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Original Article

Interleukin 17A rs2275913 G>A polymorphism is associated with the decreased risk of rheumatoid arthritis: a meta-analysis involving 6,266 subjects

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Abstract: Interleukin 17A (IL17A), a member of the IL-17 family, plays a potential role in inflamed synovium of rheumatoid arthritis (RA). Several epidemiological investigations have been performed to explore the relationship of *IL17A* rs2275913 G>A polymorphism with RA, yet the findings are conflicting and inconsistent. A literature research was performed in PubMed and Embase databases up to May 21, 2016. The association between *IL17A* rs2275913 G>A polymorphism and RA susceptibility was measured by using crude odds ratios (ORs) with 95% confidence intervals (CIs). Finally, There were seven independent studies met the inclusion criteria with 3,130 RA cases and 3,136 controls. Overall, *IL17A* rs2275913 G>A polymorphism decreased the risk of RA in three genetic models: A vs. G (OR, 0.91; 95% CI, 0.84-0.98; *P*=0.016), AA vs. GG (OR, 0.84; 95% CI, 0.72-0.99; *P*=0.043) and AA+GA vs. GG (OR, 0.87; 95% CI, 0.78-0.97; *P*=0.013). One study was not consistent with Hardy Weinberg Equilibrium. When we excluded this study, the decreased risk of RA was also found in one genetic model: (AA+GA vs. GG; OR, 0.86; 95% CI, 0.76-0.97; *P*=0.018). In a subgroup analysis by ethnicity, a significant decreased RA susceptibility was identified among Caucasians in two genetic models: A vs. G (OR, 0.91; 95% CI, 0.83-1.00; *P*=0.037) and AA+GA vs. GG (OR, 0.84; 95% CI, 0.73-0.95; *P*=0.007), and among non-Caucasians in one genetic model: AA vs. GG+GA (OR, 0.76; 95% CI, 0.59-0.98; *P*=0.033). In summary, our findings of this meta-analysis indicate that the *IL17A* rs2275913 G>A polymorphism may contribute to the decreased risk of RA, especially in Caucasians.

Keywords: Polymorphism, interleukin 17A, rheumatoid arthritis, meta-analysis

Introduction

Rheumatoid arthritis (RA) is one of commonly chronic inflammatory diseases, and leads to the small joints disability. Although the aetiology of RA is very complex and is not fully known, it is believed that RA results from the interactions of genetic predisposition and environmental factors, and eventually it triggers and maintains synovial inflammation in RA cases. Since the variants of some immune related gene may influence the function of immune, genetic factors may have a particular role in the pathogenesis of RA [1].

Interleukin 17A (IL17A), a member of IL-17 family, is secreted by Th17 cells and other immune cells, including CD8+T cells and γδT cells [2, 3]. IL17A can stimulate the expression of many factors, including cyclooxygenase-2 (COX-2), tumor necrosis factor-alpha (TNF-α), nitric oxide (NO), IL-6, and IL-1β, which may play important roles in inflammatory processes [4, 5]. An elevated levels of IL-17A have been found in the inflamed synovium of RA cases, suggesting a potential functional role for IL-17A in RA pathogenesis [6, 7]. Further studies reported that Th17 cells involve in RA, as arthritis could be suppressed by both IL17A knockout and treating with anti-

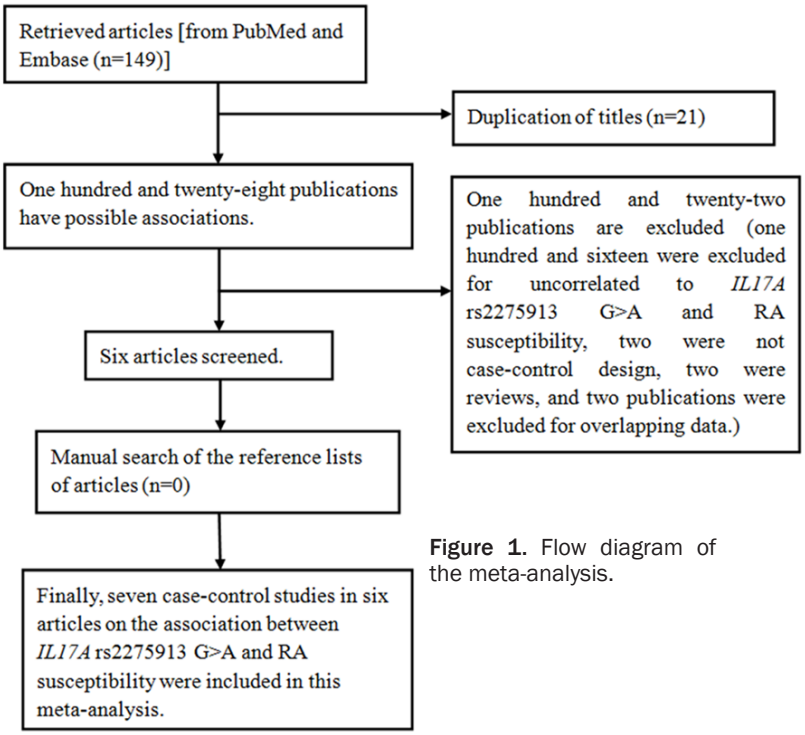

Figure 1. Flow diagram of the meta-analysis.

IL-17A in mice. The human *IL17A* gene is located on chromosome 6P12. A single nucleotide polymorphism (SNP) of *IL17A*, the rs2275913 G>A polymorphism (G197A), has been identified in the upstream variant 2KB region of *IL17A*. In recent years, the *IL17A* rs2275913 G>A polymorphism has been widely studied for its association with the susceptibility of chronic inflammatory-related diseases, such as ulcerative colitis [8-10], Crohn's disease [11], coronary artery disease [12] and asthma [13] *et al*.

Accumulating evidences suggested that the functional SNP (rs2275913 G>A) in *IL17A* gene might also contribute to the development of RA [14, 15]; however, the results were inconsistent. For instance, Nordang *et al.* suggested that *IL17A* rs2275913 G>A polymorphism might confer decreased risk of RA [15], whereas others reported null correlation of this polymorphism with RA risk [16-19]. Thus, we believed that it was essential to perform a comprehensive meta-analysis including all eligible studies to obtain a more precise evaluation of the relationship between *IL17A* rs2275913 G>A polymorphism and RA risk.

Materials and methods

Our study is reported according to PRISMA guideline (Table S1. PRISMA checklist).

Search strategy

An electronic literature research was performed in PubMed and Embase databases up to May 21, 2016 without any language restriction. Relevant publications were identified using the following searching words and strategy terms: (IL-17A or IL-17A or Interleukin-17A or Interleukin-17A) and (polymorphism or variant or SNP) and (rheumatoid arthritis or RA). Additional studies were retrieved by a manual search of references in the eligible publications and review articles.

Inclusion criteria and exclusion criteria

Studies were eligible if they met the major criteria: 1) studies that assessed the relationship between *IL17A* rs2275913 G>A and RA risk, 2) a case-control study design, and 3) provided genotype frequency of RA cases and controls to calculate the odds ratios (ORs) with 95% confidence intervals (CIs). The major exclusion criteria were: 1) case reports, treatment studies, and review articles, 2) studies without sufficient data of the genotypes and alleles of *IL17A* rs2275913 G>A polymorphism, 3) overlapping data.

Data extraction

Two reviewers (S. Zhang and Y. Wang) independently extracted the detailed data of the eligible studies. Disagreement was resolved by consulting with another reviewer (W. Tang). For each study, we collected the following data: the first author's surname, year of publication, country of origin, ethnicity, source of control, number of genotyped cases and controls and genotyping method. The ethnicity was categorized as Caucasians, Asians and mixed populations.

Statistical analysis

The distribution of *IL17A* rs2275913 G>A genotypes in controls was measured for Hardy

Table 1. Characteristics of the eligible studies

Study	Year	Country	Ethnicity	Case/Control	Genotype method
Pawlik *et al.* [16]	2016	Poland	Caucasians	422/337	TaqMan
Carvalho *et al.* [17]	2016	Brazil	Mixed	131/75	TaqMan
Louahchi *et al.* [19]	2016	Algeria	Caucasians	343/323	TaqMan
Shen *et al.* [14]	2015	China	Asians	615/839	48-Plex SNP scan™ Kit
Bogunia-Kubik *et al.* [18]	2015	Poland	Caucasians	89/125	PCR-RFLP
Nordang *et al.* [15]	2009	Norway	Caucasians	950/933	TaqMan
Nordang *et al.* [15]	2010	New Zealand	Caucasians	580/504	TaqMan

PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism.

Weinberg Equilibrium (HWE) by a web program (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl). In the present meta-analysis, all statistical analyses were conducted using the STATA 12.0 software (Stata Corp LP, College Station, Texas). *P* values (two-sided) of <0.05 were considered statistically significant. The crude ORs with 95% CIs were calculated to measure the strength of associations in the following genetic comparisons: allelic comparison (A versus G), homozygote comparison (AA versus GG), dominant comparison (AA+GA versus GG) and recessive comparison (AA versus GG+GA). The inter-study heterogeneity in meta-analysis was assessed by using a χ^2-test-based Q test. If there was significant heterogeneity based on a Q-test (I^2>50% or P<0.10) [20], a random-effects model using the DerSimonian and Laird method was used [21]. Otherwise, the Mantel-Haenszel (M-H) method (the fixed-effect model) was employed [22]. One-way sensitivity analyses were conducted to assess the stability of our findings by omission of an individual study in turn and re-calculating the ORs with 95% CIs. Both Begg's test and Egger's test were used to evaluate the potential publication bias [23], and *P* values (two-sided) of <0.10 were considered representative of statistically significant bias.

Results

Characteristics

In total, 149 publications were retrieved from the literature search. Among them, 143 literatures were excluded (21 for duplication of titles, two for non-case-control studies, two for reviews, and two for overlapping data, 116 for not relevant to *IL17A* rs2275913 G>A polymorphism and RA risk). After this step, six literatures were identified for further assessment and data extraction. After a manual search of the bibliography lists in eligible publications, none was recruited. **Figure 1** showed the major selecting and excluding process. Finally, a total of six papers concerning 3,130 RA cases and 3,136 controls were included [14-19]. One publication containing two stage case-control studies, we treated it as two independent studies [15]. Thus, seven case-control studies focusing on *IL17A* rs2275913 G>A polymorphism with RA risk were included for analysis. All of these papers were published in English. Of them, five case-control studies were from Caucasians [15, 16, 18, 19], one was from Asians [14] and one was from mixed populations [17]. Genotype distribution in controls was tested for HWE in all included studies and one was not consistent with HWE [14]. **Table 1** summarized the characteristics of the studies enrolled in the current study. The distribution of *IL17A* rs2275913 G>A variants and alleles was shown in **Table 2**.

Quantitative synthesis

There were seven independent studies met the inclusion criteria with 3,130 RA cases and 3,136 controls. Overall, *IL17A* rs2275913 G>A polymorphism decreased the risk of RA in three genetic models: A vs. G (OR, 0.91; 95% CI, 0.84-0.98; *P*=0.011), AA vs. GG (OR, 0.84; 95% CI, 0.72-0.99; *P*=0.043) and AA+GA vs. GG (OR, 0.87; 95% CI, 0.78-0.97; *P*=0.013) (**Table 3**). One case-control study was not consistent with HWE [14]. When we excluded this study, the decreased risk of RA was also found (AA+GA vs. GG; OR, 0.86; 95% CI, 0.76-0.97; *P*=0.018) (**Table 3** and **Figure 2**). In a subgroup analysis by ethnicity, a significant decreased RA susceptibility was identified among Caucasians in two genetic models: A vs. G (OR, 0.91; 95% CI, 0.83-1.00; *P*=0.037) and AA+GA vs. GG (OR, 0.84; 95% CI, 0.73-0.95; *P*=0.007), and among non-Caucasians in one genetic model: AA vs. GG+GA (OR, 0.76; 95% CI, 0.59-0.98; *P*=0.033) (**Table 3** and **Figure 3**).

Table 2. Distribution of *IL-17A* rs2275913 G>A variants and alleles

Study	Case			Control			Case		Control		HWE
	GG	GA	AA	GG	GA	AA	A	G	A	G	
Pawlik *et al.* [16]	173	193	51	118	169	50	295	539	269	405	Yes
Carvalho *et al.* [17]	74	50	7	49	20	6	64	198	32	118	Yes
Louahchi *et al.* [19]	N/A	N/A	N/A	N/A	N/A	N/A	60	283	65	258	Yes
Shen *et al.* [14]	198	292	114	255	383	194	520	688	771	893	No
Bogunia-Kubik *et al.* [18]	12	44	32	20	67	38	108	68	143	107	Yes
Nordang *et al.* [15]	396	428	114	335	461	124	656	1220	709	1131	Yes
Nordang *et al.* [15]	246	251	83	208	238	58	417	743	354	654	Yes

HWE: Hardy-Weinberg equilibrium; N/A: not available.

Tests for publication bias, sensitivity analyses

Begg's funnel plot test and Egger's linear regression test were performed to check the potential publication bias. We found that the shapes of Begg's funnel plot test were symmetry in all of the genetic models (A *vs.* G: Begg's test P=0.230, Egger's test P=0.247; AA *vs.* GG: Begg's test P=1.000, Egger's test P=0.533; AA+GA *vs.* GG: Begg's test P=0.260, Egger's test P=0.120; AA *vs.* GA+GG: Begg's test P=0.707, Egger's test P=0.690; **Figure 4**).

Sensitivity analyses were performed by sequential eliding an individual study and re-calculating the ORs with 95% CIs. **Figure 5** showed that the corresponding pooled ORs were not materially changed (data not shown), suggesting the stability of the results.

Discussion

RA, a chronic autoimmune disorder, affects less than 1% of the population worldwide and is characterized by several clinical disorders, such as persistent synovitis and systemic inflammation. Additionally, RA persistently affects the joints and promotes joint destruction. IL17A, a vital cytokine of Th17 cells, can induce the production of several pro-inflammatory cytokines (e.g., TNF-α, NO, COX-2, IL-6, and IL-1β), and then promote the pathogenesis of RA. In view of those findings, the *IL17A* rs2275913 G>A have been thought to be associated with RA. Recently, several studies focused on the relationship of this functional polymorphism in *IL17A* with RA risk; however, results of these epidemiologic studies remain controversial. In the light of the primary findings, we enrolled six independent studies with 3,130 RA cases and 3,136 controls to perform a pooled analysis and attempted to determine the susceptibility of *IL17A* rs2275913 G>A variants to RA. Our findings suggested that *IL17A* rs2275913 G>A might be a protective factor of RA, especially in Caucasians.

The most common SNP in *IL17A*, rs2275913 G>A (G197A), was associated with cancer [24], coronary artery disease [12] and tuberculosis [25] *et al*. Of late, some case-control studies have been performed to explore the relationship of *IL17A* rs2275913 G>A with the development of RA [14-19]. In 2009, Nordang *et al.* first reported that a G→A mutation in *IL17A* rs2275913 was associated with the risk of RA in Norway [15]. However, this relationship was not confirmed in a cohort from New Zeal and [15]. Thereafter, a few studies focused on the correlation of *IL17A* rs2275913 G>A polymorphism with RA [14, 16-19]. As demonstrated in this meta-analysis, we found that this SNP was associated with the decreased risk of RA, which coincide with the results of prior study [15]. A stratified analysis regarding different origin of ethnicity was also conducted for the *IL17A* rs2275913 G>A polymorphism. We found that *IL17A* rs2275913 G>A variants decreased the risk of RA in Caucasians. In our study, an individual investigation was not consistent with HWE [14]. When we excluded this study, the decreased risk of RA was also found (AA+GA vs. GG; OR, 0.86; 95% CI, 0.76-0.97; P=0.018), suggeting the robustness of our findings. Interestingly, Espinoza *et al.* reported that *IL17A* rs2275913 A allele produced significantly more IL-17 than rs2275913 G allele when T cells from healthy individuals were stimulated in vitro [26]. A recent Japanese study provided an evidence of correlation of *IL17A* rs3804513 A>T polymorphism with joint destruction in early RA, but the relationship of susceptibility of developing RA was not identified [12]. HapMap data suggest that *IL17A* rs3804513

Table 3. Meta-analysis of the *IL-17A* rs2275913 G>A polymorphism and rheumatoid arthritis

	No. of study	Allelic comparison			Homozygote comparison			Dominant comparison			Recessive comparison		
		OR (95% CI)	*P*	*P* (Q-test)	OR (95% CI)	*P*	*P* (Q-test)	OR (95% CI)	*P*	*P* (Q-test)	OR (95% CI)	*P*	*P* (Q-test)
Overall	6	0.91 (0.84-0.98)	0.011	0.312	0.84 (0.72-0.99)	0.043	0.279	0.87 (0.78-0.97)	0.013	0.280	0.91 (0.78-1.05)	0.197	0.186
Overall in HWE	5	0.92 (0.84-1.01)	0.055	0.234	0.89 (0.73-1.08)	0.231	0.235	0.86 (0.76-0.97)	0.018	0.192	0.99 (0.82-1.08)	0.880	0.282
Ethnicity													
Caucasians	4	0.91 (0.83-1.00)	0.037	0.228	0.89 (0.73-1.09)	0.254	0.139	0.84 (0.73-0.95)	0.007	0.413	1.00 (0.83-1.20)	0.972	0.211
Non-Caucasians	2	0.90 (0.78-1.04)	0.146	0.230	0.76 (0.57-1.01)	0.058	0.973	1.06 (0.69-1.63)	0.801	0.142	0.76 (0.59-0.98)	0.033	0.781

HWE: Hardy-Weinberg equilibrium.

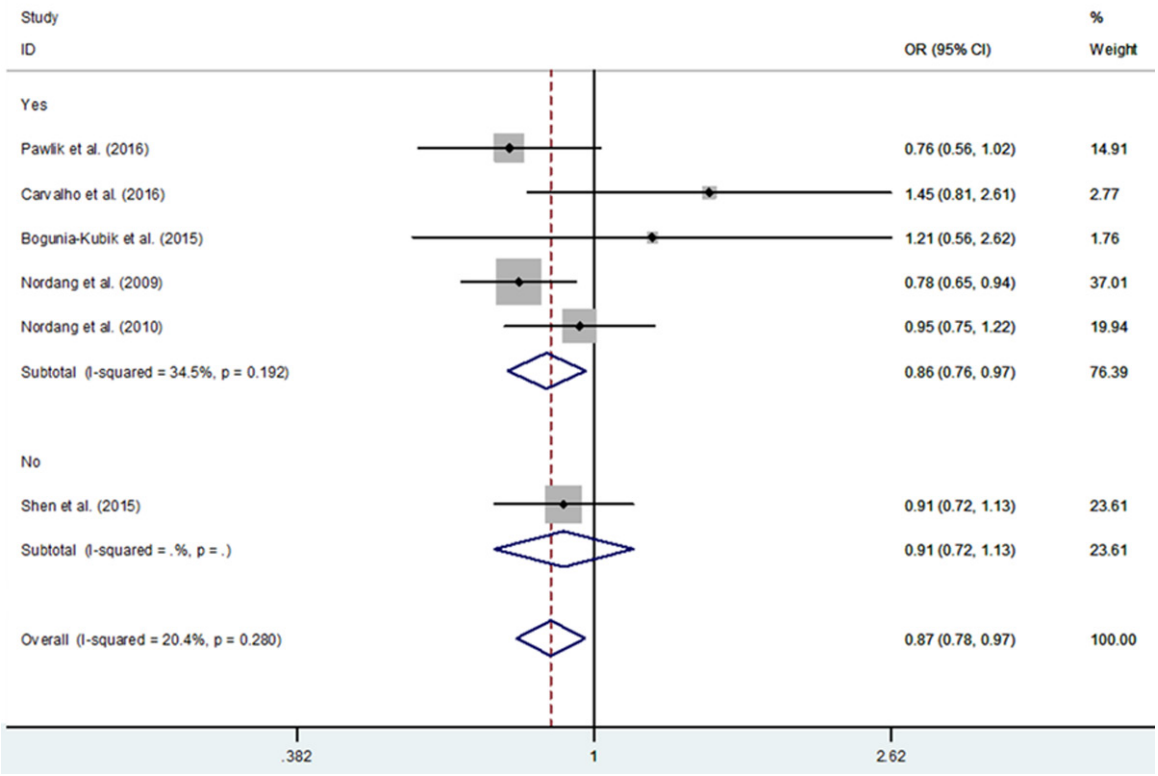

Figure 2. *IL17A* rs2275913 G>A polymorphism was associated with the decreased susceptibility of rheumatoid arthritis in overall studies and studies consistenting with Hardy-Weinberg equilibrium (AA+GA vs. GG, fixed-effects model).

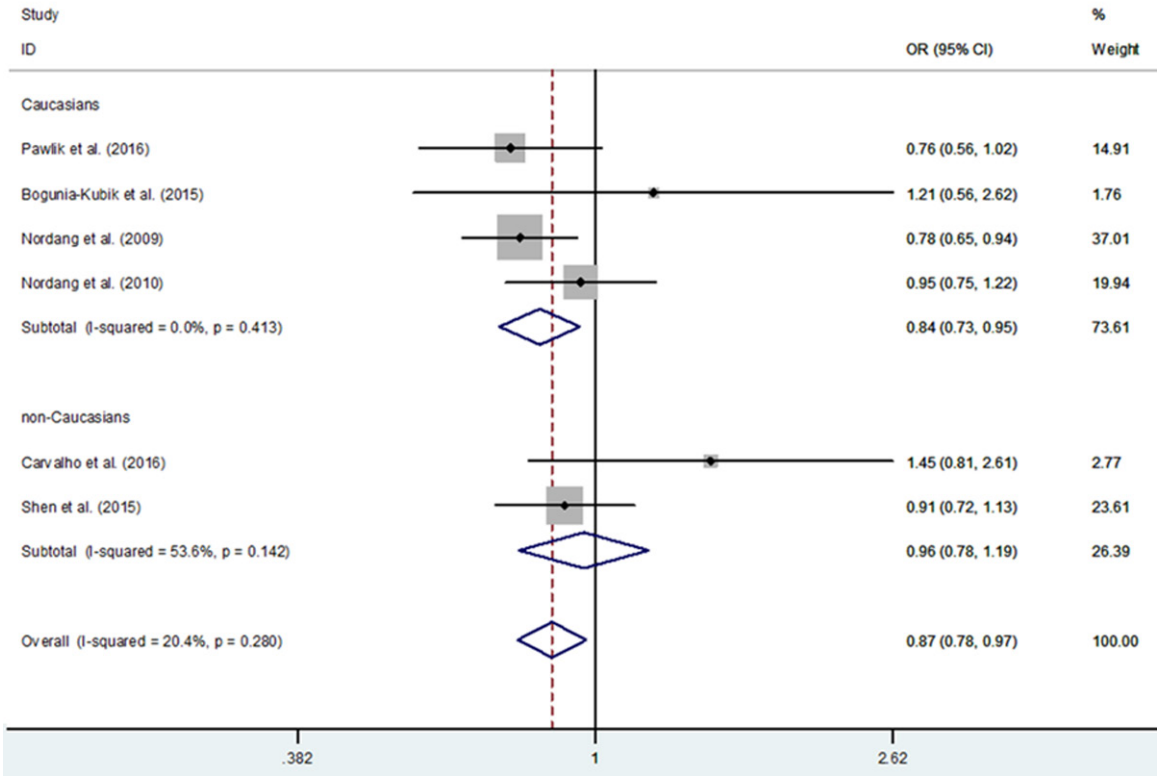

Figure 3. *IL17A* rs2275913 G>A polymorphism was associated with the decreased susceptibility of rheumatoid arthritis in Caucasians (AA+GA vs. GG, fixed-effects model).

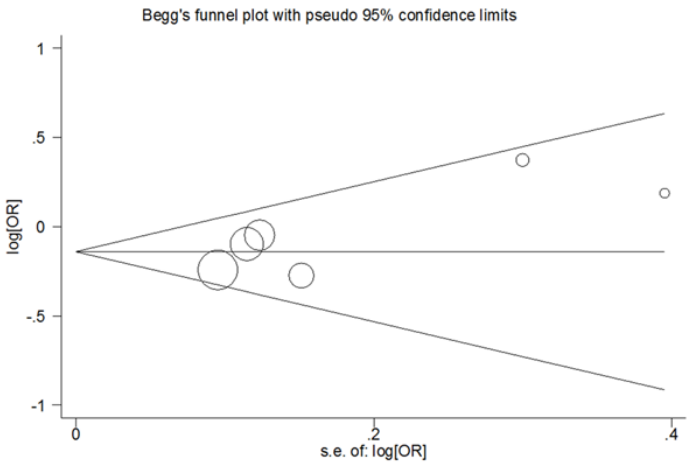

Figure 4. Begg's funnel plot of pooled-analysis of the association between *IL17A* rs2275913 G>A polymorphism and rheumatoid arthritis in (AA+GA vs. GG, fixed-effects model).

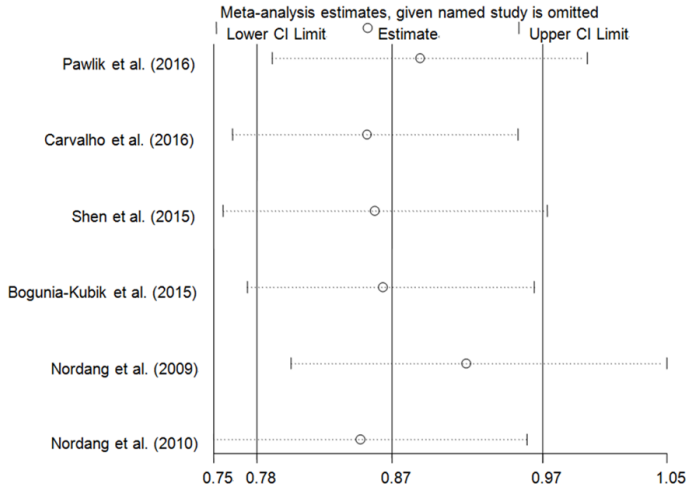

Figure 5. Sensitivity analysis for the influence of *IL17A* rs2275913 G>A polymorphism on the risk of rheumatoid arthritis (AA+GA vs. GG compare genetic model, fixed-effects estimates for).

A>T and *IL17A* rs2275913 G>A are in a Linkage disequilibrium (D'=1.0; r^2=0.12). These results could also indicate that these studies detected the same effect in some extent.

Although considerable effort and as much as possible resources were put into measuring possible correlation between *IL17A* rs2275913 G>A polymorphism and RA risk, some limitations inherited from the included publications should be acknowledged. Firstly, only seven case-control studies were enrolled in our study and some studies were designed as small sample sizes, which might limit the power to get a comprehensive analysis. Secondly, although Begg's funnel plot test and Egger's linear regression test showed no significant publication bias, only published studies were included in our analysis, the potential bias may inevitably occur. Finally, some original data of the eligible studies could not be obtained; thus, only unadjusted ORs and CIs were used to assess the relationship between this polymorphism and RA.

In summary, our findings of this meta-analysis indicate that the *IL17A* rs2275913 G>A polymorphism probably contributes to the decreased risk of RA, especially in Caucasians. Nevertheless, for practical reasons, future epidemiological investigations with an adequate methodological quality and larger sample sizes are warranted to confirm these associations.

Acknowledgements

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Disclosure of conflict of interest

None.

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Table S1. PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract section
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Introduction section, 3rd paragraph
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Introduction section, 3rd paragraph
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Materials and Methods, 3rd paragraph
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Materials and Methods, 2nd paragraph
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Materials and Methods, 2nd paragraph
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Materials and Methods, 3rd paragraph
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Materials and Methods, 4th paragraph
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Materials and Methods, 4th paragraph
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Materials and Methods, 5th paragraph
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Materials and Methods, 5th paragraph
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Materials and Methods, 5th paragraph
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Materials and Methods, 5th paragraph
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Materials and Methods, 5th paragraph
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Results, 1st paragraph and **Figure 1**
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Results, 1st paragraph, **Tables 1 and 2**
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Results 3rd paragraph and **Figure 4**
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Results, 2nd paragraph, **Figures 2 and 3**
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Results, 2nd paragraph, and **Table 3**
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Results, 3rd paragraph

Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Results, 4th paragraph
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Discussion, 1st paragraph
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Discussion, 3rd paragraph
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Discussion, 4th paragraph
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Grant support section