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Association between *TaqIB* polymorphism of cholesteryl ester transfer protein and coronary artery disease in the Chinese population*

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Abstract: Objective: To assess whether the *TaqIB* polymorphism of cholesteryl ester transfer protein (CETP) is associated with coronary artery disease (CAD) in Chinese population, we performed a meta-analysis in this paper. Methods: We searched PubMed, Embase, the Science Citation Index (SCI), the China Biological Medicine database (CBM), the China National Knowledge Infrastructure (CNKI), and the Wanfang database for relevant articles. Data were extracted, and pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Results: The literature search yielded 448 studies, in which 10 case-control studies including 1 694 cases and 1 456 controls matched the selection criteria. The combined B1 and B2 allele frequencies were 0.587 and 0.413, respectively. The pooled OR was 1.10 (95% CI, 0.89–1.34) for comparing the B1B1 or B1B2 carriers with B2B2 carriers, and was 1.27 (95% CI, 1.09–1.49) in the B1B1 carriers versus B2B2 or B1B2 carriers. Conclusions: In the present study, the *TaqIB* polymorphism of CETP was found to be associated with CAD in the Chinese population.

Key words: Cholesteryl ester transfer protein, Coronary artery disease, Polymorphism, Chinese population
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1 Introduction

Coronary artery disease (CAD) is the leading cause of death, in both China and western countries (Libby, 1995). The cholesteryl ester transfer protein (CETP) plays an important role in cholesterol metabolism by exchanging the cholesteryl ester in high-density lipoprotein (HDL) for the triglycerides in very-low-density lipoprotein (VLDL), low-density lipoprotein (LDL), or chylomicrons (Groener *et al*., 1986). The *CETP* gene contains 25 kilobases genomic DNA with 16 exons and 15 introns, and is located on chromosome 16 (Agellon *et al*., 1990). Linkage analysis has shown that a marker locus linked to the CETP locus is involved in the determination of plasma concentrations of HDL cholesterol (HDL-C) and its associated lipoproteins (Bu *et al*., 1994). Genetic variation at this locus has also been found to be associated with the variations of serum CETP activity and HDL-C concentration (Inazu *et al*., 2000). Of the known genetic variants, the *TaqIB* polymorphism is common and has been

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studied in detail. Several studies have shown an association of the *CETP* intron 1 *TaqIB2* allele with a high HDL-C level and *TaqIB1* with a low HDL-C level (Freeman *et al*., 1994; Dullaart *et al*., 1997; Kuivenhoven *et al*., 1998). A meta-analysis mainly including a Caucasian population found that the CETP *TaqIB* variant is firmly associated with HDL-C plasma levels, and as a result, with the risk of CAD (Boekholdt *et al*., 2005). However, whether the *TaqIB* polymorphism of CETP is associated with CAD remains unclear in studies mainly including Chinese subjects (Wu *et al*., 2001; Qin *et al*., 2004; Wang *et al*., 2004; Yan *et al*., 2004; Zhao *et al*., 2004; Zheng *et al*., 2004; Zhang Y. *et al*., 2003; Zhang G. *et al*., 2005; Wang, 2006; Li *et al*., 2007). Therefore, in this paper we performed a meta-analysis to assess the relationship between the *TaqIB* polymorphism of CETP and CAD in Chinese populations.

2 Materials and methods

2.1 Eligibility criteria

The inclusion criteria were: (1) un-related case-control studies; (2) complete data with genotype and allele frequencies (a genotype frequency of cases and controls is within Hardy-Weinberg equilibrium); (3) the publications that could be written in any language. Reports of duplicated studies were excluded by examining the author list, parent institution, sample size, and results.

2.2 Information sources and searches

The PubMed, Embase, the Science Citation Index (SCI), the China Biological Medicine database (CBM), the China National Knowledge Infrastructure (CNKI), and the Wanfang database for relevant articles were searched. The keywords used in literature searching included: cholesteryl ester transfer protein, coronary artery disease, polymorphism, Chinese population, CETP and variants, and genetics.

2.3 Synthesis of results

Two authors (Drs. En-qi LIU and Si-hai ZHAO) independently screened titles and abstracts for potential eligibility and the full texts for final eligibility. We extracted the data independently from the included trials for quantitative analyses, and any disagreements were subsequently resolved by discussion. The measure of association used in this meta-analysis was the odds ratio (OR) with a 95% confidence interval (CI). The summary OR with the 95% CI was calculated with Revman 5.0 software using the fixed effect model (Review Manager Version 5.0 for Windows; the Cochrane Collaboration, Oxford, UK). A statistically significant result was assumed when the 95% CI did not include 1. Heterogeneity was explored using a chi-square test, and the quantity of heterogeneity was measured using the I^2 statistics. Publication bias was assessed with funnel plot.

3 Results

3.1 Baseline characteristics of cases and controls

Fig. 1 shows the results of the study screen. The literature search yielded 448 studies, 10 of which matched the selection criteria. The combined sample size was 3150 (1694 cases; 1456 controls). There was unanimous agreement between the two authors (Drs. En-qi LIU and Si-hai ZHAO) regarding the selection of relevant articles. The baseline characteristics in the 10 included trials are summarized in Table 1.

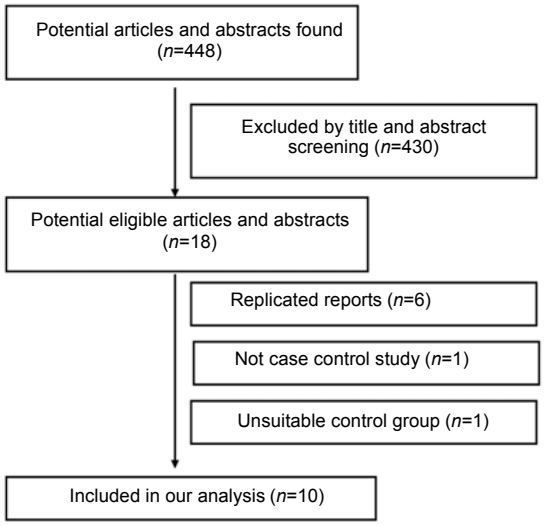

Fig. 1 Analysis of the search results

3.2 Primary meta-analysis

In this study, fixed effect model was used to analyze the ten included studies. The combined B1 and B2 allele frequencies were 0.587 and 0.413,

Table 1 Baseline characteristics of the cases and controls of included studies

Study	n_S	Mean age (year)	n_M/n_F	n_G			Allele frequency	
				B1B1	B1B2	B2B2	B1	B2
Li *et al*., 2007								
Case	176	61.7±12.5[a]		82	73	21	0.588	0.412
Control	40	55.8±13.1		15	19	6	0.584	0.416
Qin *et al*., 2004								
Case	249	58.8±8.9	169/80	81	131	37	0.588	0.412
Control	167	55.1±9.0	89/78	49	97	21	0.584	0.416
Wang *et al*., 2004								
Case	128	62.9±5.6	82/46	50	66	12	0.648	0.352
Control	247	59.5±8.4	142/105	72	123	52	0.540	0.460
Wang, 2006								
Case	123	62.36[b]	44/59	38	65	20	0.568	0.432
Control	103	48.17	84/39	33	51	19	0.573	0.427
Wu *et al*., 2001								
Case	149	20–82[c]		45	79	25	0.595	0.405
Control	274	28–83		63	159	52	0.584	0.416
Yan *et al*., 2004								
Case	106	60±9	81/25	41	46	19	0.604	0.396
Control	64	57±11	31/33	19	34	11	0.564	0.437
Zhang G. *et al*., 2005								
Case	88	65±10		31	40	17	0.580	0.420
Control	94	54±18		32	50	12	0.606	0.394
Zhang Y. *et al*., 2003								
Case	234	59.5±8.2	135/99	76	126	32	0.595	0.405
Control	164	58.2±9.3	98/66	49	95	20	0.588	0.412
Zhao *et al*., 2004								
Case	238	61.3±9.2	224/217	95	105	38	0.620	0.380
Control	203			60	109	34	0.564	0.436
Zheng *et al*., 2004								
Case	203	59.3±8.7	137/77	66	114	23	0.606	0.394
Control	100	58.4±6.5	66/34	33	55	12	0.605	0.395

n_S: number of samples; n_M/n_F: male number/female number; n_G: number of genotype. Mean age is expressed as mean±SD[a], mean[b], or range[c]

respectively. Overall, the pooled OR was 1.10 (95% CI, 0.89–1.34, P=0.38) when comparing B1B1 or B1B2 carriers with B2B2 carriers. Using OR as the measure of effect, the Cochran homogeneity test statistic yielded a P value of 0.34, and the heterogeneity was I^2=11% (Fig. 2). The pooled OR was 1.27 (95% CI, 1.09–1.49, P=0.002) when comparing B1B1 carriers with B1B2 or B2B2 carriers. The Cochran homogeneity test statistic yielded a P value of 0.79, and the heterogeneity was I^2=0% (Fig. 3).

3.3 Publication bias

We performed a funnel plot analysis to explore publication bias. All ten included studies for the comparison of B1B1 carriers with B1B2 or B2B2 carriers lied within the 95% CI line and the funnel plot did not show asymmetry. However, asymmetrical plot for comparison of B1B1 or B1B2 carriers with B2B2 carriers implied the existence of some publication bias (Fig. 4).

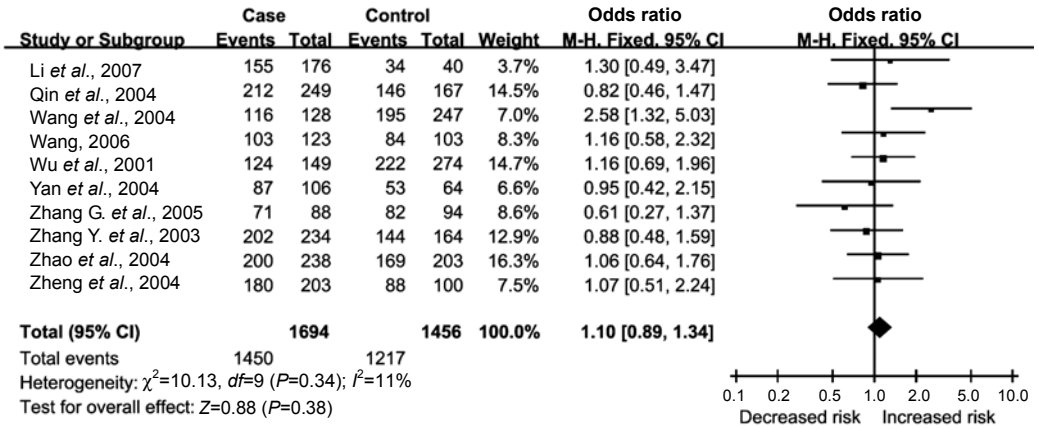

Fig. 2 Odds ratios for coronary artery disease when comparing the B1B1 or B1B2 carries with B2B2 carriers
Test for heterogeneity: chi-squared statistic with its degrees of freedom (*df*) and *P*-value; Inconsistency among results: I^2; Test for overall effect: *Z* statistic with *P*-value

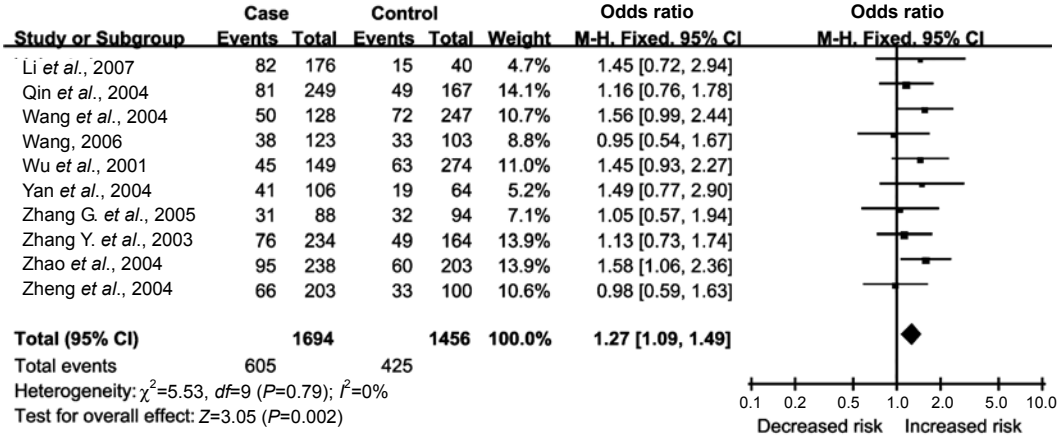

Fig. 3 Odds ratios for coronary artery disease when comparing the B1B1 carries with B1B2 or B2B2 carriers
Test for heterogeneity: chi-squared statistic with its degrees of freedom (*df*) and *P*-value; Inconsistency among results: I^2; Test for overall effect: *Z* statistic with *P*-value

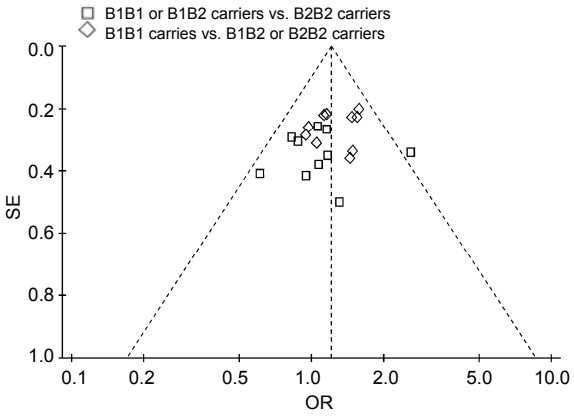

Fig. 4 Funnel plot illustrating the included trials used in this meta-analysis
Dashed lines represent the 95% CI lines. SE: standard error, expressed as logOR; OR: odds ratio

4 Discussion

As a modulator of HDL-C levels, CETP plays an important role in the molecular mechanism of human atherogenesis (Barter and Rye, 2001; Barter *et al*., 2003). The *TaqIB* polymorphism in the *CETP* gene, located in intron 1, has played a prominent role in genetic association studies investigating the relation between CETP activity, lipids, and CAD risk. The CETP *TaqIB* variant was firmly associated with the risk of CAD in Caucasians (Boekholdt *et al*., 2005). However, the association remains unclear in Chinese populations (Wu *et al*., 2001; Zhang Y. *et al*., 2003; Qin *et al*., 2004; Wang *et al*., 2004; Yan *et al*., 2004; Zhao *et al*., 2004; Zheng *et al*., 2004; Zhang G. *et al*.,

2005; Wang, 2006; Li *et al*., 2007). In this meta-analysis, we observed that the *TaqIB* polymorphism in the *CETP* gene exhibited a significant association with CAD in Chinese populations. The pooled OR was 1.27 (95% CI, 1.09–1.49) in the B1B1 carriers versus B2B2 or B1B2 carriers. The *TaqIB* genotype was still significantly associated with a higher risk of CAD in B1B1 individuals compared with B1B2 individuals and B2B2 individuals in Chinese populations. The B2 allele of the *TaqIB* polymorphism has been shown to be associated with higher HDL-C concentrations, and decreased CETP activity and CETP concentration (Kauma *et al*., 1996; Corbex *et al*., 2000; Ordovas *et al*., 2000). The *TaqIB* B1 allele has been marginally associated with the risk of developing CAD (Ordovas *et al*., 2000; Brousseau *et al*., 2002). Allele frequencies of the *TaqIB* polymorphism have been previously reported to differ by racial/ethnic groups (Cuchel *et al*., 2002; Liu *et al*., 2002). In this study, the allele frequencies of the *TaqIB* polymorphism in Chinese populations are similar to Caucasian populations reported by Tsai *et al*. (2008). In the Korean population, the B1B1 homozygote of the CETP *TaqIB* polymorphism is associated with low HDL-C levels in females and non-smoking males, and may be an independent genetic risk factor of CAD (Park *et al*., 2003). It was also reported that the B2B2 genotype in CETP *TaqIB* polymorphism may act as a protective factor against atherosclerosis in Japanese (Goto *et al*., 2001). The results of this study also agree with these previous reports in different racial populations.

In conclusion, the *TaqIB* polymorphism of CETP was found to be associated with CAD in Chinese populations. The present study suggests that allele B1 might be a genetic risk factor for CAD in Chinese populations. These results may help predict future diseases, and allow for early diagnosis and prevention of CAD. The results also help to understand the mechanism of CAD and develop new drugs for CAD-related diseases.

It is important to mention that there were limitations in this meta-analysis. Though the main worldwide biomedical databases were searched to identify potential randomized control trails (RCTs), publication bias could not be avoided completely. In our study, an asymmetrical plot for comparison of B1B1 or B1B2 carriers with B2B2 carriers was found, implying the existence of some publication bias.

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