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The effect of polymorphisms (M235T and T174M) on the angiotensinogen gene (*AGT*) in coronary artery disease in the Eastern Asian population

A systematic review and meta-analysis

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Abstract

Background: It is thought that genetic factors may play an important role in the development of coronary artery disease (CAD). Several studies report that *AGT* polymorphism is implicated in CAD susceptibility, but these results contradict those of the other studies with the associations being unclear in the Eastern Asian population. Therefore, meta-analysis was performed to evaluate this relationship.

Methods: Publication databases were used to search for eligible relevant studies and valid data were extracted from studies meeting the inclusion criteria. Subsequently, odds ratios (ORs) with 95 % confidence intervals (CIs), were used to assess the strength of the association between *AGT* polymorphism and CAD risk.

Results: Seven eligible studies published only in English were included in the present meta-analysis. In the Eastern Asian population, CAD susceptibility was shown to be related to AGT M235T under the heterozygote model (OR = 0.19). Stratified analysis indicated there was a significant relationship between AGT M235T and CAD risk in China under allelic (OR = 1.34), dominant (OR = 1.43), and heterozygote (OR = 1.62) models. The results showed that the T174M polymorphism was significantly associated with CAD risk in recessive (OR = 2.28) and homozygote (OR = 2.37) models in the Eastern Asian population.

Conclusions: In the Eastern Asian population, especially the Chinese, the M235T of *AGT* is associated with CAD susceptibility. The T174M polymorphisms were associated with CAD risk in the Eastern Asian population.

Abbreviations: AGT = angiotensinogen gene, CAD = coronary artery disease, CI = confidence interval, MI = myocardial infarction, OR = odds ratio, RAAS = renin–angiotensin-aldosterone system, SNP = single-nucleotide polymorphism.

Keywords: angiotensinogen gene, Asian population, coronary artery disease, polymorphism

1. Introduction

Coronary artery disease (CAD) as the main cause of many specific diseases, including vascular disease and myocardial infarction (MI), is well documented. It is the leading cause of human mortality worldwide, accounting for >30% of the deaths worldwide each year.[1] Common risk factors for CAD include smoking, obesity, glycolipid metabolism disorders, hypertension, and diabetes mellitus.[2] Recent evidence suggests that environmental factors and gene polymorphisms also play key roles in the occurrence and progression of CAD.[3]

With the rapid development of whole-genome sequencing, single-nucleotide polymorphism detection is becoming more accurate. Numerous in-depth genetic studies on CADs have found that several candidate genes involved in phenomena, such as regulation of lipid metabolism,[4] inflammatory factors,[5] and renin–angiotensin–aldosterone system (RAAS),[6] are closely related to the occurrence and development of diseases.

The RAAS plays an important role in the pathological mechanism of CAD. The RAAS is involved in maintaining sodium homeostasis, vascular remodeling, and blood pressure.[7] A previous study has shown that RAAS is involved in the pathological process of vascular and left ventricular remodeling.[8] The RAAS is also significantly associated with atherosclerosis and thrombosis.[9] Parangular cells secrete renin, which catalyzes the conversion of plasma angiotensin-promoting hormone (AGT) to angiotensin I. Angiotensin

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All data included in this study are available upon request by contact with the corresponding author.

The authors declare that there are no competing interests associated with the manuscript.

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is further converted into angiotensin II, III, and IV, which promote vasoconstriction.[10]

AGT is a key determinant of angiotensin II levels, and angiotensin II is an important component of RAAS. Recently, it has been found that polymorphisms of RAAS genes are closely related to the pathological process of CAD. Among them, the T175M and M235T polymorphisms of angiotensinogen (*AGT*) are the most studied. However, the relationship between *AGT* polymorphisms and CAD is contradictive and inconclusive. *AGT* M235T has been reported to be closely related to the severity of CAD.[11] Raygan et al[12] and Isordia-Salas et al[13] found that *AGT* M235T has a significant influence on CAD occurrence, while Li et al[14] and Renner et al[15] presented completely opposite results. Khatami et al[16] suggested that the T allele of AGT increases the risk of developing CAD while Min et al[17] suggested that the T allele does not increase the risk of developing CAD. In addition to the M235T polymorphism, the correlation between *AGT* T174M and the risk of developing CAD also needs to be studied. Tiret et al[18] reported a relationship between *AGT* T174M and MI for the first time in 1995, but they did not identify a significant association between T174M and the risk of developing CAD. In contrast, Nesrine et al[19] found that a significantly increased risk of developing CAD was associated with T174M.[19]

Based on the above inconsistent and contradictory results, a conclusion could not be reached as to whether or not a relationship exists between *AGT* polymorphism and the risk of developing CAD. Meta-analysis is an effective tool to evaluate the association between allele frequency and disease phenotype. The aim of this study was to collect case–control studies and meta-analyses in order to investigate the association between *AGT* polymorphisms, M235T and T174M and CAD susceptibility in the Eastern Asian populations.

2. Methods

2.1. Selection of eligible studies

Two authors (Zhang and Huang) independently searched and selected studies from PubMed, Embase, and Medline databases. The systematic searches included all study publications after January 1990. The following search terms were used: coronary artery disease, angiotensinogen, and gene polymorphism. This included all alternative locations and combinations of the terms in English.

Eastern Asia, in the present study, includes China, Japan, North Korea, South Korea, and Outer Mongolia. The Chinese refers to ethnicity, included mainland, Taiwan, Hongkong, Macau, and overseas Chinese outside China.

2.2. Inclusion and exclusion criteria

The following inclusion criteria were used: case–control study; studies investigating the association between risk of CAD and

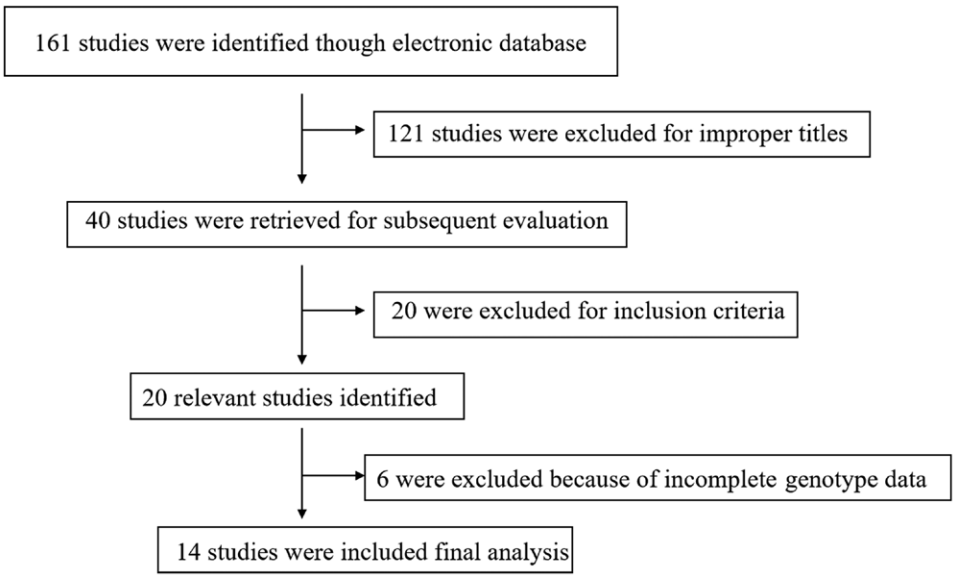

Figure 1. A flow diagram of the study selection process.

Table 1

Quality assessment included in the study (NOS).

		Case selection				Comparability between groups		Exposure factor measurement			
First author	Year	1	2	3	4	5	6	Blind method	7	Response rate	NOS score
Kamitani[20]	1995	*	*	*	*	*	*	?	*	*	8
Ichihara[21]	1997	*	*	*	*	*	*	?	*	*	7
Ko[22]	1997	*	*	*	*	*	*	?	*	?	8
Cong[23]	1998	*	*	*	*	*	*	?	*	*	8
Sheu[24]	1998	*	*	*	*	*	*	?	*	?	7
Tsai[25]	2007	*	*	*	*	*	*	?	*	*	8
Zhu[17]	2019	*	*	*	*	*	*	?	*	*	8

? = undefined, NOS = Newcastle–Ottawa Scale.

*Meet the requirement.

AGT polymorphisms, M235T and T174M; complete genotype distribution data of the AGT M235T and T174M in CAD patients and healthy controls. The following exclusion criteria were used: studies on animals, case reports, reviews, abstracts, editorial comments, and reports with incomplete data. The present study was a systematic review and meta-analysis, the ethical approval was not necessary.

2.3. Data extraction

The 2 authors read 14 eligible articles each and extracted the following information: the first author, year of publication, ethnicity, AGT genotype distribution data in CAD patients, and healthy controls.

2.4. Statistical analysis

Pooled odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were used to estimate the strength of association between *AGT* polymorphisms and CAD risk. The pooled estimate was assessed using the random-effects model (Mantel–Haenszel method) or fixed-effects model (Peto method) depending on whether the heterogeneity existed or not. We used the chi-square–based Q statistic test and I^2 statistics to evaluate the heterogeneity collected studies. The strength of association between *AGT* polymorphisms and risk of CAD was analyzed using the following 5 genetic models: additive, dominant, recessive, homozygote, and heterozygote genetic model. Publication bias was evaluated using a funnel plot. If the funnel plot was asymmetric, publication bias might exist. Egger test was also used to check publication bias. Finally, sensitivity analysis was used to determine the robustness of the results. Stratified analyses were performed based on ethnicity. All data were analyzed by Review Manager (version 5.0.0, The Cochrane collaboration) and STATA software.

3. Results

3.1. General characteristics of the included studies

The process for selecting eligible relevant studies in this meta-analysis is shown in Figure 1. Among totally 161 articles, 121 studies were excluded based on irrelevant titles and abstract, 20 studies were excluded based on inclusion criteria, and 6 studies were excluded due to incomplete genotype data.

Finally, 7[17,20–25] relevant articles from PubMed, Embase, and Medline were identified. The detailed quality assessment included in the study is shown in Table 1. All the included studies contain 1675 CAD patients and 1795 healthy controls. The extracted information, including the first author, year of publication, ethnicity, and AGT genotype distribution data of these 7 included articles, is exhibited in Table 2.

3.2. Meta-analysis results for M235T polymorphism

3.2..1. Comparison of alleles. The overall aggregated ORs and heterogeneity test results for the association of the M235T polymorphism and CAD risk in Eastern Asian are shown in Table 3. As we have seen, there was a significant difference in heterozygote model (TM vs MM; OR = 0.19, 95% CI = 0.11–0.33, $P_{\text{heterogeneity}} \leq .001$, $P_{\text{overall effects}} \leq .001$). Nevertheless, the heterogeneity test ($I^2 = 90\%$) showed that there was remarkable heterogeneity among the included studies. Thus, the subgroup analysis was conducted by region. As shown in Table 4, we discovered the M235T polymorphism exhibited a significant association with CAD in Chinese under 3 genetic models, allele (OR = 1.34, 95% CI = 1.09–1.65, $P_{\text{heterogeneity}} = .009$, $P_{\text{overall effects}} = .006$), dominant (OR = 1.43, 95% CI = 1.09–1.88, $P_{\text{heterogeneity}} = .009$, $P_{\text{overall effects}} = .006$), heterozygote (OR = 1.62, 95% CI = 1.21–2.16, $P_{\text{heterogeneity}} = .00$, $P_{\text{overall effects}} = .001$) models. Subgroup analysis suggested that Chinese carriers of the T allele are more susceptible to CAD. However, in Japanese, significance was not observed in the various genetic models.

Table 2

The characteristics of included studies.

First author	Year	Country	Age (CAD)	Outcome	Source of controls	M235T							T174M						
						CAD cases			Controls			HWE (control)	CAD cases			Controls			HWE (control)
						MM	MT	TT	MM	MT	TT		MM	TM	TT	MM	TM	TT	
Kamitani[20]	1995	Japan	52.0 ± 1.0	MI	Population	6	31	66	10	41	52	0.647	–	–	–	–	–	–	–
Ichihara[21]	1997	Japan	53.0 + 5.6	CAD	Population	15	103	209	13	112	227	0.688	6	47	274	4	57	291	0.525
Ko[22]	1997	China	61.5 ± 0.6	CAD	Population	6	36	225	4	54	279	0.453	1	45	222	2	64	270	0.387
Cong[23]	1998	Japan	–	CAD	Population	2	31	71	16	43	111	0.005	2	13	89	2	32	136	0.939
Sheu[24]	1998	China	–	CAD	Population	1	26	75	1	37	107	0.247	0	18	84	0	18	127	0.425
Tsai[25]	2007	China	63.8 ± 11.4	CAD	Population	15	195	525	5	111	403	0.381	16	133	586	7	83	428	0.202
Zhu[17]	2019	China	65.2 ± 10.7	CAD	Population	3	11	23	5	42	123	0.544	–	–	–	–	–	–	–

CAD = coronary artery disease, HWE = Hardy–Weinberg equilibrium, MI = myocardial infarction.

Table 3

The overall meta-analysis of M235T polymorphism and CAD susceptibility in East Asian

Gene model	group	n	OR	95% CI	I^2	*P* for heterogeneity	Model	*P* for overall effects	*P* for publication bias (Egger)
T vs M (allele model)	Overall	7	1.00	0.75–1.34	71	≤.001	Random	.98	.405
TT + TM vs MM (dominant model)	Overall	7	1.17	0.98–1.39	38	.07	Fixed	.08	.201
TT vs TM + MM (recessive model)	Overall	7	0.99	0.64–1.51	64	≤.001	Random	.95	.487
TT vs MM (homozygote model)	Overall	7	1.01	0.66–1.55	64	≤.001	Random	.95	.293
TM vs MM (heterozygote model)	Overall	**7**	**0.19**	**0.11–0.33**	**90**	**≤.001**	Random	**≤.001**	**.201**

Bold values denote significant association.

CAD = coronary artery disease, CI = confidence interval, OR = odds ratio.

Table 4

The subgroup meta-analysis of M235T polymorphism and CAD susceptibility.

Gene model	Group	n	OR	95% CI	I^2	*P* for heterogeneity	Model	*P* for overall effects
T vs M (allele model)	China	**4**	**1.34**	**1.09–1.65**	**86**	**.009**	Random	**.006**
	Japan	3	1.79	0.61–5.26	83	.003	Random	.29
TT + TM vs MM (dominant model)	China	**4**	**1.43**	**1.09–1.88**	**44**	**.18**	Fixed	**.009**
	Japan	3	1.64	0.56–4.75	66	.05	Random	.37
TT vs TM + MM (recessive model)	China	4	0.98	0.27–3.62	93	≤.001	Random	.98
	Japan	3	1.12	0.88–1.43	39	.19	Fixed	.35
TT vs MM (homozygote model)	China	4	1.06	0.73–1.53	91	≤.001	Random	.77
	Japan	3	1.74	0.58–5.23	67	.05	Random	.32
TM vs MM (heterozygote model)	China	**4**	**1.62**	**1.21–2.16**	**0**	**.94**	Fixed	**.001**
	Japan	3	1.49	0.51–4.37	64	.06	Random	.47

Bold values denote significant association.

CAD = coronary artery disease, CI = confidence interval, OR = odds ratio.

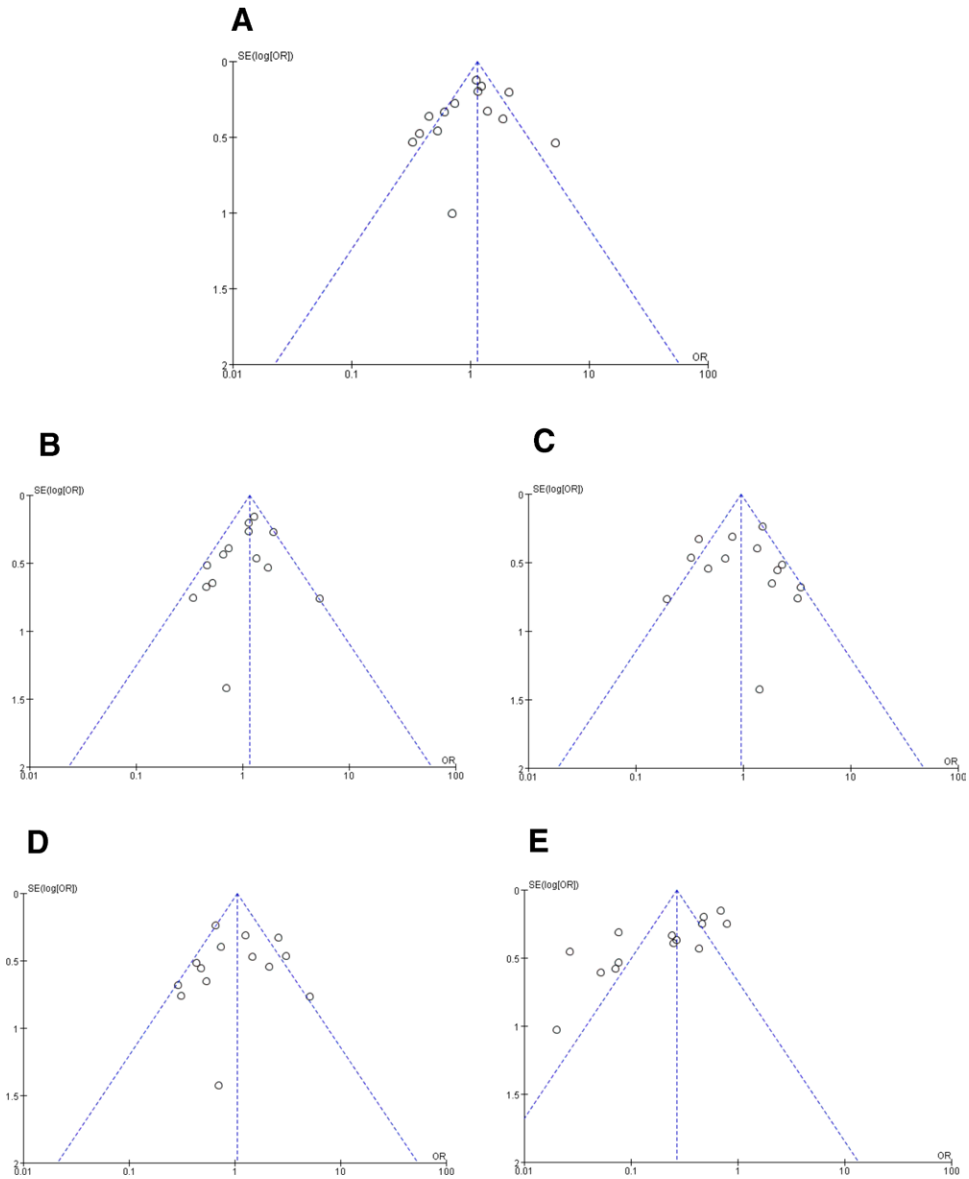

Figure 2. The results of sensitivity analysis between M235T polymorphism and susceptibility to CAD. (A) Allele model; (B) dominant model; (C) recessive model; (D) homozygous model; (E) heterozygous model. CAD = coronary artery disease, OR = odds ratio, SE = standard error.

3.2..2. Investigation of heterogeneity and publication bias. No obvious publication bias was observed in all the analyses of 5 genetic models ($P > .05$, for all; Table 3). Figure 2 shows the sensitivity analysis result of M235T polymorphism and CAD susceptibility.

3.3. Meta-analysis results for the T174M polymorphism

3.3..1. Comparison of alleles. As shown in Table 5, T174M was found to be associated with an increased risk of developing CAD in the recessive (OR = 2.28, 95% CI = 1.48–3.53, $P_{\text{heterogeneity}}$

= .26, $P_{\text{overall effects}}$ = 0.000) and homozygote models (OR = 2.37, 95% CI = 1.53–3.66, $P_{\text{heterogeneity}}$ = .24, $P_{\text{overall effects}}$ = .000) in the Eastern Asian. The results suggested that T174M was closely related to CAD susceptibility in the Eastern Asian population.

3.3..2. Investigation of heterogeneity and publication bias. The sensitivity analysis result of T174M polymorphism and CAD susceptibility is shown in Figure 3. Publication bias was calculated using the Egger test; the test did not identify bias in any of the genotypes, as the results were not significant ($P > .05$; Table 5).

4. Discussion

CAD is a multifactorial disease, and both environmental and genetic factors play an important role in its pathological process.

Table 5

The overall meta-analysis of T174M polymorphism and CAD susceptibility in East Asian.

Gene model	Group	n	OR	95% CI	I^2	*P* for heterogeneity	Model	*P* for overall effects	*P* for publication bias (Egger)
M vs T (allele model)	Overall	6	1.26	0.91–1.75	80	≤.001	Random	.16	.405
MM + MT vs TT (dominant model)	Overall	6	1.20	0.87–1.65	74	≤.001	Random	.27	.121
MM vs MT + TT (recessive model)	Overall	**6**	**2.28**	**1.48–3.53**	**21**	**.26**	Fixed	**≤.001**	**.375**
MM vs TT (homozygote model)	Overall	**6**	**2.37**	**1.53–3.66**	**24**	**.24**	Fixed	**≤.001**	**.211**
MT vs TT (heterozygote model)	Overall	6	0.98	0.84–1.14	0	0.65	Fixed	.78	.704

Bold values denote significant association.

CAD = coronary artery disease, CI = confidence interval, OR = odds ratio.

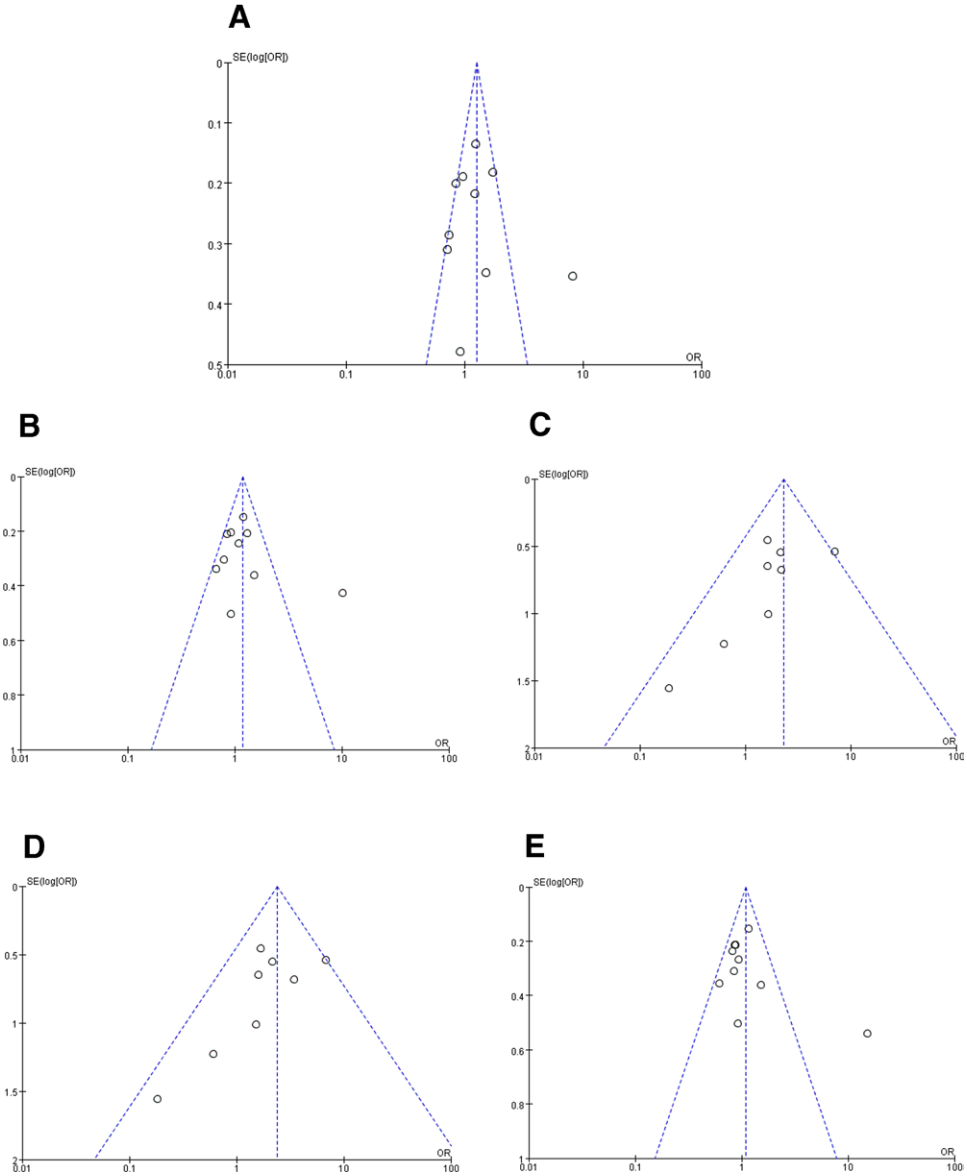

Figure 3. The results of sensitivity analysis between T174M polymorphism and susceptibility to CAD. (A) Allele model; (B) dominant model; (C) recessive model; (D) homozygous model; (E) heterozygous mode. CAD = coronary artery diseas, OR = odds ratio, SE = standard error.

Identifying the risk factors and candidate genes involved in CAD pathogenesis can help researchers understand the pathological mechanism of the disease. Parangular cells secrete renin, which catalyzes the formation of plasma AGT that plays an important role in blood pressure regulation.

In recent years, *AGT* polymorphism has attracted extensive attention from researchers. In this study, we found that *AGT* polymorphisms, which may affect transcription and expression, are closely associated with a significantly increased risk of developing CAD. In addition, *AGT* polymorphism may affect restenosis after stent implantation in patients with CAD. Therefore, studying the association between *AGT* polymorphism and CAD susceptibility is of utmost importance.

In M235T, the nucleotide T at position 704 of the second exon is substituted with C, resulting in the substitution of the methionine residue at position 235 with threonine. Alopecia M235T has been shown to alter plasma AGT levels, with patients with the T allele exhibiting elevated serum AGT levels.[26] Elevated AGT levels are closely associated with increased angiotensin II concentrations in circulation. Angiotensin II triggers cardiac myocyte hypertrophy and fibroblast proliferation by stimulating AT1 receptors.[27] In recent years, researchers have investigated the relationship between CAD susceptibility and *AGT* polymorphisms, M235T and T174M.

Our present study aims to investigate the relationship between the *AGT* polymorphisms, M235T and T174M, and the risk of developing CAD in the Eastern Asian populations. Correlation analysis investigating the association between *AGT* M235T and CAD showed that the difference in the heterozygous genetic model was significant. We found significant heterogeneity in the statistical results and, therefore, a subgroup analysis was performed. Subsequent analysis based on ethnic subgroups showed that multiple genetic models of the Chinese population were significant. Publication bias funnel plot was symmetrical and the *P* value in the Egger test was >.05, indicating that there was no publication bias. The results of the correlation analysis between *AGT* M235T and CAD susceptibility were robust; the same was also confirmed by sensitivity analysis. In the 5 gene models, T base pairing in the M235T position was a predisposing factor for CAD in the Chinese population.

The results of the correlation analysis between the T174M polymorphism and CAD risk showed that the differences were significant in recessive and homozygote models. The results suggest that there is no heterogeneity. Publication bias analysis showed that the symmetry of funnel plot for various genetic models was common, and the *P* values in the Egger test were all >.05, indicating that the conclusions were robust.

Our current results indicate that both *AGT* polymorphisms, that is, M235T and T174M are associated with CAD susceptibility in the Eastern Asian populations. A meta-analysis of Chinese patients with CAD conducted by Wang et al showed that the M235T and T174M polymorphisms were significantly correlated with CAD susceptibility.[28] The results reported in Wang et al are consistent with those of this study; however, there is a caveat, that is, the study was published in 2012. As more recent studies were included in our study, our study is a further in-depth extension of Wang et al.

However, several researchers have found contradictory results. Sui et al found a significant correlation between *AGT* T174M and CAD. However, by racial stratification, a significant association between genetic polymorphism and CAD was observed in Caucasians but not in all Asians.[29] Wen found that there was no significantly increased risk of developing CAD in Asians.[30] We speculated that discrepancy in research conclusions might be attributed to the fact that our analysis only including studies in English. Studies in other languages were excluded.

The main limitations of our meta-analysis include the following: the limited number of studies included owing to which we cannot draw complete conclusions; heterogeneity exists in various genetic models of the 2 mutations; the general condition, medical history, age, gender, medication compliance, CAD complications, and other factors of the subjects in the included literature were not considered; and the gene–gene and gene–environment interactions were not analyzed.

In conclusion, our present results showed a significant association between *AGT* polymorphisms M235T and T174M and CAD in Asian populations. However, the results of subsequent studies on gene–gene and gene–environment interactions should be taken into consideration.

Author contributions

Zhang qian and Qingning Huang retrieved literature and extracted information.
Xianen Wang and Yong Wang analyzed the data.
Xiaofang Hua supervised the project.

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