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Original Article

Association between MCP-1 A2518G polymorphism and coronary artery disease risk: evidence from 21 case-control studies

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Abstract: The MCP-1 A2518G polymorphism has been indicated to be correlated with coronary artery disease (CAD) susceptibility, but the results of studies are still debatable. Thus, a meta-analysis was carried out. The databases of PubMed, Embase, Web of Science, and CNKI (China National Knowledge Infrastructure) were searched. The related data were extracted and pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. At last, 21 case-control studies with 8,480 cases and 1,2366 controls were included in this meta-analysis. Overall, the significant association was showed (G allele vs. A allele: OR = 1.11, 95% CI: 1.02-1.21, *P* = 0.000; AG + GG vs. AA: OR = 1.14, 95% CI: 1.01-1.29, *P* = 0.000) between MCP-1 A2518G polymorphism and CAD risk. However, the evidence of heterogeneity was found among the investigated studies, and subgroup analyses were conducted according to source of population in control, ethnicity, types of CAD end points, and status of HWE. In conclusion, the meta-analysis suggests the MCP-1 A2518G polymorphism (AG + GG genotypes) is a risk factor for CAD. Further large-scale and well-designed studies are still needed to confirm the results of our meta-analysis.

Keywords: Coronary artery disease, MCP-1, meta-analysis, polymorphism

Introduction

Coronary artery disease (CAD) also known as coronary heart disease (CHD), is one of leading cause for death and disability worldwide [1]. The study pointed to a link between the risk of CAD and genetic or environmental factor, as well as their interactions [2]. The risk factors for CAD included hypercholesterolemia, hypertension, smoking, obesity and diabetes have be confirmed [3]. After adjusted risk factors, the genetic factor might predispose individuals to CAD, and the study also exhibited it has been estimated that genetic risk factors might explain approximately 20%-60% of CAD pathogenesis [4]. Numerous studies have been performed on the association of genetic variants with CAD susceptibility, the monocyte chemoattractant protein-1 (MCP-1) gene polymorphism has been also explored for CAD risk. The previous studies suggested that increased serum MCP-1 levels is associated with risk of CAD or other atherosclerotic vascular diseases, and MCP-1 has been served as a direct marker of inflammatory activity in CAD pathogenesis [5, 6].

MCP-1, also known as CCL-2 (CC chemokine ligand 2), is the key chemokine in the process of atherosclerotic vascular inflammation [7]. The human MCP-1 gene is located on chromosome 17q11.2-q21.1 [8]. A polymorphic A/G allele at the -2518 position of the promoter region of MCP-1 has been shown to increase the levels of MCP-1 [9].

In the past decade, several studies have investigated the associations between the MCP-1 A2518G polymorphism and CAD susceptibility and yielded apparently conflicting results. In consideration of the extensive role of MCP-1 A2518G polymorphism in CAD process. We therefore performed a meta-analysis of the published studies to clarify the inconsistency and to establish a comprehensive conclusion of the relationship between MCP-1 A2518G polymorphism and CAD risk.

Methods

Publication search

The electronic databases of PubMed, Embase, CNKI, and Web of Science were searched using

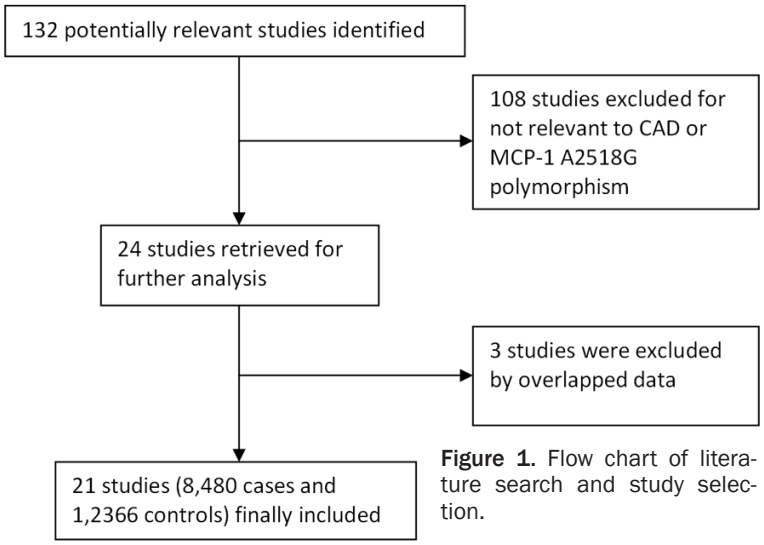

Figure 1. Flow chart of literature search and study selection.

the following terms: "CCL2 or MCP-1 or monocyte chemotactic protein 1" in combination with "acute coronary syndrome or myocardial infarction or acute myocardial infarction or cardiovascular disease or ischemic heart disease or coronary heart disease or coronary artery disease" and "polymorphism or variant or mutation" up to July 2014. Additional studies not included by our database searches were identified by reviewing the reference lists of retrieved articles.

Inclusion and exclusion criteria

All selected studies complied with the following criteria: (1) case-control or cohort study on the MCP-1 polymorphism and risk of CAD, (2) all patients diagnosed with CAD should be confirmed by clinical examinations, such as electrocardiography, echocardiography, and coronary angiography; (3) valuable data for estimation of the odds ratio (OR) and 95% confidence interval (CI). Studies should be excluded if one of the following criteria existed: (1) not relevant to CAD or MCP-1, (2) not designed as case-control studies, (3) genotype frequencies not specified, (4) animal studies, (5) editorials, reviews, and abstracts. If the published studies involved in overlap populations and the study with the largest sample size or the most recently published study would be included.

Data extraction

Data were extracted independently and entered separate databases: the first author, year of publication, geographic area, ethnicity, sample size, mean age of CAD patients and controls, the percentage of male in patients and controls, genotyping method, and Hardy-Weinberg equilibrium in controls.

Statistical analysis

The association between the MCP-1 A2518G polymorphism and CAD risk was evaluated by OR with 95% CI. Five genetic models were used in our analysis: the allele model (G allele vs. A allele), the dominant model (AG + GG vs. AA), the recessive model (GG vs. AA + AG), the homozygous model (GG vs. AA), and the heterozygous model (GG vs. GA). Genotype frequencies of controls were tested for Hardy-Weinberg equilibrium (HWE) using the χ^2 test for each study included in the meta-analysis. The heterogeneity test was performed by the χ^2-based Q test [10]. When the Q-test reported a *P* value of more than 0.10, the fixed effects model was used to calculate the pooled OR and 95% CI [11], otherwise the random effects model was used [12]. Source of controls (population or hospital based), ethnicity (Asian or Caucasian), types of CAD end points (myocardial infarction [MI] versus coronary stenosis), and status of HWE (yes or no) were prespecified as characteristics for assessment of heterogeneity. The visual funnel plot was drawn to estimate the potential publication bias, and the Egger's linear regression test was utilized to quantitatively assess the publication bias [13]. All statistical tests were carried out using STATA 12.0 software (Stata Corporation, College Station, Texas, USA). A *P* value of less than 0.05 was considered significant. All of the *P* values were two sided.

Results

Study characteristics

A total of 132 articles were retrieved after a comprehensive search, and of which 108 of these studies were excluded as not relevant to CAD risk or the AMCP-1 A2518G genetic polymorphism. Based on their full articles, a final

Table 1. Main characteristics of eligible studies

Study	Year	Country	Ethnicity	Source of control	Endpoint	Sample size (case/control)	Mean age in case/control, (years)	Gender component in case/control (% male)	Genotyping method	*HWE*
Szalai	2001	Hungary	Caucasian	PB	CAD	318/320	57.6/58.9	76.1/75.0	PCR-RFLP	0.827
Simeoni	2004	Germany	Caucasian	HB	CAD	2693/528	63.8/56.9	73.9/51.3	PCR-RFLP	0.603
Cermakova	2005	Czech	Caucasian	HB	MI	139/359	50.6/53.7	79.1/66.9	PCR-SSP	0.492
McDermott	2005	America	Caucasian	PB	MI	107/1689	NA/NA	78.5/48.3	PCR-RFLP	0.441
Bjarnadottir	2006	Iceland	Caucasian	PB	MI	455/1834	58.6/76.4	78.0/39.5	PCR-RFLP	0.954
Iwai	2006	Japan	Asian	PB	MI	364/2186	57.9/65.2	87.1/46.0	TaqMan	0.263
Kim	2007	America	Caucasian	PB	CAD	120/559	48.4/46.1	68.3/40.6	MassARRAY	0.235
Park	2007	Korea	Asian	PB	MI	169/170	62.2/62.6	75.9/67.1	single-base primer extension	0.251
Jemaa	2008	Tunisia	African	PB	MI	319/467	53.9/51.3	100/100	PCR-RFLP	0.571
Cam	2008	Turkey	Asian	PB	CAD	171/151	48.9/43.5	77.2/74.8	PCR-RFLP	0.041
Bucova	2009	Slovak	Caucasian	PB	CAD	270/499	62/64	45.1/63.3	PCR-SSP	0.955
Zhang	2009	China	Asian	PB	CAD	502/410	59.3/52.9	77.3/59.0	PCR-RFLP	0.3
van Wijk	2010	UK	Caucasian	PB	CAD	915/1691	65.2/65.2	63.8/62.8	KASPar	0.915
Zhong	2010	China	Asian	PB	CAD	132/153	52.1/51.2	48.5/45.1	TaqMan	0.315
He	2011	China	Asian	HB	MI	330/165	65.63/56.39	69.39/50.91	PCR-RFLP	0.033
El Mahgouba	2011	Egypt	Caucasian	PB	MI	30/25	54/54	86.7/88	PCR-RFLP	0.75
Lin	2012	China	Asian	PB	CAD	392/216	65.73/66.43	73.7/60.2	PCR–RFLP	0.785
Wang	2012	China	Asian	HB	MI	150/159	63.8/65.9	68/67.9	PCR–RFLP	0.016
Yang	2012	China	Asian	HB	CAD	120/60	NA/NA	NA/NA	PCR-RFLP	0.075
Kaur	2013	India	Asian	HB	CAD	150/174	59.92/49.90	NA/NA	ARMS-PCR	0.017
Xu	2013	China	Asian	HB	MI	634/601	63.0/62.0	74.0/71.4	PCR–RFLP	0.292

HB: hospital-based, PB: population-based; HWE: Hardy-Weinberg equilibrium; CAD: coronary artery disease; MI: myocardial infarction.

Table 2. Main characteristics of relevant studies selected for meta-analysis

Analysis	G vs. A		AG + GG vs. AA		GG vs. AG + AA		GG vs. AA		GG vs. AG	
	OR (95% CI)	P_h	OR (95% CI)	P_h	OR (95% CI)	P_h	OR (95% CI)	P_h	OR (95% CI)	P_h
Overall	1.11 (1.02-1.21)	0.000	1.14 (1.01-1.29)	0.000	1.13 (0.98-1.30)	0.019	1.18 (0.98-1.42)	0.001	1.08 (0.94-1.24)	0.085
Source of control										
PB	1.12 (1.01-1.24)	0.001	1.18 (1.03-1.35)	0.008	1.09 (0.90-1.33)	0.007	1.17 (0.92-1.49)	0.002	1.03(0.85-1.25)	0.027
HB	1.10 (0.93-1.31)	0.005	1.06 (0.81-1.38)	0.001	1.15 (0.97-1.36)	0.459	1.22 (0.88-1.69)	0.047	1.17(0.98-1.40)	0.812
Ethnicity										
Caucasian	1.10 (0.96-1.27)	0.001	1.13 (0.96-1.34)	0.003	1.14 (0.83-1.57)	0.006	1.17 (0.84-1.64)	0.005	1.09 (0.79-1.50)	0.012
Asian	1.10 (0.98-1.25)	0.007	1.13 (0.92-1.39)	0.003	1.08 (0.92-1.27)	0.265	1.15 (0.90-1.46)	0.021	1.05 (0.92-1.19)	0.514
HWE										
Yes	1.09 (1.00-1.20)	0.000	1.12 (0.99-1.26)	0.001	1.11 (0.95-1.31)	0.013	1.16 (0.94-1.42)	0.002	1.07 (0.92-1.24)	0.66
No	1.21 (0.92-1.59)	0.032	1.23 (0.77-1.97)	0.007	1.24 (0.93-1.65)	0.364	1.32 (0.77-2.28)	0.073	1.18 (0.87-1.59)	0.334
End point										
Coronary stenosis	1.10 (1.03-1.18)	0.302	1.12 (1.03-1.23)	0.648	1.13 (0.99-1.29)	0.104	1.26 (1.02-1.57)	0.081	1.09 (0.95-1.26)	0.187
Myocardial infarction	1.12 (0.96-1.31)	0.000	1.17 (0.92-1.47)	0.000	1.11 (0.88-1.40)	0.024	1.14 (0.84-1.55)	0.003	1.06 (0.85-1.33)	0.068

OR: odds ratio; CI: confidence interval; P_h: *P* value for heterogeneity, If *P*>0.1, ORs were calculated using fixed-effects model, otherwise the random-effects model was used; PB: population-based; HB: hospital-based.

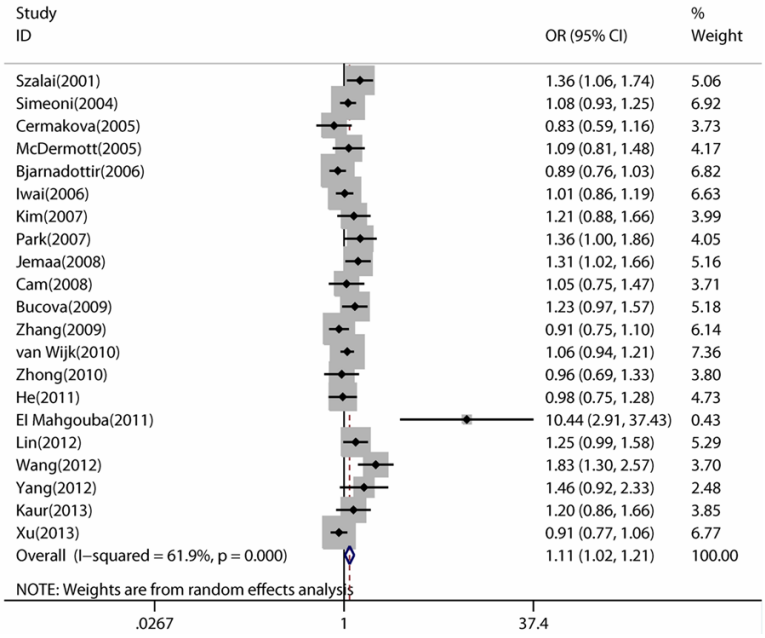

Figure 2. Forest plot for MCP-1 A2518G polymorphism and CAD risk in the genetic model of G allele vs. A allele.

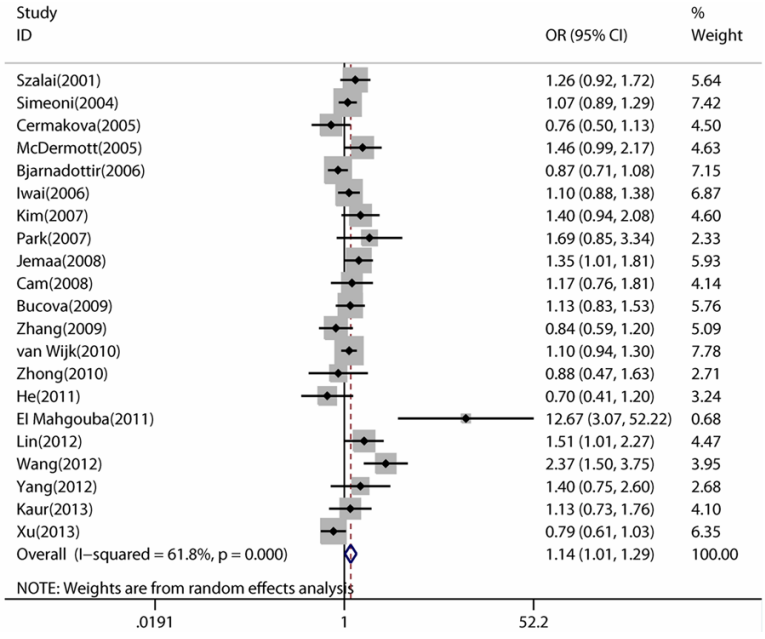

Figure 3. Forest plot for MCP-1 A2518G polymorphism and CAD risk in the genetic model of AG + GG vs. AA.

list of 24 publications were collected for meta-analysis [14-37]. Among these studies, the populations of one study [19, 23, 36] were overlapped by other two studies [22, 37]. Totally, there were 21 case-control studies with 8,480 cases and 12,366 controls included in the meta-analysis. The Flow chart of literature search was showed in **Figure 1**.

The genotype distribution in the control of all studies was consistent with Hardy-Weinberg equilibrium (HWE) except for four study (P<0.05). Among the 21 case-control studies, 10 studies included Asian population, and 9 assessed Caucasian population. The characteristics of Controls were mainly matched in terms of gender and age. One [22] of which was analyzed according to types of coronary disease (myocardial infarction and coronary stenosis) and were taken as two independent studies assessed. Seven studies were hospital-based, and fourteen were population-based. Furthermore, there were 11 studies of coronary stenosis (CS) and 11 studies of myocardial infarction (MI). The characteristics of the selected studies are summarized in **Table 1**.

Quantitative data synthesis

A summary of the meta-analysis results on the association between MCP-1 A2518G polymorphism and susceptibility to CAD was provided in **Table 2**. The meta-analysis results revealed that MCP-1 A2518G polymorphism may increase the risk of CAD (G allele vs. A allele: OR = 1.11, 95% CI: 1.02-1.21, P = 0.000; AG + GG vs. AA: OR = 1.14, 95% CI: 1.01-1.29, P = 0.000) (**Figures 2**, **3**).

In a stratified analysis by the source of controls, the significant associations of MCP-1 A2518G polymorphism with risk of CAD were found in population based on the two genetic models (G allele vs. A allele: OR = 1.12, 95% CI: 1.01-1.24, P = 0.001; AG + GG vs. AA: OR = 1.18, 95% CI:

1.03-1.35, P = 0.008). There was no significant association in the hospital-based subgroup. When studies were stratified for ethnicity, no significant associations were found for Asian or Caucasian populations in all genetic models.

In the subgroup analyses by HWE, after excluding four studies that is not in accordance with HWE, there was no evidence of significant association between MCP-1 A2518G polymorphism and the risk of CAD in any genetic model.

In the subgroup analyses by CAD end points, we found significant association between MCP-1 A2518G polymorphism and CDA risk for CS (G allele vs. A allele: OR = 1.03, 95% CI: 1.03-1.18, P = 0.302; AG + GG vs. AA: OR = 1.12, 95% CI: 1.03-1.23, P = 0.648; GG vs. AA: OR = 1.28, 95% CI: 1.02-1.60, P = 0.060), but the MCP-1 A2518G polymorphism was not related with CAD risk in MI group.

Publication bias

The shape of funnel plots did not reveal any evidence of obvious asymmetry in the overall meta-analysis. Egger's test also displayed no statistical evidence of publication bias under any genetic model, suggesting no publication bias.

Discussion

Abundant studies have suggested that MCP-1 is commonly over-expressed in a wide variety of CVD, including atherosclerosis, hypertension, coronary heart disease, and MI [38]. The study associated MCP-1 A2518G polymorphism with CAD risk firstly reported the higher frequency of G allele in CAD patients and a two-fold increase of GG homozygote in Hungarian patients [14]. A study with acute myocardial infarction (MI) patients was conducted on an Egyptian population showed a significantly higher frequency of the GA or GG genotype compared to the controls' [30]. Similar results were revealed on Slovakian men [22]. However, in a study with MI patients from Tunisia population showed a significant but not independent association of MCP-1-2518G-allele with CAD risk [20]. A series of studies have investigated the association between the MCP-1 A2518G polymorphism and CAD susceptibility, but the controversial or inconclusive results were found.

In order to provide the comprehensive and reliable conclusion, we performed the present meta-analysis of 21 independent studies with 8,480 cases and 1,2366 controls. Our meta-analysis provided the evidence that the patients with G allele carriers might have the increased risk of CAD.

Significant heterogeneity between studies was observed in the present meta-analysis. To identify the cause of heterogeneity, we stratified the data according to source of control, ethnicity, types of CAD end points and presence of HWE deviation for subgroup analyses [39]. In a stratified analysis by the source of control, the patients with G allele carriers showed the increased susceptibility of CAD compared with homozygote AA or A allele carriers among population-based but not hospital-based group. However, in some hospital-based studies, there might be the poor criteria during control subjects selected and these studies included might lead to some selected biases in the analysis. When studies were stratified for ethnicity, no significant association was found for Asian or Caucasian populations in all genetic models.

A potential false-positive association was found based on the genotype distribution deviated significantly from HWE. When the meta-analysis was restricted to those studies consistent with HWE, and no significant association was found in any genetic model.

In the subgroup analyses by CAD end points, we found significant association between MCP-1 A2518G polymorphism and CAD risk for CS group, but no significant association in MI group. Although both CS and MI result from atherosclerotic occlusion of the coronary arteries and share many of the same inflammatory factors, the pathological manifestations of CS and MI are still different.

Some limitations of this meta-analysis should be considered in interpreting the results. First, although we performed the analysis with strict criteria for study inclusion and precise data extraction, there is a significant between-study heterogeneity in all comparisons. After subgroup analysis stratified by source of control, ethnicity, types of CAD end points and presence of HWE deviation, it could be found that the heterogeneity decreased significantly.

Therefore, it can be presumed that the heterogeneity partly results from differences in source of control, ethnicity, types of CAD end points and presence of HWE deviation. Second, our results were based on unadjusted estimates, while a more precise analysis should be conducted by some adjusted factors such as age, smoking, drinking status, and so on. Third, our analysis did not consider the possibility of gene-gene interactions or the possibility of linkage disequilibrium between polymorphisms. Further investigations of the haplotypic effect of a gene and the analyses of multiple polymorphisms in different genes should be needed.

In our meta-analysis, MCP-1 A2518G might be associated with the risk of CAD. Due to above limitations in this analysis, it is critical that larger and well-designed studies should be done to confirm our conclusion.

Disclosure of conflict of interest

None.

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