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Original Article

Tumor necrosis factor-α (-308G/A, -238G/A and -863C/A) polymorphisms and coronary heart disease risk in Chinese individuals

Yanfen Guo, Xiaoqun Zhang, Jinling Fu, Xiao Zhang, Houzhi Shan, Na Shi, Liqiu Yan

Department of Cardiology, Cangzhou Central Hospital, Hebei Medical University, No. 16, Xinhua West Road, Cangzhou 061000, China

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Abstract: Previous studies investigating the association between tumor necrosis factor-alpha (TNF-α) polymorphisms and coronary heart disease (CHD) risk has provided inconsistent results. To further evaluate the influence of TNF-α polymorphisms on CHD risk, we conducted a meta-analysis in the Chinese population. To identify eligible studies, we searched on PubMed and Chinese databases through April 2016. To determine the strength of the associations, we utilized pooled odds ratios (ORs) and 95% confidence intervals (CIs). This meta-analysis included 12 studies with 3789 CHD cases and 3939 controls. In general, our findings indicated that a significant association existed between TNF-α-308G/A, -863C/A polymorphisms and the risk of CHD in the studied Chinese population (AA vs. GG: OR=1.53, 95% CI=1.05-2.23; AA vs. GG+GA: OR=1.50, 95% CI=1.03-2.18; A vs. C: OR=0.70, 95% CI=0.58-0.84; AA+CA vs. CC: OR=0.63, 95% CI=0.51-0.78). In conclusion, this meta-analysis provides evidence that TNF-α-308G/A polymorphism is a risk factor for developing CHD in the Chinese population, whereas TNF-α-863C/A polymorphism might be a protective factor for CHD. Further studies in other ethnic groups are required for definite conclusions.

Keywords: Meta-analysis, tumor necrosis factor-alpha, polymorphism, coronary heart disease

Introduction

Coronary heart disease (CHD) is widely accepted as a chronic inflammatory disease [1]. In the last century, there has been rapid increases in the global prevalence of CHD, which has become the important cause of cardiovascular mortality all over the world, is >4.5 million deaths in the developing countries [2]. A growing body of evidence indicates that several risk factors may induce CHD, including age, sex, hypertension, diabetes mellitus, hypercholesterolemia, family history and smoking history [3]. Nevertheless, CHD develops during the lifespan of only a part of the exposed individuals even in the population at risk, revealing that principal genetic predetermination might be a key factor contributing to the susceptibility of these individuals to the disease.

Recently, some commonly inherited low-penetrance genes have been recognized as genes possibly responsible for susceptibility to CHD. One of their major representatives is tumor necrosis factor-alpha (TNF-α), which is an inflammatory mediator that plays important roles in inflammatory and immune responses [4]. Several single-nucleotide polymorphisms (SNPs) have been identified in the TNF-α promoter [5]. Of these SNPs, -308G/A, -238G/A and -863C/A have been the three most extensively investigated loci of polymorphisms. Herrmann and co-workers were the first to study and report the relationship between the polymorphisms of TNF-α and CHD among the Caucasian population [6]. Thereafter, the effects of TNF-α polymorphisms on the risk of CHD was explored in a large number of investigations. Nevertheless, no evident consensus was established. This gene has been the subject of meta-analyses of examinations conducted in other ethnic groups that have led to in consistent results [7-10]. In evaluating the association of TNF-α polymorphisms with the

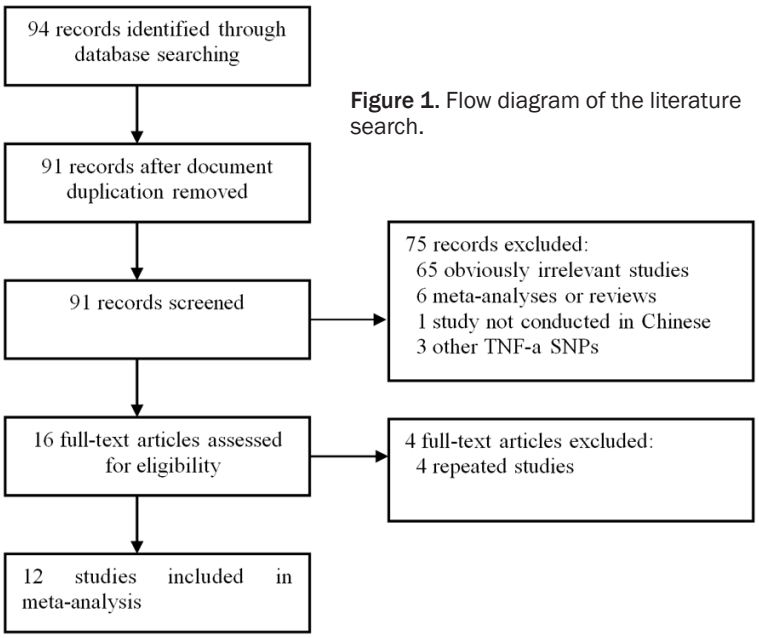

Figure 1. Flow diagram of the literature search.

risk of CHD in a solely Chinese population, we conducted the present updated meta-analysis to reduce the influence of the diverse genetic backgrounds.

Materials and methods

Search strategy and selection criteria

Using the databases of PubMed and Chinese databases, we searched all literature sources published before April 2016 for studies examining the relationship between TNF-α polymorphisms and the risk of CHD. The search keywords were used: (TNF or tumor necrosis factor) and (coronary heart disease or coronary artery heart disease) and polymorphism and (Chinese or China or Taiwan). Furthermore, we carefully inspected the lists with references of the articles and reviews that had been extracted. No language restriction was applied.

To be eligible for inclusion, the investigations had to have fulfilled the following requirements: (1) case-control or cohort studies describing the association between TNF-α-308G/A, or -238G/A or -863C/A polymorphisms and CHD, (2) studies with sufficient genetypes data in cases and controls, (3) all included participants were Chinese. The following studies were excluded: (1) non-cohort or non-case-control investigations; (2) duplicates of earlier publications; (3) their data were incomplete; (4) reviews, letters, editorial articles, or meta-analyses.

Data extraction

Two reviewers independently extracted data from each study. Disputes were settled by discussion. Titles and abstracts of all potentially relevant articles were screened to determine their relevance. Entire articles were carefully examined if they had vague titles and abstracts. We collected the following information from each study: surname of the first author, year of publication, controls sources, overall numbers of cases and controls, as well as genotypes data were identified.

Statistical analysis

We performed meta-analyses using: (1) allelic contrast, (2) contrast of homozygotes, (3) recessive, and (4) dominant models. Allele frequencies at the TNF-α polymorphisms from the respective studies were determined by the allele counting method. The association of TNF-α polymorphisms and CHD risk was estimated by odds ratio (ORs) with 95% confidence intervals (CIs). The significance of the pooled OR was determined by a Z-test. The between-study heterogeneity, and Hardy-Weinberg equilibrium (HWE) in controls were assessed by chi-square based Q-test [11]. For conducting sensitivity analyses, the methods of the random-effects model of Mantel-Haenszel and the fixed-effects model of DerSimonian and Laird were utilized. We employed Begg's funnel plot and Egger's linear regression tests to evaluate the publication bias. All statistical tests were performed using the Stata, version 12 (StataCorp LP, College Station, TX). A *P* value less than 0.05 was considered to be statistically significant.

Results

Description of included studies

As illustrated in the trial flow chart presented in **Figure 1**, a total of 91 articles that examined the association between TNF-α polymorphisms

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

References	Sources of controls	Case number	Control number	Cases			Controls			HWE	
										χ^2	*P*
TNF-α-308G/A				GG	GA	AA	GG	GA	AA		
Chen 2001	PB	40	30	29	9	2	21	8	1	0.05	0.827
Li 2003	PB	112	158	102	10	0	138	20	0	0.72	0.396
Xiang 2004	PB	162	182	148	14	0	163	19	0	0.55	0.458
Hou 2009	PB	804	914	707	94	3	802	110	2	0.77	0.379
Sun 2009	PB	73	138	54	17	2	118	20	0	0.84	0.359
Liu 2011	PB	422	283	336	28	58	241	13	29	176.91	0.000
Chu 2012	PB	955	1020	758	189	8	808	205	7	2.41	0.120
Zhao 2015	PB	783	749	627	145	11	617	126	6	0.02	0.876
TNF-α-238G/A				GG	GA	AA	GG	GA	AA		
Xiang 2004	PB	162	182	154	7	1	176	6	0	0.05	0.821
Hou 2009	PB	804	905	740	63	1	819	86	0	2.25	0.133
Sun 2009	PB	73	138	70	3	0	129	8	1	3.98	0.046
Liu 2011	PB	420	328	388	28	4	311	11	6	83.44	0.000
TNF-α-863C/A				CC	CA	AA	CC	CA	AA		
Pan 2008	PB	90	115	67	20	3	70	38	7	0.36	0.550
Zhang 2011	PB	107	115	76	22	9	74	38	3	0.53	0.466
Xiang 2004a	PB	121	115	91	29	1	72	41	2	2.03	0.155
Liu 2011	PB	435	328	316	111	8	219	99	10	0.09	0.768
Liang 2016	PB	120	120	90	26	4	67	48	5	1.00	0.317

PB: population-based.

Table 2. Association of the XRCC1 gene polymorphisms on NPC susceptibility

Polymorphism		n	Orr (95% CI)	ORf (95% CI)	P_h
TNF-α-308G/A	A vs. G	8	1.12 (0.95-1.32)	1.11 (10.99-1.24)	0.151
	AA vs. GG	6	1.51 (1.03-2.20)	1.53 (1.05-2.23)	0.854
	AA vs. GG+GA	6	1.48 (1.01-2.15)	1.50 (1.03-2.18)	0.876
	AA+GA vs. GG	8	1.09 (0.93-1.28)	1.08 (0.95-1.23)	0.260
TNF-α-238G/A	A vs. G	4	0.97 (0.72-1.30)	0.95 (0.73-1.24)	0.355
	AA vs. GG	4	0.80 (0.28-2.30)	0.86 (0.32-2.29)	0.578
	AA vs. GG+GA	4	0.79 (0.28-2.25)	0.84 (0.31-2.25)	0.562
	AA+GA vs. GG	4	1.02 (0.69-1.51)	0.96 (0.73-1.27)	0.256
TNF-α-863C/A	A vs. C	5	0.69 (0.57-0.85)	0.70 (0.58-0.84)	0.312
	AA vs. CC	5	0.74 (0.37-1.48)	0.76 (0.44-1.33)	0.264
	AA vs. CC+CA	5	0.87 (0.43-1.76)	0.89 (0.51-1.55)	0.244
	AA+CA vs. CC	5	0.63 (0.51-0.78)	0.63 (0.51-0.78)	0.382

ORr: Odd ratio for random-effects model; ORf: Odd ratio for fixed-effects model; P_h: *P* value for heterogeneity test.

and the risk of CHD were identified after document duplication in the different databases was removed. According to the inclusion and exclusion criteria, twelve studies [12-23] were included and 79 articles were excluded. The publication year of involved studies ranged from 2001 to 2016. In total, 3789 CHD cases and 3939 controls were included in this meta-analysis. The source of controls in all studies was population-based. Eight articles studied on TNF-α-308G/A, 4 articles on TNF-α-238G/A, and 5 articles on TNF-α-863C/A. The properties of included investigations are listed in **Table 1**.

Meta-analysis

The summary of the meta-analysis on the association between TNF-α gene polymorphisms and CHD in the Chinese population is shown in **Table 2**.

TNF-α-308G/A polymorphism and CHD

Eight studies determined the relationship between the TNF-α-308G/A polymorphism and CHD risk in the Chinese population [12-19]. The total sample size for patients with CHD and controls was 3351 and 3474, respectively.

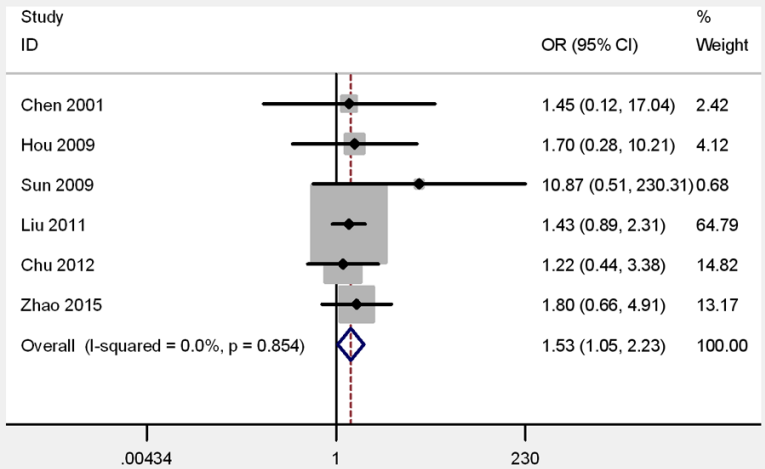

Figure 2. The forest plot on the association between TNF-α-308G/A polymorphism and CHD risk under homozygotes model.

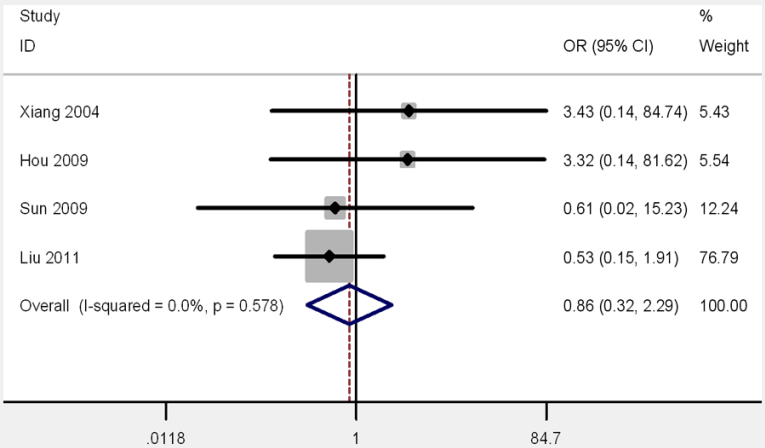

Figure 3. The forest plot on the association between TNF-α-238G/A polymorphism and CHD risk under homozygotes model.

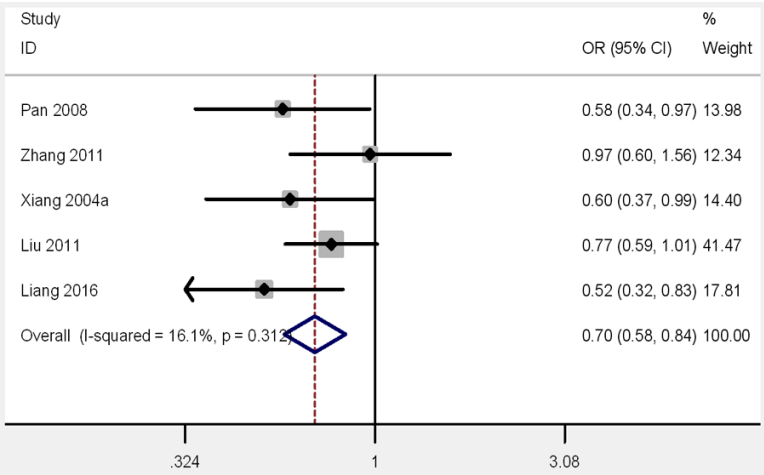

Figure 4. The forest plot on the association between TNF-α-863C/A polymorphism and CHD risk under allele model.

Meta-analysis revealed that TNF-α-308AA variant was significantly associated with an increased risk of CHD (AA vs. GG: OR=1.53, 95% CI=1.05-2.23; AA vs. GG+GA: OR=1.50, 95% CI=1.03-2.18; **Figure 2**).

TNF-α-238G/A, -863C/A polymorphisms and CHD

Four studies including 1459 cases and 1553 controls identified an association between the TNF-α-238G/A polymorphism and CHD risk in the Chinese population [14-17], while five studies including 873 cases and 793 controls for TNF-α-863C/A [17, 20-23]. No significant association was observed between TNF-α-238G/A and CHD in all the models (**Figure 3**). However, a significant decreased association was observed between TNF-α-863C/A polymorphism and CHD (A vs. C: OR=0.70, 95% CI=0.58-0.84; AA+CA vs. CC: OR=0.63, 95% CI=0.51-0.78; **Figure 4**).

Publication bias diagnosis and sensitivity analysis

The Begg's funnel plot and Egger's test were performed to access the publication bias of literatures for TNF-α and CHD. As showed in **Figures 5**, **6**, the shape of the funnel plots did not reveal obvious asymmetry. Similarly, the Egger's test indicated that there was no evidence of obvious publication bias in the reviewed studies (-308G/A: t= 0.61, *P*=0.583; -863C/A: t= -1.01, *P*=0.389).

We employed both models (the fixed-effect model and random-effect model) to compare their differences and evaluate meta-analysis sta-

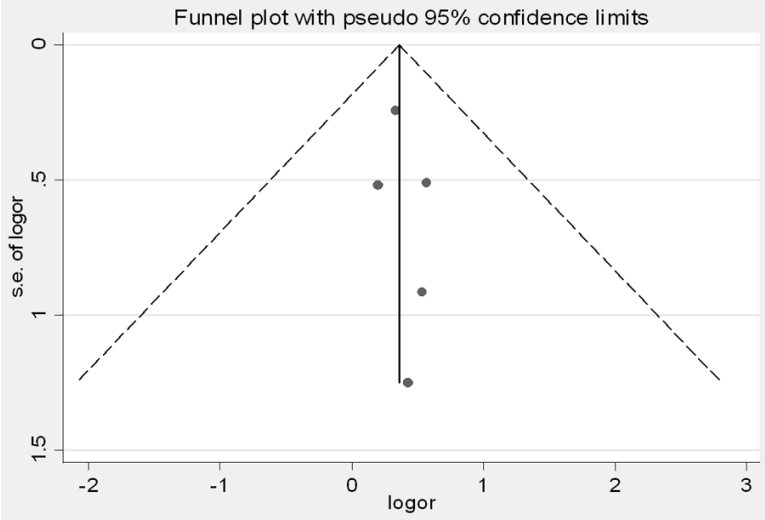

Figure 5. Publication bias assessment of TNF-α-308G/A polymorphism and CHD risk.

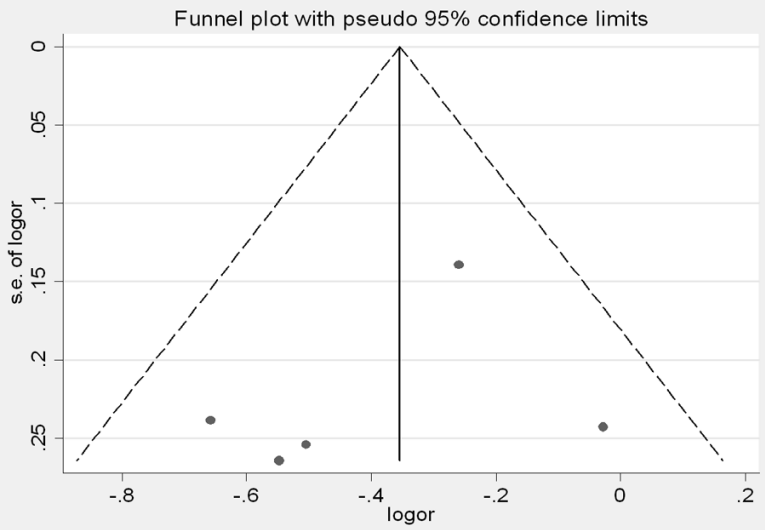

Figure 6. Publication bias assessment of TNF-α-863C/A polymorphism and CHD risk.

bility and sensitivity. No results were materially altered (**Table 2**). Thus, the sensitivity analysis results indicate that the data contained in the present meta-analysis are comparatively credible and stable.

Discussion

At present, it is accepted that CHD is a typical complex disease with multifactorial etiology. Both genetics and environmental factors could contribute to its incidence and development. This implication has promoted the considerable scientific interest and the search for discovery of the genes involved in CHD development. Since the first negative association between TNF-α and CHD was reported [6], many studies have been undertaken to investigate this relationship. However, the results of individual studies have been inconclusive so far. Regional and racial differences is one likely reason for these contradictory results [24]. This difference may be influenced by the environment and by dietary and lifestyle habits [25]; however, it remains unclear whether TNF-α affects the risk of CHD for Chinese and Western patients differently. Therefore, we conducted this meta-analysis to provide a more precise estimate of the association between TNF-α and the susceptibility to CHD in Chinese individuals, in order to reduce the impact of regional and racial differences.

Three polymorphisms in TNF-α (-308G/A, -238G/A and -863C/A) have been frequently examined in the studies on CHD susceptibility. In this meta-analysis, we found that TNF-α-308G/A polymorphism might be a low penetrent risk factor for CHD in the Chinese population, whereas TNF-α-863C/A polymorphism might be a protective factor for CHD in the Chinese population, and there may be no association between -238G/A polymorphism and CHD risk. The explanation for the results may be that functional variants in the TNF-α gene may affect the binding of p50-p50 to an NF-κB site [26]. Such as, the TNF-α-863C/A variant which binds p50-p50 results in a reduction of lipopolysaccharide-inducible gene expression in primary human monocytes [26]. The null association between TNF-α-238G/A polymorphism and CHD risk may be because there were only limited studies in the analysis.

Till now, there are several published meta-analyses regarding TNF-α polymorphisms and CHD risk [7-10, 18]. Of these, only one meta-analysis has reported that TNF-α-308A variant is associated with CHD risk in Caucasians [10], whereas other four meta-analyses reported that TNF-α polymorphisms were not associated with CHD risk [7-9, 18]. In comparison, this current meta-analysis is strengthened by investigating the association only in the Chinese ethnicity, which revealed significant results in Chinese individuals for TNF-α-308G/A and -863C/A. We were able to explore the association may not be influenced by genetic backgrounds and living environment. Sensitivity analyses and publication bias test confirmed the reliability and stability of the meta-analysis. Therefore, our results provide a persuasive indication for the existence of an association between TNF-α polymorphisms and CHD in the Chinese population.

Several limitations of this study should be figured out. First, as all the included studies were limited within Chinese patients with CHD, our conclusion may not be reasonably extrapolated for other ethnic groups. Second, lack of individual participants' data has restricted further adjustments of the results by potential valuable co-variables. Third, gene-gene, and gene-environmental interactions were not addressed in this meta-analysis because of the lack of sufficient information.

In conclusion, the results of this meta-analysis suggest that the TNF-α-308G/A polymorphism is a risk factor for developing CHD in the Chinese population, whereas TNF-α-863C/A polymorphism might be a protective factor for CHD. Ethnicity seems to play an important role in the genetic association of the disease. Further studies in other ethic groups are required in order to explore the broader role that these polymorphisms play in the pathogenesis of CHD.

Disclosure of conflict of interest

None.

Address correspondence to: Liqiu Yan, Department of Cardiology, Cangzhou Central Hospital, Hebei Medical University, No. 16, Xinhua West Road, Cangzhou 061000, China. E-mail: hbmedyan66@126.com

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