JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Original Article

Susceptibility of autoimmune diseases in three polymorphisms of infection-associated gene IRAK1

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Abstract

Introduction: Infection of pathogenic microorganisms is an important reason for autoimmune diseases (ADs). Interleukin-1 (IL-1) receptor-associated kinase-1 (IRAK1) is a key mediator in infection immunity, while the gene of IRAK1 is recognized as a risk gene in ADs. Three single nucleotide polymorphisms (SNPs) in IRAK1 (rs3027898, rs1059702, rs1059703) are considered to be associated with ADs risk. However, the results are conflicting. We conducted this study to get more precise estimations.

Methodology: PubMed, OvidSP, and CNKI databases (published prior to August 2014) were searched, and data was extracted from eligible studies. The procedure of statistical analysis was performed using STATA 12.0 software. A random effect model or fixed effect model was chosen based on the between-study heterogeneities.

Results: Of the studies involved, 11 studies included 10,705 cases (9,865 controls) for rs3027898, 9 studies included 15,005 cases (14,997 controls) for rs1059702, and 7 studies included 8,115 cases (6,815 controls) for rs1059703. Overall, the results showed that there were significant associations with ADs risk in three genetic models for rs3027898 and in four genetic models for rs1059702, but in neither model for rs1059703. Moreover, in stratified analyses, different extents of associations were found in some different genetic models for all three SNPs.

Conclusion: Our data demonstrated that these three SNPs (rs3027898, rs1059702, rs1059703) in IRAK1 were associated with ADs risk.

Key words: autoimmune diseases; susceptibility; interleukin-1 receptor-associated kinase-1; single nucleotide polymorphisms.

J Infect Dev Ctries 2015; 9(6):614-623. doi:10.3855/jidc.6776

(Received 20 February 2015 – Accepted 14 March 2015)

Introduction

Autoimmune diseases (ADs) are a group of complex disorders initiated by the loss of tolerance to self-antigen, which results in immune-mediated tissue destruction and chronic disabilities [1]. ADs comprise more than 100 diseases and syndromes, and the annual estimated treatment costs for ADs are more than US$100 billion [2]. As a group of complex diseases, the precise molecular mechanism of ADs is still not clear. However, the interaction of genes and environment is widely recognized as one of the main causes of ADs [3,4].

The sustained pathology of ADs is directly caused by a specific self-reactive immune response, including innate and adaptive immune response, which can be caused by infection with some kinds of pathogenic microorganisms [5-7]. Interleukin-1 (IL-1) receptor-associated kinases (IRAKs) are key mediators in the signaling pathways of innate immune response, especially in the Toll-like receptors (TLRs)/IL-1 receptors (IL-1Rs) pathway. There are four kinds of IRAKs: IRAK1, IRAK2, IRAK3, and IRAK4 [8]. IRAK1 is the first member identified in the IRAK family. It can be phosphorylated and induce a serious downstream signaling cascade after the activation of TLRs/IL-1Rs stimulation [8,9]. The phosphorylation of IRAK1 is associated with the activation of NF-κB in inflammatory disease, and the activity of NF-κB can be inhibited using an IRAK1 inhibitor, resulting in the suppression of the inflammatory conditions [10,11].

IRAK1 has been found play an important role in both ADs patients and in an autoimmune animal model [11-15]. Therefore, IRAK1 is recognized as a risk gene in ADs.

Single nucleotide polymorphisms (SNPs), or mutations, may alter expression of the gene and influence the susceptibility of some diseases [16-19]. Some researchers have studied the relationship between ADs risk and three polymorphisms of IRAK1: IRAK1 rs3027898 C>A, IRAK1 rs1059702 T>C, and IRAK1 rs1059703 T>C. Most of these studies were conducted in developing countries, so it is very important for these countries to make clear what the role of IRAK1 for ADs is [14,15,20-27]. However, the results among these studies remain conflicting. Therefore, we conducted this study, according the procedure published by MOOSE group [28], to find a clearer association between these three SNPs and ADs risk.

Methodology

Publication search

A systematic search was performed in PubMed, OvidSP, and Chinese National Knowledge Infrastructure (CNKI) databases covering all papers published prior to August 2014. The searching strategy was as follows: (autoimmune OR autoimmune disease OR autoimmunity) AND (polymorphism OR polymorphisms OR variation OR variations OR mutation OR mutations OR variant OR variants) AND (IRAK1 OR rs3027898 OR rs1059702 OR rs1059703). The references in the studies were also read to find additional publications on this topic. Articles included had to meet the following criteria: case-control study; evaluation of IRAK1 polymorphisms (rs3027898, rs1059702, or rs1059703) and risk of ADs; and available and usable data of genotype frequency.

Data extraction

Two authors independently extracted the data from eligible studies. The different data that were extracted were checked. The remaining disagreements were discussed and judged. The following information was extracted: first author, publication year, diseases, country, ethnicity, genotyping methods, number of cases and controls, gender distribution of cases and controls, number of genotypes and alleles, Hardy-Weinberg equilibrium (HWE) in control subjects, and frequency of major allele in controls. Ethnicities were categorized as Caucasian, Asian, African, and Latin-American. Study quality was judged according to the criteria modified from previous publications [29-31] (See Supplementary "Table S1 Scale for methodological quality assessment").

Statistical analysis

Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated as a measure of the association between the three SNPs (rs3027898, rs1059702, and rs1059703) and ADs risk. An allele model and other types of genetic models (heterozygote, homozygote, dominant, and recessive models) were used. In addition to comparing among all subjects, the stratified comparisons were also used according to different ethnicities and different diseases. The between-study heterogeneity was measured by Cochran's (Q) and Higgins's (I^2) tests. If the heterogeneity was considered significant ($p < 0.05$), the random effects model was used to estimate the pooled OR. Otherwise, the fixed effects model was used. Also, logistic meta-regression analysis was carried out, if there was obvious significant heterogeneity, to explore potential sources of heterogeneity. The examined characteristics included publication years, countries, genotyping methods, number of alleles and genotypes, number of females and males in cases, and the frequency of major allele in SNP in controls. The HWE was examined using the Chi-square test with significance set at $p < 0.05$. Sensitivity analysis was performed to evaluate the effect of each study on the combined ORs by deleting each study in each turn. Potential publication bias was determined using Funnel plots and Begg's test. An asymmetric plot and p value of less than 0.05 was recognized as significance. All statistical analyses were performed using STATA 12.0 software.

Results

Study characteristics

There were 483 articles matching the search strategy, and an additional article [20] was found by scanning the references of the original papers. After a step-by-step screening of the titles, abstracts, and full texts of the articles, as shown in Figure 1, there were 10 articles appropriate for this meta-analysis, which included 11 studies of rs3027898, 9 studies of rs1059702, and 7 studies of rs1059703.

Within all the 10 articles, six kinds of genotyping methods were used. Four races were included: Caucasian, Asian, African, and Latin-American. Four studies were not in HWE in control groups [14,15,23,24].

Table 1. Characteristics of published studies of rs3027898, rs1059702 and rs1059703

First author	Year	Diseases	Country	Ethnicity	Sample size		Female/Male		Genotyping methods	Case					Control					HWE of control (p value)	Frequency of C Allele in controls	Quality
										Genotype			Allele		Genotype			Allele				
					case	control	case	control		AA	AC	CC	A	C	AA	AC	CC	A	C			
rs3027898 C>A																						
Chatzikyriakidou	2010a	RA	Greece	Caucasian	136	147	109/27	115/32	PCR-RFLP	71	45	20	187	85	91	47	9	229	65	Y(0.385)	0.22	7
Chatzikyriakidou	2010b	PsA	Greece	Caucasian	29	66	10/19	30/36	PCR-RFLP	18	3	8	39	19	40	22	4	102	30	Y(0.679)	0.23	6
Chatzikyriakidou	2010b	AS	Greece	Caucasian	49	66	4/45	30/36	PCR-RFLP	39	1	9	79	19	40	22	4	102	30	Y(0.679)	0.23	6
Zhang	2013	RA	China	Asian	211	475			MALDI-TOF MS	28	42	141	98	324	35	103	337	173	777	N(0.000)	0.82	7
Zhai	2013	SLE	China	Asian	661	663	586/75	586/77	TaqMan	21	167	473	209	1113	40	202	421	282	1044	N(0.000)	0.79	6
Gao	2012	RA	China	Asian	123	220	105/18	196/24	PCR-LDR	4	33	86	41	205	10	54	156	74	366	Y(0.069)	0.83	7
Han	2013	RA	Korea	Asian	1158	849	1158/0	849/0	MassArray	56	383	719	495	1821	50	321	478	421	1277	Y(0.687)	0.75	8
Kaufman	2013	SLE	USA	Caucasian	3915	3462	3583/332	2337/1125	Illumina				5966	1864				5546	1378		0.20	7
Kaufman	2013	SLE	USA	Asian	1262	1256	1164/98	1106/150	Illumina				419	2105				593	1919		0.76	7
Kaufman	2013	SLE	USA	Latin-American	1487	807	1363/124	727/80	Illumina				1294	1680				867	747		0.46	7
Kaufman	2013	SLE	USA	African	1674	1920	1540/134	1342/578	Illumina				1892	1456				2170	1670		0.43	7
										CC	TC	TT	C	T	CC	TC	TT	C	T		Frequency of T Allele in controls	
rs1059702 T>C																						
Dieude	2011	SSc	France	Caucasian	1808	2217	1808/0	2217/0	TaqMan	1240	490	78	2970	646	1587	561	69	3735	699	N(0.026)	0.16	7
Han	2013	RA	Korea	Asian	1162	860	1162/0	860/0	MassArray	62	393	707	517	1807	59	336	465	454	1266	Y(0.872)	0.74	8
Zhai	2013	SLE	China	Asian	665	665	591/74	587/78	TaqMan	24	185	456	233	1097	41	220	404	302	1028	Y(0.138)	0.77	7
Carmona	2013	SSc	Spain	Caucasian	2415	2361	2415/0	2361/0	TaqMan	1729	605	81	4063	767	1746	548	67	4040	682	N(0.003)	0.14	7
Kaufman	2013	SLE	USA	Caucasian	3915	3462	3583/332	2337/1125	Illumina				6350	1480				5913	1011		0.15	7
Kaufman	2013	SLE	USA	Asian	1262	1256	1164/98	1106/150	Illumina				452	2072				631	1881		0.75	7
Kaufman	2013	SLE	USA	Latin-American	1487	807	1363/124	727/80	Illumina				1457	1517				989	625		0.39	7
Kaufman	2013	SLE	USA	African	1674	1920	1540/134	1342/578	Illumina				3150	198				3683	157		0.04	7
Marquez	2014	GCA	Spain	Caucasian	617	1449	617/0	1449/0	TaqMan	466	128	23	1060	174	1066	344	39	2476	422	Y(0.081)	0.15	8
										CC	TC	TT	C	T	CC	TC	TT	C	T		Frequency of T Allele in controls	

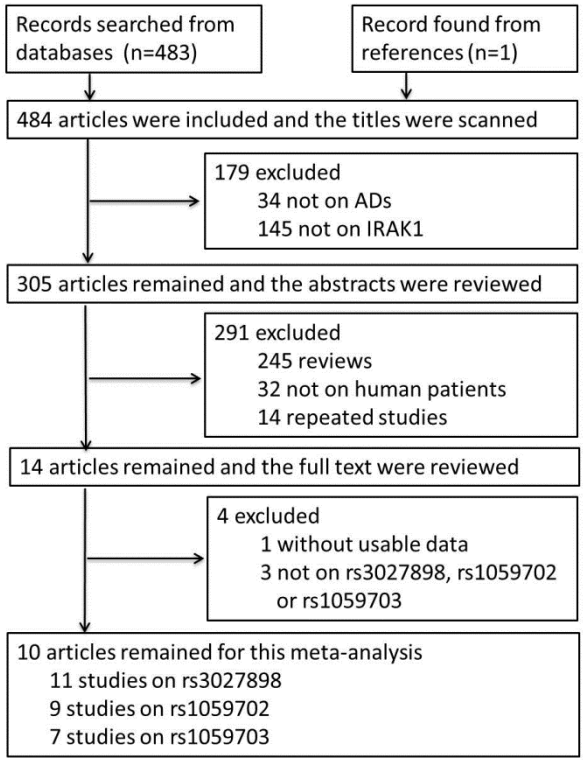
Table 1 ***(continued)*****.** Characteristics of published studies of rs3027898, rs1059702 and rs1059703

First author	Year	Diseases	Country	Ethnicity	Sample size		Female/Male		Genotyping methods	Case					Control					HWE of control (p value)	Frequency of C Allele in controls	Quality
										Genotype			Allele		Genotype			Allele				
					case	control	case	control		AA	AC	CC	A	C	AA	AC	CC	A	C			
rs1059703 T>C																						
Chatzikyriakidou	2010a	RA	Greece	Caucasian	136	147	109/27	115/32	PCR-RFLP	7	52	77	66	206	7	46	94	60	234	Y(0.656)	0.80	7
Chatzikyriakidou	2010b	PsA	Greece	Caucasian	29	66	10/19	30/36	PCR-RFLP	5	4	20	14	44	4	22	40	30	102	Y(0.679)	0.77	6
Gao	2012	RA	China	Asian	123	220	105/18	196/24	PCR-LDR	85	34	4	204	42	152	58	10	362	78	Y(0.154)	0.18	7
Han	2013	RA	Korea	Asian	1163	857	1163/0	857/0	MassArray	59	389	715	507	1819	52	337	468	441	1273	Y(0.398)	0.74	8
Kaufman	2013	SLE	USA	Caucasian	3915	3462	3583/332	2337/1125	Illumina				1527	6303				1046	5878		0.85	7
Kaufman	2013	SLE	USA	Asian	1262	1256	1164/98	1106/150	Illumina				2085	439				1902	610		0.24	7
Kaufman	2013	SLE	USA	Latin-American	1487	807	1363/124	727/80	Illumina				1627	1347				702	912		0.57	7

RA, Rheumatoid Arthristis; PsA, Psoriatic Arthritis; SLE, Systemic Lupus Erythematosus; SSc, Systemic Sclerosis; GCA, Giant Cell Arteritis.

Figure 1. Flowchart for identification of studies included in the meta-analysis

In 484 articles, 34 were found not related to ADs and 145 were found not related to IRAK1 by scanning the titles. After that, 245 articles were recognized as reviews, 32 were found not related to human patients and 14 articles were repeated papers by reviewing the abstracts. The full-text of the left 14 articles were carefully reviewed, in which 1 article was found not include usable data and 3 articles were found not about rs3027898, rs1059702 or rs1059703. At last, 10 articles were remained for this meta-analysis, which included 11 case-control studies for rs3027898, 9 studies for rs1059702 and 7 studies for rs1059703.



There was not enough data in another article [25] to generate the HWE in four studies, but the p value of HWE was not less than 0.001 according to the authors' explanation. The detail characteristics are shown in Table 1.

Association between IRAK1 rs3027898 C>A polymorphism and ADs risk

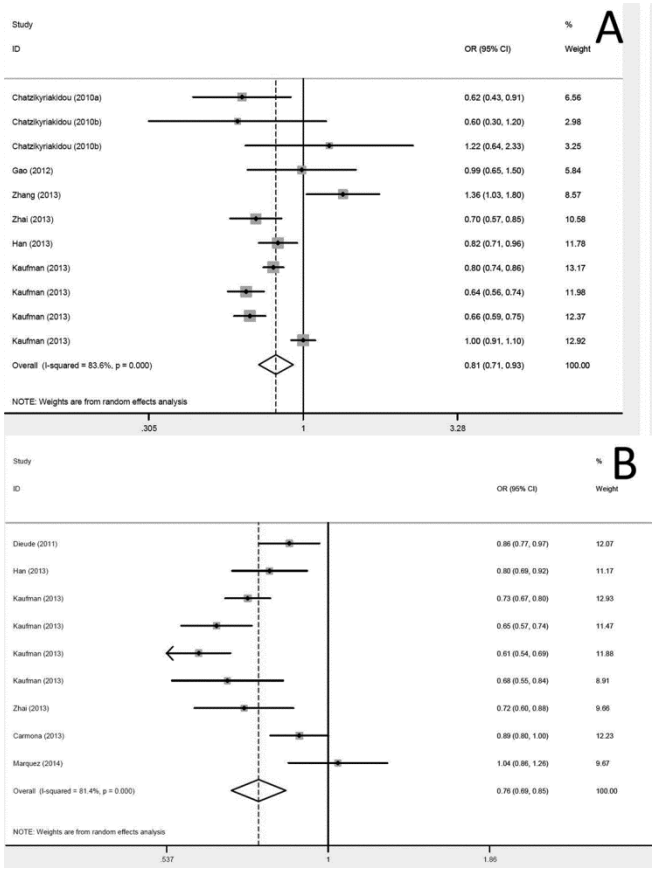
First, the association between rs3027898 C>A polymorphism and the risk of ADs was analyzed. Significant increased risk of C allele and CC genotype with ADs was observed in the allele model (A versus C: OR = 0.81, 95% CI = 0.71–0.93, p = 0.002), heterozygote model (CA versus CC: OR = 0.69, 95% CI = 0.49–0.97, p = 0.034) and dominant model (CA+AA versus CC: OR = 0.73, 95% CI = 0.55–0.98, p = 0.034) (Table 2, Figure 2A and Figure S1A, S1B).

Next, the studies were analyzed by subgroup analysis according to ethnicities or diseases. In Caucasians, there was significant increased risk of C allele and CC genotype with ADs in the allele model (A versus C: OR = 0.79, 95% CI = 0.73–0.85, p = 0.000), heterozygote model (CA versus CC, OR = 0.11, 95% CI = 0.02-0.66, p = 0.016), homozygote model (AA versus CC: OR = 0.34, 95% CI = 0.18–0.63, p = 0.001) and dominant model (CA+AA versus CC: OR = 0.30, 95% CI = 0.16–0.55, p = 0.000) (Table 2 and Figure S1E, S1F, S1G and S1H). In Asians, there was a significant increased risk in CC genotype in the heterozygote model (CA versus CC: OR = 0.81, 95% CI = 0.71–0.93, p = 0.002) (Table 2 and Figure S1I). In the systemic lupus erythematosus (SLE) subgroup, there was increased disease risk in C allele in the allele model (A versus C: OR = 0.75, 95% CI = 0.64–0.89, p = 0.001) (Table 2 and Figure S1C). In the rheumatoid arthritis (RA) subgroup, there was increased risk in CC genotype in the heterozygote model (CA versus CC: OR = 0.83, 95% CI = 0.71–0.97, p = 0.021) (Table 2 and Figure S1D).

Association between IRAK1 rs1059702 T>C polymorphism and ADs risk

For rs1059702 T>C polymorphism, significant increased risk of T allele and TT genotype with ADs was observed in the allele model (C versus T: OR = 0.76, 95% CI = 0.69–0.85, p = 0.000), heterozygote model (TC versus TT: OR = 0.77, 95% CI = 0.68–0.87, p = 0.000), hemozygote model (CC versus TT: OR = 0.71, 95% CI = 0.59–0.84, p = 0.000), and dominant model (TC+CC versus TT: OR = 0.75, 95% CI = 0.66–0.84, p = 0.000) (Table 3, Figure 2B, and Figure S2A, S2B, S2C).

Figure 2. Forest plots of overall analysis of ADs risk associated with IRAK1



(A) Forest plots of overall analysis of ADs risk associated with rs3027898. Allele model, A vs C, random model. **(B)** Forest plots of overall analysis of ADs risk associated with rs1059702. Allele model, C vs T, random model. OR: odds ratio; 95% CI: 95% confidence interval.

Stratified analyses showed that in Caucasians, there were significant increased risk of T allele and TT genotype with ADs in the allele model (C versus T: OR = 0.86, 95% CI = 0.75–0.99, p = 0.029), hemozygote model (CC versus TT: OR = 0.75, 95% CI = 0.61–0.93, p = 0.009), and dominant model (TC+CC versus TT: OR = 0.76, 95% CI = 0.62–0.95, p = 0.014) (Table 3 and Figure S2B, S2C, S2I). In Asians, there was a significant relationship between AD risk and rs1059702 in all genetic models (allele model, C versus T: OR = 0.72, 95% CI = 0.63–0.82, p = 0.000; heterozygote model, TC versus TT: OR = 0.76, 95% CI = 0.66–0.88, p = 0.000; hemozygote model, CC versus TT: OR = 0.62, 95% CI = 0.46–0.85, p = 0.002; dominant model, TC+CC versus TT: OR = 0.74, 95% CI = 0.64–0.85, p = 0.000; recessive model, CC versus TT+TC: OR = 0.69, 95% CI = 0.51–0.93, p = 0.015) (Table 3 and Figure S2B, S2C, S2J, S2K, S2L).

Table 2. Stratified analysis of association between ADs risk and rs3027898

Gene Model	Stratify		Study (n)	Effects size		Heterogeneity		Effect model
				OR(95% CI)	*p value*	I^2(%)	*p value*	
Allele model (A vs C)	Total		11	**0.81(0.71-0.93)**	**0.002**	83.6	0.000	Random
	Ethnicities	Caucasian	4	**0.79(0.73-0.85)**	**0.000**	22.8	0.274	Fixed
		Asian	5	0.84(0.67-1.06)	0.151	84.2	0.000	Random
	Diseases	RA	4	0.92(0.68-1.24)	0.575	77.7	0.004	Random
		SLE	5	**0.75(0.64-0.89)**	**0.001**	90.5	0.000	Random
Heterozygote model (CA vs CC)	Total		7	**0.69(0.49-0.97)**	**0.034**	73.2	0.001	Random
	Ethnicities	Caucasian	3	**0.11(0.02-0.66)**	**0.016**	75.3	0.017	Random
		Asian	4	**0.81(0.71-0.93)**	**0.002**	0.0	0.407	Fixed
	Diseases	RA	4	**0.83(0.71-0.97)**	**0.021**	28.0	0.244	Fixed
Homozygote model (AA vs CC)	Total		7	0.62(0.36-1.05)	0.074	72.3	0.001	Random
	Ethnicities	Caucasian	3	**0.34(0.18-0.63)**	**0.001**	0.0	0.771	Fixed
		Asian	4	0.85(0.45-1.59)	0.605	78.5	0.003	Random
	Diseases	RA	4	0.82(0.41-1.65)	0.574	77.6	0.004	Random
Dominant model (CA+AA vs CC)	Total		7	**0.73(0.55-0.98)**	**0.034**	69.1	0.004	Random
	Ethnicities	Caucasian	3	**0.30(0.16-0.55)**	**0.000**	0.0	0.590	Fixed
		Asian	4	0.87(0.69-1.10)	0.234	63.1	0.044	Random
	Diseases	RA	4	0.87(0.62-1.22)	0.422	67.1	0.028	Random
Recessive model (AA vs CC+CA)	Total		7	0.98(0.64-1.50)	0.920	69.9	0.003	Random
	Ethnicities	Caucasian	3	1.15(0.52-2.57)	0.727	72.3	0.027	Random
		Asian	4	0.89(0.49-1.61)	0.700	76.3	0.005	Random
	Diseases	RA	4	0.96(0.58-1.58)	0.861	69.4	0.020	Random

Table 3. Stratified analysis of association between ADs risk and rs1059702

Gene Model	Stratify		Study (n)	Effects size		Heterogeneity		Effect model
				OR(95% CI)	*p value*	I^2(%)	*p value*	
Allele model (C vs T)	Total		9	**0.76(0.69-0.85)**	**0.000**	81.4	0.000	Random
	Ethnicities	Caucasian	4	**0.86(0.75-0.99)**	**0.029**	80.0	0.002	Random
		Asian	3	**0.72(0.63-0.82)**	**0.000**	50.9	0.131	Random
	Diseases	SSc	2	**0.88(0.81-0.95)**	**0.002**	0.0	0.641	Fixed
		SLE	5	**0.68(0.62-0.74)**	**0.000**	42.3	0.140	Random
Heterozygote model (TC vs TT)	Total		5	**0.77(0.68-0.87)**	**0.000**	0.0	0.824	Fixed
	Ethnicities	Caucasian	3	0.80(0.64-1.01)	0.056	0.0	0.518	Fixed
		Asian	2	**0.76(0.66-0.88)**	**0.000**	0.0	0.835	Fixed
	Diseases	SSc	2	0.84(0.66-1.07)	0.163	0.0	0.502	Fixed
Homozygote model (CC vs TT)	Total		5	**0.71(0.59-0.84)**	**0.000**	0.0	0.702	Fixed
	Ethnicities	Caucasian	3	**0.75(0.61-0.93)**	**0.009**	0.0	0.776	Fixed
		Asian	2	**0.62(0.46-0.85)**	**0.002**	0.0	0.381	Fixed
	Diseases	SSc	2	**0.75(0.60-0.95)**	**0.018**	0.0	0.478	Fixed
Dominant model (TC+CC vs TT)	Total		5	**0.75(0.66-0.84)**	**0.000**	0.0	0.934	Fixed
	Ethnicities	Caucasian	3	**0.76(0.62-0.95)**	**0.014**	0.0	0.753	Fixed
		Asian	2	**0.74(0.64-0.85)**	**0.000**	0.0	0.655	Fixed
	Diseases	SSc	2	**0.77(0.61-0.98)**	**0.032**	0.0	0.483	Fixed
Recessive model (CC vs TT+TC)	Total		5	0.89(0.78-1.01)	0.070	47.3	0.108	Random
	Ethnicities	Caucasian	3	0.92(0.82-1.04)	0.206	47.5	0.149	Random
		Asian	2	**0.69(0.51-0.93)**	**0.015**	0.0	0.362	Fixed
	Diseases	SSc	2	**0.88(0.80-0.96)**	**0.006**	0.0	0.800	Fixed

In the SLE subgroup, there was an increased disease risk in T allele in the allele model (C versus T: OR = 0.68, 95% CI = 0.62–0.74, p = 0.000) (Table 3 and Figure S2E). In the systemic sclerosis (SSc) subgroup, there were increased risk in T allele, TT genotype, and TT+CC genotype in the allele model (C versus T: OR = 0.88, 95% CI = 0.81–0.95, p = 0.002), hemozygote model (CC versus TT: OR = 0.75, 95% CI = 0.60–0.95, p = 0.018), dominant model (TC+CC versus TT: OR = 0.77, 95% CI = 0.61–0.98, p = 0.032), and recessive model (CC versus TT+TC: OR = 0.88, 95% CI = 0.80–0.96, p = 0.006) (Table 3 and Figure S2D, S2F, S2G, S2H).

Association between IRAK1 rs1059703 T>C polymorphism and ADs risk

There was no significant increased risk in overall comparison in any genetic model of association between rs1059703 T>C polymorphism and the risk of ADs. However, the increased risk could be found in subgroup analysis based on ethnicities or diseases. In Caucasians, there was a significant increased risk of C allele with ADs (C versus T: OR = 1.35, 95% CI = 1.24–1.47, p = 0.000) (Table 4 and Figure S3A). In Asians, there was significant increased risk of TT allele with ADs in the heterozygote model (TC versus TT: OR = 0.77, 95% CI = 0.64–0.92, p = 0.005) and dominant model (TC+CC versus TT, OR = 0.77, 95% CI = 0.64–0.91, p = 0.003) (Table 4 and Figure S3C, S3D). In the SLE subgroup, there was an increased disease risk in C allele in the allele model (C versus T: OR = 1.47, 95% CI = 1.33–1.61, p = 0.000) (Table 4 and Figure S3E).

Evaluation of heterogeneity

The heterogeneities among studies were obvious in the overall comparisons (rs3027898: I^2 = 83.6%, Tau^2 = 0.033, p = 0.000; rs1059702: I^2 = 81.4%, Tau^2 = 0.020, p = 0.000; rs1059703: I^2 = 89.6%, Tau^2 = 0.059, p = 0.000). The meta-regression analyses were conducted to further explore sources of heterogeneity. Several factors were tested as potential sources of heterogeneity, including publication years, countries, genotyping methods, number of genotypes and alleles, number of females and males in cases, and the frequencies of major alleles for each SNP in controls. As a result, the heterogeneities could not be explained by any of the potential sources by meta-regression analysis.

Sensitivity and publication bias analysis

The sensitivity analysis to test the influence of a single study on the overall meta-analysis was performed by deleting each study one at a time. As a result, the pooled estimate did not show significant difference, which indicated that the results were reliable statistically. No evidence of publication bias was found in current meta-analysis, identified by the

Table 4. Stratified analysis of association between ADs risk and rs1059703

Gene Model	Stratify		Study (n)	Effects size		Heterogeneity		Effect model
				OR(95% CI)	*p value*	I^2(%)	*p value*	
Allele model (C vs T)	Total		7	1.23(1.00-1.52)	0.049	89.6	0.000	Random
	Ethnicities	Caucasian	3	**1.35(1.24-1.47)**	**0.000**	0.0	0.764	Fixed
		Asian	3	1.09(0.67-1.77)	0.728	94.9	0.000	Random
	Diseases	RA	3	0.97(0.73-1.29)	0.819	60.5	0.080	Random
		SLE	3	**1.47(1.33-1.61)**	**0.000**	51.8	0.126	Random
Heterozygote model (TC vs TT)	Total		4	0.90(0.56-1.46)	0.677	60.2	0.056	Random
	Ethnicities	Caucasian	2	0.79(0.22-2.89)	0.726	75.7	0.043	Random
		Asian	2	**0.77(0.64-0.92)**	**0.005**	7.6	0.298	Fixed
	Diseases	RA	3	1.02(0.62-1.69)	0.936	65.4	0.056	Random
Homozygote model (CC vs TT)	Total		4	0.89(0.63-1.24)	0.481	19.6	0.292	Fixed
	Ethnicities	Caucasian	2	1.58(0.67-3.75)	0.294	0.0	0.433	Fixed
		Asian	2	0.79(0.55-1.15)	0.220	0.0	0.322	Fixed
	Diseases	RA	3	0.83(0.59-1.18)	0.297	0.0	0.465	Fixed
Dominant model (TC+CC vs TT)	Total		4	0.94(0.64-1.39)	0.754	50.7	0.107	Random
	Ethnicities	Caucasian	2	1.18(0.77-1.79)	0.452	37.6	0.206	Fixed
		Asian	2	**0.77(0.64-0.91)**	**0.003**	6.7	0.301	Fixed
	Diseases	RA	3	1.01(0.62-1.66)	0.960	66.5	0.051	Random
Recessive model (CC vs TT+TC)	Total		4	0.95(0.72-1.26)	0.733	15.5	0.314	Fixed
	Ethnicities	Caucasian	2	1.60(0.69-3.72)	0.275	32.1	0.225	Fixed
		Asian	2	0.89(0.66-1.20)	0.453	0.0	0.543	Fixed
	Diseases	RA	3	0.90(0.68-1.21)	0.495	0.0	0.783	Fixed

Funnel plots, Egger's test (p = 0.986 for rs3027898; p = 0.875 for rs1059702; p = 0.596 for rs1059703), and Begg's test (p = 0.533 for rs3027898; p = 0.917 for rs1059702; p = 0.230 for rs1059703) (Figure 3).

Discussion

IRAK1 is a protein kinase involved in the Toll/IL-1 receptor (TIR) pathway [32], which plays an important role in the activation of NF-κB. By enhancing the communication of TLR with TNF receptor-associated factor (TRAF) 6, or by engaging into the MyD88-signaling complex, IRAK1 could trigger NF-κB, subsequently increasing the expression level of several inflammatory cytokines, such as TNF-α and IL-8 [33-35]. Several animal experiments showed that the expression level of IL-17 was decreased and inflammatory responses were dampened by depletion of IRAK1 [36], and IRAK1$^{-/-}$ mice were protected from experimental autoimmune encephalomyelitis (EAE) [13]. Moreover, IRAK1 was found to be correlated with ADs risk in several studies of patient cohorts [12,20,22].

Three SNPs of IRAK1 have been found to be related to ADs risk: rs3027898 for RA [15, 22], rs1059702 for SSc [23,24] and rs1059703 for SLE [14,25]. However, the results remain in conflict. Therefore, we conducted this meta-analysis to better understand whether these three SNPs contribute to susceptibility to ADs.

In this meta-analysis, we screened 10 manuscripts and pooled the corresponding data, including 10,705 cases (9,865 controls) for rs3027898, 15,005 cases (14,997 controls) for rs1059702, and 8,115 cases (6,815 controls) for rs1059703. We found that all these three SNPs were related to ADs risk.

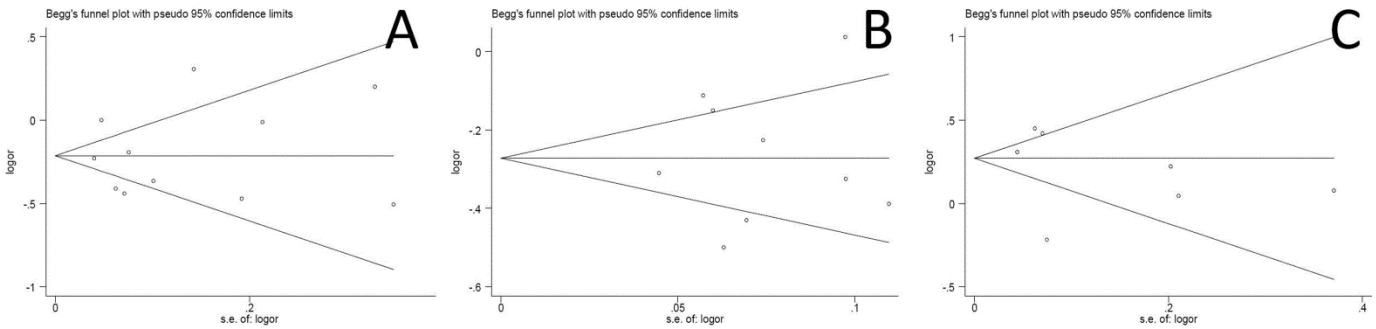
For rs3027898, C allele or CC genotype were correlated with increased disease risk in most of the genetic models, including the allele model, heterozygote model, and dominant model, both in pooled comparison and in the Caucasian subgroup. Moreover, the increased disease risk of CC genotype was also found in the homozygote model in the Caucasian subgroup. However, in the Asian subgroup, the increased ADs risk of CC genotype could only be found in the heterozygote model. In the stratified analyses based on different types of ADs, the increased susceptibility of CC genotype was found in the heterozygote model in the RA subgroup. Due to the data limitation of the SLE subgroup, we could only compare the association in the allele model, and indeed found the increased risk of C allele.

For rs1059702, either in pooled or in stratified analyses, the increased disease risk for T allele or TT genotype was found in the allele, homozygote, and dominant models. In the heterozygote model, the increased disease risk of TT genotype was found both in pooled analysis and in the Asian subgroup. In the recessive model, compared with CC genotype, the TT+TC genotype was found to be associated with increased disease risk in the Asian subgroup and SSc subgroup.

For rs1059703, there was not as much association as with rs3027898 or rs1059702. No significant relationship between ADs risk and rs1059703 could be found in pooled analyses in any genetic model. However, there were some associations shown when the stratified analyses were done. In the allele model, increased disease risk with C allele was found in the Caucasian and SLE subgroups. In contrast, increased ADs risk was found to be associated with TT genotype in the Asian subgroup, both in the heterozygote and dominant models. But for the RA subgroup, no association was found in any genetic model.

There are some limitations in this study. First, although 10 articles were included, the studies for some stratified analyses were limited. For example, there were only two studies of the Asian subgroup and two studies of the SSc subgroup in analyses for

Figure 3. Publication bias on the IRAK1 polymorphism and ADs risk



(A) Publication bias on rs3027898 and ADs risk. **(B)** Publication bias on rs1059702 and ADs risk. **(C)** Publication bias on rs1059703 and ADs risk.

rs1059702, except in the allele model. Second, there is obvious heterogeneity between different groups for some genetic models. Although the meta-regression and sensitivity analyses were conducted and no potential source of heterogeneity was found, the results still must be treated with caution. Third, only three SNPs in IRAK1 were included in this study. However, there are more SNPs in IRAK1 and more genes in the TIR signaling pathway, which would also contribute to susceptibility of ADs. The effect of these SNPs and genes, and also the interaction or network among these genetic locations, should be studied in the future. Furthermore, studies investigating the gene-environment interactions will also help to make clear of the role of these SNPs in the pathogen of ADs [37-40]. Finally, since ADs comprised diverse diseases, the relationship of these SNPs with other types of ADs, such as inflammatory bowel disease and seronegative spondyloarthropathies, should be investigated in the future.

Conclusions

The present study demonstrated that three SNPs (rs3027898, rs1059702 and rs1059703) in IRAK1 confer risk of ADs. Moreover, the associations were only within a specific genetic model, specific ethnicities, or specific disease types, not within all types of cohorts or ADs.

Acknowledgements

This work was supported by the Natural Science Foundation of China (NO. 31100661), Specialized Research Fund for the Doctoral Program of Higher Education (NO. 20114433120019, NO. 20124433120002) and the Natural Science Foundation of Guangdong Province (NO. S2011040002748, NO. S2012040006972). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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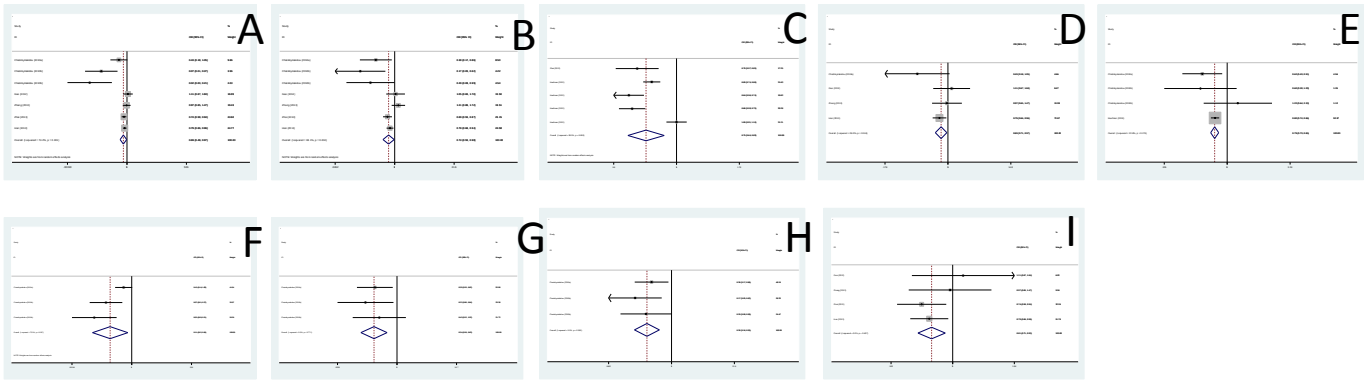
Conflict of interests: No conflict of interests is declared.

Supplementary Items

Table S1. Scale for methodological quality assessment

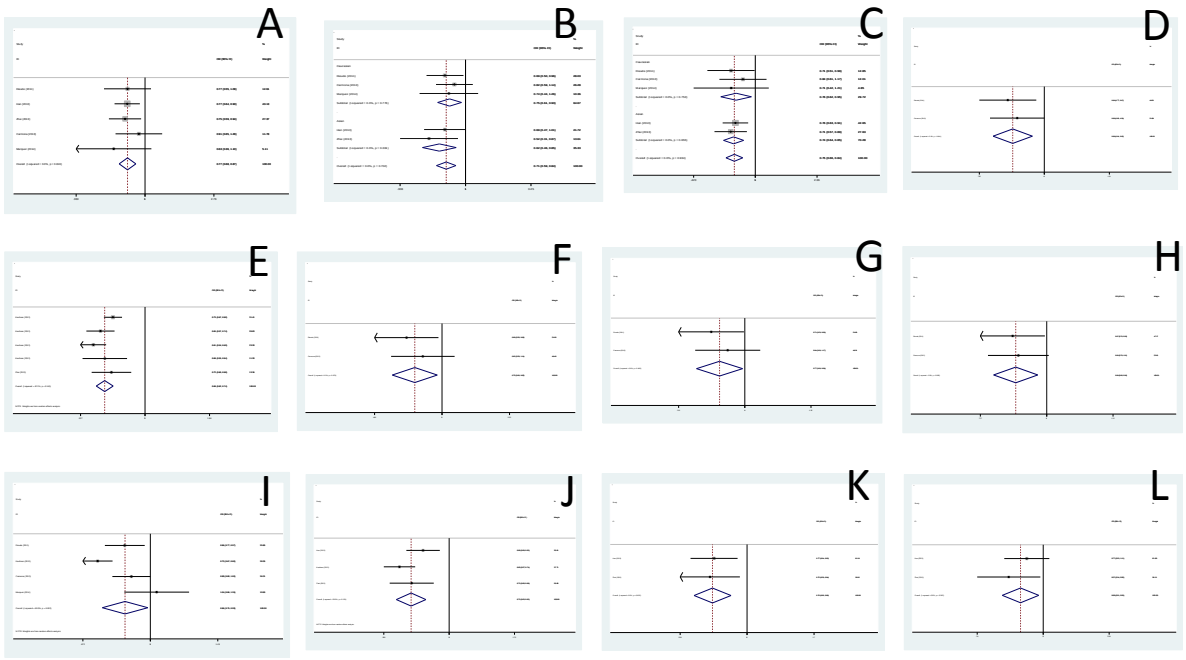
Criteria	Score
1. Representativeness of cases	
Autoimmune diseases (ADs) diagnosed according to acknowledged criteria	2
Mentioned the diagnosed criteria but not specifically described	1
Not mentioned	0
2. Source of controls	
Population or community based	3
Hospital-based ADs-free controls	2
Healthy volunteers without total description	1
ADs-free controls with related diseases	0.5
Not described	0
3. Sample size	
>300	2
200-300	1
<200	0
4. Quality control of genotyping methods	
Repetition of partial/total tested samples with a different method	2
Repetition of partial/total tested samples with the same method	1
Not described	0
5. Hardy-Weinberg equilibrium (HWE)	
Hardy-Weinberg equilibrium in control subjects	1
Hardy-Weinberg disequilibrium in control subjects	0

Figure S1. Forest plots of stratified analysis of ADs risk associated with rs3027898.



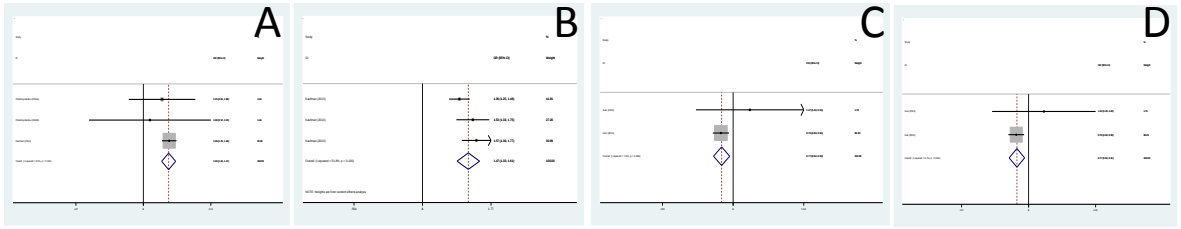
(A) Heterozygote model, CA vs CC, overall analysis, random model. **(B)** Dominant model, CA+AA vs CC, overall analysis, random model. **(C)** Allele model, A vs C, stratified analysis on SLE subgroup, random model. **(D)** Heterozygote model, CA vs CC, stratified analysis on RA subgroup, fixed model. **(E)** Allele model, A vs C, stratified analysis on Caucasian subgroup, fixed model. **(F)** Heterozygote model, CA vs CC, stratified analysis on Caucasian subgroup, random model. **(G)** Hemozygote model, AA vs CC, stratified analysis on Caucasian subgroup, fixed model. **(H)** Dominant model, CA+AA vs CC, stratified analysis on Caucasian subgroup, fixed model. **(I)** Heterozygote model, CA vs CC, stratified analysis on Asian subgroup, fixed model. OR: odds ratio; 95% CI: 95% confidence interval.

Figure S2. Forest plots of stratified analysis of ADs risk associated with rs1059702



(A) Heterozygote model, TC vs TT, overall analysis, fixed model. **(B)** Hemozygote model, CC vs TT, overall analysis and stratified analysis on Caucasian or Asian subgroup, fixed model. **(C)** Dominant model, TC+CC vs TT, overall analysis and stratified analysis on Caucasian or Asian subgroup, fixed model. **(D)** Allele model, C vs T, stratified analysis on SSc subgroup, fixed model. **(E)** Allele model, C vs T, stratified analysis on SLE subgroup, random model. **(F)** Hemozygote model, CC vs TT, stratified analysis on SSc subgroup, fixed model. **(G)** Dominant model, TC+CC vs TT, stratified analysis on SSc subgroup, fixed model. **(H)** Recessive model, CC vs TT+TC, stratified analysis on SSc subgroup, fixed model. **(I)** Allele model, C vs T, stratified analysis on Caucasian subgroup, random model. **(J)** Allele model, C vs T, stratified analysis on Asian subgroup, random model. **(K)** Heterozygote model, TC vs TT, stratified analysis on Asian subgroup, fixed model. **(L)** Recessive model, CC vs TT+TC, stratified analysis on Asian subgroup, fixed model. OR: odds ratio; 95% CI: 95% confidence interval.

Figure S3. Forest plots of stratified analysis of ADs risk associated with rs1059703



(A) Allele model, C vs T, stratified analysis on Caucasian subgroup, fixed model. **(B)** Allele model, C vs T, stratified analysis on SLE subgroup, random model. **(C)** Heterozygote model, TC vs TT, stratified analysis on Asian subgroup, fixed model. **(D)** Dominant model, TC+CC vs TT, stratified analysis on Asian subgroup, fixed model. OR: odds ratio; 95% CI: 95% confidence interval.