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Original Article

Genetic association between *TGF-β1* C509T polymorphism and IgA nephropathy susceptibility: a meta-analysis

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Abstract: Background: Several epidemiological studies have investigated the role of transforming growth factor-β1 (*TGF-β1*) C509T polymorphism in IgA nephropathy (IgAN) susceptibility. However, the results were inconsistent. Objective: This meta-analysis was designed to evaluate the genetic association between C509T polymorphism and IgAN susceptibility. Materials and methods: Thorough literature search of Pubmed, Web of science, Embase and China National Knowledge Infrastructure (CNKI), a total of 10 case-control studies were identified. Odds ratio (OR) along with 95% confidence interval (CI) was calculated to assess the association. Results: Based on the collected data consisting of 1518 IgAN cases and 1716 controls, indicating no significant association between *TGF-β1* C509T polymorphism and overall IgAN predisposed susceptibility (T vs. C, OR 1.06, 95% CI 0.96-1.17; TT vs. CC, OR 1.05, 95% CI 0.87-1.44; CT vs. CC, OR 1.13, 95% CI 0.96-1.33; TT+CT vs. CC, OR 0.89, 95% CI 0.76-1.03; TT vs. CT+CC, OR 1.03, 95% CI 0.86-1.23). However, the subgroup analysis stratified by ethnicity showed evidence for increased risk of IgAN in Caucasian populations. Conclusion: This investigation on the association between *TGF-β1* C509T polymorphism and IgAN predisposed susceptibility reveals that *TGF-β1* C509T polymorphism would not be a risk factor for IgA nephropathy.

Keywords: TGF-β1, polymorphism, IgA nephropathy, gene

Introduction

IgA nephropathy (IgAN) is one of the most common forms of primary glomerulonephritis globally and is an important cause leading to end-stage renal disease (ESRD) [1]. It is estimated that 7%-40% of patients with IgAN succumb to ESRD ultimately, which require dialysis and/or renal-replacement therapy [2]. In addition, IgAN has variable clinical expressions, depending on the interactions between environmental and genetic factors [3]. To date, there lacks well-described diagnostic approaches predicting IgAN susceptibility and the pathological mechanism of IgAN remains unclear. In recent years, a variety of studies have shown that genetic variants of immune genes might affect susceptibility to onset of IgAN [4, 5].

Transforming growth factor-β1 (TGF-β1) plays an important role in regulating biomedical events including extracellular matrix formation, tissue fibrosis and cellular growth [6]. Current evidence has demonstrated that TGF-β1 participated in the pathologic progression of IgA nephropathy [7-9]. In human IgA nephropathy, TGF-β1 can promote glomerular sclerosis through inducing cell proliferation and transforming renal tubular epithelial cells to mesenchymal cells [10]. Human *TGF-β1* gene is located on chromosome 19q13 with seven exons and six introns. The gene polymorphism can affect the genetic expression of target gene, thus altering the physiological functions of TGF-β1. Five polymorphisms of *TGF-β1* gene have been identified: 2 in the promoter region at positions -509 and -800, one in a non-translated region at position +72 and two in the signal sequence at positions +915 and +869. Among them, C509T was shown to be associated the increased secretion of TGF-β1 [11]. However, several studies designed to investigate the

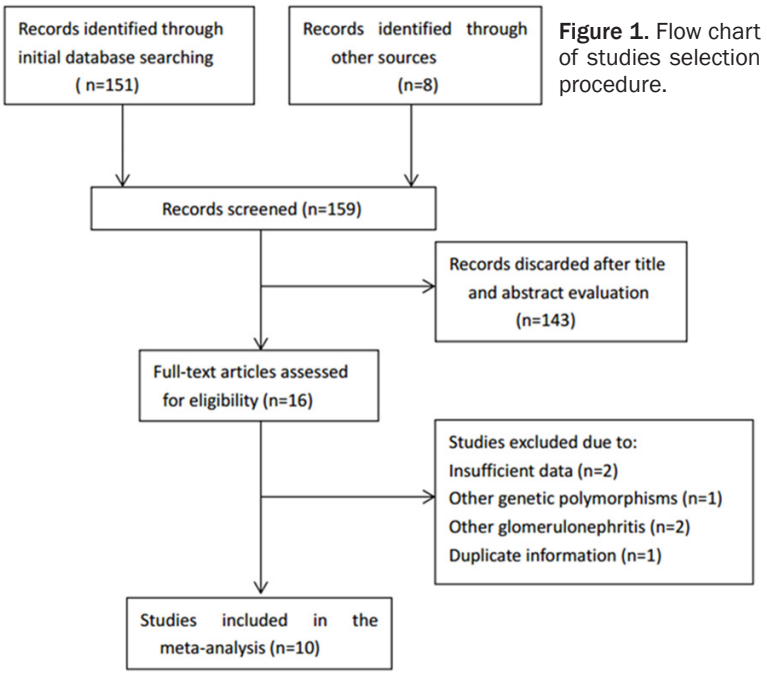

Figure 1. Flow chart of studies selection procedure.

association between this polymorphism and IgA nephropathy showed conflicting results [12-14]. Lim et al. [12] showed that *TGF-β1* C509T polymorphism were significantly different in genotype frequency between IgAN patients and healthy controls in Asian population. Another study conducted by Vuong et al. [15] also showed that *TGF-β1* C509T polymorphism were significantly different between male patients and male controls in allelic model (P=0.0006). However, Sato et al. [14] failed to find obvious difference in *TGF-β1* C509T genotype distribution in Japanese population. Brezzi et al. [13] also found no significant difference in genotype distribution of the focus polymorphism in Caucasians. Furthermore, several studies performed in Asian countries showed the controversial results [12, 14, 16-20]. The discrepancies might mainly attribute to the relatively small sample sizes and subjects with diverse ethnic backgrounds in each single study. As meta-analysis is a credible approach to handle this issue, we carried out a meta-analysis of available data to assess allelic and genotypic frequencies of *TGF-β1* C509T polymorphism in IgAN risk.

Materials and methods

Literature search

A thorough literature search was performed using the Pubmed, Web of science, Embase and China National Knowledge Infrastructure (CNKI) databases. The last search was conducted on September 20, 2015. The search strategy was as follows: (IgA nephropathy OR IgA nephritis OR IgAN) AND (transforming growth factor β1 OR TGFβ1 ORTGF beta) AND (polymorphism OR mutation OR variant). There was no language limitation. In addition, we manually searched the reference lists and reviews to identify relevant articles. The ethical approval was not necessary for our study because it was a meta-analysis.

Inclusion and exclusion criteria

The inclusion criteria were: (1) designed as case-control studies; (2) the association between *TGF-β1* C509T polymorphism and susceptibility of IgAN must be examined; (3) sufficient data available to calculate odds ratios (ORs) with 95% confidence intervals (CIs). Exclusion criteria were: (1) review articles, comments and editorials; (2) insufficient information on the distribution of *TGF-β1* C509T genotypes; (3) case-only studies; (4) animal studies. There was no language limitation. The latest paper was recruited in the final analysis if several publications reported the similar data from the same study group.

Data extraction

Based on the selection criteria listed above, two authors independently extracted the following information from each included study: first author, year of publication, study country, ethnicity, genotyping method and genotype distributions. Disagreements were resolved by consulting the third reviewer.

Statistical analysis

In order to evaluate the relationship between *TGF-β1* C509T polymorphism and the susceptibility of IgAN, the ORs and corresponding 95% CIs were calculated. The combined ORs were examined for T vs. C, TT vs. CC, CT vs. CC, TT+CT vs. CC and TT vs. CT+CC models. Subgroup

Table 1. Characteristics of studies included in this meta-analysis

Author	Year	Country	Ethnicity	Method	Case				Controls				HWE
					Sample size	CC	CT	TT	Sample size	CC	CT	TT	
Curturan [30]	2004	Italy	Caucasian	PCR-RFLP	95	36	48	11	105	39	45	21	0.23
Sato [14]	2004	Japan	Asian	PCR-RFLP	329	89	174	66	297	76	157	64	0.31
Lim [12]	2005	Korea	Asian	PCR-RFLP	82	20	29	33	55	11	31	13	0.34
Xue [16]	2005	China	Asian	PCR-RFLP	387	136	183	68	202	66	98	38	0.88
Qin [17]	2008	China	Asian	PCR-RFLP	119	28	51	40	116	34	59	23	0.78
Brezzi [13]	2009	Italy	Caucasian	PCR	105	27	55	23	200	51	95	54	0.48
Vuong [15]	2009	Sweden	Caucasian	Taqman	209	88	104	17	468	245	185	38	0.71
Li [18]	2011	China	Asian	PCR-RFLP	38	10	17	11	42	12	20	10	0.77
Jung [19]	2012	Korea	Asian	PCR	69	14	35	20	146	43	63	40	0.10
Sun [20]	2013	China	Asian	PCR	85	23	45	17	85	28	39	18	0.52

PCR-RFLP=Polymerase chain reaction-restriction fragment length polymorphism, PCR=Polymerase chain reaction, Taqman=TaqManSNP, HWE=Hardy-Weinberg equilibrium.

Table 2. Stratified analysis of the TGF-β1 C509T polymorphism on IgA nephropathy risk

Category (n)	Genetic model	Test of association	P	Analysis model	Heterogeneity	
		OR (95% CI)			*P* value	I^2 (%)
Overall (10)	T vs. C	1.06 (0.96-1.17)	0.268	F	0.256	20.3
	TT vs. CC	1.05 (0.87-1.44)	0.677	F	0.437	0
	CT vs. CC	1.13 (0.96-1.33)	0.151	F	0.327	12.6
	TT+CT vs. CC	0.89 (0.76-1.03)	0.157	F	0.686	0
	TT vs. CT+CC	1.03 (0.86-1.23)	0.767	F	0.132	34.5
Caucasian (3)	T vs. C	1.01 (0.76-1.34)	0.546	R	0.104	55.8
	TT vs. CC	0.89 (0.59-1.33)	0.57	F	0.322	11.7
	CT vs. CC	1.37 (1.05-1.78)	0.02	F	0.478	0
	TT+CT vs. CC	0.82 (0.65-1.05)	0.068	F	0.7	0
	TT vs. CT+CC	0.77 (0.54-1.11)	0.167	F	0.435	0
Asian (7)	T vs. C	1.06 (0.94-1.20)	0.353	F	0.344	11.2
	TT vs. CC	1.12 (0.87-1.44)	0.395	F	0.431	0
	CT vs. CC	1.00 (0.81-1.23)	0.987	F	0.488	0
	TT+CT vs. CC	0.93 (0.77-1.13)	0.715	F	0.518	0
	TT vs. CT+CC	1.14 (0.92-1.41)	0.239	F	0.171	33.7

F: Fixed-effects model; R: Random-effects model. When $P_{Heterogeneity}$<0.1 or I^2>50%, the random-effects model was used, otherwise the fixed-effects model was used.

analysis was conducted according to ethnicity. Hardy-Weinberg equilibrium (HWE) of the control groups was tested by the χ^2 test.

The Chi-square test based Q-statistic as well as I^2 statistic were adopted to test the heterogeneity across studies. P<0.010 or I^2>50% represented large heterogeneity, then the random-effects model [21] was used; otherwise, the fixed-effects model [22] was performed. Potential publication bias was tested by Begg's test and Egger's test [23]. All statistical analyses were performed using STATA 12.0 (Stata Corporation, College Station, TX). A level of P<0.05 was considered as statistically significant.

Results

Characteristics of the studies

Based on our search strategies, 159 papers were identified through initial searching. After the title and abstracts were screened, 143 publications were eliminated for obvious irrelevance to the study issue. 16 full-length articles were examined for eligibility, 2 of which were discarded due to insufficient data for risk estimation [24, 25]; 2 of which were excluded because the studied disease were not IgAN [26, 27]; 1 of which was eliminated because it failed to report the interest gene polymorphism [28]; 1 of which was excluded for duplicate

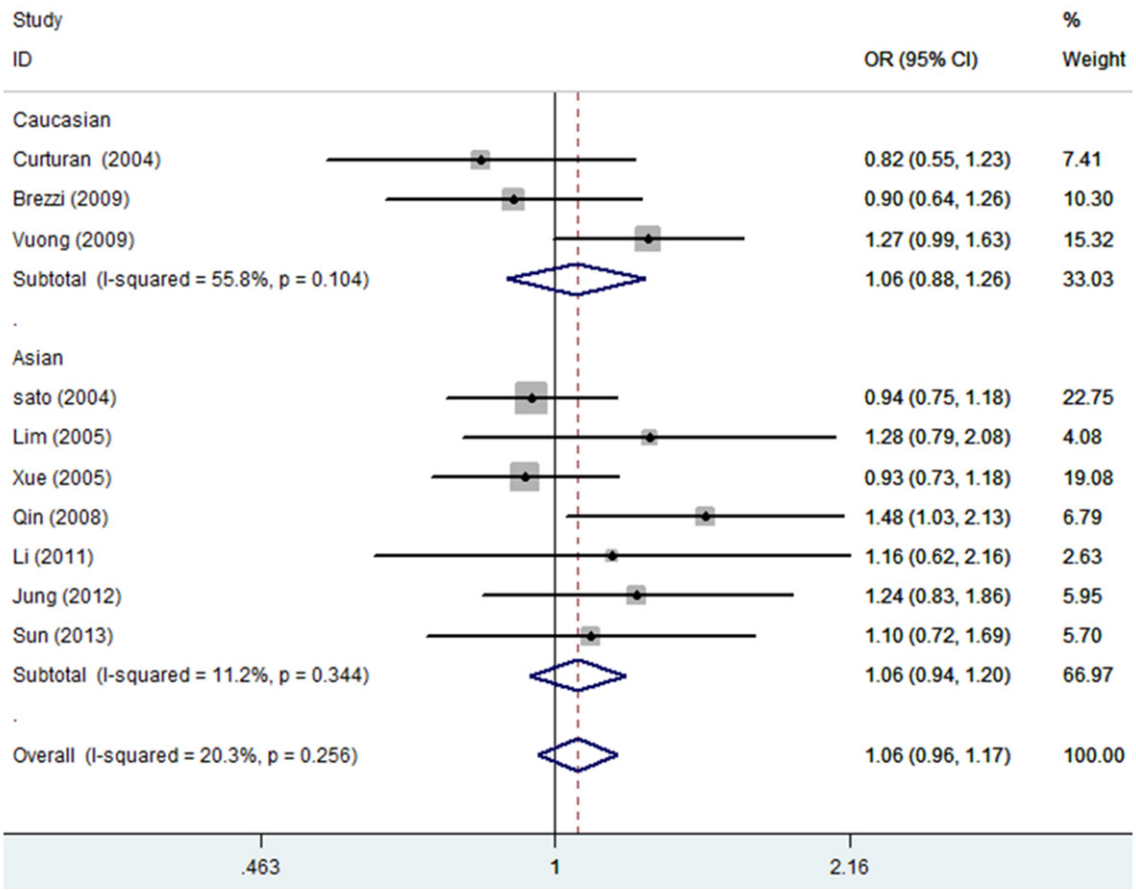

Figure 2. Forest plot of the association between *TGF-β1* C509T polymorphism and IgA nephropathy susceptibility under T vs. C genetic model.

study from the same group [29]. Finally, 10 studies published between 2004 and 2013 were included in this meta-analysis [12-20, 30]. The flow chart of the literature selection was shown in **Figure 1**. There were three studies [13, 15, 30] of Caucasian populations and seven studies [12, 14, 16-20] of Asian populations. 60% of the studies used PCR-RFLP genotyping method, 30% of the studies used PCR and 10% of the studies used Taqman. The genotype distributions of the control populations in all studies were in accordance with HWE. The characteristics of the included studies were described in **Table 1**.

Quantitative analysis

The main meta-analysis results were listed in **Table 2**. Either the fixed effects model or the random effects model was used in this analysis. Based on 1518 cases and 1716 controls for *TGF-β1* C509T, the overall analysis did not suggest statistical evidence of a significant association between *TGF-β1* C509T and IgAN susceptibility in all tested genetic models: T vs. C model: OR 1.06, 95% CI 0.96-1.17 (**Figure 2**), TT vs. CC model: OR 1.05, 95% CI 0.87-1.44 (**Figure 3**), CT vs. CC model: OR 1.13, 95% CI 0.96-1.33 (**Figure 4**), TT+CT vs. CC model: OR 0.89, 95% CI 0.76-1.03 (**Figure 5**), TT vs. CT+CC model: OR 1.03, 95% CI 0.86-1.23 (**Figure 6**). In subgroup analysis according to ethnicity, significantly increased IgA nephropathy risk was found in Caucasian populations on CT vs. CC model: OR 1.37, 95% CI 1.05-1.78 (**Table 2**). Otherwise, in other genetic models, there was no significant association between *TGF-β1* C509T and IgA nephropathy susceptibility either in Caucasians or in Asians. Generally, there was no significant heterogeneity among the studies of the *TGF-β1* C509T polymorphism and IgAN. Otherwise, in subgroup analysis, significant between-study heterogeneity was found in the T vs. C genetic model (I^2=55.8%) in

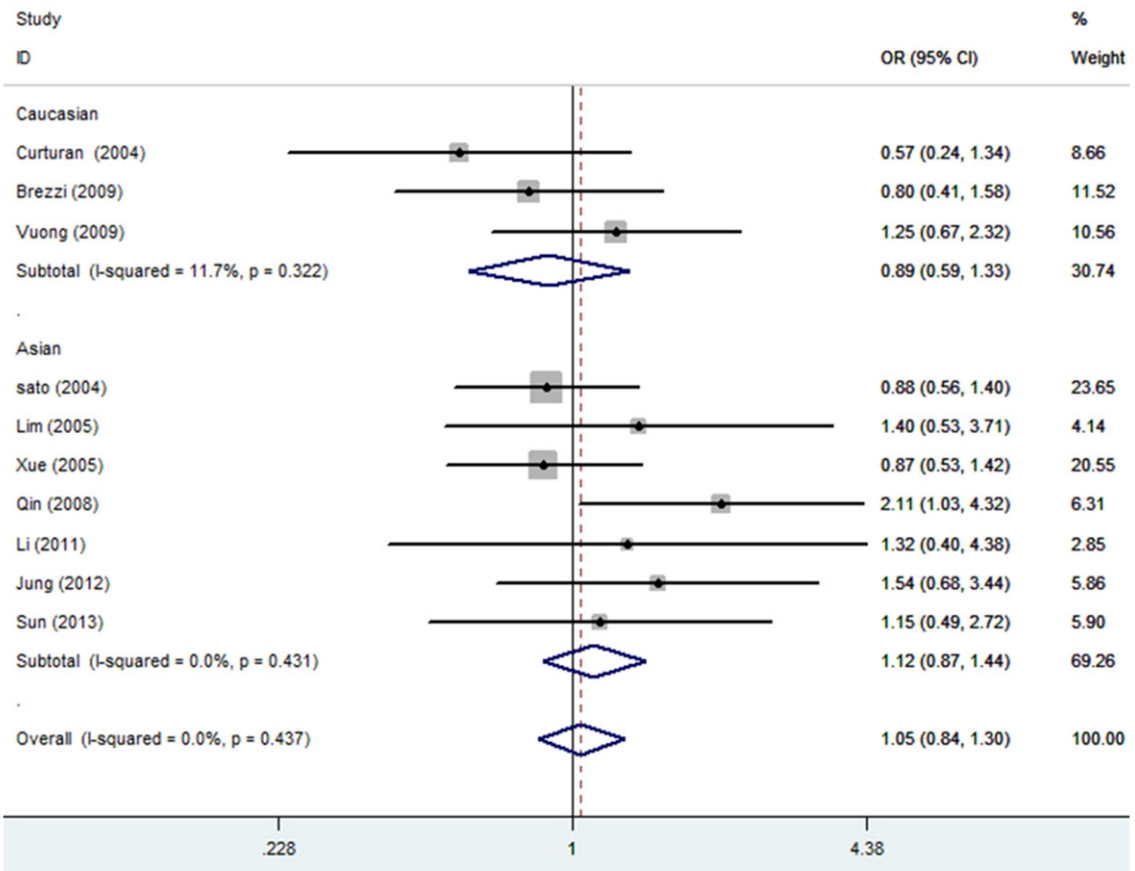

Figure 3. Forest plot of the association between *TGF-β1* C509T polymorphism and IgA nephropathy susceptibility under TT vs. CC genetic model.

Caucasian populations group, where random effects model was used correspondingly. Removing the single study one by one did not alter the substantial results of the meta-analysis, suggesting our results were statistically credible and robust.

Publication bias

According to Begg's test (**Figure 7**) and Egger's test, there was no significant publication bias in this meta-analysis (Begg's P=0.421, Egger's P=0.572, respectively).

Discussion

TGF-β1, first discovered in 1978, is a multifunctional cytokine which triggers the TGF-β1/Smad signaling pathway [31]. Through combination with the receptor on cell surface, TGF-β1 takes part in the regulating process of multimerization and phosphorylation of the downstream proteins including the R-Smads family. There existed evidence that activation of TGF-β1 plays a role in the progression of IgA nephropathy and TGF-β1 expression was elevated in severe IgA nephropathy patients [9, 32]. Genetic variants encoding could potentially influence the expression of TGF-β1, thus change the process of IgAN development. A variety of studies have explored the association between genetic susceptibility and IgA nephropathy but the results were inconsistent [13-15, 19, 30]. Thus, we performed a meta-analysis in order to look deeper into the association between candidate gene and IgAN because adequate sample size was included.

In the present study, based on 10 case-control studies including 1518 IgAN patients and 1716 controls, we showed that *TGF-β1* C509T gene polymorphism was in association with overall IgAN risk of all genetic models. Notably, subgroup analysis stratified by ethnicity revealed significantly elevated risk of IgAN in Caucasian populations, but not in Asian populations (CT

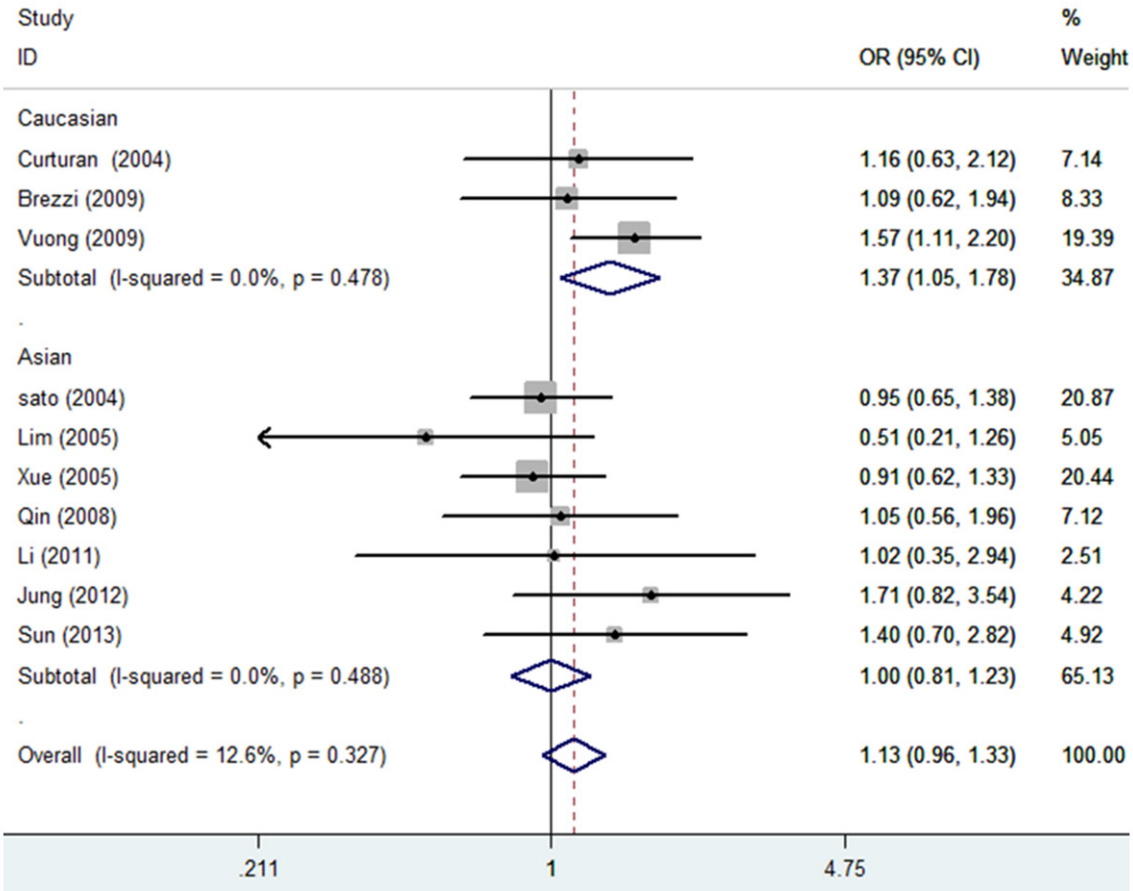

Figure 4. Forest plot of the association between *TGF-β1* C509T polymorphism and IgA nephropathy susceptibility under CT vs. CC genetic model.

vs. CC model: OR 1.37, 95% CI 1.05-1.78). There was no significant heterogeneity among the studies, indicating the uniformity of the included studies. Publication bias was not found in this meta-analysis by Egger's test and Begg's funnel plots.

A variety of studies have investigated the association between *TGF-β1* C509T polymorphism and IgAN by the approach of meta-analysis [33-36]. All of the studies failed to show statistical significance on the issue of interest. Nevertheless, the results presented disparities concerning subgroup analysis by ethnicity. Xue's study and Wang's study indicated significant association between C509CT polymorphism and IgA nephropathy risk in Caucasian populations, which was in accordance with the results of this study [33, 34]. Otherwise, Li et al failed to find this association between genetic susceptibility and IgAN neither in Caucasian nor in Asian populations [36]. There are 2 explanations for this discrepancy. First, each individual study recruited papers published in English or in both English and Chinese, which could contribute to this inconsistency due to language bias. Additionally, each study included limited number of subjects and several studies only adopted limited genetic models [34, 35] which could under power the statistical efficiency of every single meta-analysis. To the best of our knowledge, the current study included 10 original investigations, which accounts most among the published meta-analysis investigating association between *TGF-β1* C509T polymorphism and IgAN. Furthermore, both papers published in English and Chinese were retrieved, eliminating the language bias. Last but not least, we adopted five genetic models to test the stability of our results. Because of the inherent nature of meta-analysis, the sample size and inclusion of studies from diverse ethnic backgrounds are the strength factors guaranteeing the statistical power of the results. From this point of view,

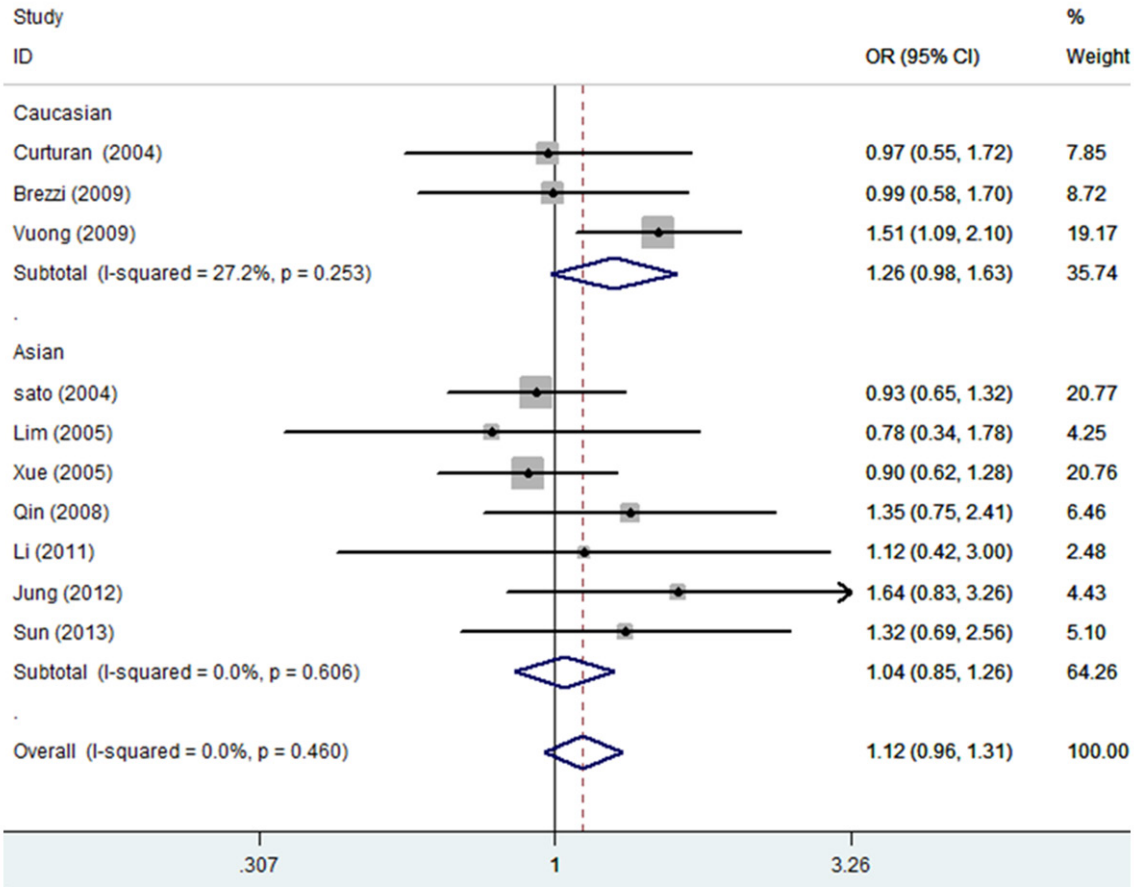

Figure 5. Forest plot of the association between *TGF-β1* C509T polymorphism and IgA nephropathy susceptibility under TT+CT vs. CC genetic model.

our study with the largest simple size and inclusion of more recent publications presented more convincible data.

Recently, a variety of genome-wide association studies (GWAS) investigated the susceptibility loci for IgAN [37-39]. Feehally et al. reported that HLA region contained strongest susceptibility alleles to IgAN in European population [37]. Gharavi et al. found that three independent lociin MHC and deletion of CFHR1 and CFHR3 were in association with increased risk of IgAN [38]. Moreover, Yu et al. showed that *TNFSF13*, *DEFA* and *MHC* gene variant were associated with IgAN risk in Chinese Han groups [39]. Notably, *TGF-β1* C509T polymorphism was not included in the susceptibility loci in the aforementioned GWAS, this discrepancy may be explained by the subjects with different races in our meta-analysis. Feehally et al. [37] only included European subjects and Yu et al. [39] only recruited Han Chinese, the results of the two studies were different which demonstrated the complexity of the susceptibility SNP with IgAN risk in different ethnicities. Although Gharavi et al. [38] also identified loci in MHC were related with risk of IgAN, which was in accordance with the results of Yu's study [39]. However, we noticed that the a large amount of subjects included in Gharavi's study were Han Chinese, which was partial identical as the subjects in Yu's study, thus, it could not be ruled out the possibility that the identical susceptibility loci was attributed to the subjects with the same ethnicity included in the two studies. Given this, our meta-analysis included both Caucasian and Asian subjects, the results of our study were more comprehensive and reliable, although we found *TGF-β1* C509 Tpolymorphism was associated with 1.37-fold higher risk of IgAN in Caucasian under CT vs. CC model, which did not surpass the allele odds ratios used in GWAS [38].

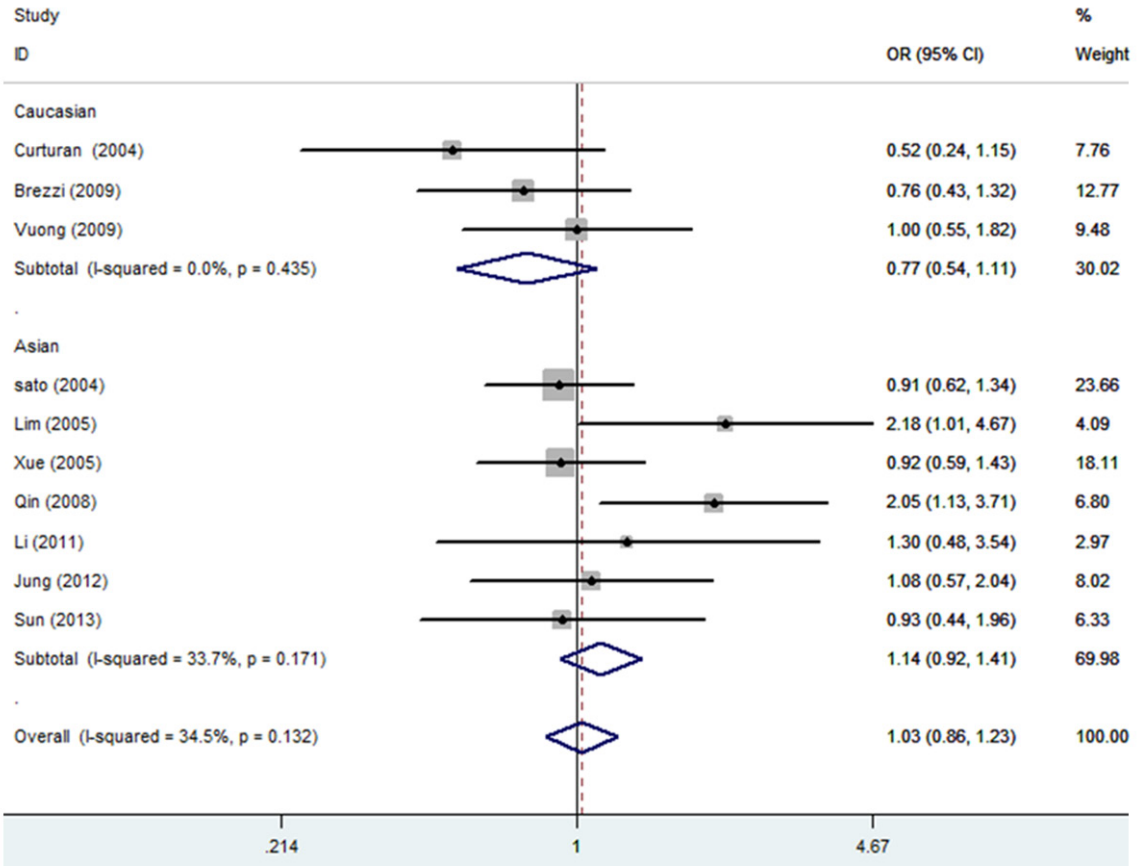

Figure 6. Forest plot of the association between *TGF-β1* C509T polymorphism and IgA nephropathy susceptibility under TT vs. CT+CC genetic model.

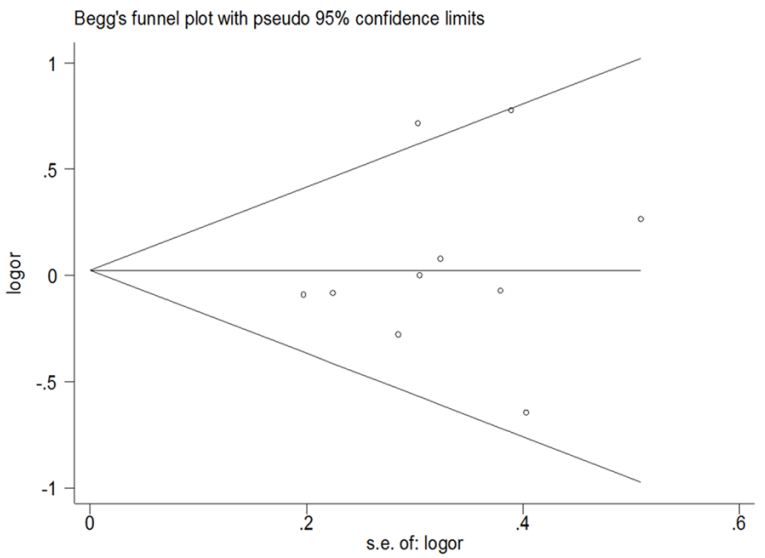

Figure 7. The funnel plot of the meta-analysis of *TGF-β1* C509T polymorphism and IgA nephropathy susceptibility (under TT+CT vs. CC model).

Several limitations should be addressed in this meta-analysis. First, subgroup analysis was conducted only divided by ethnicity. However, more potential risk confounders could not be identified because the single studies provided lacking detailed data. Furthermore, IgAN susceptibility was demonstrated to be related to *TGF-β1* C509T polymorphism in Caucasians. In the current meta-analysis, only 3 publications based on Caucasians was recruited. We could not exclude the possibility that the elevated risk was obtained by chance.

In conclusion, this study investigating the correlation between C509T polymorphism and IgAN susceptibility indicated that *TGF-β1* C509T polymorphism did not modulate overall IgA nephropathy risk. Increased risk of IgAN in

Caucasian populations with this polymorphism was found. More large sample-sized and well-designed studies are needed to clarify the genetic association between the *TGF-β1* C509T polymorphism and IgAN risk.

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Disclosure of conflict of interest

None.

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