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Original Article

Association between interleukin-15 polymorphisms and susceptibility to rheumatoid arthritis in a Chinese population

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Abstract: Background: An association between interleukin-15 (IL-15) polymorphisms and the prevalence of rheumatoid arthritis (RA) in Caucasians has been reported. We hypothesized that IL-15 polymorphisms might also affect RA susceptibility in the Chinese population. Methods: We studied the IL-15 rs10519612 A/C, rs10519613 C/A, rs17007695 T/C, rs17015014 G/C, rs35964658 A/G, and rs2228059 T/G polymorphisms in 615 RA patients and 839 controls in a Chinese population. Genotyping was performed using a custom-by-design 48-Plex SNPscan™ Kit. Results: Our results indicated that the IL-15 rs17007695 polymorphism was associated with RA, and the IL-15 rs17007695 CC genotype decreased the risk of RA. No significant associations were observed between the IL-15 rs10519612 A/C, rs10519613 C/A, rs17015014 G/C, rs35964658 A/G, or rs2228059 T/G polymorphisms and RA. The IL-15 rs17007695 CC genotype was associated with a significantly decreased RA risk, especially among male, rheumatoid factor (RF)-positive, DAS28 ≥3.20, and functional class I/II patients. The IL-15 rs17007695 C allele was also associated with a significantly decreased RA risk among ≥55 year-old patients, CRP-negative, anti-cyclic citrullinated peptide antibody (ACPA)-positive, and erythrocyte sedimentation rate (ESR) <25.00 patients. Conclusions: These findings suggest that IL-15 polymorphisms are associated with RA. Future larger studies of other ethnic populations are required to confirm these findings.

Keywords: Interleukin-15, polymorphism, rheumatoid arthritis, molecular epidemiology

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disorder that affects 0.5-1% of the adult population, and is associated with joint destruction, disability, significant morbidity, and societal costs [1]. The degree of joint destruction varies significantly among patients. Radiographic joint destruction reflects the cumulative burden of inflammation and is considered an objective measure of RA severity. RA is characterized by diverse autoantibody (Ab) production responses, with predominant synovial proliferation, a destruction of the articular cartilage, and activated T-cell and macrophage infiltration in and around the joints [2, 3]. The bone destruction based on the activity of synoviocytes and osteoclasts is mediated by altered cytokine/chemokine pathways [4]. Inflammatory markers and autoantibodies are potent risk factors for joint destruction, accounting for approximately 30% of the variance in joint destruction [5]. Many studies have suggested that genetic factors might influence the severity of joint destruction in RA although its pathophysiological etiology is incompletely understood. To increase our understanding of progression-mediating disease processes, studies have examined genetic variants of interleukin-15 (IL-15), one of the relevant cytokines, which could be a predisposing factor for a severe outcome of RA.

Cytokines are important components of the immune system, and they integrate the immunoregulatory pathways that ultimately lead to various autoimmune diseases, including RA. IL-15 is an important T cell cytokine; it plays a

Table 1. Patient demographics and risk factors in rheumatoid arthritis, all subjects

Variable*	Cases (n = 615)	Controls (n = 839)	*P*
Age (years)	54.51 (±15.19)	55.44 (±10.80)	0.170
Female/male	472/143	633/206	0.566
Age at onset, years, mean ± SD	46.06 (±13.24)	-	-
Disease duration, years, mean ± SD	8.52 (±9.24)	-	-
Treatment duration, years, mean ± SD	7.30 (±7.91)	-	-
RF-positive, no. (%)	486 (79.02%)	-	-
ACPA positive, no. (%)	321 (52.20%)	-	-
CRP-positive, no. (%)	165 (26.83%)	-	-
ESR, mm/h	35.79 (±28.70)	-	-
DAS28	4.46 (±1.50)	-	-
Functional class, no. (%)		-	-
I	78 (12.68%)	-	-
II	281 (45.69%)	-	-
III	220 (35.77%)	-	-
IV	36 (5.85%)	-	-

*RF: Rheumatoid factor; ACPA: Anti-cyclic citrullinated peptide antibodies; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; DAS28: RA disease activity score.

role in RA and shares structural similarity to interleukin-2 (IL-2) [6]. The receptor for these two cytokines is composed of IL-12/IL-15 receptor beta chains (Cluster of differentiation-122, CD-122) and a common gamma chain (Cluster of differentiation-132, CD-132). Secreted by mononuclear phagocytes, it participates in the activation and proliferation of T and natural killer cells [7]. IL-15 expressed in the synovial membrane and synovial T cells of RA patients with active RA [8]. Increased IL-15 levels may lead to the recruitment and activation of synovial T-cells, which leads to the differentiation of osteoclast progenitors, and toward bone deterioration [6, 9]. The potential therapeutic role of IL-15 in RA has also been reported. IL-15 inhibitors suppress the development of collagen-induced arthritis (CIA), while a human monoclonal antibody targeting IL-15 (HuMax-IL-15) has beneficial effects on RA in vitro and in vivo [10, 11]. Consequently, IL-15 is a gene of interest in RA.

Functional variation in the IL-15 gene may contribute to the etiology of RA because the expression of IL-15 is regulated at both the transcriptional and post-transcriptional levels, which leads to variation in the levels in the body and promotes or protects against RA in different ethnic groups. To investigate this hypothesis, we conducted a current hospital-based case-control genotype study of 615 RA patients and 839 controls.

Patients and methods

Study subjects

This work involved a case-control study, approved by the Ethics Committee of Nanjing Medical University (Nanjing, China). In total, 615 RA patients and 839 controls were included. The patients included in the case group were clinically diagnosed using the criteria for RA set by the American College of Rheumatology classification in 1987 [12]. The controls were patients without RA or other genetic diseases, matched for age (±5 years) and gender, who were recruited from the same institutions during the same time period; most of them had been admitted due to trauma. All of the included patients and controls were consecutively recruited from Changzhou First Hospital, Changzhou Second Hospital-Affiliated Hospital of Nanjing Medical University, and Changzhou Traditional Chinese Medical Hospital, between September 2010 and October 2013. All of the included patients provided written informed consent prior to participation. Then each patient was interviewed by trained personnel using a pre-tested questionnaire regarding his or her demographics and related risk factors

Table 2. Logistic regression analysis of associations between *IL-15* rs10519612 A/C, rs10519613 C/A, rs17007695 T/C, rs17015014 G/C, rs35964658 A/G, and rs2228059 T/G polymorphisms and risk of rheumatoid arthritis

Genotype	Cases* (n = 615)		Controls (n = 839)		OR (95% CI)	*P*
	n	%	n	%		
rs10519612 A/C						
AC vs. AA	306/192	52.3/32.8	417/256	50.9/44.1	0.98 (0.77-1.24)	0.858
CC vs. AA	87/192	14.9/32.8	147/256	25.3/44.1	0.79 (0.57-1.09)	0.153
CC vs. AC vs. AA						0.312
AC+CC vs. AA	393/192	67.2/32.8	564/256	68.8/44.1	0.93 (0.74-1.17)	0.525
CC vs. AA+AC	87/498	14.9/85.1	147/673	25.3/82.1	0.80 (0.60-1.07)	0.130
C allele	480	82.1	711	86.7		
rs10519613 C/A						
CA vs. CC	320/195	53.0/32.3	429/256	51.6/30.8	0.98 (0.77-1.24)	0.862
AA vs. CC	89/195	14.7/32.3	146/256	17.6/30.8	0.80 (0.58-1.11)	0.176
AA vs. CA vs. CC						0.353
CA+AA vs. CC	409/195	67.7/32.3	575/256	69.2/30.8	0.93 (0.75-1.17)	0.551
AA vs. CC+CA	89/515	14.7/85.3	146/685	17.6/82.4	0.81 (0.61-1.08)	0.153
A allele	498	82.5	721	86.8		
rs17007695 T/C						
TC vs. TT	303/212	50.6/35.4	405/274	48.8/33.0	0.97 (0.77-1.22)	0.777
CC vs. TT	84/212	14.0/35.4	151/274	18.2/33.0	**0.72 (0.52-0.99)**	**0.044**
CC vs. TC vs. TT						0.106
TC+CC vs. TT	387/212	64.6/35.4	556/274	67.0/33.0	0.90 (0.72-1.12)	0.349
CC vs. TT+TC	84/515	14.0/86.0	151/679	18.2/81.8	**0.73 (0.55-0.98)**	**0.036**
C allele	471	78.6	707	85.2		
rs17015014 G/C						
GC vs. GG	279/170	46.9/28.6	403/230	48.7/27.8	0.94 (0.73-1.20)	0.609
CC vs. GG	146/170	24.5/28.6	194/230	23.5/27.8	1.02 (0.76-1.36)	0.903
CC vs. GC vs. GG						0.785
GC+CC vs. GG	425/170	71.4/28.6	597/230	72.2/27.8	0.96 (0.76-1.22)	0.753
CC vs. GG+GC	146/449	24.5/75.5	194/633	23.5/76.5	1.06 (0.83-1.36)	0.637
C allele	571	96.0	791	95.6		
rs35964658 A/G						
AG vs. AA	315/182	52.7/30.4	429/235	51.9/28.4	0.95 (0.74-1.21)	0.666
GG vs. AA	101/182	16.9/30.4	163/235	19.7/28.4	0.80 (0.58-1.10)	0.165
GG vs. AG vs. AA						0.365
AG+GG vs. AA	416/182	70.0/30.4	592/235	71.6/28.4	0.91 (0.72-1.14)	0.409
GG vs. AA+AG	101/497	16.9/83.1	163/664	19.7/80.3	0.83 (0.63-1.09)	0.177
G allele	517	86.5	755	91.3		
rs2228059 T/G						
TG vs. TT	275/208	46.2/35.0	387/300	47.2/36.6	1.03 (0.81-1.30)	0.837
GG vs. TT	112/208	18.8/35.0	133/300	16.2/36.6	1.22 (0.89-1.65)	0.215
GG vs. TG vs. TT						0.433
TG+GG vs. TT	387/208	65.0/35.0	520/300	63.4/36.6	1.07 (0.86-1.34)	0.530
GG vs. TT+TG	112/483	18.8/81.2	133/687	16.2/83.8	1.20 (0.91-1.58)	0.202
G allele	499	83.9	653	79.6		

*The genotyping was successful in: 585 cases and 820 controls for rs10519612 A/C; 604 cases and 831 controls for rs10519613 C/A; 599 cases and 830 controls for rs17007695 T/C; 595 cases and 827 controls for rs17015014 G/C; 598 cases and 827 controls for rs35964658 A/G; 595 cases and 820 controls for rs2228059 T/G. Bold values are statistically significant ($P<0.05$).

Table 3. Stratified analyses between *IL-15* rs17007695 T/C polymorphism and the risk of rheumatoid arthritis

Variable	*IL-15* rs17007695 T/C (case/control)				OR (95% CI); *P*			
	TT	TC	CC	TC+CC	TC versus TT	CC versus TT	TC+CC versus TT	CC versus TC+TT
Sex								
Male	46/68	76/92	16/42	92/134	1.22 (0.75-1.98); 0.417	0.56 (0.28-1.12); 0.102	1.02 (0.64-1.61); 0.950	**0.50 (0.27-0.93); 0.029**
Female	166/206	227/313	68/109	295/422	0.90 (0.69-1.18); 0.438	0.77 (0.54-1.12); 0.170	0.87 (0.67-1.12); 0.271	0.82 (0.59-1.15); 0.250
Age (years)								
<55	105/133	127/162	47/66	174/228	0.99 (0.70-1.40); 0.968	0.90 (0.57-1.42); 0.656	0.97 (0.70-1.34); 0.837	0.91 (0.60-1.37); 0.637
≥55	107/141	176/243	37/85	213/328	0.95 (0.70-1.31); 0.773	**0.57 (0.36-0.91); 0.018**	0.86 (0.63-1.16); 0.316	**0.59 (0.39-0.90); 0.013**
CRP status								
Negative	96/274	130/405	31/151	161/556	0.92 (0.68-1.24); 0.574	**0.59 (0.37-0.92); 0.020**	0.83 (0.62-1.11); 0.200	**0.62 (0.41-0.93); 0.022**
Positive	116/274	173/405	53/151	226/556	1.01 (0.76-1.34); 0.950	0.83 (0.57-1.21); 0.335	0.96 (0.74-1.25); 0.764	0.83 (0.59-1.16); 0.269
ACPA status								
Negative	116/274	134/405	36/151	170/556	0.78 (0.58-1.05); 0.098	**0.56 (0.37-0.86); 0.008**	**0.72 (0.55-0.95); 0.021**	**0.65 (0.44-0.96); 0.030**
Positive	96/274	169/405	48/151	217/556	1.19 (0.89-1.60); 0.243	0.91 (0.61-1.35); 0.633	1.11 (0.84-1.48); 0.451	0.82 (0.57-1.16); 0.257
RF status								
Negative	45/274	67/405	13/151	198/556	1.01 (0.67-1.51); 0.972	0.52 (0.27-1.00); 0.051	0.88 (0.59-1.30); 0.509	**0.52 (0.29-0.95); 0.034**
Positive	167/274	236/405	71/151	307/556	0.96 (0.74-1.23); 0.725	0.77 (0.55-1.09); 0.136	0.91 (0.71-1.15); 0.415	0.79 (0.58-1.08); 0.138
ESR (mm/h)								
<25.00	112/274	129/405	30/151	159/556	0.78 (0.58-1.05); 0.099	**0.49 (0.31-0.76); 0.002**	**0.70 (0.53-0.93); 0.013**	**0.56 (0.37-0.85); 0.007**
≥25.00	100/274	174/405	54/151	228/556	1.18 (0.88-1.57); 0.270	0.98 (0.67-1.44); 0.918	1.12 (0.85-1.48); 0.408	0.89 (0.63-1.25); 0.487
DAS28								
<3.20	54/274	58/405	19/151	77/556	0.73 (0.49-1.09); 0.119	0.64 (0.37-1.12); 0.116	0.70 (0.48-1.02); 0.066	0.76 (0.46-1.28); 0.305
≥3.20	158/274	245/405	65/151	310/556	1.05 (0.82-1.35); 0.709	0.75 (0.53-1.06); 0.102	0.97 (0.76-1.23); 0.783	**0.73 (0.53-1.00); 0.046**
Functional class								
I+II	123/274	184/405	46/151	230/556	1.01 (0.77-1.33); 0.932	0.68 (0.46-1.01); 0.053	0.92 (0.71-1.20); 0.542	**0.67 (0.47-0.96); 0.030**
III+IV	89/274	119/405	38/151	157/556	0.91 (0.66-1.24); 0.532	0.78 (0.51-1.19); 0.243	0.87 (0.65-1.17); 0.356	0.82 (0.56-1.21); 0.321

Bold values are statistically significant ($P<0.05$).

for RA. After the interview, 2 mL peripheral blood was collected from each subject.

Blood samples were collected using vacutainers and transferred to test tubes containing ethylenediaminetetra-acetic acid (EDTA) using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). Single-nucleotide polymorphism (SNP) genotyping was performed using a custom-by-design 48-Plex SNP scan™ Kit (Genesky Biotechnologies Inc., Shanghai, China) as described previously [13].

Statistical analyses

Differences in age between cases and controls were evaluated using Student's t-test, and differences in gender were evaluated using the chi-square test (**Table 1**; SPSS software, version 17.0). The associations between the six IL-15 genotypes (IL-15 rs10519612 A/C, rs10519613 C/A, rs17007695 T/C, rs17015014 G/C, rs35964658 A/G, and rs2228059 T/G polymorphisms) and RA risk were estimated by computing odds ratios (ORs) and 95% confidence intervals (CIs) using logistic regression analysis (**Table 2**; SAS software, version 9.1.3; SAS Institute, Cary, NC, USA). Stratified analyses, including sex, age, CRP status, ACPA status, RF status, ESR, DAS28, and functional class, between IL-15 rs17007695 T/C polymorphism and the risk of RA, were also performed by computing odds ratios (ORs) and 95% confidence intervals (CIs) using logistic regression analysis (**Table 3**; SAS software). *P*-values of less than 0.05 were considered to indicate significance.

Results

Characteristics of the study population

The demographic and clinical characteristics of the subjects. The mean age of patients in the case group was 54.51±15.19 years (range from 19 to 90 years) versus 55.44±10.80 years (range from 20 to 88 years) for the controls. Subjects were adequately matched for age and sex (P = 0.170 and 0.566, respectively). The genotype distributions of *IL-15* rs10519612 A/C, rs10519613 C/A, rs17007695 T/C, rs17015014 G/C, rs35964658 A/G, and rs2228059 T/G for all subjects are presented in **Table 2**. The minor allele frequency (MAF) in our controls was similar to the MAF for Chinese individuals in the database for all six SNPs.

Associations between IL-15 rs10519612 A/C, rs10519613 C/A, rs17007695 T/C, rs17015014 G/C, rs35964658 A/G, and rs2228059 T/G polymorphisms and RA risk

Logistic regression analysis revealed that a significantly decreased RA susceptibility was associated with the IL-15 rs17007695 CC genotype (CC vs. TT: OR, 0.72; 95% CI, 0.52-0.99, P = 0.044; CC vs. TT+TC: OR, 0.73; 95% CI, 0.55-0.98, P = 0.036). However, the IL-15 rs10519612 A/C, rs10519613 C/A, rs17015014 G/C, rs35964658 A/G, and rs2228059 T/G polymorphisms were not associated with RA risk (**Table 2**).

Stratification analyses of the IL-15 rs17007695 T/C polymorphism and RA risk

Stratification analysis was performed according to sex, age, and C-reactive protein (CRP) status, anti-cyclic citrullinated peptide antibody (ACPA), rheumatoid factor (RF) status, erythrocyte sedimentation rate (ESR) status, disease activity score in 28 joints (DAS28) status, and functional class status (**Table 3**). The IL-15 rs17007695 CC genotype was associated with a significantly decreased RA risk, especially among male patients (CC vs. TC+TT, OR, 0.5; 95% CI, 0.27-0.93, P = 0.029), RF-positive patients (CC vs. TC+TT, OR, 0.52; 95% CI, 0.29-0.95, P = 0.034), DAS28 ≥3.20 patients (CC vs. TC+TT, OR, 0.73; 95% CI, 0.53-1.00, P = 0.046), and functional class I/II patients (CC vs. TC+TT, OR, 0.67; 95% CI, 0.47-0.96, P = 0.030).

The IL-15 rs17007695 C allele was associated with a significantly decreased RA risk among patients ≥55 years old (CC vs. TT, OR, 0.57; 95% CI, 0.36-0.91, P = 0.018; CC vs. TC+TT, OR, 0.59; 95% CI, 0.39-0.90, P = 0.013), CRP-negative patients (CC vs. TT, OR, 0.59; 95% CI, 0.37-0.92, P = 0.020; CC vs. TC+TT, OR, 0.62; 95% CI, 0.41-0.93, P = 0.022), ACPA-positive patients (CC vs. TT, OR, 0.56; 95% CI, 0.37-0.86, P = 0.008; CC vs. TC+TT, OR, 0.65; 95% CI, 0.44-0.96, P = 0.030), and ESR <25.00 patients (CC vs. TT, OR, 0.49; 95% CI, 0.31-0.76, P = 0.002; CC vs. TC+TT, OR, 0.56; 95% CI, 0.37-0.85, P = 0.007).

Discussion

IL-15 is a proinflammatory cytokine that is markedly overexpressed in patients with RA. The expression of this cytokine is regulated at both pre- and post-transcriptional levels. Overproduction of IL-15 is thought to induce T cell activation and proliferation, possibly contributing to the pathogenesis of RA [14, 15]. We performed a candidate gene study to investigate the association between IL-15 genetic variants and RA. Ultimately, an analysis of the radiological data of all 1454 subjects was performed. Only one SNP, rs17007695, had a protective effect on RA patients. We also found a significant association between the IL-15 rs17007695 polymorphism and RA factors, such as gender, age, and clinical correlation indexes.

IL-15 plays a pivotal role in the life and death of natural killer (NK) and CD8 memory T cells, and it was first described as a T cell activating factor belonging to the 4α helix cytokine super family with structural homology to IL-2 [16]. IL-15 signals through a heterotrimeric receptor involving the common gamma chain (γc) shared with IL-2, IL-4, IL-7, IL-9, and IL-21, IL-2/IL-15 receptor β (IL-15Rβ) shared with IL-2 and a private IL-15Rα subunit, which are coordinately expressed by IFN- or CD40 ligand-stimulated dendritic cells. Cell surface IL-15Rα presents IL-15 in trans to cells that express IL-2/IL-15Rβ and γc [17]. IL-15 is also an inflammatory cytokine, with pleiotropic and physiological activities in both the innate and acquired immune responses, thereby playing a role in autoimmune diseases. All of these functions are mediated through a widely distributed heterodimeric receptor (IL-15R) consisting of a β-chain shared with IL-2, a common γ-chain, and a unique α-chain [16]. These insights provide the scientific basis for clinical strategies directed toward reducing the action of IL-15. Moreover, IL-15 exerts a predominantly proinflammatory effect in diseases such as allergy, transplant rejection, and autoimmune disorders [18]. Dysregulated IL-15 expression has been demonstrated in patients with RA, inflammatory bowel disease, celiac disease, psoriasis, and alopecia areata [17].

Many RA susceptibility genes have been identified in various populations, including IL-15 polymorphisms. The associations between IL-15 polymorphisms and RA were first related to increased circulating levels of IL-15, but did not appear to play a major role in RA genetic predisposition in a Spanish Caucasian population according to Rueda et al. [19]. Similarly, Kiani et al. reported that the rs4956403 and rs3806798 SNPs of the IL-15 gene were not associated with RA in Pakistani patients [20]. Recently, an association among IL-15 polymorphisms and RA susceptibility has been reported. Knevel et al. reported that genetic variants in IL-15 are associated with the progression of joint destruction in RA in Caucasians [21], However, this phenomenon was not observed in Japanese patients with RA [22]. Recent research suggested that the polymorphisms in the 3'untranslated region affect circulating IL-15 levels and the contribution of IL-15 to immunoglobulin synthesis. Goldbergova et al. presented an association of IL-15 gene polymorphisms with RFs, including RF subtypes (RF, IgG, IgA) underlined by a relationship between increased IL-15 levels in the circulation and RFs in Caucasians [23]. Our results demonstrated a significant association of the rs17007695 polymorphism with RA in patients of Chinese origin, while no associations for the other five SNPs were found. The CC genotype of the rs17007695 SNP had a possible protective effect in RA. Further subgroup analyses showed significant associations with sex, age, and clinical indexes, including CRP, ACPA, RF, ESR, DAS28, and functional class, in RA patients compared with controls. The subgroup analyses showed that male and older patients carried higher proportions of the CC gene polymorphism and that the protective effect of the CC genotype was due to the low expressions of CRP, ACPA, RF, and ESR, as well as the low proportion of patients with functional class I+II. The patients with the CC genotype had less disease activity as measured with the DAS28 score. Our findings differed from reported findings, and the six SNPs investigated in our study have not been reported elsewhere. A possible explanation for our results may lie in the larger sample sizes, or in differences between populations.

The study's limitations include sample selection without randomization and the studied RA population size. Patient outcomes could not be observed because no follow-up data were collected. Based on functional considerations, the

polymorphisms investigated may not provide a comprehensive view of the genetic variability of IL-15, necessitating further fine-mapping studies. Finally, the sample size of this study was not sufficiently large to evaluate the low penetrance effect of the SNPs.

In summary, this study showed that the rs17007695 polymorphism of IL-15 was associated with RA in Chinese patients, and supported the protective effect of the CC genotype in male and older (age ≥55) patients. No significant association was observed between the other SNPs and RA. It may be worth investigating genes coding other molecules in the IL-15 signaling pathway as novel candidate genes. Larger well-designed studies are needed to obtain more robust results.

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Disclosure of conflict of interest

None.

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