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Association between IL-21 polymorphism and systemic lupus erythematosus: a meta-analysis

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ABSTRACT. Several case-control studies have been conducted to investigate the association between Interleukin-21 (IL-21) polymorphisms and systemic lupus erythematosus (SLE) susceptibility, and most of the studies focused on *IL-21* rs907715 and rs2221903 polymorphisms. Given the inconsistent results from these studies, the present meta-analysis aimed to obtain a more precise estimate of the association between *IL-21* rs907715 and rs2221903 polymorphisms and SLE. Studies regarding these specific polymorphisms and SLE were retrieved from PubMed, Embase, Web of Science, CNKI, and CBM. Data were extracted and meta-analysis was performed using the STATA 12.0 software. For the *IL-21* rs907715 polymorphism, seven sets of comparisons involving 7977 SLE cases and 8097 healthy controls were considered. Results showed that there were significant differences in the *IL-21* rs907715 genotype distribution between SLE patients and

healthy controls in the comparisons of all genetic models. Upon stratified analysis by ethnicity, a similar result was found in the Caucasian and African-American population. For the *IL-21* rs2221903 polymorphism, seven sets of comparisons involving 7990 SLE cases and 8098 healthy controls were considered. Results showed that there were significant differences in the *IL-21* rs2221903 genotype distribution between SLE patients and healthy controls in the comparisons of GG versus AA and GG versus GA+AA. Upon stratified analysis by ethnicity, a similar result was found in the Caucasian population. This meta-analysis suggests that the both *IL-21* rs907715 and rs2221903 polymorphisms may be associated with SLE susceptibility. As current evidence remains limited, further studies are needed to warrant the association between *IL-21* rs907715 and rs2221903 polymorphisms and SLE susceptibility.

Key words: Interleukin 21; Polymorphism; Meta-analysis; Systemic lupus erythematosus

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by the production of a range of autoantibodies (Tsokos, 2011). The exact etiology and pathogenesis of SLE has not been clarified thus far, however there is evidence that B and T cells are critical to the development of SLE (Sarra and Monteleone, 2010). Interleukin-21 (IL-21) is recognized as a member of the type I cytokine family, mainly synthesized by a range of differentiated $CD4^+$ T helper (Th) cells (Monteleone et al., 2009) and activated natural killer T (NKT) cells (Coquet et al., 2007). Studies have shown that IL-21 has an important role in the control of the growth, survival, differentiation, and function of both B (Mehta et al., 2003; Ozaki et al., 2004; Jin et al., 2004; Konforte et al., 2009) and T cells (Strengell et al., 2002; Fröhlich et al., 2007; Monteleone et al., 2008). There is increasing evidence that IL-21 contributes to the pathogenesis of SLE. For instance, elevated serum and mRNA levels of IL-21 has been detected in BXSB-Yaa mice, a mouse model which develops severe SLE-related symptoms, including hypergammaglobulinemia, autoantibody production, reduced frequencies of marginal zone B cells and monocytosis, and renal disease (Bubier et al., 2009). Conversely, IL-21 receptor (IL-21R)-deficient mice exhibited none of these abnormalities (Bubier et al., 2009). One study in humans reported that serum levels of IL-21 was markedly increased in SLE patients compared with healthy controls (Wong et al., 2010).

Although possible associations of the *IL-21* polymorphisms with SLE were reported, and many case-control studies were further performed to identify the association between *IL-21* rs907715 and rs2221903 polymorphisms and SLE (Sawalha et al., 2008; Hughes et al., 2011; Leng et al., 2012; Ding et al., 2012; Lan et al., 2014). However, results from these studies were inconsistent, which may be due to the limitations in sample size and differences in ethnic populations. Therefore, we performed a meta-analysis to evaluate comprehensively the association between the *IL-21* rs907715 and rs2221903 polymorphisms and SLE based on all eligible case-control studies.

MATERIAL AND METHODS

Literature search

The studies regarding the association between *IL-21* rs907715 and rs2221903 polymorphisms and SLE published up to October 2014 without language restrictions were independently searched by two authors in the PubMed, Embase, Web of Science, Chinese National Knowledge Infrastructure (CNKI) and Chinese Biomedical (CBM) Literature Database, using the following terms: (''Interleukin-21'' or ''IL-21'') and (''Systemic lupus erythematosus'' or ''SLE'') and (''polymorphism'' or ''SNP'' or ''single nucleotide polymorphism'' or ''variation'' or ''mutation''). The bibliographies of retrieved articles were manually searched to find additional relevant studies.

Study selection

Studies were included in this meta-analysis if they met the following criteria: (a) case-control studies focused on associations between *IL-21* rs907715 or rs2221903 polymorphisms and SLE, (b) 95% confidence interval (CI) for odds ratio (OR) were available or could be calculated, and (c) the distribution of genotypes in the control group was consistent with Hardy-Weinberg equilibrium (HWE). When met with repetitive publications, only one publication was included. Family-based studies were also excluded.

Data extraction

The following data from the studies included were extracted independently by two authors, including the first author, year of publication, country of subject recruitment, subjects' ethnicities, sample size, and genotype distributions in SLE cases and controls. In case of conflicting evaluations, disagreements were resolved through discussions between the authors.

Statistical analysis

Genotype distributions in the controls were tested for HWE using the Pearson's χ^2 test (Schaid and Jacobsen, 1999). Between-study heterogeneity was checked by the Cochran Q-statistic and I^2 test (Higgins and Thompson, 2002; Zintzaras and Ioannidis, 2005). When $P < 0.1$ for Q-test or $I^2 > 50\%$ indicated the existence of heterogeneity, a random-effect model was used; otherwise, a fixed-effect model was applied. ORs with corresponding 95% confidence intervals (CIs) were calculated to assess the association between *IL-21* rs907715 and rs2221903 polymorphisms and SLE under four genetic models: G allele versus A allele, GG versus AA, GG+GA versus AA, and GG versus GA+AA. The significance of the pooled OR was determined using the Z-test. To evaluate whether the association showed any ethnicity specific effects, we analyzed the data for separate subgroups defined by ethnicity. Sensitivity analysis was performed by sequential omission of individual studies and recalculating the results in order to assess the stability of the results. Begg's funnel plots and Egger's test were used to investigate whether publication bias might affect the validity of the estimates (Peters et al., 2006). All the statistical tests were conducted using the STATA 12.0 software.

RESULTS

Characteristics of the studies included

The flow chart of the selection of studies and specific reasons for exclusion from the meta-analysis are shown in Figure 1. The search strategy retrieved twenty-six potentially relevant studies. In accordance with the inclusion criteria, five articles were included in this meta-analysis and all of them were written in English. The publication year of the articles included ranged from 2008 to 2014. For the *IL-21* rs907715 polymorphism, seven sets of comparisons involving 7977 SLE cases and 8097 healthy controls were considered. For the *IL-21* rs2221903 polymorphism, seven sets of comparisons involving 7990 SLE cases and 8098 healthy controls were considered. Among the eligible seven sets of comparisons, three comparisons were conducted in the Asian population, two comparisons were conducted in the Caucasian population, and the remaining two comparisons were conducted in the African-American population. The distribution of genotypes within the control group of each comparison was consistent with HWE (all $P > 0.05$). The control group was chosen from healthy individuals without any systemic and dermatologic diseases. The characteristics of the included studies were summarized in Table 1.

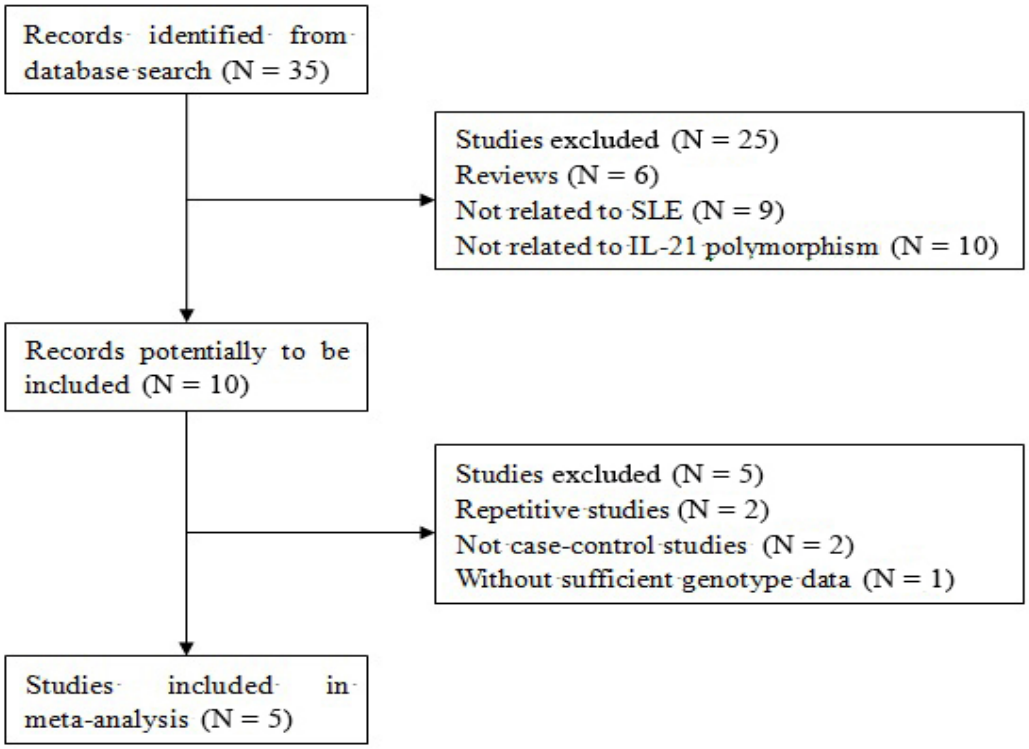

Figure 1. Selection of studies and specific reasons for exclusion from the meta-analysis.

Table 1. Characteristics of studies included in this meta-analysis.

Author	Year	Country	Ethnic	Number		Genotype					
				Case	Controls	Case			Control		
						AA	AG	GG	AA	AG	GG
rs907715											
Sawalha et al. (2008)	2008	USA	Caucasian	644	644	67	281	296	93	304	247
Sawalha et al. (2008)	2008	USA	African-American	366	366	49	170	147	61	171	134
Hughes et al. (2011)	2011	USA	Caucasian	3918	3503	387	1688	1843	417	1582	1504
Hughes et al. (2011)	2011	USA	African-American	1411	1761	199	662	550	294	851	616
Ding et al. (2012)	2012	China	Asian	605	666	124	293	188	128	339	199
Leng et al. (2012)	2012	China	Asian	858	967	151	418	289	207	481	279
Lan et al. (2014)	2014	China	Asian	175	190	41	93	41	35	97	58
rs2221903											
Sawalha et al. (2008)	2008	USA	Caucasian	644	644	298	280	66	324	275	45
Sawalha et al. (2008)	2008	USA	African-American	366	366	303	57	6	324	40	2
Hughes et al. (2011)	2011	USA	Caucasian	3928	3499	1844	1694	390	1740	1455	304
Hughes et al. (2011)	2011	USA	African-American	1414	1766	1222	185	7	1509	247	10
Ding et al. (2012)	2012	China	Asian	605	666	483	116	6	495	166	5
Leng et al. (2012)	2012	China	Asian	858	967	672	175	11	787	171	9
Lan et al. (2014)	2014	China	Asian	175	190	122	50	3	143	45	2

Meta-analysis results

For the *IL-21* rs907715 polymorphism, significant heterogeneity between studies was observed in the comparisons of G allele versus A allele, and GG versus AA with the Q test and the I^2 test ($P < 0.1$ or $I^2 > 50\%$). Therefore, the random effects model was used to pool the results. No heterogeneity between studies was observed in the comparisons of GG+GA versus AA, and GG versus GA+AA and the fixed effects model was used to pool the results. Meta-analysis results showed that there were significant differences in the *IL-21* rs907715 genotype distribution between SLE patients and healthy controls in the comparisons of G allele versus A allele, GG versus AA, GG+GA versus AA, and GG versus GA+AA (respectively: OR = 1.13, 95%CI = 1.05-1.21, P = 0.001; OR = 1.27, 95%CI = 1.09-1.48, P = 0.003; OR = 1.20, 95%CI = 1.09-1.31, P = 0.000; OR = 1.18, 95%CI = 1.11-1.26, P = 0.000). Upon stratified analysis by ethnicity, a similar result was found in Caucasian and African-American populations. Results for the *IL-21* rs907715 polymorphism were summarized in Table 2. For the *IL-21* rs2221903 polymorphism, significant heterogeneity between studies was observed in the comparisons of G allele versus A allele, and GG+GA versus AA, and the random effects model was used to pool the results. No heterogeneity between studies was observed in the comparisons of GG versus AA, and GG versus GA+AA, and the fixed effects model was used to pool the results. Meta-analysis results showed that there were significant differences in the *IL-21* rs2221903 genotype distribution between SLE patients and healthy controls in the comparisons of GG versus AA, and GG versus GA+AA. Upon stratified analysis by ethnicity, a similar result was found in the Caucasian population. Results for the *IL-21* rs2221903 polymorphism were summarized in Table 3.

Sensitivity analysis and publication bias

Sensitivity analyses were performed by sequential omission of individual studies for

all subjects and subgroups. The pooled ORs were not significantly altered in all subjects and subgroups by omitting any single study (data not shown). The results of the sensitivity analyses indicated the stability of our results. Begg's funnel plot and Egger's test showed that there were no statistically significant publication biases in all genetic models (all $P > 0.05$) (data not shown).

Table 2. Meta-analysis of the association between IL-21 rs907715 polymorphism and SLE susceptibility.

Genetic model	Population	OR (95%CI)	P	Statistical model	I^2	$P_{Heterogeneity}$
G *vs* A	Overall	**1.13 (1.05-1.21)**	**0.001**	Random	49.6%	0.064
	Caucasian	**1.17 (1.10-1.25)**	**0.000**	Fixed	41.1%	0.192
	African-American	**1.15 (1.05-1.26)**	**0.003**	Fixed	0.0%	0.958
	Asian	1.01 (0.82-1.24)	0.925	Random	74.1%	0.021
GG *vs* AA	Overall	**1.27 (1.09-1.48)**	**0.003**	Random	48.8%	0.068
	Caucasian	**1.37 (1.19-1.58)**	**0.000**	Fixed	26.3%	0.244
	African-American	**1.33 (1.10-1.61)**	**0.004**	Fixed	0.0%	0.890
	Asian	1.01 (0.66-1.53)	0.969	Random	74.4%	0.020
GG+GA *vs* AA	Overall	**1.20 (1.09-1.31)**	**0.000**	Fixed	32.0%	0.184
	Caucasian	**1.27 (1.11-1.45)**	**0.001**	Fixed	0.0%	0.378
	African-American	**1.23 (1.03-1.47)**	**0.019**	Fixed	0.0%	0.800
	Asian	1.01 (0.75-1.36)	0.972	Random	62.5%	0.069
GG *vs* GA+AA	Overall	**1.18 (1.11-1.26)**	**0.000**	Fixed	22.7%	0.256
	Caucasian	**1.21 (1.11-1.31)**	**0.000**	Fixed	30.3%	0.231
	African-American	**1.18 (1.04-1.35)**	**0.012**	Fixed	0.0%	0.899
	Asian	1.04 (0.80-1.36)	0.751	Random	63.0	0.067

OR = odds ratio; CI = confidence interval. Bold values mean that their association is significant.

Table 3. Meta-analysis of the association between IL-21 rs2221903 polymorphism and SLE susceptibility.

Genetic model	Population	OR (95%CI)	P	Statistical model	I^2	$P_{Heterogeneity}$
G *vs* A	Overall	1.09 (0.96-1.24)	0.172	Random	64.3%	0.010
	Caucasian	**1.11 (1.04-1.19)**	**0.001**	Fixed	0.0%	0.400
	African-American	1.19 (0.69-2.07)	0.527	Random	84.4%	0.011
	Asian	1.04 (0.76-1.44)	0.796	Random	75.8%	0.016
GG *vs* AA	Overall	**1.27 (1.09-1.48)**	**0.002**	Fixed	0.0%	0.732
	Caucasian	**1.26 (1.08-1.46)**	**0.003**	Fixed	33.1%	0.221
	African-American	1.28 (0.58-2.82)	0.543	Fixed	46.9%	0.170
	Asian	1.40 (0.72-2.72)	0.314	Fixed	0.0%	0.947
GG+GA *vs* AA	Overall	1.09 (0.94-1.25)	0.265	Random	64.5%	0.010
	Caucasian	**1.13 (1.04-1.23)**	**0.006**	Fixed	0.0%	0.678
	African-American	1.18 (0.69-2.02)	0.551	Random	81.5%	0.020
	Asian	1.03 (0.71-1.51)	0.865	Random	78.8%	0.009
GG *vs* GA+AA	Overall	**1.28 (1.12-1.48)**	**0.000**	Fixed	0.0%	0.811
	Caucasian	**1.28 (1.11-1.48)**	**0.001**	Fixed	0.0%	0.339
	African-American	1.25 (0.57-2.76)	0.577	Fixed	48.2%	0.165
	Asian	1.37 (0.71-2.66)	0.349	Fixed	0.0	0.958

OR = odds ratio; CI = confidence interval. Bold values mean that their association is significant.

DISCUSSION

In humans, the *IL-21* gene is located on chromosome 4q26-q27, which consists of 5 exons spanning approximately 8.44 kb of genomic DNA. Several polymorphisms in the *IL-21* gene have been identified and several studies have been carried out to identify whether *IL-21* polymorphisms were associated with SLE susceptibility (Sawalha et al., 2008; Hughes et al., 2011; Leng et al., 2012; Ding et al., 2012; Lan et al., 2014). Most of the studies focused on *IL-21* rs907715 and rs2221903 polymorphisms. However, the results from these studies were in-

consistent, which may be partly due to a small sample size in individual studies or differences in various ethnic groups. Meta-analysis has been recognized as a useful statistical method that combines findings from independent studies to precisely evaluate the effect of selected genetic polymorphisms on the risk of disease (Attia et al., 2003). To the best of our knowledge, no meta-analysis has been conducted to evaluate the association between *IL-21* polymorphisms and SLE susceptibility. We performed the present meta-analysis based on all eligible case-control studies, to provide a more complete picture of the role of *IL-21* polymorphisms in SLE susceptibility, as compared with that published in individual studies.

In this meta-analysis, all the studies checked genotypes for quality control. The genotype distribution of controls in all studies was consistent with HWE. In the meta-analysis of the rs907715 polymorphism, seven sets of comparisons involving 7977 SLE cases and 8097 healthy controls were considered. When all the eligible studies were pooled into the meta-analysis, the results showed that *IL-21* rs907715 polymorphism was associated with SLE susceptibility under all genetic models. Sensitivity analysis also showed that omission of any single study did not have a significant impact on the combined ORs. Furthermore, a funnel plot did not reveal obvious asymmetry, and the Egger test further indicated no considerable publication bias in this meta-analysis. This made the results of this meta-study more reliable to some extent. To evaluate whether the association showed any ethnicity specific effects, we analyzed the data for separate subgroups defined by ethnicity. Upon stratified analysis, a similar result was found in Caucasian and African-American populations. Moreover, no heterogeneity between studies was observed in Caucasian and African-American subgroups. For the *IL-21* rs2221903 polymorphism, seven sets of comparisons involving 7990 SLE cases and 8098 healthy controls were considered. Meta-analysis results showed that there were significant differences in the *IL-21* rs2221903 genotype distribution between SLE patients and healthy controls in the comparisons of GG versus AA, and GG versus GA+AA. Upon stratified analysis by ethnicity, a similar result was found in the Caucasian population.

Some limitations of our meta-analysis should be acknowledged. First, the completeness of evidence may be impeded by publication bias, language bias (Juni et al., 2002) and inadequate reporting (Little et al., 2009), despite the comprehensive study identification process and lack of overt publication bias in the present study. Second, the number of studies included was not sufficiently large, especially in ethnicity subgroup analysis, which may not provide enough statistical power to explore the real association between *IL-21* rs2221903 polymorphisms and SLE susceptibility. Third, SLE is polygenic and may also be modulated by several other genetic markers beyond *IL-21*, including *IL-10* (Liu et al., 2013), *MCP-1* (Zhou et al., 2014a), *CTLA-4* (Zhu et al., 2014), the vitamin D receptor (Zhou et al., 2014b), and several other candidate genes. Thus, our meta-analysis emphasizes that elucidating the pathogenesis of SLE would demand further evaluation of the potential gene-gene interactions. Finally, due to the lack of raw data, we have not considered some factors when analyzing the data, such as the factors of gender, age and the severity of the disease, which may cause serious confounding bias. However, the advantages of this meta-analysis were also obvious. First, compared with individual studies, the sample size of our study was larger, which made the results more reliable. Second the associations between *IL-21* rs907715 polymorphisms and SLE were evaluated under different genetic models.

In summary, our meta-analysis suggests that the *IL-21* rs2221903 polymorphism may be associated with SLE, especially in the Caucasian population. As few studies are available

in this field and current evidence remains limited, well-designed and large studies are needed to investigate further the association between *IL-21* rs2221903 polymorphisms and SLE.

Conflicts of interest

The authors declare no conflict of interest.

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