ORIGINAL RESEARCH

The Impacts of *IL1R1* and *IL1R2* Genetic Variants on Rheumatoid Arthritis Risk in the Chinese Han Population: A Case–Control Study

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Background: Rheumatoid arthritis (RA), an autoimmune systemic inflammatory disease, largely resulted from genetic factor. Our purpose was to explore the association for *IL1R1* and *IL1R2* genetic variants with RA susceptibility in the Chinese Han population.

Patients and Methods: A total of 508 RA patients and 494 controls were involved in this case–control study; single-nucleotide polymorphisms (SNPs) genotyping was identified by the Agena MassARRAY platform. The relationship between polymorphisms and RA susceptibility was calculated using the Pearson's Chi-square test with odds ratios and 95% confidence intervals (CIs) in multiple genetic models. The Pearson's Chi-square test and Student's *t*-test were used for sample basic characteristic analysis. And linkage disequilibrium (LD) analysis and haplotype analysis were performed by logistic regression analysis.

Results: The result from this study showed that rs2072472 (*IL1R2*) was an increased risk factor of RA (adjusted OR = 1.41, p = 0.011). Stratified analysis indicated SNPs rs10490571, rs956730, rs3917318 of *IL1R1*, and SNPs rs4851527, rs719250, rs3218896, rs3218977, rs2072472 of *IL1R2* had impacts on RA risk after stratification based on gender and average age (54 years). Finally, haplotype analysis revealed that $A_{rs3218977}A_{rs2072472}$ haplotype in *IL1R2* was related to a decreased RA risk (adjusted OR = 0.79; 95% CI = 0.65–0.94; p = 0.010). Yet, rs3917225(*IL1R1*) and rs11674595(*IL1R2*) were not significant in RA association analysis.

Conclusion: We determined SNPs (rs3917318, rs956730, rs1049057) of *IL1R1* and SNPs (rs3218977, rs719250, rs4851527, rs3218896, rs2072472) of *IL1R2* were correlated with the RA susceptibility in the Chinese Han population.

Keywords: rheumatoid arthritis, RA, *IL1R1*/*IL1R2*, single-nucleotide polymorphism, SNP, susceptibility

Introduction

Rheumatoid arthritis (RA) is a common autoimmune systemic inflammatory disease that has complex multifactorial pathogenesis finally leading to the development of synovitis, joint damage, and structural bone damage[1] and causing severe disability and reduced health-related quality of life of patients.[2] The RA population minimum prevalence is 1.16% in women and 0.44% in men.[3] RA is influenced by both genetic and environmental factors.[4] The genetic factors may explain up to 60% of the susceptibility to RA,[5] and genetic variants affect both the development and severity of rheumatoid arthritis.[6] Recent studies have expanded the number of RA susceptibility variants.[7–9] Besides, many studies have also confirmed that *IL1R1* and *IL1R2* polymorphisms were associated with the risk of certain inflammation-related diseases, such as inflammatory bowel disease,

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Alzheimer's disease.[10,11] However, the association of *IL1R1* and *IL1R2* gene polymorphisms with RA risk has not been clarified. As we all know, there were several cytokines involved in the pathogenesis of RA,[12,13] which was an inflammatory disease. Among these reported cytokines, the interleukin-1 (IL-1) family as pro-inflammatory cytokine has been illustrated to play crucial roles in the pathogenesis of RA, promoting the bone and cartilage inflammation and degradation by affecting cell proliferation and differentiation.[14] The cytokine IL-1 mediates its biological functions exactly by binding to the signaling receptor IL-1R1. Contrarily, the other receptor IL-1R2 which was known as the decoy receptor can seclude the active forms of IL-1 or obstruct the signaling complex assembly.[15] Thus, IL-1R1 and IL-1R2 played crucial roles in the process of RA development. Genetically, *IL1R1* and *IL1R2*, encoding interleukin 1 receptor type 1 (IL-1R1) and interleukin 1 receptor type 2 (IL1-R2), respectively.[16,17] IL-1α (*IL-1A*) and IL-1β (*IL-1B*) are two subtypes of IL-1, and it has been demonstrated that untreated RA patients had significant upregulation of both *IL-1B* and *IL1R* genes compared with healthy individuals,[18] which indicated the complex roles of *IL1R1* and *IL1R2* in the pathogenesis of RA. Genetic polymorphisms could affect the gene function, furthermore affecting the occurrence and development of disease. Published studies reported that *IL1R1* and *IL1R2* gene polymorphisms had an impact on the risk of osteonecrosis of the femoral head (ONFH) and aggressive periodontitis,[19,20] indicating the potential importance of *IL1R1* and *IL1R2* genetic polymorphisms in the inflammatory disease. Thus, here we try to explore the relationship between *IL1R1* and *IL1R2* gene polymorphisms and the susceptibility of RA in the Chinese Han population to elucidate the *IL1R1* and *IL1R2* risk variants may be an important factor in determining the progression in early RA.

The impacts of *IL1R1* (rs10490571, rs956730, rs3917225, rs3917318), *IL1R2* (rs11674595, rs4851527, rs719250, rs3218896, rs3218977, rs2072472) on RA risk among the Chinese Han population were investigated in this case–control study, which may provide more theoretical basis for the function of *IL1R1* and *IL1R2* in RA pathogenesis in the Chinese Han population.

Patients and Methods
Study Subjects
In total, 1002 Chinese subjects including 508 RA patients and 494 geographically ethnicity-matched healthy subjects who were from the Shanxi provincial Yanliang 630 Hospital (Xi'an City, Shaanxi, China) were enrolled in this study. All subjects were individuals without related relationship from Shaanxi province in northern China and at least three generations of Han ancestors. Before beginning the research, all participants have provided written informed consent. All experiments were carried out adhering to the protocol of Helsinki's Declaration. And the study protocol was approved by the ethics committee of the Affiliated Hospital of Xizang Minzu University (20,190–5). RA patients were diagnosed by routine biochemical blood analysis (including C-reaction protein [CRP], rheumatoid factor, erythrocyte sedimentation rate [ESR], anti-cyclic citrulline antibody [CCP]), anti-keratin auto antibody [AKA] and X-rays of small joints, and the patients were firstly diagnosed as RA according to current criteria for classifying rheumatoid arthritis.[21] All control subjects were healthy individuals who had a routine physical examination in the same period. We excluded the healthy controls with immune diseases or more aggressive metabolic and endocrinological disease. The clinical information of each participants were collected by consulting medical records.

SNP Selection and Genotyping
Firstly, a preliminary selection of SNPs with minor allele frequencies >5% was performed in the 1000 Genome Projects (http://www.internationalgenome.org/) based on the CHB (Chinese Han in Beijing) data in order to ensure the successful genotyping and valid statistical analysis in our study population. Secondly, the linkage disequilibrium (LD) haplotype analysis was observed using the haploview software (version 4.2) analysis. Then, the functional prediction of the tagSNPs which constructed the haplotypes was performed in dbSNP database (https://www.ncbi.nlm. nih.gov/snp/), which indicated these tagSNPs were introns affecting the activity of splice sites. Finally, four SNPs (rs3917318, rs956730, rs10490571 and rs3917225) in *IL1R1* and six SNPs (rs3218977, rs719250, rs4851527, rs11674595, rs3218896 and rs2072472) in *IL1R2* were selected for further research.

We isolated the genomic DNA from the blood samples using the GoldMag-Mini Whole Blood Genomic DNA Purification Kit (GoldMag. Co. Ltd., Xi'an, China) as described by the manufacturer's instructions. The extracted DNA was labeled and stored at −20°C until used. The genes of interest were amplified using appropriate primers which was designed using the Agena Bioscience Assay Design Suite V2.0 software (https:// agenacx.com/online-tools/). The information of primers

used in this study are displayed in Supplementary Table 1. Then, SNP genotyping was carried out using Agena MassARRAY platform with iPLEX gold chemistry (Agena Bioscience, San Diego, CA, USA), and data analysis was performed using Agena Bioscience TYPER, Version 4.0.

Statistical Analysis

We compared the difference of gender distribution among two groups (RA patients and controls) using Pearson's Chi-square tests, and assessed the distribution difference of age using Student's *t*-test, both of them were performed on the SPSS 19.0 (SPSS, Chicago, IL, USA) and Microsoft Excel. In the control group, Hardy-Weinberg equilibrium (HWE) of the genotype frequencies was assessed by the Fisher's exact test. The allele frequencies of two groups were also evaluated with the Pearson's Chi-square test. The correlation of *IL1R1* and *IL1R2* polymorphisms with RA susceptibility was assessed using logistic regression analysis by calculating odds ratios (ORs) and 95% confidence intervals (CIs) with adjustment for age and gender based on the multiple genetic model analysis. Besides, the gender and average age (45 years old) stratification analyses between *IL1R1* (rs10490571, rs956730, rs3917225, rs3917318), *IL1R2* (rs11674595, rs4851527, rs719250, rs3218896, rs3218977, rs2072472) and susceptibility of RA were also conducted. In addition, false discovery rate (FDR) test was performed in this study. All *p*-values were two-tailed, and *p* < 0.05 means statistical significance.

Results
Characteristics of Study Subjects

There were 508 patients (134 males and 374 females) with RA and 494 healthy individuals (124 males and 370 females) in this case–control study. The basic characteristics of all participants are shown in Table 1. The age at diagnosis of the RA patient group and the control group was 54.34 ± 12.01 years and 54.03 ± 8.83 years, respectively. The age and gender between RA cases and controls (*p* > 0.05) was well distributed while the age distribution between RA cases and controls was significantly different (*p* < 0.001).

Association Between *IL1R1* and *IL1R2* Variants and Rheumatoid Arthritis Risk

Table 2 displays the basic information about ten polymorphisms of *IL1R1* and *IL1R2*. All ten SNPs retained for their genotype distribution were in accordance with HWE (*p* > 0.05) in the control group. We found no

difference for allele frequency distribution between RA patients and controls. And we explored the correlations between *IL1R1* and *IL1R2* genetic variants and RA risk under the multiple genetic models (Table 3 and Supplemental Table 2). We noted that among these ten SNPs, only rs2072472 (*IL1R2*) was a risk factor of RA susceptibility in codominant (adjusted OR = 1.41, 95% CI: 1.08–1.84, *p* = 0.011) and dominant model (adjusted OR = 1.35, 95% CI: 1.05–1.75, *p* = 0.021). However, no statistical significance was found between other models of rs2072472 (*IL1R2*) and RA risk. And we found no significant difference for genetic models of other candidate nine loci in *IL1R1* and *IL1R2* with RA risk, either. However, after FDR analysis, we got a negative result for the association between *IL1R1* and *IL1R2* variants and RA risk in total.

The Correlation of *IL1R1* and *IL1R2* Variants with RA Risk Based on the Gender Stratification

Furthermore, we stratified our study subjects based on gender after excluding the age factor to investigate the association of the candidate SNPs in this study with RA susceptibility. As shown in Table 4, the frequency of rs3917318-A (*IL1R1*) confirmed a significantly higher probability of RA susceptibility than the G allele in males (adjusted OR = 1.44, 95% CI = 1.02–2.04, *p* = 0.040). Similarly, rs3917318 (*IL1R1*) was also associated with the elevated RA risk in codominant model (adjusted OR=1.97, 95% CI = 1.01–3.83, *p* = 0.045 for "A/A" genotype) and dominant model (adjusted OR = 1.84, 95% CI = 1.04–3.27, *p* = 0.037 for "G/A-A/A" genotype) in males but non-significant in females. Also, SNP rs10490571 (*IL1R1*) was a factor of elevated RA risk based on the dominant model (adjusted OR = 1.68, 95% CI = 1.01–2.81, *p* = 0.047) in males. However, rs956730 (*IL1R1*) was related to the decreased RA susceptibility in recessive model (adjusted OR = 0.48, 95% CI = 0.24–0.97, *p* = 0.042) in females. For SNPs in *IL1R2*, rs719250-T showed a distinctly less likelihood of RA susceptibility than the C allele in males (adjusted OR = 0.66, 95% CI = 0.45–0.97, *p* = 0.034). Similarly, it was also correlated with the reduced chances of RA susceptibility in codominant model (adjusted OR = 0.33, 95% CI = 0.12–0.91, *p* = 0.032), recessive model (adjusted OR = 0.37, 95% CI = 0.13–0.99, *p* = 0.049), and log-additive model (adjusted OR = 0.66, 95% CI = 0.44–0.97, *p* = 0.036) in males but

Table 1 Basic Characteristics of Both Cases and Controls

Variables	RA Patients (n = 508)		Controls (n = 494)		*p*
	Count(%)	Mean ± *SD*	Count (%)	Mean ± *SD*	
Gender 　Male 　Female	 134 (26%) 374 (74%)		 124 (25%) 370 (75%)		$p^a > 0.05$
Age, years (Mean ± SD) 　>54 　≤54	 261 (51%) 247 (49%)	54.34 ± 12.01	 253 (51%) 241 (49%)	54.03 ± 8.83	$p^b < 0.001$
CRP (mg/L)	508 (100%)	30.83% ± 40.23			
RF (KIU/L)	508 (100%)	164.95 ± 147.26			
ESR (mm/hr)	508 (100%)	44.15 ± 30.68			
CCP (RU/mL)	508 (100%)	136 ± 76.12			
AKA (%) 　Positive 　Weak positive 　Negative	508 (100%) 122 (24%) 46 (9%) 340 (67%)				

Notes: p^a was calculated by Chi-square test. p^b was calculated by Student's *t*-test, $p < 0.05$ indicates statistical significance. The 54 year was determined by the Mean ± SD value of age in RA patients and control groups.
Abbreviations: CCP, anti-cyclic citrullinated peptide; CRP, C-reaction protein; ESR, erythrocyte sedimentation rate; RA, rheumatoid arthritis; RF, rheumatoid factor; *SD*, standard deviation.

Table 2 The Result of Distribution Analysis of Allele Frequencies of *IL1R1/IL1R2* SNPs in Case and Control Groups

Gene	SNP	Chromosome Position (bp)	Alleles	MAF		O	E	HWE-	OR (95% CI)	p^b
			(A/B)	Control	RA Patients	(HET)	(HET)	p^a		
IL1R1	rs10490571	Chr2:102,100,877	A/G	0.178	0.204	0.311	0.325	0.879	1.18 (0.94–1.48)	0.145
	rs956730	Chr2:102,141,656	A/G	0.242	0.231	0.453	0.439	0.903	0.94 (0.77–1.16)	0.574
	rs3917225	Chr2:102,152,842	A/G	0.359	0.363	0.397	0.416	0.626	1.02 (0.85–1.22)	0.877
	rs3917318	Chr2:102,176,300	A/G	0.49	0.475	0.229	0.236	0.176	0.94 (0.79–1.12)	0.516
IL1R2	rs11674595	Chr2:101,994,530	C/T	0.204	0.227	0.358	0.358	0.333	1.14 (0.92–1.42)	0.223
	rs4851527	Chr2:102,005,914	A/G	0.326	0.297	0.298	0.317	0.539	0.87 (0.72–1.06)	0.166
	rs719250	Chr2:102,007,256	A/G	0.296	0.258	0.292	0.293	0.282	0.83 (0.68–1.01)	0.064
	rs3218896	Chr2:102,015,190	C/T	0.137	0.123	0.37	0.367	0.451	0.88 (0.68–1.15)	0.356
	rs3218977	Chr2:102,024,739	A/G	0.234	0.257	0.472	0.46	1	1.13 (0.92–1.39)	0.23
	rs2072472	Chr2:102,026,557	C/T	0.197	0.23	0.469	0.5	0.2	1.22 (0.98–1.51)	0.072

Notes: OR (95% CI): Calculated by unconditional logistic regression adjusted by gender and age. HWE- p^aCalculated by Fisher's exact test, p^bCalculated by Pearson's Chi-square test.
Abbreviations: RA, rheumatoid arthritis; *IL1R1*, interleukin-1 receptor 1; *IL1R2*, interleukin-1 receptor 2; SNP, single-nucleotide polymorphism; Position (bp), Genomic position (NCBI Build 36), A/B, minor/major alleles on the control sample frequencies, MAF, minor allele frequency; O(HET), observed heterozygosity; E(HET), expected heterozygosity; HWE, Hardy–Weinberg equilibrium; OR, odds ratio; 95% CI, 95% confidence interval.

non-significant in females. In addition, in males, rs3218977 was also (adjusted OR = 0.40, 95% CI = 0.18–0.88, p = 0.023) a protective factor in RA risk. Conversely, in females, rs2072472 (*IL1R2*) was a factor of elevated RA risk in codominant model (adjusted OR = 1.41, 95% CI = 1.03–1.92, p = 0.031). And no significant difference was found for rs3917225 of *IL1R1* and rs11674595, rs4851527, rs3218896 of *IL1R2* with RA risk in gender stratification analysis (Supplemental Table 3). However, after FDR analysis, we got a negative result for the association between *IL1R1* and *IL1R2* variants and RA risk in gender stratified analyses.

Table 3 Association Analysis Result Between *IL1R2* Rs2072472 Genetic Variants and Rheumatoid Arthritis Risk

Gene	SNP	Model	Genotype	RA Patients	Control	OR (95% CI)	*p*	FDR Test
				n (Freq)	n (Freq)			
IL1R2	rs2072472	Allele	G	234 (23.03%)	195 (19.74%)	1		
			A	782 (76.97%)	793 (80.26%)	1.22 (0.98–1.51)	0.072	0.360
		Codominant	A/A	296 (58.27%)	323 (65.38%)	1		
			A/G	190 (37.40%)	147 (29.76%)	1.41 (1.08–1.84)	**0.011**	0.275
			G/G	22 (4.33%)	24 (4.86%)	1.00 (0.55–1.82)	1	1.000
		Dominant	A/A	296 (58.27%)	323 (65.38%)	1		
			A/G-G/G	212 (41.73%)	171 (34.62%)	1.35 (1.05–1.75)	**0.021**	0.350
		Recessive	A/G-A/A	486 (95.67%)	470 (95.14%)	1		
			G/G	22 (4.33%)	24 (4.86%)	0.89 (0.49–1.60)	0.688	1.011
		Log-additive	-	-	-	1.22 (0.98–1.51)	0.073	0.608

Notes: OR (95% CI): Calculated by unconditional logistic regression adjusted by gender and age. *p* - value was calculated by two -sided χ^2 test. Bold means statistical significance.
Abbreviations: RA, rheumatoid arthritis; *IL1R2*, interleukin-1 receptor 2; SNP, single-nucleotide polymorphism; OR, odds ratio; 95% CI, 95% confidence interval; FDR, false discovery rate; freq, frequency.

The Correlation of *IL1R1* and *IL1R2* Variants with RA Risk Based on the Age Stratification

Significant differences between candidate SNPs and RA risk were also observed in the average age (54 years) stratification analysis after excluding the gender factor. As shown in Table 5, rs956730 (*IL1R1*) was a protective factor of RA risk in recessive model (adjusted OR = 0.37, 95% CI = 0.14–0.97, *p* = 0.043 for "A/A" genotype) in patients aged older than 54 years. In the codominant model of rs4851527 (*IL1R2*), both of the G/A and A/A genotypes were associated with a significantly protective effect for RA in patients aged younger than 54 years(adjusted OR = 0.63, 95% CI = 0.43–0.93, *p* = 0.023 for "G/A" genotype) and patients aged older than 54 years (adjusted OR = 0.47, 95% CI = 0.23–0.96, *p* = 0.039 for "A/A" genotype), respectively. Besides, rs4851527(*IL1R2*) was also associated with a significantly protective effect for RA in patients aged younger than 54 years based on dominant model (adjusted OR = 0.68, 95% CI = 0.47–0.97, *p* = 0.035) and patients aged older than 54 years based on recessive model (adjusted OR = 0.41, 95% CI = 0.21–0.82, *p* = 0.011). In addition, the recessive model of rs3218977 (*IL1R2*) was a protective factor of RA in patients (>54 years) (adjusted OR = 0.40, 95% CI = 0.18–0.88, *p* = 0.023), contrarily, rs3218977 (*IL1R2*) was

an elevated risk factor of RA in the log-additive model. Also, both of rs719250 (*IL1R2*) and rs3218896 (*IL1R2*) had impacts on the RA risk in patients aged younger than 54 years. In patients aged older than 54 years, rs2072472 (*IL1R2*) was an increased risk factor of RA in A/G genotype of codominant model (adjusted OR = 1.67, 95% CI = 1.14–2.45, *p* = 0.009) and dominant model (adjusted OR = 1.47, 95% CI = 1.02–2.12, *p* = 0.039). And no significant difference was found for rs10490571, rs3917225 and rs3917318 of *IL1R1* and rs11674595 of *IL1R2* with RA risk in average age (54 years) stratification analyses (Supplemental Table 4). However, no significant association between *IL1R1* and *IL1R2* variants and susceptibility to RA was observed after a FDR adjustment in the average age (54 years) stratified analysis.

LD and Haplotype Analysis

We performed the LD haplotype analysis among above ten SNPs in *IL1R1* and *IL1R2* genes at last (Figure 1). LD haplotypes in *IL1R1* and *IL1R2* genes on chromosome 2 were formed by rs3218977 (*IL1R2*) and rs2072472 (*IL1R2*), and a haplotype $A_{rs3218977}A_{rs2072472}$ which was significant with RA risk was found (adjusted OR = 0.79; 95% CI = 0.65–0.94; *p* = 0.010). In addition, the False discovery rate (FDR) test also illustrated that the $A_{rs3218977}A_{rs2072472}$ haplotype was associated with the risk of RA. Table 6 shows the frequency distribution of

Table 4 Association Analysis Result Between *IL1R1/ IL1R2* Genetic Variants and Rheumatoid Arthritis Risk Based on the Gender Stratification

Gene	SNP	Genotype	Model	Males					Females				
				RA Patients n (Freq)	Control n (Freq)	OR (95% CI)	p	FDR Test	RA Patients n (Freq)	Control n (Freq)	OR (95% CI)	p	FDR Test
IL1R1	rs3917318	Allele	G	113 (42.16%)	127 (51.21%)	—			377 (50.54%)	382 (51.76%)	—		
			A	155 (57.84%)	121 (48.79%)	1.44 (1.02–2.04)	**0.040**	0.200	369 (49.46%)	356 (48.24%)	1.05 (0.86–1.29)	0.637	0.796
		Codominant	G/G	26 (19.40%)	38 (30.65%)	—			93 (24.93%)	101 (27.37%)	—		
			G/A	61 (45.52%)	51 (41.13%)	1.97 (1.01–3.83)	**0.045**	0.450	191 (51.21%)	180 (48.78%)	1.15 (0.81–1.63)	0.427	1.334
			A/A	47 (35.07%)	35 (28.23%)	1.76 (0.94–3.27)	0.077	0.275	89 (23.86%)	88 (23.85%)	1.10 (0.73–1.65)	0.651	1.085
		Dominant	G/G	26 (19.40%)	38 (30.65%)	—			93 (24.93%)	101 (27.37%)	—		
			G/A-A/A	108 (80.60%)	86 (69.35%)	1.84 (1.04–3.27)	**0.037**	0.463	280 (75.07%)	268 (72.63%)	1.13 (0.81–1.57)	0.452	1.189
		Recessive	G/A-G/G	87 (64.93%)	89 (71.77%)	—			329 (88.20%)	324 (87.57%)	—		
			A/A	47 (35.07%)	35 (28.23%)	1.38 (0.81–2.33)	0.237	0.515	44 (11.80%)	46 (12.43%)	1.00 (0.71–1.40)	0.992	0.992
		Log-additive	—	—	—	1.39 (1.00–1.93)	0.053	0.294	—	—	1.00 (0.86–1.29)	0.636	1.097
	rs10490571	Allele	C	203 (75.75%)	120 (82.66%)	—			606 (81.02%)	607 (82.03%)	—		
			T	65 (24.25%)	43 (17.34%)	1.53 (0.99–2.35)	0.065	0.217	142 (18.98%)	133 (17.97%)	1.07 (0.82–1.39)	0.615	0.879
		Codominant	C/C	77 (57.46%)	86 (69.35%)	—			241 (64.44%)	248 (67.03%)	—		
			C/T	49 (36.57%)	33 (26.61%)	1.66 (0.97–2.84)	0.065	0.271	124 (33.16%)	111 (30.00%)	1.14 (0.84–1.57)	0.398	1.327
			T/T	8 (5.97%)	5 (4.03%)	1.84 (0.57–5.97)	0.307	0.512	9 (2.41%)	11 (2.97%)	0.84 (0.34–2.06)	0.698	1.058
		Dominant	C/C	77 (57.46%)	86 (69.35%)	—			241 (64.44%)	248 (67.03%)	—		
			C/T-T/T	57 (42.54%)	38 (30.65%)	1.68 (1.01–2.81)	**0.047**	0.392	133 (35.56%)	122 (32.97%)	1.12 (0.82–1.51)	0.477	1.193
		Recessive	C/T-C/C	126 (94.03%)	119 (95.97%)	—			365 (97.59%)	359 (97.03%)	—		
			T/T	8 (5.97%)	5 (4.03%)	1.56 (0.49–4.97)	0.454	0.649	9 (2.41%)	11 (2.97%)	0.80 (0.33–1.96)	0.624	1.156
		Log-additive	—	—	—	1.52 (0.99–2.33)	0.056	0.255	—	—	1.07 (0.82–1.40)	0.63	1.125
	rs956730	Allele	G	200 (75.19%)	184 (74.19%)	—			578 (77.48%)	565 (76.35%)	—		
			A	66 (24.81%)	64 (25.81%)	0.95 (0.64–1.41)	0.796	0.884	168 (22.52%)	175 (23.65%)	0.94 (0.74–1.20)	0.606	1.010
		Codominant	G/G	75 (56.39%)	64 (51.61%)	—			217 (58.18%)	219 (59.19%)	—		
			G/A	50 (37.59%)	56 (45.16%)	0.76 (0.46–1.26)	0.288	0.533	144 (38.61%)	127 (34.32%)	1.14 (0.84–1.55)	0.388	1.386
			A/A	8 (6.02%)	4 (3.23%)	1.70 (0.49–5.91)	0.406	0.615	12 (3.22%)	24 (6.49%)	0.50 (0.24–1.03)	0.061	0.610
		Dominant	G/G	75 (56.39%)	64 (51.61%)	—			217 (58.18%)	219 (59.19%)	—		
			G/A-A/A	58 (43.61%)	60 (48.39%)	0.82 (0.50–1.35)	0.434	0.638	156 (41.82%)	151 (40.81%)	1.04 (0.78–1.40)	0.785	0.957
		Recessive	G/A-G/G	125 (93.98%)	120 (96.77%)	—			365 (97.59%)	359 (97.03%)	—		
			A/A	8 (6.02%)	4 (3.23%)	1.92 (0.56–6.54)	0.298	0.514	9 (2.41%)	11 (2.97%)	0.48 (0.24–0.97)	**0.042**	0.700
		Log-additive	—	—	—	0.94 (0.62–1.43)	0.777	0.883	—	—	0.94 (0.73–1.2)	0.596	1.146

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IL1R2	SNP	Model	Allele	n (%)	n (%)	OR (95% CI)	p	FDR	n (%)	n (%)	OR (95% CI)	p	FDR
IL1R2	rs719250	Allele	C	204 (76.12%)	168 (67.74%)	–			545 (73.45%)	528 (71.35%)	–		
			T	64 (23.88%)	80 (32.26%)	0.66 (0.45–0.97)	**0.034**	0.340	197 (26.55%)	212 (28.65%)	0.90 (0.72–1.13)	0.366	0.915
		Codominant	C/C	76 (56.72%)	58 (46.77%)	–			203 (54.72%)	192 (51.89%)	–		
			C/T	52 (38.81%)	52 (41.94%)	0.76 (0.46–1.26)	0.288	0.533	139 (37.47%)	144 (38.92%)	0.91 (0.67–1.24)	0.559	1.215
			T/T	6 (4.48%)	14 (11.29%)	0.33 (0.12–0.91)	**0.032**	0.800	29 (7.82%)	34 (9.19%)	0.81 (0.47–1.38)	0.43	1.265
		Dominant	C/C	76 (56.72%)	58 (46.77%)	–			203 (54.72%)	192 (51.89%)	–		
			C/T-T/T	58 (43.28%)	66 (53.23%)	0.67 (0.41–1.09)	0.109	0.341	168 (45.28%)	178 (48.11%)	0.89 (0.67–1.19)	0.441	1.225
		Recessive	C/T-C/C	128 (95.52%)	110 (88.71%)	–			342 (92.18%)	336 (90.81%)	–		
			T/T	6 (4.48%)	14 (11.29%)	0.37 (0.13–0.99)	**0.049**	0.350	29 (7.82%)	34 (9.19%)	0.84 (0.50–1.41)	0.503	1.143
		Log-additive	–	–	–	0.66 (0.44–0.97)	**0.036**	0.600	–	–	0.90 (0.72–1.13)	0.377	1.450
	rs3218977	Allele	A	194 (72.39%)	185 (74.60%)	–			561 (75.00%)	572 (77.30%)	–		
			G	74 (27.61%)	63 (25.40%)	1.12 (0.76–1.66)	0.570	0.713	187 (25.00%)	168 (22.70%)	1.14 (0.89–1.44)	0.299	0.997
		Codominant	A/A	67 (50.00%)	71 (57.26%)	–			204 (54.55%)	219 (59.19%)	–		
			A/G	60 (44.78%)	43 (34.68%)	1.37 (0.94–2.00)	0.104	0.347	153 (40.91%)	134 (36.22%)	1.31 (0.90–1.90)	0.155	0.861
			G/G	7 (5.22%)	10 (8.06%)	0.45 (0.20–1.00)	0.052	0.325	17 (4.55%)	17 (4.59%)	0.44 (0.90–6.63)	0.081	0.675
		Dominant	A/A	67 (50.00%)	71 (57.26%)	–			204 (54.55%)	219 (59.19%)	–		
			A/G-G/G	67 (50.00%)	53 (42.74%)	1.17 (0.82–1.68)	0.383	0.598	170 (45.45%)	151 (40.81%)	1.38 (0.96–1.98)	0.081	
		Recessive	A/G-A/A	127 (94.78%)	114 (91.94%)	–			357 (95.45%)	353 (95.41%)	–		
			G/G	7 (5.22%)	10 (8.06%)	0.40 (0.18–0.88)	**0.023**	1.150	17 (4.55%)	17 (4.59%)	2.18 (0.81–5.84)	0.123	0.769
		Log-additive	–	–	–	0.97 (0.73–1.30)	0.843	0.937	–	–	1.39 (1.01–1.90)	**0.041**	1.025
	rs2072472	Allele	A	206 (76.87%)	201 (81.05%)	–			576 (77.01%)	592 (80.00%)	–		
			G	62 (23.13%)	47 (18.95%)	1.29 (0.84–1.97)	0.245	0.408	172 (22.99%)	148 (20.00%)	1.19 (0.93–1.53)	0.16	0.800
		Codominant	A/A	78 (58.21%)	82 (66.13%)	–			218 (58.29%)	241 (65.14%)	–		
			A/G	50 (37.31%)	37 (29.84%)	1.43 (0.84–2.42)	0.184	0.460	140 (37.43%)	110 (29.73%)	1.41 (1.03–1.92)	**0.031**	1.550
			G/G	6 (4.48%)	5 (4.03%)	1.26 (0.37–4.30)	0.712	0.848	16 (4.28%)	19 (5.14%)	0.93 (0.47–1.85)	0.834	0.970
		Dominant	A/A	78 (58.21%)	82 (66.13%)	–			218 (58.29%)	241 (65.14%)	–		
			A/G-G/G	56 (41.79%)	42 (33.87%)	1.41 (0.85–2.34)	0.185	0.440	156 (41.71%)	129 (34.86%)	1.34 (0.99–1.80)	0.056	0.700
		Recessive	A/G-A/A	128 (95.52%)	119 (95.97%)	–			358 (95.72%)	351 (94.86%)	–		
			G/G	6 (4.48%)	5 (4.03%)	1.11 (0.33–3.75)	0.862	0.917	16 (4.28%)	19 (5.14%)	0.82 (0.42–1.63)	0.577	1.202
		Log-additive	–	–	–	1.30 (0.84–1.99)	0.238	0.496	–	–	1.19 (0.93–1.53)	0.164	0.820

Notes: OR (95% CI): Calculated by unconditional logistic regression adjusted by age. p - value was calculated by two-sided χ^2 test. Bold means statistical significance.
Abbreviations: RA, rheumatoid arthritis; IL1R1, interleukin-1 receptor 1; IL1R2, interleukin-1 receptor 2; SNP, single-nucleotide polymorphism; OR, odds ratio; 95% CI, 95% confidence interval; FDR, false discovery rate; freq, frequency.

Table 5 Association Analysis Result Between *IL1R1/ IL1R2* Genetic Variants and Rheumatoid Arthritis Risk Based on the Age Stratification

Gene	SNP	Genotype	Model	Age >54 Years					Age ≤ 54 Years				
				RA Patients n (Freq)	Control n (Freq)	OR (95% CI)	p	FDR Test	RA Patients n (Freq)	Control n (Freq)	OR (95% CI)	p	FDR Test
IL1R1	rs956730	Allele	G	391 (75.48%)	375 (74.11%)	–			387 (78.34%)	374 (77.59%)	–		
			A	127 (24.52%)	131 (25.89%)	0.93 (0.70–1.23)	0.613	1.226	107 (21.66%)	108 (22.41%)	0.96 (0.71–1.30)	0.778	0.778
		Codominant	G/G	138 (53.28%)	138 (54.55%)	–			154 (62.35%)	145 (60.17%)	–		
			G/A	115 (44.40%)	99 (39.13%)	1.19 (0.83–1.72)	0.342	0.684	79 (31.98%)	84 (34.85%)	0.86 (0.58–1.26)	0.434	0.804
			A/A	6 (2.32%)	16 (6.32%)	0.40 (0.15–1.06)	0.065	0.361	14 (5.67%)	12 (4.98%)	1.28 (0.57–2.89)	0.549	0.885
		Dominant	G/G	138 (53.28%)	138 (54.55%)	–			154 (62.35%)	145 (60.17%)	–		
			G/A-A/A	121 (46.72%)	115 (45.45%)	1.08 (0.76–1.55)	0.66	0.825	93 (37.65%)	96 (39.83%)	0.91 (0.63–1.31)	0.601	0.939
		Recessive	G/A-G/G	253 (97.68%)	237 (93.68%)	–			233 (94.33%)	229 (95.02%)	–		
			A/A	6 (2.32%)	16 (6.32%)	0.37 (0.14–0.97)	**0.043**	0.358	14 (5.67%)	12 (4.98%)	1.35 (0.61–3.02)	0.462	0.797
		Log-additive	–			0.95 (0.70–1.28)	0.720	0.837			0.98 (0.72–1.32)	0.881	0.937
IL1R2	rs4851527	Allele	G	360 (68.97%)	344 (67.98%)	–			354 (71.66%)	322 (66.80%)	–		
			A	162 (31.03%)	162 (32.02%)	0.96 (0.73–1.24)	0.735	0.919	140 (28.34%)	160 (33.20%)	0.80 (0.61–1.05)	0.100	0.333
		Codominant	G/G	113 (43.30%)	119 (47.04%)	–			131 (53.04%)	102 (42.32%)	–		
			G/A	134 (51.34%)	106 (41.90%)	1.32 (0.91–1.91)	0.148	0.435	92 (37.25%)	118 (48.96%)	0.63 (0.43–0.93)	**0.019**	0.950
			A/A	14 (5.36%)	28 (11.07%)	0.47 (0.23–0.96)	**0.039**	0.488	24 (9.72%)	21 (8.71%)	0.93 (0.49–1.78)	0.831	0.944
		Dominant	G/G	113 (43.30%)	119 (47.04%)	–			131 (53.04%)	102 (42.32%)	–		
			G/A-A/A	148 (56.70%)	134 (52.96%)	1.13 (0.79–1.62)	0.490	0.766	116 (46.96%)	139 (57.68%)	0.68 (0.47–0.97)	**0.035**	0.583
		Recessive	G/G-G/A	247 (94.64%)	225 (88.93%)	–			223 (90.28%)	220 (91.29%)	–		
			A/A	14 (5.36%)	28 (11.07%)	0.41 (0.21–0.82)	**0.011**	0.275	24 (9.72%)	21 (8.71%)	1.16 (0.62–2.17)	0.641	0.971
		Log-additive	–			0.92 (0.69–1.22)	0.558	0.797			0.82 (0.62–1.08)	0.156	0.520
	rs3218977	Allele	A	396 (75.86%)	382 (75.49%)	–			359 (72.67%)	375 (77.80%)	–		
			G	126 (24.14%)	124 (24.51%)	0.98 (0.74–1.30)	0.891	0.891	135 (27.33%)	107 (22.20%)	1.32 (0.98–1.77)	0.064	0.320
		Codominant	A/A	145 (55.56%)	150 (59.29%)	–			126 (51.01%)	140 (58.09%)	–		
			A/G	106 (40.61%)	82 (32.41%)	1.37 (0.94–2.00)	0.104	0.400	107 (43.32%)	95 (39.42%)	1.00 (0.90–1.90)	0.155	0.554
			G/G	10 (3.83%)	21 (8.30%)	0.45 (0.20–1.01)	0.052	0.371	14 (5.67%)	6 (2.49%)	2.44 (0.90–6.63)	0.081	0.506
		Dominant	A/A	145 (55.56%)	150 (59.29%)	–			126 (51.01%)	140 (58.09%)	–		
			A/G-G/G	116 (44.44%)	103 (40.71%)	1.17 (0.82–1.68)	0.383	0.709	121 (48.99%)	101 (41.91%)	1.38 (0.96–1.98)	0.081	0.579
		Recessive	A/G-A/A	251 (96.17%)	232 (91.70%)	–			233 (94.33%)	235 (97.51%)	–		
			G/G	10 (3.83%)	21 (8.30%)	0.40 (0.18–0.88)	**0.023**	0.383	14 (5.67%)	6 (2.49%)	2.18 (0.81–5.84)	0.123	0.559
		Log-additive	–			0.97 (0.73–1.30)	0.843	0.878			1.39 (1.01–1.91)	**0.041**	0.513

SNP	Model	Allele/Genotype	n (%)	n (%)	OR (95% CI)	p	FDR	n (%)	n (%)	OR (95% CI)	p	FDR
rs719250	Allele	C	373 (72.29%)	359 (70.95%)	—			376 (76.11%)	337 (69.92%)	—		
		T	143 (27.71%)	147 (29.05%)	0.94 (0.71–1.23)	0.635	0.907	118 (23.89%)	145 (30.08%)	0.73 (0.55–0.97)	**0.029**	0.290
	Codominant	C/C	132 (51.16%)	129 (50.99%)	—			147 (59.51%)	121 (50.21%)	—		
		C/T	109 (42.25%)	101 (39.92%)	1.11 (0.76–1.61)	0.589	0.818	82 (33.20%)	95 (39.42%)	0.68 (0.46–1.01)	0.054	0.540
		T/T	17 (6.59%)	23 (9.09%)	0.89 (0.45–1.77)	0.739	0.821	18 (7.29%)	25 (10.37%)	0.54 (0.28–1.05)	0.070	0.583
	Dominant	C/C	132 (51.16%)	129 (50.99%)	—			147 (59.51%)	121 (50.21%)	—		
		C/T-T/T	126 (48.84%)	124 (49.01%)	1.07 (0.75–1.53)	0.709	0.865	100 (40.49%)	120 (49.79%)	0.65 (0.45–0.94)	**0.022**	0.550
	Recessive	C/T-C/C	241 (93.41%)	230 (90.91%)	—			229 (92.71%)	216 (89.63%)	—		
		T/T	17 (6.59%)	23 (9.09%)	0.85 (0.44–1.66)	0.633	0.812	18 (7.29%)	25 (10.37%)	0.63 (0.33–1.20)	0.162	0.506
	Log-additive	—	—	—	1.01 (0.76–1.34)	0.927	0.946	—	—	0.71 (0.54–0.95)	**0.019**	0.937
rs3218896	Allele	T	447 (85.63%)	429 (85.12%)	—			444 (89.88%)	422 (87.55%)	—		
		C	75 (14.37%)	75 (14.88%)	0.96 (0.68–1.36)	0.816	0.907	50 (10.12%)	60 (12.45%)	0.79 (0.53–1.18)	0.251	0.418
	Codominant	T/T	194 (74.33%)	184 (73.02%)	—			202 (81.78%)	185 (76.76%)	—		
		T/C	59 (22.61%)	61 (24.21%)	0.95 (0.62–1.45)	0.813	0.884	40 (16.19%)	52 (21.58%)	0.68 (0.43–1.08)	0.105	0.583
		C/C	8 (3.07%)	7 (2.78%)	1.46 (0.51–4.19)	0.478	0.771	5 (2.02%)	4 (1.66%)	0.80 (0.20–3.17)	0.747	0.934
	Dominant	T/T	194 (74.33%)	184 (73.02%)	—			202 (81.78%)	185 (76.76%)	—		
		T/C-C/C	67 (25.67%)	68 (26.98%)	1.00 (0.67–1.49)	0.990	0.990	45 (18.22%)	56 (23.24%)	0.69 (0.44–1.08)	0.105	0.525
	Recessive	T/T-T/C	253 (96.93%)	245 (97.22%)	—			242 (97.98%)	237 (98.34%)	—		
		C/C	8 (3.07%)	7 (2.78%)	1.48 (0.52–4.22)	0.462	0.770	5 (2.02%)	4 (1.66%)	0.86 (0.22–3.42)	**0.835**	0.928
	Log-additive	—	—	—	1.04 (0.74–1.47)	0.817	0.869	—	—	0.74 (0.50–1.10)	0.134	0.558
rs2072472	Allele	A	404 (77.39%)	407 (80.43%)	—			378 (76.52%)	386 (80.08%)	—		
		G	118 (22.61%)	99 (19.57%)	1.20 (0.89–1.62)	0.232	0.773	116 (23.48%)	96 (19.92%)	1.23 (0.91–1.68)	0.177	0.443
	Codominant	A/A	150 (57.47%)	168 (66.40%)	—			146 (59.11%)	155 (64.32%)	—		
		A/G	104 (39.85%)	71 (28.06%)	1.67 (1.14–2.45)	**0.009**	0.450	86 (34.82%)	76 (31.54%)	1.18 (0.80–1.74)	0.391	0.752
		G/G	7 (2.68%)	14 (5.53%)	0.51 (0.20–1.32)	0.163	0.408	15 (6.07%)	10 (4.15%)	1.77 (0.76–4.09)	0.185	0.544
	Dominant	A/A	150 (57.47%)	168 (66.40%)	—			146 (59.11%)	155 (64.32%)	—		
		A/G-G/G	111 (42.53%)	85 (33.60%)	1.47 (1.02–2.12)	**0.039**	0.390	101 (40.89%)	86 (35.68%)	1.25 (0.86–1.81)	0.238	0.595
	Recessive	A/G-A/A	254 (97.32%)	239 (94.47%)	—			232 (93.93%)	231 (95.85%)	—		
		G/G	7 (2.68%)	14 (5.53%)	0.42 (0.16–1.09)	0.075	0.375	15 (6.07%)	10 (4.15%)	1.67 (0.73–3.82)	0.228	0.633
	Log-additive	—	—	—	1.20 (0.88–1.63)	0.262	0.546	—	—	1.25 (0.92–1.69)	0.155	0.554

Notes: OR (95% CI): Calculated by unconditional logistic regression adjusted by gender and age. p - value was calculated by two -sided χ^2 test. Bold means statistical significance.
Abbreviations: RA, rheumatoid arthritis; IL1R1, interleukin-1 receptor 1; IL1R2, interleukin-1 receptor 2; SNP, single-nucleotide polymorphism; OR, odds ratio; 95% CI, 95% confidence interval; FDR, false discovery rate; freq, frequency.
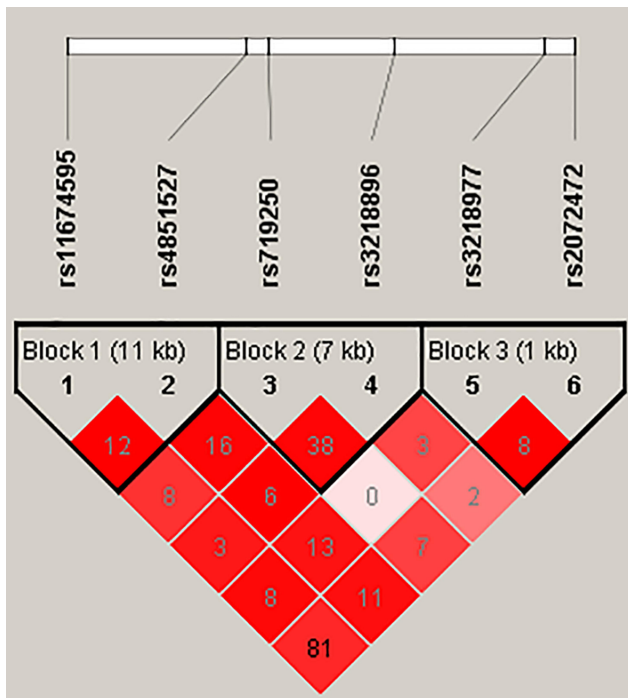
Figure 1 The LD status (r²) of six SNPs of *IL-1R2*. The number in the diamonds is the LOD score of r². The LD value is determined by r² > 0.8 analyzed by Haploview software 4.2. LD haplotype analysis provides the basis for the selection of sites for association analysis.

Chinese Han population in this study. We concluded that rs2072472, rs719250, rs4851527, and rs3218977 in *IL1R2*, and rs10490571, rs3917318, and rs956730 in *IL1R1* were associated with the RA risk.

The *IL1R1* and *IL1R2* genes play a pathogenic role in inflammation and tissue destruction of RA for encoding cytokine receptors (IL-1R1, IL-1R2) for IL-1 which plays the crucial role in the immune pathogenesis of many diseases including RA.[22] More and more studies reported that *IL1R1* and *IL1R2* gene polymorphisms had impacts on inflammation-related diseases.[10,11] *IL1R1* (on chromosome 2q12) is an important mediator involved in many cytokine-induced immune and inflammatory responses,[23] An et al reported that the rs10490571 and rs3917225 in *IL1R1* gene were associated with an increased risk of osteonecrosis of the femoral head in the allele model, codominant model, dominant model, and log-additive model, respectively.[19] Kouhia et al indicated that SNPs (rs956730, rs3917225) in the *IL1R1* gene provided evidence for association with hand osteoarthritis.[24] Another study involving the association between five SNPs polymorphisms in *IL1R1* (rs10490571, rs956730, rs3917225 and rs3917318) and osteoarthritis risk, the result found that rs3917225 in *IL1R1* was associated with increasing the risk of knee OA.[25,26] In our study, rs10490571 (*IL1R1*) was proved to be related to the increased RA risk in males. Besides, we also demonstrated that rs956730 (*IL1R1*) was also associated with the decreased RA susceptibility in females. For rs3917318 (*IL1R1*), it was related to the elevated risk of RA in males, which indicated the unfavorable effects of genetic factors in IL1R1 on RA development. Besides, we did not find the significant association between rs3917225 genetic polymorphisms and RA risk. Contrary to our

haplotypes in RA patients and control groups. The other two haplotypes A$_{rs3218977}$G$_{rs2072472}$ and G$_{rs3218977}$A$_{rs2072472}$ were also obtained; nevertheless, no significant linkage was found ($p > 0.05$) between them and RA risk.

Discussion

We explored the association between the ten SNPs on *IL1R1* and *IL1R2* genes and the RA susceptibility in the

Table 6 The Haplotype Analysis Result of *IL1R1/ IL1R2* Polymorphisms and Their Associations with Rheumatoid Arthritis Risk

Gene	SNP	Haplotype	Frequency		Without Adjusted		Adjusted		FDR Test
			RA Patients	**Control**	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	
IL1R2	rs3218977| rs2072472	AG	0.77	0.80	0.82 (0.66–1.02)	0.073	0.82 (0.66–1.02)	0.073	0.110
IL1R2	rs3218977| rs2072472	GA	0.26	0.23	1.14 (0.93–1.41)	0.218	1.14 (0.92–1.40)	0.225	0.225
IL1R2	rs3218977| rs2072472	AA	0.51	0.57	0.79 (0.65–0.94)	**0.010**	0.79 (0.65–0.94)	**0.010**	**0.030**

Notes: *p*- value was calculated by Wald test with and without adjusted by age and gender. Bold means statistical significance.
Abbreviations: RA, rheumatoid arthritis; *IL1R2*, interleukin-1 receptor 2; SNP, single-nucleotide polymorphism; OR, odds ratio; 95% CI, % confidence interval; FDR, false discovery rate, freq, frequency.

results, Chang et al confirmed that rs3917225(*IL1R1*) was a protective factor of age-related hearing impairment, in which Chronic inflammation is an important factor in Taiwan.[27] The inconsistency may result from the geographical difference.

Unlike the function of *IL1R1, IL1R2* (on chromosome 2q11.2) played an inability to signal after IL-1 binding for lacking an intracellular TIR domain,[28] thus, *IL1R2* suppressing an inflammatory response. Arend et al proved that increased concentrations of soluble forms (sIL-1R2) are found in the synovial fluid.[29] In addition, Xie et al have provided a result that *IL1R2* was a protective factor in IgA nephropathy.[30] And another suggested that IL1R2 was an important regulator of arthritis by acting specifically on macrophages as a decoy receptor for IL-1.[31] However, only several studies based on the *IL1R2* gene polymorphisms were provided. An et al concluded that the rs11674595 in *IL1R2* showed an increased risk of osteonecrosis of the femoral head in the Chinese Han population living in central China (Henan Province of China), yet, they got a negative result in the study of other five SNPs (rs4851527, rs719250, rs3218896, rs3218977, rs2072472).[19] Xia et al also observed a negative result for the impacts of rs4851527(*IL1R2*) and rs2072472 (*IL1R2*) genetic polymorphisms on ankylosing spondylitis risk in Northern Chinese Han population.[32] Nevertheless, for the rs11674595, we got a negative result in the RA risk, also, significant differences were obtained for rs719250, rs3218977, rs2072472, rs3218896 and rs4851527 in RA risk (see in Result part). Lastly, the result of haplotype analysis also concluded that haplotype $A_{rs3218977}A_{rs2072472}$ which was significant with RA risk, which was also proved by False discovery rate (FDR) test. Hence, *IL1R2* gene may play a crucial function in affecting RA. The above inconsistent result may result from the difference of geographical location, population difference lifestyle, and environmental exposure in specific Chinese population. All of candidate SNPs in this study are located in the intron sequence according to the retrieval in the dbSNP database (https://www.ncbi.nlm.nih.gov/snp/), several studies have proved that the intronic SNPs conferred susceptibilities by affecting gene expression,[33] so we suppose that these SNPs might have potential function to IL1R1 and IL1R2 expression level.

Several limitations of this investigation should be acknowledged. Firstly, the limited number of subjects with RA is a limitation of this study. Secondly, the relationship between variables such as clinical indicators and RA risk was not performed because the relevant data is incomplete. Thirdly, all the samples were collected from hospital, type false-positive error for association study may be generated. Fourthly, RA is a heterogeneous disease with many other risk factors, we did not investigate the gene–gene and gene–environment interactions because of the limited data. Last but not least, functional and molecular mechanism research were warrant to do in future. Despite the limitations mentioned above, our present results provided scientific evidence of *IL1R1* and *IL1R2* genes with RA in the future studies.

Conclusions

In conclusion, our study proved that SNPs rs3917318, rs956730, rs10490571 of *IL1R1* and rs3218977, rs719250, rs4851527, rs3218896 and rs2072472 of *IL1R2* were associated with the RA susceptibility in the Chinese Han population, which has not previously been reported and provided new genetic markers for RA susceptibility assessment. We believe that the *IL1R1* and *IL1R2* genes may be a new insight into the treatment of RA. Larger well-designed epidemiological studies with more diverse populations and functional evaluations should be conducted.

Data Sharing Statement

All relevant data are within the manuscript.

Ethical Approval and Consent to Participate

This study was performed in accordance with the World Medical Association Declaration of Helsinki and was approved by the ethics committee of the Affiliated Hospital of Xizang Minzu University (20,190-5). Written informed consent was provided from all of the subjects before participating.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation,

or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. *Lancet*. 2010;376(9746):1094–1108. doi:10.1016/S0140-6736(10)60826-4
2. Lillegraven S, Kvien TK. Measuring disability and quality of life in established rheumatoid arthritis. *Best Pract Res Clin Rheumatol*. 2007;21(5):827–840. doi:10.1016/j.berh.2007.05.004
3. Ngian GS. Rheumatoid arthritis. *Aust Fam Physician*. 2010;39 (9):626–628.
4. Elemam NM, Hannawi S, Maghazachi AA. Role of chemokines and chemokine receptors in rheumatoid arthritis. *ImmunoTargets Ther*. 2020;9:43–56. doi:10.2147/ITT.S243636
5. Perricone C, Ceccarelli F, Valesini G. An overview on the genetic of rheumatoid arthritis: a never-ending story. *Autoimmun Rev*. 2011;10 (10):599–608. doi:10.1016/j.autrev.2011.04.021
6. Deane KD, Demoruelle MK, Kelmenson LB, Kuhn KA, Norris JM, Holers VM. Genetic and environmental risk factors for rheumatoid arthritis. *Best Pract Res Clin Rheumatol*. 2017;31(1):3–18. doi:10.1016/j.berh.2017.08.003
7. Okada Y, Wu D, Trynka G, et al. Genetics of rheumatoid arthritis contributes to biology and drug discovery. *Nature*. 2014;506 (7488):376–381. doi:10.1038/nature12873
8. Leng RX, Di DS, Ni J, et al. Identification of new susceptibility loci associated with rheumatoid arthritis. *Ann Rheum Dis*. 2020;79 (12):1565–1571. doi:10.1136/annrheumdis-2020-217351
9. Raslan HM, Attia HR, Hamed Ibrahim M, et al. Association of anti-cyclic citrullinated peptide antibodies and rheumatoid factor isotypes with HLA-DRB1 shared epitope alleles in Egyptian rheumatoid arthritis patients. *Int J Rheum Dis*. 2020;23(5):647–653. doi:10.1111/1756-185X.13819
10. Latiano A, Palmieri O, Pastorelli L, et al. Associations between genetic polymorphisms in IL-33, IL1R1 and risk for inflammatory bowel disease. *PLoS One*. 2013;8(4):e62144. doi:10.1371/journal.pone.0062144
11. Chen K, Tang Y, Zhao X, Hou C, Li G, Zhang B. Association of IL1R2 rs34043159 with sporadic alzheimer's disease in southern Han Chinese. *Eur J Neurol*. 2020;27(10):1844–1847. doi:10.1111/ene.14319
12. Xu WD, Su LC, He CS, Huang AF. Plasma interleukin-38 in patients with rheumatoid arthritis. *Int Immunopharmacol*. 2018;65:1–7. doi:10.1016/j.intimp.2018.09.028
13. Kragstrup TW, Andersen T, Heftdal LD, et al. The IL-20 cytokine family in rheumatoid arthritis and spondyloarthritis. *Front Immunol*. 2018;9:2226. doi:10.3389/fimmu.2018.02226
14. Mateen S, Zafar A, Moin S, Khan AQ, Zubair S. Understanding the role of cytokines in the pathogenesis of rheumatoid arthritis. *Clin Chim Acta*. 2016;455:161–171. doi:10.1016/j.cca.2016.02.010
15. Schlüter T, Schelmbauer C, Karram K, Mufazalov IA. Regulation of IL-1 signaling by the decoy receptor IL-1R2. *J Mol Med*. 2018;96 (10):983–992. doi:10.1007/s00109-018-1684-z
16. Akdis M, Burgler S, Crameri R, et al. Interleukins, from 1 to 37, and interferon-γ: receptors, functions, and roles in diseases. *J Allergy Clin Immunol*. 2011;127(3):701–21.e1–70.
17. Li G, Cui S, Du J, et al. Association of GALC, ZNF184, IL1R2 and ELOVL7 with parkinson's disease in Southern Chinese. *Front Aging Neurosci*. 2018;10:402. doi:10.3389/fnagi.2018.00402
18. Addobbati C, da Cruz HLA, Adelino JE, et al. Polymorphisms and expression of inflammasome genes are associated with the development and severity of rheumatoid arthritis in Brazilian patients. *Inflamm Res*. 2018;67(3):255–264. doi:10.1007/s00011-017-1119-2
19. An F, Wang J, Gao H, et al. Impact of IL1R1 and IL1R2 gene polymorphisms on risk of osteonecrosis of the femoral head from a case-control study. *Mol Genet Genomic Med*. 2019;7(3):e00557. doi:10.1002/mgg3.557
20. Kamei H, Ishihara Y, Fuma D, et al. Interleukin-1 receptor gene variants are associated with aggressive periodontitis in the Japanese. *Arch Oral Biol*. 2014;59(7):756–763. doi:10.1016/j.archoralbio.2014.04.006
21. Aletaha D, Neogi T, Silman AJ, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis*. 2010;69(9):1580–1588. doi:10.1136/ard.2010.138461
22. Stříž IIL. 1 family cytokines in chronic inflammatory disorders. *Vnitr Lek*. 2019;65(2):81–85.
23. Dinarello CA. Interleukin-1, interleukin-1 receptors and interleukin-1 receptor antagonist. *Int Rev Immunol*. 1998;16(5–6):457–499. doi:10.3109/08830189809043005
24. Näkki A, Kouhia ST, Saarela J, et al. Allelic variants of IL1R1 gene associate with severe hand osteoarthritis. *BMC Med Genet*. 2010;11:50. doi:10.1186/1471-2350-11-50
25. Na Y, Bai R, Zhao Z, et al. IL1R1 gene polymorphisms are associated with knee osteoarthritis risk in the Chinese Han population. *Oncotarget*. 2017;8(3):4228–4233. doi:10.18632/oncotarget.13935
26. Smith AJ, Keen LJ, Billingham MJ, et al. Extended haplotypes and linkage disequilibrium in the IL1R1-IL1A-IL1B-IL1RN gene cluster: association with knee osteoarthritis. *Genes Immun*. 2004;5(6):451–460. doi:10.1038/sj.gene.6364107
27. Chang NC, Yang HL, Dai CY, et al. The association of genetic polymorphisms in interleukin-1 receptors type 1 and type 2 with age-related hearing impairment in a Taiwanese population: a case control study. *J Otolaryngol Head Neck Surg*. 2020;49(1):16.
28. McMahan CJ, Slack JL, Mosley B, et al. A novel IL-1 receptor, cloned from B cells by mammalian expression, is expressed in many cell types. *EMBO J*. 1991;10(10):2821–2832. doi:10.1002/j.1460-2075.1991.tb07831.x
29. Peters VA, Joesting JJ, Freund GG. IL-1 receptor 2 (IL-1R2) and its role in immune regulation. *Brain Behav Immun*. 2013;32:1–8. doi:10.1016/j.bbi.2012.11.006
30. Xie M, Zhang D, Zhang Y, et al. Association of genetic polymorphisms in IL-1R1 and IL-1R2 genes with IgA nephropathy in the Han Chinese population. *Oncotarget*. 2017;8(31):50673–50679. doi:10.18632/oncotarget.16929

31. Shimizu K, Nakajima A, Sudo K, et al. IL-1 receptor type 2 suppresses collagen-induced arthritis by inhibiting IL-1 signal on macrophages. *J Immunol*. 2015;194(7):3156–3168. doi:10.4049/jimmunol.1402155

32. Xia Y, Liu YQ, Chen K, Wang LC, Ma CY, Zhao YR. Association of IL-1R2 genetic polymorphisms with the susceptibility of ankylosing spondylitis in Northern Chinese Han population. *Mod Rheumatol*. 2015;25(6):908–912. doi:10.3109/14397595.2015.1024302

33. Zhao H, Yang W, Qiu R, et al. An intronic variant associated with systemic lupus erythematosus changes the binding affinity of Yinyang1 to downregulate WDFY4. *Genes Immun*. 2012;13 (7):536–542. doi:10.1038/gene.2012.33