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Original Article

Lack of association between GSTP1 Ile105Val polymorphism and coronary heart disease risk: a meta-analysis

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Abstract: Many epidemiological studies have evaluated the association between GSTP1 Ile105Val polymorphism and coronary heart disease risk, but the results were inconsistent. This study aims re-evaluate the association between GSTP1 Ile105Val Polymorphism and coronary heart disease risk with a meta-analysis. We performed a search in the PubMed, Springer and Elsevier and ran a meta-analysis based on 8 case-control studies that included 3,888 cases and 3,476 controls. Crude odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of the association. The results showed that there was no significant association between GSTP1 Ile105Val Polymorphism and coronary heart disease risk susceptibility in the overall population (GG vs. AA: OR = 0.98, 95% CI = 0.84-1.15; GA vs. AA: OR = 1.04, 95% CI = 0.84-1.29; GA/GG vs. AA: OR = 1.02, 95% CI = 0.84-1.25; GG vs. AA/GA: OR = 0.94, 95% CI = 0.81-1.09). Subgroup analysis stratified by ethnicity and source of control showed no significant association with any genetic model. Our meta-analysis showed that GSTP1 Ile105Val polymorphisms might not be significantly associated with coronary heart disease risk.

Keywords: GSTP1, polymorphism, meta-analysis, coronary heart disease

Introduction

Coronary heart disease (CHD) is the leading health burden and the most common cause of death worldwide [1]. The development of CHD is a multifactorial process associated with a variety of risk factors, some of which were traditional and well-known, such as hypertension, diabetes mellitus, dyslipidemia and cigarette smoking [2]. Among these factors, cigarette smoking is the most dangerous because cigarette itself contains several carcinogens, including polycyclic aromatic hydrocarbons (PAHs), N-nitrosamines and aromatic heterocyclic amines. These chemicals induce DNA damage by direct binding to form DNA adducts. Unrepaired DNA damage causes smooth muscle cell proliferation in the intima of arteries and contributing to atherosclerotic plaque formation [3]. The binding of these chemicals to DNA can be modulated by detoxification enzymes. Thus, various cellular detoxification systems may correlate with individual susceptibility to CHD.

Various cellular detoxification systems including glutathione S transferases (GSTs) protect against both endogenous and environmental toxic substances. Glutathione S-transferases (GST) are a superfamily of multifunctional enzymes that play a central role in catalyzing multiple electrophilic compounds including carcinogens, environmental toxins, and DNA products generated by carcinogens in tobacco smoke, chiefly by conjugating them with glutathione. GSTs contain various isozymes in human, such as GSTM (m), GSTS (s), GSTP (p), GSTA (a), and GSTS (s) [4]. Among those genes, GSTP1 is one of the GST superfamily, which is extremely important in detoxifying the conjugation of mutagenic electrophilic compounds with reduced glutathione forming less toxic and more water-soluble compounds. A functionally significant A to G transition in GSTP1 gene, codon 105 A to G, causes an amino acid substitution from isoleucine (Ile) to valine (Val), which could influence the enzyme activity [5]. Enzymes with the valine at amino-acid 105 may be 2-3 times less

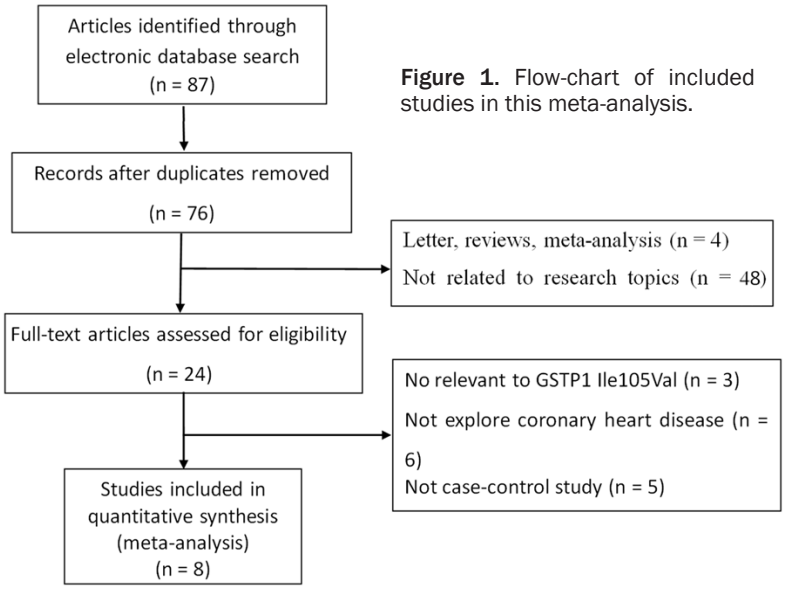

Figure 1. Flow-chart of included studies in this meta-analysis.

stable than the Ile105 enzymes and may be associated with CHD risk [6].

Many epidemiological studies have investigated the association between GSTP1 Ile105Val Polymorphism and CHD risk [7-14]. However, the results remain inconclusive, which might be caused by the limitation of individual studies with relatively small size. Therefore, we conducted a meta-analysis to better access the overall effects of the GSTP1 Ile105Val Polymorphism on risk of CHD.

Materials and methods

Search strategy

We conducted a comprehensive in PubMed, Springer and Elsevier (update to June, 2015) using a combination of the following search terms: 'GSTP1', 'Glutathione S-transferase P1', 'polymorphism', coronary heart disease, CHD, myocardial infarction and the combined phrases. Furthermore, Additional articles were identified through references cited in relevant articles on this topic. The inclusion criteria are as follows: (1) case-control or cohort studies that evaluate the association between GSTP1 Ile105Val polymorphism and coronary heart disease risk (2) providing detailed data in cases and controls for estimating an odd ratio (OR) with 95% confidence interval (CI). If several publications reported on the same population data met our criteria, only the most recent or largest report was included. In addition, family-based association studies were excluded because they use different study designs.

Exclusion criteria

Major exclusion criteria: (1) studies with no control group; (2) researches with duplicate data; (3) articles with no available genotype frequency; (4) studies with insufficient data.

Data extraction

In order to minimize the bias, two investigators extracted data independently. The following information was extracted from all eligible studies: the first author's name, publishing year, country of origin, sources of controls, ethnicity, number of different genotype in cases and controls.

Statistical analysis

The strength of association between GSTP1 Ile105Val Polymorphism and CHD risk was evaluated by using crude ORs with 95% CIs. Four different comparison models of ORs were performed for the co-dominant model (GG vs. AA, GT vs. AA), the dominant model (GA/GG vs. AA), and the recessive model (GG vs. AA/GT). Q-test and I^2 statistics were used to estimate heterogeneity among the studies. When *P* value for heterogeneity test was > 0.05, the fixed-effects model (the Mantel-Haenszel method) was used to calculate the pooled OR; otherwise the random effects model (the DerSimonian and Laird method) was applied [15]. In addition, subgroup analyses by ethnicity (Caucasians, Asian), source of controls (hospital-based, population-based). The potential publication bias of this meta-analysis was evaluated with the funnel plot and Egger's weighted regression method [16]. Statistical analyses were performed using Statistical Analysis System software (v.9.1.3; SAS Institute, Cary, NC) and Review Manage (v.5.0; Oxford, England).

Results

Eligible studies

A total of 8 eligible articles on the association between GSTP1 Ile105Val Polymorphism and

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

First author	Year	Country	Racial descent	Source of controls	Genotype distribution						P for HWE†	G
					Case			Control				
					AA	GA	GG	AA	GA	GG		
Wilson [7]	2000	UK	Caucasians	PB	155	148	48	73	94	23	0.38	0.37
Cornelis [8]	2007	Canada	Latino	PB	744	993	305	745	985	312	0.65	0.39
Ramprasath [9]	2011	India	Indian	HB	94	164	32	118	130	22	0.09	0.32
Singh [10]	2011	India	Indian	PB	140	84	6	184	95	21	0.08	0.23
Nomani [11]	2011	Iran	Iranian	PB	97	101	11	48	51	9	0.37	0.32
Phulukdaree [12]	2012	South Africa	Indian	HB	66	31	5	48	45	7	0.41	0.30
Kariz [13]	2012	Slovenia	Caucasians	PB	71	114	21	117	111	29	0.73	0.33
Yeh [14]	2013	China	Chinese	HB	333	104	21	150	51	8	0.18	0.16

G allele frequency in controls; †HWE in controls.

Table 2. Summary ORs and 95% CI of GSTP1 Ile105Val polymorphism and coronary heart disease risk

		GG vs. AA		GA vs. AA		GA/GG vs. AA		GG vs. AA/GA	
		OR 95% CI	*P**	OR 95% CI	*P**	OR 95% CI	*P**	OR 95% CI	*P**
total	8	0.98 (0.84-1.15)	0.15	1.04 (0.84-1.29)	0.004†	1.02 (0.84-1.25)	0.01†	0.97 (0.84-1.11)	0.32
Ethnicity									
Caucasians	2	1.04 (0.65-1.67)	0.72	0.82 (0.63-1.08)	0.44	0.87 (0.67-1.12)	0.47	1.17 (0.75-1.83)	0.92
Asian	5	0.82 (0.44-1.55)	0.03†	1.01 (0.73-1.40)	0.02†	0.98 (0.70-1.36)	0.01†	0.88 (0.62-1.25)	0.11
Source of control									
Population based	5	0.94 (0.80-1.11)	0.26	1.04 (0.93-1.16)	0.05	1.02 (0.91-1.13)	0.11	0.94 (0.81-1.09)	0.21
Hospital based	3	1.34 (0.85-2.10)	0.18	0.93 (0.51-1.70)	0.003†	0.95 (0.52-1.74)	0.002†	1.22 (0.79-1.88)	0.57

**P* value for heterogeneity; †Estimates for Random-effects model.

CHD risk containing 3,888 heart disease risk cases and 3,476 controls were included in our meta-analysis (**Figure 1**). The main characters of these studies are presented in **Table 1**. Among them, three studies were conducted in Asian population, 2 studies in Caucasians population, 1 study in Latino population. There were 3 studies of hospital based, 5 studies of population based.

Meta-analysis

As shown in **Table 2**, no significant associations were found between GSTP1 Ile105Val Polymorphism and CHD risk when all studies were pooled into the meta-analysis in the overall population (for GG vs. AA: OR = 0.98, 95% CI = 0.84-1.15, **Figure 2**; for GA vs. AA: OR = 1.04, 95% CI 0.84-1.29; for GA/GG vs. AA: OR = 1.02, 95% CI = 0.84-1.25; for GG vs. AA/GA: OR = 0.94, 95% CI = 0.81-1.09). In subgroup analysis by ethnicity and source of control, no significant association was detected between GSTP1 Ile105Val Polymorphism and the risk of heart disease risk.

Publication bias

Funnel plot and Egger's test was done to estimate the publication bias of literatures. As shown in **Figure 3**, no publication bias was revealed by the funnel plots. Statistical evidence from the results of Egger's test confirmed the funnel plot symmetry (GG vs. AA: t = 1.27, P = 0.3314; GA vs. AA: t = 3.14, P = 0.1184; GA/GG vs. AA: t = 3.56, P = 0.0717; GG vs. AA/GA: t = 1.51, P = 0.2692).

Discussion

To the best of our knowledge, this is the first and the most comprehensive meta-analysis investigating the association between GSTP1 Ile105Val polymorphism and CHD risk. The present meta-analysis that included 3,888 heart disease cases and 3,476 controls did not show any significant association between GSTP1 Ile105Val polymorphism and coronary heart disease risk in overall populations. Moreover, no associations were found when stratified by ethnicity and the source of control.

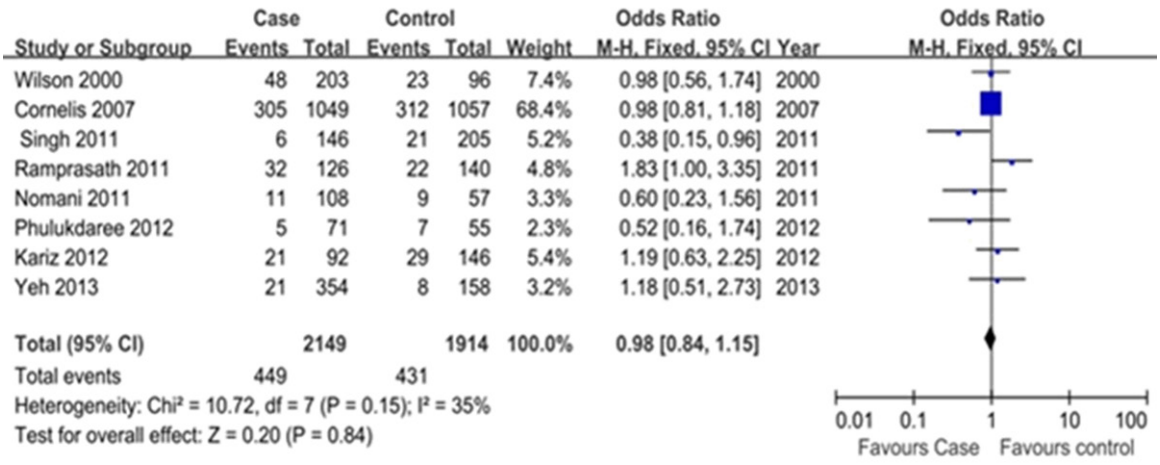

Figure 2. Forest plot for the association between GSTP1 Ile105Val polymorphism and coronary heart disease risk for the GG genotype compared with the AA genotype in overall populations.

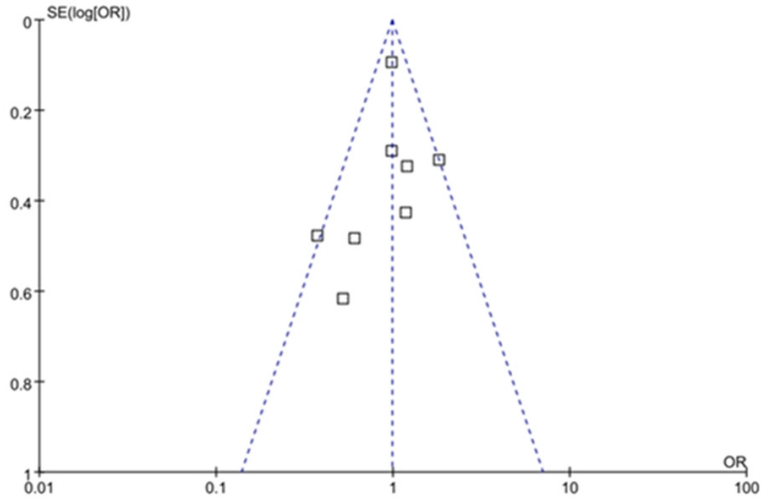

Figure 3. Funnel plot analysis to detect publication bias. Odds ratios for the main effect between GSTP1 Ile105Val polymorphism for the GG genotype compared with the AA genotype in overall populations are shown.

GSTP1 enzyme is involved in the metabolism of a variety of toxic and carcinogenetic electrophiles, including carcinogens, chemotherapeutic drugs, environmental toxins, and DNA products [17]. The GSTP1 gene is located on chromosome 11q13, which is widely expressed in normal epithelial cells, such as digestive system, urinary system and cardiovascular system [18]. GSTP1 variant results in a single amino acid change from Ile to Val at codon 105 which would reduce enzyme activity and alter susceptibility to many diseases at a certain extent. Many studies have investigated the association between GSTP1 Ile105Val polymorphism and coronary heart disease risk. Wilson [7] et al firstly explored the association between the four GST gene polymorphisms and coronary heart disease risk; however, no significant associations were observed between the GSTP1 Ile105Val polymorphism and CHD risk. In the several subsequent case-control studies, the similar results were found [9, 11, 14]. However, Singh et al [10] observed a significantly decreased risk among the Val homozygote (OR = 0.355, 95% CI = 0.141-0.896). When they checked an interactive effect of the GSTP1 Val genotypes with disease after adjusting for other risk factors, the result still have statistically significant. Phulukdaree et al [12] provides evidence that the GSTP1 Val heterozygote was associated with CAD in young South Africans of Indian ancestry. The sample size in each published study is too few to assess any genetic effects reliably. Therefore, in order to define the effect of selected genetic polymorphisms on risk of disease much more precisely, the meta-analysis was conducted and showed no significant association between GSTP1 Ile105Val polymorphism and CHD risk. The possible explanation is that the pathways of carcinogen metabolism are complex, mediated by the activities of multiple genes. There are some other phase II xenobiotic-metaboliz-

ing enzyme (XME) genes, and they may interact with GSTP1 in the metabolism of exogenous and endogenous substrates. In order to eliminate interference from the confounding factor, stratified analysis by source of controls (PB and HB) was conducted, and the result showed that the GSTP1 Ile105Val polymorphism appears to not be associated with risk of CHD in different controls, which proved the reliability of our meta-analysis.

Some limitations of our meta-analysis should be acknowledged. Firstly, the lack of sufficient data restricted the further evaluation of potential gene-gene and gene-environment interactions, thus the potential roles of GSTP1 Ile105Val polymorphism may be masked. Secondly, our results was based on unadjusted OR estimates. Third, in stratified analysis by ethnicity and source of control, the sample size was relatively small which may lead to insufficient power to detect the real relationship.

In conclusion, our meta-analysis suggested that there was no significant association between GSTP1 Ile105Val polymorphism and CHD risk. Further large-scale studies are needed to reaffirm this conclusion.

Disclosure of conflict of interest

None.

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