

Review Article

The role of hsp70-2 rs1061581 polymorphism and CAD risk: a meta-analysis

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Abstract: Background: Recently, many studies reported the association between Hsp70-2 rs1061581 polymorphism and coronary artery disease (CAD) risk. However, the results were controversial. Therefore, we performed this meta-analysis to determine this association. Method: We searched the articles using the search terms “Heat-shock protein”, “HSP”, “coronary artery disease” and “polymorphism” in PubMed, Embase and CNKI databases. The strength of association was assessed by computing odds ratio (OR) with its corresponding 95% confidence interval (CI). Results: Six studies with 1353 cases and 1211 controls that evaluated the association between Hsp70-2 rs1061581 polymorphism and CAD risk were included. Hsp70-2 rs1061581 polymorphism was associated with a significantly increased risk of CAD (OR=1.34; 95% CI, 1.19-1.50). In the race subgroup analysis, Caucasians (OR=1.39; 95% CI, 1.20-1.62) but not Asians (OR=1.26; 95% CI, 0.92-1.72) with Hsp70-2 rs1061581 polymorphism had increased CAD risk. In the subgroup analysis according to source of control, only hospital-based studied showed significantly association (OR=1.43; 95% CI, 1.23-1.65), while population-based studied did not show positive result (OR=1.21; 95% CI, 0.90-1.63). Conclusion: In conclusion, this meta-analysis suggests that individuals with Hsp70-2 rs1061581 polymorphism may have an increased CAD risk.

Keywords: Coronary artery disease, Hsp70-2, association

Introduction

Coronary artery disease (CAD) is the most common cause of morbidity and mortality in China [1]. CAD has a number of risk factors, including family history, obesity, diabetes, hypertension, high blood lipids, smoking, stress and lack of exercise [2]. It is a complex disease determined by genetic predisposition and environmental factor accumulation, which play major roles in a number of associated vessel wall abnormalities [3].

Heat-shock proteins (HSPs), in particular the HSP70 family, play important roles in intracellular trafficking and conformation of proteins by acting as a molecular chaperone, thus involving them in immune regulation [4]. Three members of the HSP gene, known as HSP70-1, -2 and -Hom, have been mapped to the class-III region of the human major histocompatibility complex (MHC); 92 kb telomeric of the complement C2

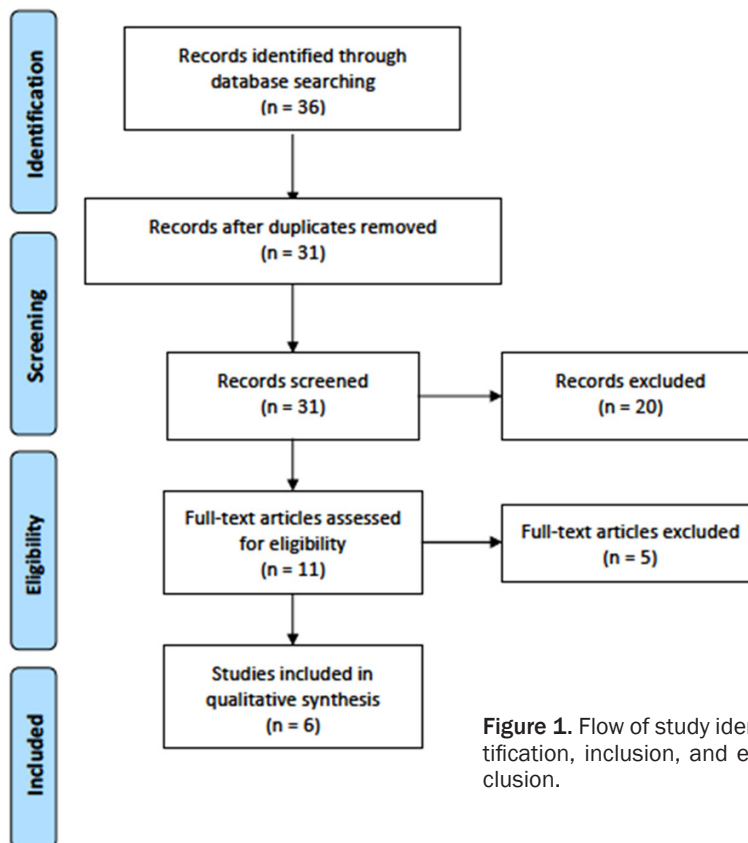
locus [5]. The majority of functions which occur in meiotic prophase in spermatocytes including chromosome condensation and pairing of homologous chromosomes are largely dependent on Hsp70-2 expression [6].

Recently, many studies reported the association between Hsp70-2 rs1061581 polymorphism and CAD risk. However, the results were controversial [7-12]. Therefore, we performed this meta-analysis to determine this association.

Materials and methods

Search for publications

We searched the articles using the search terms “Heat-shock protein”, “HSP”, “coronary artery disease” and “polymorphism” in the PubMed, Embase and CNKI databases, and the last search updated on Mar 2016. Additional



studies were identified by a hand search of references of original studies or review articles on the association between Hsp70-2 rs1061581 polymorphism and CAD risk. No publication date or language restriction was imposed.

Inclusion and exclusion criteria

The following inclusion criteria were used: (1) the study should have evaluated the association between the Hsp70-2 rs1061581 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). Studies were excluded if any of the following conditions applied: (1) irrelevant to CAD or Hsp70-2; (2) abstract or review; (3) non-clinical study; (4) studies were repeated or publications overlapped.

Data extraction

Two investigators independently extracted data and reached consensus on the following characteristics of the selected studies: the first

author's name, year of publication, country, ethnicity of the study population, numbers of cases and controls, source of control, and Hardy-Weinberg equilibrium (HWE) status.

Statistical analysis

OR and 95% CI were employed to evaluate the strength of the association between Hsp70-2 rs1061581 polymorphism and CAD risk. Departure from HWE in controls was tested by the chi-square test. The Q statistic and the I^2 statistic were used to assess the degree of heterogeneity among the studies included in the meta-analysis. If heterogeneity was observed among the studies, the random-effects model was used to estimate the pooled OR (the DerSimonian and Laird method). Otherwise, the fixed-effects model was adopted (the Mantel-Haenszel method). Subgroup analyses were carried out by ethnicity and source of control. Sensitivity analysis was performed through sequentially excluded individual studies to assess the stability of the results. The potential publication bias was examined visually in a funnel plot of log [OR] against its standard error (SE), and the degree of asymmetry was tested using Egger's test.

All statistical tests were performed using Revman 5.1 software (Nordic Cochrane Center, Copenhagen, Denmark) and STATA 11.0 software (Stata Corporation, College Station, TX, USA). A p value <0.05 was considered statistically significant, except for tests of heterogeneity where a level of 0.10 was used.

Results

Study characteristics

In total, 36 records were obtained initially through PubMed, Embase and CNKI electronic database. After screened by title, abstract and full text, 6 studies with 1353 cases and 1211

Table 1. Characteristics of included studies

Author	Year	Country	Ethnicity	Cases	Controls	HWE	Source of control
Jiang	2004	China	Asian	141	211	No	Population
Giacconi	2006	Italy	Caucasian	105	190	Yes	Population
Duan	2010	China	Asian	185	149	Yes	Hospital
Hrira	2012	Tunisia	Caucasian	252	151	Yes	Population
Wu	2014	China	Asian	237	203	Yes	Hospital
Mardan-Nik	2014	Iran	Caucasian	433	307	Yes	Hospital

HWE, Hardy-Weinberg equilibrium.

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

	No. of studies	OR (95% CI)	P Value	$P_{\text{heterogeneity}}$
Overall	6	1.34 (1.19-1.50)	<0.00001	0.18
Asian	3	1.26 (0.92-1.72)	0.15	0.04
Caucasian	3	1.39 (1.20-1.62)	<0.0001	0.83
Hospital-based	3	1.43 (1.23-1.65)	<0.00001	0.88
Population-based	3	1.21 (0.90-1.63)	0.22	0.07

controls that evaluated the association between Hsp70-2 rs1061581 polymorphism and CAD risk were included. Three studies were from China. One study was not in HWE. The flow diagram for searching and selecting articles was illustrated in **Figure 1**. Characteristics of studies were displayed in **Table 1**.

Results of the meta-analysis

The evaluations of the association between Hsp70-2 rs1061581 polymorphism and CAD risk are summarized in **Table 2**. Hsp70-2 rs1061581 polymorphism was associated with a significantly increased risk of CAD (OR=1.34; 95% CI, 1.19-1.50; **Figure 2**). In the race subgroup analysis, Caucasians (OR=1.39; 95% CI, 1.20-1.62) but not Asians (OR=1.26; 95% CI, 0.92-1.72) with Hsp70-2 rs1061581 polymorphism had increased CAD risk. In the subgroup analysis according to source of control, only hospital-based studied showed significantly association (OR=1.43; 95% CI, 1.23-1.65), while population-based studied did not show positive result (OR=1.21; 95% CI, 0.90-1.63).

To assess the robustness and reliability of the association results, we performed sensitivity analysis by removing the study without in HWE. The result did not change (OR=1.42; 95% CI, 1.26-1.61). Additionally, the heterogeneity was

disappeared. Funnel plot was performed to assess the publication bias of literatures. The shape of the funnel plot showed symmetry (**Figure 3**). Egger's test found no evidence of publication bias ($P=0.121$).

Discussion

In this meta-analysis, we investigated the association between Hsp70-2 rs1061581 polymorphism and CAD risk including 1353 cases and 1211 controls. We found that individuals with Hsp70-2 rs1061581 polymorphism showed an increased risk of CAD in the overall population. The result from this meta-analysis suggested that individuals

with Hsp70-2 rs1061581 polymorphism had a 34% increased CAD risk compared to individuals without this polymorphism. In the stratified analysis by ethnicity, the significant association was only observed in Caucasians. This result suggested that a possible influence existed among environmental exposures and different genetic backgrounds. In the subgroup analysis by source of control, only hospital-based studied showed significantly association. Only three population-based studies were included in this meta-analysis. Thus, more population-based studies are still needed to address the role of Hsp70-2 rs1061581 polymorphism on CAD risk.

Zhang et al. suggested that Hsp70 levels were significantly higher in acute coronary syndrome and stable angina [13]. Paier et al. indicated that HSP70 may have useful applications as markers of vascular dysfunction in resistance arteries [14]. Gombos et al. suggested that Hsp70 correlates with markers of heart function and hepatic injury [15]. Recently, Ali and colleagues showed that Hsp70-2 rs1061581 influenced on the electrophysiology of long QT syndrome [16]. It is possible that the functional effect of the Hsp70-2 rs1061581 polymorphism in the differential expression of Hsp70-2 mRNA [17] might influence the protein expression associated to the pathogenesis of CAD.

Hsp70-2 and CAD

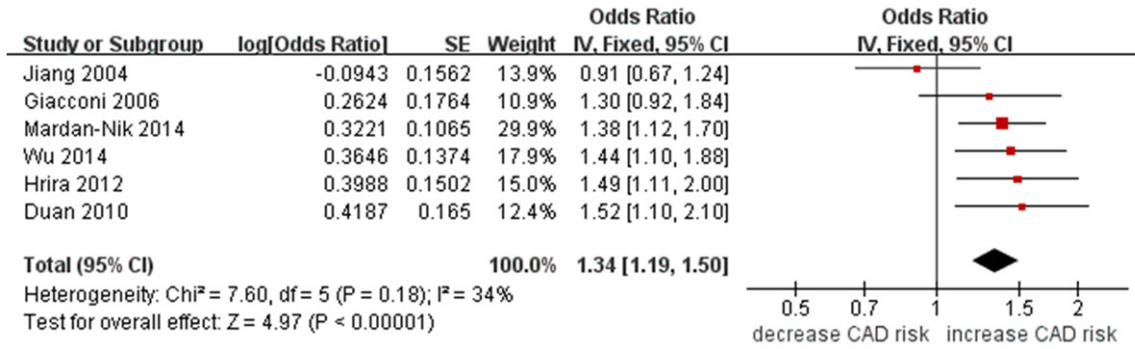


Figure 2. Meta-analysis for the association between Hsp70-2 rs1061581 polymorphism and CAD risk.

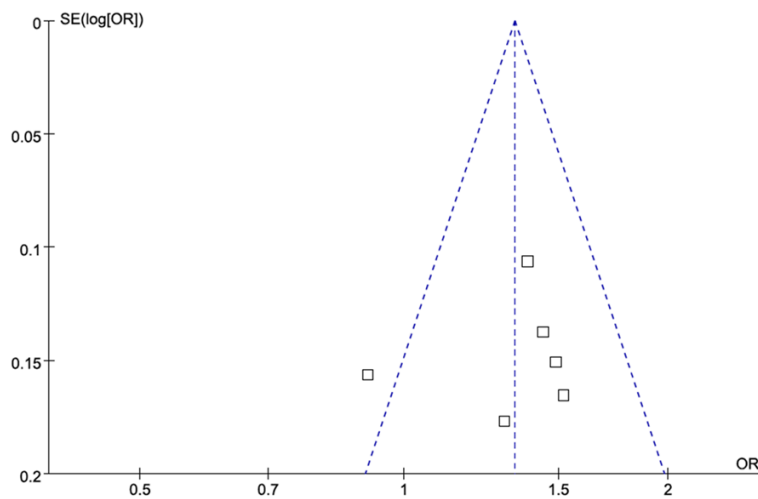


Figure 3. Funnel plot of the association between Hsp70-2 rs1061581 polymorphism and CAD risk.

body mass index (BMI), and lifestyle factors. Fourthly, the number of included studies was small. Finally, because of the complex nature of CAD, it is unlikely that a SNP in one single gene would be obviously associated with an increased CAD risk.

In conclusion, this meta-analysis suggests that individuals with Hsp70-2 rs1061581 polymorphism may have an increased CAD risk.

Disclosure of conflict of interest

None.

Heterogeneity is a potential problem that may affect the interpretation of the results. However, no significant heterogeneity existed in this meta-analysis. In addition, funnel plots and Egger's tests did not find potential publication bias. All together, these results suggested that results of this meta-analysis were reliable.

Several limitations of this meta-analysis should be considered. First, lack of the original data limited our further evaluation of potential gene-gene and gene-environment interactions. Second, all of the case-control studies were conducted in Asians and Caucasians; thus, our results may be applicable only to these ethnic groups. Third, the overall outcome was based on individual unadjusted data, while a more precise evaluation should be adjusted by other potentially suspected factors, such as age, sex,

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