

miR-499 rs3746444 polymorphism and coronary artery disease risk: a meta-analysis.

Fanbo Meng¹, Xudong Guo², Wei Wang², Baisong Lin^{2*}

¹Department of Cardiology, China-Japan Union Hospital, Jilin University, Changchun, Jilin, PR China

²Department of Cardiac Surgery, China-Japan Union Hospital, Jilin University, Changchun, Jilin, PR China

Abstract

Background: Some studies suggested that miR-499 rs3746444 polymorphism was associated with the risk of Coronary Artery Disease (CAD). However, the results were still unclear. Therefore, we conducted a meta-analysis.

Method: An electronic literature search was conducted using the following database: PubMed, Embase and China National Knowledge Infrastructure (CNKI) till to June 2017. The strength of association was investigated by pooling Odds Ratio (OR) with its corresponding 95% Confidence Interval (CI).

Results: In total, four studies with 2642 cases and 2260 controls were included in this meta-analysis. MiR-499 rs3746444 polymorphism was significantly associated with an increased risk of CAD (OR=1.30; 95% CI, 1.00-1.69). In the race subgroup analysis, Asians with miR-499 rs3746444 polymorphism did not show increased CAD risk (OR=1.25; 95% CI, 0.89-1.76). In the subgroup analysis according to source of control, hospital-based studied showed significantly association (OR=1.44; 95% CI, 1.11-1.86).

Conclusion: In conclusion, this meta-analysis suggests that miR-499 rs3746444 polymorphism was associated with CAD risk.

Keywords: Coronary artery disease (CAD), MicroRNAs, Association.

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Introduction

Coronary Artery Disease (CAD) is the primary critical cardiovascular event, causing high morbidity and mortality all over the world [1]. CAD is driven by a complex interplay of multiple genetic and environmental factors that jointly give rise to a plethora of molecular interactions resulting in a complex and heterogeneous phenotype. Hypertension, diabetes, smoking and dyslipidaemia are other established risk factors for CAD [2].

MicroRNAs (miRNAs), a family of small non-coding RNAs 20-24 nucleotides (nt) in length, are evolutionarily conserved mediators of post-transcriptional gene regulation in eukaryotes [3]. Increasing evidence indicates that dysregulation of specific miRNAs contributes to the development and progression of CAD [4]. Wang et al. found that the T allele of rs2431697 was a risk factor of CAD in the Chinese population [5]. Faccini et al. found that let-7c, miR-145 or miR-155 were powerful markers for detecting CAD [6]. Wang et al. showed that the plasma miR-146a level is significantly increased in CAD patients with good coronary collateral circulation and significantly decreased in those with poor coronary collateral circulation [7]. Some studies suggested that miR-499 rs3746444 polymorphism was associated with the risk of CAD.

However, the results were still unclear [8-11]. Therefore, we conducted a meta-analysis.

Methods

Search for publications

An electronic literature search was conducted using the following database: PubMed, Embase and China National Knowledge Infrastructure (CNKI) till to June, 2017. The following medical subject headings were used: "MicroRNA," "Coronary artery disease," and "CAD". Electronic searches were supplemented with manual searches of reference lists of all retrieved review articles, primary studies, and abstracts from meetings to identify other studies not found in the electronic searches.

Inclusion criteria

The following inclusion criteria were used: (1) The study should evaluate the association between the miR-499 rs3746444 polymorphism and CAD; (2) The study should have a case-control design; (3) Sufficient data should have been provided in order to calculate Odds Ratios (OR) and 95% Confidence Intervals (CI).

Data extraction

Two investigators independently extracted data: the first author's name, year of publication, country, ethnicity, numbers of cases and controls, source of control, and Hardy-Weinberg equilibrium (HWE).

Statistical analysis

The significance of the pooled OR's was determined by the Z-test with a P value less than 0.05 considering statistically significant. The per-allele model was examined to assess this association. Heterogeneity among studies was assessed using the Q-test and the I^2 statistic, which describes the proportion of total variation attributable to between-study heterogeneity as opposed to random error or chance. In the presence of substantial heterogeneity ($I^2 > 50\%$), the DerSimonian and Laird random effect model was applied as the pooling method, otherwise, the fixed effect model was adopted. Statistical analyses were conducted in Revman 5.1 software (Nordic Cochrane Center, Copenhagen, Denmark). All the tests were two-sided.

Results

Study characteristics

Four case-control studies met inclusion criteria. In total, 2642 cases and 2260 controls were included in this meta-analysis.

The baseline characteristics of each study included in this meta-analysis are showed in Table 1.

Table 1. Characteristics of included studies.

Author	Country	Ethnicity	Cases	Controls	HWE	Source of control
Xu	China	Asian	1003	1046	Yes	Population
Zhi	China	Asian	916	584	Yes	Hospital
Chen	China	Asian	435	480	Yes	Hospital
Labraf	Iran	Caucasian	288	150	Yes	Hospital

HWE: Hardy-Weinberg Equilibrium.

Results of the meta-analysis

Results of the meta-analysis are summarized in Table 2. MiR-499 rs3746444 polymorphism was significantly associated with an increased risk of CAD (OR=1.30; 95% CI, 1.00-1.69; Figure 1). In the race subgroup analysis, Asians with miR-499 rs3746444 polymorphism did not show increased CAD risk (OR=1.25; 95% CI, 0.89-1.76). In the subgroup analysis according to source of control, hospital-based studied showed significantly association (OR=1.44; 95% CI, 1.11-1.86).

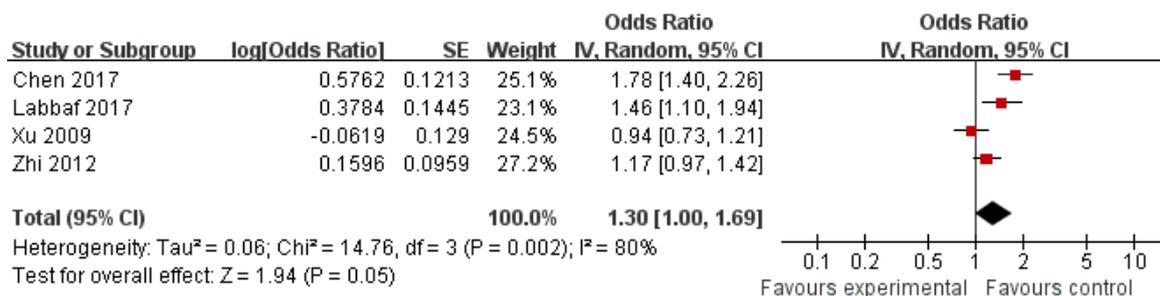


Figure 1. Meta-analysis for the association between miR-499 rs3746444 polymorphism and CAD risk.

Table 2. Summary of results from meta-analysis and subgroup analysis.

	OR (95% CI)	P value
Overall	1.30 (1.00-1.69)	0.05
Asian	1.25 (0.89-1.76)	0.2
Hospital-based	1.44 (1.11-1.86)	0.006

Discussion

This meta-analysis of 4 case-control studies aimed to investigate whether miR-499 rs3746444 polymorphism has an impact on the risk of CAD. We found that miR-499 rs3746444 polymorphism was significantly associated with an increased risk of CAD. In the race subgroup analysis, Asians with miR-499 rs3746444 polymorphism did not show increased

CAD risk. In the subgroup analysis according to source of control, hospital-based studied showed significantly association.

Zhang et al. found that rs3746444 could increase breast cancer risk in Asians and in general populations [12]. Zheng et al. suggest that miR-146a and miR-196a2 polymorphisms are associated with increased risk of hepatocellular carcinoma [13]. Luo et al. miR-499A>G (rs3746444) was related to ischemic stroke and G allele and AG genotype may increase the risk of ischemic stroke in the population of Guangxi in China [14]. Yang et al. indicated that miR-499 rs3746444 polymorphism was not significantly associated with the risk for RA [15]. Shan et al. showed that miR-499 (rs3746444) gene polymorphisms may be genetic determinants for increased risk of biliary atresia [16]. Cai et al. indicated that miR-499 rs3746444 might contribute to GC risk [17].

Several limitations of this meta-analysis should be considered. First, there were only 4 studies were included, and only one study was conducted in Caucasian. Therefore, more studies with large sample sizes are needed. Second, the overall outcomes were based on individual unadjusted ORs. The unadjusted ORs may lead to confounding bias due to lack of individual information of each study. Third, the inconsistency of the base line characteristics between the studies, such as age and gender, might increase the selection bias.

In conclusion, this meta-analysis suggests that individuals with miR-499 rs3746444 polymorphism might have an increased CAD risk.

Conflicts of Interest

None.

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*Correspondence to

Baisong Lin
Department of Cardiac Surgery
China-Japan Union Hospital
Jilin University
Changchun
Jilin
PR China