



Identification of a Single Nucleotide Polymorphism in *NFKBIA* with Different Effects on Psoriatic Arthritis and Cutaneous Psoriasis in China

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Genome-wide association studies have recently identified a number of non-major histocompatibility complex regions associated with psoriatic arthritis. However, data on Chinese patients with psoriatic arthritis and the differences between psoriatic arthritis and cutaneous psoriasis are limited. This study genotyped 12 single nucleotide polymorphisms in 379 patients with psoriatic arthritis, 376 with cutaneous psoriasis, and 760 healthy controls using Sequenom's Mass ARRAY system. The aim of the study was to expand the database for psoriatic arthritis and cutaneous psoriasis, and develop a genetic prediction system for the early diagnosis of psoriatic arthritis in the Chinese population. One variant in *NFKBIA*, rs12883343, had a significantly different association with psoriatic arthritis than with cutaneous psoriasis ($p = 4.93 \times 10^{-10}$, odds ratio 2.371). This suggests that there are differences in the pathogenesis of psoriatic arthritis and cutaneous psoriasis.

Key words: psoriatic arthritis; cutaneous psoriasis; *NFKBIA*.

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Psoriatic arthritis (PsA) is an inflammatory arthritis associated with psoriasis, characterized by seronegative rheumatoid factor. Among patients with psoriasis, the prevalence of PsA varies from 6% in the USA to 42% in South Africa (1), while published figures indicate lower prevalence rates in Asian countries (2), such as Korea (9%) (3) and Japan (1%) (4). In China, the prevalence of PsA has been estimated as 5.8% (5) based on a large cross-sectional observational study. Although the exact mechanism of PsA is unclear, host genetics, immunological, and environmental factors are thought to play a role (6).

With the development of genome-wide association studies (GWAS), 4 PsA GWAS have been published to date. Together with candidate loci analyses and Immu-

SIGNIFICANCE

A number of novel psoriatic arthritis genetic susceptibility loci have been identified recently, but data on their association with Chinese psoriatic arthritis patients are limited. In addition, the data of differences between psoriatic arthritis and cutaneous psoriasis are lacking. We performed a genetic study in a Chinese population to expand the database for psoriatic arthritis and cutaneous psoriasis and to develop a genetic prediction model for early diagnosis of psoriatic arthritis.

nochip array studies, 15 non-major histocompatibility complex (non-MHC) regions associated with PsA have shown statistical significance ($p \leq 5 \times 10^{-8}$). These include *IL-12B* (7–10), *IL-23R* (7, 10), *TNIP1* (7, 8, 10), *TRAF3IP2* (7, 9, 11, 12), *CSF2* (7), *FBXL19* (13), *REL* (7, 14), *RUNX3* (15), *TYK2* (7, 10), *NOS2* (16), *PTPN22* (16), *IFNL1* (7), *IFIH1* (7), *NFKBIA* (7) and *STAT2* (10). Current genetic studies have suggested that key pathways in the pathogenesis of PsA include the NFκB and IFN signalling pathway, and adaptive immune responses involving CD8⁺T cells and CD4⁺T helper (Th) 17-cell signalling (17–20).

Clinically, psoriasis vulgaris (PsV) is characterized by sharply demarcated, scaly, erythematous plaques. As with PsV, PsA has the common manifestation of skin lesions, but additionally manifests with peripheral arthritis, enthesitis, dactylitis, uveitis, and spondylitis (20). GWAS and candidate loci analyses have revealed differences in their genetic architecture (7). Significant differences in the strength of association between psoriasis and the MHC have been observed. It has been reported that the human leukocyte-associated antigen (*HLA*)-*Cw*0602* is strongly associated with PsV (21), while *HLA-B*27* plays an important role in PsA (22). Winchester et al. (22) hypothesized that the MHC molecules encoded by *HLA-C*0602* presented skin-specific self-peptides to T cells, whereas *B*27* molecules are mediators for the primary response to a cutaneous and joint antigen. Currently, there are 13 non-MHC regions with a nominally significant ($p < 0.05$) difference in their association for these 2 forms of psoriasis (7). However,

limited data are available for China. Yang et al. (23) reported single nucleotide polymorphisms (SNPs) at *IL12B* and *ZNF816A*, with a nominal *p*-value ($p < 0.05$) between PsA and PsV.

To address the need to expand the database for PsA and cutaneous psoriasis (PsC), 15 non-MHC PsA susceptibility loci were tested in a Chinese cohort involving 379 patients with PsA, 376 with PsC and 760 unaffected control individuals. The aim of the study was to develop a genetic prediction model for early diagnosis of PsA in the Chinese population.

METHODS

Samples

A total of 755 patients with psoriasis (379 patients with PsA and 376 with PsC) were included. All patients were recruited from the Shandong Provincial Hospital for Skin Disease. Patients were diagnosed by both a dermatologist and rheumatologist. All PsA case subjects met the Classification for Psoriatic Arthritis (CASPAR) criteria (24). PsC was defined as an individual having been a PsV patient for 10 or more years without developing any signs of PsA (7). All patients were resident in Shandong province and had no reported genetic relationship. Healthy controls in this study were all Han Chinese from the same region, with no history of psoriasis or autoimmune diseases. Clinical information was collected from the subjects through a full clinical check-up, while additional information was obtained through a questionnaire. All participants provided written informed consent. The study was approved by the ethics committee of Shandong Provincial Institute of Dermatology and Venereology and was conducted according to the principles of the Declaration of Helsinki.

Single nucleotide polymorphism selection

Fifteen SNP markers were selected from 4 GWASs and candidate-gene association studies (7–16). SNPs were selected based on the following criteria: (i) with the exception of rs9321623 at *TNFAIP3*, each SNP selected from the GWAS showed that statistically significant differences ($p \leq 5 \times 10^{-8}$) exist between PsA and control samples; (ii) all rare SNPs in Asian populations were excluded (minor allele frequency (MAF), obtained from 1,000 Genomes Phase 1 Asian data, was < 0.05); (iii) SNPs were independent of each other (linkage disequilibrium (LD) $r^2 \leq 0.5$); and (iv) SNPs were associated with coding variants or potential regulatory elements with a score ≤ 5 in the Regulomedb or < 5 in the Encode database.

Genotyping

Genotyping analysis of all the samples was conducted using Sequenom's Mass ARRAY system. DNA was amplified through multiplex PCR using 15 ng genomic DNA. PCR products were then used for locus-specific single-based extension reactions, desalted, and transferred to the SpectroCHIP array. Allele detection was performed using MALDI-TOF mass spectrometry. The mass spectrograms were analysed using Sequenom Mass ARRAY TYPER software. SNPs with a call rate $< 90\%$, or a deviation from Hardy–Weinberg equilibrium ($p < 0.01$) in the control subjects were excluded from further analysis. Of the 15 SNPs subjected to the validation study, 3 (rs9321623, rs34725611, rs35251378) failed in the genotyping analysis and were excluded from further analysis.

Statistical analysis

Associations were tested based on a logistic model grouped by PsA patients vs. controls, PsC patients vs. controls, and PsA patients vs. PsC patients using PLINK v 1.07 (25). Logistic regression for each SNP was performed by adjusting for sex. In order to correct the number of loci studied, $p < 0.004$ was accepted by a Bonferroni correction of 12.

RESULTS

Psoriatic arthritis characteristics

The demographic and clinical characteristics of patients with PsA are shown in **Table I**. The mean age at onset of patients with PsA was 42.9 years. Patients with PsA had a higher rate of severe psoriasis with a Psoriasis Area and Severity Index (PASI) score 9.83 higher than those without PsA. As demonstrated in previous reports, nail involvement was more common in patients with PsA (55.32%) than in those without PsA (21.0%) (5). Among patients with PsA, arthritis preceded psoriasis in 13.28% of cases. The temporal relationship between psoriasis and arthritis is shown in Table I. According to the Moll and Wright classification criteria (26), the manifestation of PsA included spondylitis in 15.22% of patients, oligoarthritis in 71.64%, polyarthritis in 8.66%, predominant distal interphalangeal joint (DIP) arthritis in 2.99%, and arthritis mutilans in 1.49% (**Table II**).

Compared with Asian and European data (Table I), there is not a great difference between our results and

Table I. Clinical characteristics for patients with psoriatic arthritis

Variables	This study	Japan (27)	Korean (28)	Spain (29)
Male, <i>n</i> (%)	229 (60.42)	258 (59.86)	10 (45.45)	45 (52.33)
Age, years, mean \pm SD	42.9 \pm 12.26	53.0	42.2 \pm 16.0	48.6 \pm 12.8
Mean age of psoriasis onset ^a , years	30	37	31.8	NA
Early-onset (≤ 40 years), <i>n</i> (%)	276 (78.19) ^b	NA	NA	NA
Family history of psoriasis, <i>n</i> (%)	88 (26.19)	NA	NA	NA
PASI, mean \pm SD	9.83 \pm 8.96	NA	8.9 \pm 6.1	6.6 \pm 7.2
Nail involvement, <i>n</i> (%)	156 (55.32) ^c	168 (38.98)	12 (54.55)	36 (41.86)
Temporal relationship between psoriasis and arthritis, <i>n</i> (%)				
Arthritis following psoriasis	279 (78.81) ^d	312 (72.9)	12 (54.5)	NA
Psoriasis following arthritis	47 (13.28) ^d	47 (11.0)	3 (13.6)	NA
Simultaneous onset	28 (7.91) ^d	69 (16.1)	7 (31.8)	NA

^aThe time when patients developed the symptom of the PsA including peripheral arthritis, enthesitis, dactylitis, uveitis, and spondylitis was regarded as the age of onset.

^bBased on 353 patients with psoriatic arthritis. ^cBased on 282 patients with psoriatic arthritis. ^dBased on 354 patients with psoriatic arthritis.

SD: standard deviation; PASI: Psoriasis Area and Severity Index; NA: not available.

Table II. Manifestation pattern of patients with psoriatic arthritis^a

Manifestation pattern	Cases, n (%)
Spondylitis	51 (15.22)
Spondylitis only	7
Plus oligoarthritis	26
Plus polyarthritis	18
Oligoarthritis	240 (71.64)
Polyarthritis	29 (8.66)
Predominant DIP arthritis	10 (2.99)
Arthritis mutilans	5 (1.49)

^aBased on 335 patients with psoriatic arthritis.
DIP: distal interphalangeal joint.

those of previous studies conducted in other Asia and Western countries. This study, as well as previous studies, suggests that PsA affects men more often than women. Psoriasis presented prior to PsA in >50% of patients. The mean age at onset of PsA was approximately 40–50 years and the mean age of psoriasis onset in PsA cohorts was 30–40 years. In addition, nail involvement was quite common.

Genotyping analysis

Based on the results of previous publications, 15 SNPs that were above a genome-wide significance level were selected for subsequent validation. After quality control, one patient with PsA and 11 patients with PsC were removed as the call rate was <90%. Finally, 378 PsA, 365 PsC and 760 controls samples were available for validation analysis. The characteristics of the samples are shown in **Table III**. Three SNPs failed to meet the inclusion criteria during assay design.

Firstly, the association of the SNPs with a state of psoriasis was evaluated by comparing PsA with control samples. By comparing all PsA cases against all control samples, disease association was replicated in 5 of the 12 SNPs tested. However, all SNP associations failed Bonferroni correction in the PsA cohort (**Table IV**). Mapping to *IL12B*, the strongest association was identified at a genome-wide significance level for rs2082412

Table III. Summary information for psoriatic arthritis (PsA) and cutaneous psoriasis (PsC) cases and controls

Characteristic	PsA	PsC	Controls
Total number	378	365	760
Sex (male/female), n	229/149	173/192	465/295
Ethnicity	Han Chinese	Han Chinese	Han Chinese
Age, years, mean ± SD	42.89 ± 12.26	41.17 ± 15.68	42.05 ± 6.89
Age, years, range	13–76	25–82	25–50

SD: standard deviation.

($p=4.32 \times 10^{-3}$, odds ratio (OR) 0.766), which corroborates with data reported by Yang et al. (23). Four other SNPs were found to be associated with PsA in the Chinese population in this study. This included: rs 4921485 at *IL12B* ($p=4.50 \times 10^{-3}$, OR 0.767); rs12924903 at *FBXL19* ($p=7.48 \times 10^{-3}$, OR 1.540); rs 4655683 at *IL23R* ($p=1.11 \times 10^{-2}$, OR 1.254); and rs12044149 at *IL23R* ($p=1.24 \times 10^{-2}$, OR 1.264). Within the set of positively replicated loci, *IFNL1*, *RUNX3*, *IFIH1*, *TRAF3IP2*, *NFKBIA*, and *NOS2* had not been tested in an independent replication sample, unlike the previously studies.

Next, we evaluated the disease association of the 12 SNPs by comparing the PsC and control samples. Two SNPs were associated with PsC. The rs12883343 SNP (*NFKBIA*) was significantly associated with PsC ($p=1.26 \times 10^{-8}$, OR 0.486), while the rs2082412 SNP (*IL12B*) showed borderline evidence for PsC association at a nominal p -value threshold of 0.05 ($p=1.60 \times 10^{-2}$, OR 0.798). Finally, we compared the genotypic frequencies of these SNPs across PsA and PsC cohorts. Our study demonstrated that the *NFKBIA* rs12883343 variant exhibited a significantly different association with PsA compared with PsC ($p=4.93 \times 10^{-10}$, OR 2.371). Another variant at *IL12B*, which has not been described previously, rs4921485, indicated borderline evidence for disease association ($p=2.84 \times 10^{-2}$, OR 0.785). The rs4921485 showed evidence of an association between axial and peripheral PsA subgroups ($p=7.8 \times 10^{-3}$, OR 1.548), but this failed the Bonferroni correction. We also confirmed the previous findings that the non-MHC

Table IV. Results for previously reported single nucleotide polymorphisms (SNPs) comparative strength of association of psoriatic arthritis (PsA) vs. cutaneous psoriasis (PsC)

CHR	SNP	Gene	Allele ^a	MAF			PsA vs. Control			PsA vs. PsC			PsC vs. Control		
				F_PsA	F_PsC	F_cont	p -value ^b	OR ^b	CI ^b	p -value ^b	OR ^b	CI ^b	p -value ^b	OR ^b	CI ^b
1	rs7540214	<i>IFNL1</i>	T/C	0.169	0.162	0.181	2.23E-01	0.870	0.695–1.089	5.87E-01	1.076	0.825–1.404	9.67E-02	0.820	0.649–1.036
1	rs4649038	<i>RUNX3</i>	T/C	0.359	0.389	0.389	1.59E-01	0.878	0.733–1.052	2.64E-01	0.884	0.712–1.098	8.50E-01	0.982	0.816–1.182
1	rs12044149	<i>IL23R</i>	T/G	0.344	0.296	0.292	1.24E-02	1.264	1.052–1.520	7.40E-02	1.217	0.981–1.510	5.69E-01	1.058	0.871–1.285
1	rs4655683	<i>IL23R</i>	A/G	0.456	0.403	0.400	1.11E-02	1.254	1.053–1.494	2.56E-02	1.273	1.030–1.572	7.17E-01	1.034	0.863–1.238
2	rs1990760	<i>IFIH1</i>	T/C	0.223	0.201	0.210	6.62E-01	1.048	0.849–1.294	3.81E-01	1.118	0.871–1.435	4.71E-01	0.921	0.737–1.152
2	rs3747517	<i>IFIH1</i>	C/T	0.348	0.336	0.343	9.55E-01	1.005	0.836–1.209	6.66E-01	1.049	0.846–1.300	5.97E-01	0.950	0.786–1.149
5	rs2082412	<i>IL12B</i>	A/G	0.369	0.382	0.415	4.32E-03	0.766	0.638–0.920	7.62E-01	0.967	0.778–1.202	1.60E-02	0.798	0.664–0.959
5	rs4921485	<i>IL12B</i>	T/C	0.333	0.390	0.394	4.50E-03	0.767	0.639–0.921	2.84E-02	0.785	0.633–0.975	7.28E-01	0.969	0.809–1.160
6	rs13210247	<i>TRAF3IP2</i>	G/A	0.050	0.045	0.055	3.45E-01	0.826	0.555–1.228	5.70E-01	1.149	0.711–1.857	2.01E-01	0.765	0.507–1.154
14	rs12883343	<i>NFKBIA</i>	C/G	0.439	0.292	0.376	1.78E-01	1.145	0.940–1.395	4.93E-10	2.371	1.806–3.112	1.26E-08	0.486	0.379–0.623
16	rs12924903	<i>FBXL19</i>	A/G	0.101	0.088	0.075	7.48E-03	1.540	1.122–2.112	5.61E-01	1.113	0.776–1.597	8.12E-02	1.343	0.964–1.871
17	rs4795067	<i>NOS2</i>	G/A	0.397	0.378	0.374	4.10E-01	1.055	0.929–1.199	7.01E-01	1.030	0.887–1.195	7.80E-01	1.019	0.894–1.161

CHR: chromosome; MAF: minor allele frequency; F-PsA: frequency of psoriatic arthritis; F-PsC: frequency of cutaneous psoriasis; F-Con: frequency of control; PsA: psoriatic arthritis; PsC: cutaneous psoriasis; OR: odds ratio; CI: confidence interval.
Bold: significant findings.

^aAllele, Minor allele/major allele. ^b p -value, OR, and CIs were adjusted by sex. OR is with respect to the minor allele.

variant rs 4655683 at IL23R is associated with disease ($p=2.56 \times 10^{-2}$, OR 1.273).

DISCUSSION

PsA has a complex genetic background. Recently, a large number of loci that are confidently associated with the risk of developing this disease were identified in large GWAS population cohorts (7). However, data representative of the Chinese population are limited. This study provides significant evidence for the genetic associations of PsA and PsC in the Chinese population. A genetic association between PsA and PsC was also identified. We furthermore found that the *NFKB1A* locus was involved in PsC susceptibility. Finally, we also discovered and describe a previously unknown, independent variant that is differentially associated with PsA compared with PsC.

In 78.8% patients with PsA in our study skin manifestations preceded joint symptoms. Therefore, it is vital to not only identify new therapeutic targets, but also pinpoint disease-specific genetic risk factors in order to predict which psoriasis patients are at high risk of developing PsA. We discovered a variant in the *NFKB1A* region (rs12883343), which exhibited a significantly different association with PsA and PsC. *NFKB1A* as well as *NKBI* and *RelA* are the components of the nuclear factor- κ B (NF- κ B) complex. *NFKB1A* encodes I-kappa-B (NFKB1 α), which blocks the NF- κ B nuclear localizing sequence, thereby inactivating the complex in the cytoplasm (30). Many NF- κ B-activating agents enable I-kappa-B (IKBKA or IKBKB) kinases to phosphorylate serine residues on the NFKB1 α protein, thereby causing degradation via ubiquitination (31). Transcriptional products of NF- κ B include tumour necrosis factor alpha (TNF- α), which plays a central role in psoriasis or PsA pathophysiology (32). rs12883343 is located at the 3' of the *NFKB1A* gene. Although we found no evidence that this SNP is a cis-eQTL for *NFKB1A* mRNA levels in skin tissue, it could be regarded as a regulatory element in

many cell types relevant to PsC and PsA. These include keratinocytes, Th 17 cells, neutrophils, CD14⁺ monocytes, fibroblasts, and osteoblasts (33). This may provide us with a new method by which to predict the risk of developing PsA and to acquire evidence indicating that PsA and PsC are genetically different. This is different from the results of previous studies. Explanations for this difference could include the presence of heterogeneous associations within different populations, or a lack of power in moderately sized case-control cohorts.

We also found a PsA-specific variant (rs 4921485) in the *IL12B* region, which appeared to be borderline evidence for PsA association ($p=4.50 \times 10^{-3}$, OR 0.767), with no detectable association with PsC ($p=0.728$, OR 0.969). It is the first time that this variant and its associated findings relative to PsA and PsC have been reported. Our results replicate the previously described association (Table V) of 5 alleles, which showed borderline evidence at a nominal p -value threshold of 0.05, with the risk of developing PsA. Four variants in *IL23R* and *IL12B* were included. This reveals the important role of the IL-12/IL-23 pathway in the pathogenesis of PsA and provides an explanation for the effective treatment of this condition using ustekinumab; a monoclonal antibody against IL-12 and IL-23 (34).

This study supports the hypothesis that there are differences in the underlying genetic architecture between PsA and PsC. The study was based on a limited number of PsA, PsC and control subjects from the Chinese population. Although we gave a more stringent definition of PsC to decreasing the patients who will go on to develop PsA, the PsC subset may still include patients who will ultimately develop PsA. Therefore, more studies that include a large number of affected case subjects are needed to detect or confirm the differential association between PsA and PsC. In parallel, studies investigating a large number of SNPs, GWAS in large sample sets, meta-analyses of genome-wide scan results, and large-scale analyses of rarer variants are needed to identify additional susceptibility loci in the Chinese population.

Table V. Single-nucleotide polymorphisms (SNPs) in previous studies

Chromosome	SNP	Gene	Allele (risk/non-risk)	Psoriatic arthritis vs. Control		Psoriatic arthritis vs. cutaneous psoriasis		Cutaneous psoriasis vs. Control	
				p -value*	OR*	p -value*	OR*	p -value*	OR*
1	rs7540214	<i>IFNL1</i>	C/T	1.60E-08	1.403	3.10E-01	1.084	2.40E-05	1.294
1	rs4649038	<i>RUNX3</i>	C	1.40E-08	1.240	NA	NA	NA	NA
1	rs12044149	<i>IL23R</i>	T/G	2.50E-12	1.296	1.80E-04	1.196	2.30E-02	1.084
1	rs4655683	<i>IL23R</i>	A/G	7.80E-14	1.319	7.50E-03	1.135	1.60E-05	1.162
2	rs1990760	<i>IFIH1</i>	T/C	1.00E-14	1.585	1.70E-01	1.112	7.60E-10	1.425
2	rs3747517	<i>IFIH1</i>	T/C	3.20E-08	1.422	3.80E-01	1.076	8.10E-06	1.322
5	rs2082412	<i>IL12B</i>	G/A	2.00E-28	1.440	NA	NA	NA	NA
5	rs4921485	<i>IL12B</i>	C/T	2.80E-16	1.375	1.10E-01	1.080	1.00E-11	1.273
6	rs13210247	<i>TRAF3IP2</i>	G	1.73E-14	1.690	NA	NA	NA	NA
14	rs12883343	<i>NFKB1A</i>	G/C	2.60E-09	1.223	3.80E-01	1.040	1.30E-06	1.176
16	rs12924903	<i>FBXL19</i>	A/G	1.00E-09	1.160	NA	NA	NA	NA
17	rs4795067	<i>NOS2</i>	G/A	5.27E-09	1.220	NA	NA	NA	NA

* p -value and odds ratio in previous studies.

OR: odds ratio; CI: confidence interval; NA: not available.

The current study found a previously unreported variant in *NFKB1A*, showing that a significant difference exists between PsA and PsC. The results contribute towards understanding the genetic aetiology of PsC in the Chinese population, as well as the differences in the genetic architecture of PsA and PsC. Further research is needed to identify the biological mechanisms that are most relevant to each clinical subtype, and to provide new targets for treatment.

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The authors have no conflicts of interest to declare.

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