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Original Article

Myeloperoxidase G-463A polymorphism and coronary artery disease susceptibility in the Chinese population: an updated meta-analysis and review

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Abstract: Objective: Although a number of studies have been conducted on the association between myeloperoxidase (MPO) G-463A polymorphism and coronary artery disease (CAD), this association remains elusive and controversial. To assess the effects of MPO G-463A polymorphism on the risk of CAD in the Chinese population, an updated meta-analysis was performed. Methods: Related studies were identified from PubMed, Springer Link, Ovid, Chinese Wanfang Data Knowledge Service Platform, Chinese National Knowledge Infrastructure (CNKI), and Chinese Biology Medicine (CBM) up to 28th March 2015. Pooled ORs and 95% CIs were used to assess the strength of the associations. Results: A total of ten studies including 1808 CAD cases and 1030 controls were involved in this meta-analysis. In overall analysis, MPO -436 A variant genotype reduces the risk of CAD in the Chinese population (A vs. G: OR = 0.53, 95% CI = 0.43-0.66; AA vs. GG: OR = 0.25, 95% CI = 0.15-0.40; AA vs. GA: OR = 0.45, 95% CI = 0.33-0.62; AA and GA combined vs. GG: OR = 0.51, 95% CI = 0.40-0.66; AA vs. GA and GG: OR = 0.34, 95% CI = 0.25-0.46). In subgroups stratified by geographical location and source of controls, significant associations were found in North China, in South China, in hospital-based studies and population-based studies. Conclusions: This meta-analysis showed that the MPO G-463A variants may influence CAD risk in Chinese. Studies with larger sample sizes and wider spectrum of populations are warranted to verify this finding.

Keywords: Myeloperoxidase, polymorphism, oronary artery disease, meta-analysis

Introduction

Coronary artery disease (CAD), is mostly fatal if remain untreated result into atherosclerosis in the epicardial coronary arteries. In the last century, there has been rapid increases in the global prevalence of CAD, which has become the important cause of cardiovascular mortality all over the world, is >4.5 million deaths in the developing countries [1, 2]. In China, cardiovascular disease is already the leading cause of mortality, and CAD is the 4th leading cause [3]. Numerous epidemiological studies have identified several risk factors for CAD, including age, sex, hypertension, diabetes mellitus, hypercholesterolemia, family history and smoking history [4]. However, only a subset of individuals exposed to these risk factors eventually develop CAD, indicating a pivotal role of genetic factors in the susceptibility to CAD. Most recently, genomics researches have revealed a series of new candidate markers that may contribute to the pathogenesis of CAD [5]. An important one is myeloperoxidase (MPO), which is expressed in activated neutrophils, monocytes and macrophages in human atherosclerotic plaque [6]. Evidence suggests that MPO plays a crucial role in the promotion and propagation of atherosclerosis [7, 8]; increased serum levels of MPO have been shown to predict the prevalence of CAD [9, 10].

MPO is a member of the heme peroxidase superfamily with gene coding locating in chromosome 17q23.1 [11]. Several single-nucleotide polymorphisms in the MPO gene have been

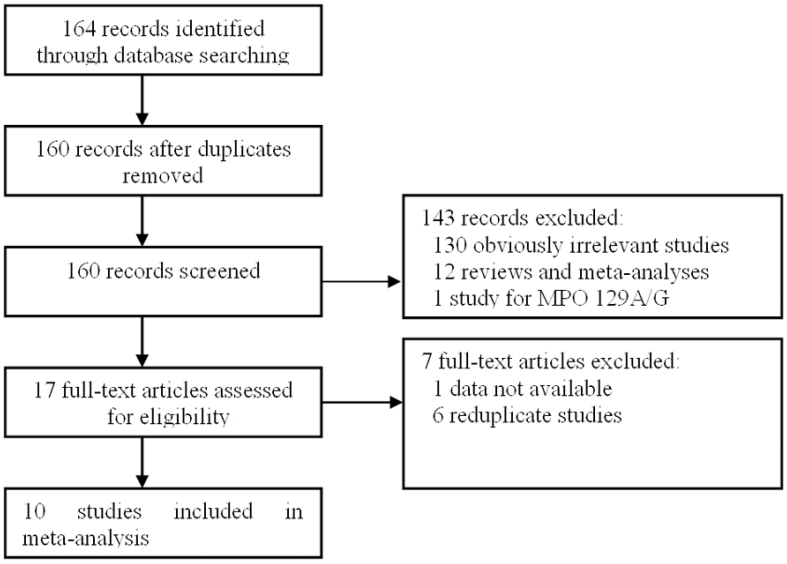

Figure 1. Flow diagram of the literature search.

identified [12-14]. One of the most frequently studied polymorphisms, MPO G-463A (rs233-3227), has been reported to be associated with significantly decreased transcriptional activity, because of the disruption of an SP1-binding site in an Alu hormone-responsive element (HRE) [15]. The first research of the association between MPO G-463A polymorphism and CAD was reported by Nikpoor and co-workers in 2001 among the French-Canadian population [16]. As a consequence, many studies analyzed the influence of MPO G-463A polymorphism on CAD risk, however, no clear consensus was reached. Meta-analyses of studies on the gene in other ethnic groups have been reported elsewhere and produced conflicting results [17-19]. In order to lessen the impact of different genetic background, we performed this meta-analysis to assess the relationship of MPO G-463A polymorphism with risk of CAD in the Chinese population.

Materials and methods

Literature search

A comprehensive literature search was performed using the PubMed, Springer Link, Ovid, Chinese Wanfang Data Knowledge Service Platform, Chinese National Knowledge Infrastructure (CNKI), and Chinese Biology Medicine (CBM) for relevant articles published with the following Mesh terms: (MPO or myeloperoxidase) and (genetic polymorphism or gene or polymorphism) and (coronary artery disease or CAD) and (China or Chinese or Taiwan). An upper date limit of 28 March 2015 was applied and no lower date limit was used. The search was performed without any restrictions on language and focused on studies conducted in humans. Concurrently, the reference lists of reviews and retrieved articles were searched manually.

Inclusion/exclusion criteria

For inclusion, the studies must have met the following criteria: (1) case-control study or cohort study on association between the MPO G-463A polymorphism and CAD risk; (2) all patients diagnosis based on angiographic features, clinical or laboratory findings; (3) sufficient published data about sample size, odds ratio (OR), and their 95% confidence interval (CI); (4) all participants were Chinese; (5) provided detailed information on genotype frequency. Studies were excluded when they were: (1) not case-control study or cohort study; (2) duplicate of previous publication; (3) based on incomplete data; (4) meta-analyses, letters, reviews, or editorial articles.

Data extraction

Information was extracted carefully from all eligible studies independently by two investigators according to the inclusion criteria listed above. Disagreements were resolved through a discussion between the two authors, and if consensus was not achieved the decision was made by all the reviewers. The title and abstract of all potentially relevant articles were screened to determine their relevance. Full articles were also scrutinized if the title and abstract were ambiguous. The following data was collected from each study: first author's surname, year of publication, geographical location, and source of controls, ethnicity of study population, sample size, and the number of subjects with MPO G-463A genotypes. If data from any category were not reported in the primary study, the items were designated 'not stated'. We did not contact the author of the primary study to request the information.

Table 1. Characteristics of studies included in the meta-analysis

Reference	Source of controls	Geographical location	Case number	Control number	Case			Control			HWE	
					GG	GA	AA	GG	GA	AA	χ^2	*P*
Hao 2006 [28]	PB	Shandong	105	105	68	35	2	53	39	13	1.80	0.179
Zhang 2006 [29]	HB	Gansu	171	111	135	36	0	71	38	2	1.49	0.222
Li 2007 [30]	HB + PB	Anhui	79	69	68	10	1	48	20	1	0.46	0.498
Zhang 2009 [31]	PB	Fujian	220	105	148	69	3	55	44	6	0.54	0.464
Zhang 2009a [32]	HB	Jiangsu	141	76	78	52	11	14	33	29	0.71	0.401
Zhong 2009 [33]	HB	Jiangsu	229	230	152	69	8	135	74	21	4.97	0.026
Du 2010 [34]	HB	Anhui	191	95	109	60	22	39	32	24	9.08	0.003
Li 2010 [35]	HB	Jiangsu	219	70	64	116	39	9	44	17	5.24	0.022
Han 2011 [36]	HB	Fujian	157	78	101	49	7	39	28	11	2.41	0.120
Lin 2011 [37]	HB	Tianjin	296	91	217	70	9	66	22	3	0.46	0.496

PB Population-based, HB hospital-based.

Table 2. Main results in the total and subgroup analysis

Analysis model	Study groups	n	Random-effect model	Fixed-effect model	Heterogeneity	
			OR (95% CI)	OR (95% CI)	χ^2	P
A vs. G	Total analysis	10	0.53 (0.43-0.66)	0.54 (0.48-0.62)	23.76	0.005
	PB	2	0.54 (0.40-0.73)	0.54 (0.40-0.73)	0.12	0.732
	HB	7	0.54 (0.40-0.73)	0.55 (0.47-0.64)	23.28	0.001
	South China	5	0.50 (0.35-0.72)	0.52 (0.44-0.62)	17.11	0.002
	North China	5	0.57 (0.44-0.75)	0.57 (0.40-0.70)	6.21	0.184
AA vs. GG	Total analysis	10	0.25 (0.15-0.40)	0.25 (0.18-0.34)	14.98	0.092
	PB	2	0.15 (0.05-0.43)	0.15 (0.05-0.41)	0.17	0.676
	HB	7	0.26 (0.15-0.47)	0.26 (0.18-0.37)	13.34	0.038
	South China	5	0.20 (0.11-0.38)	0.21 (0.14-0.32)	8.26	0.082
	North China	5	0.34 (0.17-0.67)	0.32 (0.19-0.54)	4.77	0.312
AA vs. GA	Total analysis	10	0.46 (0.32-0.65)	0.45 (0.33-0.62)	10.28	0.328
	PB	2	0.24 (0.08-0.69)	0.23 (0.08-0.65)	0.34	0.563
	HB	7	0.48 (0.32-0.71)	0.48 (0.35-0.67)	7.35	0.290
	South China	5	0.43 (0.26-0.72)	0.45 (0.31-0.66)	6.42	0.170
	North China	5	0.49 (0.28-0.86)	0.46 (0.27-0.79)	3.85	0.427
AA + GA vs. GG	Total analysis	10	0.51 (0.40-0.66)	0.53 (0.45-0.63)	19.19	0.024
	PB	2	0.54 (0.38-0.78)	0.54 (0.38-0.78)	0.01	0.924
	HB	7	0.51 (0.35-0.72)	0.54 (0.44-0.65)	18.34	0.005
	South China	5	0.45 (0.29-0.70)	0.50 (0.40-0.62)	13.28	0.028
	North China	5	0.57 (0.42-0.77)	0.58 (0.45-0.74)	5.42	0.247
AA vs. GG + GA	Total analysis	10	0.34 (0.22-0.51)	0.34 (0.25-0.46)	14.63	0.102
	PB	2	0.18 (0.06-0.51)	0.17 (0.06-0.48)	0.24	0.625
	HB	7	0.36 (0.22-0.59)	0.38 (0.27-0.50)	12.28	0.056
	South China	5	0.31 (0.16-0.57)	0.33 (0.23-0.47)	4.32	0.365
	North China	5	0.39 (0.22-0.70)	0.36 (0.22-0.60)	10.11	0.039

PB Population-based, HB hospital-based, South China including Jiangsu and Fujian; North China including Shandong, Anhui, Gansu and Tianjin.

Statistical analysis

Crude odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of association between the MPO G-463A polymorphism and CAD risk. The significance of the pooled OR was determined by the Z test. Between-study heterogeneity was assessed by the Q-statistics with *P*-values < 0.1. Dependent on the results of heterogeneity test among indi-

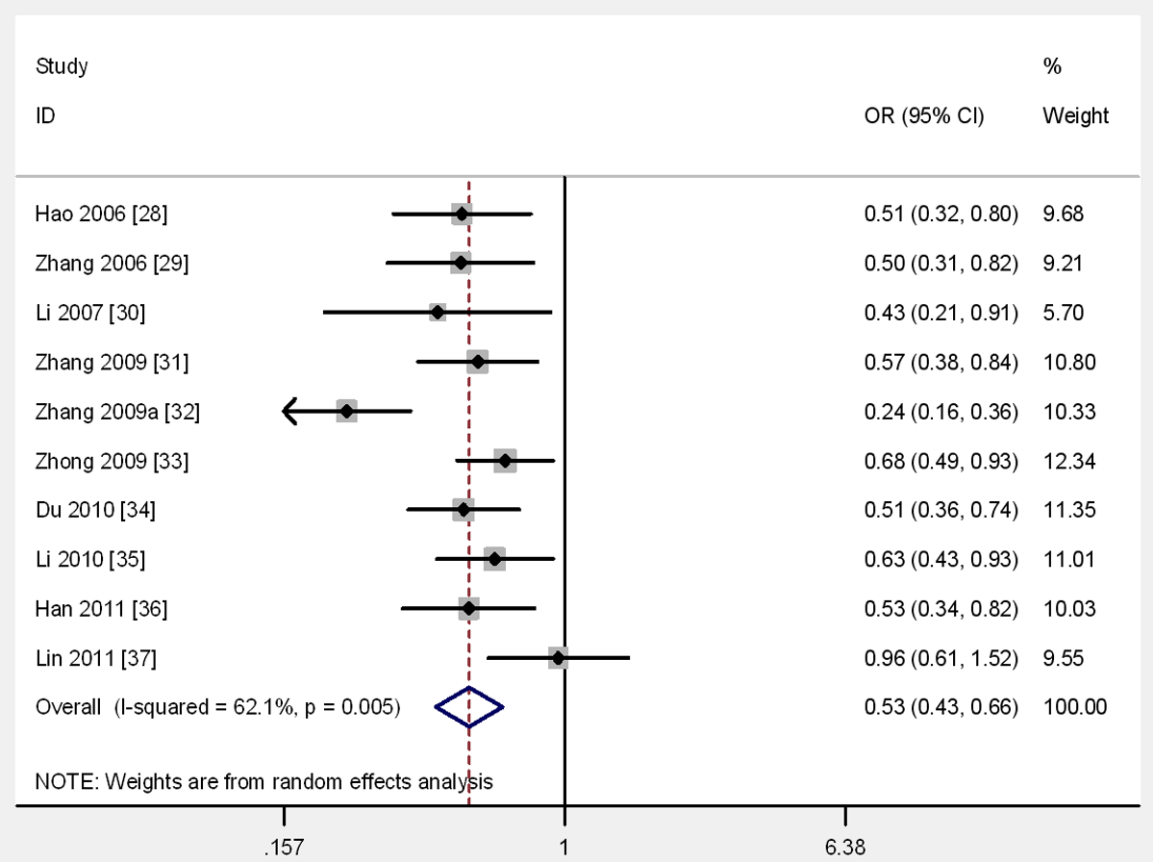

Figure 2. The forest plot of MPO G-463A polymorphism and CAD risk under allele genetic model.

vidual studies, the fixed-effect model (Mantel-Haenszel) or random-effect model (DerSimonian and Laird) was selected to summarize the combined ORs and their 95% CIs. Hardy-Weinberg equilibrium (HWE) was calculated by using the goodness-of-fit test, and deviation was considered when $P < 0.05$. Sensitivity analysis was conducted to verify stability of the meta-analysis using both models (the fixed effect model and random effect model). Begg's funnel plots and Egger's linear regression test were used to assess publication bias. In addition to the comparison among all subjects, we also performed stratification analyses by geographical location and source of controls. All the statistical analysis was conducted by using STATA statistical package (version 10, STATA, College Station, TX).

Results

Eligible studies

Figure 1 graphically illustrates the trial flow chart. A total of 164 articles regarding MPO G-463A polymorphism with respect to CAD were identified. After screening the titles and abstracts, 147 articles were excluded because they were review articles, duplicates, or irrelevant to the current study. Of the 17 potentially relevant articles [20-36] identified for full study retrieval, one article [20] was excluded because of insufficient genotyping data, six [21-26] were excluded because they concerned subjects included in an expanded series [29, 30, 32, 34, 35]. Finally, ten studies [27-36] including 1808 CAD cases and 1030 controls were involved in this meta-analysis according to the inclusion criteria. The publication year of studies ranged from 2006 to 2011. Nine of these studies were written in Chinese, one study in English. The characteristics of the included studies are summarized in **Table 1**.

Meta-analysis results

Table 2 lists the primary results. Overall, the variant genotypes of MPO G-463A polymorphism were associated with decreased risk of CAD in all the models (for AA vs. GG: OR = 0.25,

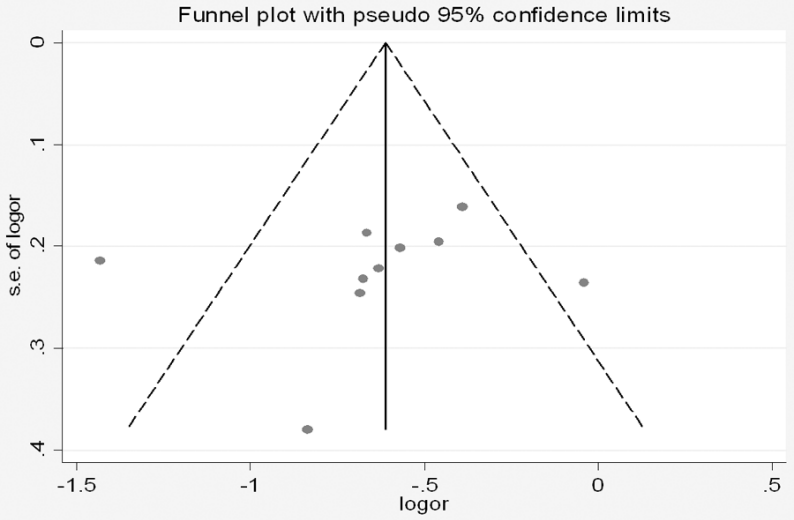

Figure 3. Begg's funnel plot of MPO G-463A polymorphism and CAD risk under the allele genetic model.

95% CI = 0.15-0.40, P = 0.092 for heterogeneity; for AA vs. GA: OR = 0.45, 95% CI = 0.33-0.62, P = 0.328 for heterogeneity; for AA and GA combined vs. GG: OR = 0.51, 95% CI = 0.40-0.66, P = 0.024 for heterogeneity; for AA vs. GA and GG: OR = 0.34, 95% CI = 0.25-0.46, P = 0.102 for heterogeneity). For the allele A versus allele G, the pooled OR was 0.53 (95% CI = 0.43-0.66, P = 0.005 for heterogeneity) (**Figure 2**). However, there was significant heterogeneity between studies in some model (A vs. G; AA vs. GG; and AA + GA vs. GG). Hence, we then performed subgroup analysis by geographical location and source of controls. In the stratified analysis by geographical location, significant associations were found both in North China (A vs. G: OR = 0.57, 95% CI = 0.40-0.70; AA vs. GG: OR = 0.32, 95% CI = 0.19-0.54; AA vs. GA: OR = 0.46, 95% CI = 0.27-0.79; AA + GA vs. GG: OR = 0.58, 95% CI = 0.45-0.74; AA vs. GG + GA: OR = 0.39, 95% CI = 0.22-0.70) and South China (A vs. G: OR = 0.50, 95% CI = 0.35-0.72; AA vs. GG: OR = 0.21, 95% CI = 0.14-0.32; AA vs. GA: OR = 0.45, 95% CI = 0.31-0.66; AA + GA vs. GG: OR = 0.45, 95% CI = 0.29-0.70; AA vs. GG + GA: OR = 0.33, 95% CI = 0.23-0.47). In the stratified analysis by source of controls, significant results were also found both in the population-based studies (A vs. G: OR = 0.54, 95% CI = 0.40-0.73; AA vs. GG: OR = 0.15, 95% CI = 0.05-0.41; AA vs. GA: OR = 0.23, 95% CI = 0.08-0.65; AA + GA vs. GG: OR = 0.54, 95% CI = 0.38-0.78; AA vs. GG + GA: OR = 0.17, 95% CI = 0.06-0.48) and hospital-based studies (A vs. G: OR = 0.54, 95% CI = 0.40-0.73; AA vs. GG: OR = 0.26, 95% CI = 0.15-0.47; AA vs. GA: OR = 0.48, 95% CI = 0.35-0.67; AA + GA vs. GG: OR = 0.51, 95% CI = 0.35-0.72; AA vs. GG + GA: OR = 0.38, 95% CI = 0.27-0.50).

Sensitive analysis and bias diagnosis

In order to compare the difference and evaluate the sensitivity of the meta-analyses, we used both models (the fixed-effect model and random-effect model) to evaluate the stability of the meta-analysis. All the significant results were not materially altered (**Table 2**). Hence, results of the sensitivity analysis suggest that the data in this meta-analysis are relatively stable and credible. The Begg's funnel plot and Egger's test were performed to assess the publication bias of literatures. The shape of the funnel plots did not reveal obvious asymmetry (**Figure 3**). Then, the Egger's test was used to provide statistical evidence of funnel plot symmetry. The Egger's test indicated that there were no obvious publication bias under the allele model in overall analyses (t = -0.81, *P* = 0.443).

Discussion

Since the identification of MPO G-463A polymorphism, a number of studies have investigated the genetic effect of this polymorphism on CAD susceptibility, but the results are varied and inconclusive. Meta-analysis as a powerful statistical method could improve the reliability of the conflicting results about the same topic and identify the reason for the variation. So we did this updated meta-analysis to estimate the relationship between MPO G-463A polymorphism and susceptibility to CAD among the Chinese population, in order to lessen the impact of genetic background and gene-environment interactions. This meta-analysis involved 10 articles with 1808 CAD cases and 1030 controls. The results showed that there

was a significant genetic effect of the MPO G-463A gene polymorphism on CAD in the Chinese population. The sensitivity analysis confirmed the reliability and stability of the meta-analysis and no publication bias was found among studies by Egger's test. Therefore, the findings from our meta-analysis provide a strong evidence for the association between MPO G-463A polymorphism and CAD in the Chinese population. Our results were consistent with a previously published meta-analysis, which indicated significantly decreased risks in Chinese populations (AA vs. GG: OR = 0.21, 95% CI = 0.10-0.43; GA vs. GG: OR = 0.57, 95% CI = 0.44-0.74), but not in Caucasians (AA vs. GG: OR = 0.59, 95% CI = 0.22-1.57; GA vs. GG: OR = 0.93, 95% CI = 0.80-1.09) [17].

Considering the existence of heterogeneity, we performed a stratified analysis based on geographical location and source of controls. The results showed that the MPO G-463A polymorphism significantly decreased risk for CAD in North China, in South China, in hospital-based studies and population-based studies. However, Tang et al.' meta-analysis indicated significant associations in studies with hospital-based controls, but not in studies with population-based controls [17]. The inconsistent results may be explained, at least in part, by the inherent bias brought by different populations (Caucasians and Chinese), since ethnically diverse subjects may have unique cultures and lifestyles that can contribute to different genetic characteristics. Another factor that might be related to the inconsistency in the findings is that, only 2 publications were population-based study, and it is too little for the meta-analysis. Thus, the results on study design should be more cautious for interpretation.

Some limitations of this meta-analysis should be addressed. First, the present meta-analysis was based primarily on unadjusted effect estimates and confidence intervals and the confounding factors were not controlled. Second, only published studies included in our study, we cannot exclude the possibility of publication bias, although neither Egger's test nor funnel plots found evidence for a publication bias. Third, the sample size is still relatively small and may not provide sufficient power to estimate the association between MPO G-463A gene polymorphism and CAD risk in Chinese, especially in subgroup analyses. Finally, although we minimized this likelihood by performing a careful search of published studies and subgroup analyses, significant inter-study heterogeneity nevertheless existed in the some comparisons.

Conclusion

This meta-analysis suggests that MPO -436 A variant genotype reduces the risk of CAD in Chinese population. Concerning CAD with multifactorial etiology, to further evaluate gene-gene and gene-environment interactions on MPO G-463A polymorphism and CAD, larger studies in selected populations with different environmental background or other risk factors are required. Such studies may eventually lead to have a better, comprehensive understanding of the association between the MPO G-463A polymorphism and CAD risk.

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Disclosure of conflict of interest

None.

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