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Association between single nucleotide polymorphisms in thrombospondins genes and coronary artery disease: A meta-analysis

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ABSTRACT

Objective: This study aimed to assess the association between single nucleotide polymorphisms in thrombospondin-1 (THBS1), thrombospondin-2 (THBS2), thrombospondin-4 (THBS4) and coronary artery disease (CAD) risk.
Methods: Electronic databases were searched before June, 2014 to obtain articles associated with thrombospondin polymorphisms and CAD risk. After identifying case-control studies, odds ratios (ORs) and 95% confidence intervals (95% CIs) were used to pool effect sizes. Different effect models were used according to heterogeneity. Meta-regression and sensitivity analyses were performed to examine the heterogeneity source. Begg's funnel plot and Egger's test were conducted for publication bias.
Results: 13 studies involving 10,801 cases and 9,381 controls were included. Associations were observed between the THBS1 N700S polymorphism and CAD risk in general population(heterozygote model: OR = 1.14, 95% CI: 1.03-1.26; dominant model: OR = 1.13, 95% CI: 1.00-1.29), European population (heterozygote model: OR = 1.13, 95% CI: 1.00-1.27) and Asian population (heterozygote model: OR = 1.57, 95% CI: 1.01-2.44; dominant model: OR = 1.56, 95% CI: 1.00-2.43). The THBS2 3' untranslated region (UTR) polymorphism and THBS4 A387P polymorphism were not associated with overall CAD risk. However, an association was observed between the THBS4 A387P polymorphism and CAD risk in the American population (allele model: OR = 1.09, 95% CI: 1.00-1.18; homozygote model: OR = 1.29, 95% CI: 1.04-1.61; recessive model: OR = 1.27, 95% CI: 1.02-1.58).
Conclusions: The THBS1 N700S polymorphism was associated with increased CAD risk, especially in Asian and European populations. No association was observed between the THBS2 3' UTR polymorphism and CAD risk. The THBS4 A387P polymorphism was associated with increased CAD risk in the American population.

Introduction

Coronary artery disease (CAD) greatly threatens human health. In 2008, approximately 17.3 million individuals died from cardiovascular disease, accounting for 30% of global deaths [1], and approximately 7.3 million of these deaths were due to CAD [2]. CAD has a complex pathophysiology generated by interactions between genes and the environment [3]. Environmental risk factors, such as smoking, diet and alcohol consumption, have only partially explained why individuals develop CAD [4]. The general genetic contribution CAD development is estimated to range from 20% to 60%. [5] Despite years of research, the genetic basis of CAD has not yet been fully explained.

Recently, because of their potential function in the formation and damage process of atherosclerosis CAD and myocardial infarction (MI), thrombospondins (TSPs) have been widely investigated. TSPs are multi-domain, multi-function calcium-biding extracellular glycoproteins that contain at least 5 family members: TSP-1, TSP-2, TSP-3, TSP-4 and TSP-5 or cartilage oligomeric matrix protein (COMP). TSPs play important roles in cell proliferation and migration, the regulation of platelet aggregation, the inflammatory response, wound repair and the regulation of angiogenesis [6,7]. In 2001, Topol et al first reported the potential association of premature CAD/MI and a single nucleotide polymorphism (SNP) in THBS1 (Asn700Ser, 2210A/G, *rs2228262*), an SNP in THBS4 (Ala387Pro, 1186G/C, *rs1866389*) and an SNP in the 3' untranslated region (UTR) of THBS2 (3949 T/G, *rs8089*). The authors suggested that both the variant in THBS1 N700S and the variant in THBS4 A387P might increase the risk of CAD and MI, whereas the variant in

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the 3' UTR of THBS2 might have a protective effect against MI [8]. Several subsequent studies have confirmed these associations [9,10], whereas some have failed to reproduce the above-mentioned results [11–13].

Therefore, we identified studies investigating the association between THBS polymorphisms and CAD and performed a meta-analysis using the fundamental principle and methods of evidence-based medicine to provide an evidence-based medical verification of CAD genetic predisposition.

Method

Search and Selection Process

We conducted a systematic search of PubMed, Embase, Web of Science, and The Cochrane Library, with the last search updated on June 1, 2014. We searched the databases using keywords of "Thrombospondin or TSP or THBS", "coronary heart disease or coronary artery disease or myocardial infarction or acute coronary syndrome" and "polymorphism or variant". In addition, references of relevant articles were also reviewed by hand searching to investigate additional literature that was not indexed. All searches were restricted to articles in English. The research was independently conducted by two investigators.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) case-control studies; (2) studies investigating the association between THBS polymorphisms and CAD risk; (3) studies with detailed genotype data acquired to calculate the odds ratios and 95% confidence intervals; (4) studies with genotype frequencies of controls conforming to the Hardy-Weinberg equilibrium. The exclusion criteria were as follows: (1) duplicated studies; (2) studies with no controls; (3) studies with no detailed genotype frequency.

Unpublished reports, abstracts and comments were not considered. Eligible studies were independently obtained by two reviewers according to the inclusion and exclusion criteria, and disagreement was resolved by discussion.

Data Extraction

Data extraction was conducted independently by two reviewers, and disagreements were resolved by discussion. The following data were extracted from eligible studies: first author, publication year, country, ethnicity, number of cases and controls, information about genotype and allele frequency in cases and controls, disease condition, Hardy-Weinberg equilibrium (HWE, $p < 0.05$ was considered a significant departure from HWE). Ethnicities were divided into American, European and Asian.

Methodological Quality Assessment for Individual Studies

The quality of the included studies was independently evaluated by two reviewers, and dissent was resolved by discussion. The quality of the studies was evaluated using the methodological quality assessment scale (Table 1) adjusted from previous publications [14,15].

Five aspects of the studies were assessed (representativeness of cases, source of controls, sample size, quality control of genotyping methods and HWE of controls). Studies with a quality score equal to or higher than six were considered high quality.

Statistical Analysis

Odds ratios (ORs) and 95% confidence intervals (95% CIs) were used to measure the associations between the THBS polymorphisms and CAD risk. In the current meta-analysis, we evaluated the association in five genetic models: the allelic model (THBS1: G versus A; THBS2: G versus T; THBS4: C versus G), homozygote model (THBS1: GG versus AA; THBS2: GG versus TT; THBS4: CC versus GG), heterozygote model (THBS1: GA versus AA; THBS2: GT versus TT; THBS4: CG versus GG), dominant model (THBS1: GG/GA versus AA; THBS2: GG/GT versus TT; THBS4: CC/CG versus GG) and recessive model (THBS1: GG versus GA/AA; THBS2: GG versus GT/TT; THBS4: CC versus CG/GG). A Chi-squared-based Q test [16] was used to evaluate the heterogeneity between studies, with extent assessed by I^2 [17]. A p value for heterogeneity ($P_{Heterogeneity}$, P_H) <0.1 was considered statistically significant, and the pooled CAD risk was estimated by the random-effects model [18]; in all other cases, a fixed-effects model [19] was applied. Subgroup analyses were conducted to explore the effect of ethnicity (American, European or Asian). A meta-regression analysis was performed to determine the potential source of heterogeneity, and $p < 0.05$ was considered significant [20]. Begg's funnel plot [21] and Egger's test [22] were performed to examine potential publication bias, with $p < 0.05$ considered statistically significant.

All statistical analyses were conducted with STATA 11.2 software.

Table 1
Scale for methodological quality assessment.

Criteria	Score
1. Representativeness of cases	
CAD diagnosed according to acknowledged criteria	2
Mentioned the diagnosed criteria but not specifically described	1
Not mentioned	0
2. Source of controls	
Population or community based	3
Hospital-based CAD-free controls	2
Healthy volunteers without total description	1
CAD-free controls with related diseases	0.5
Not described	0
3. Sample size	
>300	2
200-300	1
<200	0
4. Quality control of genotyping methods	
Repetition of partial/total tested samples with a different method	2
Repetition of partial/total tested samples with the same method	1
Not described	0
5. Hardy-Weinberg equilibrium (HWE)	
Hardy-Weinberg equilibrium in control subjects	1
Hardy-Weinberg disequilibrium in control subjects	0

Results

Characteristics of Eligible Studies

As shown in Fig. 1, a total of 210 potentially eligible studies were identified through database searching. Among these studies, 194 were excluded after reviewing the study abstracts, leaving 16 studies for a more detailed evaluation. An additional 2 eligible studies were identified by reviewing the references of relevant articles. Among the 18 studies, 5 were excluded for the following reasons: duplicated report ($n = 1$), English article unavailable ($n = 2$), no detailed data ($n = 1$), and only abstract available ($n = 1$). The characteristics of the studies are shown in Table 2.

In total, 13 studies [8–13,23–29] were included in the current meta-analysis. Among the 13 studies, eight investigated the THBS1 N700S polymorphism [8,9,12,23–25,28,29]; five investigated the polymorphism located in THBS2 3'UTR [8,23,24,28,29] and nine investigated the THBS4 A387P polymorphism [8–11,23,24,26–28]. Six were performed in an American population [8,10,13,23,26,27]. Three were performed in a European population [9,24,28] and four were performed in an Asian population [11,12,25,29].