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Review Article

Polymorphisms in the *interleukin-10* gene and Graves' disease: a meta-analysis

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Abstract: The correlation between interleukin-10 (*IL-10*) common polymorphisms (rs1800896 A>G, rs1800872 A>C and rs3021097 C>T) and Gravesdisease (GD) has been widely studied; however, the findings remain conflicting. The objective of this meta-analysis was to address the relationship of polymorphisms in the *IL-10* gene with the risk of GD. PubMed, China National Knowledge Infrastructure (CNKI) and Chinese BioMedical Disc (CBM) databases were systematically searched by two reviewers independently to identify relevant studies before March19, 2016. Pooled odds ratios (ORs) and their 95% confidence intervals (CIs) for the correlation of *IL-10* gene polymorphisms with GD susceptibility were calculated by Stata 12.0 software. Tests for publication bias, sensitivity analyses, and heterogeneity were also assessed in our meta-analysis. A total of six publications comprising sixteen case-control studies concerning the IL-10 rs1800896 A>G, rs1800872 A>C and rs3021097 C>T polymorphisms were included in our study. The pooled results suggested that *IL-10* rs1800896 A>G polymorphism was correlated with an increased GD risk (G vs. A: OR = 1.58, 95% CI = 1.14-2.20, P = 0.007; GG vs. AA: OR = 5.01, 95% CI = 2.81-8.94, P<0.001; GG+AG vs. AA: OR = 1.75, 95% CI = 1.24-2.48, P = 0.001 and GG vs. AA+AG: OR = 3.84, 95% CI = 2.32-6.37, P<0.001). In a stratified analysis by ethnicity, an increased GD risk was found among Asians and Caucasians. However, for *IL-10* rs1800872 A>C and rs3021097 C>T polymorphisms, the results showed that they were not associated with GD risk. In summary, these findings demonstrate that *IL-10* rs1800896 A>G polymorphism may be a risk factor for GD.

Keywords: Polymorphism, *IL-10*, Graves' disease, susceptibility, meta-analysis

Introduction

Graves' disease (GD) is a common autoimmune disorder, approximately 2% of women and 0.2% of men affected. It is characterized by the presence of anti-thyroid stimulating antibodies leading to diffuse goiter, hyperthyroidism, Graves' ophthalmopathy and Graves' dermopathy [1]. Genetic predisposition and multiple environmental factors may be responsible for the development of GD. Recently, an inherited predisposition to GD was found [2]. However, the etiology of GD is complicated and remains largely unclear.

The human *interleukin-10* (*IL-10*) gene is located on chromosome 1q32.2. The IL-10 is a homodimer; each of its subunits has 178 amino acid residue [3]. IL-10, also known as human cytokine synthesis inhibitory factor, plays pleiotropic effects in anti-inflammatory and immunosuppression. It inhibits the expression of Th1 cytokines, co-stimulatory molecules and major histocompatibility complex class II antigens on macrophages. IL-10 inhibits lipopolysaccharide and bacterial product mediated induction of the pro-inflammatory cytokines predominantly, such as TNFα, IL-1β, IL-12, IFNγ and so on [4-6]. Previous studies indicated that single nucleotide polymorphisms (SNPs) in *IL-10* gene were correlated with the susceptibility of multiple human autoimmune diseases, such as rheumatoid arthritis [7, 8], systemic lupus erythemato-

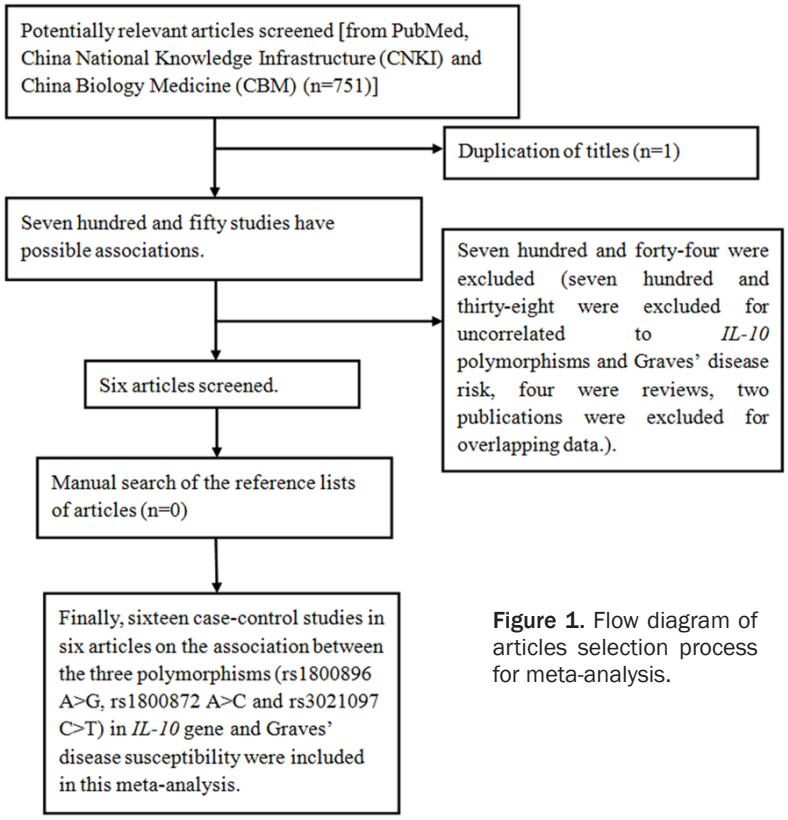

Figure 1. Flow diagram of articles selection process for meta-analysis.

sus [9], Behcets disease [10] and inflammatory bowel disease [11] *et al.*

Recently, accumulating evidences highlighted *IL-10* SNPs and haplotypes might play important roles in the development of GD [12, 13], specifically by influencing IL-10 expression levels [14]. *IL-10* gene is polymorphic, and more than 1,200 SNPs have been established (http://www.ncbi.nlm.nih.gov/snp), such as rs1800896 A>G (-1082 A>G), rs1800872 A>C (-592 A>C), rs3021097 C>T (-819 C>T), rs3021094, rs3024496 and rs3790622 polymorphisms etc. Among them, the *IL-10* rs1800896 A>G, rs1800872 A>C and rs3021097 C>TSNPs were extensively studied for their implication in GD risk. However, all available findings from previous epidemiologic studies were conflicting rather than conclusive. Considering the vital role of *IL-10* SNPs in the development of GD, we performed this meta-analysis on all eligible case-control studies to assess the GD susceptibility associated with *IL-10* rs1800896 A>G, rs1800872 A>C and rs3021097 C>T polymorphisms. As far as we know, the present study is the most comprehensive meta-analysis carried out to date with respect to the relationship of *IL-10* polymorphisms with GD risk.

Materials and methods

Search strategy

To identify all potentially publications on the association between *IL-10* polymorphisms and GD risk, we performed a systematic search on PubMed, China National Knowledge Infrastructure (CNKI) and Chinese BioMedical Disc (CBM) databases, covering all papers published up to March 19, 2016 without any language restrictions, by using the following terms: 'IL10/IL-10/interleukin-10/interleukin10', 'polymorphism/variant/SNP', 'GD/Graves disease'. References provided in retrieved articles and review articles were manually searched.

Inclusion and exclusion criteria

The major selection criteria were: (a) full-text study, (b) evaluating the correlation of *IL-10* rs1800896 A>G, rs1800872 A>C and rs3021097 C>T polymorphisms with GD susceptibility, (c) unrelated case-control design, (d) containing sufficient data on genotype and allele frequency for estimating the odds ratios (ORs) with their 95% confidence intervals (CIs). Publications containing two or more case-control studies were considered as several independent investigations. Accordingly, papers without sufficient data, not case-control study design, letters, duplicated data, comments and reviews were excluded.

Data extraction

Two authors (X. Wei and Y. Wang) independently reviewed and extracted the following original data from all publications: the first author' surname, published year, country/ethnicity, number of case/control, genotyping method and data of allele and genotype frequency. In case of a conflicting evaluation, discrepancy was addressed by a detailed discussion among all authors.

Table 1. Characteristics of the eligible studies included in the meta-analysis

Study	Year	Country	Ethnicity	No. of case/ control	Genotype method	polymorphisms
Liang *et al.* [14]	2015	China	Asians	118/138	PCR-RFLP	rs1800896 A>G
Jurecka-Lubieniecka *et al.* [23]	2013	Poland	Caucasians	735/1216	PCR-ARMS	rs1800896 A>G
Liu *et al.* [13]	2011	China	Asians	727/701	Taqman	rs1800896 A>G and rs1800872 A>C
Liu *et al.* [13]	2011	China	Asians	376/318	Taqman	rs1800896 A>G and rs1800872 A>C
Khalilzadeh *et al.* [21]	2010	Iran	Caucasians	57/140	PCR-SSP	rs1800896 A>G, rs1800872 A>C and rs3021097 C>T
Khalilzadeh *et al.* [21]	2010	Iran	Caucasians	50/140	PCR-SSP	rs1800896 A>G, rs1800872 A>C and rs3021097 C>T
Shiau *et al.* [20]	2007	China	Asians	137/189	PCR-RFLP	rs1800872 A>C and rs3021097 C>T
Tait *et al.* [22]	2004	UK	Caucasians	630/864	Taqman	rs1800872 A>C and rs3021097 C>T

PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism; PCR-ARMS: polymerase chain reaction-amplification refractory mutation system; PCR-SSP: polymerase chain reaction-sequence specific primer.

Table 2. Distribution of *IL-10* polymorphisms genotype and allele

Polymorphism	Study	Case			Control			Case		Control		HWE
rs1800896 A>G		AA	AG	GG	AA	AG	GG	A	G	A	G	
	Liang et al.	74	37	7	87	49	2	185	51	223	53	0.09
	Jurecka-Lubieniecka et al.	N/A	N/A	N/A	N/A	N/A	N/A	257	343	262	360	N/A
	Liu et al.	608	109	10	629	69	3	1325	129	1327	75	0.458
	Liu et al.	318	54	4	290	27	1	690	62	607	29	0.662
	Khalilzadeh et al.	14	32	11	53	75	12	60	54	181	99	0.042
	Khalilzadeh et al.	6	26	18	53	75	12	38	62	181	99	0.042
rs1800872 A>C		AA	AC	CC	AA	AC	CC	A	C	A	C	
	Liu et al.	321	326	78	299	310	87	968	482	908	484	0.633
	Liu et al.	169	163	44	133	152	33	501	251	418	218	0.278
	Khalilzadeh et al.	8	32	17	12	57	71	48	66	81	199	0.907
	Khalilzadeh et al.	16	26	8	12	57	71	58	42	81	199	0.907
	Shiau et al.	62	54	17	72	52	10	178	88	196	72	0.885
	Tait et al.	32	234	364	35	290	521	298	962	360	1332	0.498
rs3021097 C>T		CC	CT	TT	CC	CT	TT	C	T	C	T	
	Khalilzadeh et al.	15	34	8	71	57	12	64	50	199	81	0.907
	Khalilzadeh et al.	6	28	16	71	57	12	40	60	199	81	0.907
	Shiau et al.	19	57	59	13	71	91	95	175	97	253	0.868
	Tait et al.	377	248	31	512	280	34	1002	310	1304	348	0.579

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

Statistical analysis

We first evaluated the departure of frequencies of *IL-10* rs1800896 A>G, rs1800872 A>C and rs3021097 C>T variants from expectation under Hardy-Weinberg equilibrium (HWE) in controls by using an online goodness-of-fit test (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl) [15, 16]. Crude Ors with their 95% CIs were used to measure the strength of the association between *IL-10* rs1800896 A>G, rs1800872 A>C and rs3021097 C>T polymorphisms and GD risk. The statistical significance of the pooled ORs was assessed by the Z-test, and a $P<0.05$ was accepted as statistical significance. For *IL-10* rs1800896 A>G, we measured the correlation between genetic variants and GD risk in allelic comparison (G vs. A), homozygote comparison (GG vs. AA), dominant comparison (GG+AG vs. AA) and recessive comparison (GG vs. AG+AA), respectively. The same method was harnessed to assess *IL-10* rs1800872 A>C and rs3021097 C>T polymorphisms. A Chi-square-based Q-test was used to assess heterogeneity among the included studies. $I^2>50\%$ or $P<0.10$ (two-sided) suggesting the significant heterogeneity, the random-effects model (the DerSimonian-Laird method) was used to pool the data

Table 3. Meta-analysis of the *IL*-10 polymorphisms and Graves' disease

Polymorphism		No. of study	Alleliccomparison			Homozygote comparison			Dominantcomparison			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)
rs1800896A>G	Overall	6	1.58 (1.14-2.20)	0.007	<0.001	5.01 (2.81-8.94)	<0.001	0.422	1.75 (1.24-2.48)	0.001	0.075	3.84 (2.32-6.37)	<0.001	0.729
	Overall in HWE	4	1.36 (0.96-1.91)	0.080	0.006	3.69 (1.48-9.22)	0.005	0.986	1.57 (1.25-1.98)	<0.001	0.158	3.59 (1.44-8.94)	0.006	0.964
	Asians	3	1.60 (1.29-1.98)	<0.001	0.239	3.69 (1.48-9.22)	0.005	0.986	1.57 (1.25-1.98)	<0.001	0.158	3.59 (1.44-8.94)	0.006	0.964
	Caucasians	3	1.64 (0.84-3.21)	0.146	<0.001	6.63 (1.78-24.64)	0.005	0.081	2.67 (1.55-4.60)	<0.001	0.137	4.00 (2.20-7.25)	<0.001	0.166
rs1800872 A>C	Overall	6	0.79 (0.61-1.03)	0.078	<0.001	0.65 (0.37-1.15)	0.143	<0.001	0.79 (0.57-1.10)	0.161	0.006	0.74 (0.50-1.10)	0.133	<0.001
	Asians	3	0.98 (0.87-1.10)	0.728	0.203	0.97 (0.75-1.27)	0.849	0.174	0.96 (0.82-1.13)	0.661	0.352	0.99 (0.77-1.28)	0.964	0.184
	Caucasians	3	0.54 (0.28-1.03)	0.062	<0.001	0.30 (0.08-1.12)	0.073	0.001	0.47 (0.20-1.11)	0.086	0.019	0.43 (0.18-1.05)	0.064	<0.001
rs3021097 C>T	Overall	4	1.51 (0.85-2.68)	0.156	<0.001	2.15 (0.61-7.62)	0.237	<0.001	1.81 (0.75-4.34)	0.184	<0.001	1.54 (0.72-3.27)	0.265	<0.001

HWE: Hardy-Weinberg equilibrium.

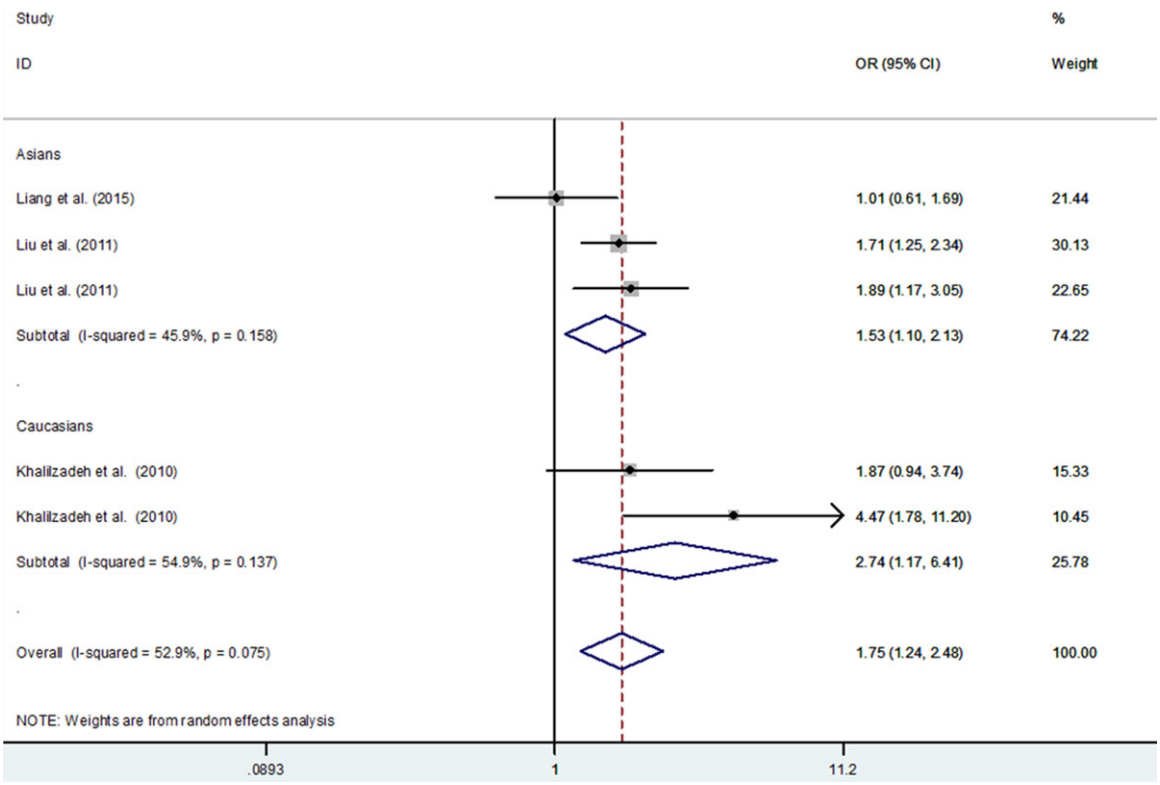

Figure 2. Meta-analysis with a random-effects model for the relationship of *IL-10* rs1800896 A>G polymorphism with Graves' disease (GG+AG vs. AA compare genetic model).

[17], otherwise the fixed-effects model (the Mantel-Haenszel method) was utilized [18]. Subgroup analyses were performed according to ethnicity (Asians and Caucasians). Begg's funnel plot and Egger's linear regression test were harnessed to measure potential publication bias [19]. One-way sensitivity analysis was performed to examine whether an individual study would affect the stability of our results. For publication bias, a $P<0.1$ (two-sided) was designated as statistical significance. All statistical analyses were performed using STATA software (version 12.0, Stata Corporation, USA).

Results

Characteristics

In total of 754 relevant papers were retrieved. The detailed selecting and excluding process were listed in **Figure 1**. Finally, a total of sixteen case-control studies from six publications were identified. Overall, there were four publications (including six case-control studies) on the *IL-10* rs1800896 A>G polymorphism, four articles (including six case-control studies) on the *IL-10* rs1800872 A>C polymorphism and three publications (including four case-control studies) on the *IL-10* rs3021097 C>T polymorphism. The characteristics of these included studies and the distribution of *IL-10* rs1800896 A>G, rs1800872 A>C and rs3021097 C>T variants as well as alleles are summarized in **Tables 1** and **2**, respectively.

Quantitative synthesis

IL-10 rs1800896 A>G polymorphism: There were four publications met the major selecting criteria with 1,328GD cases and 1,437 controls [13, 14, 20-23]. Two articles (Liu *et al.* and Khalilzadeh *et al.*) containing two case-control studies in each of them were considered as several independent investigations [13, 21]. In total, there were six case-control studies included in the present meta-analysis. Among these studies, three were Asian [13, 14, 20], three were Caucasian [21-23]. Overall, *IL-10* rs1800896 A>G polymorphism was associated with overall GD risk (OR, 1.58; 95% CI, 1.14-2.20; $P = 0.007$ for G vs. A; OR, 5.01; 95% CI,

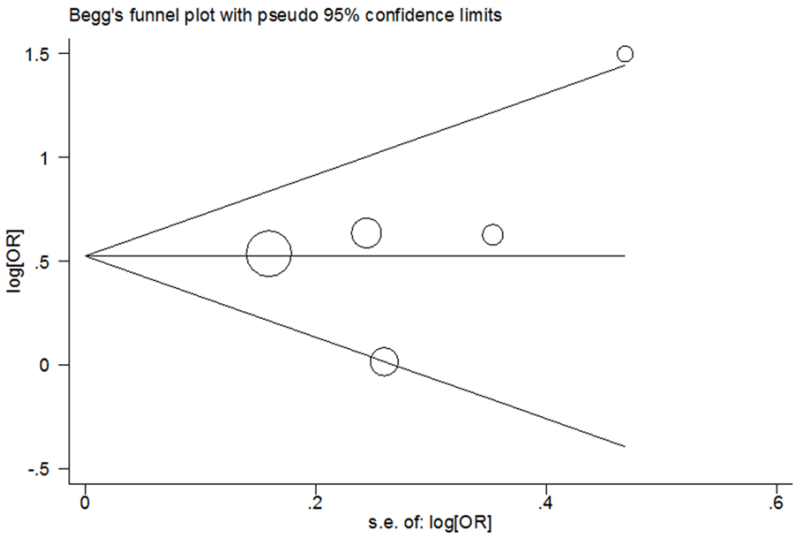

Figure 3. Begg's funnel plot of meta-analysis of the relationship between *IL-10* rs1800896 A>G polymorphism and the risk of Graves' disease (GG+AG vs. AA compare genetic model).

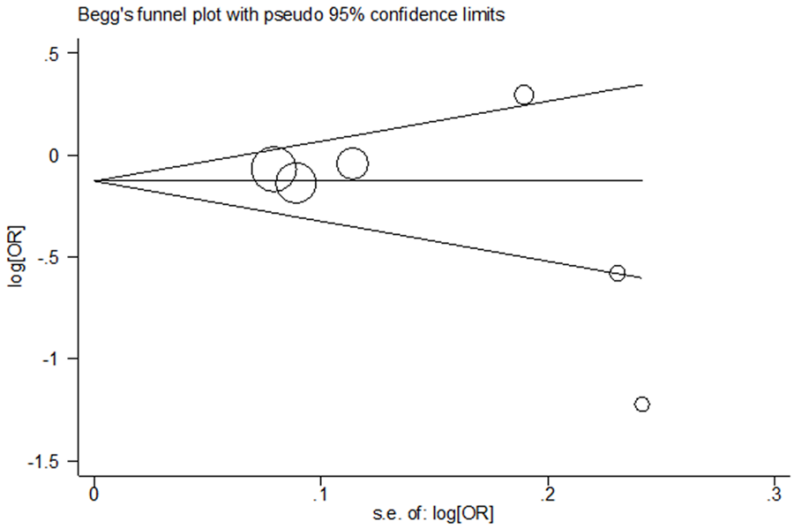

Figure 4. Begg's funnel plot of meta-analysis of the relationship between *IL-10* rs1800872 A>C polymorphism and the risk of Graves' disease (C vs. A compare genetic model).

2.81-8.94; *P*<0.001 for GG vs. AA; OR, 1.75; 95% CI, 1.24-2.48; *P* = 0.001 for GG+AG vs. AA and OR, 3.84; 95% CI, 2.32-6.37; *P*<0.001 for GG vs. AA+AG) (**Table 3** and **Figure 2**). In a subgroup analysis by ethnicity, a significant increased GD risk was identified among Asians (OR, 1.60; 95% CI, 1.29-1.98; *P*<0.001 for G vs. A; OR, 3.69; 95% CI, 1.48-9.22; *P* = 0.005 for GG vs. AA; OR, 1.57; 95% CI, 1.25-1.98; *P*<0.001 for GG+AG vs. AA and OR, 3.59; 95% CI, 1.44-8.94; *P* = 0.006 for GG vs. AA+AG) and Caucasians (OR, 6.63; 95% CI, 1.78-24.64; *P* = 0.005 for GG vs. AA; OR, 2.67; 95% CI, 1.55-4.60; *P*<0.001 for GG+AG vs. AA and OR, 4.00; 95% CI, 2.20-7.25; *P*<0.001 for GG vs. AA+AG). Other comparison results are listed in **Table 3**.

IL-10 rs1800872 A>C polymorphism: There were four papers met the inclusion criteria with 1,971 GD cases and 2,274 controls. Two articles (Liu *et al.* and Khalilzadeh *et al.*) provided two subgroups in each of them; thus, reviewers treated them separately [13, 21]. In total, there were six case-control studies included in this mata-analysis. Among them, three case-control studies were Caucasian and three were Asian. Overall, there was null correlation of *IL-10* rs1800872 A>C polymorphism with GD risk (**Table 3**). In a subgroup analysis by ethnicity, the similar findings were found in Asians and Caucasians (**Table 3**).

IL-10 rs3021097 C>T polymorphism: A total of 898-GD cases and 1,281 controls from four case-control studies were included on the relationship between *IL-10* rs3021097 C>T polymorphism and GD susceptibility. One case-control study was Asian and three were Caucasian. Results of this study did not show any statistical evidence of an association between *IL-10* rs3021097 C>T polymorphism and GD susceptibility (**Table 3**). For limited data, subgroup analyses were not performed.

Tests for publication bias, sensitivity analyses, and heterogeneity

As reflected by Begg's funnel plot and Egger's linear regression test (**Figures 3** and **4**), there

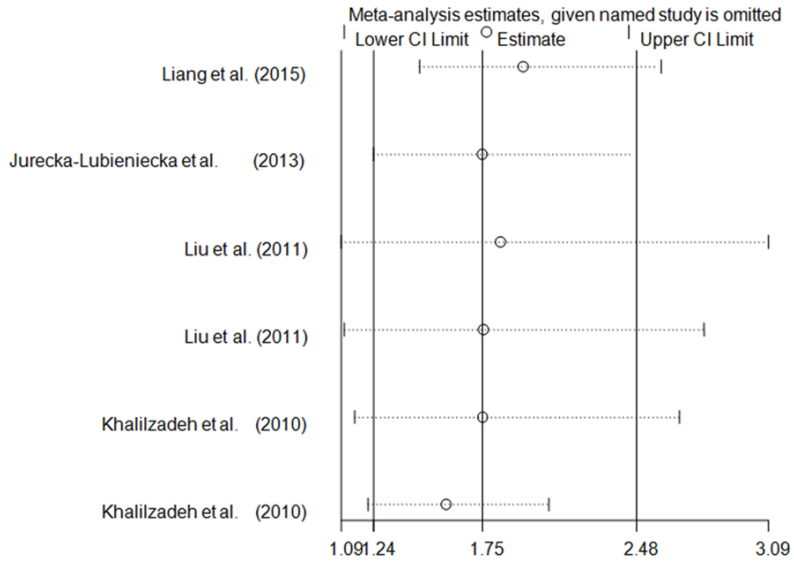

Figure 5. Sensitivity analysis of the influence of GG+AG vs. AA comparison (random-effects estimates for *IL-10* rs1800896 A>G polymorphism).

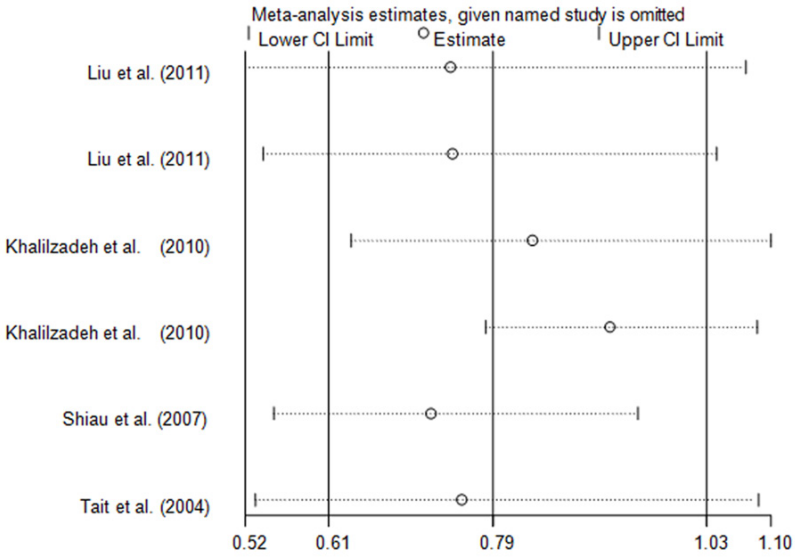

Figure 6. Sensitivity analysis of the influence of C vs. A compare genetic model (random-effects estimates for *IL-10* rs1800872 A>C polymorphism).

was no publication bias in this meta-analysis (*IL-10* rs1800896 A>G polymorphism: G vs. A: Begg's test $P = 0.133$, Egger's linear regression test $P = 0.105$; GG vs. AA: Begg's test $P = 0.806$, Egger's linear regression test $P = 0.736$; GG+AG vs. AA: Begg's test $P = 0.462$, Egger's linear regression test $P = 0.488$; GG vs. AG+AA: Begg's test $P = 1.000$, Egger's linear regression test $P = 0.786$; *IL-10* rs1800872 A>C polymorphism: C vs. A: Begg's test $P = 0.260$, Egger's linear regression test $P = 0.292$; CC vs. AA: Begg's test $P = 0.452$, Egger's linear regression test $P = 0.361$; CC+AC vs. AA: Begg's test $P = 0.133$, Egger's linear regression test $P = 0.237$; CC vs. AC+AA: Begg's test $P = 0.707$, Egger's linear regression test $P = 0.533$).

For *IL-10* rs1800896 A>G and rs1800872 A>C polymorphism, we conducted one-way sensitivity analyses to measure the effect of an individual study on pooled ORs and CIs (**Figures 5** and **6**). The pooled ORs and CIs were similar before and after omitting of each study in turn, suggesting that our findings were relatively stable. As listed in **Table 3**, significant heterogeneity was found in our study. Thus, we assessed the sources of heterogeneity by subgroup meta-analysis (**Table 3**). The results showed that Caucasians subgroup may contribute to the major sources of heterogeneity for both *IL-10* rs1800896 A>G and rs1800872 A>C polymorphism (**Table 3**).

Discussion

GD is an autoimmune disorder and causes the majority of hyperthyroidism cases. Recently, some studies have highlighted that GD is a complex disease with genetic predisposition [24, 25]. Interaction among multiple genetic variants may alter the susceptibility of GD [12-14]. IL-10 has pleiotropic anti-inflammatory and immuno-suppressive effects by inhibiting the production of pro-inflammatory mediators, and decreasing T cell stimulation and/or energy. The level of serum IL-10 is significantly low in healthy subjects; however, it is elevated with GD [14]. These studies also indicated that IL-10 may be a potential biomarker which was correlated with the development of GD [14, 26].

Recently, several epidemiological studies have focused on the association of *IL-10* common polymorphisms with GD risk. The rs1800896 A>G polymorphism in *IL-10* gene has been extensively studied. In 2010, Khalilzadeh *et al.* reported that an A→G intron variant in rs1800896 polymorphism was associated with GD susceptibility [21]. Subsequently, Liu *et al.* reported a similar finding [13]. In this meta-analysis, we found that *IL-10* rs1800896 A>G polymorphism significantly increased the risk of GD, suggesting the presence of the G allele, which led to higher IL-10 serum level, might increase the risk of GD [27]. In a subgroup analysis for ethnicity, *IL-10* rs1800896 A>G polymorphism was associated with the increased risk of GD in Asians and Caucasians. Two case-control studies did not conform to HWE [21]. When we discarded these studies, the association between *IL-10* rs1800896 A>G polymorphism and GD risk was also significant in homozygote comparison, dominant comparison and recessive comparison models (OR, 3.69; 95% CI, 1.48-9.22; $P = 0.005$ for GG vs. AA; OR, 1.57; 95% CI, 1.25-1.98; $P<0.001$ for GG+AG vs. AA and OR, 3.59; 95% CI, 1.44-8.94; $P = 0.006$ for GG vs. AG+AA; **Table 3**), suggesting the robustness of our results.

There were six case-control studies for *IL-10* rs1800872 A>C polymorphism and GD risk. *Shiau et al.* reported a positive signal of *IL-10* rs1800872 A>C polymorphism with GD susceptibility [20]; the other study found that *IL-10* rs1800872 A>C polymorphism was associated with the decrease the risk of GD [21]. As shown in **Table 3**, we found that *IL-10* rs1800872 A>C polymorphism was not associated with the risk of GD. However, *IL-10* rs1800872 A>C variants were correlated with a borderline statistically decreased susceptibility of GD in overall and Caucasians (**Table 3**). For this meta-analysis, only six studies were included, which may restrict power to measure a real influence of *IL-10* rs1800872 A>C polymorphism with GD. Large heterogeneities among the included studies should also be taken into account. In the future, more large scale studies are needed to further explore this potential association. For *IL-10* rs3021097 C>T polymorphism, four case-control studies with 898 GD cases and 1,281 controls were included on the relationship between this polymorphism and GD susceptibility. As listed in **Table 3**, *IL-10* rs3021097 C>T polymorphism was not associated with the risk of GD. For limited data, a subgroup analysis was not performed.

In interpreting these findings, certain limitations in our study should be addressed. Firstly, due to lack of detailed data presented in the included publications, the possible effect of vital risk factors to GD was not assessed, such as age, sex, family history and environmental factors *et al.* Secondly, the sample size of this meta-analysis is relatively small. Thirdly, significant heterogeneity existed in our study, the results should be interpreted with very cautiously. Finally, although Begg's funnel plot and Egger's linear regression test did not detect any bias in the current study, we should also admit the potential of publication bias. Some studies may not have been enrolled online or negative/non-significant studies may be unpublished so far.

In conclusion, despite these limitations, this meta-analysis highlights that *IL-10* rs1800896 A>G polymorphism may contribute to increased susceptibility of GD. Nevertheless, for practical reasons, well-designed association studies with large sample sizes in diverse ethnicities incorporating with functional assessments are warranted.

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Disclosure of conflict of interest

None.

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