

Association of IL-23R gene rs7517847 T>G SNP and susceptibility to systemic lupus erythematosus: A systematic review and meta-analysis

Danyal Imani¹, Ramazan Rezaei¹, Arash Poorsheikhani², Shahab Alizadeh³, Mahdi Mahmoudi^{4*}

¹ Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

² Department of Medical Genetics, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

³ Department of Cellular and Molecular Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran

⁴ Rheumatology Research Center, Tehran University of Medical Sciences, Tehran, Iran

Previous articles have evaluated the association between IL-23R gene rs7517847 T>G SNP and systemic lupus erythematosus (SLE). Nevertheless, the results of these studies have been inconclusive. The current study is a meta-analysis that assesses the association between IL-23R gene rs7517847 T>G SNP and SLE susceptibility. Literature searches of Medline, Web of Science, and EMBASE databases were performed to recognize all eligible studies published before August, 2016, and the search was updated in July, 2017. The identified studies were independently reviewed by two authors for eligibility based on inclusion criteria. Odds ratios (ORs) and 95% confidence intervals (CIs) were applied to assess the strength of association in the allelic model, dominant model, recessive model, heterozygotes contrast, and homozygotes contrast. Because evidence of heterogeneity was detected across the studies, the data was pooled using a random-effects model. A sum of four case-control studies with 1348 SLE patients and 1754 healthy subjects were considered in this study. In the combined analysis, no significant association between the IL-23R gene rs7517847 T>G SNP and SLE disease risk was found in any of the genetic models (dominant model: OR = 0.95, 95% CI = 0.72-1.18; allelic model: OR = 1.08, 95% CI = 0.95-1.21; recessive model: OR = 1.13, 95% CI = 0.80-1.46; TG vs. TT: OR = 0.86, 95% CI = 0.63-1.08; and GG vs. TT: OR = 1.20, 95% CI = 0.81-1.60). Moreover, no publication bias was observed in any genetic models ($p > 0.05$). First, this study was based on unadjusted ORs. Second, the number of included case-control articles was small. Third, only published English language studies were imported to this meta-analysis. The current meta-analysis suggests that the IL-23R gene rs7517847 T>G SNP might not be related with risk of SLE. More studies are essential to confirm these results. No association was found between the IL-23R gene rs7517847 T>G SNP and SLE risk.

Keywords: interleukin-23R, polymorphism, SLE, meta-analysis.

Introduction

Systemic lupus erythematosus (SLE) is an inflammatory disorder which involves multiple organs such as the skin, kidneys, and the nervous system [1]. It is characterized by chronic inflammation in tissues, autoantibody secretion, and severe organ damage [2]. While there are no exact figures for SLE prevalence in different parts of the world, it is estimated that approximately 12-64 in 100,000 people suffer from SLE, and SLE is 10 times more prevalent in females than males [3]. SLE has heterogeneous clinical manifestations and complicated genetic features [4]. Although the exact pathogenesis of SLE remains unclear, recent evidence has described a significant familial trend of SLE in monozygotic twins in comparison to healthy subjects [5]. Furthermore, the familial occurrence of SLE has revealed evidence of

genetics in the pathogenesis of the disease [6].

Accumulating data has indicated that cytokines and their receptors play crucial roles in the progression of inflammatory disorders such as SLE [7-9]. IL-23 and its receptor (IL-23R) are involved in the pathogenesis of autoimmune disease [10]. The p19 and p40 subunits of IL-23 are expressed mainly by activating phagocytes and dendritic cells [11]. It has been shown that IL-23 plays an essential role in the development and maintenance of IL-17 producing cells [12]. IL-17 induces the synthesis of proinflammatory cytokines including IL-6, TNF- α (Tumor Necrosis Factor), various chemokines, matrix metalloproteinase, and the recruitment of neutrophils from tissue which ultimately leads to chronic inflammation and the destruction of joints and organs [13].

IL-23 exerts its effects through high-affinity

* Corresponding Author: Mahdi Mahmoudi, Email: mahmoudim@tums.ac.ir, Tele-fax: +98-218-822-0067

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binding to the IL-23 receptor (IL-23R) complex [14]. IL-23R includes a common IL-23 receptor and an IL-12 receptor β 1 subunit which are mostly expressed on activated and memory T cells [15]. The IL-23R gene is located on the short arm of chromosome 1, at region 31.3. This gene spans 2.8 kb and contains 11 exons and 10 introns. The promoter region of the human IL-23R gene are distributed with many single nucleotide polymorphisms [16]. Many studies have demonstrated a strong association between IL-23R polymorphisms and the progression and outcome of several autoimmune disorders, such as ankylosing spondylitis [17], ophthalmopathy [18], Crohn's disease [19], and rheumatoid arthritis [20].

A relatively large number of case-control studies have investigated the association between the IL-23R gene rs7517847 T>G SNP and SLE risk. However, inconsistent and inconclusive results have been reported, probably due to the different ethnicity of populations and limited sample sizes. Although some studies have reported a significant association between the IL-23R gene rs7517847 T>G SNP and SLE risk, others have failed to find this association. The current meta-analysis was conducted to obtain an exact estimation of the effect of the IL-23R gene rs7517847 T>G SNP and SLE susceptibility.

Evidence Acquisition/ Methods

This study was performed in accordance with MOOSE (Meta-analysis of observational studies in epidemiology) guidelines [21].

Searches and Data sources

For this study, a systematic literature search was done on the electronic databases Medline, EMBASE, and Web of Science prior to August, 2016 for all observational studies that had examined the associations between the IL-23R gene rs7517847 T>G SNP and SLE susceptibility; the search was updated in July, 2017. The following syntaxes were used: (interleukin 23 receptor OR IL-23R) AND (Systemic Lupus Erythematosus OR SLE) AND (polymorphism OR polymorphisms OR SNP OR variation OR mutation). The search strategy was restricted to articles written in the English language and studies involving human populations.

Inclusion criteria

The articles used in this study were included using the following criteria:

1. Case-control studies that assessed the association of the IL-23R gene rs7517847 T>G SNP with SLE

susceptibility;

2. Risk estimates with 95% confidence intervals that could be extracted or calculated; and
3. Genotype or allele frequency of case and control groups provided by the studies.

The exclusion criteria were as follow:

1. Studies with insufficient information regarding genotype or allele frequency;
2. Abstracts, reviews, comments, and letters; and
3. Republished studies and studies with overlapping subjects.

The identified studies were independently reviewed by two authors for eligibility based on inclusion criteria, and discrepancies were resolved through consensus. The Kappa coefficient as the agreement coefficient between the two investigators was equal to 0.72, showing an overall good agreement between reviewers.

Extraction of data and quality assessment

For this meta-analysis, the following information was extracted with the use of a standardized data extraction form: the author's first name, journal and date of publication, ethnicity, country, average age, gender, number of case and control subjects, genotyping method, and the genotype or allele frequency. The Newcastle-Ottawa Scale (NOS) method was employed to evaluate the methodological quality [22]. This quality assessment tool judges studies on the basis of a star system; for this analysis, studies awarded 0-3, 4-6, or 7-9 stars were considered to be low, moderate, or high-quality studies, respectively. The quality assessment and data extraction were performed independently by two investigators.

Statistical analysis

Adherence to the Hardy-Weinberg equilibrium (HWE) constant was confirmed using the chi-square test [23]. ORs and their 95% CI were applied to assess the strength of the association between the IL-23R gene rs7517847 T>G SNP and the risk of lupus erythematosus in the following five genetic models: dominant (GG+ TG vs. TT), homozygote comparison (GG vs. TT), recessive (GG vs. TG + TT), heterozygote comparison (TG vs. TT), and allelic (G vs. T) models among groups. In the current meta-analysis, the heterogeneity among studies was assessed using the X^2 -based Q test and I^2 statistics. Significance level for heterogeneity was set at $p < 0.1$ [24]. Because of the remarkable heterogeneity among included studies, a random-effects model was applied. Visual

inspection of asymmetry in funnel plots, Begg's, and Egger's tests were done to evaluate publication bias ($p < 0.05$ was considered statistically significant) [25]. All statistical analyses were performed with the use of STATA (Version 13.0; Stata Corporation, College Station, TX).

Results

Characteristics of eligible studies

The procedures for including/ excluding potential studies are presented in Figure 1. The initial search yielded 463 potentially relevant articles. According to the inclusion criteria, a total of four case-control studies with 1348 SLE cases and 1754 healthy subjects were included in this meta-analysis [26-29]. The studies were done in different regions: one in China [26], one in Hungary [27], one in Spain [28], and one in South Korea [29]. Study publication years ranged from 2007 to 2010. Study characteristics and the genotype and allele frequency of the selected articles are represented in Tables 1 and 2. The genotype frequency of rs7517847 T>G SNP among SLE patients was 32% in the "TT" genotype, 46% in the "TG" genotype, and 22% in the "GG" genotype, while the frequency of the "T" allele between SLE patients was 55% and that of the "G" allele was 45%.

Quantitative synthesis

Heterogeneity and publication bias

Based on the inclusion criteria, four studies with 1348 cases and 1754 healthy subjects were analyzed. The summarized results and heterogeneity tests for association between the IL-23R gene rs7517847 T>G SNP and the risk of SLE in different genetic models are shown in Table 3. Virtual inspection of funnel plots revealed no evidence of publication bias (Fig. 2).

Meta-analysis for IL-23R (rs7517847) polymorphism and SLE

The results of analysis revealed that there was no association between the IL-23R gene rs7517847 T>G SNP and the risk of SLE disease in all of the genetic models tested (dominant model (GG+ TG vs. TT): OR= 0.95, 95% CI = 0.72-1.18; allelic model (G vs. T): OR= 1.08, 95% CI= 0.95-1.21; recessive model (GG vs. TG + TT): OR= 1.13, 95% CI= 0.80-1.46; heterozygote comparison (TG vs. TT): OR= 0.86, 95% CI= 0.63-1.08; and homozygote comparison (GG vs. TT): OR= 1.20, 95% CI= 0.81-1.60.) (Table 3 and Fig. 3).

Discussion

The pathogenesis of SLE is a complex process in *Rheum. Res., Vol. 3, No. 1, Jan. 2018*

which both genetic and environmental elements play important roles in its onset and progression [30]. The inflammatory reactions mediated through Th17 lymphocytes are also related to SLE development [31]. IL-23 is one of the important proinflammatory cytokines that is associated with multiple autoimmune diseases, including SLE [32]. Recently several studies have evaluated the association between the IL-23R gene rs7517847 T>G SNP and SLE susceptibility [26-29]. Because of inconsistencies in the results, a meta-analysis was needed. Meta-analysis is a strong statistical methodology that combines the findings of independent eligible studies to assess the effects of certain genetic variations on the risk of a disease. The current study is a meta-analysis of published articles which was conducted to evaluate the association between the IL-23R gene rs7517847 T>G SNP and the risk of SLE.

To the best of the authors' knowledge, this was the first meta-analysis study to evaluate the association between the IL-23R gene rs7517847 T>G SNP and SLE risk. Following the literature search, 4 case-control articles were involved in this study, including a total of 1348 SLE patients and 1754 healthy subjects. The results of the current study revealed no significant association between the IL-23R gene rs7517847 T>G SNP and SLE susceptibility in any genetic model in the overall samples.

The role of IL-23R in the onset and progression of many autoimmune and inflammatory disorders has been elucidated [33]. Moreover, IL-23R polymorphisms have been related with the progression of various autoimmune diseases [34-37]. The IL-23R signaling pathway is involved in the development of a pathogenic CD4⁺ T-cell fate, which is determined by the secretion of TNF- α , IL-17, IL-17F and IL-6 [38]. Therefore, considering its important function in the growth and differentiation of lymphocytes, IL-23R might augment the inflammation and production of autoantibodies during the course of a disease [32, 39]. In addition, the possible significance of IL-23 in the inflammatory process was further revealed by a more recent study demonstrating that the Th1-associated transcription factor, T-bet, could enhance the expression of the IL-23 receptor and, finally, the differentiation of Th17 and Th1 cells in autoimmune diseases [40]. In this regard, CK Wong et al. reported that IL-23 promotes the activation of IL-17-producing cells in SLE patients. It is possible that this process is affected by the production of IL-18, which regulates the inflammation of SLE [41].

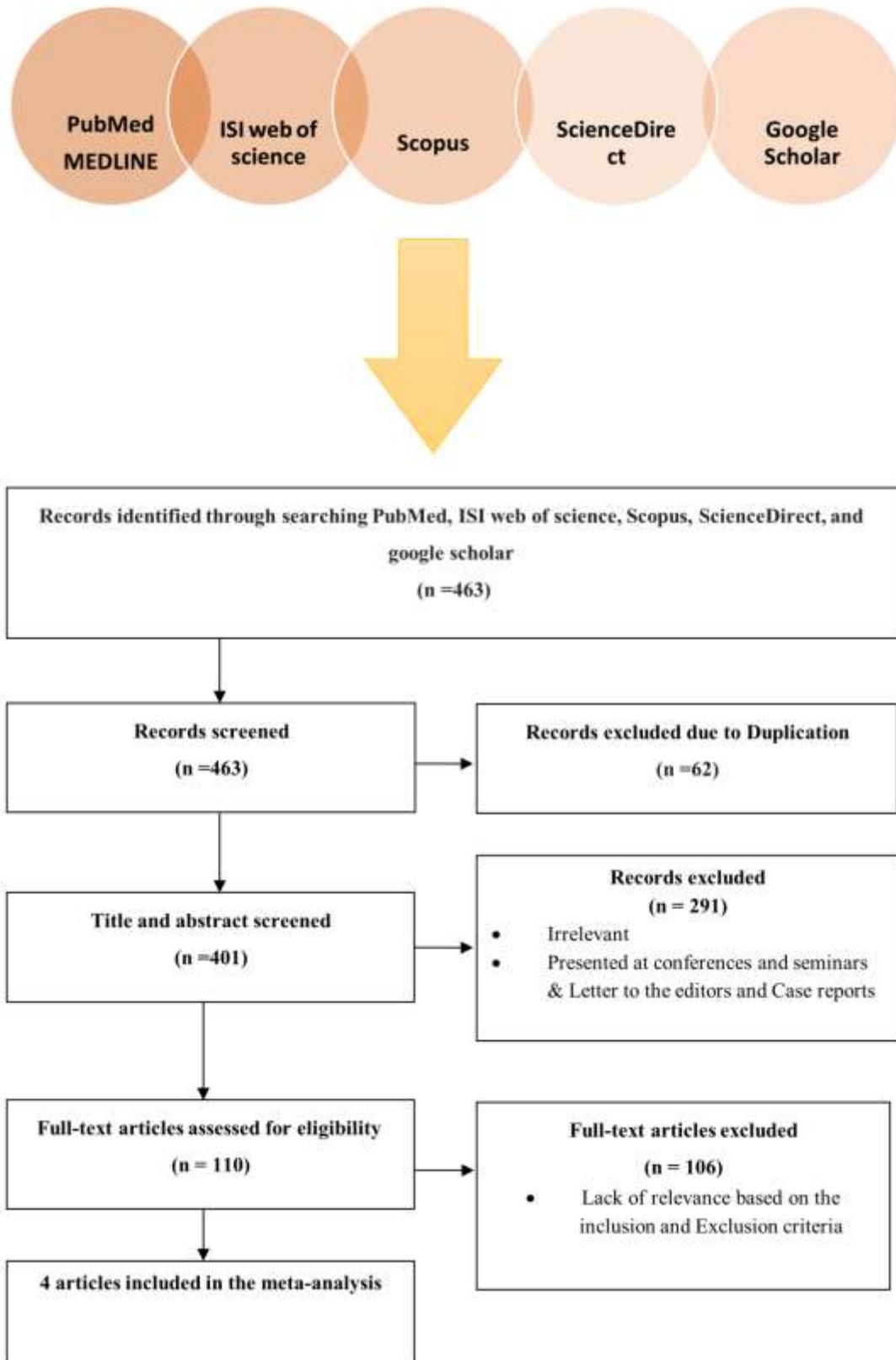


Fig. 1. The procedures for including/ excluding potential studies

Table 1. Characteristics of studies included in meta-analysis of overall SLE disease

Study author	Year	Country	Ethnicity	Sex	Total cases/controls	Case age/control age (Mean±SD)	Genotype method	Outcome	Quality score
Li et al. [26]	2010	China	Caucasian	M/F	139/168	33.5/34.5	PCR-RFLP	SLE	7
Safrany et al. [27]	2010	Hungarian	Caucasian	M/F	383/253	NR/NR	PCR-RFLP	SLE	8
Sanchez et al. [28]	2007	Spain	Caucasian	M/F	224/342	NR/NR	PCR-RFLP	SLE	8
Kim et al. [29]	2009	S. Korea	Caucasian	M/F	602/991	32.4/37.4	PCR-RFLP	SLE	7

NR: not reported; M: male; F: female; SLE: systemic lupus erythematosus

Table 2. Distribution of genotype and allele among SLE patients and controls

Study author	SLE cases					Healthy controls					P-HWE	MAF
	TT	TG	GG	T	G	TT	TG	GG	T	G		
Li et al. [26]	46	59	34	151	127	55	79	34	189	147	0.56	0.43
Safrany et al. [27]	125	176	82	426	340	73	139	41	285	221	0.06	0.43
Sanchez et al. [28]	69	106	49	244	202	121	153	68	395	289	0.12	0.42
Kim et al. [29]	NA	NA	NA	688	516	NA	NA	NA	1180	802	NA	0.40

P-HWE: p-value for Hardy–Weinberg equilibrium; MAF: minor allele frequency of control group; NA: not available. Other abbreviated as Table 1.

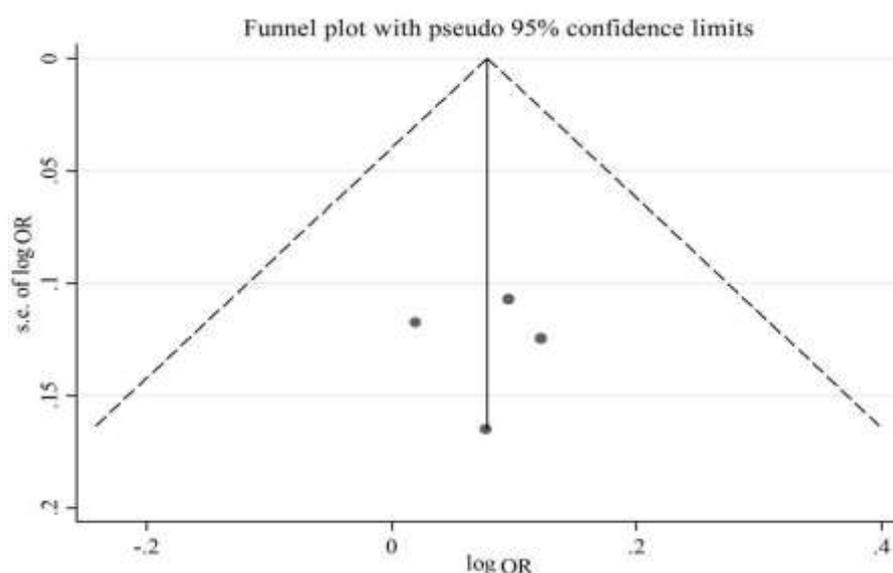


Fig. 2. Funnel plot on IL-23R (rs7517847 T>G) gene SNP to evaluate the publication bias of the literature

Table 3. Main results of pooled ORs in meta-analysis of IL-23R (rs7517847) polymorphism

Disease	Genetic model	Sample size Case/Control	Test of association		Test of heterogeneity		Test of publication bias			
			OR	95%CI	I ² (%)	P	Begg's		Egger's	
							Z	P	t	P
SLE	Dominant model	1348/1754	0.95	0.72-1.18	0.0	0.39	0.52	0.60	0.11	0.93
	Recessive model	1348/1754	1.13	0.80-1.46	0.0	0.80	0.52	0.60	0.27	0.83
	Allelic model	1348/1754	1.08	0.95-1.21	0.0	0.94	0.0	1.0	0.01	0.99
	GG vs. TT	1348/1754	1.20	0.81-1.60	0.0	0.97	0.52	0.60	0.23	0.85
	TG vs. TT	1348/1754	0.86	0.63-1.08	0.0	0.50	0.52	0.60	0.06	0.96

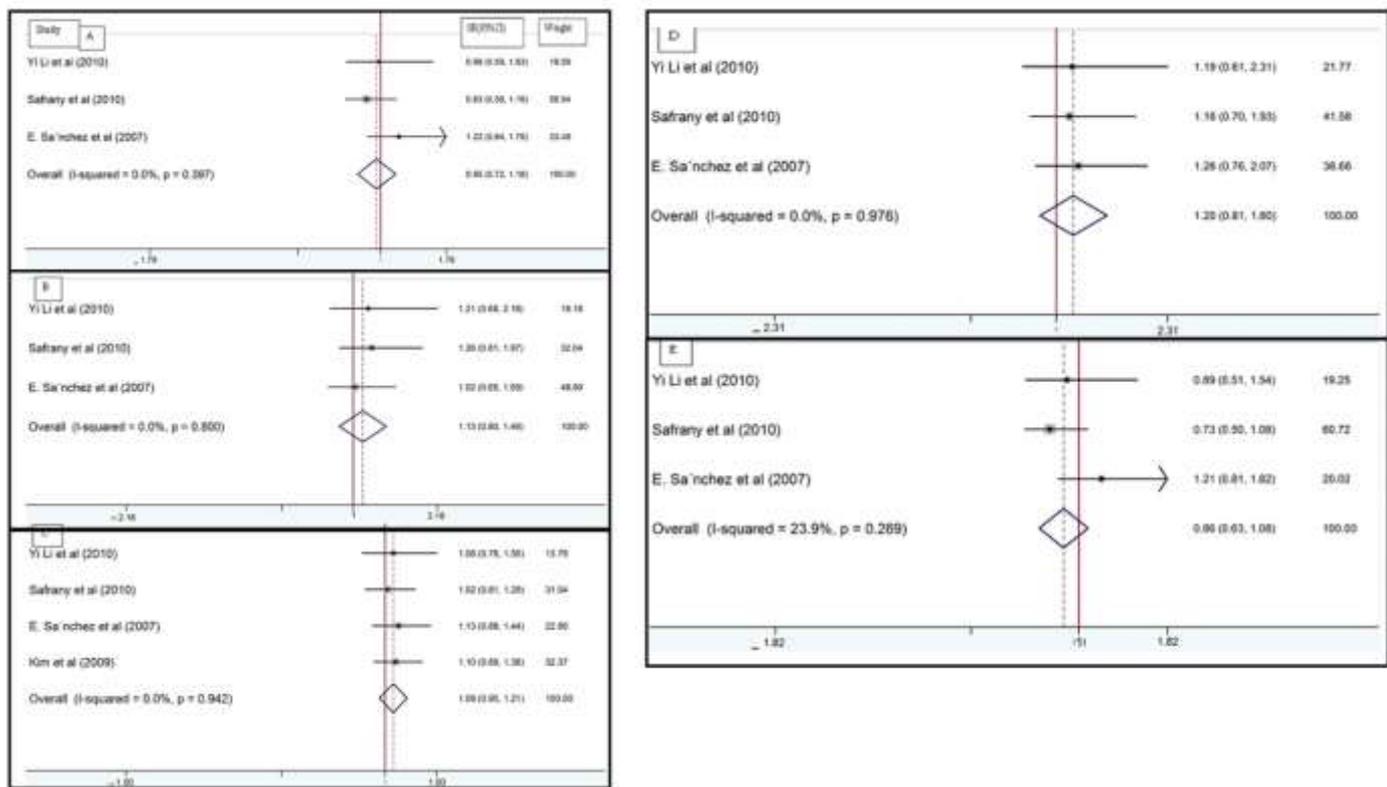


Fig. 3. Forest plot of association between IL-23R (rs7517847 T>G) gene SNP and SLE disease risk. Dominant model (A), Recessive model (B), Allelic model (C), GG vs. TT (D), and TG vs. TT (E)

The present study had some limitations. First, it was based on unadjusted ORs without adjustment for potential confounders; thus, the results should be interpreted with caution. Second, the number of included case-control articles was small. Third, only published English language studies were imported into this meta-analysis, and that probably led to the exclusion of some relevant publications in other languages. Finally, since included studies did not report data regarding the interactions of this polymorphism with other polymorphisms or environmental factors, the potential interactions between gene-gene and gene-environmental factors

could not be further evaluated, and this shortage might have affected the results.

Overall, the current study suggests that the IL-23R gene rs7517847 T>G SNP is not associated with the risk of SLE. Because of the scarcity of current evidence and to obtain a more conclusive result, additional large-scale and well-designed investigations are necessary to assess the association of the IL-23R gene rs7517847 T>G SNP and SLE risk.

Conclusion

The current meta-analysis suggests that the IL-23R (rs7517847 T>G) gene SNP might not be related with

the risk of SLE. More studies are essential to confirm these results.

Conflicts of interest

The authors declare no conflicts of interest.

Authors' Contributions

Each author confirms that s/he has participated in the

work in a substantive way and is prepared to take full responsibility for the work.

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