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Correlation between *IL-3* and *IL-13* gene polymorphisms in Chinese patients and rheumatoid arthritis

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ABSTRACT. The aim of this study was to examine the association between polymorphisms in the interleukin-3 and -13 (*IL-3* and *IL-13*) genes and rheumatoid arthritis (RA). In this hospital-based case-control study, we analyzed the *IL-3* rs2073506 G/A, *IL-3* rs40401 C/T, and *IL-13* rs1800925 C/T polymorphisms in 615 RA patients and 839 controls from a Chinese Han population. Genotyping was performed using a custom-by-design 48-Plex single nucleotide polymorphism scan™ kit. Our results indicated that the *IL-3* rs2073506 G/A, *IL-3* rs40401 C/T, and *IL-13* rs1800925 C/T polymorphisms were not associated with RA. However, stratification analyses suggested that the *IL-13* rs1800925 CT and CT/CC genotypes increased the risk of RA in patients with erythrocyte sedimentation rate (ESR) <25.00. To sum up, these findings suggest that the *IL-13* rs1800925 C/T polymorphism may be associated with increased risk of RA in ESR <25.00 patients. Future studies with

larger sample sizes and inclusion of other ethnic populations must be conducted to confirm the findings of this study.

Key words: IL-3; IL-13; Single nucleotide polymorphism; Rheumatoid arthritis

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease that primarily affects the joints of the hands and feet. The pathogenesis of RA is still quite unclear; however, is believed to be multifactorial, involving both genetic and environmental factors (Kalinina et al., 2014). Genetic studies have indicated that the susceptibility to RA has a genetic component (Choi et al., 2006). The genes coding for several cytokines are believed to be associated with autoimmune disease (Seldin et al., 1999; Qu et al., 2015), while other such genes may not be correlated with it (Zhu et al., 2013; Ye et al., 2015). Our previous studies have led to the discovery of several single nucleotide polymorphisms (SNPs) in genes coding for various cytokines, including interleukin-10 (*IL-10*), *IL-12*, and *IL-17A*, that are correlated with RA (Ge et al., 2015; Shen et al., 2015a,b).

RA progression is significantly associated with immune mechanisms and components that affect the immune system, including cytokines, inflammatory mediators produced mainly by immune cells, and other cells and tissues. Graves' disease (GD) is another common autoimmune disease. Genome-wide analyses have revealed a correlation between GD and chromosome 5q31-q33, which encodes a number of cytokines and inflammatory mediators, including *IL-3*, *IL-4*, *IL-5*, *IL-9*, and *IL-13*. Particularly, polymorphisms in the *IL-3* and *IL-13* genes have been associated with GD (Hiromatsu et al., 2005; Simmonds et al., 2010). Moreover, chromosome 5q31-q33 has also been identified as a susceptibility locus for the development of asthma or atopic dermatitis (Renauld, 2001). It is well understood that some groups of genetic diseases may have a similar pathophysiology. Autoimmune diseases such as GD, systemic lupus erythematosus (SLE), and RA have been shown to possess some common genetic linkages (Becker et al., 1998; Cookson, 1999). This has led to the hypothesis that various inflammatory diseases, such as RA and GD, may have common underlying genes. The correlation between GD and polymorphisms in the *IL-3* and *IL-13* genes led to the hypothesis that functional SNPs in the *IL-3* (rs2073506 G/A and rs40401 C/T) and *IL-13* (rs1800925 C/T) genes may also be associated with the risk of RA. Therefore, we genotyped the three SNPs (*IL-3* rs2073506 G/A, *IL-3* rs40401 C/T, and *IL-13*rs1800925 C/T) in 615 RA patients and 839 controls in a Chinese Han population.

PATIENTS AND METHODS

Subjects

The study protocol was approved by the Ethics Committee of Nanjing Medical University (Nanjing, China). Written informed consent was obtained from all included patients and control subjects. Six hundred and fifteen RA patients who fulfilled the criteria for RA set by the American College of Rheumatology classification in 1987 (Arnett et al., 1988) were recruited from the Changzhou Second Hospital-Affiliated Hospital of Nanjing Medical

University (Changzhou, China), the Changzhou First Hospital (Changzhou, China), and the Changzhou Traditional Chinese Medical Hospital (Changzhou, China) between September 2010 and October 2013. The controls were age- (±5 years) and gender-matched subjects without RA recruited from the same institutions during the same time period; most of the controls were admitted to the hospitals for trauma treatment.

Each patient was interviewed by trained personnel using a pre-designed questionnaire, in order to obtain information regarding the patient demographics and risk factors 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 ethylenediaminetetraacetic acid (EDTA), using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). SNP genotyping was performed using a custom-by-design 48-Plex SNP scan™ kit (Genesky Biotechnologies Inc., Shanghai, China), as described in a previous study (Zheng et al., 2013).

Statistical analysis

Differences in demographics, variables, and genotypes of the *IL-3* rs2073506 G/A, *IL-3* rs40401 C/T, and *IL-13* rs1800925 C/T polymorphic variants were evaluated using a chi-squared test. The associations between the *IL-3* rs2073506 G/A, *IL-3* rs40401 C/T, and *IL-13* rs1800925 C/T genotypes and risk of RA were estimated by computing the odds ratios (ORs) with their corresponding 95% confidence intervals (CIs) using logistic regression analyses, and by using crude ORs. The observed genotype frequencies were compared against the expected frequencies among controls by testing for conformance with the Hardy-Weinberg equilibrium (HWE) using a goodness-of-fit chi-squared test. All statistical analyses were performed using the SAS software (v.9.1.3; SAS Institute, Cary, NC, USA).

RESULTS

Characteristics of the study population

The demographic and clinical characteristics of all subjects are summarized in Table 1. The subjects were adequately matched for age and gender (P = 0.170 and 0.566, respectively) between RA patients and control subjects. Genotyping for the *IL-3* rs2073506 G/A and *IL-3* rs40401 C/T polymorphisms were successful in 603 (98.0%) RA patients and 832 (99.2%) controls and 592 (96.3%) RA patients and 820 (97.7%) controls, respectively; on the other hand, genotyping for *IL-13* rs1800925 C/T was successful in 595 (96.7%) RA patients and 828 (98.7%) controls (Table 2). The observed genotype frequencies for the *IL-3* rs2073506 G/A (P = 0.284), *IL-3* rs40401 C/T (P = 0.364), *IL-13* rs1800925 C/T (P = 0.612) polymorphisms in the control subjects were in HWE.

Associations between the *IL-3* rs2073506 G/A, *IL-3* rs40401 C/T, and *IL-13*rs1800925 C/T polymorphisms and risk of RA

The genotype distributions of the *IL-3* rs2073506 G/A, *IL-3* rs40401 C/T, and *IL-13* rs1800925 C/T polymorphisms did not differ significantly between the cases and controls. Logistic regression analyses revealed that the *IL-3* rs2073506 G/A, *IL-3* rs40401 C/T, and *IL-13* rs1800925 C/T polymorphisms were not associated with risk of RA (Table 2). The data

were stratified according to age, gender, rheumatoid factor (RF) status, disease activity score in 28 joints (DAS28), C-reactive protein (CRP) status, erythrocyte sedimentation rate (ESR) status, functional class, and anti-cyclic citrullinated peptide antibody (ACPA) status (Table 3). The *IL-13* rs1800925 CT and CT/CC genotypes were associated with increased RA risk when the *IL-13* rs1800925 CC homozygote genotype was used as the reference group (CT *vs* CC: 1.46 (1.08-1.97); P = 0.014 and CT+CC *vs* CC: 1.46 (1.09-1.96); P = 0.011) among patients with ESR < 25.00 (Table 3). We did not identify any correlation between the *IL-13* rs1800925 C/T polymorphism and the gender, age, CRP status, ACPA status, RF status, and functional class (Table 3).

Table 1. Patient demographics and risk factors for rheumatoid arthritis in all cases and controls.

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), means ± SD	46.06 (± 13.24)	-	-
Disease duration (years), means ± SD	8.52 (± 9.24)	-	-
Treatment duration (years), means ± SD	7.30 (±7.91)	-	-
RF-positive (%)	486 (79.02%)	-	-
ACPA positive (%)	321 (52.20%)	-	-
CRP-positive (%)	165 (26.83%)	-	-
ESR mm/h	35.79 (±28.70)	-	-
DAS28	4.46 (±1.50)	-	-
Functional class (%)		-	-
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 = disease activity score of 28 joints.

Table 2. Logistic regression analysis of associations between *IL-3* rs2073506 G/A, *IL-3* rs40401 C/T, and *IL-13* rs1800925 C/T polymorphisms and risk of rheumatoid arthritis.

Genotype	Cases* (N = 615)		Controls (N = 839)		OR (95%CI)	P
	N	%	N	%		
rs2073506 G/A						
GA *vs* GG	184/405	30.5/67.2	221/584	26.6/70.2	0.98 (0.77-1.24)	0.858
AA *vs* GG	14/405	2.3/67.2	27/584	3.2/70.2	0.79 (0.57-1.09)	0.153
AA *vs* GA *vs* GG						0.312
GA+AA *vs* GG	198/405	32.8/67.2	248/584	29.8/70.2	1.19 (0.94-1.50)	0.141
AA *vs* GG+GA	14/589	2.3/97.6	27/805	3.2/96.8	0.81 (0.60-1.09)	0.165
A allele	212	17.6	275	16.4		
rs40401 C/T						
CT *vs* CC	312/135	52.7/22.8	397/214	48.4/26.1	1.13 (0.88-1.47)	0.345
TT *vs* CC	145/135	24.5/22.8	209/214	25.5/26.1	0.91 (0.67-1.23)	0.537
TT *vs* CT *vs* CC						0.234
CT+TT *vs* CC	457/135	77.2/22.8	606/214	73.9/26.1	1.05 (0.83-1.35)	0.671
TT *vs* CC+CT	145/447	24.5/75.5	209/611	25.5/74.5	0.84 (0.65-1.07)	0.157
T allele	602	50.8	815	49.7		
rs1800925 C/T						
CT *vs* CC	171/410	28.7/68.9	211/601	25.5/72.6	1.12 (0.94-1.51)	0.155
TT *vs* CC	14/410	2.4/68.9	16/601	2.0/72.6	1.28 (0.62-2.66)	0.503
TT *vs* CT *vs* CC						0.314
CT+TT *vs* CC	185/410	31.1/68.9	228/601	27.5/72.6	1.20 (0.95-1.51)	0.132
TT *vs* CC+CT	14/581	2.4/97.6	16/812	2.0/98.1	1.22 (0.59-2.53)	0.587
T allele	199	33.4	243	29.3		

*Genotyping was successful in 603 cases and 832 controls for *IL-3* rs2073506 G/A, 592 cases and 820 controls for *IL-3* rs40401 C/T, and 595 cases and 828 controls for *IL-13* rs1800925 C/T.

Table 3. Stratified analyses between *IL-13* rs1800925 C/T polymorphisms and the risk of rheumatoid arthritis.

Variable	*IL-13* rs1800935 C/T (case/control)				OR (95%CI); P		
	CC	CT	TT	CT+TT	CT versus CC	TT versus CC	CT+CC versus CC	TT versus CT+CC
Gender								
Male	91/132	45/65	4/5	49/70	1.00 (0.63-1.60); 0.986	1.16 (0.30-4.44); 0.828	1.02 (0.65-1.60); 0.947	1.16 (0.31-4.39); 0.828
Female	319/469	126/146	10/11	136/157	1.27 (0.96-1.68); 0.093	1.34 (0.56-3.18); 0.513	1.27 (0.97-1.67); 0.079	1.26 (0.53-2.98); 0.605
Age (years)								
<55	184/261	84/93	6/5	90/98	1.28 (0.90-1.82); 0.166	1.70 (0.51-5.66); 0.386	1.30 (0.93-1.84); 0.131	1.59 (0.48-5.25); 0.451
≥55	226/340	87/118	8/11	95/129	1.11 (0.80-1.53); 0.531	1.09 (0.43-2.76); 0.849	1.11 (0.81-1.52); 0.522	1.07 (0.42-2.68); 0.894
CRP status								
Negative	170/601	74/211	7/16	81/227	1.24 (0.91-1.70); 0.181	1.55 (0.63-3.82); 0.344	1.26 (0.93-1.71); 0.136	1.46 (0.59-3.58); 0.413
Positive	240/601	97/211	7/16	104/227	1.15 (0.87-1.53); 0.330	1.10 (0.45-2.70); 0.843	01.15 (0.87-1.51); 0.330	1.06 (0.43-2.59); 0.907
ACPA status								
Negative	192/601	78/211	10/16	88/227	1.16 (0.85-1.57); 0.350	1.96 (0.87-4.39); 0.103	1.21 (0.90-1.63); 0.199	1.88 (0.84-4.19); 0.123
Positive	218/601	93/211	4/16	97/227	1.22 (0.91-1.62); 0.186	0.69 (0.23-2.09); 0.510	1.18 (0.89-1.57); 0.258	0.65 (0.22-1.97); 0.449
RF status								
Negative	90/601	32/211	1/16	33/227	1.01 (0.66-1.56); 0.954	0.42 (0.06-3.19); 0.400	0.97 (0.63-1.49); 0.892	0.42 (0.06-3.17); 0.397
Positive	320/601	139/211	13/16	152/227	1.24 (0.96-1.59); 0.100	1.53 (0.73-3.21); 0.266	1.26 (0.98-1.61); 0.068	1.44 (0.69-3.02); 0.337
ESR (mm/h)								
<25.00	172/601	88/211	7/16	95/227	**1.46 (1.08-1.97); 0.014**	1.53 (0.621-3.78); 0.358	**1.46 (1.09-1.96); 0.011**	1.37 (0.56-3.36); 0.496
≥25.00	238/601	83/211	7/16	90/227	0.99 (0.74-1.33); 0.965	1.11 (0.45-2.72); 0.828	1.00 (0.75-1.33); 0.994	1.11 (0.45-2.72); 0.825
DAS28								
<3.20	83/601	41/211	5/16	46/227	1.41 (0.94-2.11); 0.099	2.26 (0.81-6.34); 0.120	1.47 (0.998-2.17); 0.055	2.05 (0.74-5.69); 0.170
≥3.20	327/601	130/211	9/16	139/227	1.13 (0.88-1.46); 0.343	1.03 (0.45-2.37); 0.937	1.13 (0.88-1.45); 0.355	1.00 (0.44-2.28); 0.100
Functional class								
I + II	238/601	103/211	7/16	110/227	1.23 (0.93-1.63); 0.142	1.11 (0.45-2.72); 0.828	1.22 (0.93-1.61); 0.147	1.04 (0.43-2.56); 0.928
III + IV	172/601	68/211	7/16	75/227	1.13 (0.82-1.55); 0.469	1.53 (0.62-3.78); 0.357	1.15 (0.85-1.58); 0.366	1.48 (0.60-3.64); 0.393

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

DISCUSSION

In this hospital-based case-control study, we analyzed the association between three SNPs in the *IL-3* and *IL-13* genes and RA susceptibility. We found that polymorphisms in the *IL-3* and *IL-13* genes were not associated with RA. However, stratification analyses suggested that *IL-13* rs1800925 CT and CT/CC genotypes increased the risk of RA in patients with ESR < 25.00.

RA is a common complex genetic disease. A large number of genes, including cytokine genes, are believed to be associated with RA. IL-13, an immunoregulatory protein produced mainly by activated Th2 cells, is involved in the maturation and differentiation of autoimmune disorders (Chomarat and Banchereau, 1998). Th2 cells are involved in antibody production and humoral immune responses, participate in the inflammatory process via the secretion of cytokines such as IL-4, IL-5, IL-9, and IL-13. Imbalance between the Th1 and Th2 subtypes may result in the development of autoimmune diseases such as RA (Zhu et al., 2010). It has been reported that IL-13 may inhibit the development of arthritis in animal models (Heinzmann et al., 2003). Pertovaara et al. (2006) revealed that the Th2 cytokine genotypes (including *IL-13*) are associated with a milder form of primary Sjogren's syndrome. Heinzmann et al. (2003), on the other hand, found no correlation between the *IL-13* variant Arg110Gln and juvenile idiopathic arthritis compared to the controls. Several studies have indicated that a polymorphism in the *IL-13* gene (rs1800925 C/T) was strongly associated with psoriatic arthritis (PsA) (Duffin et al. 2009; Bowes et al., 2011; Eder et al., 2011). Moreover, it has been proposed that similar pathogenic mechanisms may be shared among other autoimmune diseases. Therefore, we hypothesized that the *IL-13* rs1800925 C/T polymorphism may be associated with RA. The results of this study indicated the lack of any correlation between *IL-13* rs1800925 C/T and RA susceptibility. However, stratification analyses indicated that *IL-13* rs1800925 CT and CT/CC genotypes increased the risk of RA in ESR < 25.00 patients. These results were also seen in two previous studies conducted in Caucasian populations (Marinou et al., 2008; Pavkova Goldbergova et al., 2014). Marinou et al. (2008) first reported that *IL-13* rs1800925 C/T did not significantly contribute to RA susceptibility and radiological severity in an English Caucasian population, while a subsequent Czech study conducted by Pavkova Goldbergova et al. (2014) reported the lack of any association between RA and *IL-13* rs1800925 C/T; however, the latter study demonstrated an association between the T allele of *IL-13* rs1800925 C/T and faster RA progression. Furthermore, they did not report any association between this promoter polymorphism and serum IL-13 levels (Pavkova Goldbergova et al., 2014).

IL-3 is a product of activated T cells. Heller et al. (1997) reported its expression in synoviocytes and chondrocytes of RA tissue. IL-3 represents a potential candidate for RA as it regulates the proliferation, differentiation, and function of three hematopoietic lineages in the bone marrow (Yamada et al., 2001). A previous study conducted by Yamada et al. (2001) in a Japanese population indicated that the *IL-3* gene polymorphism was associated with RA, particularly in females with earlier-onset RA. However, no association was observed between *IL-3* rs40401 C/T and RA in this study. We attributed the discrepancy between these results to environmental differences. This study also indicated that the *IL-3* rs2073506 G/A polymorphism was not associated with RA. To the best of our knowledge, this is the first study investigating the association between RA and the *IL-3* gene polymorphisms in a Chinese Han population. Larger-scale studies are required to identify the association between *IL-3* gene polymorphisms and RA in the Chinese Han population.

This study has several limitations. First, as this is a hospital-based case-control study,

selection bias was unavoidable. Second, analyses of a single SNP locus may not provide us with a comprehensive understanding of the genetic effects of these candidate genes; therefore, further fine-mapping analyses of the susceptible region are warranted. Third, our sample size was not large enough to evaluate the low-penetrance effects of the SNPs. Therefore, further studies with a larger sample size must be conducted to confirm our findings. Finally, our results should be interpreted with caution because of the potential influence of confounding factors, such as environmental and inflammatory factors, on RA.

In conclusion, no association was observed between polymorphisms in the *IL-3* and *IL-13* genes and RA in this study. However, stratification analyses suggested that the *IL-13* rs1800925 C/T genotype increased the risk of RA in ESR < 25.00 patients. Well-designed studies with larger sample sizes and ethnically diverse populations are required to further evaluate the impact of these and other polymorphisms on RA susceptibility.

Conflicts of interest

The authors declare no conflict of interest.

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