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ORIGINAL ARTICLE

Association of TNF-α promoter-308 A/G polymorphism with susceptibility to systemic lupus erythematosus: a meta-analysis

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Abstract Published data on the association between tumor necrosis factor-alpha (TNF-α) promoter-308 A/G polymorphism and systemic lupus erythematosus (SLE) risk are inconclusive. To derive a more precise estimation of the relationship, a meta-analysis was performed. A total of 28 studies including 2,992 cases and 4,326 controls (5,924 cases and 8,484 controls in A versus G comparison) were involved in this meta-analysis. Meta-analysis was performed for genotypes A/A (recessive effect), A/A+A/G (dominant effect), and A allele in fixed or random effects models. In addition, we also performed a "model-free" analysis by considering the G/G genotype as the reference and estimated the OR for the A/A versus G/G and A/G versus G/G genotype. Overall, an association of TNF-α promoter-308 A/G polymorphism with SLE was found (A versus G: OR = 1.686, 95% CI = 1.400–2.032, $P < 0.001$; A/A versus A/G+G/G: OR = 3.043, 95% CI = 2.185–4.238, $P < 0.001$; A/A+A/G versus G/G: OR = 1.822, 95% CI = 1.379–2.407, $P < 0.001$; A/A versus G/G: OR = 3.686, 95% CI = 2.628–5.172, $P < 0.001$; A/G versus G/G: OR = 1.691, 95% CI = 1.291–2.215, $P < 0.001$). However, stratification by ethnicity indicated that the risk A allele was not associated with SLE in Asian (A versus G: OR = 1.207, 95% CI = 0.856–1.702, $P = 0.283$) and African population (A versus G: OR = 1.225, 95% CI = 0.597–2.516, $P = 0.580$). In summary, this meta-analysis indicated that TNF-α promoter-308-A/G polymorphism is associated with susceptibility to SLE.

Keywords Meta-analysis · Susceptibility · Systemic lupus erythematosus · TNF-α

Introduction

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease, characterized by the production of multiple autoantibodies, complement activation, and immune-complex deposition, resulting in tissue and organ damage. The etiology and pathogenetic mechanisms of SLE are still unclear [1].

Many pro-inflammatory cytokines have been implicated in the pathogenesis of SLE. Tumor necrosis factor-alpha (TNF-α) is a potential pro-inflammatory cytokine that plays an important role in inflammatory and immune responses in SLE [2]. TNF-α stimulates cytokine production, enhancing expression of adhesion molecules and neutrophil activation and acts as a costimulator for T cell activation and antibody production.

TNF-α gene is located on chromosome 6, within the class III region of MHC [3]. Many polymorphisms of the TNF-α gene have been identified. Recently, these polymorphisms have attracted widespread attention, especially the TNF-α promoter-308 A/G polymorphism. A number of case–control studies have been conducted to investigate the association of this polymorphism with autoimmune diseases

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including systemic lupus erythematosus. However, many studies have shown inconclusive or contradictory results. This inconsistency may be due to studies with inadequate statistical power, racial and ethnic differences, publication bias, or uncorrected multiple hypothesis testing. Although it is unclear whether the TNF-α promoter-308 A/G polymorphism has a functional significance, several evidences suggest that there may be a small but significant effect of the TNF-α promoter-308 A/G polymorphism, with the A allele being associated with slightly greater levels of TNF-α transcription [4].

Meta-analysis is a means of increasing the effective sample size under investigation through the pooling of data from individual association studies, thus enhancing the statistical power of the analysis for the estimation of genetic effects [5]. Using meta-analysis, Lee et al. has demonstrated that the TNF-α promoter-308 A/G polymorphism may confer susceptibility to SLE, especially in European-derived population. In this study, we present an update to Lee's meta-analysis with recently published studies, to further investigate whether the TNF-α promoter-308 A/G polymorphism is a risk factor to the SLE susceptibility.

Methods

Identification of eligible studies and data extraction

We performed an exhaustive search on studies that examined the association of the TNF-α promoter-308 A/G

Table 1 Characteristics of individual studies included in meta-analysis

Study [Reference]	Country (Ethnicity)	Numbers		OR for A versus G allele	95% CI	HWE (*P* value)	Power ($\alpha = 0.05$, OR = 1.5)
		Control	Case				
McHugh et al. [6]	European	234	147	1.2	0.8–1.8	NA	49.7
Hrycek et al. [7]	European	36	24	0.4	0.2–1.0	0.84	12.1
Suárez et al. [8]	European	343	248	2.4	1.8–3.3	0.39	68.1
Schotte et al. [9]	European	157	205	2.7	1.9–4.0	0.88	47.7
Parks et al. [10]	European	203	86	2.0	1.3–3.0	0.44	39.8
May et al. [11]	European	57	47	2.7	1.3–5.6	0.33	17.5
Van der Linden et al. [12]	European	253	91	2.6	1.7–4.0	0.22	45.8
Rood et al. [13]	European	177	99	4.1	2.6–6.3	0.65	38.3
Rudwaleit et al. [14]	European	96	49	1.8	1.0–3.2	NA	22.6
D'Alfonso et al. [15]	European	174	123	1.1	0.7–1.7	NA	40.7
Danis et al. [16]	European	57	40	3.3	1.6–7.0	NA	16.6
Wilson et al. [17]	European	168	81	1.6	1.0–2.5	NA	35.1
Goldstein et al. [18]	European	91	91	1.4	0.9–2.2	0.83	27.1
Fugger et al. [19]	European	131	20	2.2	1.1–4.4	0.20	23.3
Lin et al. [20]	Asian	211	161	1.1	0.7–1.8	0.87	48.8
Hirankarn et al. [21]	Asian	154	154	0.9	0.5–1.5	0.67	41.9
Azizah et al. [22]	Asian	59	70	1.6	0.9–2.9	NA	20.6
Wang et al. [23]	Asian	70	89	2.6	1.6–4.1	0.17	24.3
Wang et al. [24]	Asian	187	51	0.9	0.4–2.1	0.25	33.8
Chen et al. [25]	Asian	107	100	0.6	0.4–1.2	0.93	30.1
Fong et al. [26]	Asian	89	67	1.5	0.8–2.9	NA	23.9
Tomita et al. [27]	Asian	23	20	2.9	1.2–7.5	NA	10.1
Atsumi et al. [28]	Asian	20	74	0.6	0.3–1.3	0.59	16.3
Parks et al. [10]	African	73	144	0.9	0.5–1.6	0.55	31.3
Sullivan et al. [29]	African	88	64	2.7	1.3–5.8	NA	23.4
Rudwaleit et al. [14]	African	81	49	0.8	0.4–1.5	NA	20.7
Guarnizo-Zuccardi et al. [30]	South American	102	120	2.2	1.2–4.1	0.06	31.9
Correa et al. [31]	South American	430	100	2.6	1.8–3.8	0.82	63.4
Jimênez-Morales et al. [32]	Mexican	400	327	2.4	1.4–4.2	0.46	77.0
Zuniga et al. [33]	Mexican	55	51	3.0	0.8–11.8	0.84	17.7

NA not available, *OR* odds ratio, *CI* confidence interval, *HWE* Hardy–Weinberg equilibrium of genotypes of controls

polymorphism with SLE. A search of the literature was made using MEDLINE and PubMed to identify available articles in which the TNF-α promoter-308 A/G polymorphism was determined in patients with SLE and control (most recent one was Nov 2009). References in the studies were reviewed to identify additional studies not indexed by MEDLINE or PubMed. "Tumor necrosis factor", "TNF-α", "polymorphism", "systemic lupus erythematosus" and "SLE" were entered as both medical subject heading (MeSH) terms and text words. No language restrictions were applied. A study was included in the analysis if (1) it was published up to Nov 2009, (2) it was original data (independence among studies), and (3) it provided enough data to calculate odds ratio (OR). When a study reported the results on different subpopulation, we treated them as a separate study in the meta-analysis. We excluded the following: (1) studies that contained overlapping data, (2) studies in which the number of null and wild genotypes could not be ascertained, and (3) studies in which family members had been studied because their analysis is based on linkage considerations. From each study, we extracted the available genotype and allele frequency information from the TNF-α promoter-308 A/G polymorphism.

The literature search identified 81 potentially relevant publications. Among them, 53 studies were excluded because they did not meet the inclusion criteria. They were studies on other TNF polymorphism such as TNF receptor genes (24 publications), studies on other diseases (22 publications) or animal studies (5 publications), or family study (1 publication) or repeat study (1 publications). There were no studies in which the number of null and wild genotypes could not be ascertained. A total of 28 relevant studies with TNF-α promoter-308 A/G polymorphism and SLE were selected for the meta-analysis [6–33]. Among them, two of the eligible studies contained data on two different ethnic groups [10, 14], and we treated them independently. Therefore, a total of 30 separate

Table 2 Meta-analysis of the TNF-alpha promoter-308 A/G polymorphism in SLE

Comparison	Population	Sample size		No. of studies	Test of association			Model	Test of heterogeneity		
		Case	Control		OR	95% CI	*P* value		X^2	*P* value	I^2
A versus G	Overall	5,924	8,484	30	1.686	1.400–2.032	<0.001	R	101.38	<0.001	71.4
	European	2,642	4,186	14	1.970	1.547–2.508	<0.001	R	45.45	<0.001	71.4
	Asian	1,572	1,840	9	1.207	0.856–1.702	0.283	R	20.93	0.007	61.8
	African	514	484	3	1.225	0.597–2.516	0.580	R	7.34	0.026	72.7
	South American	440	1,064	2	2.452	1.768–3.399	<0.001	R	0.15	0.697	0.0
	Mexican	756	910	2	2.505	1.548–4.056	<0.001	R	0.09	0.766	0.0
AA versus AG+GG	Overall	2,195	3,050	18	3.043	2.185–4.238	<0.001	F	15.99	0.525	0.0
	European	928	1,448	9	3.720	2.520–5.491	<0.001	F	9.02	0.340	11.3
	Asian	504	542	4	0.992	0.379–2.601	0.987	F	1.57	0.666	0.0
	South American	220	532	2	2.693	0.891–8.136	0.079	F	0.40	0.530	0.0
	Mexican	399	455	2	3.377	0.348–32.760	0.294	F	0.00	0.984	0.0
AA+AG versus GG	Overall	2,246	3,237	19	1.822	1.379–2.407	<0.001	R	70.75	<0.001	74.6
	European	928	1,448	9	2.418	1.733–3.375	<0.001	R	23.34	0.003	65.7
	Asian	555	729	5	1.021	0.684–1.522	0.920	R	7.36	0.118	45.7
	South American	220	532	2	2.837	1.898–4.243	<0.001	R	1.08	0.298	7.5
	Mexican	399	455	2	2.362	1.440–3.873	0.001	R	0.05	0.818	0.0
AA versus GG	Overall	1,582	2,417	18	3.686	2.628–5.172	<0.001	F	19.93	0.278	14.7
	European	562	1,062	9	4.727	3.168–7.053	<0.001	F	11.81	0.160	32.2
	Asian	403	440	4	1.079	0.412–2.824	0.877	F	1.73	0.630	0.0
	South American	153	433	2	3.353	1.066–10.543	0.038	F	0.14	0.708	0.0
	Mexican	351	429	2	3.623	0.373–35.177	0.267	F	0.00	0.984	0.0
AG versus GG	Overall	2,129	3,177	19	1.691	1.291–2.215	<0.001	R	61.52	<0.001	70.7
	European	836	1,404	9	2.142	1.550–2.961	<0.001	R	20.10	0.010	60.2
	Asian	547	721	5	1.028	0.684–1.546	0.895	R	7.27	0.122	45.0
	South American	210	525	2	2.629	1.473–4.692	0.001	R	1.81	0.179	44.7
	Mexican	397	455	2	2.270	1.380–3.734	0.001	R	0.00	0.953	0.0

OR odds ratio, *CI* confidence interval, *R* random effects model, *F* fixed effects model

comparisons were considered in our meta-analysis. These 30 studies consisted of 14 European, 9 Asian, 3 African, 2 South American, and 2 Mexican population samples (Table 1). Although the allele frequency of the TNF-α promoter-308 A/G polymorphism was extracted from 30 studies, the genotype frequency was available from 19 studies. Therefore, the meta-analysis was performed with 19 studies overall and 14 (9 European and 5 Asian) when divided by ethnical origin for genotype-based analysis. We have performed group-specific meta-analysis in European, Asian, South American, Mexican, and African-derived populations. As the genotype data on TNF-α-308 A/G polymorphism was available for one of three studies in African population [10], meta-analysis was performed only on A allele of TNF-α promoter-308 in African population.

Evaluation of publication bias

An estimate of potential publication bias was carried out by the funnel plot, in which the standard error of log (OR) of each study was plotted against its log (OR). An asymmetric plot suggests a possible publication bias. Funnel plot asymmetry was assessed by the method of Egger's linear regression test, a linear regression approach to measure funnel plot asymmetry on the natural logarithm scale of the OR. The significance of the intercept was determined by the t test suggested by Egger ($P < 0.05$ was considered representative of statistically significant publication bias).

Evaluation of the statistical association

Allele frequencies at the TNF-α promoter-308 A/G polymorphism from the respective study were determined by the allele counting method. A chi-square test was used to determine whether the observed genotype frequencies in the controls conformed to Hardy–Weinberg (H–W) expectations. We examined the contrast of the allelic effect of A (minor allele) versus G (common allele) and also examined the contrast of A/A versus A/G+G/G genotypes as well as the contrast of A/A+A/G versus G/G genotypes. These contrasts correspond to the recessive and dominant effects of the A allele, respectively. The point estimates of the risk, the OR, and its 95% confidence interval (CI) were estimated for each study. We assessed the within- and between-study variation or heterogeneity by testing Cochran's Q statistic [34]. This heterogeneity test assessed the null hypothesis that all studies were evaluating the same effect. A significant Q statistic ($P < 0.10$) indicated heterogeneity across studies, and then the random effect

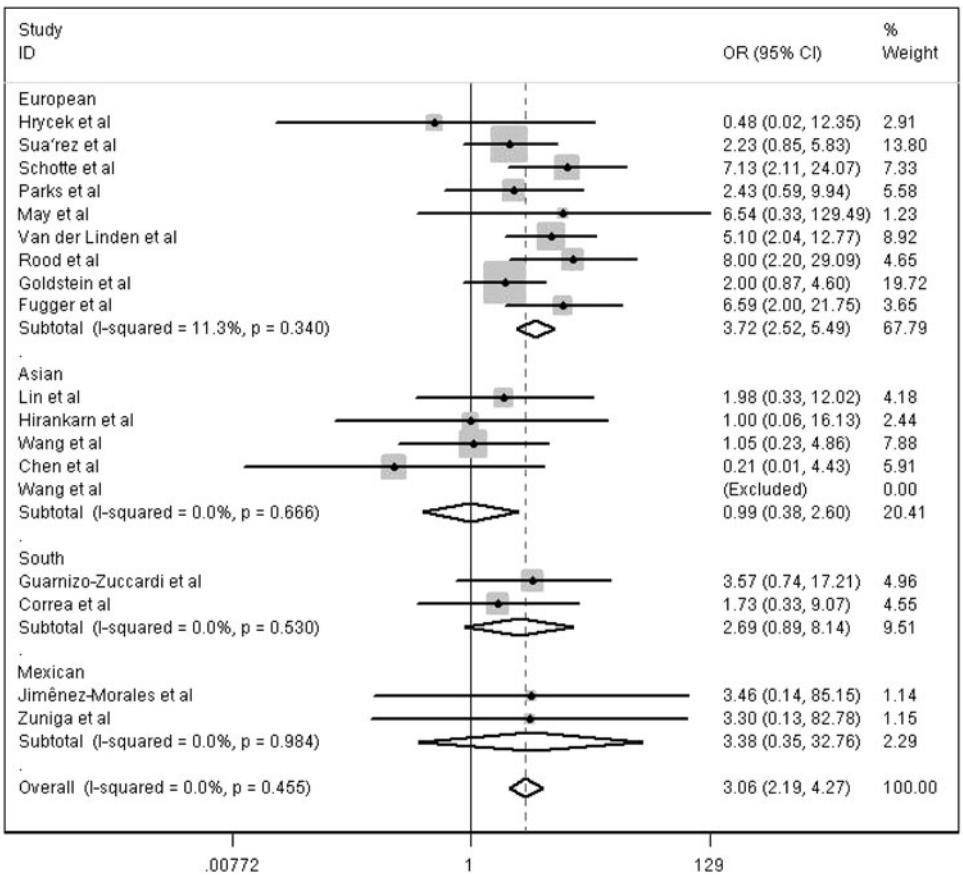

Fig. 1 OR and 95% CI of individual studies and pooled data for TNF-α-308 A/A versus A/G+G/G genotype

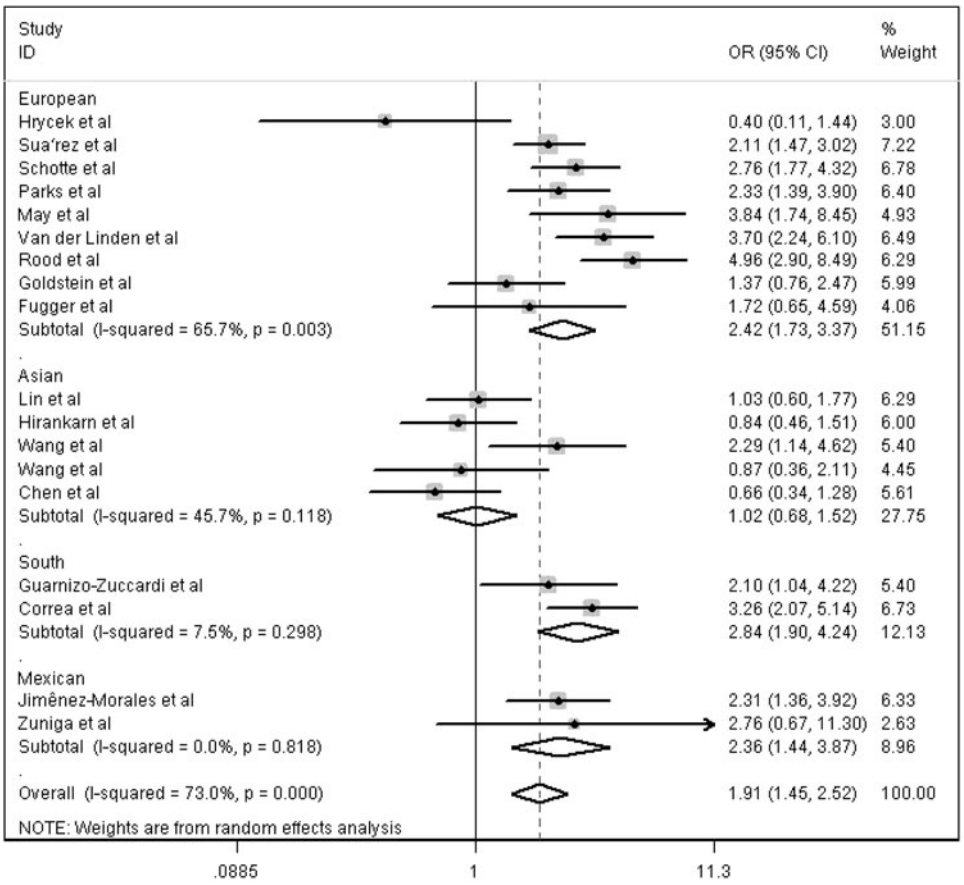

Fig. 2 OR and 95% CI of individual studies and pooled data for the association of the TNF-α-308 A/A+A/G versus G/G genotype

model was used for meta-analysis. Otherwise, the fixed effect model was used. Fixed effect model assumes that all of the studies are estimating the same underlying effect and considers only within-study variation. We also quantified the effect of heterogeneity using a recently developed measure, $I^2 = 100\% \times (Q - df)/Q$ [35]. The I statistic measures the degree of inconsistency in the studies by calculating what percentage of the total variation across studies is due to heterogeneity rather than by chance [36]. Finally, the overall or pooled estimate of risk (OR) was obtained by a random effects (DerSimonian–Laird) or a fixed effects model (Mantel–Haenszel) in the presence ($P \leq 0.1$ or $I^2 > 50\%$) or absence ($P > 0.1$ and $I^2 \leq 50\%$) of heterogeneity, respectively. Pooled OR in the meta-analysis was performed weighting individual OR by the inverse of their variance. Statistical manipulations for the meta-analysis were conducted by STATA version 8.0 (Stata Corporation, College Station, TX). The power of each study was computed as the probability of detecting an association between the TNF-α-308 A/G SNP and SLE at the 0.05 level of significance, assuming an OR of 1.5 (small effect size). The power analysis was performed using the statistical program G*Power. (http://www.psycho.uni-duesseldorf.de/aap/projects/gpower).

Results

Studies included in the meta-analysis

Selected characteristics of 28 case–control studies for TNF-α-308 A/G polymorphism and the risk of SLE are summarized in Table 1. Also, Table 1 shows the expected power of each individual study to demonstrate an association between this polymorphism and SLE. The statistical power of each study ranged from 10.1 to 77.0%. Interestingly, none of the 28 individual studies had more than 80% statistical power to an effect (Table 1). We also calculate the distribution of genotype for H–W equilibrium in control group.

Evaluation of study quality

The distribution of the genotype in the control group of each study (if the genotype data are available in a study) was consistent with H–W equilibrium. Deviation from H–W equilibrium among controls could imply some potential biases in the selection of control or genotyping errors, but excluding the study with the absence of H–W equilibrium in controls did not materially affect the overall

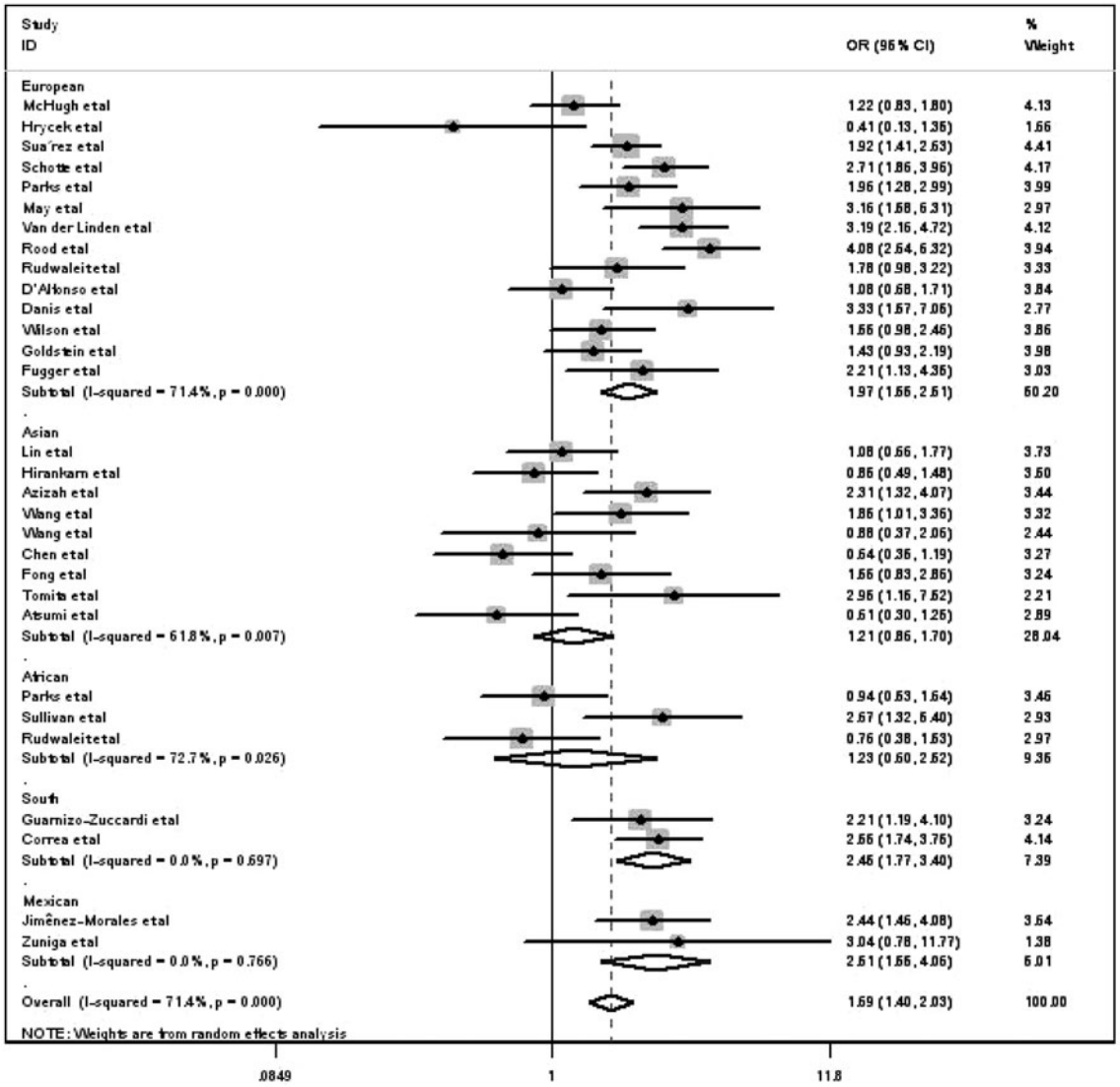

Fig. 3 OR and 95% CI of individual studies and pooled data for the association of the TNF-α-308 A versus G allele

results [37]. So, presentation of the meta-analysis is based on a combined data by adding the data which we can only get the alleles distribution.

Evaluation of A/G polymorphism and SLE association

The summary of meta-analysis for the TNF-α-308 A/G polymorphism with SLE is shown (Table 2). The *Q* test of heterogeneity was almost always significant, and we conducted analyses using random effect models except in one case that was in a subgroup analysis, and the *Q* test was likely to have been not statistically significant owing to lack of power. So, we also performed the subgroup analysis using random effect model.

An association between SLE and A/A risk genotype (assuming A allele as recessive allele) was found in the overall population (OR = 3.043, 95% CI = 2.185–4.238, $P < 0.001$) (Table 2; Fig. 1). However, stratification by ethnicity indicates that the A/A genotype is significantly associated with SLE only in Europeans (OR = 3.720, 95% CI = 2.520–5.491, $P < 0.001$). Conversely, there was no association detected for the A/A genotype with SLE patients from other population. Genotype data on TNF-α-308 A/G polymorphism were available for one of three studies in African population; therefore, genotype-specific meta-analysis was not performed in African samples. Assuming A allele as dominant allele, the overall OR for the combined A/A+A/G genotypes was 1.822 (95% CI = 1.379–2.407, $P < 0.001$) (Table 2; Fig. 2). Similarly, using ethnic-specific analysis, OR was increased significantly in the European samples (OR = 2.418, 95% CI = 1.733–3.375, $P < 0.001$), South American (OR = 2.837, 95% CI = 1.898–4.243, $P < 0.001$), and Mexican (OR = 2.362, 95% CI = 1.440–3.873, $P = 0.001$), but not in Asians

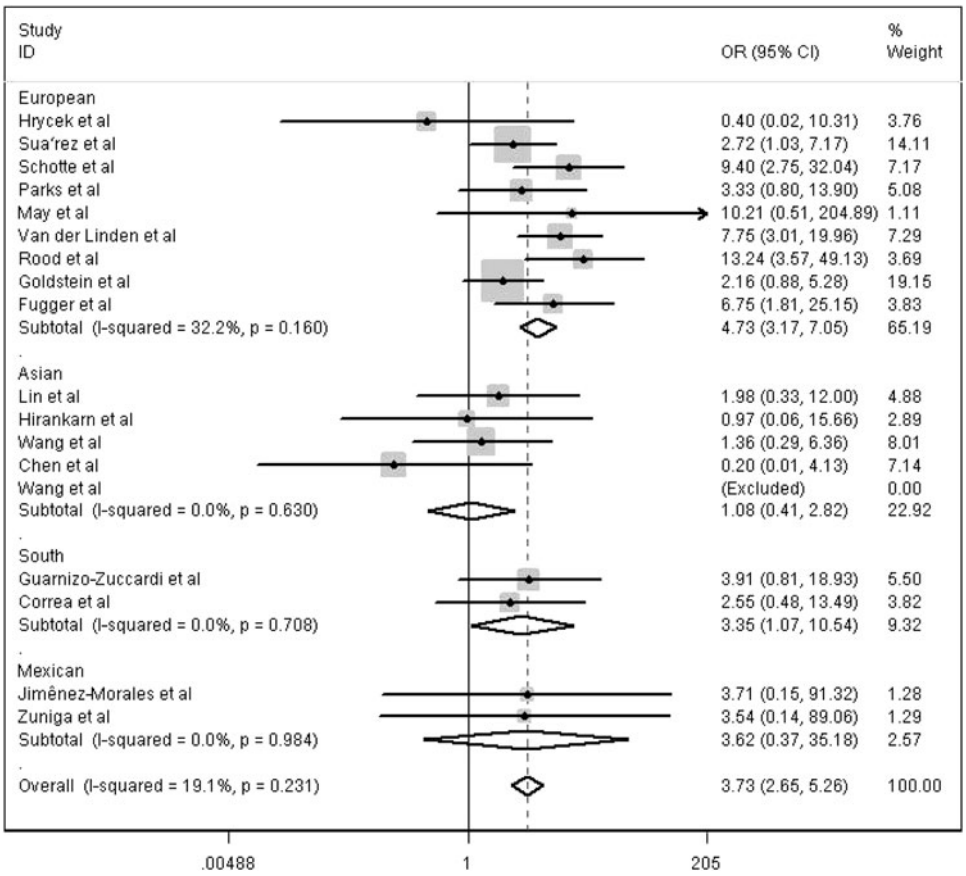

Fig. 4 OR and 95% CI of individual studies and pooled data for the association of the TNF-α-308 A/A versus G/G genotype

(OR = 1.021, 95% CI = 0.684–1.522, $P = 0.920$). The overall OR for the A allele of the TNF-α-308 A/G was 1.686 (95% CI = 1.400–2.032, $P < 0.001$) (Table 2; Fig. 3). Stratification by ethnicity indicates that the A allele is a risk factor for SLE in European (OR = 1.970, 95% CI = 1.547–2.508, $P < 0.001$), South American (OR = 2.452, 95% CI = 1.768–3.399, $P < 0.001$), Mexican (OR = 2.505, 95% CI = 1.548–4.056, $P < 0.001$), but not in Asian (OR = 1.207, 95% CI = 0.856–1.702, $P = 0.283$) or African (OR = 1.225, 95% CI = 0.597–2.516, $P = 0.580$). We also performed a "model-free" analysis by considering the G/G genotype as the reference and estimated the OR for the A/A versus G/G and A/G versus G/G genotype (Table 2; Figs. 4, 5). We found gene dosage effect of the A allele.

Overall, the meta-analysis of the TNF-α-308 A/G genotype (recessive effect), A/A+A/G genotype (dominant effect), and the risk allele A was associated with susceptibility to SLE in Europeans. However, in the subgroup analysis by ethnicity, there were differences in different populations.

Publication bias

Begg's funnel plot and Egger's test were performed to access the publication bias of literatures. The shapes of the funnel plots did not reveal any evidence of obvious asymmetry (The figures are not shown). Then, the Egger's test was used to provide statistical evidence of funnel plot symmetry. The results still did not demonstrate any evidence of publication bias (Table 3).

Discussion

It is well recognized that there is individual susceptibility to SLE even with the same environmental exposure. Host factors, including polymorphisms of genes involved in SLE may have accounted for this difference. Therefore, genetic susceptibility to SLE has been a research focus in scientific community. Recently, genetic variants of the TNF-α gene in the etiology of several autoimmune diseases have drawn increasing attention. Growing number of studies have suggested that -308 A in the promoter region of the TNF-α gene was emerging as a susceptibility allele for SLE. However, the results are inconclusive. To better understanding of the association between this polymorphism and SLE risk, a pooled analysis with a large sample, subgroup analysis performed, and heterogeneity explored is needed.

Overall, our results indicated that TNF-α promoter-308-A/G polymorphism is associated with susceptibility to

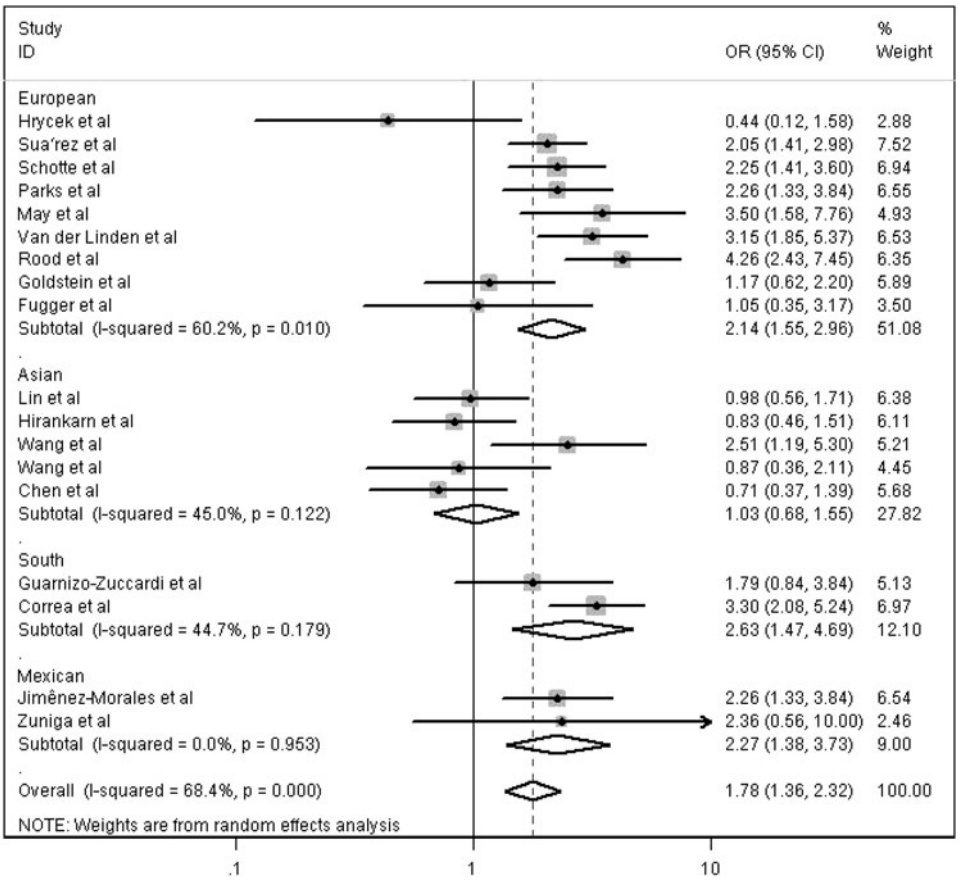

Fig. 5 OR and 95% CI of individual studies and pooled data for the association of the TNF-α-308 A/G versus G/G genotype

Table 3 Tests for publication bias (Egger's test) in population (overall)

Comparison	Egger's test (*P* value)
A versus G	0.190
AA versus AG+GG	0.208
AA+AG versus GG	0.143
AA versus GG	0.160
AG versus GG	0.116

SLE. These results were similar to that observed by Lee et al. in another previous meta-analysis [38]. However, in the subgroup analysis by ethnicity, there were differences among different populations, suggesting a possible role of ethnic differences in genetic backgrounds and the environment they lived in. In addition, the influence of the TNF-α-308 A allele might be masked by the presence of other as-yet unidentified causal genes involved in SLE development.

Some limitations of this meta-analysis should be acknowledged. Firstly, the controls were not uniformly defined. Although most of the controls were selected mainly from healthy populations, some had benign disease. Therefore, non-differential misclassification bias was possible because these studies may have included the control groups who have different risks of developing SLE. Secondly, in the subgroup analyses, the number of Africans was relatively small, not having enough statistical power to explore the real association. In spite of these limitations, our meta-analysis also had some advantages. First, substantial number of cases and controls were pooled from different studies, which significantly increased the statistical power of the analysis. Second, no publication bias were detected, indicating that the whole pooled results may be unbiased.

In summary, this meta-analysis suggests that the TNF-α promoter-308-A/G polymorphism is associated with SLE susceptibility. However, large sample studies including different ethnic groups with a careful matching between cases and controls should be considered in future association studies to confirm the results from our meta-analysis. Also, further evaluating the effect of gene–gene and gene-environment interactions on the TNF-α promoter-308-A/G polymorphism and SLE risk is necessary.

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