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Original Article

The SNP rs4804611 in ZNF627 gene and the risk of myocardial infarction: a meta-analysis

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Abstract: A single nucleotide polymorphism (rs4804611) in zinc finger protein 627 (ZNF627) gene has been demonstrated to be associated with the susceptibility to myocardial infarction (MI), but the results are inconsistent. Therefore, a meta-analysis of eligible studies reporting the association between rs4804611 and MI was carried out to enhance the reliability of published results. A systematic literature search was performed using PubMed, Web of Science, Cochrane Library to search English articles concerning the relation between rs4804611 and MI up to January, 2015. Summary odds ratios (OR) and 95% confidence interval (CI) were used to evaluate the risk of MI. The heterogeneity and publication bias of this study were also evaluated. Five eligible studies involving 11639 subjects (6299 patients and 5340 healthy controls) were included in this meta-analysis. Overall, the results indicated that rs4804611 polymorphism was associated with the risk of MI (GG vs. AA/AG: OR = 0.833, 95% CI = 0.704-0.985, *P* = 0.033). Furthermore, subgroup analyses also showed that rs4804611 polymorphism was associated with the risk of MI in Caucasian (GG vs. AA/AG: OR = 0.839, 95% CI = 0.704-0.999, *P* = 0.048). In conclusion, our meta-analysis suggests that the rs4804611 polymorphism in ZNF627 gene is associated with the risk of MI. However, further large scale case-control studies with rigorous design should be conducted to confirm the conclusion in the future.

Keywords: Zinc finger protein 627, single nucleotide polymorphism, coronary artery disease, myocardial infarction, meta-analysis

Introduction

Ischemic heart disease, especially myocardial infarction (MI), accounts for the largest causes of death worldwide [1]. MI usually occurs when the coronary artery is suddenly occluded by a ruptured atherosclerotic plaque. Multiple factors, including living environment, dietary pattern, and genetic factor, contribute to the onset and progression of MI [2-4]. Some studies have found that genetic variant is associated with the susceptibility to MI for the reason that it may lead to the development of hypertension, hypercholesterolemia, and diabetes, which are the common risk factors of MI [5].

Zinc finger protein is characterized as a transcription factor, which might be associated with many diseases such as cancer, lipid metabolism disorder and cardiovascular disease [6-9]. Zinc finger protein 627 (ZNF627) is a newfound zinc finger protein and its encoding gene locates in 19p13.2. A genome-wide association study identified a novel single nucleotide polymorphism (SNP) in ZNF627 gene (rs4804611) was associated with the risk of MI [10]. However, subsequent replicated studies in different population showed inconsistent results [11-14]. Therefore, in the present study, we performed a meta-analysis to evaluate the association between rs4804611 polymorphism in ZNF627 gene and the risk of MI.

Materials and methods

Search strategy

A systematic search assembling the following terms: “genetic polymorphism”, “single nucleotide polymorphism”, “gene mutation”, “genetic variants”, “coronary atherosclerosis”, “myocardial ischemia”, “acute coronary syndrome”,

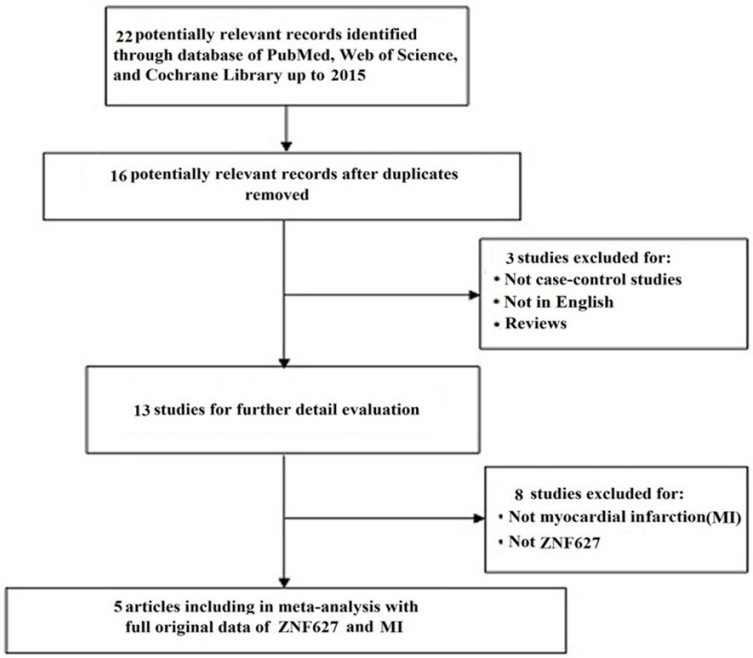

Figure 1. Flow diagram of the study selection process.

"coronary disease", "myocardial infarction", "ischemic heart disease", "zinc finger protein 627", "ZNF627", "rs4804611", was conducted in PubMed, Web of Science, Cochrane Library databases up to January 1st, 2015 to identify all potentially relevant studies. Hand-searching was carried out to determine other potential eligible studies through scanning the references cited in the retrieved articles. The full-text articles were further reviewed to determine whether they were included in the final analysis strictly based on eligibility criteria. If the two reviewers (Nan Wu and Xiaowen Zhang) disagreed, all the authors critically evaluated the studies to judge of the inclusion or exclusion of a certain study.

Eligibility criteria

All the eligible articles were supposed to meet the major inclusion criteria: (i) assessment of the association between ZNF627 gene polymorphism and MI; (ii) unrelated case-control or cohort studies; (iii) data provided by articles about allele frequency should be sufficient for calculating genotypic odds ratio (OR) with corresponding 95% confidence interval (95% CI) in cases and controls. Studies were excluded when they were (i) duplicated data; (ii) not written in English; (iii) case report, review articles and editorial comment. The diagnosis of the MI case was based on a history of MI, typical electrocardiographic change, left ventricular angiography, and coronary angiography. All healthy controls were identified according to patient history, electrocardiograph test and coronary angiography.

Data extraction

Data extraction was performed independently by two authors (Nan Wu and Xiaowen Zhang) using a standardized data extraction form including following elements: 1) author's name, year of publication; 2) patient characteristics of each group; 3) number of participants in cases and controls; 4) study type; 5) genotyping method; 6) *P* value of Hardy-Weinberg equilibrium (HWE) test in the control; 7) OR and 95% CI for association with MI. In order to assess the quality of studies, Newcastle-Ottawa Scale (NOS) was performed as previous described [15]. Briefly, two authors (Nan Wu and Pengyu Jia) of this article independently evaluated the quality of studies based on eight items and scored the studies from 0 to 9 points. Studies with a score not less than 7 points were considered to be of high quality. Discrepancy was settled as described above.

Statistical analysis

Firstly, the genotype frequencies of rs4804611 polymorphism among the controls of all included studies were assessed under HWE using a chi-square goodness-of-fit test. OR with corresponding 95% CI was used to estimate the strength of association between rs4804611 polymorphism and MI. The between-study heterogeneity across all eligible comparisons was test by the chi-square based Q statistic. Heterogeneity was considered significant when *P* value was less than 0.10. When the heterogeneity exists, the random effects model was performed to calculate the pooled OR of each eligible study, otherwise, the fixed effect model was used. Generally, we assessed the associa-

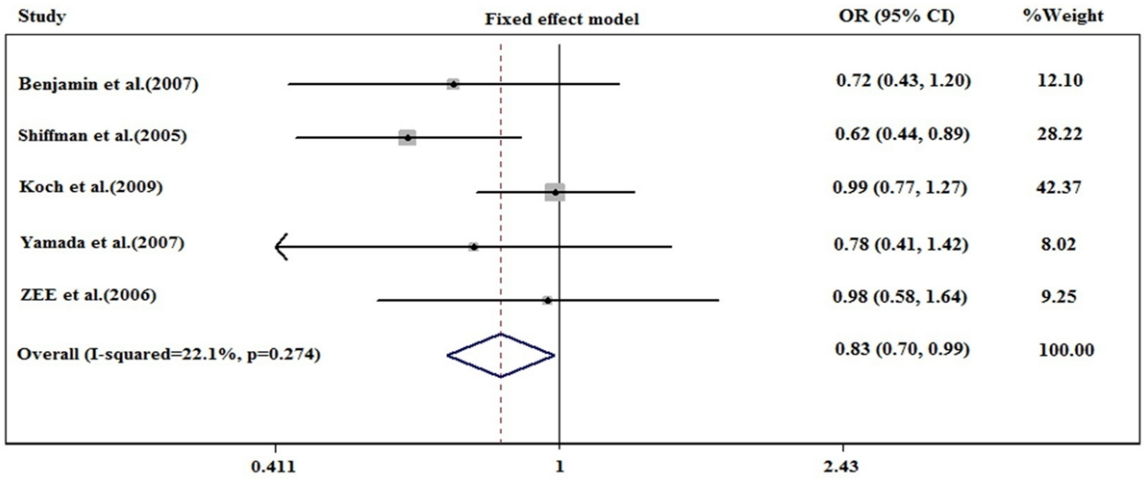

Figure 2. Flow diagram of the study selection process.

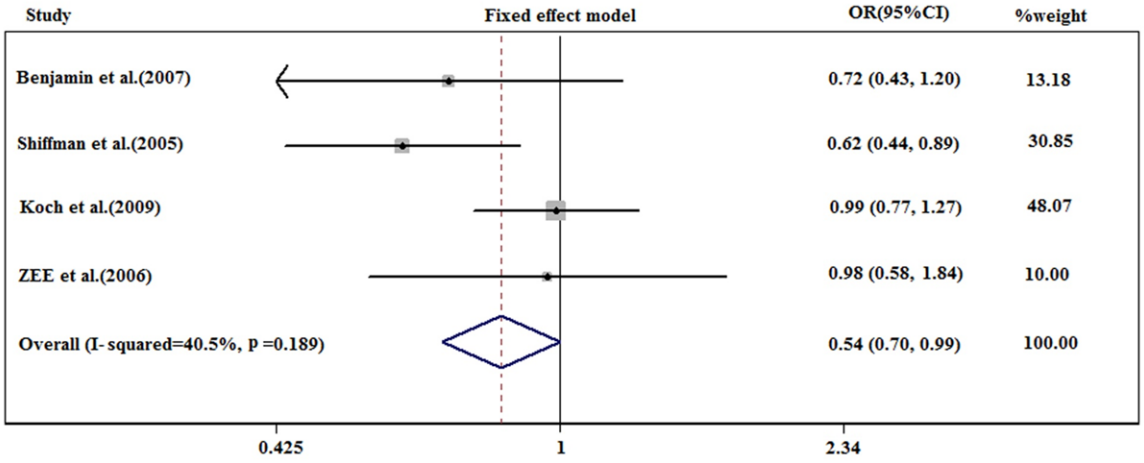

Figure 3. Forest plots for rs4804611 and myocardial infarction in Caucasian under recessive model (GG versus AG/AA) using fixed effect model.

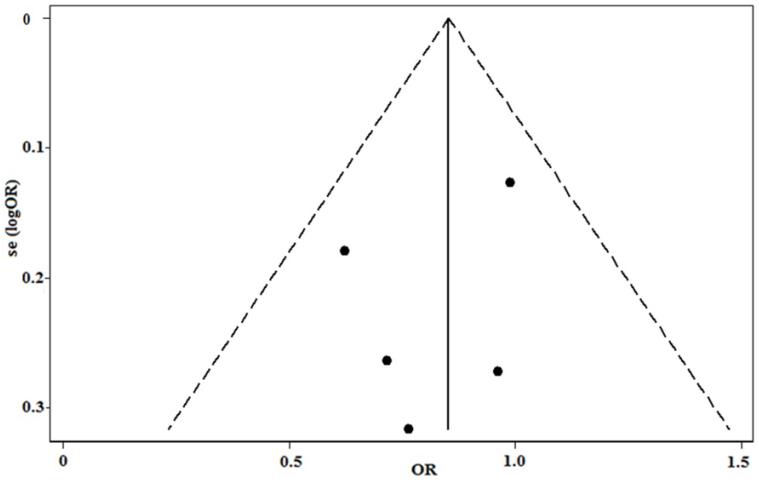

Figure 4. Funnel plots for rs4804611 and myocardial infarction in recessive model (GG versus AG/AA).

tion between rs4804611 polymorphism and MI in five genetic models: allele model (G vs. A), homozygote (co-dominant) model (GG vs. AA), heterozygote (co-dominant) model (AG vs. AA), dominant model (GG/AG vs. AA) and recessive model (GG vs. AG/AA). Subgroup analyses were further performed according to ethnicity (Asian and Caucasian). Publication bias was analyzed using the Egger's linear regression test and funnel plot. Publication bias was considered present when *P* value was less than

Table 1. Main characteristics of studies included in the meta-analysis

Studies	Country	Ethnicity	Number (case/control)	Age, year (case/control)	Male,% (case/control)	Hypertensionn% (case/control)	Study type	Primary outcome	Genotype method	NOS score	HWE test (control)
Benjamin et al. (2007)	America	Caucasian	413/792	50.7/73.9	50/51	60/57	Case-control study	MI	PCR-RFLP	9	Yes
Shiffman et al. (2005)	America	Caucasian	560/891	62/66	45/37	62/33	Case-control study	MI	PCR-RFLP	9	Yes
Koch et al. (2009)	Germany	Caucasian	3657/1211	NA	75.80/50.62	NA	Case-control study	MI	PCR-RFLP	9	Yes
Yamada et al. (2007)	Japan	Asian	1328/2105	63.3/67.6	78.0/42.5	72.7/30.3	Case-control study	MI	sequence-specific probes array	9	Yes
Zee et al. (2006)	America	Caucasian	341/341	NA	100/100	NA	Case-control study	MI	PCR-RFLP	9	Yes

HWE: Hardy-Weinberg equilibrium; MI: myocardial infarction; NA: not available.

Table 2. Main results of the meta-analysis of the pooled OR

Variable	Cases/controls (n)	ORb (95% CI) *P* value				
		Allele (G vs. A)	Homozygote (GG vs. AA)	Heterzygote = (AG vs. AA)	Dominant (GG/AG vs. AA)	Recessive (GG vs. AG/AA)
All subjects	6299/5340	1.002 (0.878-1.142) 0.980	0.841 (0.707-1.000) 0.050a	1.088 (0.947-1.249) 0.233	1.046 (0.903-1.213) 0.550	0.833 (0.704-0.985) 0.033a
Ethnicity						
Caucasian	4971/3235	0.954 (0.841-1.082) 0.465	0.844 (0.705-1.011) 0.065a	1.027 (0.929-1.135) 0.604a	0.995 (0.905-1.095) 0.921a	0.839 (0.704-0.999) 0.048a

Ph, *P* value for Cochran's Q test for between-study heterogeneity in each genetic comparison model. a: A fixed effects model was used when the *P* value for Cochran's Q test for heterogeneity was more than 0.1. Otherwise, a random effects model was used. b: Crude OR.

Table 3. Sensitivity analysis

Study omitted	Cases/controls (n)	Crude OR 95% CI				
		Allele (G vs. A)	Homozygote (GG vs. AA)	Heterzygote (AG vs. AA)	Dominant (GG/AG vs. AA)	Recessive (GG vs. AG/AA)
Benjamin et al. (2007)	413/792	1.01 (0.84, 1.17)	0.88 (0.69, 1.06)	1.07 (0.89, 1.26)	1.04 (0.85, 1.23)	0.87 (0.69, 1.05)
Shiffman et al. (2005)	560/891	1.07 (0.97, 1.16)	0.95 (0.75, 1.15)	1.15 (0.99, 1.30)	1.12 (0.99, 1.25)	0.92 (0.73, 1.12)
Koch et al. (2009)	3657/1211	1.01 (0.82, 1.20)	0.74 (0.49, 0.98)	1.11 (0.90, 1.32)	1.06 (0.84, 1.28)	0.73 (0.49, 0.97)
Yamada et al. (2007)	1328/2105	0.96 (0.85, 1.07)	0.87 (0.69, 1.05)	1.03 (0.92, 1.14)	1.00 (0.87, 1.12)	0.86 (0.68, 1.04)
Zee et al. (2006)	341/341	1.01 (0.86, 1.17)	0.85 (0.67, 1.04)	1.11 (0.93, 1.29)	1.07 (0.89, 1.25)	0.84 (0.66, 1.02)

Abbreviation: OR, odds ratio; 95% CI, 95% confidence interval.

0.05. Sensitivity analysis was also carried out to evaluate the stability of the meta-analysis. Briefly, a new analysis was performed through omitting one study at a time to test its influence on the overall estimate. All statistical analyses were done using STATA 11.0 (STATA Corp., College Station, TX, USA). All *P* values were two-tailed.

Results

Characteristics of included studies

22 potential eligible articles were initially identified through literature search. After different levels of screening, 5 articles in accordance with the inclusion criteria were finally included, and 17 articles, including 6 articles that were duplicated, 3 article that were not written in English, 3 articles were not about MI, 5 articles were not concerning ZNF627, were excluded in this meta-analysis (**Figure 1**) [10-14].

Overall, a total of 11639 subjects, including 6299 MI patients and 5340 healthy controls, were finally included from 5 independent researches in this meta-analysis. Among 5 eligible studies, 4 studies were conducted in Caucasian and 1 study was carried out in Asian. The genotype distribution of the controls in all studies conformed to the law of HWE. The characteristics of the included studies are summarized in **Table 1**.

Quantitative data synthesis

As shown in **Figure 2**, rs4804611 polymorphism was significantly associated with the risk of MI under recessive model (GG vs. AA/AG: Fixed effect model, OR = 0.833, 95% CI = 0.704-0.985, *P* = 0.033), but none of association was found under allele model, homozygote model, heterozygote model, and dominant model when pooling all the data in the meta-analysis (**Table 2**). We further performed the subgroup analysis by ethnicity and the result showed that statistical significant association existed between the rs4804611 polymorphism and the risk of MI in Caucasian under recessive model (GG vs. AA/AG: Fixed effect model, OR = 0.839, 95% CI = 0.704-0.999, *P* = 0.048) (**Figure 3**).

Sensitivity analysis

The aim of sensitivity analysis was to evaluate the influence of each study on the pooled OR and ensure that none of solo study was completely responsible for the combined results. The results of sensitivity analysis showed that the pooled OR was not materially affected by omitting any individual study under all genetic models, confirming that our results were robust (**Table 3**).

Publication bias

Visual inspection of the funnel plot did not reveal any evidence of obvious asymmetry for recessive model (**Figure 4**). In addition, the result of Egger's regression test suggested no publication bias existed under recessive model (*P* = 0.023, 95% CI: 0.269-1.814 for recessive model).

Discussion

Zinc finger gene family is one of major human gene families and plays a key role in the modulation of transcription. Several zinc finger proteins have been involved in the cardiovascular-related diseases. Variants of zinc finger protein 202 gene have been discovered to be strongly associated with coronary heart disease and atherosclerosis [9]. Variants in the zinc finger protein 259 gene are associated with the risk of hyperlipidaemia [8]. Recent studies have also found that variants of zinc finger protein 627 gene are associated with the risk of coronary heart disease, especially MI [10, 16, 17]. However, some researchers argue against the association of rs4804611 polymorphism in ZNF627 gene with MI [11, 12, 14]. Considering these inconsistent results, meta-analysis is a good approach to combine the results of various studies on the same topic, and to further estimate and explain their diversity [18].

To our knowledge, our study was the first report to pool published studies to estimate the association between rs4804611 and the susceptibility to MI. This meta-analysis included 11639 subjects (6299 MI patients and 5340 healthy controls) from 5 independent studies. The results demonstrated that rs4804611 polymorphism was significantly associated with the risk of MI under recessive model with little heterogeneity across studies. Meanwhile, the Egger's test and funnel plots indicated no publication bias existed and the sensitivity analysis suggested that none of single study influenced the pooled OR of all included studies. These data further enhance the reliability and stability of the meta-analysis results. In addition, a sub-

group analysis of ethnicity also displayed that a significant association existed between rs480 4611 polymorphism and the susceptibility to MI in Caucasian with little heterogeneity across studies.

Similar to other meta-analyses, two limitations existed in our meta-analysis. On the one hand, only 5 published studies with total 11639 subjects were included in the final meta-analysis. The sample size is still relatively small and may not provide sufficient statistical power to estimate the correlation between rs4804611 polymorphism in the ZNF627 gene and the susceptibility to MI. More studies with larger sample size are still needed to accurately provide a more representative statistical analysis. On the other hand, four out of five studies were conducted in Caucasian, only one study was carried out in Asian, and none was in African. Therefore, this meta-analysis should be included more studies conducted in Asian and African to improve the reliability of the final conclusion.

Conclusions

Our meta-analysis suggests that SNP rs480-4611 in ZNF627 gene is associated with the susceptibility to MI. However, further large scale case-control studies with rigorous design should be conducted to confirm above conclusions in the future. Despite of some limitations, this meta-analysis still gives us new insight into ZNF627 gene associated with the development and progression of MI.

Disclosure of conflict of interest

None.

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