Lack of association between CYP1A1 T6235C polymorphism and coronary artery disease: Evidence from a meta-analysis

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Abstract. A number of studies have evaluated the correlation between the cytochrome P450 1A1 (CYP1A1) T6235C polymorphism and coronary artery disease (CAD) risk, however, at present the results remain inconclusive. To provide a more robust investigation of this correlation, a meta-analysis was performed. In the present study, a systematic search of PubMed, Embase and CBM databases for studies published prior to June 6, 2012 was performed. The correlation between the CYP1A1 T6235C polymorphism and CAD risk was assessed by calculating pooled odds ratios (ORs) and 95% confidence intervals (95% CIs). Seven studies with a total of 2,903 cases and 2,304 controls were included in the meta-analysis. Overall, the CYP1A1 T6235C polymorphism was not correlated with CAD risk (C vs. T: OR=1.03; 95% CI, 0.87-1.22; P=0.728; CC vs. TT: OR=1.04; 95% CI, 0.84-1.19; P=0.699; CC+TC vs. TT: OR=1.04; 95% CI, 0.93-1.18; P=0.478; CC vs. TC+TT: OR=1.04; 95% CI, 0.85-1.28; P=0.704). A meta-analysis of five high-quality studies demonstrated that the CYP1A1 T6235C polymorphism is not correlated with risk of CAD in 4 genetic models. Ethnic subgroup analyses identified no significant correlation in Caucasian, Asian and African populations. The present meta-analysis study indicates that the CYP1A1 T6235C polymorphism is not correlated with CAD risk. Additional studies with a larger sample size and consistent design must be performed to confirm the present hypothesis.

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Introduction

Coronary artery disease (CAD), including its most severe complication, myocardial infarction, is the leading cause of mortality worldwide (1,2). There are several traditional risk factors of CAD, including hypertension, diabetes mellitus, dyslipidemia and smoking, however, these factors explain only two-thirds of the observed clinical events (3,4). In addition, not all individuals exposed to those risk factors develop CAD, which is indicative of other causes, including genetic susceptibility, which may contribute to variations in host susceptibility to CAD. Identification of CAD susceptibility genes highlights the link between CAD and inflammation and immunity, as well as the biological insights that may be gained from a genetic understanding of CAD (5,6).

Environmental pollutants, including polycyclic aromatic hydrocarbons (PAHs), aldehydes and metals, contribute to the incidence, severity and risk of CAD by affecting atherogenesis, thrombosis and blood pressure. Cytochrome P450 1A1 (CYP1A1) is a member of the super family of cytochrome P450 enzymes important for detoxification of PAHs (7,8). The CYP1A1 gene codes for a phase I enzyme associated with detoxification pathways that protect against damage caused by reactive metabolites of a number of chemicals, including steroids. Numerous mutations in CYP1A1 have been described and a T→C mutation in the non-coding 3'-flanking region of the gene (MspI, T6235C polymorphism, rs4646903) is the most commonly studied polymorphism (9). CYP1A1 T6235C in the 3'-flanking region, is associated with increased transcript half-life and therefore increased enzyme activity leading to elevated levels of activated metabolites (9,10). The CYP1A1 T6235C polymorphism is one of the most extensively studied genes for susceptibility to various diseases over the last two decades. A number of studies have investigated the correlation between the CYP1A1 T6235C polymorphism and CAD risk, however, the results remain inconclusive (11-16). Primarily, single studies have been performed to investigate the correlation between the CYP1A1 T6235C polymorphism and CAD risk. In the present study, a meta-analysis was performed to increase the statistical power to examine the correlation between the CYP1A1 T6235C polymorphism and CAD risk. The meta-analysis of observational studies in epidemiology (MOOSE) consensus statement was followed

during stages of design, implementation and reporting of this meta-analysis (17).

Materials and methods

Search strategy. A comprehensive search of PubMed, Embase and the Chinese Biomedical Database (CBM) databases prior to June 6, 2012 was performed. Search terms for the CYP1A1 T6235C polymorphism and CAD risk were combined and included 'cytochrome P4501A1', 'CYP1A1', 'T6235C', 'rs4646903' or 'MspI'; and 'coronary artery disease', 'coronary heart disease' or 'myocardial infarction'. There was no language limitation. Review articles and bibliographies of relevant literature were manually scanned to identify additional eligible studies.

Study eligibility. The criteria used for the study selection were: i) Evaluation of the correlation between the CYP1A1 T6235C polymorphism and CAD risk; ii) studies with case-control design; iii) studies with full text articles; and iv) sufficient data for estimating an odds ratio (OR) with its corresponding 95% confidence interval (CI). Studies investigating progression, severity, phenotype modification, response to treatment or survival were excluded from the present meta-analysis. Family-based association studies were also excluded due to utilization of various study designs. In cases where multiple articles publishing data on the same population were identified, the publication with the most complete data set was included.

Data extraction. Two investigators independently extracted data using a standardized data extraction form. Discrepancies were resolved by discussion and if consensus was not achieved the decision was made by a third investigator. The information sought from each publication included author, year of publication, source of controls, country of origin, ethnicity of participants, adjustment for known confounding variables and genotype information. In studies of multiple ethnic groups, data were extracted separately for each ethnic group. Ethnicity of the participants was categorized as Caucasian, Asian and Africans.

Quality assessment. Quality assessment for case-control studies was assessed using the Newcastle Ottawa scale (NOS) as recommended by the Cochrane Non-Randomized Studies Methods Working Group (18-20). This instrument was developed to assess the quality of non-randomized studies, specifically cohort and case-control. Based on the NOS, case-control studies were judged based on three broad perspectives: selection of study groups (4 criteria), comparability of study groups (1 criteria) and ascertainment of outcome of interest (3 criteria). Considering the variability in quality of observational studies identified on our initial literature search, we considered studies that met ≥5 of the NOS criteria as high quality (18-20). Hardy-Weinberg Equilibrium (HWE) served as a surrogate to assess study quality. The effect of HWE was associated with problems in the design and conduct of genetic association studies and therefore studies with departures from HWE were judged as low quality (21).

Statistical analysis. For assessment of deviation from HWE in the reported genotype frequencies among controls, the appropriate goodness-of-fit χ^2 test was carried out (21). Pooled ORs and 95% CIs were performed to assess the strength of the correlation between the CYP1A1 T6235C polymorphism and CAD risk. Pooled ORs with corresponding 95% CIs for all studies were calculated and subgroup analyses were then performed in the ethnic groups (Caucasians, Asians and Africans). Pooled ORs were performed for the allele (C vs. T), homozygous (CC vs. TT), dominant (CC+CT vs. TT) and recessive models (CC vs. CT+TT). Statistical heterogeneity among studies was estimated with Q and I^2 statistics (22,23). A P-value for the Q statistic >0.10 or I^2 value <50% indicated a lack of marked heterogeneity among the studies. On the basis of heterogeneity test results, the fixed-effects (Mantel-Haenszel) or random-effects model (DerSimonian and Laird) was selected to calculate pooled OR (24,25). Potential publication bias was investigated using the Begg's funnel plot and an asymmetric plot indicated possible publication bias. Funnel-plot asymmetry was further determined by the Egger's linear regression test method (26). Stata Version 12 (Stata Corp, College Station, TX, USA) was used for statistical analyses. Two-sided P<0.05 was considered to indicate a statistically significant difference for all analyses.

Results

Characteristics of included studies. The search criteria identified 38 abstracts. Following elimination of studies that did not meet the criteria and exclusion of 19 records, 9 full-text publications were preliminarily identified for further evaluation (11-16,27-29). Each original manuscript was reviewed and data were extracted. Two publications were excluded, including a case-only study(27) and a study with limited data (28). Therefore, 7 studies with a total of 2,903 CAD cases and 2,304 controls were included in the meta-analysis (11-16,29). All 7 studies were hospital-based case-control studies. There were 4 studies on Caucasian populations (11,12,14,15), 2 on Asians (16,29) and 1 on Africans (13). The number of cases varied between 114 and 873 and controls varied between 53 and 932. The CYP1A1 T6235C genotype distribution in the control groups were all consistent with HWE, with the exception of 1 study (29). According to the quality criteria, there were 5 studies with high quality (12-16). The remaining studies were considered low quality (11,29).

Quantitative synthesis. Pooled ORs and the corresponding 95% CIs are shown in Table I. Overall, the CYP1A1 T6235C polymorphism was not correlated with CAD risk (C vs. T: OR=1.03; 95% CI, 0.87-1.22; P=0.728; CC vs. TT: OR=1.04; 95% CI, 0.84-1.29; P=0.699; CC+TC vs. TT: OR=1.04, 95% CI, 0.93-1.18; P=0.478; CC vs. TC+TT: OR=1.04, 95% CI, 0.85-1.28; P=0.704; Figs. 1-4). Meta-analyses of the 5 high-quality studies demonstrated that the CYP1A1 T6235C polymorphism was not correlated with risk of CAD in 4 genetic models (Table I). Ethnic subgroup analyses revealed no significant correlation was detected in Caucasians, Asians and Africans (Table I).

Publication bias. Begg's funnel plot and Egger's test were performed to assess publication bias. The shapes of the funnel plots did not reveal any evidence of marked asymmetry in all comparison models. Egger's test was further

Table I. Meta-analysis of the correlation between the CYP1A1 T6235C polymorphism and CAD risk.

Studies	Contrast model	Participants[a]	OR (95% CI)	P_{OR}	I^2 (%)
Total	C vs. T	6 (4511)	1.03 (0.87-1.22)	0.728	55.8
	CC vs. TT	6 (4511)	1.04 (0.84-1.29)	0.699	46.6
	CC/CT vs. TT	7 (5207)	1.04 (0.93-1.18)	0.478	23.4
	CC vs. CT/TT	6 (4511)	1.04 (0.85-1.28)	0.704	38.1
High quality	C vs. T	5 (3758)	0.98 (0.88-1.09)	0.698	48.6
	CC vs. TT	5 (3758)	0.92 (0.71-1.18)	0.513	30.8
	CC/CT vs. TT	5 (3758)	0.99 (0.86-1.13)	0.861	23.5
	CC vs. CT/TT	5 (3758)	0.93 (0.73-1.19)	0.573	24.4
Caucasian	C vs. T	3 (2286)	0.94 (0.58-1.52)	0.792	72.3
	CC vs. TT	3 (2286)	0.82 (0.31-2.13)	0.680	54.6
	CC/CT vs. TT	4 (2982)	1.02 (0.73-1.41)	0.919	50.5
	CC vs. CT/TT	3 (2286)	0.91 (0.69-1.21)	0.526	48.2
Asian	C vs. T	2 (1442)	1.14 (0.98-1.34)	0.099	0.0
	CC vs. TT	2 (1442)	1.33 (0.95-1.84)	0.093	0.0
	CC/CT vs. TT	2 (1442)	1.14 (0.92-1.42)	0.234	0.0
	CC vs. CT/TT	2 (1442)	1.27 (0.93-1.73)	0.127	0.0
African	C vs. T	1 (783)	1.02 (0.75-1.38)	0.897	NA
	CC vs. TT	1 (783)	0.53 (0.16-1.79)	0.310	NA
	CC/CT vs. TT	1 (783)	1.08 (0.78-1.51)	0.648	NA
	CC vs. CT/TT	1 (783)	0.52 (0.16-1.74)	0.289	NA

[a]Study number (cases per study); OR, odds ratio; CI, confidence interval; P_{OR}, the P-value of OR; NA, not applicable. CAD, coronary artery disease; CYP1A1, cytochrome P450 1A1.

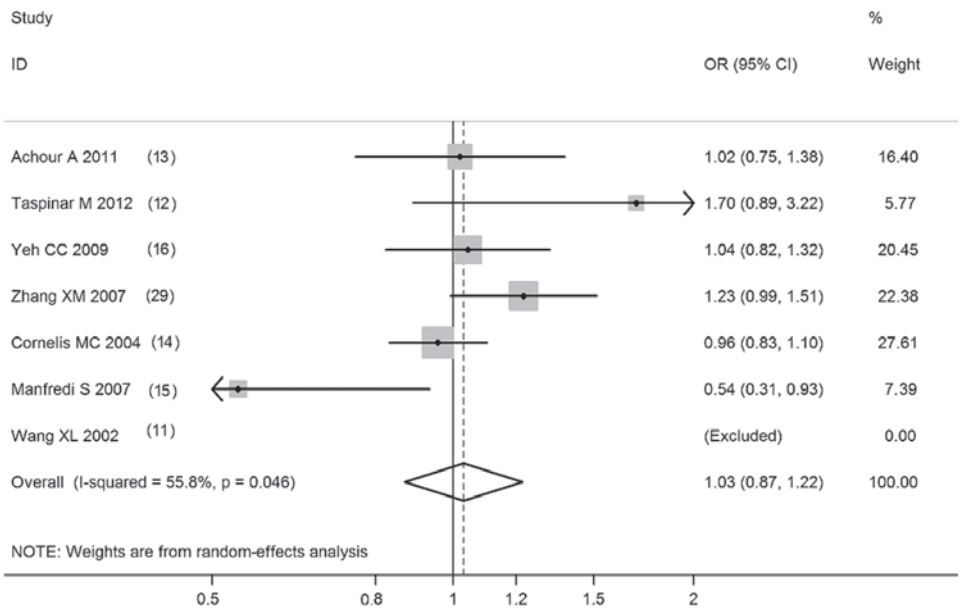

Figure 1. Meta-analysis of the correlation between the CYP1A1 T6235C polymorphism and CAD risk (C vs. T). CYP1A1, cytochrome P450 1A1; CAD, coronary artery disease; OR, odds ratio; CI, confidence interval.

used to provide statistical evidence of funnel plot asymmetry and the results were consistent with no evidence of publication bias (Egger's test values: C vs. T: P=0.690; CC vs. TT: P=0.661; CC/TC vs. TT: P=0.450; CC vs. TC/TT: P=0.693). Therefore, a low risk of publication bias was detected in the present meta-analysis.

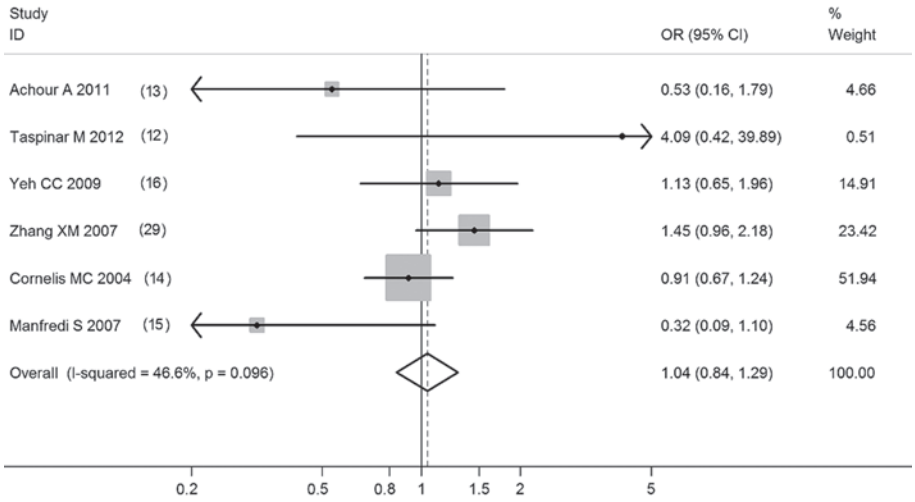

Figure 2. Meta-analysis of the correlation between the CYP1A1 T6235C polymorphism and CAD risk (CC vs. TT). CYP1A1, cytochrome P450 1A1; CAD, coronary artery disease; OR, odds ratio; CI, confidence interval.

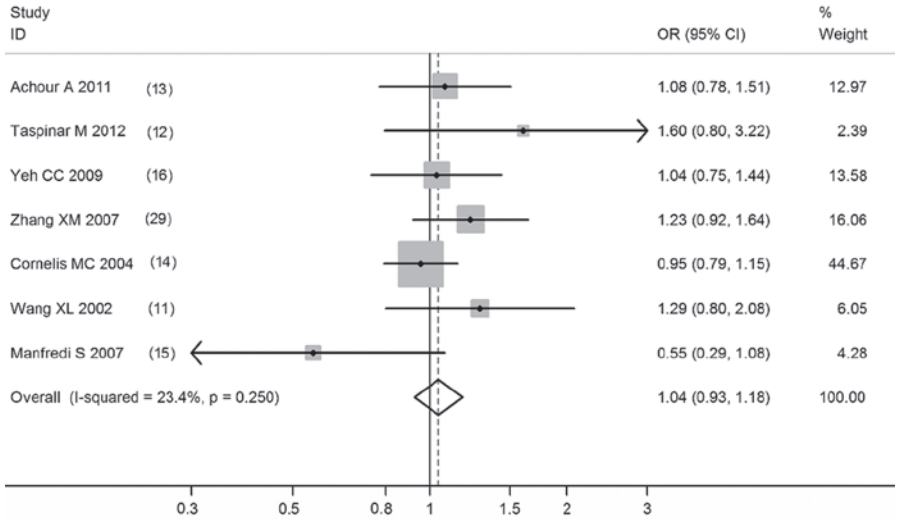

Figure 3. Meta-analysis of the correlation between the CYP1A1 T6235C polymorphism and CAD risk (CC/CT vs. TT). CYP1A1, cytochrome P450 1A1; CAD, coronary artery disease; OR, odds ratio; CI, confidence interval.

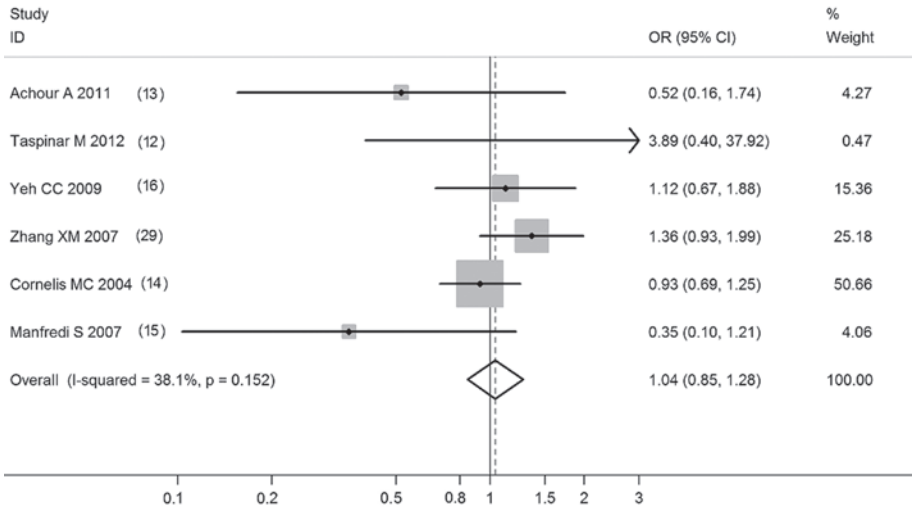

Figure 4. Meta-analysis of the correlation between the CYP1A1 T6235C polymorphism and CAD risk (CC vs. TT/CT). CYP1A1, cytochrome P450 1A1; CAD, coronary artery disease; OR, odds ratio; CI, confidence interval.

Discussion

CYP1A1 is a phase I extrahepatic metabolic enzyme involved in the bioactivation of carcinogenic PAHs, including benzopyrene. PAHs present in smoked foods, tobacco smoke and ubiquitous in urban environments in large cities are considered to be responsible for an elevated risk of specific types of cancer and cardiovascular diseases. Considering the importance of CYP1A1, it is biologically plausible that CYP1A1 polymorphisms may modulate the risk of cancer and it is well documented that CYP1A1 is important in arachidonic acid metabolism. The metabolites generated by the process are associated with cardiovascular physiology (16,30,31). In addition, CYP1A1 is involved in the metabolic activation of tobacco-derived PAHs, molecules associated with carcinogenesis and atherosclerosis. A number of CYP1A1 polymorphisms increase transcript half-life, leading to increased enzyme activity and a subsequent elevation in levels of activated metabolites (9,10). Therefore, a correlation between CYP1A1 polymorphisms and CAD risk is possible.

A number of previous studies have evaluated the correlation between the CYP1A1 T6235C polymorphism and CAD risk, however, the effect of this polymorphism on CAD remains inconclusive. Previously, small sample genetic association studies were performed. These studies had various designs and methodologies and insufficient power, qualities associated with an increased risk of false results. Combining data from all eligible studies by meta-analysis reduces random error and increases the accuracy of genetic association data. To provide a more robust estimate of the hypothesized correlation, a meta-analysis was performed. In the present study, a comprehensive meta-analysis of literature on the correlation between the CYP1A1 T6235C polymorphism and CAD risk was performed. On the basis of our inclusion criteria, 7 studies with a total of 2,903 cases and 2,304 controls were included in the meta-analysis. Overall, the CYP1A1 T6235C polymorphism was not correlated with CAD risk (C vs. T: OR=1.03; 95% CI, 0.87-1.22; P=0.728; CC vs. TT: OR=1.04; 95% CI, 0.84-1.29; P=0.699; CC+TC vs. TT: OR=1.04; 95% CI, 0.93-1.18; P=0.478; CC vs. TC+TT: OR=1.04; 95% CI, 0.85-1.28; P=0.704). Meta-analyses of five high-quality studies demonstrated that the CYP1A1 T6235C polymorphism was not correlated with risk of CAD in four genetic models. Ethnic subgroup analyses revealed that no significant correlation was identified in Caucasian, Asian and African populations. Therefore, this meta-analysis indicates that the CYP1A1 T6235C polymorphism is not correlated with CAD risk.

Four polymorphisms, including T6235C (a substitution in the 3' non-coding region), A2455G (isoleucine to valine transition at codon 462), T3205C (a transition mutation in the 3' non-coding region) and C2453A (threonine to asparagine transition at codon 461) were previously identified in the CYP1A1 gene (32). C2453A is extremely rare and T3205C exists only in African and African-American individuals. Therefore, the majority of studies have focused on the CYP1A1 T6235C and CYP1A1 A2455G polymorphisms (32). The CYP1A1 A2455G polymorphism was previously found to be correlated with risk of several common types of cancer, however, the CYP1A1 T6235C polymorphism is not correlated with this risk (33-35). These outcomes indicate that the CYP1A1 A2455G polymorphism may have additional effects on the CYP1A1 enzyme compared with the CYP1A1 T6235C polymorphism. Previous studies have concentrated on the correlation between the CYP1A1 T6235C polymorphism and CAD risk, however, limited studies have analyzed this correlation with respect to the CYP1A1 A2455G polymorphism. Therefore, additional studies are required to assess this correlation.

The present study is associated with several limitations that must be considered when interpreting the results. Firstly, inclusion of only seven studies with relatively small sample sizes and poor validation was the main limitation of the meta-analysis. In addition, only two studies on Asian and four on Caucasian populations were included in the analysis. Two methods were utilized to assess publication bias, however, these methods may be associated with low power for the detection of publication bias risk in cases of limited study numbers. Therefore, additional studies of larger sample size and consistent design are required for comprehensive analysis of this correlation. Secondly, the main analysis was based on unadjusted estimates due to lack of adjusted estimates. A more precise analysis is achieved when adjusted estimates are available for all studies (36). Considerable variability in study design and control selection was revealed in the present meta-analysis. To obtain results from meta-analysis of homogeneous studies, additional studies with adjusted estimates are required. Thirdly, gene-environmental factor interactions were not fully addressed due to insufficient data. Future studies must further assess the possible gene-environmental interactions, including gene-smoking interactions, in the correlation between the CYP1A1 T6235C polymorphism and CAD risk.

In conclusion, the present study has demonstrated that the CYP1A1 T6235C polymorphism is not correlated with CAD risk. Additional studies with larger sample size and consistent design must be performed to confirm this finding.

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