.3           |
| BSA>3%                 | 25 (41.7)    | 64.0          | 29.4          | 39.0         | 15.7           | 11.0   | 15.7| 13.4| 79.9   | 44.7           |
| p value                | 0.40         | 0.67          | <0.001        | <0.001       | 0.07           | 0.63   | 0.23| 0.004| 0.89   | 0.003          |

Table 3. Demographic features of patient had 3% BSA involvement or less.

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Kgs lighter, with lower concurrent PsA prevalence (or history of PsA), shorter disease duration since diagnosis, and higher baseline psoriasis severity compared to Western subjects[15]. In the lack of Asian demographic data in pivotal PsA studies, the current results provided important information regarding the clinical and HLA features of Chinese patients with PsA. The demographics in our patients were in consistent with the pivotal studies, namely the mean age, duration of PsA, duration of psoriasis and PASI. For the genders, there is mild male predominance, although the gender predilection varied significantly among studies, with ethnic and geographic differences [1, 17]. In a previous Taiwanese study[18], like Korean [3, 19], spondylitis was the most common pattern of PsA. However, to homogenize the patient group, we excluded patients with only spondyloarthritis and due to reimbursement criteria, only patients with polyarthritis was included. In the majority of our patients, PsA was preceded by psoriasis, which is consistent with previous data. The mean (± SD) onset age for cutaneous psoriasis was 31.0 ± 13.1 years and the mean age of onset of PsA was 38.2 ± 11.9 years. The mean duration between psoriasis and PsA was 7.2 years and in patients who had skin manifestations before arthritis, the latency period was 9.1±7.8 years, which was compatible with previous pivotal studies of PsA[20–24].

Some differences in demographics exist for our patients. First, the body weight is lower in our patients. The mean total swollen and tender joints counts were also lower. Compared with previous pivotal PsA studies, about 44.7~85.0% of patients who were candidate for biologic agents has more than 3% BSA involvement, and among them, the average PASI score was 6.7~13.8 [20–31]. Only 41.7% of our patients had more than 3% BSA involvement, which might imply that Asian PsA patients had less severe psoriasis. Alternatively, it might be due to better skin care by dermatologists in this study as compared to by rheumatologists who conducted most of the PsA trials. However, patients with more severe psoriasis should be more common in dermatologists’ clinic, and the higher concomitant use of both methotrexate (up to 30mg/week) and systemic corticosteroid (10mg/day) in PsA pivotal trials compared to our patients should theoretically favor less psoriasis lesions in global studies. Thus, the lower percentage of severe psoriasis in high need PsA patients may be a true feature of our PsA patients. However, in those who had more than 3% BSA involvement, the PASI score and BSA involvement were comparable to previous pivotal studies. In fact, some Asian subgroup analysis of psoriasis studies showed an even higher PASI and BSA in Asian subjects[15].

### Table 4. HLA genotyping results in 47 patients with moderate to severe PsA.

| HLA-Cw | Positivity | Frequencies N = 47 (%) | HLA-DRB1 | Positivity | Frequencies N = 47 (%) |
|--------|------------|------------------------|-----------|------------|------------------------|
| HLA-Cw allele | N = 94 (%) | | HLA-DRB1 allele | N = 94 (%) | |
| Cw’01 | 01:02 | 19(40.4) | 22(23.4) | DRB1’04 | 04:03 | 7(14.9) | 7(7.4) |
|      | 01:03 | 3(6.4) | 3(3.2) |      | 04:04 | 1(2.1) | 1(1.1) |
| Cw’06 | 06:02 | 3(6.4) | 3(3.2) |      | 04:06 | 1(2.1) | 2(2.1) |
| Cw’07 | 07:02 | 26(55.3) | 28(29.8) |      | 04 | 18(38.3) | 19(20.2) |
| Cw’08 | 08:01 | 6(12.8) | 6(6.4) | DRB1’07 | 07:01 | 3(6.4) | 3(3.2) |
|      | 08:03 | 1(2.1) | 1(1.1) | DRB1’08 | 08:02 | 1(2.1) | 1(1.1) |
|      | 08 | 7(14.9) | 7(7.4) |      | 08:03 | 14(29.8) | 14(14.9) |
| Cw’12 | 12:02 | 2(4.3) | 3(3.2) |      | 08 | 15(31.9) | 15(16.0) |
|      | 12:03 | 1(2.1) | 1(1.1) | DRB1’13 | - | 0(0.0) | 0(0.0) |
|      | 12 | 3(6.4) | 4(4.3) | DRB1’17 | 03:01 | 2(4.3) | 2(2.1) |

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findings, differences are known to exist between study populations in randomized clinical trials and real life studies[32]. Among our study population, some were classified as medically ineligible, which mean that they had medical conditions within the exclusion criteria. Besides, parts of our patient had concomitant treatments like topical medications and cDMARDs other than methotrexate. The difference between the study groups, may affect the baseline demographic characteristics and disease severity. As for dactylitis, there were 10 patients (16.7%) who had dactylitis in our study group, the rate is lower than previous pivotal studies of PsA (ranging from 17.1% to 61.9%)[20–31]. However, the rate is close to previous Chinese study [33], which dactylitis presented in 13.4% of random PsA patients. The results may indicate less dactylitis in Chinese PsA patients, although data about moderate to severe PsA patients were relatively lacking.

The relationship between the extent of psoriasis and the severity of the PsA had shown inconsistent results[16]. The results of meta-analysis suggested a trend for an association between high psoriasis severity and PsA risk[34]. However, there were few studies discussing whether the extent of psoriasis had a positive correlation with the severity of PsA among PsA patients. Our study showed that compared to patients with less than 3% BSA involvement of psoriasis, patients with more than 3% BSA involvement had positive trends of more tender joint counts and swollen joint counts. Another interesting finding is the longer latency between psoriasis and onset of PsA in type I psoriasis. The exact reason is unknown. Previously, the annual incidence of PsA was found to remain constant following initial diagnosis of psoriasis among patients seen in European dermatologic clinics[35]. In addition, repeated mechanical stress or microtrauma has been shown to trigger the occurrence of PsA[36], and patients whose psoriasis has onset before 40 could have theoretically more physical activity and hence more exercise associated trauma. One possible explanation is the need of other factors such as aging related degenerative changes in the pathogenesis of PsA.

Previously, compared to Indian patients, Chinese patients were found to be less likely to be using biological therapies, and have fewer tender joint counts[37]. Our study results had similar results. When compared with Western patients, our PsA patients had fewer tender joints. Ethnicity, genetic or social factors might play a pathogenic role in the manifestation of disease activity of PsA.

HLA-Cw*06 is known to be one of the most strongly associated psoriasis susceptibility allele and presence of HLA-Cw*06 has been shown to affect different aspects of psoriasis and PsA [38, 39]. In Caucasians, frequency of the HLA-Cw*06 allele in the psoriatic disease was higher than that in the control group and it is associated with earlier disease onset of psoriasis in uncomplicated psoriasis and psoriatic arthritis patients[9–11]. Multiple studies have indicated an increase in HLA-Cw*06 frequency in PsA patients[40–45], although some studies found that the frequency of the allele was comparable to psoriasis patients[43, 44]. Besides, HLA-Cw*06 prevalence is known to be lower in Chinese, and especially lower in high need moderate to severe psoriasis patients who failed previous conventional systemic agents [14]. It is also known that the presence of HLA-Cw*06 combined with HLA-DRB1*07 was a negative predictor factor for severe PsA in United Kingdom[12]. The HLA-Cw*06 frequency in our study was similar to normal population in Taiwan[7, 46], which might suggest that it is not a susceptibility factor in Chinese patients with patients with PsA refractory to conventional DMARDs.

There were fewer reports regarding the association of HLA-Cw*07 and psoriatic disease. There were reports to show no association between HLA-Cw*07 and psoriatic disease, and PsA cases were less likely to be carriers of the HLA-Cw*07[47, 48]. In one Spanish study, HLA-Cw*0701 was found under-represented in PsA patients compared to controls and there was a positive association between psoriatic spondylitis and HLA-Cw*0702[11]. In our
previous study, psoriasis vulgaris patients were more likely (not statistically significant) to be carriers of HLA-Cw*07 compared with the control group[7]. In this study, twenty-six (55.3%) patients carried at least one HLA-Cw*0702 allele and it was the most frequent allele and more prevalent compared with psoriasis patients and normal population in Taiwan[7, 14, 46], which may indicate that HLA-Cw*0702 might also be a susceptibility allele for Chinese PsA patients. Besides, compared with random PsA patients[49], our group had higher positivity rate and frequency of HLA-Cw*0702, which may indicate that there is an association between moderate to severe PsA patients and HLA-Cw*0702.

The association between HLA-Cw*12 and psoriasis has been controversial. One genome-wide association study had demonstrated HLA-Cw*12 was significantly associated with psoriasis in Caucasians, but not in Han Chinese[50]. For PsA, Chandran et al. found that HLA-Cw*12 is present in about 20% of patients with PsA, with significant difference compared with control group[51]. Similarly, a study by Liao et al.[49] showed that HLA-Cw*12 was more common in PsA patients than in psoriasis patients in Chinese population, which may indicate that HLA-Cw*12 plays a more important role in the development of PsA. However, our data differs from the above studies and the frequency of HLA-Cw*12 in our study was lower (4.3%), which may indicate it was not a risk factor for Chinese PsA patients refractory to conventional DMARDs.

Although HLA-DRB1 alleles were not found to be associated with PsA susceptibility in several reports[52, 53], HLA-DRB1 antigen may play a minor role in the susceptibility of psoriasis and psoriatic arthritis and may modify the clinical presentation of PsA. HLA-DRB1*04, the most common allele in this study, was reported to be a risk for rheumatoid-like psoriatic arthritis[54, 55] and was associated with early-onset of arthritis[56], although some study found no association or even under-representation in PsA patients[57, 58]. Study by Schmitt-Egenolf et al. revealed positive association between HLA-DRB1*07 and type I psoriasis[59] and our previous study revealed that HLA-DRB1*0701 allele was positively associated with both type I and type II psoriasis[60]. In PsA patients, increased frequency of HLA-DRB1*0701 compared with controls had been reported[61], but its frequency was lower than uncomplicated psoriasis patients[49, 52, 62]. HLA-DRB1*0701 had been associated with oligoarthritis[58] and milder PsA disease [52, 63]. HLA-DRB1*08 was found to be associated with psoriatic polyarthritis[58], and it was the second most common allele in our study, with higher frequency compared with psoriasis patient and normal population in Taiwan[49, 64, 65], which may indicate it is a risk factor for psoriatic polyarthritis.

This study had several limitations. First, our sample size is small. Second, despite similar inclusion criteria of PsA severity, PsA patients in the pivotal trials of biologics did not have to fail at least two conventional DMARDs (disease modifying antirheumatic drugs) including leflunomide (not approved in United states for PsA) and more patients in PsA trials used concomitant systemic agents. Previously, HLA-Cw*06 positive psoriasis patients were shown to respond better to conventional treatment and ustekinumab[38, 39, 66–69]. Thus, our PsA patients who failed multiple conventional DMARDs might have different severity of psoriasis and also different HLA-Cw allele distribution compared to PsA patients in pivotal biologics studies. Third, lower percentage of our patients used baseline systemic corticosteroid and methotrexate compared to controlled clinical trials which could affected the presence and severity of psoriasis. Fourth, data regarding enthesitis and nail involvement are not included in the reimbursement criteria and were not assess.

To the best of our knowledge, this is the largest genetic study in PsA patients who had inadequate response to disease-modifying antirheumatic drugs in Chinese population. Compared with Western population, our patients had less psoriasis and PsA burden, but in those who had more than 3% BSA involvement, their PASI score and BSA involvement were comparable.
to the Western subjects. The frequencies of HLA-Cw*06 and HLA-Cw*12, two well-documented alleles associated with psoriasis and PsA in Chinese, respectively, was not increased in our cohort. In contrast, HLA-Cw*0702 and HLA-DRB1*08 allele frequencies were increased compared with normal population and psoriasis patients in Taiwan. Due to the heterogeneous natures of PsA and the small sample sizes, future studies are still needed to characterize the demographic and genetic features among patients of PsA who needed biologic treatment.

Supporting information
S1 Table. HLA genotyping results in patients with or without dactylitis.
(DOCX)
S2 Table. Demographic features of patients with HLA data and patients without HLA data.
(DOCX)

Author Contributions
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