Hindawi Publishing Corporation
BioMed Research International
Volume 2016, Article ID 5896906, 9 pages
http://dx.doi.org/10.1155/2016/5896906

Research Article

Lack of Association between Genetic Polymorphisms of JAK-STAT Signaling Pathway Genes and Acute Anterior Uveitis in Han Chinese

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Received 2 June 2016; Revised 14 September 2016; Accepted 16 October 2016

Academic Editor: Juan-Manuel Anaya

Purpose. This study aimed to investigate the association between single nucleotide polymorphisms (SNPs) of JAK-STAT signaling pathway genes and acute anterior uveitis (AAU) with or without ankylosing spondylitis (AS) in the Han Chinese population. *Methods*. Eleven SNPs of the *JAK1*, *JAK2*, *STAT1*, *IRF1*, and *NOS2* genes were analyzed in 443 AAU patients with AS, 486 AAU patients without AS, and 714 healthy controls. Genotyping was performed by PCR-RFLP assay or TaqMan® probe assay. The Chi-squared (χ^2) test and multivariate logistic regression analysis were used to compare the distributions of alleles and genotypes between patients and controls. P values were adjusted using Bonferroni correction. *Results*. We did not observe significant differences in the genotype and allele frequencies of any SNP between AAU patients with or without AS and healthy controls. Stratification analyses by gender and HLA-B27 status showed a boundary significant association between two SNPs (rs10975003 and rs10758669) in *JAK2* and AAU ($P = 0.052$ and $P = 0.053$, resp.). *Conclusions*. Our results indicated that genetic polymorphisms of the JAK-STAT signaling pathway genes may not be associated with AAU in the Han Chinese population.

1. Introduction

Uveitis is one of the major ocular diseases leading to blindness and visual impairment. The prevalence of uveitis is 111.3 per 100,000 persons in Taiwan [1] compared with 40.4 per 100,000 persons in Japan [2] and 115.3 per 100,000 persons in United States [3]. In the clinic, acute anterior uveitis (AAU), which may be accompanied by complicated phenotypes including cataract and glaucoma [4], is the most common type of uveitis [5]. Evidence suggests that the occurrence of AAU is associated with the prognosis of ankylosing spondylitis (AS) [6, 7]. The frequency of AAU, which is characterized by positive human leukocyte antigen- (HLA-) B27, varies across different ethnic populations [8–10]. In the United States and Western Europe, the prevalence of HLA-B27 with AAU is up to 50% [5, 8, 11]. Previous studies have reported that there is a strong association between AS and HLA-B27 in various ethnic groups [12–14]. Further study showed that the percentage of AAU accompanied by AS is 30–40%, suggesting that there may be linked pathogenesis between AAU and AS [15]. AAU and AS may share certain genetic associations, but several susceptibility genes seem to be unique for each disease [16]. Genes including *TNFSF15*, *TRAF5*, and *FoxO1* have been reported to be associated with AAU [17–19]. However, a lack of association with AAU has been demonstrated for other genes, including *CTLA4* and *PTPN22* [20, 21]. A recent study revealed that T lymphocyte subsets (Th1 and Th17) and $CD4^+$ $CD25^+$ Treg cells were involved in the development of HLA-B27 positive AAU [22, 23]. Furthermore, a higher level of Th17 cells has been observed in the peripheral blood of patients with AS [24].

The Janus kinase-signal transducer and activator of transcription (JAK-STAT) signaling pathway plays a major role in T lymphocyte differentiation and function [25, 26]. *JAK1* and *JAK2* have been reported to play an important role in Th1 and Th17 cell differentiation [27]. *STAT1* is critical to T lymphocyte differentiation and function [25, 26, 28]. *STAT1* is activated by type I interferons (IFNs) and IFN-γ and plays

an important role in immune responses [29]. *IRF1* is the first member identified in the IRF family and is involved in many innate and adaptive immune responses [30]. Impaired or absent Th1-type immune responses favor Th2 differentiation in *IRF1*-deficient mice [31, 32]. *NOS2*-derived NO, a key factor in immunoregulation [33], can inhibit Th1 as well as Th2 cytokine production and regulate the development of FoxP3$^+$ Treg cells [34, 35]. In summary, JAK-STAT signaling pathway genes, including *JAK1, JAK2, STAT1, IRF1*, and *NOS2*, have been suggested to be strongly linked with T cells and may be involved in the pathophysiology of AAU with or without AS.

Thus, we conducted the present case-control study to investigate whether JAK-STAT signaling pathway genes confer susceptibility to AAU risk in a Chinese Han population.

2. Materials and Methods

2.1. Subjects. A total of 929 AAU patients were enrolled in this study, including 443 patients with AS (AAU$^+$AS$^+$) and 486 patients without AS (AAU$^+$AS$^-$), as well as 714 gender- and race-matched healthy controls. All subjects were Han Chinese recruited from the Department of Ophthalmology in the First Affiliated Hospital of Chongqing Medical University (Chongqing, China) between June 2008 and May 2015. All AAU patients were diagnosed based on medical records, physical examinations, and the anatomic location of inflammation as previously described by Jabs et al. [36]. The diagnosis of AS followed the modified New York Criteria [37]. All subjects gave written informed consent before blood collection. This study was approved by the Human Ethics Committee of the First Affiliated Hospital of Chongqing Medical University (Approval number: 2009-201008) and followed the tenets of the Declaration of Helsinki.

2.2. SNP Selection. We selected candidate single nucleotide polymorphisms (SNPs) based on previously published studies and included only those SNPs significantly associated with autoimmune diseases [38–45]. We used HaploView 4.2 software to evaluate the linkage disequilibrium (LD) and minor allele frequency (MAF) of the SNPs. Five SNPs of *JAK1*, rs2780815, rs3790532, rs310230, rs310236, and rs310241 [41, 42], were selected. Since the SNPs rs3790532, rs310230, rs310236, and rs310241 are in strong LD with each other ($r^2 > 0.8$, Figure 1), we only used rs310241 in our study. Furthermore, we also eliminated SNPs that were not polymorphic in the Chinese population. Finally, eleven SNPs in five JAK-STAT signaling pathway genes were tested in our study, including two SNPs in the intron region of the *JAK1* gene (rs310241, rs2780815) [41], two SNPs in the exon region and 3′UTR of the *JAK2* gene (rs10758669, rs10975003) [38, 45], one SNP in the intron region of the *IRF1* gene (rs2070721), four SNPs in the exon region and intron region of the *STAT1* gene (rs2066802, rs1547550, rs6718902, and rs10199181) [39, 40], and two SNPs in the exon region and intron region of the *NOS2* gene (rs2297518, rs4795067) [43, 44].

2.3. DNA Extraction and Genotyping. Peripheral blood samples were collected from subjects, and genomic DNA extraction was performed using the QIAamp DNA Blood Mini Kit (Qiagen, Valencia, CA, USA). The genomic DNA was quantified with NanoDrop 2000 (Thermal Fisher Scientific, Delaware, USA) and stored at −20°C until use. Three SNPs (rs2780815, rs2070721, and rs10199181) were genotyped by TaqMan probe (Applied Biosystems, Foster City, CA), and the others were genotyped by polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) assay. The specific primers for PCR and restriction enzymes are described in Table 1. The PCR reactions were performed under the following conditions: denaturation at 95°C for 5 minutes, 33 to 36 cycles of denaturation at 95°C for 30 seconds, annealing at 56–64°C for 30 s, and extension at 72°C for 30 seconds and a final extension at 72°C for 5 minutes. The enzyme-digested products were visualized on 3% or 4% agarose gels and stained with GoldView (SBS Genetech, Beijing, China). Direct sequencing was carried out randomly on 10% of the study samples to assure the validity of the SNP genotyping method used. The success rate of all SNP genotyping ranged from 97.3% to 100%.

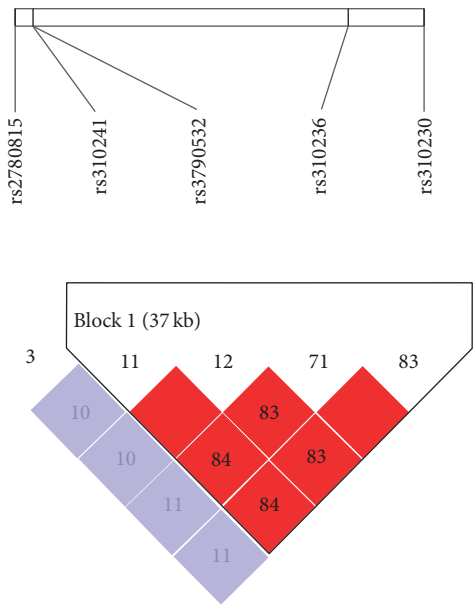

Figure 1: Linkage disequilibrium (LD) analysis of rs2780815, rs310241, rs3790532, rs310236, and rs310230 in the *JAK1* gene. The LD block was estimated by HaploView software version 4.2 using the Chinese Han HapMap data. The number in the square indicates the r^2 value.

2.4. Statistical Analysis. Hardy-Weinberg equilibrium (HWE) was analyzed by the χ^2 test. The distributions of the allele and genotype frequencies between the patients and controls were compared by the χ^2 test. Multivariate logistic regression model adjusted for age and gender was further adopted to test the associations between the SNPs and AAU. The risk effect of each SNP was measured by odds ratios (OR) and 95% confidence intervals (CI). There were four different models of inheritance in our study, including additive models, codominant models, dominant models, and recessive models. P values were corrected using the Bonferroni correction

Table 1: PCR primer sequences and restriction enzymes.

SNP	Primers	Restriction enzyme
rs310241	5′ AACCACCAGCTCAACATTCCTAG 3′ 5′ CAGCCAGGTCTCCCGTAGG 3′	BseDI
rs6718902	5′ CGGACAAAAGCATGCACTAGA 3′ 5′ CCACCACCATTAATAGGTGACTTTA 3′	DraI
rs2297518	5′ TGAGCTCTTTCAGCATGAAGATC 3′ 5′ CTTCCGTGGTGGGCTGTG 3′	TaqI
rs10758669	5′ TGATGTAGAGACAAGGACATGCTGAGGTAC 3′ 5′ GCCAAAAGACAAAGGCAAGGGG 3′	BanI
rs10975003	5′ GGCCAGTCAAGAAAAAACCAGTT 3′ 5′ TTCGGAGTCTTGTCTGAGCATGT 3′	HpaI
rs4795067	5′ GCACTCATTCATTCATGCAAACATA 3′ 5′ GGCAGAACTTGAACCCCAGCT 3′	NdeI
rs1547550	5′ CTTCTCTAGGAGGCCCAGCA 3′ 5′ TGGGCACCACGATATGAGAG 3′	BstMAI
rs2066802	5′ ATTCCTGGAGCAGGTTCACAAG 3′ 5′ AAACATGGCCCCAAGTCACT 3′	HindIII

method considering multiple tests. Statistical significance level was defined as a corrected P value < 0.05. Statistical analyses were performed using SPSS version 17.0 (SPSS, Inc., Chicago, IL, USA).

3. Results

3.1. Clinical Features of AAU Patients. The detailed clinical features and demographic characteristics of the AAU patients are presented in Table 2. All 929 AAU patients include 569 (61.2%) males and 360 (38.8%) females. The 714 control subjects consisted of 428 (59.9%) males and 286 (40.1%) females. The average age was 39.8 ± 12.3 in AAU patients and 39.5 ± 10.8 in the controls, respectively. There were no significant differences in age and gender between the cases and controls. In addition, 546 AAU patients (68.9%) were HLA-B27-positive, whereas 246 AAU patients (31.1%) were HLA-B27-negative.

3.2. The Genotype and Allele Frequency Distribution of the Tested SNPs in AAU. Eleven SNPs of the JAK-STAT signaling pathway genes (*JAK1, JAK2, STAT1, IRF1*, and *NOS2*) were successfully genotyped. There were no significant deviations of HWE in either the cases or controls. We did not observe significant differences in the genotype and allele distributions of any of the SNPs between the AAU patients and control subjects after Bonferroni correction (see Supplementary Table S1 in Supplementary Material available online at http://dx.doi.org/10.1155/2016/5896906). Further stratified analyses of gender, AS, and HLA-B27 status showed a boundary significant association of two SNPs (rs10975003 and rs10758669) of *JAK2* with AAU. In female AS-positive AAU patients, there was a decreased frequency of the TT genotype of rs10975003 compared to the female controls (OR = 0.55; $P = 1.59 \times 10^{-3}$; $P_{\text{Bonferroni}} = 0.052$, Table 3), whereas no significant differences were observed in the genotype and allele frequencies of the other ten SNPs ($P_{\text{Bonferroni}} > 0.05$, Table 3). Similarly, there were no significant differences in the genotype and allele frequencies of the SNPs between the male AAU patients and male controls ($P_{\text{Bonferroni}} > 0.05$, Supplementary Table S2).

Table 2: Clinical characteristics of the investigated subjects.

Clinical features	Total	Percentage
AAU patients	929	100
Mean age ± SD (years)	39.8 ± 12.3	
AAU with AS	443	47.7
AAU without AS	486	52.3
AAU male	569	61.2
AAU female	360	38.8
AAU with AS (male)	326 (443 tested)	73.6
AAU with AS (female)	117 (443 tested)	26.4
AAU without AS (male)	243 (486 tested)	50
AAU without AS (female)	243 (486 tested)	50
HLA-B27$^+$ AAU	546 (792 tested)	68.9
HLA-B27$^+$ AAU AS$^+$	348 (428 tested)	81.3
HLA-B27$^+$ AAU AS$^-$	198 (364 tested)	54.4
Control	714	100
Mean age ± SD (years)	39.5 ± 10.8	
Male	428	59.9
Female	286	40.1

In addition, an increased frequency of the AC genotype in rs10758669 was observed in HLA-B27-positive AAU patients compared to the healthy controls (OR = 1.44; $P = 1.62\times10^{-3}$; $P_{\text{Bonferroni}} = 0.053$, Table 4), whereas there were no significant differences in the genotype and allele frequencies of the other ten SNPs between the HLA-B27-positive AAU patients and the control subjects ($P_{\text{Bonferroni}} > 0.05$, Table 4).

However, an increased frequency of the rs10758669/AC genotype was observed in HLA-B27-positive AS-positive AAU patients compared to healthy controls (OR = 1.49; $P = 2.56\times10^{-3}$; $P_{\text{Bonferroni}} = 0.084$, Table 5), whereas no significant

Table 3: Allele and genotype frequencies in female AAU patients and female controls.

Gene	SNP	Allele and genotype	AAU^+AS^+ (female)	AAU^+AS^- (female)	Controls (female)	P (AS^+)	Pc (AS^+)	OR (95% CI)	P (AS^-)	Pc (AS^-)	OR (95% CI)
JAK1	rs310241	C	80 (33.3%)	138 (29.6%)	156 (28.7%)	0.19	NS	1.24 (0.90–1.72)	0.74	NS	1.05 (0.80–1.37)
		CC	12 (10.0%)	14 (6.0%)	17 (6.2%)	0.19	NS	1.67 (0.77–3.61)	0.91	NS	0.96 (0.46–2.00)
		CT	56 (46.7%)	110 (47.2%)	122 (44.9%)	0.74	NS	1.08 (0.70–1.66)	0.60	NS	1.10 (0.77–1.56)
		TT	52 (43.3%)	109 (46.8%)	133 (48.9%)	0.31	NS	0.80 (0.52–1.23)	0.64	NS	0.92 (0.65–1.30)
	rs2780815	G	159 (78.7%)	400 (87.0%)	495 (85.3%)	0.03	NS	0.64 (0.42–0.96)	0.45	NS	1.15 (0.80–1.63)
		GG	63 (62.4%)	175 (76.1%)	212 (73.1%)	0.04	NS	0.61 (0.38–0.99)	0.44	NS	1.17 (0.79–1.75)
		GT	33 (32.6%)	50 (21.7%)	71 (24.5%)	0.11	NS	1.50 (0.91–2.45)	0.46	NS	0.86 (0.57–1.29)
		TT	5 (5.0%)	5 (2.2%)	7 (2.4%)	0.20	NS	2.11 (0.65–6.80)	0.86	NS	0.90 (0.28–2.87)
JAK2	rs10758669	A	170 (73.9%)	328 (67.5%)	399 (72.3%)	0.64	NS	1.09 (0.77–1.54)	0.10	NS	0.80 (0.61–1.04)
		AA	59 (51.3%)	104 (42.8%)	144 (52.2%)	0.88	NS	0.97 (0.63–1.49)	0.03	NS	0.69 (0.49–1.00)
		AC	52 (45.2%)	120 (49.4%)	111 (40.2%)	0.36	NS	1.23 (0.79–1.90)	0.04	NS	1.45 (1.02–2.05)
		CC	4 (3.5%)	19 (7.8%)	21 (7.6%)	0.13	NS	0.44 (0.15–1.30)	0.93	NS	1.03 (0.54–1.97)
	rs10975003	C	44 (20.6%)	117 (25.8%)	93 (17.9%)	0.40	NS	1.19 (0.80–1.77)	2.83×10^{-3}	0.09	1.59 (1.17–2.17)
		CC	2 (1.9%)	11 (4.8%)	8 (3.1%)	0.52	NS	0.60 (0.13–2.87)	0.32	NS	1.60 (0.63–4.06)
		CT	40 (37.4%)	95 (41.9%)	77 (29.6%)	0.15	NS	1.42 (0.88–2.28)	4.83×10^{-3}	NS	1.71 (1.18–2.49)
		TT	65 (60.7%)	121 (53.3%)	175 (67.3%)	0.23	NS	0.75 (0.47–1.20)	1.59×10^{-3}	0.052	0.55 (0.38–0.80)
STAT1	rs1547550	C	205 (86.9%)	411 (88.6%)	423 (87.0%)	0.95	NS	0.99 (0.62–1.56)	0.47	NS	1.16 (0.78–1.71)
		CC	88 (74.6%)	182 (78.4%)	185 (76.1%)	0.75	NS	0.92 (0.55–1.53)	0.55	NS	1.14 (0.74–1.75)
		CG	29 (24.6%)	47 (20.3%)	53 (21.8%)	0.56	NS	1.17 (0.70–1.96)	0.68	NS	0.91 (0.59–1.42)
		GG	1 (0.8%)	3 (1.3%)	5 (2.1%)	0.40	NS	0.41 (0.05–3.52)	0.56	NS	0.65 (0.15–2.76)
	rs2066802	C	46 (20.4%)	81 (17.4%)	113 (21.2%)	0.80	NS	0.95 (0.65–1.40)	0.13	NS	0.78 (0.57–1.08)
		CC	1 (0.9%)	6 (2.6%)	8 (3.0%)	0.22	NS	0.29 (0.04–2.34)	0.78	NS	0.86 (0.29–2.50)
		CT	44 (38.9%)	69 (29.6%)	97 (36.3%)	0.63	NS	1.12 (0.71–1.76)	0.11	NS	0.74 (0.51–1.07)
		TT	68 (60.2%)	158 (67.8%)	162 (60.7%)	0.93	NS	0.98 (0.63–1.54)	0.10	NS	1.37 (0.95–1.97)
	rs6718902	C	132 (60.0%)	259 (54.2%)	308 (53.8%)	0.12	NS	1.29 (0.94–1.76)	0.91	NS	1.01 (0.79–1.29)
		CC	36 (32.7%)	72 (30.1%)	82 (28.7%)	0.43	NS	1.21 (0.75–1.94)	0.72	NS	1.07 (0.74–1.56)
		CT	60 (54.5%)	115 (48.1%)	144 (50.3%)	0.45	NS	1.18 (0.76–1.84)	0.61	NS	0.92 (0.65–1.29)
		TT	14 (12.7%)	52 (21.8%)	60 (21.0%)	0.06	NS	0.55 (0.29–1.03)	0.83	NS	1.05 (0.69–1.59)
	rs10199181	A	51 (24.8%)	117 (26.1%)	148 (25.2%)	0.91	NS	0.98 (0.68–1.41)	0.73	NS	1.05 (0.79–1.39)
		AA	6 (5.8%)	20 (8.9%)	19 (6.5%)	0.82	NS	0.90 (0.35–2.31)	0.29	NS	1.42 (0.74–2.73)
		AT	39 (37.9%)	77 (34.4%)	110 (37.4%)	0.94	NS	1.02 (0.64–1.62)	0.48	NS	0.88 (0.61–1.26)
		TT	58 (56.3%)	127 (56.7%)	165 (56.1%)	0.97	NS	1.01 (0.64–1.58)	0.90	NS	1.02 (0.72–1.45)
IRF1	rs2070721	A	86 (40.6%)	154 (33.9%)	216 (34.3%)	0.10	NS	1.31 (0.95–1.80)	0.90	NS	0.98 (0.76–1.27)
		AA	15 (14.2%)	26 (11.5%)	29 (9.2%)	0.15	NS	1.63 (0.84–3.17)	0.39	NS	1.28 (0.73–2.23)
		AC	56 (52.8%)	102 (44.9%)	158 (50.2%)	0.63	NS	1.11 (0.72–1.73)	0.23	NS	0.81 (0.58–1.14)
		CC	35 (33.0%)	99 (43.6%)	128 (40.6%)	0.16	NS	0.72 (0.45–1.14)	0.49	NS	1.13 (0.80–1.60)
NOS2	rs2297518	A	52 (20.5%)	69 (15.2%)	74 (15.7%)	0.10	NS	1.39 (0.94–2.05)	0.84	NS	0.96 (0.68–1.38)
		AA	3 (2.4%)	6 (2.6%)	2 (0.8%)	0.24	NS	2.83 (0.47–17.17)	0.14	NS	3.18 (0.63–15.90)
		AG	46 (36.2%)	57 (25.2%)	70 (29.7%)	0.20	NS	1.35 (0.85–2.13)	0.27	NS	0.80 (0.53–1.20)
		GG	78 (61.4%)	164 (72.2%)	164 (69.5%)	0.12	NS	0.70 (0.45–1.10)	0.51	NS	1.14 (0.77–1.71)
	rs4795067	A	173 (73.9%)	369 (75.9%)	439 (77.8%)	0.24	NS	0.81 (0.57–1.15)	0.46	NS	0.90 (0.67–1.20)
		AA	62 (53.0%)	145 (59.7%)	169 (59.9%)	0.20	NS	0.75 (0.49–1.16)	0.95	NS	0.99 (0.70–1.40)
		AG	49 (41.9%)	79 (32.5%)	101 (35.8%)	0.26	NS	1.29 (0.83–2.01)	0.43	NS	0.86 (0.60–1.24)
		GG	6 (5.1%)	19 (7.8%)	12 (4.3%)	0.70	NS	1.22 (0.45–3.32)	0.08	NS	1.91 (0.91–4.02)

OR = odds ratio; 95% CI = 95% confidence interval.
Pc = P value adjusted by Bonferroni correction.

Table 4: Allele and genotype frequencies of SNPs in patients with AAU versus control subjects stratified by HLA-B27 status.

Gene	SNP	Allele and genotype	AAU HLA-B27	Control	*P*	Pc	OR (95% CI)
JAK1	rs310241	C	324 (31.0%)	392 (27.5%)	0.06	NS	1.18 (1.00–1.41)
		CC	41 (7.9%)	45 (6.3%)	0.29	NS	1.27 (0.82–1.96)
		CT	242 (46.4%)	302 (42.4%)	0.16	NS	1.18 (0.94–1.48)
		TT	239 (45.7%)	366 (51.3%)	0.05	NS	0.80 (0.64–1.00)
	rs2780815	G	878 (86.2%)	1250 (87.5%)	0.35	NS	0.89 (0.70–1.13)
		GG	381 (74.8%)	548 (76.7%)	0.44	NS	0.90 (0.69–1.18)
		GT	116 (22.8%)	154 (21.6%)	0.61	NS	1.07 (0.82–1.41)
		TT	12 (2.4%)	12 (1.7%)	0.40	NS	1.41 (0.63–3.17)
JAK2	rs10758669	A	705 (65.9%)	980 (69.0%)	0.10	NS	0.87 (0.73–1.03)
		AA	220 (41.1%)	346 (48.7%)	0.08	NS	0.74 (0.59–0.92)
		AC	265 (49.5%)	288 (40.6%)	1.62×10^{-3}	0.053	1.44 (1.15–1.80)
		CC	50 (9.4%)	76 (10.7%)	0.43	NS	0.86 (0.59–1.25)
	rs10975003	C	251 (24.5%)	272 (21.2%)	0.05	NS	1.21 (1.00–1.47)
		CC	26 (5.1%)	28 (4.4%)	0.56	NS	1.18 (0.68–2.03)
		CT	199 (38.8%)	216 (33.5%)	0.06	NS	1.26 (0.99–1.60)
		TT	287 (56.1%)	399 (62.1%)	0.03	NS	0.77 (0.61–0.98)
STAT1	rs1547550	C	937 (87.2%)	1254 (87.8%)	0.67	NS	0.95 (0.75–1.21)
		CC	407 (75.8%)	555 (77.7%)	0.42	NS	0.90 (0.69–1.17)
		CG	123 (22.9%)	144 (20.2%)	0.24	NS	1.18 (0.90–1.54)
		GG	7 (1.3%)	15 (2.1%)	0.29	NS	0.62 (0.25–1.52)
	rs2066802	C	190 (19.3%)	288 (20.7%)	0.39	NS	0.91 (0.74–1.12)
		CC	15 (3.0%)	27 (3.9%)	0.44	NS	0.78 (0.41–1.48)
		CT	160 (32.5%)	234 (33.7%)	0.66	NS	0.95 (0.74–1.21)
		TT	318 (64.5%)	434 (62.4%)	0.47	NS	1.09 (0.86–1.39)
	rs6718902	C	584 (56.5%)	778 (54.5%)	0.33	NS	1.08 (0.92–1.27)
		CC	163 (31.5%)	209 (29.3%)	0.40	NS	1.11 (0.87–1.42)
		CT	258 (49.9%)	360 (50.4%)	0.86	NS	0.98 (0.78–1.23)
		TT	96 (18.6%)	145 (20.3%)	0.45	NS	0.90 (0.67–1.19)
	rs10199181	A	270 (27.2%)	397 (27.8%)	0.75	NS	0.97 (0.81–1.16)
		AA	43 (8.7%)	55 (7.7%)	0.55	NS	1.14 (0.75–1.73)
		AT	184 (37.1%)	287 (40.2%)	0.28	NS	0.88 (0.69–1.11)
		TT	269 (54.2%)	372 (52.1%)	0.47	NS	1.09 (0.87–1.37)
IRF1	rs2070721	A	356 (35.7%)	487 (34.1%)	0.40	NS	1.08(0.91–1.27)
		AA	61 (12.2%)	74 (10.4%)	0.30	NS	1.21 (0.84–1.73)
		AC	234 (47.0%)	339 (47.4%)	0.87	NS	0.98 (0.78–1.23)
		CC	203 (40.8%)	301 (42.2%)	0.63	NS	0.94 (0.75–1.19)
NOS2	rs2297518	A	194 (18.1%)	209 (16.2%)	0.21	NS	1.15 (0.93–1.42)
		AA	12 (2.3%)	12 (1.9%)	0.64	NS	1.21 (0.54–2.72)
		AG	170 (31.7%)	185 (28.6%)	0.24	NS	1.16 (0.90–1.49)
		GG	354 (66.0%)	450 (69.5%)	0.20	NS	0.85 (0.67–1.09)
	rs4795067	A	797 (74.3%)	1008 (76.1%)	0.35	NS	0.92 (0.76–1.10)
		AA	293 (54.6%)	382 (57.7%)	0.33	NS	0.89 (0.71–1.23)
		AG	211 (39.4%)	244 (36.9%)	0.37	NS	1.11 (0.88–1.41)
		GG	32 (6.0%)	36 (5.4%)	0.69	NS	1.10 (0.68–1.80)

OR = odds ratio; 95% CI = 95% confidence interval.
Pc = *P* value adjusted by Bonferroni correction.

Table 5: Allele and genotype frequencies of SNPs in patients with AAU versus control subjects stratified by AS and HLA-B27 status.

Gene	SNP	Allele and genotype	AAU^+AS^+ HLA-B27	AAU^+AS^- HLA-B27	Control	P (AS^+)	Pc (AS^+)	OR (95% CI)	P (AS^-)	Pc (AS^-)	OR (95% CI)
JAK1	rs310241	C	205 (31.6%)	119 (29.9%)	392 (27.5%)	0.05	NS	1.22 (1.00–1.49)	0.32	NS	1.13 (0.88–1.45)
		CC	30 (9.3%)	11 (5.5%)	45 (6.3%)	0.09	NS	1.52 (0.94–2.45)	0.70	NS	0.87 (0.44–1.72)
		CT	145 (44.7%)	97 (48.7%)	302 (42.4%)	0.47	NS	1.10 (0.85–1.44)	0.10	NS	1.31 (0.95–1.79)
		TT	149 (46.0%)	90 (45.7%)	366 (51.3%)	0.11	NS	0.81 (0.62–1.05)	0.14	NS	0.79 (0.58–1.08)
	rs2780815	G	543 (84.3%)	335 (89.6%)	1250 (87.5%)	0.05	NS	0.77 (0.59–1.00)	0.28	NS	1.22 (0.85–1.77)
		GG	230 (71.4%)	151 (80.7%)	548 (76.7%)	0.07	NS	0.76 (0.56–1.02)	0.24	NS	1.27 (0.85–1.90)
		GT	83 (25.8%)	33 (17.6%)	154 (21.6%)	0.14	NS	1.26 (0.93–1.72)	0.23	NS	0.78 (0.51–1.18)
		TT	9 (2.8%)	3 (1.7%)	12 (1.7%)	0.24	NS	1.68 (0.70–4.03)	0.94	NS	0.95 (0.27–3.42)
JAK2	rs10758669	A	449 (66.2%)	256 (65.3%)	980 (69.0%)	0.20	NS	0.88 (0.72–1.70)	0.16	NS	0.85 (0.67–1.07)
		AA	139 (41.0%)	81 (41.3%)	346 (48.7%)	0.02	NS	0.73 (0.56–0.95)	0.07	NS	0.74 (0.54–1.02)
		AC	171 (50.4%)	94 (48.0%)	288 (40.6%)	2.56×10^{-3}	0.084	1.49 (1.15–1.94)	0.06	NS	1.35 (0.98–1.86)
		CC	29 (8.6%)	21 (10.7%)	76 (10.7%)	0.28	NS	0.78 (0.50–1.22)	1.00	NS	1.00 (0.60–1.67)
	rs10975003	C	165 (25.7%)	86 (22.5%)	272 (21.2%)	0.03	NS	1.29 (1.03–1.61)	0.57	NS	1.08 (0.82–1.43)
		CC	18 (5.6%)	8 (4.2%)	28 (4.4%)	0.39	NS	1.31 (0.71–2.40)	0.92	NS	0.96 (0.43–2.14)
		CT	129 (40.2%)	70 (36.6%)	216 (33.5%)	0.04	NS	1.33 (1.01–1.75)	0.44	NS	1.14 (0.82–1.60)
		TT	174 (54.2%)	113 (59.2%)	399 (62.1%)	0.01	NS	0.72 (0.55–0.95)	0.47	NS	0.89 (0.64–1.23)
STAT1	rs1547550	C	608 (88.1%)	329 (85.7%)	1254 (87.8%)	0.84	NS	1.03 (0.78–1.36)	0.26	NS	0.83 (0.60–1.15)
		CC	264 (76.5%)	143 (74.5%)	555 (77.7%)	0.66	NS	0.93 (0.69–1.27)	0.34	NS	0.84 (0.58–1.21)
		CG	80 (23.2%)	43 (22.4%)	144 (20.2%)	0.26	NS	1.20 (0.88–1.63)	0.50	NS	1.14 (0.78–1.68)
		GG	1 (0.3%)	6 (3.1%)	15 (2.1%)	0.02	NS	0.14 (0.02–103)	0.40	NS	1.50 (0.58–3.93)
	rs2066802	C	130 (20.7%)	60 (16.8%)	288 (20.7%)	0.99	NS	1.00 (0.79–1.26)	0.09	NS	0.77 (0.57–1.05)
		CC	11 (3.5%)	4 (2.2%)	27 (3.9%)	0.77	NS	0.90 (0.44–1.83)	0.29	NS	0.57 (0.20–1.64)
		CT	108 (34.4%)	52 (29.1%)	234 (33.7%)	0.82	NS	1.03 (0.78–1.37)	0.24	NS	0.81 (0.56–1.16)
		TT	195 (62.1%)	123 (68.7%)	434 (62.4%)	0.92	NS	0.99 (0.75–1.30)	0.12	NS	1.32 (0.93–1.88)
	rs6718902	C	368 (57.7%)	216 (54.5%)	778 (54.5%)	0.18	NS	1.14 (0.94–1.38)	0.98	NS	1.00 (0.80–1.25)
		CC	103 (32.3%)	60 (30.3%)	209 (29.3%)	0.33	NS	1.15 (0.87–1.53)	0.78	NS	1.05 (0.75–1.48)
		CT	162 (50.8%)	96 (48.5%)	360 (50.4%)	0.91	NS	1.02 (0.78–1.32)	0.63	NS	0.93 (0.68–1.27)
		TT	54 (16.9%)	42 (21.2%)	145 (20.3%)	0.20	NS	0.80 (0.57–1.13)	0.78	NS	1.06 (0.72–1.56)
	rs10199181	A	170 (26.9%)	100 (27.8%)	397 (27.8%)	0.67	NS	0.96 (0.77–1.18)	0.99	NS	1.00 (0.77–1.29)
		AA	25 (7.9%)	18 (10.0%)	55 (7.7%)	0.91	NS	1.03 (0.63–1.68)	0.32	NS	1.33 (0.76–2.33)
		AT	120 (38.0%)	64 (35.6%)	287 (40.2%)	0.50	NS	0.91 (0.69–1.20)	0.26	NS	0.82 (0.58–1.15)
		TT	171 (54.1%)	98 (54.4%)	372 (52.1%)	0.55	NS	1.08 (0.83–1.41)	0.57	NS	1.10 (0.79–1.53)
IRF1	rs2070721	A	221 (34.9%)	135 (37.3%)	487 (34.1%)	0.73	NS	1.03 (0.85–1.26)	0.25	NS	1.15 (0.90-1.46)
		AA	37 (11.7%)	24 (13.3%)	74 (10.4%)	0.53	NS	1.14 (0.75–1.74)	0.26	NS	1.32 (0.81–2.16)
		AC	147 (46.4%)	87 (48.1%)	339 (47.4%)	0.74	NS	0.96 (0.73–1.25)	0.89	NS	1.02 (0.74–1.42)
		CC	133 (42.0%)	70 (38.6%)	301 (42.2%)	0.95	NS	0.99 (0.76–1.30)	0.40	NS	0.97 (0.62–1.21)
NOS2	rs2297518	A	130 (19.0%)	64 (16.5%)	209 (16.2%)	0.11	NS	1.22 (0.96–1.55)	0.87	NS	1.03 (0.76–1.39)
		AA	7 (2.0%)	5 (2.6%)	12 (1.9%)	0.83	NS	1.11 (0.43–2.84)	0.53	NS	1.40 (0.49–4.02)
		AG	116 (33.9%)	54 (27.8%)	185 (28.6%)	0.08	NS	1.28 (0.97–1.70)	0.84	NS	0.96 (0.67–1.38)
		GG	219 (64.1%)	135 (69.6%)	450 (69.5%)	0.07	NS	0.78 (0.59–1.03)	0.99	NS	1.00 (0.71–1.42)
	rs4795067	A	512 (73.6%)	295 (74.5%)	1008 (76.1%)	0.20	NS	0.87 (0.71–1.08)	0.61	NS	0.92 (0.71–1.19)
		AA	184 (52.9%)	109 (55.1%)	382 (57.7%)	0.14	NS	0.82 (0.63–1.07)	0.51	NS	0.90 (0.65–1.24)
		AG	144 (41.4%)	77 (38.8%)	244 (36.9%)	0.16	NS	1.21 (0.93–1.58)	0.60	NS	1.09 (0.79–1.51)
		GG	20 (5.7%)	12 (6.1%)	36 (5.4%)	0.84	NS	1.06 (0.60–1.86)	0.74	NS	1.12 (0.57–2.20)

OR = odds ratio; 95% CI = 95% confidence interval.
Pc = P value adjusted by Bonferroni correction.

differences in the genotype and allele frequencies of the other 10 SNPs were observed between the HLA-B27-positive AS-positive AAU patients and healthy controls ($P_{\text{Bonferroni}} > 0.05$, Table 5). In addition, there were no significant differences in the genotype and allele frequencies of the tested SNPs between the AS-positive AAU patients and control subjects ($P_{\text{Bonferroni}} > 0.05$, Supplementary Table S3).

3.3. Logistic Regression Analysis of SNPs in AAU. We further investigated the SNPs rs10758669 and rs10975003 using additive, codominant, dominant, and recessive genetic models using a multivariate logistic regression model adjusted for age and gender. We observed that the frequency of the CA genotype of rs10758669 was significantly higher in AAU patients, which suggests that patients with the rs10758669 CA genotype have increased susceptibility to AAU (46.8% versus 40.6%, OR = 1.28, $P = 0.02$, Supplementary Table S4). An increased frequency of the AC genotype of rs10758669 was also observed in HLA-B27-positive AAU patients and AS-positive AAU patients compared to the healthy controls (49.5% versus 40.6%, OR = 1.43, $P = 3.50 \times 10^{-3}$ and 49.2% versus 40.6%, OR = 1.36, $P = 0.02$, Supplementary Table S4). For SNP rs10975003, the frequency of the heterozygous CT genotype was significantly higher in female AAU patients compared to the healthy controls (40.4% versus 33.6%, OR = 1.57, $P = 0.01$, Supplementary Table S5). A similar result was observed when we combined CT and CC to construct a dominant model (44.3% versus 38.0%, OR = 1.57, $P = 9.10 \times 10^{-3}$, Supplementary Table S5). However, none of the observed associations for the two SNPs retained statistical significance after Bonferroni correction ($P_{\text{Bonferroni}} > 0.05$). Furthermore, no significance associations were found between the other SNPs and AAU, even after stratification by gender, AS, and HLA-B27 status (data not shown).

4. Discussion

In this study, we first investigated whether genetic polymorphisms of JAK-STAT signaling pathway genes, including *JAK1, JAK2, STAT1, IRF1*, and *NOS2*, confer susceptibility to AAU with or without AS in a Chinese Han population. Our results suggest that none of these SNPs exhibit statistically different frequencies of genotypes and alleles between healthy controls and AAU patients. However, we observed a boundary significant association for two SNPs (rs10975003 and rs10758669) of *JAK2* by stratification analysis by gender and HLA-B27 status.

We highlighted two issues at the time of study design to obtain unbiased association results. First, we followed strict criteria for the diagnosis of AAU patients. Patients with AAU were diagnosed as previously described by Jabs et al. [36] and patients with AS were diagnosed with the modified New York Criteria [37]. In addition, the AAU patients and healthy controls were strictly matched by ethnicity and age to avoid a possible influence of population stratification. Furthermore, we only enrolled controls who had detailed histories and physical examinations and excluded controls with any autoimmune or immune-related diseases. Finally, 20% of the samples were randomly chosen and analyzed by direct sequencing, and the results of different genotyping methods were consistent.

AAU is defined as inflammation confined to the anterior segment of the eye that involves the iris and anterior part of the ciliary body. The HLA-B27 is considered to be strongly associated with both AAU and AS [5, 8, 10, 14]. Recent genetic studies have revealed that five candidate genes in the JAK-STAT signaling pathway were considered genetic predisposing factors for different autoimmune-mediated diseases [38–45]. SNPs (rs10758669 and 10975003) in *JAK2* are considered susceptibility factors for Crohn's disease (CD) in the German population and ulcerative colitis (UC) in the Korean population [38, 45]. One SNP (rs2070721) in *IRF1* and SNPs (rs2297518 and rs4795067) in *NOS2* are also associated with autoimmune diseases, such as multiple sclerosis (MS) in Italy, AS in Europe, and psoriasis in Pakistan [39, 43, 44]. Four SNPs (rs6718902, rs10199181, rs2066802, and rs1547550) in the *STAT1* gene were observed to be associated with MS in Italy and IgA nephropathy (IgAN) in Korea [39, 40]. In addition, an association was found between SNPs (rs2780815, rs310241, rs3790532, rs310230, and rs310236) in *JAK1* and Behçet disease (BD) as well as Vogt-Koyanagi-Harada (VKH) syndrome [41, 42], two other common uveitis entities in China. There has been no report of associations between JAK-STAT signaling pathway genes and AAU, and thus we performed this case-control study to detect whether the five candidate genes were associated with AAU in a Chinese Han population. Our results showed that there were no significant associations between the genetic polymorphisms of the five candidate genes in the JAK-STAT signaling pathway and AAU. These results are not consistent with those observed for other autoimmune diseases reported in German, European, and some other Asian populations [38, 43, 45]. This discrepancy may be attributable to differences in the etiology and pathogenesis of AAU compared with BD, VKH syndrome, and autoimmune-mediated diseases.

Consistent with our results, a recent study also reported no significant association of JAK-STAT signaling pathway gene polymorphisms with rheumatoid arthritis stratified by the presence/absence of cardiovascular disease [46]. Conversely, an influence of NFKB1 signaling pathway polymorphisms on the development of cardiovascular events in patients with rheumatoid arthritis has been observed [47]. Furthermore, NFKB1 signaling pathway polymorphisms have been described to play a critical role in the development of many autoimmune and inflammatory diseases, and thus the evaluation of the potential relationships between *NFKB1* polymorphisms and the development of AAU could be a promising research line for the future.

There were several limitations of our study. We had a limited sample size to detect SNPs with weak effects while considering multiple corrections. Even for SNPs rs10758669 and rs10975003, we only had 70.0% power using a genetic power calculator [48]. In addition, our samples were restricted to the Han Chinese population, and all patients were enrolled from the ophthalmology department. Further studies with a larger sample size and other ethnic populations as well as patients enrolled from multiple sources are warranted to confirm our

findings. Additionally, we only focused on eleven SNPs in the JAK-STAT pathway, and it is possible that other unknown SNPs might be associated with AAU risk.

In conclusion, this study reveals that genetic polymorphisms of JAK-STAT pathway genes, including *JAK1, JAK2, STAT1, IRF1*, and *NOS2*, may not be involved in susceptibility to AAU risk in the Han Chinese population.

Competing Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors' Contributions

Ling Cheng and Hongsong Yu contributed equally to this work.

Acknowledgments

The authors would like to thank Professor Peizeng Yang for his great help in our study. They are also grateful to all donors enrolled in this study. This work was supported by the National Natural Science Foundation Project (81200678, 81670844), Fundamental and Advanced Research Program of Chongqing (cstc2015jcyjA10022), Science and Technology Project of Chongqing Municipal Education Commission (KJ1500236), Scientific Research Program of Science and Technology Commission of Yuzhong District of Chongqing (20150102), and National Key Clinical Specialties Construction Program of China.

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