

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

L. Tang<sup>1\*</sup>, B. Chen<sup>2\*</sup>, B. Ma<sup>3</sup> and S. Nie<sup>4</sup>

<sup>1</sup>School of Basic Medical Sciences, Changsha Medical University, Changsha, China
<sup>2</sup>School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Shatin, Hong Kong, China
<sup>3</sup>Yunnan Walvax Biotechnology Co., Ltd., Kunming, Yunnan, China
<sup>4</sup>School of Forensic Medicine, Kunming Medical University, Kunming, Yunnan, China

\*These authors contributed equally to this study. Corresponding author: S. Nie E-mail: nieshengjie@126.com

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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

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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

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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 (rs2004640rs2280714) 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.,

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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 = 1.42-1.94, 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

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SNP	Reference	Country	Year	Diseases		No.	OR*,	Power <sup>a</sup>
							P value	$(\alpha = 0.05, OR = 1.5)$
					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	/55	1.95, 3.75 x 10 <sup>-1</sup>	85.4
				KA	515		1.19, 0.029	94.0
	Cigurdacon et el	Sweden (E)	2005	JIA SLE	404	256	1.19, 0.04/	4 77.4
	Siguiasson et al.	Sweden (E)	2003	SLE	480	121	1.51, 2.50 X 10	5 22.0
	Ship at al	Finanu (E)	2007	SLE	580	050	1.04, 9.30 X 10	07.5
	Graham et al	Argenting (LA)	2007	SLE	284	270	1.52, 0.0003	57.5
	Granani et al.	Snain (E)	2000	SEL	444	541	1.42 0.00016	88.1
		Sweden (E)			208	254	1 31 0 0426	33.3
		USA (E)			725	1434	$1.47, 3.6 \times 10^{-9}$	99.6
	Sigurdsson et al.	Swedish (E)	2008	SLE	485	563	$1.57, 5.70 \times 10^{-1}$	7 89.9
	Kristiansdottir 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	KA	140	185	1.10, 0.30	43.7
	Vuong et al. Poddy ot al	Sweden (E) Movicens (LA)	2010	SLE	180	307	$1.81, 0.1/ \times 10$ 2.18 < 0.001	58.2
	Song et al	Chinese $(\Delta)$	2007	SLE	92	282	1.78 < 0.001	26.9
	Ito et al	Iananese (A)	2009	SSC	281	477	1.70, <0.03	78.6
	Löføren et al	Mexico (LA)	2010	SLE	178	265	$2.35 \times 72 \times 10^{-1}$	<sup>9</sup> 55.8
	Loigion et ui.	Argentina (LA)	2010	0LL	241	249	$1.53, 3.56 \times 10^{-1}$	4 60.0
		Spain (E)			596	520	1.45, 4.37 x 10 <sup>-</sup>	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	55	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	1084	/9/	0.84, 0.13	96.7
	Cigurdacon et el	Swedisn (E)	2005	SLE	1084	256	0.96, 0.68	99.7
	Sigurusson et al.	Finland (E)	2005	JLE	100	121	0.65 0.23	32.0
	Shin et al	Korean $(\Delta)$	2007	SLE	580	950	0.05, 0.25	32.9 97.5
	Vuong et al	Sweden (F)	2007	SLE	272	307	0.64 0.007	67.2
	Kim et al	Korean (A)	2010	RA	1193	950	0.97 0.67	99.6
			2000		105	5(2	1 44 0 10 10	4 00.0

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

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SNP	Reference	Country	Year	Diseases	1	No.	OR*,	Power <sup>a</sup>
					Case	Control	P value	$(\alpha = 0.05, \text{OR} = 1.5)$
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 x 10 <sup>-5</sup>	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 x 10 <sup>-7</sup>	68.0
	e	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 x 10 <sup>-4</sup>	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 x 10 <sup>-9</sup>	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
	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 x 10 <sup>-2</sup>	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. \*Power calculations assume  $\alpha$  = 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).

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	Diseases	Population	Samp	le size	No. of studies		Test of associat	ion	Test	of heterogen	eity	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	Ч	0.27	17.7	0.568
		Asian	1592	1831	5	1.34	1.21-1.48	< 0.00001	ц	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	Ц	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	ц	0.20	39.0	NA
	SSc	Total	1835	2087	3	1.25	1.13-1.38	< 0.00001	ц	0.32	12.0	0.200
	JIA	Total	485	945	2	1.06	0.90-1.24	0.48	ц	0.55	0.00	NA
rs2280714	SLE	Total	2730	3326	9	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	9	1.01	0.94 - 1.09	0.80	Ц	0.12	43.0	0.784
		European	2291	2663	3	1.00	0.94-1.07	0.92	ц	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	9	1.42	1.30-1.56	< 0.00001	Ц	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	ц	0.35	0.00	NA
	MS	Total	2350	2573	2	1.13	1.03-1.25	0.01	н	0.36	0.00	NA
	SSc	Total	1242	1459	2	1.21	1.07-1.36	0.002	ц	0.41	0.00	NA
rs2070197	SLE	Total	408	401	2	1.66	1.42-1.94	< 0.00001	ц	0.47	0.00	NA
Exon 6	SLE	Total	772	729	2	1.31	1.16-1.49	< 0.0001	Ŀ	0.29	11.0	NA
Haplotype <sup>a</sup>	SLE	TT/GG	1208	1592	2	1.25	1.13-1.38	< 0.0001	Ц	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	ŝ	1.12	1.00-1.26	0.05	Ľ.	0.62	0.00	0.213
		GT/GG	323	370	3	0.94	0.80-1.10	0.43	ц	0.69	0.00	0.203

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Study cost         Funds         Total         Venants         Total         Venants         All         Random         20% CI         M-H. Random         20% CI           Damint 2006         0.09         418         740         442         242         24%         1.30 [107.158]         -           Caraham-2006         0.09         688         688         688         688         688         1.30 [107.158]         -         -           Caraham-2006         209         1.46         1.44         1.42 [119.177]         -         -         -           Caraham-2006         209         2.45         1.27 [11.37.23.0]         -<		SLE		cont	rol		Odds Ratio	Odds Ratio
1.1.1 $r_{2004640_{0}SLE}$ Demiral 2006 418 740 462 924 2.8% 1.30 [1.07, 1.58] Graham 2.2006 59 688 589 245 588 2.7% 1.42 [1.18, 1.70] The second	Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Random, 95% CI	M-H. Random, 95% Cl
Demics 2006 418 740 462 924 28% 1.30 107.158 Graham 22006 509 888 589 1082 29% 1.32 [12.0, 13.8] Graham 22006 509 888 589 1082 29% 1.32 [12.0, 13.8] Graham 22006 209 2064 528 588 2.6% 1.31 [10.1, 17.1] Graham 22001 193 224 929 2064 3.2% 1.27 [13.1.43] Kelly 2008 1139 224 929 2064 3.2% 1.24 [14.1.68] Kelly 2007 234 378 241 564 2.2% 1.53 [14.7, 284] Teddy 2007 234 378 241 564 2.2% 1.53 [14.7, 284] Teddy 2007 234 378 241 564 2.2% 1.53 [14.7, 284] Teddy 2007 234 428 219 468 2.5% 1.53 [14.1.68] Sarae Lotgren 2.010 263 482 219 468 2.5% 1.53 [14.1.68] Sarae Lotgren 2.010 3.09 526 225 7494 2.5% 1.51 [13.1.88] Sarae Lotgren 2.010 3.09 526 225 7494 2.5% 1.51 [13.1.88] Sarae Lotgren 2.010 3.09 526 212 2.7% 1.51 [13.1.89] Sarae Lotgren 2.010 3.09 526 212 2.7% 1.51 [13.1.89] Sarae Lotgren 2.010 3.09 526 102 2.7% 1.28 [14.1.10.3, 168] Sarae Lotgren 2.010 3.09 544 315 176 1.2% 1.44 [12.7, 287] Sarae Lotgren 2.010 3.09 544 315 176 1.2% 1.48 [1.0.1.69] Sarae Lotgren 2.010 3.09 544 315 176 1.2% 1.64 [1.4.1.61] Sarae Lotgren 2.006 502 5164 2.2% 1.58 [1.4.1.137] Satubota (6% CI) 1932 21 1919 56.6% 1.28 [1.4.0, 1.61] Satubota (6% CI) 1932 21 (17 = 0.000.1) 1.12 ra204440 PA Amala 2006 165 200 203 370 2.1% 1.18 [0.86, 1.62] Blanca Runds 2.206 507 263 568 2.6% 1.24 [0.98, 1.57] Ted I wents Sarae 2.2 [1.7, 1.2] [1.2, 1.2] Satubota (6% CI) 1932 21 (17 = 0.000.1) 1.14 ra204440 PA Amala 2006 165 200 203 370 2.1% 1.18 [0.04, 1.62] Satubota (6% CI) 208 244 64 2.3 % 1.08 [0.05, 1.2] Blanca Runds 2.206 505 570 283 546 2.6% 1.24 [0.98, 1.57] Ted I wents C1 = 0.07 (P = 0.45); P = 0.05; P = 0	1.1.1 rs2004640_SLE							
$ \begin{array}{c} \text{Garlam: 2006} & 309 & 568 & 246 & 568 & 246 & 1.42 [110, 1.71] \\ \text{Garlam: 32006} & 200 & 416 & 224 & 508 & 246 & 1.31 [101, 1.71] \\ \text{Garlam: 32006} & 200 & 416 & 224 & 508 & 246 & 1.31 [101, 1.71] \\ \text{Garlam: 32006} & 113 & 554 & 121 & 402 & 235 & 1.24 [104, 1.64] \\ \text{Garlam: 32006} & 113 & 254 & 121 & 402 & 235 & 1.24 [104, 1.64] \\ \text{Garlam: 32006} & 113 & 224 & 920 & 422 & 11 & 402 & 235 & 1.24 [104, 1.72] \\ \text{Garlam: 32006} & 113 & 224 & 920 & 422 & 115 & 1.27 [113, 1.64] \\ \text{Garlam: 32007} & 124 & 378 & 244 & 526 & 516 & 2.75 & 1.27 [113, 1.64] \\ \text{Garlam: 32007} & 224 & 328 & 224 & 530 & 2.35 & 2.35 [1.78, 3.09] \\ \text{Sarae Logren: 32010} & 228 & 326 & 224 & 530 & 2.35 & 2.35 [1.78, 3.09] \\ \text{Sarae Logren: 32010} & 228 & 428 & 219 & 1090 & 3.15 & 1.31 [110, 3.168] \\ \text{Sarae Logren: 32010} & 228 & 426 & 216 & 1.33 [114, 1.66] \\ \text{Sarae Logren: 32010} & 228 & 526 & 227 & 442 & 2.55 & 1.31 [110, 3.168] \\ \text{Sarae Logren: 3200 & 656 & 267 & 227 & 1.51 [121, 1.67] \\ \text{Sarae Logren: 3200 & 656 & 520 & 226 & 512 & 2.75 & 1.51 [114, 1.66] \\ \text{Sarae Logren: 5200 & 626 & 527 & 1229 & 205 & 1.76 [148, 2.10] \\ \text{Sarae Logren: 5200 & 626 & 512 & 2.75 & 1.58 [114, 1.24] \\ \text{Sarae Logren: 5200 & 626 & 512 & 2.75 & 1.58 [114, 2.46] \\ \text{Sarae Logren: 5200 & 57 & 544 & 315 & 614 & 2.65 & 1.81 [143, 2.30] \\ \text{Sarae Logren: 5200 & 577 & 544 & 315 & 614 & 2.65 & 1.81 [143, 2.30] \\ \text{Sarae Logren: 5200 & 577 & 544 & 315 & 614 & 2.65 & 1.81 [143, 2.30] \\ \text{Sarae Logren: 5200 & 528 & 200 & 370 & 2.15 & 1.59 [104, 2.46] \\ \text{Total events} & 6673 & 6697 & 1969 & 66.65 \\ \text{Hetrogeneity: Tat' = 0.05 (1.164 & 6.038 & 1.160 [164, 0.28] \\ \text{Hetrogeneity: Tat' = 0.05 (1.17 & 1.55 & 4.17 (1.6 \times 1.59) \\ \text{Sarae Logren: 5200 & 528 & 223 & 525 & 1.38 [1.00, 1.46] \\ \text{Total events} & 6446 & 638 & 1504 & 2.355 & 1.28 [104, 1.61] \\ \text{Total events} & 6164 & 678 & 1700 & 3.15 & 1.28 [10, 0.4, 0.8] \\ Hetrogeneity: Tat' = 0.05 (1.16 \times 2.16 & 1.77 (1.60 \times 1.59) \\ \text{Hetrogeneity: Tat' = 0.00 & (1.16 \times 2.16 & 1.77 (1.6 \times 1.59) \\ \text{Total even$	Demirci 2006	418	740	462	924	2.8%	1.30 [1.07, 1.58]	1
Samalling and the set of the set	Graham-1 2006	309	568	245	558	2.6%	1.52 [1.20, 1.93]	12
$ \frac{1}{12} $	Graham-2 2006 Graham-3 2006	260	416	284	1082	2.9%	1.42 [1.19, 1.70]	-
$ \begin{array}{c} \mbox{tr} y B, k \ Nording 2011 & 208 & 306 & 823 & 1910 & 2.4% & 177 (137, 2.30) \\ \mbox{tr} y B, K \ Nording 2011 & 308 & 305 & 412 & 402 & 2.3\% & 1.27 (13, 1.4.9) \\ \mbox{tr} kelly 2008 & 1139 & 2234 & 929 & 2064 & 32\% & 1.27 (13, 1.4.9) \\ \mbox{tr} kelly 2010 & 201 & 398 & 115 & 564 & 2.2\% & 1.58 (1, 14, 2.08) \\ \mbox{tr} kelly 2017 & 224 & 378 & 241 & 564 & 2.4\% & 2.16 [167, 2.84] \\ \mbox{tr} kelly 2017 & 224 & 378 & 241 & 564 & 2.4\% & 2.16 [167, 2.84] \\ \mbox{tr} kelly 2017 & 223 & 326 & 224 & 219 & 468 & 2.5\% & 1.53 (1, 19, 197) \\ strane.Ldgren+2010 & 228 & 326 & 227 & 494 & 2.5\% & 1.31 (103, 168] \\ \mbox{strane.Ldgren+2010 & 309 & 526 & 257 & 494 & 2.5\% & 1.31 [113, 1.68] \\ \mbox{strane.Ldgren+2010 & 309 & 526 & 257 & 494 & 2.5\% & 1.31 [113, 1.46] \\ \mbox{Strane.Ldgren+2010 & 309 & 526 & 257 & 494 & 2.5\% & 1.31 [113, 1.46] \\ \mbox{Strane.Ldgren+2010 & 309 & 526 & 257 & 494 & 2.5\% & 1.31 [114, 1.54] \\ \mbox{Strane.Ldgren+2010 & 309 & 526 & 257 & 494 & 2.5\% & 1.31 [114, 1.54] \\ \mbox{Strane.Sigurdsson 2006 & 613 & 674 & 656 1 12.9 & 2.0\% & 1.76 [1.46, 2.10] \\ \mbox{Strane.Sigurdsson 2008 & 613 & 674 & 656 1 12.9 & 2.0\% & 1.76 [1.46, 2.10] \\ \mbox{Strane.Sigurdsson 2008 & 614 & 626 & 12.2 & 7\% & 1.31 [1.44, 1.54] \\ \mbox{Strane.Sigurdsson 2008 & 165 & 200 & 273 & 1.12\% & 1.18 [1.64, 2.20] \\ \mbox{Strane.Sigurdsson 2008 & 165 & 200 & 203 & 370 & 2.1\% & 1.18 [1.64, 1.20] \\ \mbox{Strane.Sigurdsson 2008 & 165 & 200 & 203 & 370 & 2.1\% & 1.18 [1.64, 1.20] \\ \mbox{Strane.Sigurdsson 2008 & 165 & 200 & 203 & 370 & 2.1\% & 1.31 [1.44, 1.54] \\ \mbox{Strane.Sigurdsson 2008 & 165 & 200 & 203 & 370 & 2.1\% & 1.18 [1.64, 1.20] \\ \mbox{Strane.Sigurdsson 2006 & 165 & 200 & 203 & 370 & 2.1\% & 1.31 [1.44, 1.20] \\ \mbox{Strane.Sigurdsson 2006 & 165 & 200 & 203 & 370 & 2.1\% & 1.31 [1.60, 1.62] \\ \mbox{Strane.Sigurdsson 2006 & 165 & 200 & 203 & 370 & 2.1\% & 1.31 [1.60, 1.62] \\ \mbox{Strane.Sigurdsson 2006 & 165 & 200 & 203 & 570 & 2356 & 2.5\% & 1.32 [1.00, 1.40] \\ \mbox{Strane.Sigurdsson 2006 & 165 & 200 & 203 & 526$	Graham-4 2006	879	1450	1467	2868	3 2%	1.47 [1.01, 1.71]	-
Taximaski 2008 1193 554 121 402 2.35 124 [0.94, 1.64] Evely 2008 1193 224 629 2064 3.25 127 [1.13, 1.43] LLANKUNG DIN 2010 158 380 115 364 2.25 127 [1.57, 2.64] Same Lofgren 2010 225 356 224 530 2.35 2.35 [1.76, 3.09] Same Lofgren 2010 225 356 224 530 2.35 1.55 [1.19, 1.57] Same Lofgren 2010 78 1192 668 1040 3.05 145 [1.22, 1.72] Same Lofgren 2010 78 1192 668 1040 3.05 145 [1.22, 1.72] Same Lofgren 2010 224 482 2.74 44 2.55 1.55 [1.19, 1.57] Same Lofgren 2010 224 482 2.75 1.31 [1.03, 1.68] Same Lofgren 2010 224 88 210 820 2.75 1.31 [1.03, 1.68] Same Lofgren 2010 224 88 211 820 2.75 1.33 [1.04, 1.57] Sugurdsson 2006 122 2.88 211 820 2.75 1.38 [1.04, 1.57] Sugurdsson 2006 122 2.88 211 820 2.75 1.38 [1.04, 1.57] Sugurdsson 2006 122 2.88 2.17 15 1.55 1.10 [1.04, 1.57] Sugurdsson 2006 124 148 52 176 1.55 1.50 [1.06] 1.04 2.49] Subtack (15% CL) 1582 2.16 14 2.26 15 1.55 1.50 [1.06] 1.04 2.49] Wong 2010 357 544 315 14 2.26 15 1.55 1.50 [1.06] 1.04 2.49] Wong 2010 357 544 315 14 2.26 1.10 [1.04, 2.49] Tate for ownall effect 2 = 11.38 (1.04, 1.57] Subtack (15% CL) 1582 2.17 129 2.16 1.15 1.55 1.50 [1.60 [1.04, 2.49] Wong 2010 357 544 315 1.44 2.01 1.50 [1.06] 1.42 2.01 Tate results and the 2 = 11.36 (1.42, 2.01 1.50 [1.44, 2.01 1.57] Subtack (15% CL) 1582 2.17 (1.50 [1.54 1.26 [1.55 1.50 [1.56 [1.52]] Binca Runda 2.206 36 52 5 1570 2.55 568 2.56 1.24 [0.90, 1.57] Wong N. Nocdancy 2.011 4.52 (1.09 (2.31 160 3.35 0.09 [0.87, 1.06 [0.85, 1.23] Wong N. Nocdancy 2.011 54 12.28 612 1000 3.25 1.00 3.05 1.100 [0.95, 1.23] Wong N. Nocdancy 2.011 54.48 1064 2.35 55 1.30 [0.85, 1.11] Total events 24 0.7 (P = 0.35); P = 0.55; Test for ownall effect 2 = 0.7 (P = 0.35); P = 0.55; Test for ownall effect 2 = 0.7 (P = 0.35); P = 0.55; Test for ownall effect 2 = 0.7 (P = 0.25); P = 0.55; Test for ownall effect 2 = 0.7 (P = 0.25); P = 0.55; Test for ownall effect 2 = 0.7 (P = 0.45) 1.17 (1.00, 1.33] P. Deucle 2000 199 662 287 954 2.75 1.159 [1.00, 1.34] 1.14 re200640, S56 Nue No 2009 199 662 287 954 2.75 1.1	Gry B. N. Nordang 2011	208	306	823	1510	2.4%	1.77 [1.37, 2.30]	-
Kelly 2008 1139 2234 929 2064 3.2% 127 [1.13, 1.43] redy 2007 224 378 241 564 2.4% 2.16 [1.67, 2.84] stare_Lofgren-2010 225 365 224 530 2.3% 1.25 [1.14, 2.86] stare_Lofgren-2010 223 482 219 488 2.5% 1.53 [1.19, 1.57] stare_Lofgren-2010 293 482 219 488 2.5% 1.53 [1.19, 1.57] stare_Lofgren-2010 293 482 219 488 2.5% 1.53 [1.19, 1.57] stare_Lofgren-2010 299 526 257 444 2.5% 1.31 [1.03, 1.88] stare_Lofgren-2010 299 526 257 444 2.5% 1.31 [1.03, 1.88] stare_Lofgren-2010 299 526 257 444 2.5% 1.31 [1.04, 1.87] stare_Lofgren-2010 299 526 560 2.66 512 2.7% 1.51 [1.21, 1.87] stare_Lofgren-2010 299 526 560 2.65 122 2.7% 1.51 [1.21, 1.87] stare_Lofgren-2010 299 526 560 2.65 122 2.7% 1.51 [1.21, 1.87] stare_Lofgren-2005 137 218 116 242 1.5% 1.50 [1.04, 2.49] stare_Lofgren-2006 203 677 244 2.5% 1.51 [1.14, 2.20] stare_Lofgren-2006 203 677 244 2.1% 1.50 [1.04, 2.49] stare_Lofgren-2006 203 667 14 144 52 176 15.% 1.50 [1.04, 2.49] stare_Lofgren-2006 203 6667 14 144 2.7% 0.99 [0.80, 1.22] stare_Lofgren-2006 203 66 662 516 944 2.7% 0.99 [0.80, 1.22] Blanca Ruada-2006 203 577 2.55 568 2.6% 1.29 [0.90, 1.57] crast for overall effect 2 = 11.38 [P < 0.0001'] 1.12 rs20440, RA Maaig 2008 165 200 538 2.446 547 2.4% 0.99 [0.80, 1.22] Blanca Ruada-2006 220 5288 2464 6472 3.4% 0.99 [0.80, 1.22] Blanca Ruada-2006 220 5288 2464 6472 3.4% 0.91 [0.44, 0.88] red for overall effect 2 = 0.77 (P = 0.03); P = 55% Test for overall effect 2 = 0.77 (P = 0.03); P = 55% Test for overall effect 2 = 0.004 1 1.14 rs204440, MS G Kreilignaschir.2 2001 145 103 045 1594 3.1% 1.28 [1.10, 1.48] red for overall effect 2 = 0.004 1 1.14 rs204440, S5 Keeting provide Stare 2.20 (Ch <sup>2</sup> = 0.32; P = 0.5%; Test for overall effect 2 = 0.24; P = 0.00; P = 3.9% Test for overall effect 2 = 0.24 (P = 0.05); P = 0.5% Test for overall effect 2 = 0.24 (P = 0.05); P = 0.5% Test for overall effect 2 = 0.44 (P < 0.00001); P = 0.5%; Te 0.5% Test for overall effect 2 = 0.44 (P < 0.00001); P = 0.5%; Te 0.5% Test for overall effect 2 = 0.44 (P < 0.000	Kawasaki 2008	193	554	121	402	2.3%	1.24 [0.94, 1.64]	+
LIANKING CIN 2010 158 380 115 364 2.2% 1.54 [1.4, 2.68] weight 2007 24 376 2.41 576 2.44 2.16 [1.67, 2.44] Sarae Lofgren 2010 225 356 224 530 2.3% 2.35 [1.78, 3.09] Sarae Lofgren 2010 228 482 219 486 2.5% 1.53 [1.19, 1.57] Sarae Lofgren 2010 249 420 188 370 2.3% 1.41 [1.06, 1.87] Sarae Lofgren 2010 249 420 188 370 2.3% 1.41 [1.06, 1.87] Sarae Lofgren 2010 249 420 188 370 2.3% 1.41 [1.06, 1.87] Sarae Lofgren 2010 249 420 188 370 2.3% 1.41 [1.06, 1.87] Siguitsion 2020 5137 2.18 118 242 1.5% 1.50 [1.14, 1.54] Siguitsion 2020 5137 2.18 118 242 1.5% 1.58 [1.16] 1.42, 2.67] Sarae Lofgren 2.005 137 2.18 118 242 1.5% 1.58 [1.16] [1.4, 2.61] wong 2010 2.25 157 2.18 118 242 1.5% 1.58 [1.60 [1.04, 2.69] wong 2010 374 464 52 176 15% 1.60 [1.04, 2.69] wong 2010 374 464 52 176 15% 1.60 [1.04, 2.69] Total events 673 8867 Total events 673 8867 Total events 1.66 (2.2 - 1.16) (1.4, 2.69] Wong 2010 53 55 570 263 568 2.6% 1.26 [1.40 [1.4, 2.60] Total events 673 8867 Total events 206 362 577 2.83 568 2.6% 1.26 [1.40 [1.4, 2.60] Wong 2010 528 2.248 1022 3166 3.3% 0.96 [0.87, 1.66] Blanca Runda 206 165 280 203 370 2.1% 1.18 [0.86, 1.62] Blanca Runda 206 206 366 422 51510 3.0% 1.10 [0.41, 1.29] Blanca Runda 206 205 577 2.83 568 2.6% 1.24 [0.99, 1.57] Total events 646 4638 1022 3166 3.3% 0.96 [0.87, 1.66] Blanca Runda 2006 205 528 2.848 472 3.4% 0.97 [0.64, 0.89] YUN JUNK KM 2008 811 2.286 612 1900 3.2% 1.08 [0.95, 1.11] Total events 646 4638 1024 2.35% 1.08 [0.95, 1.13] Total events 646 4638 1024 2.35% 1.38 [1.10, 1.48] Total events 646 122 0.27 (P = 0.20); P = 30% Text for overall effect. 2 = 0.7 (P = 0.20); P = 30% Text for overall effect. 2 = 0.7 (P = 0.20); P = 30% Text for overall effect. 2 = 0.24 (P = 0.20); P = 30% Text for overall effect. 2 = 0.24 (P = 0.20); P = 30% Text for overall effect. 2 = 0.24 (P = 0.20); P = 30% Text for overall effect. 2 = 0.24 (P = 0.20); P = 30% Text for overall effect. 2 = 0.24 (P = 0.25); P = 0.26; Text for overall effect. 2 = 0.24 (P = 0.25); P = 0.26; Text	Kelly 2008	1139	2234	929	2064	3.2%	1.27 [1.13, 1.43]	-
redy 2007 244 376 241 564 24% 2.18 [1.67, 2.84] The same Logrem - 2010 253 482 219 486 2.5% 1.53 [1.19, 1.57] Same Logrem - 2010 283 482 219 486 2.5% 1.53 [1.19, 1.57] Same Logrem - 2010 283 482 219 486 2.5% 1.53 [1.19, 1.57] Same Logrem - 2010 283 482 219 486 2.5% 1.53 [1.10, 1.68] Same Logrem - 2010 283 482 219 486 2.5% 1.53 [1.10, 1.68] Same Logrem - 2010 284 41 177 610 1900 3.1% 1.51 [1.21, 1.67] Same Logrem - 2010 282 882 128 830 2.7% 1.51 [1.21, 1.67] Sigurisson - 2005 95 560 2.66 512 2.7% 1.51 [1.21, 1.67] Sigurisson - 2005 95 70 557 1129 2.5% 1.68 [1.04, 1.67] Same Logrem - 2010 249 420 188 200 2.7% 1.28 [1.04, 1.67] Same Logrem - 2010 249 420 188 200 2.7% 1.28 [1.04, 1.67] Same Visual and Visual 248, df = 21 [1.66, 1.62] Same Logrem - 2010 244 26, df = 21 [1.66, 1.62] Total events 267 3 867 Heter ogeneity: Tau' = 0.01: Ch' = 428, df = 21 [1.66, 1.62] Subtola (15% Ch) 1582 11916 9.66 9% 1.50 [1.40, 1.61] Total events 267 3 1428 591 1084 3.0% 1.18 [1.43, 2.30] Same Audiot 2006 165 200 203 370 2.1% 118 [0.68, 1.62] Heter ogeneity: Tau' = 0.01: Ch' = 428, df = 21 [1.00, 2.37] Subtola (15% Ch) 1582 100 2.33 1510 3.0% 1.09 [0.20, 1.67] For worall effect 2 = 11.33 [P < 0.0001) 1.1.2 rs200440, PA A mala 2006 122 288 1468 2316 3.5% 1.09 [1.60, 1.67] For worall effect 2 = 0.77 (P = 0.44) 1.1.3 rs2004440, MS C Kreignasoditri - 2006 777 1200 245 1594 3.1% 1.28 [1.10, 1.48] C Kreignasoditri - 2006 777 1200 245 1594 3.1% 1.08 [0.91, 1.28] Method (pers) Ch 1544 100 44 2.35% 1.103 [0.95, 1.11] 1.14 rs206460, JA C Kreignasoditri - 2006 777 1200 445 1594 3.1% 1.18 [1.10, 1.48] C Kreignasoditri - 2006 777 120 - 0.43; 171 [1.00, 1.30] For worall effect 2 = 0.77 (P = 0.44) 1.14 rs206460, JA C Kreignasoditri - 2006 777 1200 445 1594 3.1% 1.15 [1.10, 1.38] P. Bucked 0.916 44 (683 1.40] Subtoal (65% Ch) 3468 237 510 3.0% 1.22 [1.21, 1.42] 1.14 rs204440, JA C Kreignasoditri - 2006 (Ch' = 2.33, df = 1 (P = 0.25); P = 35% Test for overall effect 2 = 0.21 (P = 0.25); P = 35% Test for over	LIANXIANG QIN 2010	158	380	115	364	2.2%	1.54 [1.14, 2.08]	-
Same Logren 2010 225 356 224 530 2.3% 2.35 [1.76, 3.09] Same Logren 2010 234 482 219 486 2.5% 1.55 [1.19, 1.97] Same Logren 2010 249 420 188 370 2.3% 1.45 [1.22, 1.72] Same Logren 2010 249 420 188 370 2.3% 1.41 [1.06, 1.87] Same Logren 2010 249 420 188 370 2.3% 1.41 [1.06, 1.87] Same Logren 2010 249 420 188 370 2.3% 1.41 [1.06, 1.87] Same Logren 2010 249 420 188 370 2.3% 1.41 [1.06, 1.87] Same Logren 2010 249 420 188 370 2.3% 1.41 [1.06, 1.87] Same Logren 2010 357 544 315 614 2.26% 1.58 [1.19, 1.43] Saugutsson 2006 613 970 557 1129 2.9% 1.76 [1.48, 2.10] Same 2008 74 184 52 176 1.5% 1.60 [1.04, 2.49] Subtoal (95% CI) 1582 109 68.7% 1.59 [1.40, 1.81] Subtoal (95% CI) 15832 19169 56.8% 1.59 [1.40, 1.81] Subtoal (95% CI) 15832 19169 56.8% 1.19 [1.43, 2.30] Total events 867 442.6, df = 21 ( $P = 0.022$ ; $P = 53\%$ Test for overall effect 2 = 1.13.3 ( $P < 0.0000$ ) 1.12 rs200440 ,RA A Maalg 2008 165 280 203 370 2.1% 1.18 [0.66, 1.62] Blanca Ruadis 2006 823 1448 591 1004 3.0% 1.10 [0.94, 1.29] Blanca Ruadis 2006 220 528 248 6472 3.4% 0.99 [0.80, 1.22] Blanca Ruadis 2006 220 528 248 6472 3.4% 0.99 [0.87, 1.66] Rebeca 2008 720 528 248 4672 3.4% 0.99 [0.87, 1.66] Rebeca 2008 720 528 248 477 ( $P = 0.03$ ; $P = 55\%$ Test for overall effect 2 = 1.128 (1.47 ( $P = 0.33$ ; $P = 55\%$ Test for overall effect 2 = 0.44) 1.1.3 rs200440 ,MS C Kreigmaddim 2001 Ch <sup>2</sup> = 1.54, df = 7 ( $P = 0.33$ ; $P = 55\%$ Test for overall effect 2 = 0.74 ( $P = 0.35$ ; $P = 0.5\%$ Test for overall effect 2 = 0.74 ( $P = 0.35$ ; $P = 0.5\%$ Test for overall effect 2 = 0.74 ( $P = 0.35$ ; $P = 0.5\%$ Test for overall effect 2 = 0.74 ( $P = 0.35$ ; $P = 0.5\%$ Test for overall effect 2 = 0.74 ( $P = 0.35$ ; $P = 0.5\%$ Test for overall effect 2 = 0.74 ( $P = 0.35$ ; $P = 0.5\%$ Test for overall effect 2 = 0.74 ( $P = 0.35$ ; $P = 0.5\%$ Test for overall effect 2 = 0.74 ( $P = 0.35$ ; $P = 0.5\%$ Test for overall effect 2 = 0.74 ( $P = 0.35$ ; $P = 0.5\%$ Test for overall effect 2 = 0.74 ( $P = 0.35$ ; $P = 0.5\%$ Test for overall effect 2 = 0.74 ( $P $	reddy 2007	234	378	241	564	2.4%	2.18 [1.67, 2.84]	
Same Lofgren 2 2010 263 482 219 488 2.5% 1.53 [1.19, 1.97] Same Lofgren 2 2010 788 1192 568 1040 3.0% 1.45 [1.22, 1.72] Same Lofgren 2 2010 244 220 188 102 55% 1.31 [1.02, 1.68] Sin 2007 454 1178 610 1900 3.1% 1.33 [1.4, 1.54] Sin 2007 454 1178 610 1900 3.1% 1.33 [1.4, 1.54] Sigurisson 2 2005 137 218 116 242 1.8% 1.44 [1.27, 2.67] Sigurisson 2 2005 208 22 888 219 820 2.7% 1.28 [1.04, 1.57] Same Lofgren 2 2005 137 7 184 216 2.26% 1.76 [1.44, 2.10] Same Lofgren 2 2005 137 7 184 2176 1.5% 1.60 [1.04, 2.49] subtotal (8% C) 1582 1916 56.6% 1.50 [1.44, 1.51] Total events 1001 Che 673 8087 Heterogenety, Tat <sup>2</sup> = 0.01 Che <sup>2</sup> 442.6 (d = 21 (P = 0.02); P = 53% Test for overall effect 2 = 11.83 (P < 0.0001) 1.12 re200440 PA Managi 2006 165 280 203 37 2.1% 1.9 [1.06, 1.62] Bimora Ruech-2 2005 908 562 516 944 2.7% 99 [1.06, 1.62] Bimora Ruech-2 2005 908 562 516 944 2.7% 99 [1.06, 1.22] Bimora Ruech-2 2005 928 570 2.35 568 2.26% 1.24 [1.09, 1.57] Cy B N Nordang-1 2011 582 1030 823 1510 3.0% 1.10 [1.04, 1.29] Bimora Ruech-2 2005 928 570 2.35 568 2.5% 1.24 [1.99, 1.57] Cy B N Nordang-1 2011 582 1030 823 1510 3.0% 1.10 [1.04, 1.29] Bimora Ruech-2 2005 928 2246 6472 3.4% 9.91 [0.81, 1.09] Cy B N Nordang-1 2011 1228 61 12900 3.23 % 1.04 [1.09, 1.12] Subtotal (95% C) 15448 10644 2.35% 1.03 [0.95, 1.11] Total events 644 6038 Heterogenetity. Tat' = 0.01; Chr = 1.54, d = 7 (P = 0.3); P = 55% Test for overall effect; 2 = 0.17 (P = 0.44) 1.1.3 re200440_MS C Knisjanadotti-1 2008 767 100 845 1594 3.1% 1.28 [1.10, 1.48] C Knisjanadotti-2 200 5.17 (P = 0.43); P = 0.39; P = 55% Test for overall effect; 2 = 0.17 (P = 0.3); P = 0.39; P = 55% Test for overall effect; 2 = 0.17 (P = 0.3); P = 0.39; P = 55% Test for overall effect; 2 = 0.17 (P = 0.3); P = 0.39; P = 12% Test for overall effect; 2 = 0.17 (P = 0.3); P = 0.30; P = 55% Test for overall effect; 2 = 0.17 (P = 0.3); P = 0.30; P = 12% Test for overall effect; 2 = 0.17 (P = 0.3); P = 12% Test for overall effect; 2 = 0	Sarae.Lofgren-1 2010	225	356	224	530	2.3%	2.35 [1.78, 3.09]	
Sarae.Logren-2010 768 1192 568 1040 3.0% 1.48 [122,172] Sarae.Logren-2101 200 526 27 444 2.5% 1.3 [10.1,16] Sarae.Logren-2010 249 420 188 370 2.3% 1.41 [10.6, 187] Sarae.Logren-2005 137 218 116 242 118% 1.44 [1.7, 2.67] Sugurdsson-22005 137 218 116 242 118% 1.44 [1.7, 2.67] Su 2008 242 688 219 820 2.7% 1.28 [1.44, 1.57] song 2008 242 688 219 820 2.7% 1.28 [1.44, 1.57] song 2008 242 888 219 820 2.7% 1.28 [1.44, 1.57] song 2008 242 888 219 820 2.7% 1.28 [1.44, 1.57] song 2008 242 888 219 820 2.7% 1.28 [1.44, 1.57] song 2008 242 888 219 820 2.7% 1.28 [1.44, 2.40] Total events 0.01 7.04* 44.28, df = 21 (P = 0.002); P = 53% Test for overall effect; 2 = 11.83 (P < 0.0002); P = 53% Test for overall effect; 2 = 11.83 (P < 0.0002); P = 55% Test for overall effect; 2 = 12.82 884 1002 3150 3.0% 1.00 [0.4, 1.29] Bianca Rueds-2006 822 1448 591 1004 3.0% 1.100 [0.4, 1.29] Bianca Rueds-2006 822 1448 591 1004 3.0% 1.00 [0.4, 1.29] Bianca Rueds-2006 822 1448 591 1004 3.0% 1.00 [0.4, 1.29] Bianca Rueds-2006 822 1448 591 1004 2.3% 0.99 [0.6, 1.22] FX Simane 2.012 12 128 284 1022 3166 3.3% 0.99 [0.6, 1.22] Subtoal (95% Cf) 152 2864 1022 3166 3.3% 0.99 [0.6, 1.20] Subtoal (95% Cf) 1528 612 1900 3.2% 1.08 [0.92, 1.27] VI J.UN KIM 2008 767 1300 845 1594 3.1%, 1.28 [1.10, 1.48] Heterogeneity: Tau* 0.07 (Ch* = 15.5, df = 7 (P = 0.03); P = 55% Test for overall effect; 2 = 0.77 (P = 0.44) 1.1.3 rs2004440_MS C Kraiganadottri 2008 767 1300 845 1594 3.1%, 1.28 [1.10, 1.48] Subtoal (95% Cf) 159 2070 1998 4.7%, 1.13 [1.00, 1.27] Subtoal (95% Cf) 1999 207 1456 808 823 1510 3.0%, 1.08 [0.91, 1.28] Heterogeneity: Tau* 0.07 (Ch* = 1.5, df = 1 (P = 0.20); P = 39% Test for overall effect; 2 = -3.77 (P = 0.04) 1.1.4 rs200440_JSC Intal events 1959 2070 1456 808 823 1510 3.0%, 1.08 [0.91, 1.28] Notation (95% Cf) 199 540 2.28 94 4.2.7%, 1.27 [1.02, 1.59] P.Buade 2000 69 199 562 287 964 2.7%, 1.27 [1.02, 1.59] P.Buade 2009 69 199 562 287 964 2.7%, 1.27 [1.02, 1.59] P.Buade 2009 69 199 562 287 964 2.7%, 1.27 [1.02, 1.	Sarae.Lofgren-2 2010	263	482	219	498	2.5%	1.53 [1.19, 1.97]	I
Same Longren 2010 309 5.26 227 494 2.5% 1.31 [1.03, 1.80] Same Longren 2010 4420 1186 370 2.25% 1.44 [1.03, 1.80] Sin 2007 454 1178 610 1900 3.1% 1.33 [1.44, 1.54] Sin 2007 454 1178 610 1900 3.1% 1.33 [1.44, 1.54] Sigurdsson-12005 969 960 266 512 2.7% 1.26 [1.04, 1.57] Sigurdsson-2005 137 218 116 242 18% 1.44 [1.27, 2.67] Same Visual 2008 282 888 219 820 2.7% 1.28 [1.04, 1.57] Sneaver Sigurdsson 2008 613 970 557 1129 2.9% 1.76 [1.48, 2.10] subtotal (19% C) 15832 19189 56.8% 1.50 [1.40, 1.61] Total events 8673 6867 Heterogeneity: Tat' = 0.01; Ch <sup>2</sup> 442.6gt = 21 ( $P = 0.02$ ); P = 53% Test for overall effect: 2 = 11.83 ( $P < 0.00001$ ) 1.12 rs200460_RA A Maniej 2008 165 280 203 370 2.1% 1.18 [0.66, 1.62] Bianca Rueda-2006 306 562 510 944 2.7% 0.99 [0.61, 1.29] Bianca Rueda-2006 306 562 510 944 2.7% 0.99 [0.61, 1.29] Bianca Rueda-2006 2205 257 283 568 2.6% 1.24 [0.99, 1.57] Cy B. N. Kordan-12011 524 2030 823 1510 3.0% 1.08 [0.95, 1.23] Subtotal (19% C) 1548 10644 2.3% 0.91 [0.84, 0.99] VIN JUNG KIM 2008 811 2386 612 1900 3.2% 1.08 [0.95, 1.13] Total events 6464 6938 Heterogeneity: Tat' = 0.0; Ch <sup>2</sup> = 0.55; P = 0.3; P = 55% Test for overall effect: 2 = 0.77 ( $P = 0.43$ ) 1.13 rs200460_MS CKristjanadotti-2 2008 1192 2168 1229 2344 3.2% 1.13 [1.00, 1.27] Subtotal (19%; C) 3468 3958 6.3% 1.19 [1.66, 1.34] Total events 1959 2074 Heterogeneity: Tat' = 0.0; Ch <sup>2</sup> = 2.8, ( $P = 0.03$ ; $P = 55\%$ Test for overall effect: 2 = 0.71 ( $P = 0.43$ ) 1.14 rs2004640_MS CKristjanadotti-2 2008 1192 2168 1229 2364 3.2% 1.13 [1.00, 1.27] Subtotal (19%; C) 3567 4174 8.9% 1.28 [1.10, 1.48] CKristjanadotti-2 200 Reg 246 7170 7180 4.7% 1.08 [0.91, 1.28] Total events 1959 P. Deude 2009 Reg 2162 752 1460 3.1% 1.28 [1.10, 1.48] CKristjanadotti-2 200 Reg 246 2475 246 4.27% 1.27 [1.02, 1.59] P. Deude 2009 Reg 2162 752 1460 3.1% 1.34 [1.15, 1.64] Total events 1954 20750 Heterogeneity: Tat' = 0.0; Ch' = 2.28, df = 2 ( $P = 0.32$ ; $P = 12\%$ Total events 1954 1468 6.97 1470 1.35 [1.13, 1.38] Total events 1954 1468	Sarae.Lofgren-3 2010	758	1192	568	1040	3.0%	1.45 [1.22, 1.72]	
Saria Logien-2.2010 249 4.20 168 3.70 2.3% 1.41 [1.06, 1.47] Sigurdsson-12005 595 960 266 512 2.7% 1.51 [1.21, 1.87] Sigurdsson-22005 137 218 116 242 1.8% 1.44 [1.27, 2.67] Su 2008 242 8.88 219 8.20 2.7% 1.28 [1.04, 1.57] song 2008 74 194 52 176 1.5% 1.60 [1.04, 2.49] song 2009 74 194 52 176 1.5% 1.60 [1.04, 2.49] Subtrat [95% C] 15832 19169 56.8% 1.50 [1.40, 1.61] Total events 8673 8867 Heterogeneity. Tau' = 0.01; Chr = 44.26, df = 21 ( $P = 0.02$ ); $P = 53\%$ Test for overall effect: 2 = 11.83 ( $P < 0.000$ )1) 1.12 rs2004640_RA A Maalg 2008 165 280 203 370 2.1% 1.18 [0.66, 1.62] Blanca Rueda-12006 622 1448 591 1004 3.0% 1.00 [0.94, 1.29] Blanca Rueda-2006 306 562 516 944 2.7% 0.99 [0.80, 1.22] Blanca Rueda-2006 300 5662 516 944 2.7% 0.99 [0.80, 1.22] Blanca Rueda-2006 300 5662 516 944 2.7% 0.99 [0.80, 1.22] Blanca Rueda-2006 302 1448 510 04.3.0% 1.10 [0.94, 1.29] Blanca Rueda-2006 322 1448 5472 3.4% 0.91 [0.84, 0.99] 1.571 Gry B. N. Nerdang-1 2011 582 1030 823 1510 3.0% 1.08 [0.92, 1.27] VUN JUNG KIM 2008 112 286 41 [2400 2.37% 1.03 [0.95, 1.11] Total events 6464 6038 Heterogeneity. Tau' = 0.01; Chr = 15.54, df = 7 ( $P = 0.03$ ); $P = 55\%$ Test for overall effect: Z = 0.77 ( $P = 0.44$ ) 1.1.3 rs2004440_MS C Kristjamadctin-2 2006 1132 2168 1229 2344 3.2% 1.13 [1.00, 1.27] Subtrat (195% C) 15448 3958 3.1% 1.28 [1.10, 1.48] C Kristjamadctin-2 2006 1132 2168 1229 2344 3.2% 1.13 [1.00, 1.27] Subtrat (195% C) 3488 3958 4.31 151 0.0% 1.08 [0.91, 1.28] Maskatsu 2011 456 80.08 823 1510 3.0% 1.08 [0.91, 1.28] Maskatsu 2011 456 80.08 823 1510 3.0% 1.08 [0.91, 1.28] Heterogeneity. Tau' = 0.00; Chr = 2.58, df = 7 ( $P = 0.35$ ); $P = 0\%$ Total events 1959 2074 Heterogeneity. Tau' = 0.00; Chr = 2.28, df = 0.00; $P = 0.55$ ; $P = 0\%$ Test for overall effect: Z = 0.57 ( $P = 0.48$ ) 1.1.5 rs200440_SSC Heterogeneity. Tau' = 0.00; Chr = 2.28, df = 0.000; $P = 55\%$ 1.22 [1.0, 1.59] P. Deude 2009 692 622 752 1460 3.1% 1.32 [1.23, 1.42] Maskatsu 2011 456 80.68 823 1510 3.0% 1.32 [1.23, 1.42] F Demodem	Sarae.Lofgren-4 2010	309	526	257	494	2.5%	1.31 [1.03, 1.68]	<u> </u>
Sint 2007 454 110 610 1500 5.7% 1.55 [1.4, 1.54] Sigurdsson-22005 137 218 116 242 1.8% 1.44 [127, 247] Sigurdsson-22005 137 218 116 242 1.8% 1.44 [127, 247] Sint 2008 2008 21 24 288 219 20 2.7% 1.28 [104, 1.57] Snaver Sigurdsson 2008 61 970 557 1129 2.9% 1.76 [1.48, 2.10] Total events 8673 687 Heterogeneity: Tau* = 0.01; Ch* = 42.8; dt = 21 (P = 0.02); P = 53% Test for overall effect: Z = 11.83; P < 0.0001) 1.1.2 rs200440_RA Amalej 200 126 22 1448 591 1084 3.0% 1.10 [0.64, 1.62] Blanca Rueds-2006 305 22 548 244 45 561 24%, 0.9% 1.08 [0.57, 1.66] Blanca Rueds-2006 306 562 510 944 2.7% 0.99 [0.61, 122] Blanca Rueds-2006 306 562 510 944 2.5% 1.44 [0.99, 1.57] CK Shimana 2012 1282 3844 1082 3166 3.3% 0.96 [0.67, 1.66] Ruebca 2008 212448 591 1084 3.0% 1.08 [0.95, 1.21] K Shimana 2012 1282 3844 1082 3166 3.3% 0.96 [0.67, 1.66] Ruebca 2008 200 5288 2546 4727 3.3% 1.08 [0.95, 1.11] Total events 6464 6638 Heterogeneity: Tau* = 0.01; Ch* = 15.5, dt = 7 (P = 0.03); P = 55% Test for overall effect: Z = 0.77 (P = 0.44) 1.1.3 rs200440_MS CKreignandottri-2008 112 246 1229 2074 Heterogeneity: Tau* = 0.05; Ch* = 15.5, dt = 7 (P = 0.20); P = 39% Test for overall effect: Z = 0.77 (P = 0.44) 1.1.4 rs200440_UNS CKreignandottri-2008 1192 2168 1229 2344 3.2% 1.13 [1.00, 1.27] Subtrotal (95%; Ch) 3468 3958 6.37% 1.08 [0.91, 1.28] Masakatus 2011 456 808 823 1510 3.0% 1.08 [0.91, 1.28] Masakatus 2011 456 808 823 1510 3.0% 1.08 [0.91, 1.28] Masakatus 2011 456 808 823 1510 3.0% 1.08 [0.91, 1.28] Masakatus 2011 456 808 823 1510 3.0% 1.08 [0.91, 1.28] Masakatus 2011 456 808 823 1510 3.0% 1.08 [0.91, 1.28] Masakatus 2011 456 808 823 1510 3.0% 1.08 [0.91, 1.28] Masakatus 2011 456 808 823 1510 3.0% 1.08 [0.91, 1.28] Masakatus 2011 456 808 823 1510 3.0% 1.08 [0.91, 1.28] Masakatus 2011 456 807 970 4174 8.9% 1.25 [1.13, 1.38] Masakatus 2011 456 807 970 4174 8.9% 1.25 [1.13, 1.38] Masakatus 2010 491 1486 671 7700 3.1% 1.34 [1.17, 1.54] Masakatus 2010 491 1486 77 770 4174 8.9% 1.32 [1.23, 1.42] Masakatus 201	Sarae.Lotgren-5 2010	249	420	188	370	2.3%	1.41 [1.06, 1.87]	
Significan-22005 137 218 12 21.5% 1.5% 1.5% 1.5% 1.5% 1.5% 1.5% 1.5%	Sigurderop 1 2005	404	060	266	1900	3.1%	1.33 [1.14, 1.34]	-
Subtrain (2000) 105 113 119 129 205 105 1129 129 205 105 117 [148, 210] Snaever Sigurdson 2008 613 970 557 1129 2.9% 1.76 [148, 210] song 2009 74 164 52 176 155% 1.60 [1.04, 249] vuong 2010 357 544 315 614 2.6% 1.81 [1.43, 2.30] Total events 8673 8687 Heterogeneity: Tau" = 0.01: Ch <sup>+</sup> = 42.8, df = 21 (P = 0.002); P = 53% Test for overall effect Z = 11.83 (P < 0.0001) 1.12 rs2004640_FA A Maaiej 2006 165 280 203 370 2.1% 1.18 [0.86, 1.62] Blanca Rueda-2006 805 652 516 944 2.7% 0.99 (0.80, 1.22] Blanca Rueda-2006 205 5570 283 568 2.8% 1.24 (0.96, 1.57] Gry B. N. Nordang-1 2011 552 1030 843 1510 3.0% 0.96 (0.87, 1.26] VUN JUNG KIM 2008 2190 5288 248 6472 2.4% 0.91 (0.84, 2.17] K Shimana 2012 1282 3884 1082 3196 3.3% 0.96 (0.87, 1.66] VUN JUNG KIM 2008 2190 5288 248 6472 2.4% 0.91 (0.84, 1.27] Subtrai (95% CI) 6444 6938 Heterogeneity: Tau" = 0.01; Ch <sup>+</sup> = 1.54, df = 7 (P = 0.03); P = 55% Test for overall effect Z = 0.77 (P = 0.43) 1.13 rs204640_MS C Krisignasotin-2 2006 767 1300 845 1594 3.1% 1.28 [1.10, 1.48] G Krisignasotin-2 2006 767 1300 845 1594 3.1% 1.28 [1.10, 1.48] Heterogeneity: Tau" = 0.00; Ch <sup>+</sup> = 1.63, df = 1 (P = 0.20); P = 39% Test for overall effect Z = 0.77 (P = 0.35); f = 1 (P = 0.20); P = 39% Test for overall effect Z = 0.77 (P = 0.35); f = 1 (P = 0.25); P = 0% Test for overall effect Z = 0.71 (P = 0.48) 1.13 rs204640_JK GY Kisignasotin-1 2000 769 131 380 4.7% 1.06 [0.94, 1.28] Total events 1959 2074 Heterogeneity: Tau" = 0.00; Ch <sup>+</sup> = 0.35, df = 1 (P = 0.25); P = 0% Test for overall effect Z = 0.71 (P = 0.48) 1.15 rs204640_JK GY B. N. Nordang-2 2011 456 808 823 1510 3.0% 1.08 [0.94, 1.28] Total events 1959 2074 Heterogeneity: Tau" = 0.00; Ch <sup>+</sup> = 0.35, df = 1 (P = 0.25); P = 0% Test for overall effect Z = 0.71 (P = 0.48) 1.15 rs204640_JSC Kou to 2000 892 1622 752 1460 3.1% 1.32 [1.23, 1.42] Total events 1940 1917 Heterogeneity: Tau" = 0.00; Ch <sup>+</sup> = 2.88, df = 2 (P = 0.32); P = 12% Test for overall effect Z = 2.75 (P < 0.00001) Test for overall effect Z = 2.	Sigurdsson-2 2005	137	218	116	342	1.8%	1.84 [1.27, 2.67]	
$ \begin{array}{c} \text{Subtract} Sigurdsson 2006 & 13 & 970 & 557 & 1128 & 2.9\% & 1.76 & 1.5\% & 1.60 [1.04, 2.49] \\ \text{song 2009 } 74 & 164 & 52 & 176 & 1.5\% & 1.60 [1.04, 2.49] \\ \text{subtract} [95\%; C] & 15332 & 19169 & 56.6\% & 1.56 [1.40, 2.49] \\ \text{Total events } & 6673 & 6867 & 1.56 [1.40, 2.49] \\ \text{Hetrogeneity: Tau" = 0.01; Ch" = 44.26, df = 21 (P = 0.002); P = 53\% \\ \text{Test for overall effect Z = 11.83 (P < 0.00001) \\ \textbf{1.12 rs2004640_RA \\ \text{A Masiej 2008 } & 165 & 280 & 203 & 370 & 2.1\% & 1.18 [0.86, 1.62] \\ \text{Blanca Ruedn-2006 } & 253 & 1448 & 591 & 1064 & 30\% & 1.10 [0.94, 1.29] \\ \text{Blanca Ruedn-2006 } & 255 & 570 & 263 & 568 & 2.6\% & 1.24 [0.90, 1.27] \\ \text{Blanca Ruedn-2006 } & 255 & 570 & 263 & 568 & 2.6\% & 1.24 [0.90, 1.27] \\ \text{Blanca Ruedn-2006 } & 225 & 570 & 263 & 568 & 2.6\% & 1.24 [0.90, 1.27] \\ \text{Blanca Ruedn-2006 } & 225 & 570 & 263 & 568 & 2.6\% & 1.24 [0.90, 1.27] \\ \text{Rowtang-2012 } & 1282 & 3864 & 1082 & 3196 & 3.3\% & 0.96 [0.87, .06] \\ \text{Rowtang-2012 } & 1282 & 3864 & 1082 & 3196 & 3.3\% & 0.96 [0.87, .06] \\ \text{Rowtang-12011 } & 582 & 612 & 1900 & 3.2\% & 1.08 [0.95, 1.23] \\ \text{Subtral} [95\%; C] & 15448 & 16044 & 2.3\% & 1.03 [0.95, 1.23] \\ \text{Subtral} [95\%; C] & 15448 & 1229 & 2364 & 3.7\% & 1.13 [1.00, 1.27] \\ \text{Subtral} [95\%; C] & 1543 & 1229 & 2364 & 3.7\% & 1.13 [1.00, 1.27] \\ \text{Total events } & 6464 & 6938 & 633 & 1.19 [1.06, 1.34] \\ \text{Total events } & 1959 & 2074 & 1899 & 4.7\% & 1.08 [0.91, 1.28] \\ \text{Metrogeneiny: Tau" = 0.00; Ch" = 1.63, df = 1 (P = 0.25); P = 0\% \\ \text{Test for overall effect: Z = 2.84 (P = 0.004) \\ 1.1.4 rs204640_JIA \\ \text{Gy B. N. Nordang-2 2011 } & 456 & 808 & 823 & 1510 & 3.0\% & 1.08 [0.91, 1.28] \\ \text{Meartogeneiny: Tau" = 0.00; Ch" = 0.35, df = 1 (P = 0.55); P = 0\% \\ \text{Test for overall effect: Z = 0.71 (P = 0.43) \\ 1.15 rs204640_JSC \\ \text{Iue Ito 2009 } & 199 & 562 & 287 & 954 & 2.7\% & 1.27 [1.02, 1.59] \\ \text{P. Deude 2000 } & 892 & 1622 & 752 & 1460 & 3.1\% & 1.32 [1.21, 1.3] \\ \text{Dol events } & 1940 & 1917 \\ Heterogeneiny: Tau" = 0.00; Ch" = 2.28, df = 2 (P = 0.32); P = 12\% \\ \text{Test for overal$	Sig 2008	282	888	219	820	2 7%	1 28 [1 04 1 57]	
sorg 2006	Snaevar Sigurdsson 2008	613	970	557	1129	2.9%	1.76 [1.48, 2.10]	-
$\begin{aligned} & \text{using 2010} & 377 & 544 & 315 & 614 & 2.6\% & 1.61 [1.43, 2.30] \\ & \text{Subtotal (95% C)} & 15832 & 19169 & 56.6\% & 1.50 [1.40, 1.61] \\ & \text{Total events} & 8673 & 8867 \\ & \text{Heterogeneity. Tau" = 0.01; Ch" = 44.26, df = 21 (P = 0.002); P = 53\% \\ & \text{Test for overall effect. 2 = 11.83 (P < 0.00001)} \\ & \text{1.12 rs2004640_RA} \\ & \text{A Maalej 2006} & 165 & 280 & 203 & 370 & 2.1\% & 1.18 [0.86, 1.62] \\ & \text{Blanca Rueda-1 2006} & 522 & 1448 & 591 & 1064 & 3.0\% & 1.10 [0.54, 1.29] \\ & \text{Blanca Rueda-2 2006} & 306 & 562 & 516 & 944 & 2.7\% & 0.99 [0.80, 1.22] \\ & \text{Blanca Rueda-3 2006} & 2285 & 570 & 2283 & 568 & 25\% & 1.24 [0.99, 1.57] & 696 [0.87, 1.06] \\ & \text{Reteca 2008} & 2280 & 5288 & 2486 & 6472 & 3.4\% & 0.96 [0.87, 1.06] \\ & \text{Reteca 2009} & 2280 & 5288 & 2486 & 6472 & 3.4\% & 0.96 [0.87, 1.06] \\ & \text{Reteca 2008} & 11 & 2386 & 612 & 1900 & 3.2\% & 1.08 [0.95, 1.23] \\ & \text{Subtotal (95% C)} & 1544 & 6938 & 46424 & 2.5\% & 1.08 [0.95, 1.23] \\ & \text{Subtotal (95% C)} & 1544 & 6938 & 46424 & 2.5\% & 1.08 [0.95, 1.23] \\ & \text{Reterogeneity: Tau" = 0.01; Ch" = 15.8, df = 7 (P = 0.03;)! = 55\% \\ & \text{Test for overall effect. 2 = 0.77 (P = 0.44) & 1.13 [1.00, 1.27] \\ & \text{Subtotal (95% C)} & 3468 & 3395 & 6.3\% & 1.19 [1.06, 1.34] \\ & \text{Total events} & 1959 & 2074 \\ & \text{Heterogeneity: Tau" = 0.00; Ch" = 1.63, df = 1 (P = 0.26); P = 9\% \\ & \text{Test for overall effect. 2 = 2.54 (P = 0.004) & 1.19 [1.02, 1.59] \\ & \text{Total events} & 510 & 954 \\ & \text{Heterogeneity: Tau" = 0.00; Ch" = 0.35, df = 1 (P = 0.55); P = 0\% \\ & \text{Test for overall effect. 2 = 0.71 (P = 0.46) & 1.17 \\ & \text{Subtotal (95\% C)} & 3928 & 4523 & 1510 & 3.0\% & 1.38 [1.01, 1.48] \\ & \text{For graneity: Tau" = 0.00; Ch" = 0.35, df = 1 (P = 0.55); P = 0\% \\ & \text{Test for overall effect. 2 = 0.71 (P = 0.46) & 1.17 \\ & \text{Subtotal (95\% C)} & 3938 & 45235 & 100.0\% & 1.32 [1.25, 1.16] \\ & \text{Total events} & 510 & 954 \\ & \text{Heterogeneity: Tau" = 0.00; Ch" = 2.8, df = 2 (P = -0.32); P = 12\% \\ & \text{Test for overall effect. 2 = 7.57 (P < 0.00001) \\ & \text{Total events} & 19440 & 1917 \\ & Hetero$	song 2009	74	184	52	176	1.5%	1.60 [1.04, 2.49]	
Subtotal (95% CI) 1582 19169 56.6% 1.50 [1.40, 1.61] Total events 8073 8087 Test for overall effect: $Z = 11.83$ ( $P < 0.0001$ ) 1.12 re200440_RA A Maakej 2006 165 280 203 370 2.1% 1.18 [0.86, 1.62] Blanca Rueda-2006 623 1448 591 1084 3.0% 1.10 [0.44, 1.29] Blanca Rueda-2006 295 570 263 568 2.6% 1.24 [0.99, 1.57] GY B. N. Nordang-1 2011 582 1030 823 1510 3.0% 1.08 [0.92, 1.27] GY B. N. Nordang-1 2011 582 1030 823 1510 3.0% 1.08 [0.95, 1.31] VUN JUNG KIM 2008 811 228 612 1900 3.2% 1.08 [0.95, 1.32] Subtotal (95% CI) 15448 10644 23.5% 1.28 [1.10, 1.48] G Krisijansdotti-2 2008 1192 2168 1229 2364 3.1% 1.28 [1.10, 1.48] G Krisijansdotti-2 2008 1192 2168 1229 2364 3.2% 1.13 [1.00, 1.27] Subtotal (95% CI) 3468 308 6.3% 1.08 [0.91, 1.28] G Krisijansdotti-2 2008 1192 2168 1229 2364 3.2% 1.08 [0.91, 1.28] G Krisijansdotti-2 2008 1192 2168 1229 2364 3.2% 1.08 [0.91, 1.28] G Krisijansdotti-2 2008 1192 2168 1229 2364 3.1% 1.28 [1.10, 1.48] G Krisijansdotti-2 2008 1192 2168 1229 2364 3.2% 1.09 [0.95, 1.11] Total events 1959 2074 Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 1.38, df = 1 (P - 0.20); P = 39% Test for overall effect: $Z = 2.84$ (P = 0.004) 1.1.4 re200440_JIA G Yr B. N. Nordang-2 2011 456 808 823 1510 3.0% 1.08 [0.91, 1.28] Masketu/ 2011 551 951 G YB. N. Nordang-2 2011 456 808 823 1510 3.0% 1.08 [0.91, 1.28] Masketu/ 2011 551 951; P = 0% Test for overall effect: $Z = 0.71$ (P = 0.48) 1.1.5 re2004440_SLC Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 0.38; df = (P = 0.35; F = 0% Test for overall effect: $Z = 0.77$ (P = 0.44) 1.1.5 re2004460_SLC Hue to 2009 199 562 287 964 2.7% 1.27 [1.02, 1.59] P. Deude 200; B 92 1622 752 1460 3.1% 1.34 [1.71, 1.54] Subtotal (95% CI) 39388 45235 100.0% 1.32 [1.23, 1.42] Total events 1940 1917 Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 2.84, df = 2 (P = 0.32; F = 12% Test for overall effect: $Z = 7.57$ (P < 0.00001) Total events 1940 1917 Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 2.84, df = 2 (P = 0.0001); F = 83% Total events 19546 20750 Heterorgeneity: Tau <sup>2</sup> = 0.	vuong 2010	357	544	315	614	2.6%	1.81 [1.43, 2.30]	-
Total events 8673 6867 Heterogeneity: Tau" = 0.1; Chi" = 44.26, df = 21 (P = 0.002); P = 53%. Test for overall effect: Z = 11.83 (P < 0.00001) 1.1.2 rs200440_RA A Maalej 2006 165 220 203 370 2.1%, 1.18 [0.86, 1.62] Blanca Rueda-12005 652 1448 591 1084 0.0%, 1.10 [0.94, 1.29] Blanca Rueda-2 2006 306 562 516 944 2.7%, 0.99 [0.80, 1.27] Gry B. N. Nordang-1 2011 582 1030 623 1510 3.0%, 1.08 [0.82, 1.27] Gry B. N. Nordang-1 2011 582 1030 623 1510 3.0%, 1.08 [0.82, 1.27] K. Shimane 2012 1282 3844 1062 3196 3.3%, 0.96 [0.87, 1.06] Rebeca 2008 2200 5288 2448 6472 3.4%, 0.91 [0.44, 0.89] YUJ JUNG K10 208 611 2288 612 1900 2.2%, 1.08 [0.95, 1.31] Total rownts 6464 6938 Heterogeneity: Tau" = 0.01; Chi" = 15.4, df = 7 (P = 0.03); P = 55% Test for overall effect: Z = 0.77 (P = 0.44) 1.1.3 rs2004460_JIA GK ristgiansdotti-2 2008 1192 2168 1229 2.364 3.2%, 1.13 [1.00, 1.27] Subtotal (95% CI) 3468 3395 6.3% 1.08 [0.95, 1.28] Total events 1959 2074 Heterogeneity: Tau" = 0.00; Chi" = 1.63, df = 1 (P = 0.20); P = 39% Test for overall effect: Z = 2.84 (P = 0.004) 1.1.4 rs2004460_JIA GY B. N. Nordang-2 2011 456 808 823 1510 3.0%, 1.08 [0.91, 1.28] Masakatsu 2011 454 162 131 380 1.8%, 0.95 [0.64, 1.40] Subtotal (95% CI) 3948 452 1594 2.7%, 1.27 [1.02, 1.59] P. Deudo 2009 999 662 287 954 2.7%, 1.27 [1.02, 1.59] P. Deudo 2009 199 662 287 954 2.7%, 1.27 [1.02, 1.59] P. Deudo 2009 199 662 287 954 2.7%, 1.27 [1.02, 1.59] P. Deudo 2009 199 662 287 954 2.7%, 1.27 [1.02, 1.59] P. Deudo 2009 199 662 287 954 2.7%, 1.27 [1.02, 1.59] P. Deudo 2009 199 662 287 954 2.7%, 1.28 [1.13, 1.38] Total events 1940 1917 Heterogeneity: Tau" = 0.00; Chi" = 2.35, df = 2 (P = -0.32); F = 12%, Test for overall effect: Z = 7.57 (P < 0.00001) Total (95% CI) 3938 45235 100.0%, 1.32 [1.23, 1.42] Total events 1954 0.00; Chi" = 2.58, df = 2 (P = -0.32); F = 12%, Test for overall effect: Z = 7.57 (P < 0.00001) Test for overall effect: Z = 7.57 (P < 0.00001) Test for overall effect: Z = 7.57 (P < 0.00001) Test for overalle effec	Subtotal (95% CI)		15832		19169	56.6%	1.50 [1.40, 1.61]	+
Heterogeneity: Tau <sup>2</sup> = 0.01; Ch <sup>2</sup> = 4.28, df = 21 ( $P = 0.002$ ); $P = 53\%$ Test for overall effect: Z = 11.83 ( $P < 0.00001$ ) 1.1.2 rs2004640_RA A Maskie 2006 165 280 203 370 2.1% 1.18 [0.86, 1.62] Blanca Rueds-2006 823 1448 591 1084 3.0% 1.10 [0.94, 1.29] Blanca Rueds-2006 285 570 263 568 2.6% 1.24 [0.99, 1.57] Gry B. N. Nordang-1 2011 582 1030 823 1510 3.0% 1.08 [0.87, 1.06] Prebeca 2006 2200 528 2486 6472 3.4% 0.961 [0.84, 0.98] YUN JUNG KIM 2008 811 2386 612 1900 3.2% 1.08 [0.95, 1.23] Subtotal (95% CI) 15448 16044 23.5% 1.93 [0.35, 1.11] Total events 6444 6038 Heterogeneity: Tau <sup>2</sup> = 0.01; Ch <sup>2</sup> = 15.54, df = 7 ( $P = 0.03$ ); $P = 55\%$ Test for overall effect: Z = 0.77 ( $P = 0.44$ ) 1.1.3 rs2004640_MS G Knsjiansdottir-2 2008 787 1300 845 1594 3.1% 1.28 [1.10, 1.48] G Knsjiansdottir-2 2008 787 1300 845 1594 3.1% 1.28 [1.10, 1.48] G Knsjiansdottir-2 2008 787 1300 845 1594 3.1% 1.28 [1.10, 1.48] G Knsjiansdottir-2 2008 787 1300 845 1594 3.1% 1.28 [1.10, 1.48] G Knsjiansdottir-2 2008 787 1300 845 1594 3.1% 1.28 [1.10, 1.48] G Knsjiansdottir-2 2008 787 1300 845 1594 3.1% 1.28 [1.10, 1.48] G Knsjiansdottir-2 2008 787 1300 845 1594 3.1% 1.08 [0.91, 1.27] Subtotal (95% CI) 970 1890 4.7% 1.06 [0.90, 1.24] Total events 1959 2074 Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 0.35, df = 1 ( $P = 0.55$ ); $P = 0\%$ Test for overall effect: Z = 2.84 ( $P = 0.004$ ) 1.1.4 rs2004640_JIA Gry B. N. Nordang-2 2011 456 808 823 1510 3.0% 1.08 [0.91, 1.28] Maskatsu 2011 54 162 752 1460 3.1% 1.36 [0.90, 1.24] Total events 510 954 2.752 4160 3.1% 1.25 [1.13, 1.38] Total events 1940 1917 Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 2.38, df = 2 ( $P = 0.32$ ); $P = 12\%$ Test for overall effect: Z = 0.27 ( $P = 2.62$ ); $P = 12\%$ Test for overall effect: Z = 7.57 ( $P < 0.00001$ ); $P = 83\%$ Total events 1940 1917 Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 2.88, df = 2 ( $P = 0.00001$ ); $P = 83\%$ Total events 1940 1917 Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 2.88, df = 2 ( $P = 0.00001$ ); $P = 83\%$ Test for overall effect: Z = 7	Total events	8673		8867				
Test for overall effect: $Z = 11.83$ ( $P < 0.0001$ ) 1.1.2 rs2004640_RA A Mateig 2008 165 280 203 370 2.1% 1.18 [0.86, 1.62] Blanca Rueds-1 2006 366 562 516 944 2.7% 0.99 [0.80, 1.22] Blanca Rueds-2 2006 366 562 516 944 2.7% 0.99 [0.80, 1.22] Blanca Rueds-2 2006 328 570 263 568 2.6% 1.24 [0.99, 1.57] Gry B. N. Nordang-1 2011 582 1030 823 1510 3.0% 1.08 [0.92, 1.27] K Shimare 2012 1282 384 1082 3196 3.3% 0.96 [0.87, 1.06] Rebeca 2008 2200 5288 2446 6472 3.4% 0.91 [0.84, 0.98] YUN JUNG KIM 2008 811 2386 612 1000 3.2% 1.08 [0.95, 1.23] Subtotal (95% CI) 1544 644 6938 Heterogeneity: Tau <sup>2</sup> = 0.01; Chi <sup>2</sup> = 15.54, df = 7 ( $P = 0.03$ ); $P = 55\%$ Test for overall effect: $Z = 0.77$ ( $P = 0.44$ ) 1.1.3 rs2004640_MS G Kristjansdottir-2 2008 1152 2168 1229 2364 3.2% 1.13 [1.00, 1.27] Subtotal (95% CI) 3448 3958 6.3% 1.19 [1.06, 1.34] Total events 1959 2074 Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 1.63, df = 1 ( $P = 0.20$ ); $P = 39\%$ Test for overall effect: $Z = 2.84$ ( $P = 0.004$ ) 1.1.4 rs2004640_JIA Gry B. N. Nordang-2 2011 456 808 823 1510 3.0% 1.08 [0.91, 1.28] Maskatsu 2011 54 162 131 380 1.8% 0.95 [0.64, 1.40] Subtotal (95% CI) 970 1899 4.7% 1.25 [1.13, 1.38] Total events 510 964 Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.35; $P = 0\%$ Test for overall effect: $Z = 0.71$ ( $P = 0.45$ ); $P = 0\%$ Test for overall effect: $Z = 0.71$ ( $P = 0.45$ ); $P = 0\%$ Test for overall effect: $Z = 0.71$ ( $P = 0.45$ ); $P = 0\%$ Test for overall effect: $Z = 0.71$ ( $P = 0.45$ ); $P = 0\%$ Test for overall effect: $Z = 0.71$ ( $P = 0.45$ ); $P = 0\%$ Test for overall effect: $Z = 0.71$ ( $P = 0.45$ ); $P = 0\%$ Test for overall effect: $Z = 0.71$ ( $P = 0.45$ ); $P = 0\%$ Test for overall effect: $Z = 0.71$ ( $P = 0.45$ ); $P = 0\%$ Test for overall effect: $Z = 0.71$ ( $P = 0.45$ ); $P = 0\%$ Total (95% CI) 3670 4174 84 42.25% 100.0% 1.22 [1.13, 1.38] Total events 1940 1917 Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 2.28, df = 2 ( $P = 0.00001$ ); $P = 83\%$ Test for overall effect: $Z = 7.57$ ( $P < 0.00001$ ) Teal for swratin	Heterogeneity: Tau <sup>2</sup> = 0.01;	Chi <sup>2</sup> = 44.3	26, df =	21 (P = 0	.002); l <sup>2</sup>	= 53%		
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Test for overall effect: Z = 1	1.83 (P < 0	.00001)					
1.1.2 ra2004640_RA Amale 2006 165 220 203 370 2.1% 1.18 [0.86, 1.62] Blanca Rueda-12006 823 1448 591 1084 3.0% 1.10 [0.94, 1.22] Blanca Rueda-2006 306 562 516 944 2.7% 0.99 [0.80, 1.22] Blanca Rueda-2006 2255 570 253 568 2.6% 1.24 [0.99, 1.57] Gry B. N. Nordang-12011 582 1030 623 1510 3.0% 0.96 [0.87, 1.06] Rebeca 2008 2200 5288 2848 6472 3.4% 0.91 [0.84, 0.98] VUN JUNG KIM 2008 811 2286 612 1900 3.2% 1.08 [0.95, 1.23] Subtotal (95% CI) 15448 16044 23.5% 1.08 [0.95, 1.23] Subtotal (95% CI) 15448 16044 23.5% 1.08 [0.95, 1.23] Gri Gri and State 1.200 877 ( $P = 0.44$ ) 1.1.3 ra2004640_MS G Krisijansdotir-2008 1192 2168 1229 2364 3.2% 1.13 [1.00, 1.27] Subtotal (95% CI) 3468 3956 6.3% 1.19 [1.06, 1.34] Total events 1959 2074 Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 1.63, df = 1 ( $P = 0.20$ ); $P = 39\%$ Test for overall effect: $Z = 2.84$ ( $P = 0.004$ ) 1.1.4 rs2004640_MS G Krisijansdotir-2008 1192 2168 1229 2364 3.2% 1.13 [1.00, 1.27] Subtotal (95% CI) 3468 0.823 1510 3.0% 1.08 [0.91, 1.28] Masakatu 2011 54 162 131 380 1.8% 0.95 [0.64, 1.40] Subtotal (95% CI) 970 1890 4.7% 1.06 [0.90, 1.24] Total events 510 964 Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 1.63, df = 1 ( $P = 0.55$ ); $P = 0\%$ Test for overall effect: $Z = 0.71$ ( $P = 0.48$ ) 1.1.5 rs2004640_JIA Gry B. N. Nordang-22011 456 808 823 1510 3.0% 1.08 [0.91, 1.28] Masakatu 2011 54 162 131 380 1.8% 0.95 [0.64, 1.40] Subtotal (95% CI) 970 1890 4.7% 1.25 [1.13, 1.38] Total events 510 964 Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 2.84, df = 2 ( $P = 0.35$ ); $P = 0\%$ Test for overall effect: $Z = 0.71$ ( $P = 0.48$ ) 1.1.5 rs2004640_SSc livue to 2009 199 562 287 954 2.7% 1.27 [1.02, 1.59] P. Deude 2009 199 562 287 954 2.7% 1.25 [1.13, 1.38] Total events 1940 1917 Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 2.84, df = 2 ( $P = 0.32$ ); $P = 12\%$ Test for overall effect: $Z = 7.57$ ( $P < 0.00001$ ); $P = 83\%$ Test for overall effect: $Z = 7.57$ ( $P < 0.00001$ ); $P = 83\%$ Test for overall effect: $Z = 7.57$ ( $P < 0.00001$ ); $P = 83\%$ Test for overall eff								
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Blanca Rueda-2 2006 306 562 516 944 2.7% 0.99 [0.80, 1.22] Blanca Rueda-3 2006 2295 570 263 568 2.6% 1.24 [0.99, 1.57] Gry B. N. Nordang-1 2011 562 1030 823 1510 3.0% 1.06 [0.92, 1.27] K Shimane 2012 1282 3884 1082 3196 3.3% 0.96 [0.87, 1.06] Rebeca 2008 2200 5288 2848 6472 3.4% 0.97 [0.84, 0.98] YUN JUNC KIM 2008 811 2386 612 1900 3.2% 1.08 [0.95, 1.23] Subtotal (95% CI) 15448 16044 23.5% Heterogeneity: Tau <sup>2</sup> = 0.01; Ch <sup>2</sup> = 15.64, df = 7 (P = 0.03); P = 55% Test for overall effect: Z = 0.77 (P = 0.44) 1.1.3 rs2004640_MS G Krisijansdotti-2 2008 1192 2168 1229 2364 3.2% Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 1.63, df = 1 (P = 0.20); P = 39% Test for overall effect: Z = 0.77 (P = 0.04) 1.1.4 rs2004640_JIA Gry B. N. Nordang-2 2011 456 808 823 1510 3.0% Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 1.63, df = 1 (P = 0.55); P = 0% Test for overall effect: Z = 0.71 (P = 0.48) 1.1.5 rs2004640_SSc Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 0.35, df = 1 (P = 0.55); P = 0% Test for overall effect: Z = 0.71 (P = 0.48) 1.1.5 rs2004640_SSc Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 0.35, df = 1 (P = 0.55); P = 0% Test for overall effect: Z = 0.71 (P = 0.48) 1.1.5 rs2004640_SSc Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 0.35, df = 1 (P = 0.55); P = 0% Test for overall effect: Z = 0.71 (P = 0.48) 1.1.5 rs2004640_SSc Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 2.83, df = 1 (P = 0.55); P = 0% Test for overall effect: Z = 0.71 (P = 0.48) 1.1.5 rs2004640_SSc Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 2.84 (P = 0.00001) Total (95% CI) 39388 45235 100.0% 1.32 [1.23, 1.42] Total events 1940 1917 Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 2.84 (P = 0.00001); P = 83% Test for overall effect: Z = 7.57 (P < 0.00001); P = 83% Test for overall effect: Z = 7.57 (P < 0.00001) Total (95% CI) 39388 45235 100.0% Test for overall effect: Z = 7.57 (P < 0.00001) Test for several effect: Z = 7.57 (P < 0.00001) Test for several effect: Z = 7.57 (P < 0.00001) Heterogeneity and the foure 2 = 7.57 (P < 0.00001) Heterogeneity and the foure 2 = 0.0	Blanca Rueda-1 2006	823	1448	591	1084	3.0%	1.10 [0.94, 1.29]	r
Blanca Rueda-3 2006 295 570 283 588 2.6% 1.24 [0.99, 1.57] Gry B. N. Mordang-1 2011 582 1030 823 31510 3.0% 1.08 [0.87, 1.06] Rebeca 2008 2200 5288 2848 6472 3.4% 0.91 [0.84, 0.98] YUN JUNS KIM 2008 210 5288 2848 6472 3.4% 0.91 [0.84, 0.98] YUN JUNS KIM 2008 210 5288 612 1900 3.2% 1.08 [0.95, 1.23] Subtotal (95% CI) 1544 646 46938 Heterogeneity: Tau <sup>2</sup> = 0.01; Chi <sup>2</sup> = 15.54, df = 7 (P = 0.03); P = 55% Test for overall effect: Z = 0.77 (P = 0.44) 1.1.3 rs2004640_MS G Krisignasdottin-2 2008 1192 2168 1229 2364 3.2% 1.13 [1.00, 1.27] Subtotal (95% CI) 3468 3958 6.3% 1.19 [1.06, 1.34] Otal events 1959 2074 Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 1.63, df = 1 (P = 0.20); P = 39% Test for overall effect: Z = 0.71 (P = 0.004) 1.1.4 rs2004640_JIA Gry B. N. Mordang-2 2011 456 808 823 1510 3.0% 1.08 [0.91, 1.28] Masakatsu 2011 541 162 131 380 4.7% 1.06 [0.90, 1.24] Total events 1959 70 1890 4.7% 1.06 [0.90, 1.24] Total events 510 954 Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 1.63, ff = 1 (P = 0.55); P = 0% Test for overall effect: Z = 0.71 (P = 0.48) 1.1.5 rs2004640_SSc Ikue Ito 2009 199 562 287 954 2.7% 1.27 [1.02, 1.59] P. Dieude 2009 882 1622 752 1460 3.1% 1.34 [1.71, 1.54] P. Dieude 2009 199 562 287 954 2.7% 1.25 [1.13, 1.38] Total events 1940 1917 Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 2.28, df = 2 (P = 0.32); P = 12% Test for overall effect: Z = 4.44 (P < 0.00001) Total (95% CI) 3938 45235 100.0% 1.32 [1.23, 1.42] Total events 19546 20750 Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 2.28, df = 2 (P = 0.02); P = 83% Test for overall effect: Z = 7.57 (P < 0.00001) Total (95% CI) 39388 45235 100.0% 1.32 [1.23, 1.42] Total events 19546 20750 Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 2.28, df = 2 (P = 0.002); P = 83% Test for overall effect: Z = 7.57 (P < 0.00001) Total (95% CI) 39388 45235 100.0% 1.32 [1.23, 1.42] Total events 19546 20750 Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 2.48, df = 4.40 = 0.00001) H = 83.00 Control SLE	Blanca Rueda-2 2006	306	562	516	944	2.7%	0.99 [0.80, 1.22]	L
Gry B. N. Nordang-1 2011 562 1030 823 1510 3.0% 1.08 [0.92, 1.27] K Shimane 2012 1282 3884 1082 3196 3.3% 0.96 [0.87, 1.06] Rebeca 2008 2200 5288 2848 6472 3.4% 0.91 [0.84, 0.98] YUN JUNG KIM 2008 811 2386 612 1900 3.2% 1.08 [0.95, 1.23] Subtotal (95% CI) 15448 16044 23.5% 1.08 [0.95, 1.23] Subtotal (95% CI) 15448 16044 23.5% 1.08 [0.95, 1.11] Total events 6444 6938 Heterogeneity: Tau" = 0.01; Chi" = 15.54, df = 7 (P = 0.03); P = 55% Test for overall effect: Z = 0.77 (P = 0.44) 1.1.3 rs2004440_MS G Kristjansdottin-1 2008 767 1300 845 1594 3.1% 1.28 [1.10, 1.48] G Kristjansdottin-2 2008 1192 2168 1229 2364 3.2% 1.13 [1.00, 1.27] Subtotal (95% CI) 3468 3958 6.3% 1.18 [1.06, 1.34] Total events 1959 2074 Heterogeneity: Tau" = 0.00; Chi" = 1.63, df = 1 (P = 0.20); P = 39% Test for overall effect: Z = 0.77 (P = 0.45) 1.1.5 rs2004640_JIA Gry B. N. Nordang-2 2011 456 808 823 1510 3.0% 1.08 [0.91, 1.28] Masakatsu 2011 54 162 131 380 1.8% 0.96 [0.64, 1.40] Subtotal (95% CI) 970 1890 4.7% 1.06 [0.90, 1.24] Total events 510 954 Heterogeneity: Tau" = 0.00; Chi" = 0.35; df = 1 (P = 0.55); P = 0% Test for overall effect: Z = 0.71 (P = 0.48) 1.1.5 rs2004640_SSC Ikue Ito 2009 199 562 287 954 2.7% 1.27 [1.02, 1.59] P. Dicude 2009 882 1622 752 1460 3.1% 1.34 [1.71, 1.54] Subtotal (95% CI) 3670 4174 8.8% 1.25 [1.13, 1.38] Total events 1940 1917 Heterogeneity: Tau" = 0.00; Chi" = 2.28, df = 2 (P = 0.32); P = 12% Test for overall effect: Z = 7.57 (P < 0.00001) Total (95% CI) 39388 45235 100.0% 1.32 [1.23, 1.42] Total events 1956 20.2 df = 36 (P < 0.00001); P = 83% Test for overall effect: Z = 7.57 (P < 0.00001) Total (95% CI) 39388 45235 100.0% 1.32 [1.23, 1.42] Total events 1956 20.750 Heterogeneity: Tau" = 0.00; Chi" = 2.28, df = 2 (P = 0.020); P = 83% Test for overall effect: Z = 7.57 (P < 0.00001) Total (95% CI) 39388 45235 100.0% 1.32 [1.23, 1.42] Total events (Dhi" = 2.40, df = 4 (P < 0.00001); P = 83% Test for overall effect: Z = 7.57 (P < 0.00001) Exter scherourd diffeceroce: Chi" = 5	Blanca Rueda-3 2006	295	570	263	568	2.6%	1.24 [0.99, 1.57]	
K Shimane 2012 1282 3884 1082 3196 3.3% 0.96 [0.87, 1.06] Rebeca 2008 2200 528 248 6472 3.4% 0.91 [0.84, 0.98] YUN JUNG KIM 2008 811 2386 612 1900 3.2% 1.08 [0.95, 1.23] Subtotal (95% CI) 15448 16044 23.5% 1.03 [0.95, 1.11] Total events 6464 6938 Heterogeneity: Tau <sup>2</sup> = 0.01; Ch <sup>2</sup> = 15.54, df = 7 (P = 0.03); P = 55% Test for overall effect: Z = 0.77 (P = 0.44) 1.1.3 rs2004640_MS G Kristjanadottir-2 2008 1192 2168 1229 2364 3.2% 1.13 [1.00, 1.27] Subtotal (95% CI) 3468 3958 6.3% 1.19 [1.06, 1.34] Total events 1959 2074 Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 1.63, df = 1 (P = 0.20); P = 39% Test for overall effect: Z = 0.71 (P = 0.04) 1.1.4 rs2004640_JIA Gr ys b. Nordang-2 2011 456 808 823 1510 3.0% 1.08 [0.91, 1.28] Masakatsu 2011 54 162 131 380 1.8% 0.95 [0.64, 1.40] Subtotal (95% CI) 970 1890 4.7% 1.06 [0.90, 1.24] Total events 510 954 Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 0.35, df = 1 (P = 0.55); P = 0% Test for overall effect: Z = 0.71 (P = 0.48) 1.1.5 rs2004640_SSc Ikue Ito 2009 199 562 287 954 2.7% 1.27 [1.02, 1.59] P. Dieude 2009 892 1622 752 1466 3.1% 1.15 [1.00, 1.33] Total events 1946 174 8.9% 1.25 [1.13, 1.38] Total events 1946 1917 Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 2.28, df = 2 (P = 0.32); P = 12% Test for overall effect: Z = -6.71 (P = 0.32); I <sup>2</sup> = 12% Test for overall effect: Z = -7.57 (P < 0.00001) Total events 19546 20750 Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 2.28, df = 2 (P = 0.32); I <sup>2</sup> = 12% Test for overall effect: Z = -7.57 (P < 0.00001) Total (95% CI) 39388 45235 100.0% 1.32 [1.23, 1.42] 0.01 0.1 1 0 100 control SLE	Gry B. N. Nordang-1 2011	582	1030	823	1510	3.0%	1.08 [0.92, 1.27]	1
Rebeca 2008 2200 528 2448 647 2 3.4% 0.9 [0.8, 0.96] VIN JUKK M2008 811 236 612 1900 3.2% 1.08 [0.95, 1.23] Subtotal (95% CI) 15448 16044 23.5% 1.03 [0.95, 1.11] Total events 6464 6938 Heterogeneity: Tau <sup>2</sup> = 0.01; Ch <sup>2</sup> = 15.54, df = 7 (P = 0.03); P = 55% Test for overall effect: $Z = 0.77 (P = 0.44)$ 1.1.3 rs2004640_MS G Kristjansdottir-2 2008 767 1300 845 1594 3.1% 1.28 [1.10, 1.48] G Kristjansdottir-2 2008 767 1300 845 1594 3.1% 1.28 [1.10, 1.49] G Kristjansdottir-2 2008 767 1300 845 1594 3.1% 1.28 [1.10, 1.48] G Kristjansdottir-2 2008 767 1300 845 1594 3.1% 1.28 [1.10, 1.48] G Kristjansdottir-2 2008 767 1300 845 1594 3.1% 1.28 [1.10, 1.48] G Kristjansdottir-2 2008 767 1300 845 1594 3.1% 1.28 [1.10, 1.48] Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 1.63, df = 1 (P = 0.20); P = 39% Test for overall effect: Z = 2.84 (P = 0.004) 1.1.4 rs2004640_JIA Gry B. N. Nordang-2 2011 456 808 823 1510 3.0% 1.08 [0.91, 1.28] Masakatsu 2011 54 162 131 380 1.8% 0.96 [0.64, 1.40] Subtotal (95% CI) 970 1890 4.7% 1.06 [0.90, 1.24] Total events 510 954 Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 0.35; df = 1 (P = 0.55); P = 0% Test for overall effect: Z = 0.71 (P = 0.48) 1.1.5 rs2004640_SSc Ikue Ito 2009 892 1622 752 1460 3.1% 1.34 [1.17, 1.54] Subtotal (95% CI) 3670 4174 8.9% 1.25 [1.13, 1.38] Total events 19546 20750 Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 2.28, df = 2 (P = 0.32); P = 12% Test for overall effect: Z = 4.44 (P < 0.00001) Total (95% CI) 39388 45235 100.0% 1.32 [1.23, 1.42] Total events 19546 20750 Heterogeneity: Tau <sup>2</sup> = 0.04; Ch <sup>2</sup> = 2.8, df = 2 (P < 0.0001); P = 83% Test for overall effect: Z = -57; P < 0.00001; Total (95% CI) 39388 45235 100.0% 1.32 [1.23, 1.42] Total events 19546 20750 Heterogeneity: Tau <sup>2</sup> = 0.04; Ch <sup>2</sup> = 2.8, df = 2 (P < 0.00001); P = 83% Test for overall effect: Z = -57; P < 0.00001; Total events (195% CI) 93838 45235 100.0% 1.32 [1.23, 1.42] Total events (195% CI) 939388 45235 100.0% 1.32 [1.23, 1.42] Total events (195% CI) 939388 45235 100.0% 1.32 [1.23, 1.42] 0	K Shimane 2012	1282	3884	1082	3196	3.3%	0.96 [0.87, 1.06]	1
YON JONG KM 2008 611 2366 612 1900 3.2% 1.08 [0.95, 1.23] Subtotal (95% CI) 15448 16044 23.5% 1.03 [0.95, 1.24] Total events 6464 6938 Heterogeneity: Tau <sup>2</sup> = 0.01; Ch <sup>2</sup> = 15.54, df = 7 (P = 0.03); P = 55% Test for overall effect: Z = 0.77 (P = 0.04) 1.1.3 rs2004640_MS G Kristjanadotlir-2 2008 179 2 2168 1229 2364 3.2% 1.13 [1.00, 1.27] Subtotal (95% CI) 3468 3958 6.3% 1.19 [1.06, 1.34] Total events 1959 2074 Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 1.63, df = 1 (P = 0.20); P = 39% Test for overall effect: Z = 2.84 (P = 0.004) 1.1.4 rs2004640_JIA Gry B. N. Nordang-2 2011 456 808 823 1510 3.0% 1.08 [0.91, 1.28] Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 0.35, df = 1 (P = 0.55); P = 0% Test for overall effect: Z = 0.71 (P = 0.48) 1.1.5 rs2004640_SSc likue lio 2009 199 562 287 954 2.7% 1.27 [1.02, 1.59] P. Dieude-2 2010 649 1486 878 1760 3.1% 1.34 [1.17, 1.54] Subtotal (95% CI) 370 4174 8.9% 1.25 [1.13, 1.38] Total events 1940 1917 Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 2.28, df = 2 (P = 0.32); P = 12% Test for overall effect: Z = 4.44 (P < 0.00001) Total events 19546 20750 Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 2.28, df = 2 (P = 0.32); P = 12% Test for overall effect: Z = -57 (P < 0.00001) Total events 19546 20750 Heterogeneity: Tau <sup>2</sup> = 0.04; Ch <sup>2</sup> = 2.28, df = 2 (P = 0.02); P = 83% Test for overall effect: Z = -57 (P < 0.00001) Total events 19546 20750 Heterogeneity: Tau <sup>2</sup> = 0.04; Ch <sup>2</sup> = 2.48, df = 4 (P < 0.00001); P = 83% Test for overall effect: Z = -57 (P < 0.00001) Total events 19548 20750 Heterogeneity: Tau <sup>2</sup> = 0.04; Ch <sup>2</sup> = 2.57 (P < 0.00001); P = 83% Test for overall effect: Z = -57 (P < 0.00001) Total events Ch <sup>2</sup> = 2.58 df = 2 (P < 0.00001); P = 83% Test for overall effect: Z = -57 (P < 0.00001) Control SLE	Rebeca 2008	2200	5288	2848	6472	3.4%	0.91 [0.84, 0.98]	1
Subtraction (55% CI) 1940 to 100 2.5.0 x 1.05 [0.50, 1.11] Total events 644 6338 Heterogeneity: Tau <sup>2</sup> = 0.01; Ch <sup>2</sup> = 15.54, df = 7 (P = 0.03); P = 55% Test for overall effect: $Z = 0.77$ (P = 0.44) 1.1.3 rs2004640_MS G Kristjansdottir-2 2006 1192 2168 1229 2364 3.2% 1.13 [1.00, 1.27] Subtotal (95% CI) 3468 3998 6.3% 1.19 [1.06, 1.34] Total events 1959 2074 Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 1.63, df = 1 (P = 0.20); P = 39% Test for overall effect: $Z = 2.84$ (P = 0.004) 1.1.4 rs2004640_JIA Gry B. N. Nordang-2 2011 456 808 823 1510 3.0% 1.08 [0.91, 1.28] Masakatsu 2011 54 162 131 380 1.8% 0.95 [0.64, 1.40] Subtotal (95% CI) 970 1890 4.7% 1.06 [0.90, 1.24] Total events 510 954 Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 0.35, df = 1 (P = 0.55); P = 0% Test for overall effect: $Z = 0.71$ (P = 0.48) 1.1.5 rs2004640_SSc Ikue Ito 2009 199 562 287 954 2.7% 1.27 [1.02, 1.59] P. Dieude-2 2010 849 1486 878 1760 3.1% 1.34 [1.17, 1.54] Subtotal (95% CI) 3670 4174 8.9% 1.25 [1.13, 1.38] Total events 1940 1917 Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 2.28, df = 2 (P = 0.32); P = 12% Test for overall effect: $Z = 7.57$ (P = 0.00001) Total events 1940 1917 Heterogeneity: Tau <sup>2</sup> = 0.04; Ch <sup>2</sup> = 2.60, df = 36 (P < 0.00001); P = 83% Test for overall effect: $Z = 7.57$ (P < 0.00001) Total events 1940 1917 Heterogeneity: Tau <sup>2</sup> = 0.04; Ch <sup>2</sup> = 2.60, df = 36 (P < 0.00001); P = 83% Test for overall effect: $Z = 7.57$ (P < 0.00001) Total events 19546 20750 Heterogeneity: Tau <sup>2</sup> = 0.04; Ch <sup>2</sup> = 2.60, df = 36 (P < 0.00001); P = 83% Test for overall effect: $Z = 7.57$ (P < 0.00001) LE 90 00000	YUN JUNG KIM 2008	811	2380	012	1900	3.2%	1.08 [0.95, 1.23]	
Total events 510 954 40 0 505 10 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	Total quants	RARA	10440	6039	10044	20.070	1.00 [0.00, 1.11]	
Total events 1954 to use 1000 (1000)	Heterogeneity: Tau <sup>2</sup> = 0.01:	ChP = 15	54 df =	7 (P = 0 (	13): 12 =	55%		
<b>1.1.3</b> rs2004640_MS G Kristjansdottir-1 2008 767 1300 845 1594 3.1% 1.28 [1.10, 1.48] G Kristjansdottir-2 2008 1192 2168 1229 2364 3.2% 1.13 [1.00, 1.27] Subtotal (95% CI) 3468 3998 6.3% 1.19 [1.06, 1.34] Total events 1959 2074 Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 1.63, df = 1 (P = 0.20); P = 39% Test for overall effect: $Z = 2.84$ (P = 0.004) <b>1.1.4 rs2004640_JIA</b> Gry B N. Nordang-2 2011 456 808 823 1510 3.0% 1.08 [0.91, 1.28] Masekatsu 2011 54 162 131 380 1.8% 0.95 [0.64, 1.40] Subtotal (95% CI) 970 1880 4.7% 1.06 [0.90, 1.24] Total events 510 954 Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 0.35, df = 1 (P = 0.55); P = 0% Test for overall effect: $Z = 0.71$ (P = 0.48) <b>1.1.5 rs2004640_SSC</b> Ikwa Ito 2009 199 562 287 954 2.7% 1.27 [1.02, 1.59] P. Dieude 2009 892 1622 752 1460 3.1% 1.15 [1.00, 1.33] P. Dieude-2010 849 1486 878 1760 3.1% 1.34 [1.17, 1.54] Subtotal (95% CI) 39388 45235 100.0% Total events 1940 1917 Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 2.28, df = 2 (P = 0.32); P = 12% Test for overall effect: $Z = 7.57$ (P < 0.00001) Total events 19546 20750 Heterogeneity: Tau <sup>2</sup> = 0.04; Ch <sup>2</sup> = 2.602, df = 36 (P < 0.00001); P = 83% Test for overall effect: $Z = 7.57$ (P < 0.00001) Total events 19546 20750 Heterogeneity: Tau <sup>2</sup> = 0.04; Ch <sup>2</sup> = 248, df = 4 (P < 0.00001); P = 83% Test for overall effect: $Z = 7.57$ (P < 0.00001) Total events 19546 4.00 control SLE	Test for overall effect: Z = 0.	77 (P = 0.4	44)	. (				
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	1140-0-0 0.000 0000-00000-00							
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	1.1.3 rs2004640_MS							
G Kristjansdottir-2 2008 1192 2168 1229 2364 3.2% 1.13 [1.00, 1.27] Subtotal (95% CI) 3468 3958 6.3% 1.19 [1.06, 1.34] Total events 1959 2074 Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 1.63, df = 1 (P = 0.20); P = 39% Test for overall effect: Z = 2.84 (P = 0.004) 1.1.4 rs2004640_JIA Gry B. N. Nordang-2 2011 456 808 823 1510 3.0% 1.08 [0.91, 1.28] Masakatsu 2011 54 162 131 380 1.8% 0.95 [0.64, 1.40] Subtotal (95% CI) 970 1890 4.7% 1.06 [0.90, 1.24] Total events 510 954 Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 0.35, df = 1 (P = 0.55); P = 0% Test for overall effect: Z = 0.71 (P = 0.48) 1.1.5 rs2004640_SSc Ikue Ito 2009 199 562 287 954 2.7% 1.27 [1.02, 1.59] P. Dieude 2009 892 1622 752 1460 3.1% 1.15 [1.00, 1.33] P. Dieude-2 2010 849 1486 878 1760 3.1% 1.34 [1.77, 1.54] Subtotal (95% CI) 3938 45235 100.0% 1.32 [1.33, 1.38] Total events 1940 1917 Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 2.28, df = 2 (P = 0.32); P = 12% Test for overall effect: Z = 7.57 (P < 0.00001) Total events 19546 20750 Heterogeneity: Tau <sup>2</sup> = 0.04; Ch <sup>2</sup> = 2.69, df = 36 (P < 0.00001); P = 83% Test for overall effect: Z = 7.57 (P < 0.00001) Total events 19548 4.0 e overall effect: Z = 7.57 (P < 0.00001); I <sup>2</sup> = 83% Test for overall effect: Z = 7.57 (P < 0.00001) I <sup>2</sup> = 0.00001; I <sup>2</sup> = 83% Test for overall effect: Z = 7.57 (P < 0.00001) I <sup>2</sup> = 83%	G Kristjansdottir-1 2008	767	1300	845	1594	3.1%	1.28 [1.10, 1.48]	-
Subtotal (95% CI) 3468 3958 6.3% 1.19 [1.06, 1.34] Total events 1959 2074 Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 1.63, df = 1 ( $P = 0.20$ ); $P = 39\%$ Test for overall effect: $Z = 2.84$ ( $P = 0.004$ ) 1.1.4 rs2004640_JIA Gry B. N. Nordang-2 2011 458 808 823 1510 3.0% 1.08 [0.91, 1.28] Masakatsu 2011 54 162 131 380 1.8% 0.95 [0.64, 1.40] Subtotal (95% CI) 970 1890 4.7% 1.06 [0.90, 1.24] Total events 510 954 Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 0.35, df = 1 ( $P = 0.55$ ); $P = 0\%$ Test for overall effect: $Z = 0.71$ ( $P = 0.48$ ) 1.1.5 rs2004640_SSC Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 2.87, 954 2.7% 1.27 [1.02, 1.59] P. Dieude-2009 892 1622 752 1460 3.1% 1.15 [1.00, 1.33] P. Dieude-2010 849 1486 878 1760 3.1% 1.34 [1.77, 1.54] Subtotal (95% CI) 39388 45235 100.0% 1.32 [1.23, 1.42] Total events 1940 1917 Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 2.88, df = 2 ( $P = 0.32$ ); $P = 12\%$ Test for overall effect: $Z = 7.57$ ( $P < 0.00001$ ) Total (95% CI) 39388 45235 100.0% 1.32 [1.23, 1.42] Total events 19546 20750 Heterogeneity: Tau <sup>2</sup> = 0.04; Ch <sup>2</sup> = 2.60, df = 36 ( $P < 0.00001$ ); $P = 83\%$ Test for overall effect: $Z = 7.57$ ( $P < 0.00001$ ) Total (95% CI) 39388 45235 100.0% 1.32 [1.23, 1.42] Total events 19546 20750 Heterogeneity: Tau <sup>2</sup> = 0.04; Ch <sup>2</sup> = 2.60, df = 36 ( $P < 0.00001$ ); $P = 83\%$ Test for overall effect: $Z = 7.57$ ( $P < 0.00001$ )	G Kristjansdottir-2 2008	1192	2168	1229	2364	3.2%	1.13 [1.00, 1.27]	
Total events 1959 2074 Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 1.63, df = 1 (P = 0.20); P = 39% Test for overall effect: Z = 2.84 (P = 0.004) 1.1.4 rs2004640_JIA Gry B. N. Nordang-2 2011 456 808 823 1510 3.0% 1.08 [0.91, 1.28] Masakatsu 2011 54 162 131 380 1.8% 0.95 [0.64, 1.40] Subtotal (95% CI) 970 1890 4.7% 1.06 [0.90, 1.24] Total events 510 954 Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 0.35, df = 1 (P = 0.55); P = 0% Test for overall effect: Z = 0.71 (P = 0.48) 1.1.5 rs2004640_SSc Ikue Ito 2009 199 562 287 954 2.7% 1.27 [1.02, 1.59] P. Dieude 2009 882 1622 752 1460 3.1% 1.15 [1.00, 1.33] P. Dieude 2009 882 1622 752 1460 3.1% 1.25 [1.13, 1.38] Total events 1940 1917 Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 2.28, df = 2 (P = 0.32); P = 12% Test for overall effect: Z = 4.44 (P < 0.00001) Total events 19546 20750 Heterogeneity: Tau <sup>2</sup> = 0.04; Ch <sup>2</sup> = 216.02, df = 36 (P < 0.00001); P = 83% Test for overall effect: Z = 7.57 (P < 0.00001) Test for overall effect: Z = 7.57 (P < 0.00001) LE 90.000	Subtotal (95% CI)		3468		3958	6.3%	1.19 [1.06, 1.34]	•
Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 1.63, df = 1 (P = 0.20); P = 39% Test for overall effect: Z = 2.84 (P = 0.004) 1.1.4 rs2004640_JIA Gry B. N. Nexdang-2 2011 456 808 823 1510 3.0% 1.08 [0.91, 1.28] Masekatsu 2011 54 162 131 380 1.8% 0.95 [0.64, 1.40] Subtoal (95% CI) 970 1880 4.7% 1.06 [0.90, 1.24] Total events 510 954 Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 0.35, df = 1 (P = 0.55); P = 0% Test for overall effect: Z = 0.71 (P = 0.46) 1.1.5 rs2004640_SSc likue lio 2009 199 562 287 954 2.7% 1.27 [1.02, 1.59] P. Dieude 2009 882 1622 752 1460 3.1% 1.15 [1.10, 1.33] P. Dieude 2009 882 1622 752 1460 3.1% 1.34 [1.17, 1.54] Subtoal (95% CI) 3670 4174 8.9% 1.25 [1.13, 1.38] Total events 1940 1917 Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 2.28, df = 2 (P = 0.32); P = 12% Test for overall effect: Z = 4.44 (P < 0.00001) Total (95% CI) 39388 45235 100.0% 1.32 [1.23, 1.42] Total events 19546 20750 Heterogeneity: Tau <sup>2</sup> = 0.04; Ch <sup>2</sup> = 216.02, df = 36 (P < 0.00001); P = 83% Test for overall effect: Z = 7.57 (P < 0.00001) Total (95% CI) 39388 45235 100.0% 1.32 [1.23, 1.42] Total events 19546 20750 Heterogeneity: Tau <sup>2</sup> = 0.04; Ch <sup>2</sup> = 216.02, df = 36 (P < 0.00001); P = 83% Test for overall effect: Z = 7.57 (P < 0.00001) Le 93 006	Total events	1959		2074				
Test for overall effect: $Z = 2.84$ (P = 0.004) 1.1.4 rs2004640_JIA Gry B. N. Nordang-2 2011 456 808 823 1510 3.0% 1.08 [0.91, 1.28] Masakatsu 2011 54 162 131 380 1.8% 0.95 [0.64, 1.40] Subtotal (95% Ci) 970 1880 4.7% 1.06 [0.90, 1.24] Total events 510 954 Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 0.35, df = 1 (P = 0.55); l <sup>2</sup> = 0% Test for overall effect: $Z = 0.71$ (P = 0.48) 1.1.5 rs2004640_SSC Ikwa Ito 2009 199 562 287 954 2.7% 1.27 [1.02, 1.59] P. Dieude 2009 892 1622 752 1460 3.1% 1.15 [1.00, 1.33] P. Dieude-2010 849 1486 878 1760 3.1% 1.34 [1.17, 1.54] Subtotal (95% Ci) 39388 45235 100.0% Test for overall effect: $Z = 4.44$ (P < 0.00001) Total events 1940 1917 Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 2.28, df = 2 (P = 0.32); l <sup>2</sup> = 12% Test for overall effect: $Z = 7.57$ (P < 0.00001) Total events 19546 20750 Heterogeneity: Tau <sup>2</sup> = 0.04; Ch <sup>2</sup> = 2.60, df = 36 (P < 0.00001); l <sup>2</sup> = 83% Test for overall effect: $Z = 7.57$ (P < 0.00001) LE 93 0%	Heterogeneity: Tau <sup>2</sup> = 0.00;	Chi <sup>2</sup> = 1.63	3, df = 1	(P = 0.20	<ol> <li>); l<sup>2</sup> = 3</li> </ol>	9%		
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Test for overall effect: Z = 2.	.84 (P = 0.1	004)					
$\begin{array}{cccc} 1.1.5 \ rsz009690_{2.14} \\ \mbox{Gry B. N. Nextang-2 2011 456 808 823 1510 3.0\% 1.08 [0.91, 1.28]} \\ \mbox{Masekatsu 2011 54 162 131 380 1.8\% 0.95 [0.64, 1.40]} \\ \mbox{Subtoal (95\% CI) 970 1880 4.7\% 1.06 [0.90, 1.24]} \\ \mbox{Total events 510 954} \\ \mbox{Heterogeneity: Tau^2 = 0.00; Ch^2 = 0.35, df = 1 (P = 0.55); P = 0\% \\ \mbox{Test for overall effect: Z = 0.71 (P = 0.46)} \\ \mbox{1.1.5 rs2004640_SSc} \\ \mbox{Ikue 2009 199 562 287 954 2.7\% 1.27 [1.02, 1.59]} \\ \mbox{P. Dieude 2009 882 1622 752 1460 3.1\% 1.15 [1.00, 1.33]} \\ \mbox{P. Dieude 2009 882 1622 752 1460 3.1\% 1.34 [1.17, 1.54]} \\ \mbox{Subtoal (95\% CI) 3670 4174 8.9\% 1.25 [1.13, 1.38]} \\ \mbox{Total events 1940 1917} \\ \mbox{Heterogeneity: Tau^2 = 0.00; Ch^2 = 2.28, df = 2 (P = 0.32); P = 12\% \\ \mbox{Test for overall effect: Z = 4.44 (P < 0.00001)} \\ Total events 19546 20750 \\ \mbox{Heterogeneity: Tau^2 = 0.04; Ch^2 = 216.02, df = 36 (P < 0.00001); P = 83\% \\ \mbox{Test for overall effect: Z = 7.57 (P < 0.00001) \\ \mbox{Let or overall effect: Z = 7.57 (P < 0.00001) \\ \mbox{Let or overall effect: Z = 7.57 (P < 0.00001) \\ \mbox{Let or overall effect: Z = 7.57 (P < 0.00001) \\ \mbox{Let or overall effect: Z = 7.57 (P < 0.00001) \\ \mbox{Let or overall effect: Z = 7.57 (P < 0.00001) \\ \mbox{Let or overall effect: Z = 7.57 (P < 0.00001) \\ \mbox{Let or overall effect: Z = 7.57 (P < 0.00001) \\ \mbox{Let or overall effect: Z = 7.57 (P < 0.00001) \\ \mbox{Let or overall effect: Z = 7.57 (P < 0.00001) \\ \mbox{Let or overall effect: Z = 7.57 (P < 0.00001) \\ \mbox{Let or overall effect: Z = 7.57 (P < 0.00001) \\ \mbox{Let or overall effect: Z = 7.57 (P < 0.00001) \\ \mbox{Let or overall effect: Z = 7.57 (P < 0.00001) \\ \mbox{Let or overall effect: Z = 7.57 (P < 0.00001) \\ \mbox{Let or overall effect: Z = 7.57 (P < 0.00001) \\ \mbox{Let or overall effect: Z = 7.57 (P < 0.00001) \\ \mbox{Let or overall effect: Z = 7.57 (P < 0.00001) \\ \mbox{Let or overall effect: Z = 7.57 (P < 0.00001) \\ \mbox{Let or overall effect: Z = 7.57 (P < 0.00001) \\ \mbox{Let or ov$	4.4.4							
$ \begin{array}{c} cry {\rm p. n. norcatarg-2 U11} & 496 & 606 & 62.3 \ \mbox{ 1510} & 3.0\% & 1.08 \ [0.91, 1.28] \\ \mbox{Masakatsu 2011} & 54 & 162 & 131 & 380 & 1.8\% & 0.95 \ [0.64, 1.40] \\ \mbox{Subtotal (95\% CI)} & 970 & 1890 & 4.7\% & 1.06 \ [0.90, 1.24] \\ \mbox{Test for overall effect: Z = 0.71 \ [P = 0.35, df = 1 \ [P = 0.55); l^2 = 0\% \\ \mbox{Test for overall effect: Z = 0.71 \ [P = 0.48] \\ \mbox{1.1.5 rs2004640_SSc} \\ \mbox{Ikue lo 2009} & 199 & 562 & 287 & 954 & 2.7\% & 1.27 \ [1.02, 1.59] \\ \mbox{P. Dieude 2009} & 892 & 1622 & 752 & 1460 & 3.1\% & 1.15 \ [1.00, 1.33] \\ \mbox{P. Dieude 2009} & 892 & 1622 & 752 & 1460 & 3.1\% & 1.34 \ [1.7, 1.54] \\ \mbox{Subtotal (95\% CI)} & 3670 & 4174 & 8.9\% & 1.25 \ [1.13, 1.38] \\ \mbox{Total events} & 1940 & 1917 \\ \mbox{Heterogeneity: Tau2 = 0.00; Ch2 = 2.28, df = 2 \ (P = 0.32); l2 = 12\% \\ \mbox{Test for overall effect: Z = 4.44 \ (P < 0.00001) \\ \mbox{Total events} & 1946 & 20750 \\ \mbox{Heterogeneity: Tau2 = 0.04; Ch2 = 216.02, df = 36 \ (P < 0.00001); l2 = 83\% \\ \mbox{Test for overall effect: Z = 7.57 \ (P < 0.00001) \\ \mbox{Control SLE} \\ \end{tabular}$	1.1.4 rsz004640_JIA	100	par		-	0.00	1.00.00.01.1.000	L.
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Gry B. N. Nordang-2 2011 Manakataw 2014	456	808	823	1510	3.0%	1.08 [0.91, 1.28]	+
$\begin{array}{c} \text{Contain (p.r. Gr)} & Site of the set of the $	Subtotal (95% CI)	54	970	131	1890	4 7%	0.95 [0.64, 1.40]	•
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Total events	610	510	054	1000	4.7 /0	1.00 [0.80, 1.24]	
1.1.5 rs2004640_SSc         1kue 1to 2009       199       562       287       954       2.7%       1.27 [1.02, 1.59]         P. Dieude 2009       892       1622       752       1460       3.1%       1.15 [1.00, 1.33]         P. Dieude 2009       892       1622       752       1460       3.1%       1.15 [1.00, 1.33]         P. Dieude 2009       892       1622       752       1460       3.1%       1.34 [1.17, 1.54]         Subtotal (95% Cl)       3670       4174       8.9%       1.25 [1.13, 1.38]       1.34 [1.77, 1.54]         Total events       1940       1917       1.25 [1.13, 1.38]       1.32 [1.23, 1.42]         Test for overall effect: Z = 4.44 (P < 0.00001)	Heterogeneity: Tau <sup>2</sup> = 0.00:	Chi2 = 0.3	5 df = 1	(P = 0.54	5): P = 0	96		
1.1.5 rs 2004640_SSc         Ikue ito 2009       199       562       287       954       2.7%       1.27 [1.02, 1.59]         P. Dieude 2009       892       1622       752       1460       3.1%       1.15 [1.00, 1.33]         P. Dieude 2009       892       1622       752       1460       3.1%       1.51 [1.00, 1.33]         P. Dieude 2009       892       1622       752       1460       3.1%       1.34 [1.17, 1.54]         Subtotal (95% CI)       3670       4174       8.9%       1.25 [1.13, 1.38]       1.32 [1.23, 1.42]         Total events       1940       1917       1.32 [1.23, 1.42]       1.32 [1.23, 1.42]         Total events       19546       20750       1.32 [1.23, 1.42]       0.01       0.1       1.0       100         Test for overall effect: $Z = 7.57 (P < 0.00001)$ $P = 83\%$ 0.01       0.1       1       10       100         Control       SLE       0.01       1       10       100       control       SLE	Test for overall effect: 7 = 0	71 (P = 0.0	48)	11 - 0.01	J, I - 0	10		
$\begin{array}{c c c c c c c c c c c c c c c c c c c $		110 - 0.	10/					
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	1.1.5 rs2004640 SSc							
P. Dieude 2009 892 1622 752 1460 3.1% 1.15 [1.00, 1.33] P. Dieude-2 2010 849 1486 878 1760 3.1% 1.34 [1.77, 1.54] Subtotal (95% CI) 3670 4174 8.9% 1.25 [1.13, 1.38] Total events 1940 1917 Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 2.28, df = 2 (P = 0.32); P <sup>2</sup> = 12% Test for overall effect: Z = 4.44 (P < 0.00001) Total (95% CI) 39388 45235 100.0% 1.32 [1.23, 1.42] Total events 19546 20750 Heterogeneity: Tau <sup>2</sup> = 0.04; Ch <sup>2</sup> = 216.02, df = 36 (P < 0.00001); P <sup>2</sup> = 83% Test for overall effect: Z = 7.57 (P < 0.00001) Test for subround difference: Ch <sup>2</sup> = 67.89, df = 4 (P < 0.00001); I <sup>2</sup> = 830 0.01 0.1 1 10 100 control SLE	Ikue Ito 2009	199	562	287	954	2.7%	1.27 [1.02, 1.59]	2 T
P. Dieude-2 2010 849 1486 878 1760 3.1% 1.34 [1.17, 1.54] Subtotal (95% CI) 3670 4174 8.9% 1.25 [1.13, 1.38] Total events 1940 1917 Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 2.28, df = 2 (P = 0.32); l <sup>2</sup> = 12% Test for overall effect: Z = 4.44 (P < 0.00001) Total (95% CI) 39388 45235 100.0% 1.32 [1.23, 1.42] Total events 19546 20750 Heterogeneity: Tau <sup>2</sup> = 0.04; Ch <sup>2</sup> = 216.02, df = 36 (P < 0.00001); l <sup>2</sup> = 83% Test for overall effect: Z = 7.57 (P < 0.00001) Test for subrown difference: Ch <sup>2</sup> = 67.84, df = 4 (P < 0.00001) l <sup>2</sup> = 93.0%	P. Dieude 2009	892	1622	752	1460	3.1%	1.15 [1.00, 1.33]	
Subtotal (95% CI)         3670         4174         8.9%         1.25 [1.13, 1.38]           Total events         1940         1917           Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 2.28, df = 2 (P = 0.32); l <sup>2</sup> = 12%         Test for overall effect: Z = 4.44 (P < 0.00001)	P. Dieude-2 2010	849	1486	878	1760	3.1%	1.34 [1.17, 1.54]	
Total events         1940         1917           Heterogeneity:         Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 2.28, df = 2 (P = 0.32); l <sup>2</sup> = 12%           Test for overall effect:         Z = 4.44 (P < 0.00001)	Subtotal (95% CI)		3670		4174	8.9%	1.25 [1.13, 1.38]	+
Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 2.28, df = 2 (P = 0.32); l <sup>2</sup> = 12% Test for overall effect: Z = 4.44 (P < 0.00001) Total (95% Cl) 39388 45235 100.0% 1.32 [1.23, 1.42] Total events 19546 20750 Heterogeneity: Tau <sup>2</sup> = 0.04; Ch <sup>2</sup> = 216.02, df = 36 (P < 0.00001); l <sup>2</sup> = 83% Test for overall effect: Z = 7.57 (P < 0.00001) Test for subround differences: Ch <sup>2</sup> = 6.48, df = 4 (P < 0.00001); l <sup>2</sup> = 03.0%	Total events	1940		1917				
Test for overall effect: Z = 4.44 (P < 0.00001)	Heterogeneity: Tau <sup>2</sup> = 0.00;	Chi <sup>2</sup> = 2.23	8, df = 2	(P = 0.32	2);  2 = 1	2%		
Total (95% CI)         39388         45235         100.0%         1.32 [1.23, 1.42]           Total events         19546         20750         1.32 [1.23, 1.42]           Heterogeneity: Tau <sup>2</sup> = 0.04; Chi <sup>2</sup> = 216.02, df = 36 (P < 0.00001); l <sup>2</sup> = 83%         0.01         0.1         1         10         100           Test for overall effect: Z = 7.57 (P < 0.00001)	Test for overall effect: Z = 4.	44 (P < 0.0	00001)					
Total (95% CI)         39388         45235         100.0%         1.32 [1.23, 1.42]           Total events         19546         20750         1.32 [1.23, 1.42]         1           Heterogeneity:         Tau <sup>2</sup> = 0.04; Chi <sup>2</sup> = 216.02, df = 36 (P < 0.00001); P = 83%			22222		10000	00000000		
Total events         19546         20750           Heterogeneity: Tau <sup>2</sup> = 0.04; Ch <sup>2</sup> = 216.02; df = 36 (P < 0.00001); l <sup>2</sup> = 83%         0.01         0.1         1         10         100           Test for overall effect: Z = 7.57 (P < 0.00001); l <sup>2</sup> = 63.48; df = 4 (P < 0.00001); l <sup>2</sup> = 03.0%         0.01         0.1         1         10         100	Total (95% CI)		39388		45235	100.0%	1.32 [1.23, 1.42]	1
Heterogenetty: Tau* = 0.04; Chr = 216.02; df = 36 (P < 0.00001); P = 83% Test for overall effect: Z = 7.57 (P < 0.00001) Test for superall effect: Z = 7.57 (P < 0.00001) Test for superall effect: Z = 7.57 (P < 0.00001) Test for superall effect: Z = 7.57 (P < 0.00001) Test for superall effect: Z = 7.57 (P < 0.00001) Test for superall effect: Z = 7.57 (P < 0.00001) Test for superall effect: Z = 7.57 (P < 0.00001) Test for superall effect: Z = 7.57 (P < 0.00001) Test for superall effect: Z = 7.57 (P < 0.00001) Test for superall effect: Z = 7.57 (P < 0.00001) Test for superall effect: Z = 7.57 (P < 0.00001) Test for superall effect: Z = 7.57 (P < 0.00001) Test for superall effect: Z = 7.57 (P < 0.00001) Test for superall effect: Z = 7.57 (P < 0.00001) Test for superall effect: Z = 7.57 (P < 0.00001) Test for superall effect: Z = 7.57 (P < 0.00001) Test for superall effect: Z = 7.57 (P < 0.00001) Test for superall effect: Z = 7.57 (P < 0.00001) Test for superall effect: Z = 7.57 (P < 0.00001) Test for superall effect: Z = 7.57 (P < 0.00001) Test for superall effect: Z = 7.57 (P < 0.00001) Test for superall effect: Z = 7.57 (P < 0.00001) Test for superall effect: Z = 7.57 (P < 0.00001) Test for superall effect: Z = 7.57 (P < 0.00001) Test for superall effect: Z = 7.57 (P < 0.00001) Test for superall effect: Z = 7.57 (P < 0.00001) Test for superall effect: Z = 7.57 (P < 0.00001) Test for superall effect: Z = 7.57 (P < 0.00001) Test for superall effect: Z = 7.57 (P < 0.00001) Test for superall effect: Z = 7.57 (P < 0.00001) Test for superall effect: Z = 7.57 (P < 0.00001) Test for superall effect: Z = 7.57 (P < 0.00001) Test for superall effect: Z = 7.57 (P < 0.00001) Test for superall effect: Z = 7.57 (P < 0.00001) Test for superall effect: Z = 7.57 (P < 0.00001) Test for superall effect: Z = 7.57 (P < 0.00001) Test for superall effect: Z = 7.57 (P < 0.00001) Test for superall effect: Z = 7.57 (P < 0.00001) Test for superall effect: Z = 7.57 (P < 0.00001) Test for superall effec	Total events	19546		20750				
rest for overall effect: $z = r_{-D}r_{\parallel}r_{\parallel} < 0.00001$ control SLE Tast for subgroup differences: ( $D_{\perp} = 57.84$ ( $d = 4.0 < 0.00001$ ) $B = 93.0%$	Heterogeneity: Tau <sup>2</sup> = 0.04;	Chr = 216	0.02, df =	= 36 (P <	0.00001	); l* = 83%	,	0.01 0.1 1 10 100
	Test for subgroup difference	or (P < 0.1	7 48 -4	= 4 /P -	0.00004	) 12 = 0.2 0	196	control SLE

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

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	SLE		Cont	rol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H. Random, 95% CI
1.1.1 2280714_SLE							
Kelly 2008	849	2234	846	2064	8.9%	0.88 [0.78, 1.00]	-
Shin 2007	465	1178	764	1900	8.0%	0.97 [0.84, 1.12]	+
Sigurdsson-1 2005	278	960	149	512	5.5%	0.99 [0.78, 1.26]	+
Sigurdsson-2 2005	48	218	73	242	2.6%	0.65 [0.43, 1.00]	
Snaevar Sigurdsson 2008	243	970	361	1129	6.7%	0.71 [0.59, 0.86]	-
vuong 2010	121	544	190	614	4.8%	0.64 [0.49, 0.83]	-
Subtotal (95% CI)		6104		6461	36.4%	0.82 [0.72, 0.95]	•
Total events	2004		2383				
Heterogeneity: Tau <sup>2</sup> = 0.02;	Chi² = 14.	35, df =	5 (P = 0.0	01); I <sup>2</sup> =	65%		
Test for overall effect: Z = 2	.73 (P = 0.	006)					
1.1.2 rs2280714 RA							
Blanca Rueda-1 2006	475	1448	345	1084	7.4%	1.05 (0.88, 1.24)	+
Blanca Rueda-2 2006	171	546	299	948	5.7%	0.99 [0.79, 1.24]	+
Blanca Rueda-3 2006	208	570	238	568	5.4%	0.80 [0.63, 1.01]	-
K Shimane 2012	1765	3884	1364	3196	9.8%	1.12 [1.02, 1.23]	
Rebeca Dieguez 2008	1645	5288	2019	6472	10.2%	1.00 [0.92, 1.08]	+
YUN JUNG KIM 2008	943	2386	762	1900	8.8%	0.98 [0.86, 1,10]	+
Subtotal (95% CI)		14122		14168	47.3%	1.01 [0.94, 1.09]	
Total events	5207		5027				
Heterogeneity: Tau <sup>2</sup> = 0.00;	Chi <sup>2</sup> = 8.8	1, df = 5	6 (P = 0.12	2); $ ^2 = 4$	3%		
Test for overall effect: Z = 0	.25 (P = 0.	80)					
1.1.3 rs2280714 MS							
G Kristiansdottir-1 2008	351	1300	510	1594	7.6%	0.79 [0.67, 0.92]	-
G Kristiansdottir-2 2008	629	2168	709	2364	8.7%	0.95 [0.84, 1.08]	•
Subtotal (95% CI)		3468		3958	16.3%	0.87 [0.72, 1.05]	•
Total events	980		1219				
Heterogeneity: Tau <sup>2</sup> = 0.01;	Chi <sup>2</sup> = 3.3	9, df = 1	(P = 0.07	7);  2 = 7	1%		
Test for overall effect: Z = 1	.42 (P = 0.	16)	1.1.1				
Total (95% CI)		23694		24587	100.0%	0.91 [0.84, 0.98]	
Total events	8191		8629			[ere il ere il	
Heterogeneity: Tau <sup>2</sup> = 0.01	Chi <sup>2</sup> = 43	86. df =	13 (P < 0	.00011	<sup>2</sup> = 70%		
Test for overall effect: Z = 2	38 (P = 0.	02)					0.01 0.1 1 10 100
Test for subgroup difference	s: Chi2 = 7	.50. df	= 2 (P = 0	.02), 12 :	= 73.3%		control SLE

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

	SLE		Cont	rol		Odds Ratio		Odds Ratio
Study or Subaroup	Events	Total	Events	Total	Weight	M-H. Random, 95% C	Year	M-H. Random, 95% CI
1.1.1 rs10954213_SLE								
eddy 2007	241	360	311	564	9.3%	1.65 [1.25, 2.17]	2007	-
Kawasaki 2008	242	554	190	402	0.0%	0.87 [0.67, 1.12]	2008	
celly 2008	906	1590	1174	2258	0.0%	1.22 [1.07, 1.39]	2008	
inaevar Sigurdsson 2008	692	970	674	1129	0.0%	1.68 [1.40, 2.02]	2008	
iiu 2008	424	888	413	820	0.0%	0.90 [0.74, 1.09]	2008	
Song 2009	112	184	84	176	0.0%	1.70 [1.12, 2.59]	2009	
nna Hellquist 2009	388	554	441	712	0.0%	1.44 [1.13, 1.82]	2009	
arae.Lofgren-1 2010	247	356	274	530	9.2%	2.12 [1.60, 2.81]	2010	
arae.Lofgren-3 2010	840	1192	689	1040	0.0%	1.22 [1.02, 1.45]	2010	10.00
uong 2010	402	544	398	614	0.0%	1.54 [1.19, 1.98]	2010	
arae.Lofgren-5 2010	285	420	222	370	0.0%	1.41 [1.05, 1.88]	2010	
arae.Lofgren-2 2010	282	482	264	498	9.8%	1.25 [0.97, 1.61]	2010	-
arae.Lofgren-4 2010	344	526	293	494	0.0%	1.30 [1.01, 1.67]	2010	
ubtotal (95% CI)		1198		1592	28.3%	1.63 [1.20, 2.20]		•
otal events	770		849					1.1
leterogeneity: Tau <sup>2</sup> = 0.05:	Chi2 = 7.4	9, df = 2	P = 0.0	2); l <sup>2</sup> = 7	3%			
est for overall effect: Z = 3.	15 (P = 0.	002)						
.1.2 rs10954213_RA								-
ebeca Dieguez 2008	1745	5288	2343	6472	12.9%	0.87 [0.80, 0.94]	2008	
UN JUNG KIM 2008	1138	2386	941	1900	12.3%	0.93 [0.82, 1.05]	2008	
ubtotal (95% CI)		7674		8372	25.2%	0.89 [0.83, 0.94]		
otal events	2883		3284					
leterogeneity: Tau <sup>2</sup> = 0.00:	Chi <sup>2</sup> = 0.8	8. df = 1	(P = 0.3)	5); l <sup>2</sup> = 0	1%			
est for overall effect: Z = 3.	70 (P = 0.	0002)						
.1.3 rs10954213_MS								1.1
Kristiansdottir-2 2008	1453	2168	1537	2364	12.3%	1.09 (0.97, 1.24)	2008	
Kristiansdottir-1 2008	897	1300	1036	1594	11.7%	1.20 [1.03, 1.40]	2008	
ubtotal (95% CI)		3468		3958	24.0%	1.13 [1.03, 1.25]		,
otal events	2350		2573					
leterogeneity: Tau <sup>2</sup> = 0.00:	Chi <sup>2</sup> = 0.8	2. df = 1	(P = 0.3)	6);   <sup>2</sup> = 0	9%			
est for overall effect: Z = 2.	.53 (P = 0.	01)	S 833					
.1.4 rs10954213_SSc								
kue Ito 2009	291	562	432	954	10.7%	1.30 [1.05, 1.60]	2009	-
. DIEUDE 2010	951	1486	1063	1760	11.9%	1.17 [1.01, 1.34]	2010	
ubtotal (95% CI)		2048		2714	22.6%	1.21 [1.07, 1.36]		•
otal events	1242		1495					
leterogeneity: Tau <sup>2</sup> = 0.00;	Chi <sup>2</sup> = 0.6	9, df = 1	(P = 0.4)	1); I <sup>2</sup> = 0	9%			
est for overall effect: Z = 3.	12 (P = 0.	002)						
otal (95% CI)		14388		16636	100.0%	1.21 [1.04, 1.41]		•
otal events	7245		8201					
leterogeneity: Tau <sup>2</sup> = 0.05;	Chi <sup>2</sup> = 72.	46, df =	8 (P < 0.	00001);	l² = 89%			
est for overall effect: Z = 2.	40 (P = 0.	02)						0.01 0.1 1 10
est for subgroup difference	s: Chi2 = 3	19.66. d	f = 3 (P <	0.0000	1), $ ^2 = 92.4$	4%		control SLE

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

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	SLE		Contr	ol		Odds Ratio			0	dds Rati	o	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year		M-H.	Fixed, 9	5% CI	
reddy-1 2007	169	378	175	564	32.9%	1.80 [1.37, 2.35]	2007			-		
Kelly et al-1 2008	239	1590	226	2258	67.1%	1.59 [1.31, 1.93]	2008					
Total (95% CI)		1968		2822	100.0%	1.66 [1.42, 1.94]				٠		
Total events	408		401									
Heterogeneity: Chi <sup>2</sup> = (	0.52, df = 1	(P = (	).47); l <sup>2</sup> =	0%				0.01	0.1	-	10	100
Test for overall effect: Z = 6.29 (P < 0.00001)									conre	eol SLE	- 10	100

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

	SLE	2	Control Odds Ratio						Odds Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Fixed, 95% C	Year		M-H, F	ixed, 95	% CI		
Kawasaki et al-1 2008	313	554	212	402	26.0%	1.16 [0.90, 1.51]	2008			<b>.</b>			
Snaevar Sigurdsson-1 2008	459	1590	517	2258	74.0%	1.37 [1.18, 1.58]	2008						
Total (95% CI)		2144		2660	100.0%	1.31 [1.16, 1.49]				•			
Total events	772		729										
Heterogeneity: Chi <sup>2</sup> = 1.13, df	= 1 (P = 0	.29); I <sup>z</sup>	= 11%					0.01	0.1	1	10	100	
Test for overall effect: Z = 4.2	0 (P < 0.00	001)						0.01	contr	ol SLE	10	100	

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,

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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- $\alpha$  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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