Association of IL-18 polymorphisms with rheumatoid arthritis: a meta-analysis

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ABSTRACT. Interleukin-18 (IL-18), an important proinflammatory cytokine, has been reported to play a potential pathological role in rheumatoid arthritis (RA). Results from previous studies on the association between IL-18 polymorphisms and RA are conflicting. To clarify this, an updated meta-analysis of all available studies on IL-18 polymorphisms and RA was conducted. Eligible articles were identified by searching databases, including PubMed, Ovid, Cochrane Library, EMBASE, and China Knowledge Resource Integrated Database, for the period up to May 1, 2015. The pooled odds ratios (ORs) with 95% confidence intervals (95%CIs) were used to assess the strength of association in the homozygote, heterozygote, dominant, recessive, and additive models. The software STATA (Version 13.0) was used for statistical analysis. Finally, 14 articles were included in the present meta-analysis. The IL-18 -607C/A polymorphism showed pooled ORs and 95%CIs for the homozygote model (AA *vs* CC: OR = 0.598; 95%CI = 0.395-0.907), and the association between

the IL-18 -137G/C polymorphism and RA showed pooled ORs and 95%CIs for the homozygote (CC *vs* GG: OR = 0.699; 95%CI = 0.364-1.342) and heterozygote (CG *vs* GG: OR = 0.924; 95%CI = 0.803-1.064) models. In summary, the current meta-analysis, which was based on the most current studies, showed that the -607A/C, -920C/T, and -105A/C polymorphisms in IL-18 were significantly associated with increased RA risk. However, the -137C/G polymorphism was not associated with RA risk under any genetic model. More evidence is needed to support or deny such a conclusion.

Key words: IL-18; Polymorphism; Rheumatoid arthritis; Meta-analysis

INTRODUCTION

Rheumatoid arthritis (RA) is a common immune-mediated inflammatory disease characterized by the chronic inflammation of primarily synovial tissue, leading to joint destruction, functional disability, and even death (Harris, 1990). The precise etiology of RA is not completely clear, but a large number of studies have indicated that environmental and genetic factors are responsible for the susceptibility and phenotype (Perricone et al., 2011). More than 30 loci have been identified to be involved in RA pathogenesis by large genome-wide association studies (de Vries, 2011). Human leukocyte antigen (HLA) alleles, such as HLA-DRB1*01, HLA-DRB1*13, and HLA-DRB1*15, have been reported to be implicated in the pathogenesis of RA (Kurko et al., 2013). Non-HLA genes, such as peptidylarginine deiminase type 4, protein tyrosine phosphatase non-receptor 22, interleukin-23 receptor, interleukin-1β (IL-1β), macrophage migration inhibitory factor, tumor necrosis factor alpha (TNF-α), and CD40, have also been shown to be involved in the pathogenesis of RA (Suzuki et al., 2013).

The imbalance of T helper type 1 and 2 cells (Th1 and Th2, respectively), which could be induced by IL-18, or cytokines has been observed to be involved in the occurrence and development of RA (Kawashima and Miossec, 2005). Previous studies have demonstrated that IL-18 is significantly elevated in sera, synovial fluid, and synovial tissues in osteoarthritic patients compared to healthy controls (Munakata et al., 2001). In the RA synovium, the expression of IL-18 is associated with that of IL-1β and TNF-α and is correlated with the acute-phase response, demonstrating that IL-18 is an important proinflammatory cytokine that drives the local production of IL-1β and TNF-α in RA patients (Joosten et al., 2003). Dai et al. (2007) reported that IL-18 contributes to the development and maintenance of an acquired immune response in RA by promoting the differentiation and chemotaxis of T cells. All these reports indicate that IL-18 plays an important role in the pathogenesis of RA.

Many single nucleotide polymorphisms (SNPs) in the IL-18 gene region have been identified, including -607C/A and -137G/C in the IL-18 promoter regions and 148G/C and 105A/C in regulatory sequences. SNPs in the IL-18 promoter at positions -607C/A (rs1946518) and -137G/C (rs187238) have been repeatedly found to be associated with alterations in transcriptional activity (Giedraitis et al., 2001). Many studies concerning the association of IL-18 gene polymorphisms with RA have focused on these two polymorphisms, but results from these studies remain inconclusive and controversial. Meta-analysis is a powerful statistical method to combine the results from multiple studies in an effort to increase power, improve estimates of the size of the effect, and/or to resolve uncertainty when reports disagree. However, results from previous meta-

analyses (published between 2012 and 2014) are still conflicting. Chen et al. (2012) conducted a meta-analysis and concluded that the -607A/C SNP but not the -137G/C SNP in IL-18 may confer susceptibility to RA in a Chinese population, but this cannot be extrapolated to all Asians. However, results from another meta-analysis demonstrated that the IL-18 137G/C SNP was a risk factor for RA (Wen et al., 2014). Ji and Lee (2013) performed a meta-analysis and concluded that no significant association was found between two IL-18 SNPs (-607C/A and -137G/C) and RA susceptibility in all subjects, even upon subgroup analysis. Cai et al. (2014) conducted a meta-analysis based on published studies between 2003 and 2012 and concluded that the IL-18 -607A/C (not -137G/C) polymorphism in the promoter region may be associated with RA risk. Considering these conflicting results, we conducted an updated meta-analysis to derive a more precise estimation of the association between IL-18 gene polymorphisms and RA risk.

MATERIAL AND METHODS

Search strategy

This meta-analysis was performed according to the methodology advocated by the PRISMA statement (Panic et al., 2013). All studies included in the meta-analysis were selected by searching PubMed, Ovid, Cochrane Library, EMBASE, and China Knowledge Resource Integrated Database up to May 1, 2015 using the following keywords: "(polymorphism OR variants OR mutation OR genotype) AND (IL-18 OR Interleukin-18) AND (rheumatoid arthritis OR RA)". There was no restriction on time period, sample size, population, or type of report. However, only studies published in English or Chinese were included. All eligible studies were retrieved and their references were checked for other relevant studies. The literature retrieval was performed in duplicate by two independent reviewers. When multiple publications reported on the same or overlapping data, the most recent or largest population was chosen. When a study reported the results on different subpopulations, each subpopulation was treated as a separate study in the meta-analysis.

Inclusion criteria

All of the studies met the following inclusion criteria: 1) case-control design; 2) association between IL-18 gene polymorphisms and RA risk; 3) application of standardized clinical or pathologic criteria for the diagnosis of RA; and 4) sufficient genotype distributions for calculation of odds ratios (ORs) with 95% confidence intervals (95%CIs). The following were cause for exclusion: 1) not related to the IL-18 gene polymorphisms and RA risk; 2) not a primary case-control study; 3) no usable or insufficient genotype data reported; 4) studies where the allele frequency in the control population deviated from the Hardy-Weinberg equilibrium (HWE) at a P value equal to or less than 0.01; and 5) case reports, letter to editor, book chapters, or reviews. The study inclusion and exclusion procedures are summarized in Figure 1.

Data extraction

Two investigators independently extracted the data from all qualified studies according to the selection standard listed above. Discrepancies were resolved through discussion until

agreement was reached. The following information was extracted: the first author's name, year of publication, the country in which the study was conducted, source of the control group, genotyping methods, sample size, number of cases and controls, risk allele frequency in controls, and results of HWE in controls.

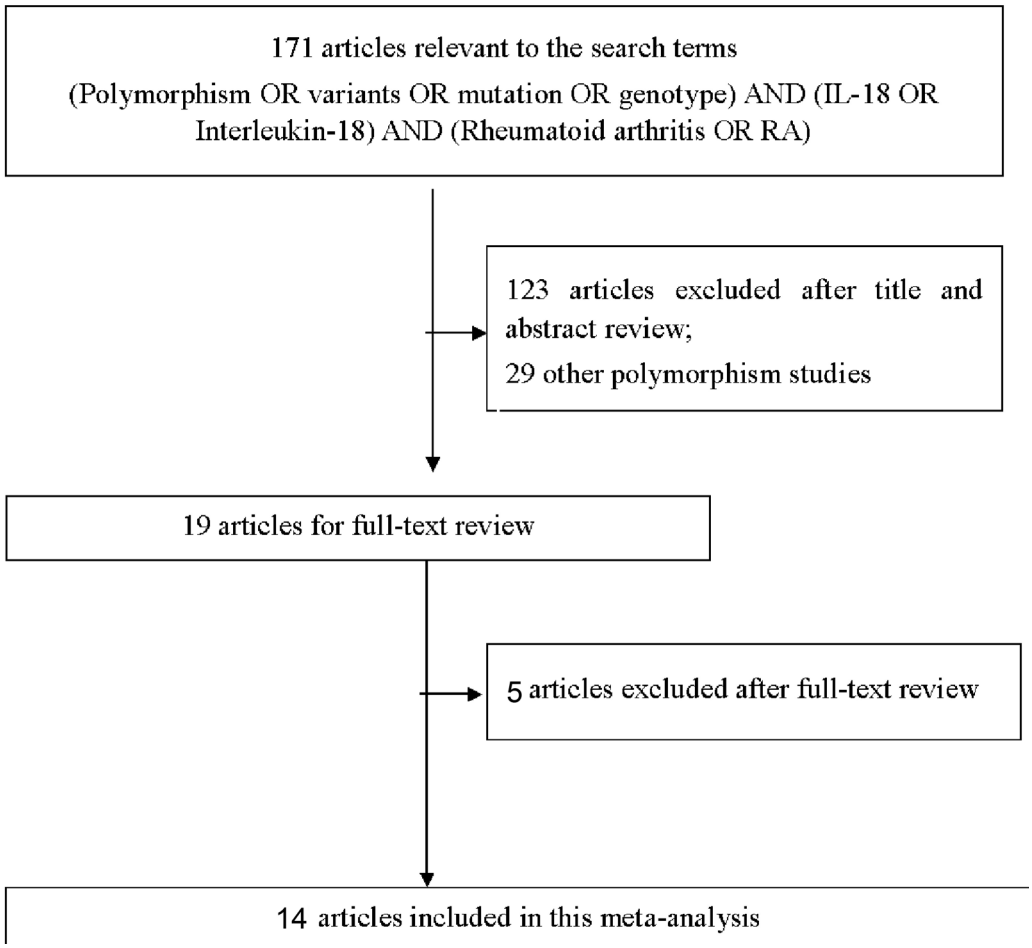

Figure 1. Inclusion and exclusion procedures for publications included in the meta-analysis.

Statistical analysis

All statistical analyses were performed using the STATA software 13.0 (StataCrop, College Station, TX, USA). Two-sided P values less than 0.05 were considered to be statistically significant. The strength of the association between the IL-18 polymorphisms and RA risk was assessed by the ORs with 95%CIs. The pooled ORs were calculated for the homozygote, heterozygote, dominant, recessive, and additive models (Lee and Bae, 2015). We also conducted subgroup analysis by ethnicity, genotyping methods, and source of control. Cochran's Q-statistic and the I^2 metric were conducted to assess heterogeneity between studies. We classified

heterogeneity into three categories: high ($I^2 > 50\%$), middle ($25 < I^2 < 50\%$), and low ($I^2 < 25\%$) (Higgins and Thompson, 2002). If the heterogeneity test result resulted in $P > 0.1$, the pooled ORs were analyzed using the random-effects model; otherwise, the fixed effects model was used. The distribution of genotypes in the controls was checked for HWE (Salanti et al., 2005). Sensitivity analyses were also performed after sequential removal of each study (Wen et al., 2015). Last, publication bias was investigated by both Begg's funnel plot and the Egger linear regression test.

RESULTS

Study characteristics

A total of 171 relevant articles were initially identified from PubMed, Ovid, Cochrane Library, EMBASE, and China Knowledge Resource Integrated Database. After titles and abstracts were screened, 152 articles were excluded because of irrelevant data. The full texts of the remaining 19 records were carefully reviewed. Finally, 14 articles were included in the present meta-analysis (Sivalingam et al., 2003; Gracie et al., 2005; Rueda et al., 2005; Pawlik et al., 2006; Lee et al., 2007; Huang et al., 2007; Pawlik et al., 2009; Shi et al., 2011; Sugiura et al., 2011; Ying et al., 2011; Hashaad et al., 2012; Song et al., 2012; Farias et al., 2013; Gurram et al., 2014). All of the 14 articles were published between 2003 and 2014. Eleven articles were published in English and three were published in Chinese. Of the 14 eligible studies, 6 were conducted in Caucasian populations, 6 were in Asian populations, and 2 were in mixed populations. Thirteen studies were population-based and one was unclear. The genotype distributions in the controls for all studies were consistent with the Hardy-Weinberg equilibrium (Norton and Neel, 1965), except for three studies (Sivalingam et al., 2003; Rueda et al., 2005; Gurram et al., 2014). The characteristics of all included studies are summarized in Table 1.

Results of the overall meta-analysis

The results of the overall meta-analysis are summarized in Table 2. The IL-18 -607C/A polymorphism showed pooled ORs and 95%CI for the homozygote (AA *vs* CC: OR = 0.598; 95%CI = 0.395-0.907), heterozygote (AC *vs* CC: OR = 0.699; 95%CI = 0.540-0.906), dominant (AA + AC *vs* CC: OR = 0.677; 95%CI = 0.518-0.884), recessive (AA *vs* AC + CC: OR = 0.771; 95%CI = 0.558-1.065), and additive (A *vs* C: OR = 0.766; 95%CI = 0.633-0.927) models. The association between the IL-18 -137G/C polymorphism and RA showed pooled ORs and 95%CI for the homozygote (CC *vs* GG: OR = 0.699; 95%CI = 0.364-1.342), heterozygote (CG *vs* GG: OR = 0.924; 95%CI = 0.803-1.064), dominant (CG + CC *vs* GG: OR = 0.810; 95%CI = 0.633-1.038), recessive (CC *vs* CG + GG: OR = 0.725; 95%CI = 0.383-1.371), and additive (G *vs* C: OR = 0.777; 95%CI = 0.583-1.036) models. The IL-18 -920C/T polymorphism showed pooled ORs and 95%CI for the homozygote (TT *vs* CC: OR = 0.297; 95%CI = 0.026-3.352), heterozygote (CT *vs* CC: OR = 1.010; 95%CI = 0.841-1.214), dominant (CT + TT *vs* CC: OR = 0.905; 95%CI = 0.761-1.076), recessive (TT *vs* CT + CC: OR = 0.295; 95%CI = 0.026-3.358), and additive (T *vs* C: OR = 0.848; 95%CI = 0.759-0.949) models (Figures 2 and 3).

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

Author	Year	Region	Ethnicity	Disease duration	Age (year)		Genotype method	Source of control	Case				Control				H-W (P)
-607C/A					Case	Control			Total	CC	CA	AA	Total	CC	CA	AA	
Hashaad et al.	2012	Egypt	Caucasian	4.7 ± 3.5	37.7 ± 6.1	38.2 ± 10.3	PCR-SSP	PB	80	22	42	16	80	20	42	18	0.650486
Gurram et al.	2014	India	Caucasian	5 ± 5	46 ± 12	48 ± 12	PCR	PB	80	42	35	3	100	10	52	38	0.198889
Pawlik et al.	2006	Poland	Caucasian	Unclear	21-75	19-74	PCR	PB	309	126	143	40	305	107	145	53	0.747805
Rueda et al.	2005	Spain	Caucasian	Unclear	Unclear	45 ± 12	PCR	PB	362	128	178	56	339	111	193	35	0.00025
Farias et al.	2013	Brazil	Mixed	Unclear	54.63 ± 12.48	48.00 ± 15.56	PCR-SSP	PB	97	31	46	20	151	48	78	25	0.478681
Gracie et al.*	2005	Germany	Caucasian	Unclear	59	46	PCR-SSP	PB	102	50	32	20	98	26	57	15	0.07787
Gracie et al.	2005	Scotland	Caucasian	Unclear	62	44	PCR-SSP	PB	225	81	112	32	185	71	96	18	0.075599
Sivalingam et al.	2003	Singapore	Mixed	10	50	Unclear	PCR	PB	106	30	73	3	273	59	183	31	4.52E-09
Sugiura et al.	2011	Japan	Asian	Unclear	Unclear	Unclear	Taqman	PB	1462	238	724	500	970	195	446	329	0.051508
Shi et al.	2011	China	Asian	Unclear	52.4 ± 16 .8	50 .5 ± 14 .2	PCR-SSP	PB	107	53	42	12	100	31	56	13	0.115249
Song et al.	2012	China	Asian	0.5-16	33.5 ± 3.2	34.2 ± 4. 6	PCR	PB	110	54	43	13	100	30	58	12	0.046765
Huang et al.	2007	China	Asian	Unclear	48.48 ± 14.98	45.18 ± 8.11	PCR	PB	120	33	83	3	168	29	94	45	0.093778
Pawlik et al.	2009	Poland	Caucasian	Unclear	21-75	Unclear	PCR–RFLP	PB	404	151	197	56	148	56	65	27	0.292376
Ying et al.	2011	China	Asian	Unclear	49.17 ± 11.25	47.13 ± 9.10	PCR–RFLP	PB	164	71	67	26	196	66	99	31	0.542726
-137G/C									Total	GG	GC	CC	Total	GG	GC	CC	
Hashaad et al.	2012	Egypt	Caucasian	4.7 ± 3.5	37.7 ± 6.1	38.2 ± 10.3	PCR-SSP	PB	80	38	38	4	80	33	35	12	0.589992
Pawlik et al.	2006	Poland	Caucasian	Unclear	21-75	19-74	PCR	PB	309	169	123	17	305	162	112	31	0.082446
Rueda et al.	2005	Spain	Caucasian	Unclear	Unclear	45 ± 12	PCR	PB	362	192	140	30	339	175	145	19	0.116379
Farias et al.	2013	Brazil	Mixed	Unclear	54.63 ± 12.48	48.00 ± 15.56	PCR-SSP	PB	97	45	45	7	151	70	74	7	0.021776
Gracie et al.	2005	Germany	Caucasian	Unclear	59	46	PCR-SSP	PB	102	54	39	9	98	53	35	10	0.253248
Gracie et al.	2005	Scotland	Caucasian	Unclear	62	44	PCR-SSP	PB	225	125	73	27	185	105	72	8	0.317445
Gurram et al.	2014	India	Caucasian	5 ± 5	46 ± 12	48 ± 12	PCR	Unclear	70	42	19	9	100	20	19	61	5.568E-08
Sivalingam et al.	2003	Singapore	Mixed	10	50	Unclear	PCR	PB	106	79	24	3	273	206	63	4	0.741612
Shi et al.	2011	China	Asian	Unclear	52.4 ± 16.8	50.5 ± 14 .2	PCR-SSP	PB	107	85	20	2	100	70	28	2	0.676922
Huang et al.	2007	China	Asian	Unclear	48.48 ± 14.98	45.18 ± 8.11	PCR	PB	120	102	17	1	168	127	35	6	0.081932
Pawlik et al.	2009	Poland	Caucasian	Unclear	21-75	Unclear	PCR-RFLP	PB	404	207	169	28	148	81	51	16	0.075494
-920C/T									Total	CC	CT	TT	Total	CC	CT	TT	
Sugiura et al.	2011	Japan	Asian	Unclear	Unclear	Unclear	Taqman	PB	1469	406	762	301	943	241	451	251	0.182913
Pawlik et al.	2009	Poland	Caucasian	Unclear	21-75	Unclear	PCRRFLP	PB	404	331	73	0	148	120	25	3	0.22746
-105A/C									Total	AA	AC	CC	Total	AA	AC	CC	
Lee et al.	2007	Taiwan	Asian	Unclear	Unclear	Unclear	PCR–RFLP	PB	201	158	38	5	218	122	91	5	0.010807

PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism; PCR = polymerase chain reaction; PCR-SSP = polymerase chain reaction-single specific primer; PB = population based; H-W (P) = Hardy-Weinberg equilibrium; *Gracie et al. reported two studies in the one paper.

Table 2. Results of the overall meta-analysis.

Polymorphism	OR (95%CI)	Heterogeneity	Z and P values
IL-18 -607C/A			
AA vs CC	0.598 (0.395-0.907)	chi-squared = 74.16 (d.f. = 13), P = 0.000 I-squared = 82.5%	Z = 2.42, P = 0.015
AC vs CC	0.699 (0.540-0.906)	chi-squared = 57.34 (d.f. = 13), P = 0.000 I-squared = 77.3%	Z = 2.70, P = 0.007
AA + AC vs CC	0.677 (0.518-0.884)	chi-squared = 67.95 (d.f. = 13), P = 0.000 I-squared = 80.9%	Z = 2.86, P = 0.004
AA vs AC + CC	0.771 (0.558-1.065)	chi-squared = 56.36 (d.f. = 13), P = 0.000 I-squared = 76.9%	Z = 1.58, P = 0.114
A vs C	0.766 (0.633-0.927)	chi-squared = 81.36 (d.f. = 13), P = 0.000 I-squared = 84.0%	Z = 2.74, P = 0.006
IL-18 -137G/C			
CC vs GG	0.699 (0.364-1.342)	chi-squared = 50.47 (d.f. = 10), P = 0.000 I-squared = 80.2%	Z = 1.08, P = 0.282
CG vs GG	0.924 (0.803-1.064)	chi-squared = 9.89 (d.f. = 10), P = 0.450 I-squared = 0.0%	Z = 1.09, P = 0.274
CG + CC vs GG	0.810 (0.633-1.038)	chi-squared = 30.68 (d.f. = 10), P = 0.001 I-squared = 67.4%	Z = 1.67, P = 0.095
CC vs CG + GG	0.725 (0.383-1.371)	chi-squared = 51.03 (d.f. = 10), P = 0.000 I-squared = 80.4%	Z = 0.99, P = 0.322
C vs G	0.777 (0.583-1.036)	chi-squared = 66.08 (d.f. = 10), P = 0.000 I-squared = 84.9%	Z = 1.72, P = 0.086
IL-18 -920C/T			
TT vs CC	0.297 (0.026-3.352)	chi-squared = 2.98 (d.f. = 1), P = 0.085 I-squared = 66.4%	Z = 0.98, P = 0.326
CT vs CC	1.010 (0.841-1.214)	chi-squared = 0.04 (d.f. = 1), P = 0.844 I-squared = 0.0%	Z = 0.11, P = 0.913
CT + TT vs CC	0.905 (0.761-1.076)	chi-squared = 0.04 (d.f. = 1), P = 0.849 I-squared = 0.0%	Z = 1.13, P = 0.257
TT vs CT + CC	0.295 (0.026-3.358)	chi-squared = 3.00 (d.f. = 1), P = 0.083 I-squared = 66.7%	Z = 0.98, P = 0.325
T vs C	0.848 (0.759-0.949)	chi-squared = 0.00 (d.f. = 1), P = 0.997 I-squared = 0.0%	Z = 2.88, P = 0.004

OR = odds ratio; d.f. = degrees of freedom; CI = confidence interval

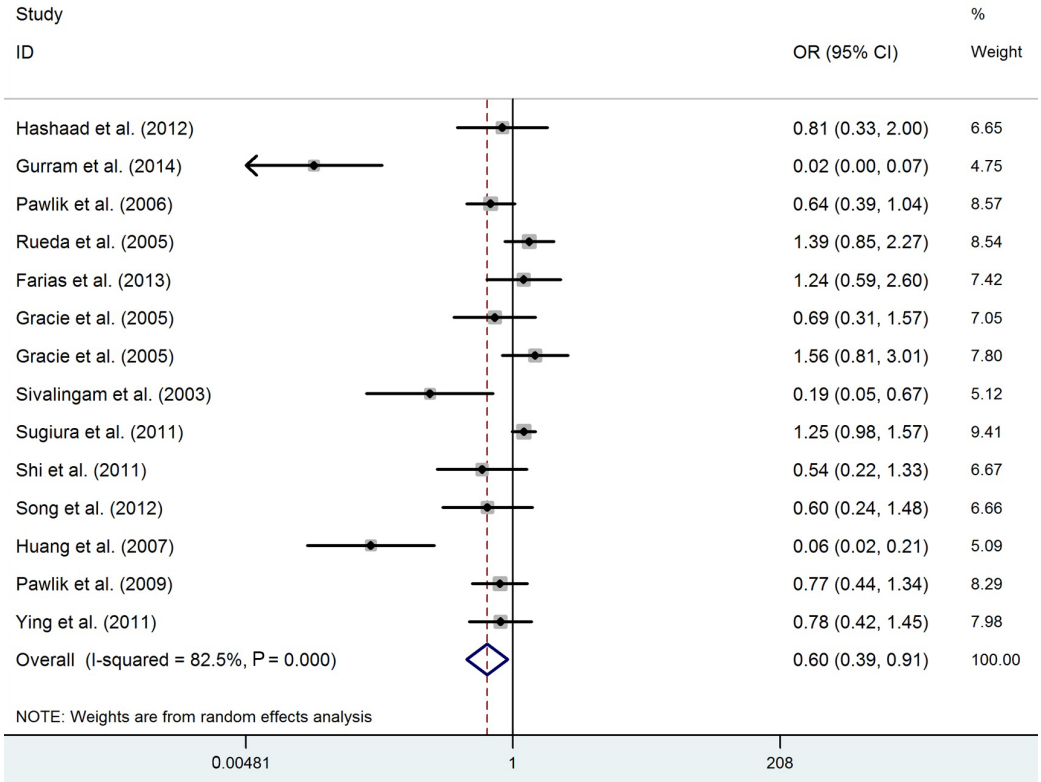

Figure 2. Random effect forest plot of homozygote model (AA *vs* CC) of IL-18 -607A/C polymorphism.

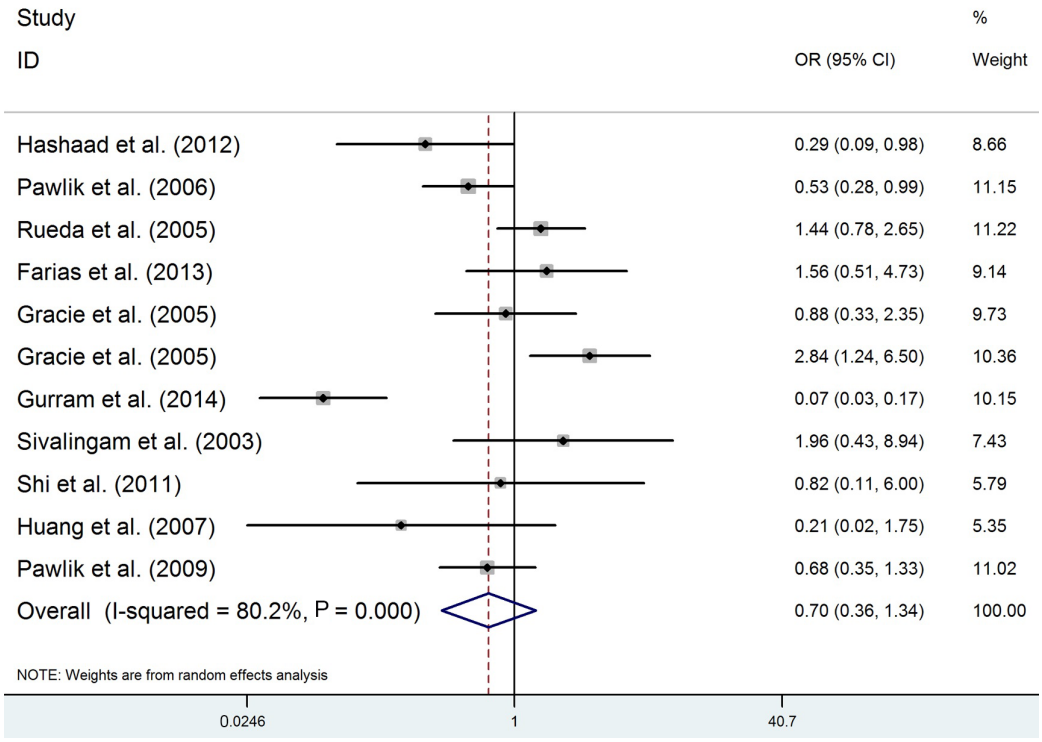

Figure 3. Random effect forest plot of homozygote model (CC *vs* GG) of IL-18 -137C/G polymorphism.

Sub-group analysis

We next performed a sub-group analysis stratified by ethnicity. For the IL-18-607C/A polymorphism, 7 studies were conducted in Caucasian populations, 5 studies were conducted in Asian populations, and 2 were conducted in mixed populations. For the IL-18 -137G/C gene polymorphism, 7 studies were conducted in Caucasian populations, 2 studies were conducted in Asian populations, and 2 were conducted in mixed populations. For the IL-18 -920C/T polymorphism, one study was conducted in a Caucasian population and one study was conducted in an Asian population. The results of the sub-group analysis are shown in detail in Table 3.

Test of heterogeneity and sensitivity analysis

We assessed the source of heterogeneity by region, publication year, control source, and sample size. However, we did not observe any sources that contributed to substantial heterogeneity. Sensitivity analyses were conducted to ascertain the primary origin of the heterogeneity. No individual study significantly affected the pooled OR because no substantial change was found (Figures 4 and 5).

Table 3. Results of sub-group analysis stratified by ethnicity.

Polymorphism	N	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
IL-18 -607C/A		AA *vs* CC	AC *vs* CC	AA + AC *vs* CC	AA *vs* AC + CC	A *vs* C
Ethnicity						
Caucasian	7	0.626 (0.327-1.199)	0.666 (0.450-0.986)	0.644 (0.421-0.984)	0.817 (0.486-1.374)	0.750 (0.539-1.045)
Mixed	2	0.521 (0.081-3.341)	0.839 (0.570-1.234)	0.823 (0.566-1.195)	0.587 (0.102-3.387)	0.881 (0.599-1.296)
Asian	5	0.526 (0.242-1.141)	0.674 (0.400-1.137)	0.647 (0.388-1.078)	0.681 (0.373-1.245)	0.730 (0.523-1.017)
Overall	14	0.598 (0.395-0.907)	0.699 (0.540-0.906)	0.677 (0.518-0.884)	0.771 (0.558-1.065)	0.766 (0.633-0.927)
IL-18 -137G/C		CC *vs* GG	CG *vs* GG	CG + CC *vs* GG	CC *vs* CG + GG	C *vs* G
Ethnicity						
Caucasian	7	0.611 (0.269-1.386)	0.970 (0.825-1.140)	0.812 (0.580-1.137)	0.631 (0.285-1.396)	0.753 (0.508-1.116)
Mixed	2	1.685 (0.687-4.134)	0.969 (0.665-1.412)	1.024 (0.712-1.473)	1.713 (0.711-4.127)	1.080 (0.800-1.456)
Asian	2	0.434 (0.102-1.858)	0.597 (0.378-0.942)	0.574 (0.369-0.891)	0.485 (0.114-2.066)	0.591 (0.397-0.881)
Overall	11	0.699 (0.364-1.342)	0.924 (0.803-1.064)	0.810 (0.633-1.038)	0.725 (0.383-1.371)	0.777 (0.583-1.036)
IL-18 -920C/T		TT *vs* CC	CT *vs* CC	CT + TT *vs* CC	TT *vs* CT + CC	T *vs* C
Ethnicity						
Caucasian	1	0.052 (0.003-1.013)	1.059 (0.642-1.745)	0.945 (0.583-1.532)	0.051 (0.003-1.001)	0.849 (0.545-1.322)
Asian	1	0.712 (0.565-0.897)	1.003 (0.823-1.222)	0.899 (0.747-1.082)	0.710 (0.586-0.861)	0.848 (0.756-0.953)
Overall	2	0.297 (0.026-3.352)	1.010 (0.841-1.214)	0.905 (0.761-1.076)	0.295 (0.026-3.358)	0.848 (0.759-0.949)

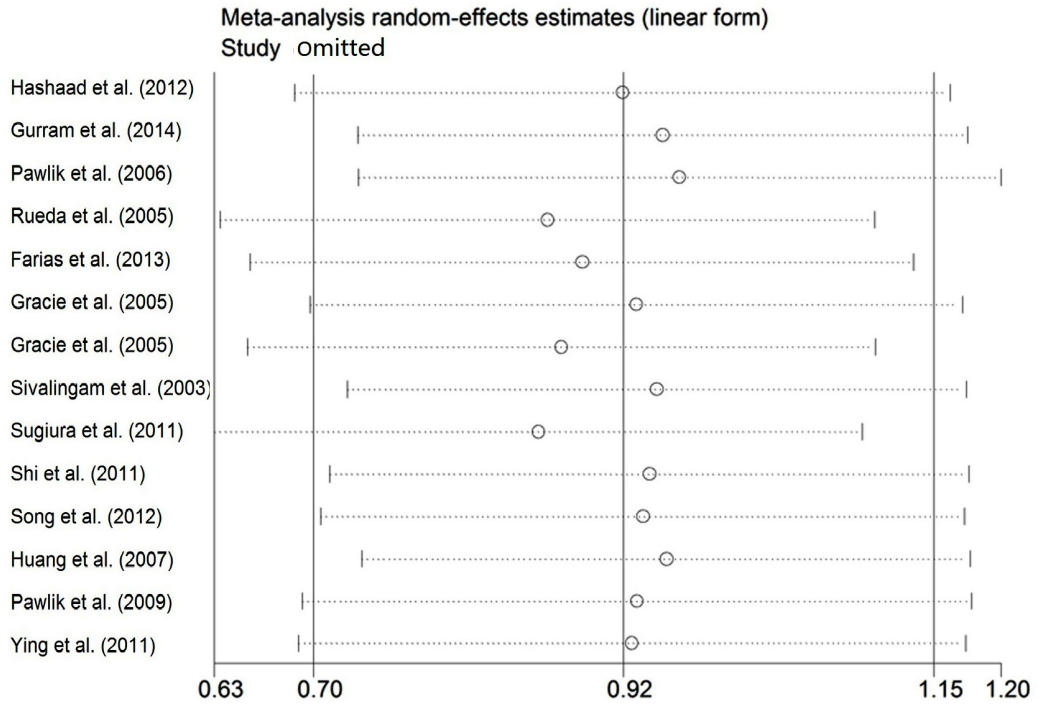

Figure 4. Sensitivity analysis for IL-18 -607A/C polymorphism.

Publication bias

Funnel plots were generated to assess publication bias. The Begg test was performed to statistically evaluate funnel plot symmetry. The results showed no publication bias: Begg's test

Pr > |Z| = 0.052 for the IL-18 -137G/C polymorphism and Pr > |Z| = 0.055 for the IL-18 -607C/A polymorphism. The results suggest that publication bias was not a factor in this meta-analysis (Figures 6 and 7).

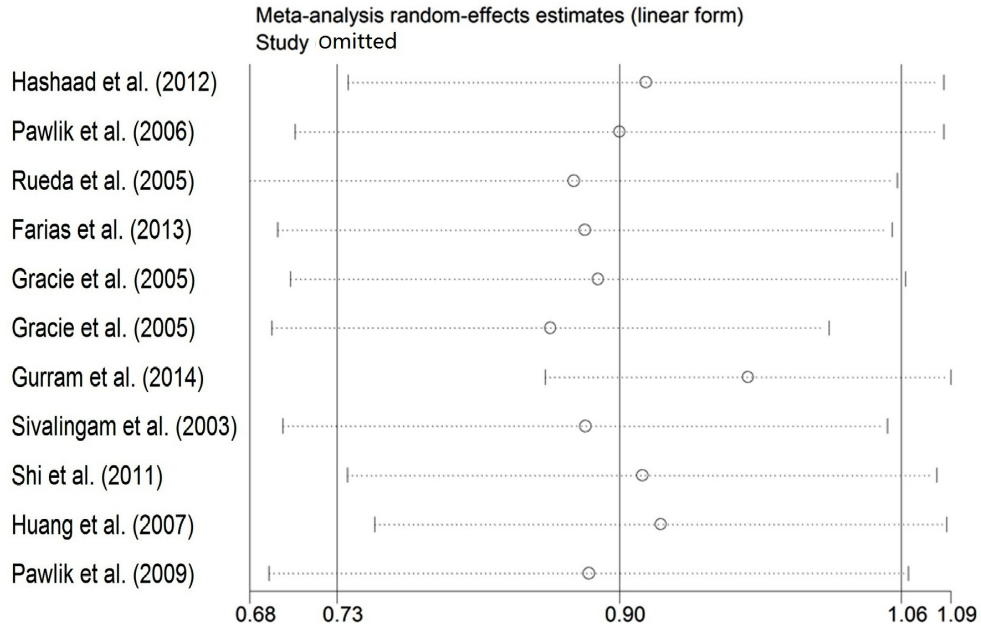

Figure 5. Sensitivity analysis for IL-18 -137C/G polymorphism.

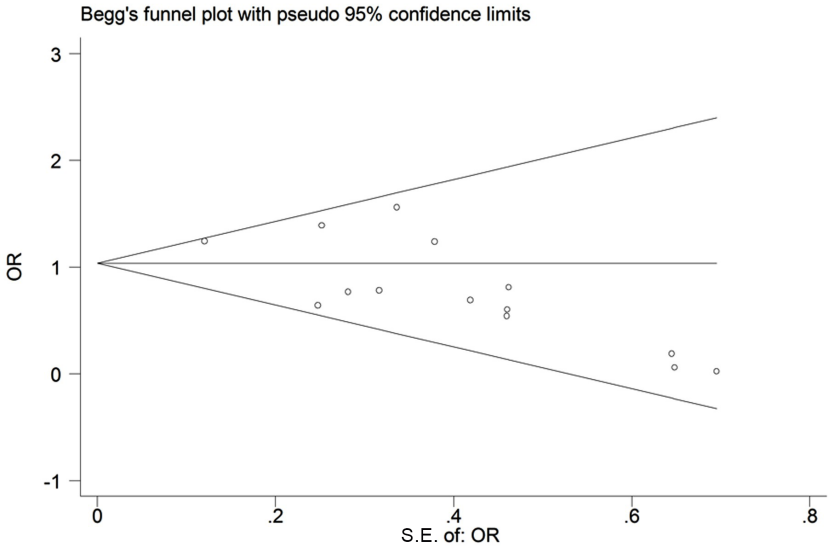

Figure 6. Publication bias test for IL-18 -607 A/C polymorphism. OR = odds ratio; S.E. = standard error.

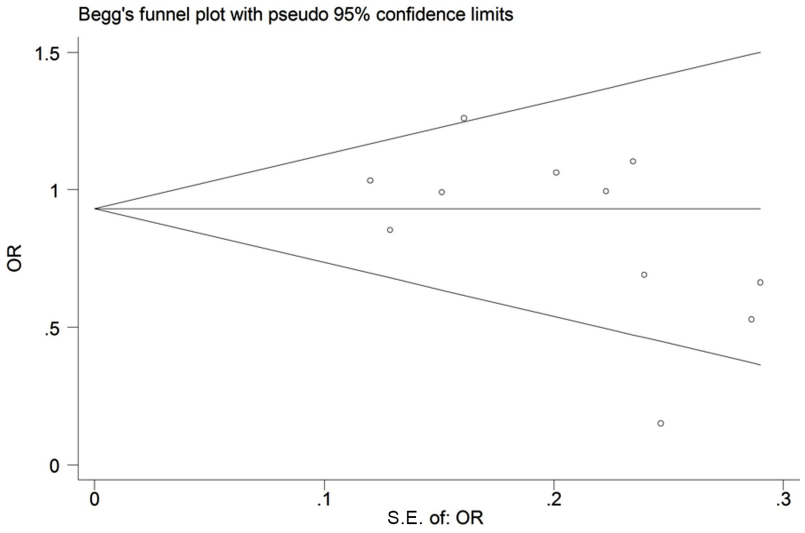

Figure 7. Publication bias test for IL-18 -137C/G polymorphism. OR = odds ratio; S.E. = standard error.

DISCUSSION

Previous studies have demonstrated that the imbalance of Th1 and Th2 cells plays an important role in the induction and development of RA. IL-18 can promote upregulation of Th1 cells and inhibit Th2 cells in RA patients, which results in a greater imbalance of Th1 and Th2 cells (Shao et al., 2009). The IL-18 promoter region regulates IL-18 protein expression. Two SNPs in this region are -137C/G and -607A/C, which are located at the binding sites for cAMP response-element binding transcription factor and the H4TF-1 nuclear factor, respectively. Higher frequencies of A alleles at position -607 and/or higher frequencies of C alleles at position -137 were thought to have some protective effects against the development of RA.

Many studies have explored the association between IL-18 gene polymorphisms and RA risk, but results from these studies remain inconclusive and controversial. Meta-analysis is regarded as a powerful tool to more precisely define the effects of select genetic polymorphisms on the risk for disease and to identify potentially important sources of between-study heterogeneity. However, results from previous meta-analyses are still conflicting. Hence, we performed this meta-analysis including all available studies to provide the most comprehensive assessment of the association between the IL-18 gene polymorphisms and RA risk. For the IL-18 -607A/C polymorphism, there were 14 studies with 3728 cases and 3213 controls included in our meta-analysis. For the -137C/G polymorphism, there were 11 studies with 1982 cases and 1947 controls included. The results from this meta-analysis suggest that the IL-18-607A/C and -920C/T polymorphisms are significantly associated with increased RA risk. However, for the -137C/G polymorphism, we failed to find any association with RA risk under all genetic models. Additionally, for the IL-18 -105A/C polymorphism, there was just one study included in this meta-analysis and the results of this study provided genetic evidence that the IL-18 -105A/C polymorphism may play a role in RA (Lee et al., 2007).

Of course, we should be careful to conclude that there is no association between the -137C/G polymorphism and RA risk merely on the basis of the negative results in this study. If a

putative genetic association is of a small magnitude with point estimates of less than 1.5, the small and underpowered studies may be unable to identify true genetic associations (Ioannidis, 2003; Ioannidis et al., 2006; Hindorff et al., 2009). Thus, more evidence is needed to support or deny such an association. By means of a meta-analysis, a statistical technique for combining the results from independent studies, we drew a more reliable conclusion on the influence of IL-18 polymorphisms on RA risk. However, as RA might be a result of multiple factors, future research should focus not only on individual genes, but also on gene-gene interactions.

Meta-analysis is regarded as a useful method for synthesizing data from all eligible studies to obtain greater statistical power. However, several potential limitations of this meta-analysis should be noted: 1) although the funnel plot and the Begg test showed no publication bias, selection bias may have occurred because only studies published in English or Chinese were selected; and 2) there was significant heterogeneity. However, our meta-analysis has some clear advantages: 1) the most recent studies were examined; 2) we performed a sub-group analysis stratified by ethnicity; 3) sensitivity analysis showed no individual study had a marked effect on the overall results; 4) the scientific search and selection method significantly increased the applicability of this meta-analysis; and 5) no publication bias was detected.

In summary, this meta-analysis, which is based on the most current information, showed that the -607A/C, -920C/T and -105A/C polymorphisms in IL-18 were significantly associated with increased RA risk. However, the -137C/G polymorphism was not associated with RA risk under any genetic model. Of course, more evidence is needed to support or deny such a conclusion.

Conflicts of interest

The authors declare no conflict of interest.

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