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REVIEW ARTICLE

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Are genetic variations in IL-21–IL-23R–IL-17A cytokine axis involved in a pathogenic pathway of rheumatoid arthritis? Bayesian hierarchical meta-analysis

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Abstract

Inflammatory cytokines have been established to be involved in the pathogenesis of rheumatoid arthritis (RA). The genetic polymorphisms in the interleukin (IL) 23 receptor (IL23R), IL21, and IL17 have been associated with RA risk. However, there is no conclusive understanding of the genes encoding the immunoinflammatory IL-21–IL-23R–IL-17A pathway in RA aetiopathogenesis. This meta-analysis was conducted to attain this goal. A comprehensive literature search was conducted in Scopus and PubMed to look for the relevant case–control studies up until 2018. A Bayesian hierarchical meta-analysis was carried out to assess the association between the polymorphisms and the risk of RA. The association was estimated by calculating the logarithm of odds ratio (Log OR) and 95% credible interval (95% CI). In this meta-analysis, 37 case–control studies comprising 23,506 RA patients and 25,984 healthy individuals were found for analyzing the *IL23R*, *IL21*, *and IL1A* gene polymorphism and risk of RA. In the *IL23R* gene rs1343151 SNP, the minor A allele significantly increased the risk of RA (Log OR = 0.085, 95% CI = 0.008, 0.156). Moreover, the minor AA genotype was significantly associated with increased RA risk (Log OR = 0.176, 95% CI = 0.028, 0.321). In addition, the C allele of the *IL23R* gene rs2201841 SNP significantly decreased the disease risk (Log OR = −0.544, 95% CI = −1.0, −0.065). Since Bayesian meta-analysis is a powerful strategy to pool the data, it can be mentioned that genetic polymorphisms of *IL23R*, but not *IL21* and *IL17A*, are involved in susceptibility to RA.

KEYWORDS
Bayesian hierarchical meta-analysis, inflammatory cytokine, polymorphism, rheumatoid arthritis

1 | INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune rheumatic disease that is characterized by inflammation in the joints. The exact etiology of the disease has poorly been disclosed, but genetics, environment, and immune system collaborate in a network in this regard (Aslani et al., 2016; Buch & Emery, 2018; Mahmoudi, Aslani, Fadaei, & Jamshidi, 2017; Mousavi et al., 2018). With the immune system viewpoint, CD4+ T cells and related cytokines have been postulated to take a major part in the initiation and perpetuation of the pathogenic inflammatory settings (Brennan & McInnes, 2008). It has been indicated that two of the T cell-associated cytokines, namely interleukin-21 (IL-21) and IL-23, are major modulators of inflammation in RA patients. In fact, IL-21 and IL-23 produced by CD4+ T cells and dendritic cells, respectively, induce the development of the IL-17A-producing proinflammatory T helper 17 (Th17) cells

(Korn et al., 2007; Nurieva et al., 2007; Zhou et al., 2007). In addition, IL-21 receptor (IL-21R) is upregulated in the synovia of RA patients, and blocking of IL-21 culminates in a diminished inflammatory state, as presented by decreased production of inflammatory cytokines like IL-1β, IL-6, and tumor necrosis factor-α (Andersson, Feldmann, & Brennan, 2008; Jüngel et al., 2004). To further support the inflammatory role of IL-21, interfering with the function of this cytokine in animal models of arthritis results in disease amelioration (Jang et al., 2009; Young et al., 2007). On the contrary, increased plasma levels of IL-23 in chronic RA patients was associated with disease activity (Melis et al., 2010). In mice, blocking of the IL-23 pathway leads to deceleration of the inflammatory condition development (Langrish et al., 2005; Nakae, Nambu, Sudo, & Iwakura, 2003). It seems that IL-23 and IL-21 are involved in the development of Th17 cells, which in turn produce IL-17 that are involved in inflammatory conditions in RA patients (Dinesh & Rasool, 2018; Lubberts, 2015).

Evidence has indicated that common genetic variants can modulate the immune system and confer susceptibility to autoimmune or inflammatory disease. According to the genome-wide association studies (GWASs), IL-23R, IL-21, IL-17A single-nucleotide polymorphisms (SNPs) has been shown to be a potential candidate contributing to autoimmune disease, including RA (Hollis-Moffatt et al., 2010; Kurkó et al., 2013). To date, several association studies have attempted to find the role of single nucleotide polymorphisms (SNPs) in genes encoding IL-23R, IL-21, and IL-17A in altered risk of RA development. However, the findings were sometimes conflicting, which could be due to a relatively small sample size of each study. Hence, an accumulative analysis is required to combine data from all the individual studies to attain a more comprehensive and valid estimation via meta-analysis. Meta-analysis permits pooling of the existing data from different studies to generate a single approximate of the main effect with higher precision. Bayesian hierarchical meta-analysis, however, provides a more accurate pooled effect size in comparison to classical analysis approaches (Lunn, Barrett, Sweeting, & Thompson, 2013). Therefore, in this study, a Bayesian hierarchical meta-analysis was carried out to gain a vivid and precise estimation of the association between *IL23R* gene rs1343151, rs1004819, rs10489629, rs11209026, rs2201841, rs7517847, rs10889677 polymorphisms, *IL21* gene rs6822844 polymorphism, and *IL17A* gene rs2275913 polymorphism and risk of RA.

2 | METHODS

The preparation process of the manuscript met the PRISMA guidelines (Moher et al., 2015).

2.1 | Search strategies

Here we conducted a comprehensive literature search with respect to the association between *IL23R*, *IL21*, and *IL17A* gene polymorphism and risk of RA through PubMed and Scopus databases to find relevant publications up until November 2018. For identification of gray publications, relevant experts and research centers were interviewed. The systematic search was conducted using the combination of following keywords "interleukin 23 receptor"/"interleukin 21 or rs6822844"/"interleukin 17 A or rs2275913" AND "polymorphism or variant" AND "rheumatoid arthritis." The titles, abstracts, and keywords of all the papers were scanned and irrelevant studies were excluded. Moreover, the eligible publications in the reference list of the relevant papers were also assessed. During the literature search, we did not set a limitation with respect to language, ethnicity, race, or geographic area.

2.2 | Inclusion and exclusion criteria

The eligibility of the studies was evaluated according to the following inclusion criteria: (a) only case–control studies, which (b) evaluated the *IL23R*, or *IL21*, or *IL17A* gene polymorphisms and RA risk, and (c) provided sufficient data about allele or genotype frequencies which could be expressed as odds ratio (OR) and corresponding 95% confidence interval. Articles were excluded if they met the following reasons: (a) duplication of previous publication; (b) studies that were letter, review, comment, or abstract supplying insufficient or irrelevant data.

2.3 | Data extraction and quality assessment

Data were collected independently and checked for discrepancies by at least two experts. In case of disagreement, a third reviewer was consulted to resolve it. Information on the first author's name, year of publication, ethnicity of participants, numbers of cases and controls and frequency of alleles and genotypes was collected from each study. The methodology of studies was evaluated for quality using the Newcastle–Ottawa Scale (NOS). According to this scale, studies were classified as low (scores 0–3), moderate (scores 4–6), and high (scores 7–9) qualities (Zeng et al., 2015). According to NOS criteria of included studies, the mean (range) of the scores was 7.7 (7–9), and all of the included studies were classified as high quality.

2.4 | Statistical methods

In this meta-analysis, the following comparisons for *IL23R*, *IL21*, and *IL17A* polymorphism were evaluated: allele model (minor allele *vs.* reference allele), homozygous model (minor genotype vs. reference genotype), heterozygous model (heterozygote genotype vs. reference genotype), dominant inheritance model (minor genotype + heterozygote genotype vs. reference genotype), and recessive inheritance model (minor genotype vs. heterozygote genotype + reference genotype).

2.5 | Bayesian meta-analysis method

The different patient characteristics and practice patterns may explain that the true effect is likely to vary between the studies

included in meta-analysis. Therefore, a fixed-effect meta-analysis and sometimes a random effect meta-analysis also would not account for these between-study variations. The Bayesian hierarchical random-effect model is an alternative to the classical analysis for measuring accurate pooled effect size especially in situations with a small number of studies (Babapulle, Joseph, Bélisle, Brophy, & Eisenberg, 2004; Huynh et al., 2009; Rhodes, Turner, & Higgins, 2016). This model also accounts heterogeneity within and between the included studies. In Bayesian meta-analysis, any information about the unknown parameters has been specified in the analysis as prior information. To model the between-study variability, the logarithm of the OR as the effect size of the association with 95% credible interval (CI) is assumed to follow a normal distribution. The model supposes that the mean of the normal distribution of Log (ORs) has a low-informative normal distribution (mean = 0, variance = 100) and the variance of the normal distribution of log (ORs) has low-informative inverse-γ distribution (0.01, 0.01). Furthermore, the robustness of Bayesian analysis was confirmed by several sensitivity analyses. Sensitivity analyses with different choices of low-information prior distributions showed robustness to this choice. I^2 and τ^2 were used for calculating the total variation and between studies variation (Huedo-Medina, Sánchez-Meca, Marín-Martínez, & Botella, 2006). Forest plot displayed Log (OR) and 95% CI for both the individual trials and for the pooled results from this meta-analysis. In addition, heterogeneity plot displayed joint posterior density of the two parameters of the random-effects meta-analysis model, Log (OR), and τ parameters. All statistical analyses were conducted using "bayesmeta" R package (https://cran.r-project.org/web/packages/bayesmeta/index.html).

3 | RESULTS

3.1 | Characteristics of the eligible studies

On the basis of the inclusion and exclusion criteria, 37 case–control studies comprising 23,506 RA patients and 25,984 healthy individuals were analyzed in the meta-analysis (Figure 1). In details, 10,012 cases and 11,806 healthy subjects for *IL23R* rs1343151, rs1004819, rs10489629, rs11209026, rs2201841, rs7517847, rs10889677 SNPs (from 17 studies), 10,079 cases and 10,742 healthy subjects for *IL21* rs6822844 SNP (from 10 studies), and 3,415 cases and 3,436 healthy subjects for *IL17A* rs2275913 SNP (from 10 studies) were included in the final meta-analysis. Among these investigated case–control studies, nineteen case–control studies were performed in European populations, one in Asians, five in African, two in North America, four in South America, and six case–control studies were conducted in Australia and New Zealand. The NOS score of the included studies ranged between 7 and 9. Publication year of these studies was ranged from 2007 to 2018. The key characteristics of the included studies in this meta-analysis are presented in Table 1.

3.2 | Main results, subgroup, and sensitivity analysis

The main results of Bayesian hierarchical meta-analysis were calculated as the median of the marginal posterior distribution of the Log (ORs) and τ parameters. The Hardy–Weinberg equilibrium (HWE) for distribution of genotypes in controls indicated that only *IL23R* gene rs10889677 SNP deviated from HWE. On the basis of the Bayesian hierarchical meta-analysis, two SNPs in the *IL23R* gene were significantly associated with the risk of RA (Table 2). In the *IL23R* gene rs1343151 SNP (Figure 2a), the minor A allele significantly increased the risk of RA (Log OR = 0.085, 95% CI = 0.008, 0.156). Moreover, the minor AA genotype was significantly associated with increased RA risk (Log OR = 0.176, 95% CI = 0.028, 0.321). In addition, the minor C allele of the *IL23R* gene rs2201841 SNP (Figure 2b) significantly decreased the disease risk (Log OR = −0.544, 95% CI = −1.0, −0.065). However, alleles and genotypes in other polymorphisms were not significantly associated with the risk of RA. Furthermore, the *IL21* gene rs6822844 SNP and *IL17A* gene rs2275913 SNP did not disclose significant associations with RA susceptibility (Tables 3 and 4).

3.3 | Heterogeneity and publication bias

Evaluation of the heterogeneity of the studies was analyzed with the τ^2 test. $I^2 > 0.50$ was considered as high value for heterogeneity. On the basis of forest and heterogeneity plots and I^2 value, in most of the meta-analyses, the total heterogeneity and between studies heterogeneity were not high, for example, rs1343151 (Figure 3a). But, these results for rs2201841 was significantly high (Figure 3b).

Publication bias was evaluated by Egger's and Begg's tests. Publication bias was found in GA versus GG comparison of the *IL23R* gene rs1343151 SNP (Begg's test $p = 0.04$; Egger's test $p = 0.02$; Table 2) and in AA versus CC comparison of the IL23R gene rs10889677 SNP (Begg's test $p = 0.22$; Egger's test $p = 0.01$; Table 2).

4 | DISCUSSION

In this study, we conducted a Bayesian hierarchical meta-analysis to attain a vivid and precise approximation of the associations between *IL23R* gene rs1343151, rs1004819, rs10489629, rs11209026, rs2201841, rs7517847, rs10889677 SNP, IL21 gene rs6822844 SNP, and *IL17A* gene rs2275913 SNP and risk of RA susceptibility. In fact, we biologically hypothesized that the immune interactions of IL-21–IL-23R–IL17A simultaneously in the development of RA and considered the contribution of their haplotype tagging SNPs simultaneously in susceptibility to this disease. In contrast to the classical meta-analysis performed already with lower studies and patients and controls included, the Bayesian hierarchical meta-analysis exerted here indicated that only two SNPs in the IL23R gene are associated with RA risk. Nonetheless, we also performed a classical meta-analysis of the current data (results were not

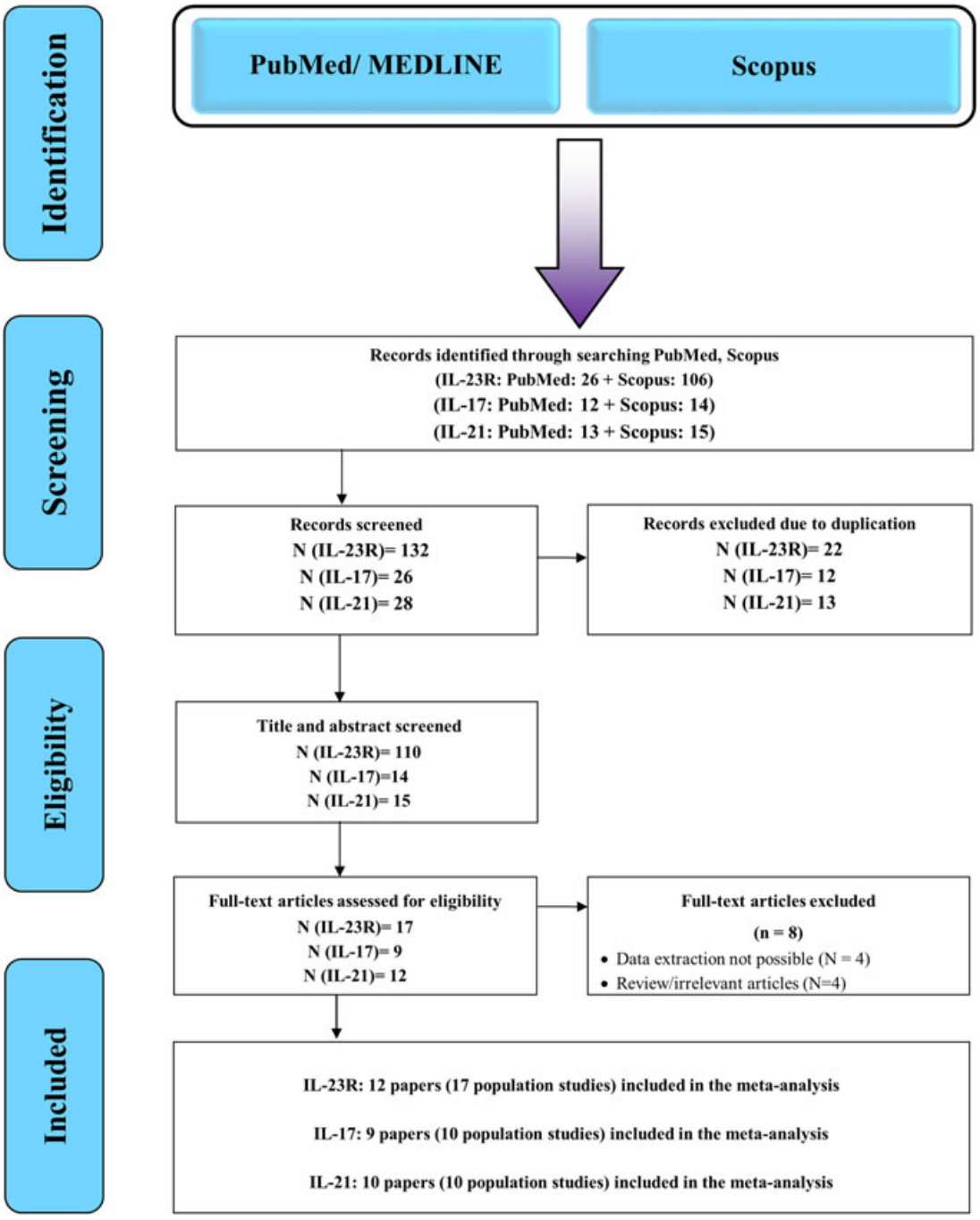

FIGURE 1 Flowchart of the procedure for the literature search and study selection. IL: interleukin; IL-23R: IL-23 receptor [Color figure can be viewed at wileyonlinelibrary.com]

mentioned) that demonstrated the association of most of the SNPs. However, since the Bayesian hierarchical meta-analysis is much more sensitive and confers much precise estimation, it seems that only rs1343151 and rs2201841 SNPs in the *IL23R* gene are bona fide genetic variations that provide a risk association with RA predisposition.

When conducting a classical meta-analysis of studies with a binary outcome, a normal approximation for the summary risk effect size in each trial is inappropriate in the common situation where some of the trials in the meta-analysis are small, or the observed risks are close to 0 or 1 (Warn, Thompson, & Spiegelhalter, 2002). On the contrary, if the risk effect size is determined to be a fixed effect, both two types of meta-analysis (Bayesian hierarchical and classical) can be used. But when the random effect is adopted, if the number of included studies is <20, Bayesian hierarchical meta-analysis should be the choice. However, if the number of included studies is >20, both two types of meta-analysis can be used (Wei, Shouying, Ying, Jie, & Zhang, 2015). The number of included studies is <11 in each studied SNP in our meta-analysis, hence Bayesian hierarchical meta-analysis was used. The

TABLE 1 Characteristics of the studies included in the meta-analysis

References	Published year	Country/race	Detection technique	RA patients, *N*	Healthy controls, *N*	Evaluated SNP	NOS score
IL-23R							
Faragó et al. (2008)	2007	Hungary/Caucasian	PCR-RFLP	412	220	rs2201841, rs10889677	7
Orozco, Rueda, Robledo, García, and Martín (2007)	2007	Spain/Caucasian	TaqMan Real-time PCR	322	342	rs1343151, rs1004819, rs10489629, rs11209026, rs7517847, rs10889677	8
WTCC Consortium (2007)	2007	United Kingdom /European	GeneChip 500K Mapping Array Set (Affymetrix chip)	1,856	2,932	rs1343151, rs1004819, rs10489629, rs11209026, rs2201841, rs7517847	8
Chang et al. (2008)	2008	North America/Caucasian	Multiplexed PCR	471	475	rs11209026	8
Chang et al. (2008)	2008	North America/Caucasian	Multiplexed PCR	658	1,318	rs11209026	8
Chang et al. (2008)	2008	Netherlands/Dutch	Multiplexed PCR	590	700	rs11209026	7
Hollis-Moffatt et al. (2009)	2008	New Zealand/Caucasian	TaqMan Real-time PCR	812	555	rs1343151, rs1004819, rs10489629, rs11209026, rs2201841, rs7517847	9
Varade et al. (2009)	2009	Spain/European	TaqMan Real-time PCR	550	546	rs11209026, rs7517847	8
Chen-Xu et al. (2012)	2011	Australasian/Caucasian	TaqMan Real-time PCR	216	1,188	rs1343151, rs10489629, rs7517847	7
Chen-Xu et al. (2012)	2011	UK/Caucasian	TaqMan Real-time PCR	981	662	rs1343151, rs10489629, rs7517847	7
Chen-Xu et al. (2012)	2011	Norway/Caucasian	TaqMan Real-time PCR	792	913	rs1343151, rs10489629, rs7517847	8
Chen-Xu et al. (2012)	2011	Spain/Caucasian	TaqMan Real-time PCR	1,206	1,131	rs1343151, rs10489629, rs7517847	8
Szabo et al. (2013)	2012	Hungary/European	PCR–RFLP	396	182	rs1343151, rs1004819, rs2201841, rs7517847, rs10889677	8
Hazlett, Stamp, Merriman, Highton, and Hessian (2012)	2012	New Zealand/Caucasian	TaqMan Real-time PCR	81	NA	rs11209026	8
Hamdy et al. (2015)	2015	Egypt/Egyptians	TaqMan Real-time PCR	120	120	rs11209026, rs2201841, rs10889677	7
da Silva et al. (2017)	2017	Brazil/Brazilian	RFLP-PCR	127	134	rs10889677	7
Paradowska-Gorycka et al. (2018)	2018	Poland/European	TaqMan Real-time PCR	422	388	rs11209026, rs2201841, rs10889677	7
IL-17							
Nordang et al. (2009)	2009	Norway/Caucasian	TaqMan Real-time PCR	938	920	rs2275913	7

(Continues)

TABLE 1 (Continued)

References	Published year	Country/race	Detection technique	RA patients, *N*	Healthy controls, *N*	Evaluated SNP	NOS score
Nordang et al. (2009)	2009	New Zealand/Caucasian	TaqMan Real-time PCR	580	504	rs2275913	7
Bogunia-Kubik et al. (2015)	2015	Poland/Caucasian	PCR-RFLP	88	125	rs2275913	7
Shen, Zhang, Yan, Zhou, and Liu (2015)	2015	China/Asian	Custom-by-design 48-Plex SNP Scan Kit	604	832	rs2275913	9
Carvalho et al. (2016)	2016	Brazil/Brazilizan	TaqMan Real-time PCR	100	75	rs2275913	7
Pawlik et al. (2016)	2016	Poland/Caucasian	TaqMan Real-time PCR	422	337	rs2275913	7
Louahchi, Allam, Berkani, et al. (2016)	2016	Algeria/Caucasian	TaqMan Real-time PCR	343	323	rs2275913	8
da Silva et al. (2017)	2017	Brazil/Brazilizan	RFLP-PCR	127	134	rs2275913	8
Dhaouadi et al. (2018)	2018	Tunis/Tunisian	PCR-RFLP	115	91	rs2275913	7
Elfasakhany, Eldamarawi, and Khalil (2018)	2018	Egypt/Caucasian	PCR-RFLP	98	95	rs2275913	7
IL-21							
WTCC Consortium (2007)	2007	UK/Caucasian	GeneChip 500K Mapping Array Set (Affymetrix chip)	1,856	2,933	rs6822844	8
Zhernakova et al. (2007)	2007	Netherlands/Dutch	TaqMan Real-time PCR	1,012	924	rs6822844	8
Daha et al. (2009)	2009	Netherlands/Caucasian	MassArray matrix-assisted laser desorption ionization time of-flight mass spectrometry	877	866	rs6822844	8
Teixeira et al. (2009)	2009	Mixed European/Caucasian	TaqMan Real-time PCR	434	434	rs6822844	8
Barton et al. (2009)	2009	UK/Caucasian	Sequenom iPlex Platform	3,886	3,454	rs6822844	8
Hollis-Moffatt et al. (2010)	2010	New Zealand/Australia/ Australasian European Caucasian	TaqMan Real-time PCR	834	1,102	rs6822844	9
Maiti et al. (2010)	2010	Colombia/Colombians	TaqMan Real-time PCR	354	368	rs6822844	7
Hazlett, Stamp, Merriman, Highton, and Hessian (2012)	2012	New Zealand/Caucasian	TaqMan Real-time PCR	81	NA	rs6822844	8
Louahchi, Allam, Raaf, et al. (2016)	2016	Algeria/African	TaqMan Real-time PCR	323	323	rs6822844	7
Malinowski, Paradowska-Gorycka, Safranow, and Pawlik (2017)	2017	Poland/Caucasian	TaqMan Real-time PCR	422	338	rs6822844	7

Note. IL: interleukin; IL-23R: IL-23 receptor; NOS: Newcastle–Ottawa Scale; PCR: polymerase chain reaction; RA: rheumatoid arthritis; RFLP: restriction fragment length polymorphism; SNP: single nucleotide polymorphism.

TABLE 2 Bayesian hierarchical meta-analysis of the pooled associations between *IL23R* gene rs1343151 (G>A), rs1004819 (G>A), rs10489629 (A>G), rs11209026 (G>A), rs2201841 (T>C), rs7517847 (T>G), rs10889677 (C>A) polymorphisms and risk of RA disease

SNPs	Variations	Frequency		Percentage heterogeneity	Association test		Absolute heterogeneity test τ^2 (95% CI)	Publication bias (Begg's test, *p* value; Egger's test, *p* value)
		Case	Control	I^2	Pooled Log (OR)	95% Credible interval)		
rs1343151 (G>A), 8 studies	G	8,416	10,475					
	A	4,749	5,335					
	GG	2,682	3,465					
	GA	3,052	3,545					
	AA	847	895					
	A vs. G			0.239	**0.085**	0.008, 0.156	0.04 (0.0, 0.14)	0.17, 0.16
	AA vs. GG			0.171	**0.176**	0.028, 0.321	0.08 (0.0, 0.25)	0.71, 0.63
	GA vs. GG			0.409	0.078	−0.25, 0.353	0.09 (0.0, 0.25)	0.04, 0.02
	AA + GA vs. GG			0.343	0.096	−0.025, 0.199	0.07 (0.0, 0.22)	0.41, 0.32
	AA vs. GA + GG			0.159	0.101	−0.035, 0.235	0.07 (0.0, 0.22)	0.82, 0.95
	HWE for controls = 0.79							
rs1004819 (G>A), 4 studies	G	4,682	5,487					
	A	2,142	2,541					
	GG	1,635	1,888					
	GA	1,448	1,711					
	AA	347	415					
	A vs. G			0.684	−0.006	−0.231, 0.249	0.13 (0.0, 0.42)	0.31, 0.18
	AA vs. GG			0.529	−0.054	−0.414, 0.352	0.21 (0.0, 0.62)	0.31, 0.49
	GA vs. GG			0.553	−0.021	−0.252, 0.274	0.13 (0.0, 0.46)	0.31, 0.15
	AA + GA vs. GG			0.603	−0.054	−0.294, 0.25	0.14 (0.0, 0.48)	0.31, 0.23
	AA vs. GA + GG			0.441	−0.046	−0.374, 0.302	0.17 (0.0, 0.56)	0.31, 0.43
	HWE for controls = 0.34							
rs10489629 (A>G), 7 studies	A	6,403	8,354					
	G	5,813	6,982					
	AA	1,670	2,290					
	AG	3,063	3,774					
	GG	1,375	1,604					
	G vs. A			0.169	−0.066	−0.161, 0.042	0.08 (0.0, 0.20)	0.55, 0.23
	GG vs. AA			0.211	0.112	−0.108, 0.31	0.18 (0.0, 0.41)	0.55, 0.33
	AG vs. AA			0.195	0.067	−0.111, 0.212	0.12 (0.0, 0.32)	0.13, 0.33
	GG + AG vs. AA			0.205	0.082	−0.098, 0.232	0.14 (0.0, 0.33)	0.41, 0.56
	GG vs. AG + GG			0.148	0.089	−0.039, 0.217	0.07 (0.0, 0.24)	0.50, 0.29
	HWE for controls = 0.49							
rs11209026 (G>A), 10 studies	G	11,043	1,3719					
	A	803	945					
	GG	5,154	6,408					
	GA	735	901					
	AA	34	21					
	A vs. G			0.876	−0.018	−0.439, 0.304	0.43 (0.0, 0.82)	0.75, 0.69
	AA vs. GG			0.099	0.602	−0.068, 1.271	0.31 (0.0, 0.82)	0.71, 0.44
	GA vs. GG			0.909	−0.085	−0.554, 0.319	0.5 (0.14, 1.0)	0.92, 0.85
	AA + GA vs. GG			0.925	−0.048	−0.531, 0.39	0.60 (0.24, 1.02)	0.66, 0.57
	AA vs. GA + GG			0.088	0.630	−0.031, 1.292	0.29 (0.0, 0.79)	0.69, 0.41
	HWE for controls = 0.07							
rs2201841 (T>C), 6 studies	T	5,356	5,969					
	C	2,350	5,585					
	TT	1,873	2,070					
	CT	1,610	1,829					
	CC	370	380					
	C vs. T			0.965	**−0.544**	−1.0, −0.065	0.49 (0.24, 0.86)	0.06, 0.28
	CC vs. TT			0.813	0.367	−0.232, 0.994	0.57 (0.24, 1.01)	0.81, 0.15
	CT vs. TT			0.137	−0.035	−0.173, 0.102	0.06 (0.0, 0.21)	0.71, 0.71
	CC + CT vs. TT			0.208	−0.003	−0.142, 0.154	0.07 (0.0, 0.25)	0.75, 0.46
	CC vs. CT + TT			0.828	0.389	−0.217, 1.02	0.58 (0.26, 1.02)	0.83, 0.55
	HWE for controls = 0.39							
rs7517847 (T>G), 9 studies	T	7,885	9,454					
	G	6,341	7,252					
	TT	2,202	2,696					
	TG	3,481	4,062					

(Continues)

TABLE 2 (Continued)

SNPs	Variations	Frequency		Percentage heterogeneity	Association test		Absolute heterogeneity test τ^2 (95% CI)	Publication bias (Begg's test, p value; Egger's test, p value)
		Case	Control	I^2	Pooled Log (OR)	95% Credible interval)		
	GG	1,430	1,595					
	G vs. T			0.681	0.044	−0.06, 0.143	0.11 (0.02, 0.23)	0.25, 0.36
	GG vs. TT			0.603	0.093	−0.096, 0.271	0.18 (0.0, 0.37)	0.47, 0.46
	TG vs. TT			0.713	0.022	−0.156, 0.186	0.19 (0.05, 0.38)	0.60, 0.23
	GG + TG vs. TT			0.745	0.045	−0.13, 0.211	0.19 (0.06, 0.38)	0.51, 0.16
	GG vs. TG + TT			0.221	0.081	−0.034, 0.194	0.07 (0.0, 0.21)	0.43, 0.32
	HWE for controls = 0.35							
rs10889677 (C>A), 6 studies	C	2,323	1,732					
	A	1,275	944					
	CC	771	585					
	CA	781	562					
	AA	247	191					
	A vs. C			0.668	0.083	−0.164, 0.343	0.20 (0.0, 0.48)	0.45, 0.50
	AA vs. CC			0.671	0.290	−0.304, 0.935	0.53 (0.13, 1.03)	0.22, 0.01
	CA vs. CC			0.682	0.090	−0.274, 0.489	0.30 (0.0, 0.67)	0.99, 0.17
	AA + CA vs. CC			0.657	0.111	−0.226, 0.494	0.27 (0.0, 0.64)	0.38, 0.14
	AA vs. CA + CC			0.721	0.159	−0.360, 0.718	0.51 (0.14, 0.97)	0.27, 0.10
	HWE for controls = 0.003							

Note. Marginal posterior summary, bold pooled Log (OR) indicated as statistical significant at 0.05 level, I^2: relative heterogeneity.
CI: credible interval; HWE: Hardy-Weinberg equilibrium; OR: odds ratio; SNP: single nucleotide polymorphism.

results of this meta-analysis are consistent and conservative against any false significant association.

IL-23 belongs to the IL-12 cytokine family and plays an inflammatory function in both the innate and adaptive immunity and participates in the differentiation of CD4+ T cells into Th17 cells (Murphy et al., 2003). Th17 cells, by generating inflammatory IL-17 cytokine, have been indicated to impose tissue damage in joints (Steinman, 2007). Role IL-23 in the autoinflammatory process has been reported in animal models of collagen-induce arthritis and inflammatory bowel disease (IBD; Murphy et al., 2003). *IL23* gene knocking down results in a disease-resistant state in collagen-induced arthritis. In addition, serum and synovial fluid levels of IL-23 in patients with RA are high (Kim et al., 2006). IL-23 mediates its biological function through ligation to the IL-23R, which is encoded by the *IL23R* gene on chromosome 1p31. A GWAS indicated that *IL23R* gene rs112096, rs2201841, and rs10889677 polymorphisms associated with IBD and psoriasis (Cargill et al., 2007). Haplotype tagging SNPs of the *IL23R* gene have also been associated with RA. The previous meta-analysis of *IL23R* gene polymorphisms performed by Song, Bae, Choi, Ji, and Lee (2012) and published in 2012, included 13 case–control studies in comparison to 17 studies in the current meta-analysis and performed a classical analysis. They indicated the association of rs1343151 with a strong p value (4.7×10^{-6}), in which the minor A allele increased the risk of RA 1.1 times. Our Bayesian hierarchical meta-analysis also validates the previous significant association in minor A allele of *IL23R* gene rs1343151 SNP. However, the rs2201841 was not significantly associated with RA in the previous classical meta-analysis; nonetheless, our analysis indicated that the minor C allele of this polymorphisms is a protective allele against RA risk. Moreover, our analysis did not support the association of rs10489629 SNP with RA that was reported in the previous analysis. In classical meta-analysis, the significance of pooled OR is tested by Z test, and $p < 0.05$ is considered as statistically significant. Heterogeneity may be observed between included studies. Despite significant results in the classical meta-analysis, the number of included studies was not considerably large (in a statistical viewpoint), and thus the results should be interpreted with caution. In the Bayesian hierarchical meta-analysis, the credible interval is slightly wider than that of classical meta-analysis and the results tend to be more consistent. Therefore, the significant result of Bayesian hierarchical meta-analysis is conservative and more reliable in comparison with the classical meta-analysis (Lunn, Barrett, Sweeting, & Thompson, 2013; Wei et al., 2015).

IL-21 is mainly produced by human activated CD4+ T and, like as IL-23, is required for differentiation of human naive CD4+ T cells into Th17 cells (Khatonier et al., 2018). Studies have indicated that the frequency of the IL-21 receptor (IL-21R) expressing cells in the inflammatory synovial tissues from RA patients is increased. Moreover, IL-21 upmodulated the local activation, proliferation, and inflammatory cytokine production in T cells in RA involved tissues (Li, Shen, Kong, & Liu, 2006). If the genetic polymorphisms in the IL21 gene results in a nonfunctional IL-21 cytokine, the differentiation of CD4+ T cells toward pathogenic Th17 cells might occur slowly, culminating in decreased inflammatory settings. Hollis-Moffatt et al. (2010) studied the association of rs6822844 within the *KIAA1109-TENR-IL2-IL21* gene cluster in Australian RA patients in 2010 and tried to meta-analyze the data with already published data. Despite this SNP was not associated with RA in the Australian population, when the data were combined in a meta-analysis using data from a total of 9,772 cases and 10,909 controls (including the North

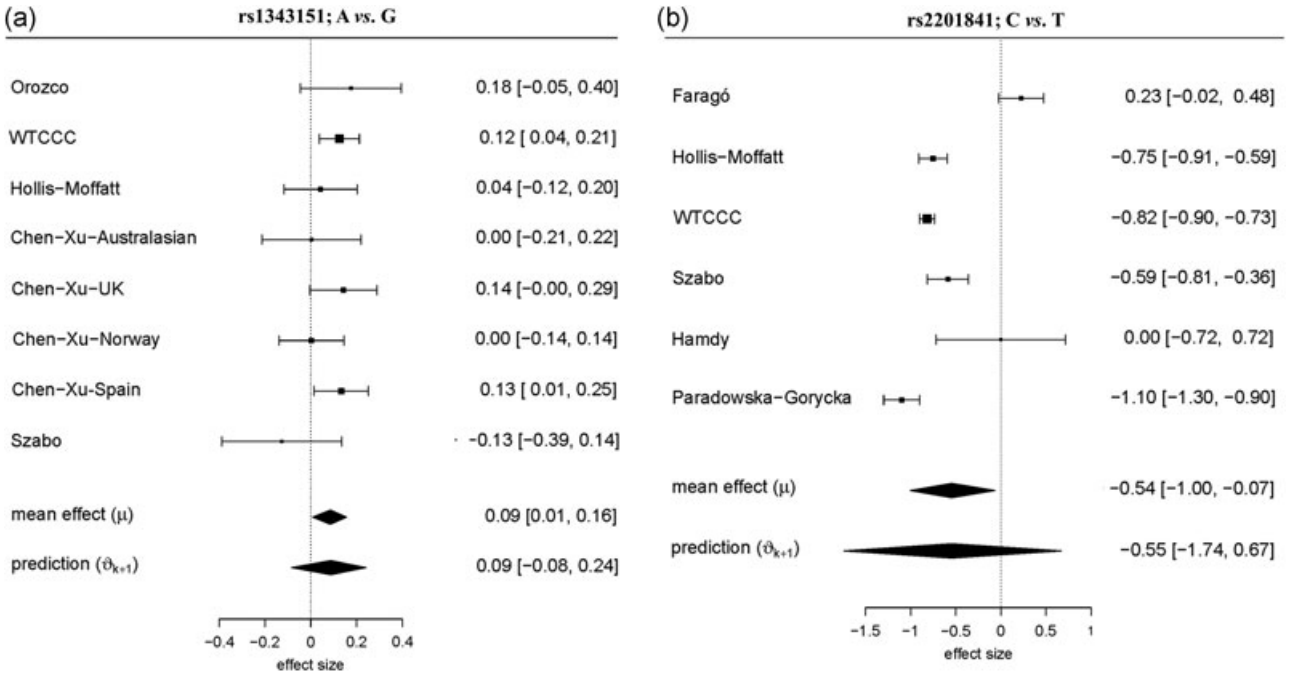

FIGURE 2 Forest plots displayed Log (OR) and 95% credible intervals for both the individual trials and for the pooled results, (a) rs1343151; A versus G, (b) rs2201841; C versus T. OR: odds ratio

American Rheumatoid Arthritis Consortium data with $p = 2.1 \times 10^{-8}$), there was a genome-wide level of significance of rs6822844 SNP association with RA. Our Bayesian hierarchical meta-analysis included 10,079 cases and 10,742 healthy subjects for *IL21* gene rs6822844 SNP from 10 studies; nonetheless, we could not have access to the North American Rheumatoid Arthritis Consortium data. However, Bayesian hierarchical meta-analysis analysis did not support the significant association of *IL21* gene rs6822844 SNP with RA risk. In contrast, our classical meta-analysis of the current data (results not provided in the current paper) also demonstrated a significant association of minor T allele with decreased RA risk. However, Bayesian hierarchical in contrast to its classical counterpart has reasonable accuracy even when the study population underlying meta-sample is small (Moeltner, Boyle, & Paterson, 2007).

TABLE 3 Bayesian hierarchical meta-analysis of the pooled association between *IL21*, rs6822844 (G>T) polymorphism and risk of RA disease, 10 studies

	Frequency		Percentage heterogeneity	Association test			
Variations	Case	Control	I^2	Pooled Log (OR)	95% Credible interval)	Absolute heterogeneity test τ^2 (95% CI)	Publication bias (Begg's Test, *p* value; Egger's test, *p* value)
G	17,018	17,638					
T	3,134	3,846					
GG	6,278	6,364					
GT	2,329	2,840					
TT	238	304					
T vs. G			0.913	−0.205	−0.48, 0.04	0.26 (0.05, 0.56)	0.35, 0.27
TT vs. GG			0.489	−0.232	−0.57, 0.11	0.25 (0.0, 0.59)	0.77, 0.78
GT vs. GG			0.904	−0.238	−0.55, 0.03	0.30 (0.03, 0.62)	0.37, 0.32
TT + GT vs. GG			0.910	−0.240	−0.54, 0.03	0.30 (0.05, 0.62)	0.22, 0.40
TT vs. GT + GG			0.474	−0.178	−0.50, 0.16	0.25 (0.0, 0.57)	0.63, 0.62
HWE for controls = 0.55							

Note. Marginal posterior summary, bold pooled Log (OR) indicated as statistically significant at 0.05 level, I^2: relative heterogeneity.
CI: credible interval; HWE: Hardy–Weinberg equilibrium; IL-21: interleukin-21; OR: odds ratio; RA: rheumatoid arthritis.

TABLE 4 Bayesian hierarchical meta-analysis of the pooled association between *IL17A*, rs2275913 (G>A) polymorphism and risk of RA disease, 10 studies

Variations	Frequency		Percentage heterogeneity	Association test		Absolute heterogeneity test τ^2 (95% CI)	Publication bias (Begg's test, *p* value; Egger's test, *p* value)
	Case	Control	I-squared	Pooled Log (OR)	95% Credible Interval)		
G	4,119	3,949					
A	2,358	2,600					
GG	1,214	1,099					
GA	1,412	1,493					
AA	443	521					
A vs. G			0.977	−0.201	−0.77, 0.36	0.79 (0.49, 1.17)	0.86, 0.54
AA vs. GG			0.302	−0.173	−0.47, 0.12	0.19 (0.0, 0.50)	0.75, 0.86
GA vs. GG			0.186	−0.130	−0.29, 0.04	0.08 (0.0, 0.28)	0.35, 0.25
AA + GA vs. GG			0.188	−0.148	−0.30, 0.01	0.08 (0.0, 0.27)	0.38, 0.24
AA vs. GA + GG			0.293	−0.113	−0.33, 0.10	0.15 (0.0, 0.39)	0.66, 0.74
HWE for controls = 0.71							

Note. Marginal posterior summary, bold pooled Log (OR) indicated as statistically significant at 0.05 level, I^2: relative heterogeneity.
CI: credible interval; HWE: Hardy–Weinberg equilibrium; IL-17A: interleukin-17A; OR: odds ratio; RA: rheumatoid arthritis.

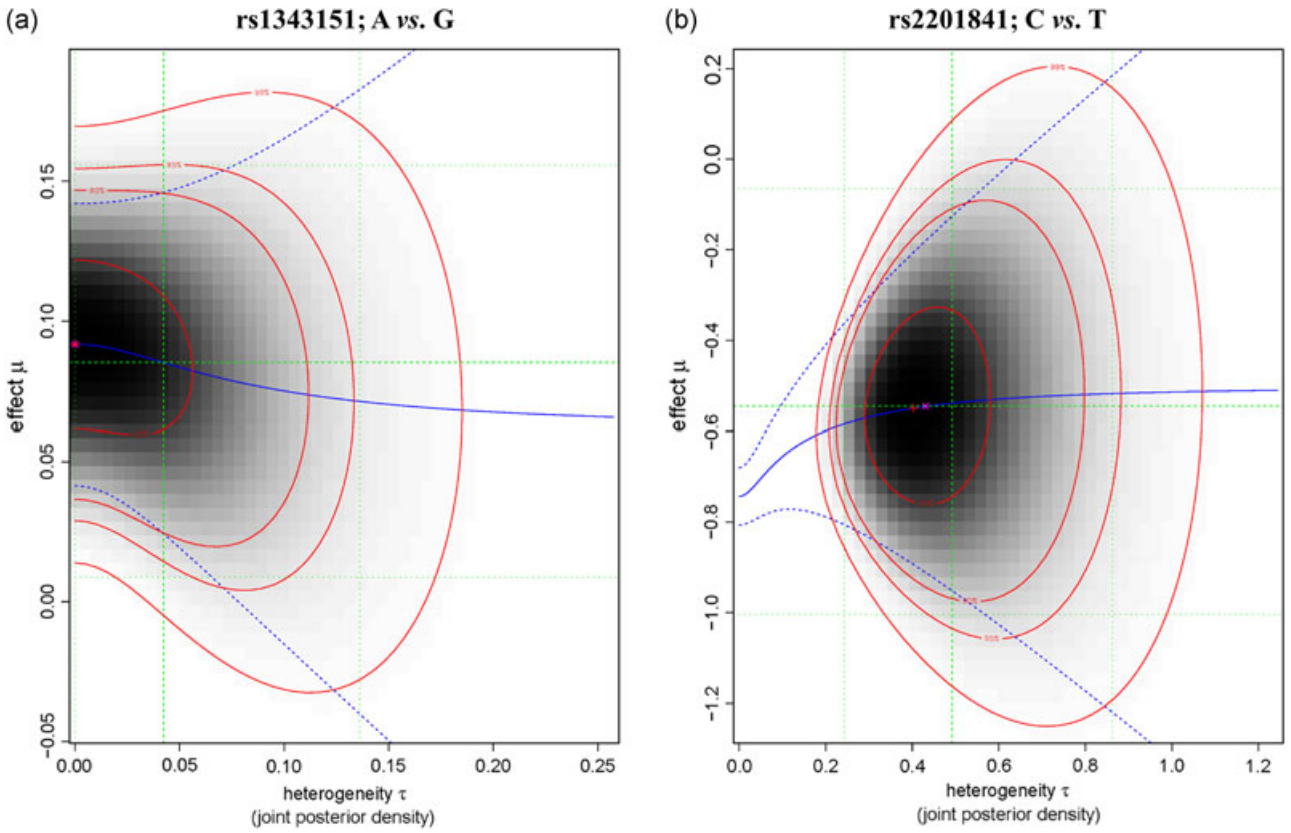

FIGURE 3 Heterogeneity plots, red lines trace the contours of constant density corresponding to approximate two-dimentional credible regions (based on a χ^2 approximation to the logarithmic posterior density) as labeled. The credible regions are only an approximation based on a "well-behaved," unimodal posterior; contour lines are omitted if the posterior mode is not finite. Blue lines show the conditional mean effect (Log OR) as a function of the heterogeneity τ (solid line) along with conditional 95% confidence bounds (dashed lines). Green lines indicate marginal medians and shortest 95% credible intervals for Log (OR) and τ. (a) rs1343151; A versus G and (b) rs2201841; C versus T [Color figure can be viewed at wileyonlinelibrary.com]

IL17A is a member of IL-17 family and is produced mainly by Th17 cells (Korn, Bettelli, Oukka, & Kuchroo, 2009). IL17A, in turn, can trigger the production of inflammatory factors (Brennan & McInnes, 2008). Increased IL-17A level has been reported in the synovium of RA patients. In addition, interfering with the function of IL-17 in animal models has been associated with amelioration of disease course, suggesting a pathologic role of IL-17 in RA disease (Hueber et al., 2010). The human *IL17A* gene, located on chromosome 6p12, harbors the rs2275913 G > A polymorphism (G197A), which has been evaluated in association with the susceptibility to ulcerative colitis (Arisawa et al., 2008) and Crohn's disease (McGovern et al., 2009). The first evidence of the association of *IL17A* gene rs2275913 G > A polymorphism came from a study by Nordang et al. (2009) in Norwegian population, while the association was not replicated in a cohort from New Zealand. After that, the other eight studies in different countries have tried to disclose this association (Table 1). Zhang et al. (2016) performed a classical meta-analysis of *IL17A* gene rs2275913 polymorphism by evaluating 3,130 RA cases and 3,136 controls extracted from seven case–control association studies. They indicated that *IL17A* gene rs2275913 polymorphism decreased the risk of RA in three genetic models of A versus G, AA versus GG and AA + GA versus GG. In contrast, we performed a Bayesian hierarchical meta-analysis of 3,415 cases and 3,436 healthy individuals obtained from 10 studies. However, our analysis did not support the significant association of *IL17A* gene rs2275913 polymorphism with RA risk. Again, this could be due to the difference in the method of analysis, as our classical analysis (the result of this analysis were not included in this study) also demonstrated a significant decreased association risk of *IL17A* gene rs2275913 polymorphism in RA patients. In all of the Bayesian hierarchical meta-analysis, we assumed the Log (OR) follows a normal distribution (mean = 0, variance = 100), meaning independence between rs2275913 and the disease risk. Therefore, the results of Bayesian hierarchical meta-analysis are conservative against false significant associations.

This meta-analysis is attributed to some limitations. First, because of the insufficient original data, we could not perform a subgroup analysis with respect to the ethnicity of populations (e.g., Asians, Europeans, Americans, etc.). Second, due to lack of sufficient amount of data, it was not possible to stratify the data according to the baseline variables, such as sex, autoantibody status (like cyclic citrullinated peptide antibody or rheumatoid factor), and other clinicopathological characteristics, as the genetic polymorphisms are associated with the severity of RA. Third, the heterogeneity observed in these studies might be due to variations in demographic specifications among the studies, geographic factors, different genotyping techniques, and differences in the inclusion criteria for the study populations.

In consideration of all, this Bayesian hierarchical meta-analysis intended to disclose the possible association of the polymorphisms in *IL23R*, *IL21*, and *IL17A* genes by pooling the available data and considering the immunological pathway of the three molecules (IL21-IL-23R-IL-17) that has been implicated in the pathogenesis of RA. The analysis resulted in identification of association of rs1343151 and rs2201841 polymorphisms in the *IL23R* gene with the risk of RA. However, a gene–gene interaction analysis is still required to further describe the role of genetic variants in immunological pathway of IL21-IL-23R-IL-17 in the pathogenesis of RA.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

F. S. M. performed the literature search, conducted data acquisition, and participated in manuscript drafting. S. A. conducted data acquisition, designed the tables, and participated in manuscript drafting. S. M. performed the statistical analysis and participated in manuscript drafting. A. J. developed the main idea, involved in conception and design, and participated in manuscript drafting. P. R. performed statistical analysis and participated in manuscript drafting. M. M. developed the main idea, participated in manuscript drafting, and read the manuscript critically.

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