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Association between IRF5 polymorphisms and autoimmune diseases: a meta-analysis

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ABSTRACT. In this study, we investigated the association between 5 interferon regulatory factor-5 (IRF5) single nucleotide polymorphisms (SNPs) and autoimmune diseases using the Medline citation index. Twenty-eight studies with 74 comparisons, including 16 rheumatoid arthritis (RA), 43 systemic lupus erythematous (SLE), 2 juvenile idiopathic arthritis (JIA), 6 multiple sclerosis (MS), and 5 systemic sclerosis (SSc) studies, were examined in the meta-analysis. The SNP rs2004640 was significantly associated with SLE, MS, and SSc, but not with JIA [odds ratio (OR) = 1.06, 95% confidence interval (CI) = 0.90-1.24, P = 0.48] or RA (OR = 1.03, 95%CI = 0.95-1.11, P = 0.44). A significant association was observed between rs2280714 and SLE, MS, and SSc, but not RA (OR = 1.01, 95%CI = 0.94-1.09, P = 0.80). Rs10954213 was associated with the pathogenesis of SLE, RA, MS, and SSc. rs2070197 and the exon 6 insertion were significantly associated

with SLE. Haplotypes containing rs2004640T and rs2280714T were significantly associated with an increased risk of SLE, but not with RA. This meta-analysis certified that IRF5 polymorphisms confer susceptibility to SLE, MS, and SSc. To further confirm the correlations between polymorphisms of IRF5 and autoimmune disease susceptibility, studies involving a larger number of patients worldwide are necessary.

Key words: IRF5; Autoimmune diseases; Meta-analysis

INTRODUCTION

Autoimmune diseases are complex diseases influenced by both genetic background and environmental triggers (Tsonis et al., 2007). Recently, several key susceptible genes have been identified, including those in the type I interferon (IFN) family (Banchereau and Pascual, 2006).

The type I IFN system has been found to be associated with the pathogenesis of autoimmune diseases. IRF-5, a member of the IFN regulatory factor (IRF) family (IRFs 1-9), plays a crucial role in the Toll-like receptor signaling pathway, and is thought to be a major transcription factor in the activation of inflammatory cytokine genes.

The gene encoding IRF5 (*IRF5*; OMIM 607218) is located on chromosome 7q32, and its expression is associated with atopic diseases (Garnier et al., 2007). An important polymorphism at the intron-exon border of exon 1B (rs2004640) creates a splice donor site and leads to alternative splicing of exon 1B (Graham et al., 2007). In addition, a second single nucleotide polymorphism (SNP) in the 3'-flanking region (rs2280714) was confirmed to be associated with the IRF5 mRNA level, in which the rs2280714 T-allele can upregulate the expression of IRF5 (Cunninghame Graham et al., 2007). In addition, several other variants, such as rs10954213, rs2070197, and exon 6 insertions/deletions, were reported to be associated with autoimmune diseases.

Further investigations implied that IRF5 polymorphisms are associated with an increased risk of developing autoimmune diseases such as systemic lupus erythematous (SLE), multiple sclerosis (MS), Sjögren's syndrome (SS), systemic sclerosis (SSc), and inflammatory bowel disease (IBD). However, studies using rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA) cohorts of Caucasian and Asian subjects have shown that IRF5 polymorphisms did not increase the genetic susceptibility to RA and JIA.

A combination of evidence should be taken into account to assess the correlation between IRF5 polymorphisms and autoimmune diseases. In the present study, we carried out a meta-analysis to evaluate the association between IRF5 polymorphisms and autoimmune disease risk among different ethnic groups.

MATERIAL AND METHODS

Identification of eligible studies

The keywords "interferon regulatory factor", "IRF5", and "autoimmune disease" were searched in the PubMed database to identify relevant publications. Studies examining the association between the *IRF5* gene and autoimmune diseases were considered, with the most

recent article dated December 16, 2011. Studies were not restricted to any particular language. Only the data from published papers were collected. A study was included if: i) an unrelated case-control design was used; ii) allele frequency or genotypes were available; iii) frequencies of SNPs were in Hardy-Weinberg (HW) equilibrium.

Data extraction

Information of first author, year of publication, type of study design, ethnicity, total sample size, number of cases and controls, and distribution of haplotype (rs2004640-rs2280714) were extracted, respectively. Extraction from each study was conducted independently by 2 authors (L.T. and B.C.), and consensus was achieved for all data.

Evaluation of the statistical association

Odds ratios (ORs) and 95% confidence intervals (95%CIs) were calculated for each study. Variation and heterogeneity were evaluated by using Cochran's *Q*-statistic. $P < 0.10$ indicated significant heterogeneity across studies, and the random effects model was used for meta-analysis; otherwise, the fixed effect model was used. The I^2 statistic, calculated as 100% x (Q - df) / Q, was also used to measure the effect of heterogeneity. Calculation power was obtained at the 0.05 level of significance, assuming an OR of 1.5 (small effect size). The G*Power software was used to perform the power analysis (http://www.gpower.hhu.de).

Publication bias

Publication bias was assessed by using the Egger test. A P value <0.05 was considered to be significant for significant publication bias. Sensitivity analysis excluding individual studies was performed in the meta-analysis. All statistical analyses were conducted using the program RevMan 5 (Oxford, UK) and STATA10.0 (http://www.stata.com).

RESULTS

Studies included in the meta-analysis

There were 28 relevant studies with *IRF5* SNPs and autoimmune diseases identified through the Medline search and a review of references (most recent search, December 16, 2011). Five studies were excluded because they were family-based studies (Graham et al., 2007; Cunninghame Graham et al., 2007; Qu et al., 2007; Dawidowicz et al., 2011) or duplicated data (Kozyrev et al., 2007). Data from 15 studies (Sigurdsson et al., 2005; Rueda et al., 2006; Graham et al., 2006; Shin et al., 2007; Demirci et al., 2007; Reddy et al., 2007; Kawasaki et al., 2008; Kelly et al., 2008; Siu et al., 2008; Dieguez-Gonzalez et al., 2008; Kim et al., 2008; Hellquist et al., 2009; Song et al., 2009; Löfgren et al., 2010; Vuong et al., 2010) overlapped in studies by Lee and Song (2009), Han et al. (2009), and Hu and Ren (2011), and the latter three studies were included in the analysis. In addition, the most recent studies (Dideberg et al., 2007; Miceli-Richard et al., 2007; Kristjansdottir et al., 2008; Sigurdsson et al., 2008; Maalej et al., 2008; Ito et al., 2009; Shimane et al., 2009; Dieude et al., 2009, 2010; Wieczorek et al.,

2010; Qin et al., 2010;Yanagimachi et al., 2011; Nordang et al., 2011) on the polymorphisms of *IRF5* and autoimmune diseases such as MS, SSc, SS, WG, IBD, and JIA were included in this study. The characteristics of the selected studies for 5 *IRF5* SNPs and autoimmune diseases are summarized in Table 1. All eligible studies included 19,566 autoimmune disease patients and 20,750 healthy controls. Each population was treated independently. A total of 84 separate comparisons were available. A meta-analysis was performed if there were at least 2 comparisons. A total of 74 comparisons were considered in this meta-analysis (Table 1).

Association between *IRF5* SNPs and susceptibility of autoimmune diseases

A significant association was found between rs2004640 and SLE (OR = 1.50, 95%CI = 1.40-1.61, P < 0.00001), MS (OR = 1.18, 95%CI = 1.06-1.34, P = 0.004), and SSc (OR = 1.25, 95%CI = 1.13-1.38, P < 0.00001), but not JIA (OR = 1.06, 95%CI = 0.90-1.24, P = 0.48) or RA (OR = 1.06, 95%CI = 0.90-1.24, P = 0.48) (Table 2 and Figure 1). The rs2280714G allele appeared to be a risk factor for SLE (OR = 0.82, 95%CI = 0.72-0.95, P < 0.006), but not for RA (OR = 1.01, 95%CI = 0.94-1.09, P = 0.80) and MS (OR = 0.87, 95%CI = 0.72-1.05, P = 0.16), (Table 2 and Figure 2). The rs10954213 A allele was significantly associated with SLE (OR = 1.63, 95%CI = 1.20-2.20, P < 0.002), MS (OR = 1.13, 95%CI =1.03-1.25, P = 0.01), and SSc (OR = 1.21, 95%CI = 1.07-1.36, P = 0. 002). However, it appears to be a protective factor in RA (OR = 0.89, 95%CI = 0.83-0.94, P = 0.0002) (Table 2 and Figure 3). In addition, rs2070197C and the exon 6 insertion were significantly associated with SLE (OR = 1.66, 95%CI = 1.42-1.94, P < 0.00001 for rs2070197; OR = 1.31, 95%CI = 1.16-1.49, P < 0.0001 for exon 6 insertion) (Table 2, Figures 4 and 5).

No difference was detected between rs2004640 and SLE, RA, JIA, MS, SSc, and rs2280714 and RA in terms of ethnicity. In addition, rs2280714 was not associated with SLE in European, Asian, and African American subjects. A significant association was observed between rs10954213 and SLE in subjects of European and Latin American origin, but not in Asian subjects.

For haplotypes, the results showed that haplotypes containing rs2004640T and rs2280714T significantly increased the risk of SLE (T-T *vs* G-G: OR = 1.25, 95%CI = 1.13-1.38, P < 0.0001). Haplotypes containing rs2004640G and rs2280714T (G-T *vs* G-G: OR = 0.81, 95%CI = 0.70-0.94, P = 0.03) appeared to not be risk factors of SLE. Neither haplotype was significantly associated with RA (T-T *vs* G-G: OR = 1.12, 95%CI 1.00-1.26, P = 0.05; G-T *vs* G-G: OR = 0.94, 95%CI 0.80-1.10, P = 0.43) (Table 2). Haplotype information of SS, SSc, MS, and JIA are not supplied because of a lack of data.

Evaluation of study quality and heterogeneity

Significant heterogeneity was detected in rs2004640, rs2280714, and rs10954213 (Table 2). For rs2004640, significant heterogeneity was observed among studies of SLE in Latin American origin, but not in European and Asian studies. Significant heterogeneity among studies of RA was observed in European origin, not in Latin American and Asian origin. For rs2280714, European origin contributed to significant heterogeneity in SLE (Table 2). In addition, Latin American and Asian origin contributed to significant heterogeneity in SLE. However, sensitivity analysis was performed in the meta-analysis, and similar results were observed after excluding

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

SNP	Reference	Country	Year	Diseases	No.		OR*, P value	Power[a] ($\alpha = 0.05$, OR = 1.5)
					Case	Control		
rs2004640 T	Demirci et al.	USA (E)	2007	SLE	370	462	1.30, 0.008	82.2
	Rueda et al.	Spanish (E)	2006	RA	724	542	1.09, 0.25	94.5
		Swedish (E)			281	472	0.99, 0.92	78.3
		Argentinean (LA)			284	285	1.24, 0.07	66.5
	Miceli-Richard et al.	USA (E)	2007	SS	210	154	1.36, 0.04	47.9
	Qin et al.	Chinese (A)	2010	SLE	190	182	1.60, 0.002	48.8
	Kawasaki et al.	Japanese (A)	2008	SLE	277	201	1.24, 0.12	58.9
	Nordang et al.	Norwegian (E)	2011	SLE	153	755	1.95, 3.75×10^{-7}	85.4
				RA	515		1.19, 0.029	94.6
				JIA	404		1.19, 0.047	92.6
	Sigurdsson et al.	Sweden (E)	2005	SLE	480	256	1.51, 2.50×10^{-4}	77.4
		Finland (E)			109	121	1.84, 9.50×10^{-5}	32.9
	Shin et al.	Korean (A)	2007	SLE	589	950	1.32, 0.0003	97.5
	Graham et al.	Argentina (LA)	2006	SLE	284	279	1.52, 0.00035	66.0
		Spain (E)			444	541	1.42, 0.00016	88.1
		Sweden (E)			208	254	1.31, 0.0426	33.3
		USA (E)			725	1434	1.47, 3.6×10^{-9}	99.6
	Sigurdsson et al.	Swedish (E)	2008	SLE	485	563	1.57, 5.70×10^{-7}	89.9
	Kristjansdottir et al.	Spanish (E)	2008	MS	650	797	1.28, 0.0011	96.7
		Swedish (E)			1084	1182	1.11, 0.082	99.7
	Dieguez-Gonzalez et al.	Spanish (E)	2008	RA	2644	3236	0.91, 0.07	99.9
	Dieude et al.	French (E)	2009	SSc	811	730	1.25, 0.002	97.5
	Kelly et al.	African A (AF)	2008	SLE	795	1129	1.30, 0.0001	99.2
	Shimane et al.	Japanese (A)	2009	RA	1942	1598	1.05, 0.31	99.9
	Siu et al.	Chinese (A)	2008	SLE	444	410	1.32, 0.056	83.2
	Yanagimachi et al.	Japanese (A)	2011	JIA	81	190	1.05, 0.80	37.7
	Kim et al.	Korean (A)	2008	RA	1193	950	1.13, 0.66	99.6
	Dideberg et al.	Belgium (E)	2007	IBD	1661	534	1.11, 0.16	99.7
				CD	1027		1.06, 0.46	97.7
				UC	429		1.24, 0.027	87.4
	Dieude et al.	French (E)	2010	SSc	743	880	1.41, 0.008	98.0
	Wieczorek et al.	German (E)	2010	WG	642	920	0.82, 0.00662	97.7
	Maalej et al.	Tunisian (A)	2008	RA	140	185	1.10, 0.30	43.7
	Vuong et al.	Sweden (E)	2010	SLE	272	307	1.81, 6.17×10^{-5}	67.2
	Reddy et al.	Mexicans (LA)	2007	SLE	189	282	2.18, <0.001	58.3
	Song et al.	Chinese (A)	2009	SLE	92	88	1.78, <0.05	26.9
	Ito et al.	Japanese (A)	2009	SSc	281	477	1.27, 0.032	78.6
	Löfgren et al.	Mexico (LA)	2010	SLE	178	265	2.35, 8.72×10^{-9}	55.8
		Argentina (LA)			241	249	1.53, 3.56×10^{-4}	60.0
		Spain (E)			596	520	1.45, 4.37×10^{-5}	91.6
		Italy (E)			263	247	1.31, 0.042	61.7
		Germany (E)			210	185	1.41, 0.007	51.1
rs2280714 G	Rueda et al.	Spanish (E)	2006	RA	724	542	1.05, 0.603	94.5
		Swedish (E)			273	474	0.99, 0.92	78.0
		Argentinean (LA)			284	285	0.80, 0.06	66.5
	Dieguez-Gonzalez et al.	Spanish (E)	2008	RA	2644	3236	0.99, 0.92	99.9
	Ito et al.	Japanese (A)	2009	SSc	281	477	1.42, 0.0012	78.6
	Kelly et al.	African A (AF)	2008	SLE	795	1129	0.88, 0.06	99.2
	Shimane et al.	Japanese (A)	2009	RA	1942	1598	1.12, 0.023	99.9
	Miceli-Richard et al.	USA (E)	2007	SS	213	154	0.75, 0.07	48.2
	Yanagimachi et al.	Japanese (A)	2011	JIA	81	190	1.19, 0.38	37.7
	Kristjansdottir et al.	Spanish (E)	2008	MS	650	797	0.84, 0.13	96.7
		Swedish (E)			1084	1182	0.96, 0.68	99.7
	Sigurdsson et al.	Sweden (E)	2005	SLE	480	256	1.00, 0.82	77.4
		Finland (E)			109	121	0.65, 0.23	32.9
	Shin et al.	Korean (A)	2007	SLE	589	950	0.97, 0.697	97.5
	Vuong et al.	Sweden (E)	2010	SLE	272	307	0.64, 0.007	67.2
	Kim et al.	Korean (A)	2008	RA	1193	950	0.97, 0.67	99.6
	Sigurdsson et al.	Swedish (E)	2008	SLE	485	563	1.44, 2.10×10^{-4}	89.9

Continued on next page

Table 1. Continued.

SNP	Reference	Country	Year	Diseases	No.		OR*, P value	Power[a] (α = 0.05, OR = 1.5)
					Case	Control		
rs10954213 A	Kawasaki et al.	Japanese (A)	2008	SLE	277	201	0.87, 0.038	70.9
	Sigurdsson et al.	Swedish (E)	2008	SLE	485	563	1.45, 8.60×10^{-5}	94.6
	Kelly et al.	African American (AF)	2008	SLE	795	1129	1.30, 0.0006	99.7
	Siu et al.	Chinese (A)	2008	SLE	444	410	0.90, 0.28	90.1
	Löfgren et al.	Mexican (LA)	2010	SLE	178	265	2.12, 7.7×10^{-7}	68.0
		Argentina (LA)			241	249	1.27, 0.042	71.8
		Spain (E)			596	520	1.22, 0.055	95.6
		Italy (E)			263	247	1.30, 1.58×10^{-4}	73.3
		Germany (E)			210	185	1.39, 0.011	63.7
	Hellquist et al.	Finland (E)	2009	SLE	277	356	1.42, 0.0043	81.1
	Vuong et al.	Sweden (E)	2010	SLE	272	307	1.53, 0.0009	78.0
	Song et al.	Chinese (A)	2009	SLE	92	88	1.70, 0.05	38.1
	Reddy et al.	Mexican (LA)	2007	SLE	189	282	1.65, 1.78×10^{-9}	70.0
	Kim et al.	Korean (A)	2008	RA	1193	950	0.93, 0.34	99.8
	Dieguez-Gonzalez et al.	Spanish (E)	2008	RA	2644	3236	0.87, 0.016	99.9
	Kristjansdottir et al.	Spanish (E)	2008	MS	650	797	1.19, 0.031	98.5
		Swedish (E)	2008	MS	1084	1182	1.09, 0.15	99.8
	Ito et al.	Japanese (A)	2009	SSc	281	477	1.30, 0.014	86.6
	Dieude et al.	French (E)	2010	SSc	743	880	1.17, 0.035	99.7
rs2070197 C	Kelly et al.	African American (AF)	2008	SLE	795	1129	1.59, <0.0001	99.7
	Kim et al.	Korean (A)	2008	RA	1193	950	NS	99.8
	Reddy et al.	Mexican (LA)	2007	SLE	189	282	1.80, 1.26×10^{-21}	70.3
Exon 6 in	Sigurdsson et al.	Swedish (E)	2008	SLE	485	563	1.37, 0.45	95.2
	Kawasaki et al.	Japanese (A)	2008	SLE	277	201	1.16, 0.25	70.9
	Kim et al.	Korean (A)	2008	RA	1193	950	0.94, 0.43	99.8

*OR = odds ratio; NS = not significant; SLE = systemic lupus erythematosus; RA = rheumatoid arthritis; SS = Sjogren's syndrome; JIA = juvenile idiopathic arthritis; MS = multiple sclerosis; SSc = systemic sclerosis; IBD = inflammatory bowel disease; CD = Crohn disease; UC = ulcerative colitis; WG = Wegener granulomatosis. [a]Power calculations assume α = 0.05 and small effect size (0.1) or OR = 1.5. E = European; LA = Latin-American; A = Asian; AF = African-American.

individual studies, indicating the reliability of the meta-analysis results. No evidence of publication bias was identified when the Egger test was used (Table 2; $P > 0.5$). The statistical power of each study ranged from 32.9-99.9% (Table 1). Forty-eight of the 84 studies examined in the meta-analysis showed more than 80% statistical power to detect an effect.

DISCUSSION

In the present study, we conducted a meta-analysis to determine the genetic association between IRF5 polymorphisms and autoimmune diseases. The results provided strong evidence of an association of rs2004640T, rs2280714T, rs10954213A, rs2070197C, and the exon 6 insertion with autoimmune diseases, including SLE, MS, and SSc.

Genetic factors are thought to play an important role in the pathogenesis of autoimmune diseases. Case-control design studies have been carried out to examine the correlation between IRF5 polymorphisms and autoimmune diseases (Demirci et al., 2007). Individual studies and family-based association studies have demonstrated that the rs2004640T allele was a risk factor for SLE (Sigurdsson et al., 2005). Subsequently, correlation studies between rs2004640 T and autoimmune diseases such as RA, SSc, MS, and JIA were conducted in different cohorts. A haplotype in Caucasians carrying 4 polymorphisms (rs2004640T, exon 6 insertion, rs2070197C, and rs10954213A) was reported to be a risk factor for SLE (Ferreiro-Neira et al., 2007).

Table 2. Main results of interferon regulatory factor 5 (IRF5), in terms of autoimmune risk in the meta-analysis.

	Diseases	Population	Sample size		No. of studies	Test of association			Test of heterogeneity			Publication bias
			Disease	Control		OR*	95%CI	P value	Model	P value	I^2	P value (Egger's test)
rs2004640	SLE	Total	7594	9680	22	1.50	1.40-1.61	<0.00001	R	0.002	53.0	0.919
		European	4315	5645	12	1.50	1.42-1.59	<0.00001	F	0.27	17.7	0.568
		Asian	1592	1831	5	1.34	1.21-1.48	<0.00001	F	0.74	0.00	0.977
		LA	892	1075	4	1.82	1.60-2.07	<0.00001	R	0.03	66.7	0.084
		AA	795	1129	1	1.30	1.10-1.50	0.0001	-	-	-	-
	RA	Total	7723	8023	8	1.03	0.95-1.11	0.44	R	0.03	55.0	0.276
		European	4164	5005	4	0.96	0.91-1.02	0.19	R	0.06	59.7	0.053
		Asian	3275	2733	3	1.02	0.94-1.01	0.69	F	0.22	33.0	0.187
		LA	284	285	1	1.24	0.99-1.57	0.07	-	-	-	-
	MS	Total	1734	1979	2	1.18	1.06-1.34	0.004	F	0.20	39.0	NA
	SSc	Total	1835	2087	3	1.25	1.13-1.38	<0.00001	F	0.32	12.0	0.200
	JIA	Total	485	945	2	1.06	0.90-1.24	0.48	F	0.55	0.00	NA
rs2280714	SLE	Total	2730	3326	6	0.82	0.72-0.95	0.006	R	0.01	65.0	0.067
		European	1346	1247	4	0.93	0.83-10.5	0.25	R	0.001	81.2	0.281
		Asian	589	950	1	0.97	0.84-1.13	0.69	-	-	-	-
		AA	795	1129	1	0.88	0.77-1.00	0.06	-	-	-	-
	RA	Total	7670	7085	6	1.01	0.94-1.09	0.80	F	0.12	43.0	0.784
		European	2291	2663	3	1.00	0.94-1.07	0.92	F	0.87	0.00	0.521
		Asian	2708	2126	2	1.06	0.99-1.15	0.11	R	0.08	0.66	NA
		AA	2644	3236	1	0.99	0.90-1.10	NS	-	-	-	-
	MS	Total	1734	1979	2	0.87	0.72-1.05	0.16	R	0.07	71.0	NA
rs10954213	SLE	Total	5405	5427	13	1.63	1.20-2.20	0.002	R	0.02	73.0	0.350
		European	4206	4359	6	1.42	1.30-1.56	<0.00001	F	0.22	29.0	0.799
		Asian	1626	1398	3	0.96	0.83-1.11	0.57	R	0.02	76.0	0.476
		LA	1198	1592	3	1.60	1.37-1.87	<0.00001	R	0.02	73	0.072
		AA	795	1129	1	1.20	1.00-1.50	NS	-	-	-	-
	RA	Total	2883	3284	2	0.89	0.83-0.94	0.0002	F	0.35	0.00	NA
	MS	Total	2350	2573	2	1.13	1.03-1.25	0.01	F	0.36	0.00	NA
	SSc	Total	1242	1459	2	1.21	1.07-1.36	0.002	F	0.41	0.00	NA
rs2070197	SLE	Total	408	401	2	1.66	1.42-1.94	<0.00001	F	0.47	0.00	NA
Exon 6	SLE	Total	772	729	2	1.31	1.16-1.49	<0.0001	F	0.29	11.0	NA
Haplotype[a]	SLE	TT/GG	1208	1592	2	1.25	1.13-1.38	<0.0001	F	0.16	48.3	NA
		GT/GG	347	652	2	0.81	0.70-0.94	0.03	R	0.002	89.1	NA
	RA	TT/GG	1270	1313	3	1.12	1.00-1.26	0.05	F	0.62	0.00	0.213
		GT/GG	323	370	3	0.94	0.80-1.10	0.43	F	0.69	0.00	0.203

*OR = odds ratio; NS = not significant; NA = not available; MS = multiple sclerosis; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; SSc = systemic sclerosis; JIA = juvenile idiopathic arthritis; AA = African American; LA = Latin American. [a]Haplotype of rs2004640-rs2280714, data from Kelly et al. (2008), Shin et al. (2007), Rueda et al. (2006), and Kim et al. (2008).

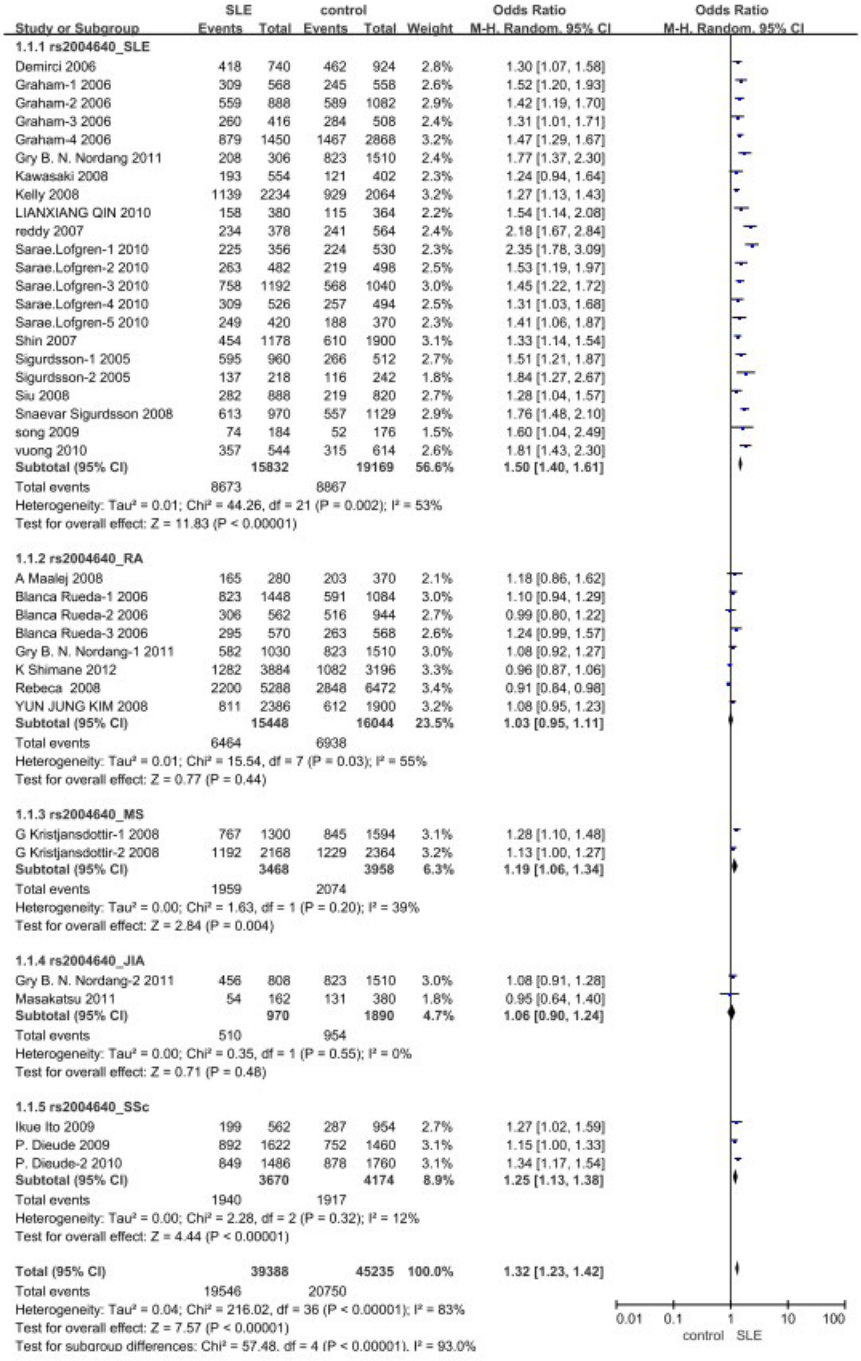

Figure 1. Forest plots of individual and pooled ORs and 95%CI from individual studies testing association of the rs2004640 polymorphism and autoimmune diseases.

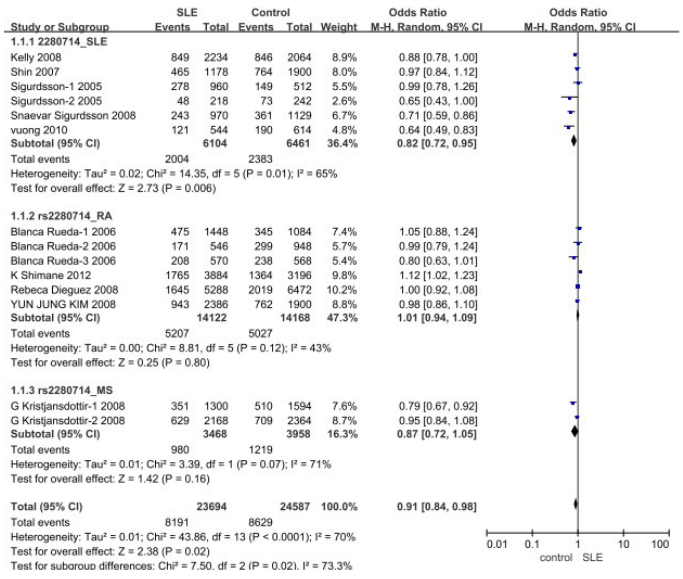

Figure 2. Forest plots of individual and pooled ORs and 95%CI from individual studies testing association of the rs2280714 polymorphism and autoimmune diseases.

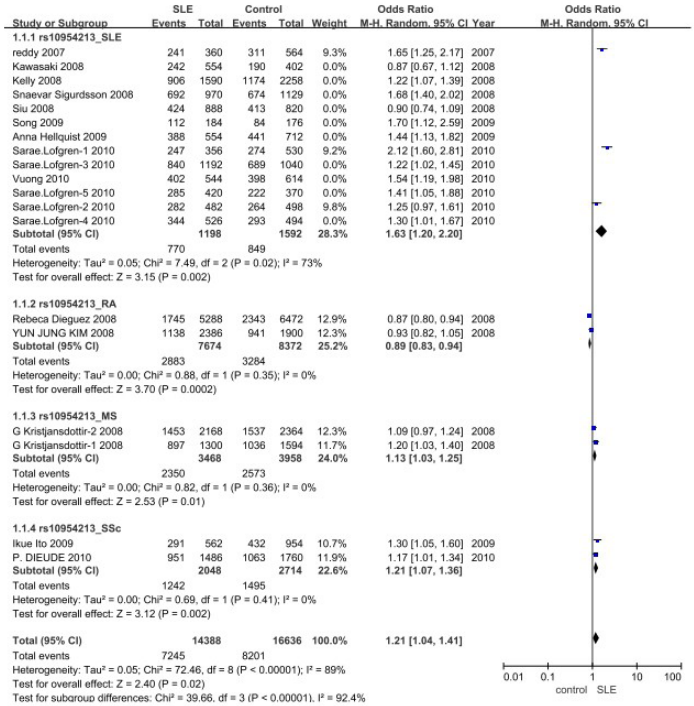

Figure 3. Forest plots of individual and pooled ORs and 95%CI from individual studies testing association of the rs10954213 polymorphism and autoimmune diseases.

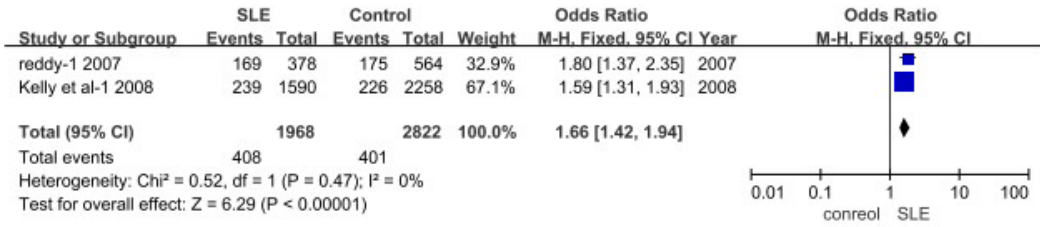

Figure 4. Forest plots of individual and pooled ORs and 95%CI from individual studies testing association of the rs2070197 polymorphism and autoimmune diseases.

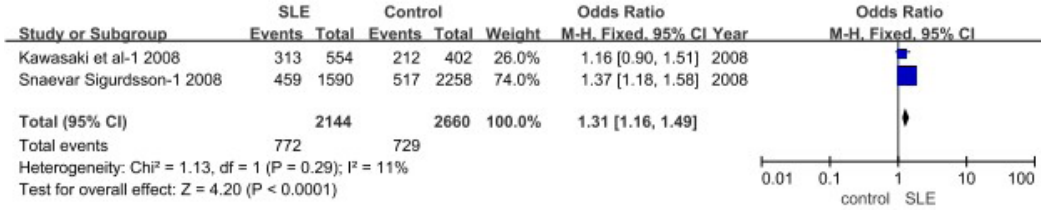

Figure 5. Forest plots of individual and pooled ORs and 95%CI from individual studies testing association of the exon 6 polymorphism and autoimmune diseases.

Compared with previous meta-analyses conducted by Lee and Song (2009), Hu and Ren (2011), and Han et al. (2009), this study revealed a significant association between 5 SNPs and SLE. Studies in population- and family-based cohorts with SLE have demonstrated that 5 SNPs were associated with SLE, indicating an important role for the type-I IFN signaling system in the pathogenesis of SLE. Furthermore, this meta-analysis revealed an association of rs2004640, rs2280714, and rs10954213 with JIA, MS, and SSc susceptibility, and of rs2070197 and the exon 6 insertion with SLE.

rs2004640 and rs10954213 were significantly associated with MS and SSc. Because of the small number of appropriate studies, we could not determine whether rs2280714, rs2070197, or the exon 6 insertion were risk factors for MS and SSc. Combined evidence indicated that MS and SSc may share several pathways with IRF5.

Three SNPs of *IRF5*, including rs2004640, rs2280714, and rs10954213 were not implicated in RA. Varying genetic backgrounds may have contributed to the different results in individual studies. Because of the crucial role of the IRF family in immune responses, other variants of IRF5 or other IRF family members may be involved in the pathogenesis leading to RA. In addition, rs2004640T is unlikely to be associated with JIA. However, we could not rule out the genetic effect of rs2004640T in the pathogenesis of JIA, possibly owing to a lack of sufficient power to detect a true association (power = 0.56) and an insufficient number of studies. The source of the varying results between Nordang et al. (2011) and Yanagimachi et al. (2011) may be due to chance or variation in the populations tested. Although RA and SLE share several pathogenic mechanisms, important differences in molecular pathways leading to the development of these diseases may exist. One of the main features that differentiates RA and SLE might be the type of IFN responses that are predominantly induced in each condition.

The rs2280714G allele was not associated with the development of SLE in Asians,

Europeans, or African Americans, which may be due to the low number of ethnic subgroups contained in the meta-analysis. The rs10954213A allele was associated with SLE in Europeans and Latin Americans, but not in Asians, which may indicate differences in genetic backgrounds between the populations.

rs2280714 is in high linkage disequilibrium with rs2004640, which allows for examination of haplotype association. In a study of SLE, carriers of a high-risk IRF5 haplotype showed higher IFN-α levels than those without the haplotype (Niewold et al., 2008), suggesting that risk variants may contribute to the pathophysiology of SLE. Our results indicated that the T-T haplotype (rs2004640T-rs2280714T) was significantly associated with an increased risk of SLE, but not RA. The haplotype containing rs2280714T without rs2004640T was not a risk haplotype in SLE, supporting the results that genetic susceptibility to SLE is mediated by the presence of exon 1B (supported by the rs2004640T allele) rather than by the overexpression of IRF5 (supported by the rs2280714T allele). Overexpression of IRF5 in the absence of the exon 1B splice site does not confer a risk of SLE.

Several limitations of this meta-analysis must be considered. First, when determining the association of rs2004640, rs2280714, rs10954213, with SLE, heterogeneity was discovered. However, the overall effect was not influenced by the heterogeneity based on the results of sensitivity analysis. Second, the number of studies and subjects collected in this meta-analysis were relatively small. Subgroup analysis for SSc, MS, and JIA included only 2 studies for the meta-analysis. Therefore, additional studies are required for further analysis. Although the available genetic data implicate IRF5 variants as determinant of autoimmune disease susceptibility, the possibility that there are other functional variants of IRF5 involved in autoimmune diseases needs to be examined.

In conclusion, this meta-analysis demonstrated that *IRF5* rs2004640 is associated with SLE, MS, and SSc, but not RA and JIA. rs2280714 may be associated with SLE, but not RA and MS. rs10954213 was significantly associated with SLE, RA, MS, and SSc. rs2070197 and the exon 6 insertion may be risk factors for SLE. The haplotype results provided further evidence that overexpression of *IRF5* in the absence of the exon 1B splice site does not confer a risk of autoimmune diseases. The finding that 5 important polymorphic sites of the same gene are associated with different diseases in different populations may provide evidence for supporting the role of this gene in diseases.

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