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T174M polymorphism in the angiotensinogen gene and risk of myocardial infarction: a meta-analysis

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ABSTRACT. Numerous studies have evaluated the association between the T174M polymorphism in the angiotensinogen (*AGT*) gene and myocardial infarction (MI) risk. However, the specific association remains controversial because of small sample sizes and varied study designs among different studies. We performed a meta-analysis to assess this correlation. A comprehensive search was conducted to identify all published articles regarding the association between the *AGT* gene T174M polymorphism and MI risk from different databases. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated, and heterogeneity and publication bias were assessed. A total of 1032 patients with lung cancer and 1286 controls from 6 comparative studies were included in this meta-analysis. The results revealed a significant association between the *AGT* gene T174M polymorphism and MI risk (MM *vs* TT: OR = 2.87, 95%CI = 1.71-4.83; dominant model: OR = 1.57, 95%CI = 1.10-2.25; recessive model: OR = 0.41, 95%CI = 0.25-0.66). In subgroup analysis by nationality, we observed a significant association between the *AGT* gene T174M polymorphism and susceptibility to MI

in both Caucasian and Asian populations. In conclusion, the T174M polymorphism in the *AGT* gene may be related to an increased risk of MI. Further larger studies are needed to confirm these conclusions.

Key words: Angiotensinogen; Gene polymorphism; Meta-analysis; Myocardial infarction

INTRODUCTION

Myocardial infarction (MI) is a severe type of cardiovascular disease and one of the major causes of morbidity and mortality worldwide (Oerkild et al., 2012). The American Heart Association reported that approximately 600,000 new patients sustain an MI and 320,000 patients have an episode of recurrent MI annually in the United States, incurring 31 billion dollars in hospital costs (Yin et al., 2014). Projections show that by 2030, an additional 8 million people may have coronary artery disease, representing a 16.6% increase in prevalence from 2010 (Roger et al., 2012). Although a large number of studies have been conducted, the causes are not fully understood. The INTER-HEART study identified several risk factors for MI, including family history, body mass index, smoking habits, hypertension, diabetes mellitus, and serum lipid levels (Ounpuu et al., 2001). In addition, genetic factors play important role in MI development (Wang and Staessen, 2000; Sekuri et al., 2005).

As a liver protein, angiotensinogen (AGT) can interact with renin to produce angiotensin I, which is the pro-hormone of angiotensin II. Angiotensin II has been shown in studies using both human and animal models to be involved in the development of cardiomyocyte hypertrophy, as well as in cardiac fibrosis and modulation of cardiac fibroblast growth and collagen synthesis. The *AGT* gene is located at lq42-43 and consists of 5 exons. A threonine to methionine substitution at amino acid 174 is a common polymorphism known as T174M (rs699), designating the T and M alleles, respectively (Sivitskaia et al., 2008). This variation can alter AGT function, eventually inducing the development of cardiovascular disease.

Over the past decade, a number of epidemiological studies have assessed the association between the T174M polymorphism and MI risk; however, controversial results have been reported. A meta-analysis is useful for detecting an association that could otherwise remain masked in studies with small sample sizes, particularly in those evaluating rare allele frequency polymorphisms (Attia et al., 2003). Thus, we conducted this meta-analysis of all published case-control studies to confirm whether the T174M polymorphism in the *AGT* gene increased the risk of MI.

MATERIAL AND METHODS

Selection of studies

The Google Scholar, PubMed, and China National Knowledge Infrastructure (CNKI) databases were searched for all articles examining the association between the T174M polymorphism and MI risk without language restrictions (January 1995 to April 2014), using the following key words: ‘AGT/angiotensinogen’, ‘T174M’, ‘MI/myocardial infarction’, and ‘gene polymorphism’. The reference lists of major textbooks, reviews, and included articles were identified through manual searches to identify other potentially eligible studies.

Selection criteria

Any human-associated study, regardless of sample size, was included if it met the following criteria: i) case-control studies that addressed MI patients and healthy controls; ii) studies that evaluated the association between the T174M polymorphism and MI risk; iii) genotype frequencies of healthy controls were in Hardy-Weinberg equilibrium (HWE). Studies were excluded when they were: i) not case-control studies that evaluated the association between the T174M polymorphism and MI risk; ii) case reports, letters, reviews, or editorial articles; iii) studies that were based on incomplete raw data and no usable data reported; iv) duplicate data were contained in the studies; v) healthy controls were not in HWE.

Data extraction

Using a standardized form, data from published studies were extracted independently by 2 reviewers (P.Y. Hu and Y.W. Wang). Disagreements were resolved by discussion. For each study, the following information was recorded: first author, year of publication, area, ethnicity, number of cases and controls, genotypes for cases and controls, and evidence of HWE in controls. For subjects of different ethnicities, data were extracted separately and categorized as Caucasians or Asians (Table 1).

Statistical analysis

The Fisher exact test was used to assess deviations from HWE for each genotype distribution in the control group. The strengths of the associations between the T174M polymorphism and susceptibility to MI were estimated by the odds ratio (OR) and 95% confidence interval (95%CI) using a homozygote comparison (MM *vs* TT), a heterozygote comparison (MT *vs* TT), a dominant model (MM+MT *vs* TT), and a recessive model (TT+MT *vs* MM) between groups. Heterogeneity among studies was assessed by the I^2 statistic, which describes the proportion of the total variation attributable to between-study differences or heterogeneity compared to random error or chance. If $I^2 > 50\%$, the DerSimonian and Laird random-effect model was adopted as the pooling method; otherwise, the fixed-effect model was used. To evaluate ethnicity-specific effects, subgroup analyses were performed to explore the diversity among the results of different studies. Sensitivity analysis was performed by altering the statistical models to ensure the stability of measuring the results. Publication bias was examined by plotting a Begg's funnel plot ($P < 0.05$ was considered statistically significant publication bias). Meta-analysis was performed using the STATA package version 12.0 (Stata Corporation, College Station, TX, USA). All reported probabilities were two-tailed, with $P < 0.05$ considered to be statistically significant.

RESULTS

Studies included in the meta-analysis

The search strategy retrieved 32 potentially relevant studies. Based on the inclusion criteria, only 6 full-text case-control studies (Tiret et al., 1995; Frossard et al., 1998; Chistiakov et al., 1999; Zhang et al., 2005; Sun et al., 2006, Konopka et al., 2011) were included in this meta-analysis and 26 studies were excluded. The flow chart of study selection is summarized in Figure 1. These 6 case-control studies included a total of 1032 MI cases and 1286 healthy

controls. All studies included were case-control studies that evaluated the association between the T174M polymorphism and susceptibility to MI. The publication year of the studies included ranged from 1995 to 2014. Three studies were conducted in Europe and 3 in Asia. The source of controls was based on healthy populations. The HWE test was performed on the genotype distribution of the controls, and all were in HWE. The study characteristics are presented in Table 1.

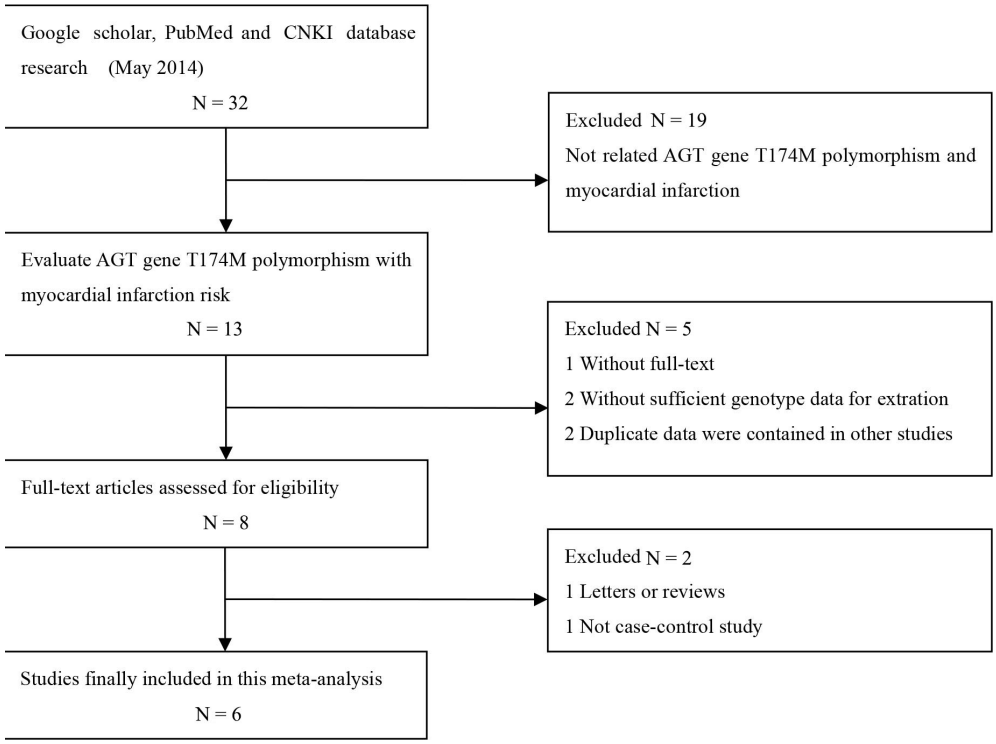

Figure 1. Flow chart showing the study selection procedure.

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

Study included	Year	Area	Race	Cases/controls	Genotypes for cases			Genotypes for controls			HWE test
					MM	MT	TT	MM	MT	TT	
Tiret et al.	1995	France	Caucasians	630/741	12	125	493	9	154	578	0.73
Frossard et al.	1998	UAE	Asians	40/61	14	18	8	16	26	19	0.26
Chistiakov et al.	1999	Russia	Caucasians	45/60	2	17	26	1	11	48	0.69
Zhang et al.	2005	China	Asians	105/201	8	19	78	3	32	166	0.32
Sun et al.	2006	China	Asians	112/128	10	18	84	2	21	105	0.43
Konopka et al.	2011	Poland	Caucasians	100/95	5	41	54	1	27	67	0.34

Quantitative synthesis

The combined results of the association between the T174M polymorphism and MI risk are summarized in Figure 2 and Table 2. In this study, we found a statistically significant

relationship between the *AGT* gene T174M polymorphism and MI (MM *vs* TT: OR = 2.87, 95%CI = 1.71-4.83; dominant model: OR = 1.57, 95%CI = 1.10-2.25; recessive model: OR = 0.41, 95%CI = 0.25-0.66). In the stratified analysis by ethnicity, we found a significant association between the *AGT* gene T174M polymorphism and susceptibility to MI in both Caucasians (MM *vs* TT: OR = 2.12, 95%CI = 1.00-4.49) and Asians (MM *vs* TT: OR = 3.78, 95%CI = 1.82-7.83; dominant model: OR = 1.62, 95%CI = 1.11-2.38; recessive model: OR = 0.36, 95%CI = 0.19-0.67).

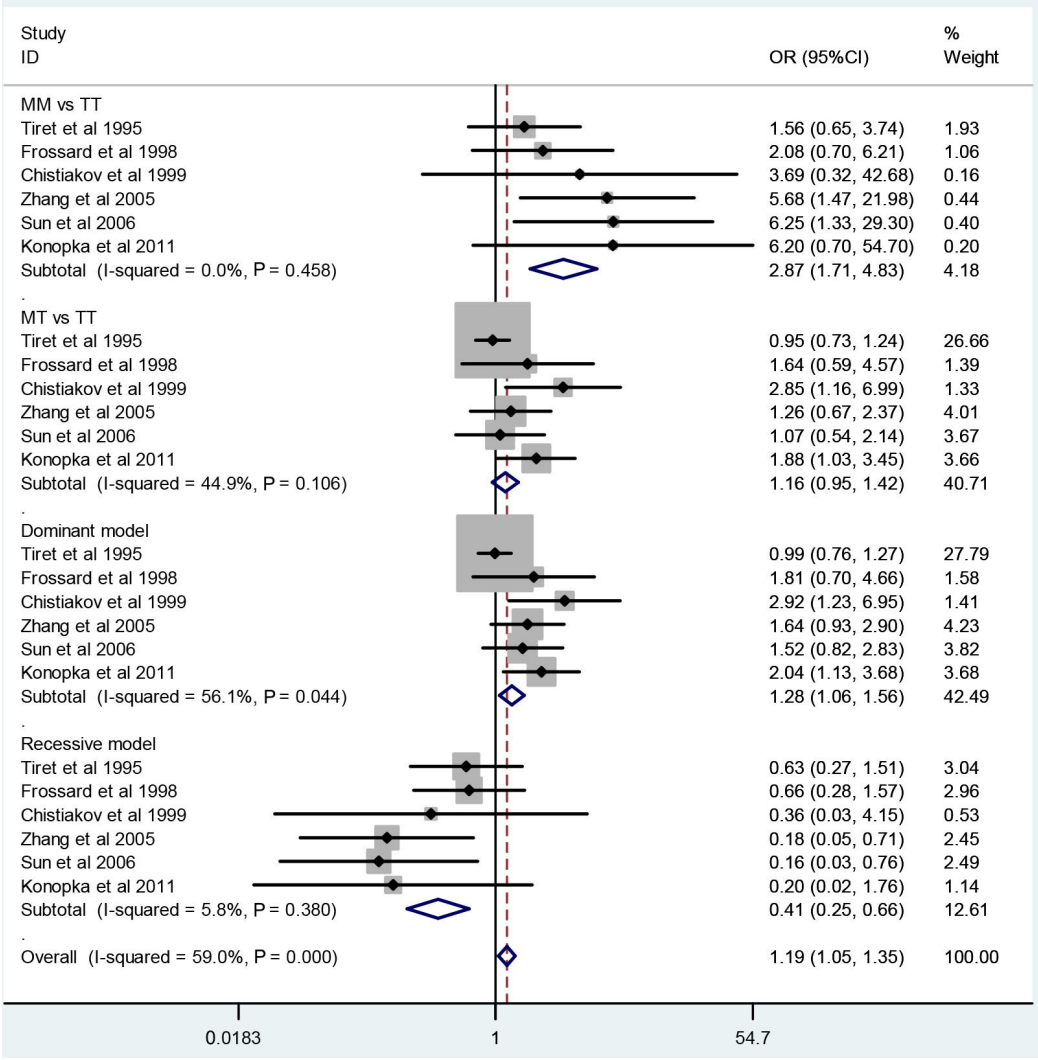

Figure 2. Forest plot of MI risk associated with the *AGT* gene T174M polymorphism in overall population. The squares and horizontal lines correspond to the study-specific odds ratios (OR) and 95% confidence intervals (CI).

Table 2. Summary ORs and 95%CI of the *AGT* T174M gene polymorphism and myocardial infarction risk.

Subgroup	Genetic model	Sample size		Type of model	Test of heterogeneity		Test of association	Test of publication bias	
		Case	Control		I^2	P	OR (95%CI)	z	P
Overall	MM *vs* TT	1032	1286	Fixed	0.0%	0.46	2.87 (1.71-4.83)	0.00	1.00
	MT *vs* TT			Fixed	44.9%	0.11	1.16 (0.95-1.42)	0.00	1.00
	Dominant model			Random	56.1%	0.04	1.57 (1.10-2.25)	0.00	1.00
	Recessive model			Fixed	5.8%	0.38	0.41 (0.25-0.66)	0.00	1.00
Caucasians	MM *vs* TT	775	896	Fixed	0.0%	0.45	2.12 (1.00-4.49)	0.00	1.00
	MT *vs* TT			Random	76.4%	0.01	1.57 (0.81-3.05)	0.00	1.00
	Dominant model			Random	78.7%	0.01	1.66 (0.84-3.28)	0.00	1.00
	Recessive model			Fixed	0.0%	0.60	0.50 (0.23-1.06)	0.00	1.00
Asians	MM *vs* TT	257	390	Fixed	0.0%	0.39	3.78 (1.82-7.83)	1.04	0.30
	MT *vs* TT			Fixed	0.0%	0.79	1.24 (0.82-1.90)	1.04	0.30
	Dominant model			Fixed	0.0%	0.95	1.62 (1.11-2.38)	1.04	0.30
	Recessive model			Fixed	48.6%	0.14	0.36 (0.19-0.67)	1.04	0.30

Publication bias and sensitivity analysis

The Begg's funnel plot was constructed to assess the publication bias in the reports included in the meta-analysis. The shape of funnel plots showed no evidence of publication bias (Figure 3 and Table 2). Sensitivity analysis was conducted to evaluate the influence of each eligible study and changing the regression model on the pooled OR and the overall effect. After altering the statistical models, the pooled ORs and P values for the overall effect of the null genotype did not significantly change, suggesting that the results of the meta-analysis were statistically robust.

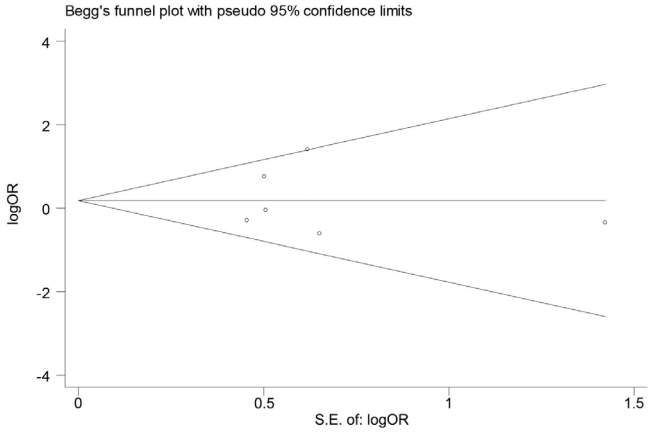

Figure 3. Funnel plot of the *AGT* gene T174M polymorphism and susceptibility of MI.

DISCUSSION

The renin-angiotensin system (RAS) plays an important role in the regulation of blood pressure, vascular remodeling, and sodium homeostasis (Wang and Staessen, 2000). AGT is a component of the RAS that is released from the liver and is cleaved by renin. AGT has been shown to play a vital role in affecting the cardiovascular system, and the ECTIM study was the

first to evaluate the association between the *AGT* gene T174M polymorphism and MI using a population-based case-control study (Tiret et al., 1995). The study included 630 cases who had survived MI and 741 controls drawn from the corresponding populations, and no significant impact of the *AGT* locus on the risk of MI was detected. In contrast, several recent studies have confirmed the association between the T174M polymorphism and an increased risk for MI. However, these studies included a small sample number, and thus it is possible that the observed associations between the T174M polymorphism and increased MI risk reflect chance observations rather than true associations. To help clarify these inconsistent findings, we conducted a meta-analysis of published genetic association studies of the T174M polymorphism and risk of MI.

This is the first meta-analysis to examine the association between the T174M variant and MI risk. The present meta-analysis included 6 studies with a total of 1032 MI cases and 1286 controls. When all eligible studies were pooled, the results showed that the T174M polymorphism was associated with a significantly increased risk of MI. We also performed an ethnicity-related subgroup analysis and found significant associations in Asians and Europeans. Further sensitivity analysis confirmed the significant association between the maternal T174M gene polymorphism and MI risk. No publication bias was observed in this meta-analysis for the T174M gene polymorphism ($P > 0.05$). Because the eligible study number was small in this meta-analysis of the T174M polymorphism, these results require further confirmation.

Serum AGT level is not altered in subjects with the T174M variant (Pilbrow et al., 2007). Therefore, the mechanism of how the *AGT* T174M polymorphism is related to MI risk remains unclear. The influence of the T174M polymorphism may be affected by gene-gene interactions. A missense mutation in exon 2 of the *AGT* gene (M235T) and T174M variants are in linkage disequilibrium, and M235T has been associated with elevated levels of AGT, which interacts with renin to produce angiotensin II. Angiotensin II activates vascular cell apoptosis, contributing to vascular remodeling and cardiomyocyte loss in ischemia-reperfusion and MI (Horiuchi et al., 1999). The linkage disequilibrium between M235T and T174M may synergistically increase the risk of MI.

There were some limitations to this meta-analysis. First, because of incomplete raw data or publication limitations, some relevant studies could not be included in our analysis. Second, the number of published studies was not sufficiently large for a comprehensive analysis, and some included studies of small size may not have had sufficient statistical power to determine the real association between the T174M polymorphism and susceptibility to MI. Finally, our meta-analysis was based on unadjusted OR estimates because not all published studies presented adjusted ORs, or when they did, the ORs were not adjusted by the same potential confounders such as age, gender, and environmental exposure. This may have resulted in serious confounding bias.

In conclusion, the results of this meta-analysis indicate that the *AGT* gene T174M polymorphism may be not associated with MI risk. Large-scale case-control and population-based association studies are necessary to validate the risk identified in the current meta-analysis and investigate potential gene-gene and gene-environment interactions on MI risk.

Conflicts of interest

The authors declare no conflict of interest.

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