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. Common risk factors for CAD include smoking, obesity, glycolipid metabolism disorders, hypertension, and diabetes mellitus. Recent evidence suggests that environmental factors and gene polymorphisms also play key roles in the occurrence and progression of CAD.

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, inflammatory factors, and renin-angiotensin-aldosterone system (RAAS), 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. A previous study has shown that RAAS is involved in the pathological process of vascular and left ventricular remodeling. The RAAS is also significantly associated with atherosclerosis and thrombosis. Parangual cells secrete renin, which catalyzes the conversion of plasma angiotensin-promoting hormone (AGT) to angiotensin I. Angiotensin...
is further converted into angiotensin II, III, and IV, which promote vasoconstriction.\cite{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 contradictory and inconclusive. AGT M235T has been reported to be closely related to the severity of CAD.\cite{11} Raygan et al\cite{12} and Isordia-Salas et al\cite{13} found that AGT M235T has a significant influence on CAD occurrence, while Li et al\cite{14} and Renner et al\cite{15} presented completely opposite results. Khatami et al\cite{16} suggested that the T allele of AGT increases the risk of developing CAD while Min et al\cite{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\cite{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\cite{19} found that a significantly increased risk of developing CAD was associated with T174M.\cite{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

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Table 1

| First author | Year | Case selection | Comparability between groups | Exposure factor measurement |
|--------------|------|----------------|----------------------------|-----------------------------|
| Kamitani\cite{20} | 1995 | * * * * | * * | * * |
| Ichihara\cite{21} | 1997 | * * * * | * * | * * |
| Ko\cite{22} | 1997 | * * * * | * * | * * |
| Cong\cite{23} | 1998 | * * * * | * * | * * |
| Sheu\cite{24} | 1998 | * * * * | * * | * * |
| Tsai\cite{25} | 2007 | * * * * | * * | * * |
| Zhu\cite{26} | 2019 | * * * * | * * | * * |

*= 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 I² 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, 16 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, $P_{\text{heterogeneity}} = .001, \ P_{\text{overall effects}} = .001$). 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 | CAD cases | Controls | HWE (control) | CAD cases | Controls | HWE (control) |
|--------------|------|---------|-----------|---------|--------------------|-----------|----------|--------------|-----------|----------|--------------|
| Kamitani[20] | 1995 | Japan   | 52.0 ± 1.0 | MI      | Population         | 6         | 31       | 66           | 10        | 41       | 52           |
| Ichihara[21] | 1997 | Japan   | 53.0 ± 5.6 | CAD     | Population         | 15        | 103      | 209          | 13        | 112      | 227          |
| KG[22]       | 1997 | China   | 61.5 ± 0.6 | CAD     | Population         | 6         | 36       | 225          | 4         | 54       | 279          |
| Cong[23]     | 1998 | Japan   | 53.0 ± 1.0 | MI      | Population         | 2         | 31       | 71           | 16        | 43       | 111          |
| Sheu[24]     | 1998 | China   | –         | CAD     | Population         | 1         | 26       | 75           | 1         | 37       | 107          |
| Tsai[25]     | 2007 | China   | 63.8 ± 11.4 | CAD     | Population         | 15        | 195      | 525          | 5         | 111      | 403          |
| Zhu[26]      | 2019 | China   | 65.2 ± 10.7 | CAD     | Population         | 3         | 11       | 23           | 5         | 42       | 123          |

**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 | $P$ | $P$ 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 | 0.66 | 0.44–1.03 | 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.
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, $P_{\text{heterogeneity}}$)

### Table 4

| Gene model                              | Group | $n$ | OR   | 95% CI | I² | $P$ for heterogeneity | Model | $P$ for overall effects |
|-----------------------------------------|-------|-----|------|--------|----|-----------------------|-------|------------------------|
| T vs M (allele model)                   | China | 4   | 1.34 | 1.09–1.65 | 86 | .099                  | 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 | 0.58–6.23 | 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.

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

| Gene model                          | Group | n   | OR   | 95% CI | $P_{\text{heterogeneity}}$ | Model  | $P_{\text{overall effects}}$ | $P_{\text{for publication bias (Egger)}}$ |
|-------------------------------------|-------|-----|------|--------|---------------------------|--------|-----------------------------|------------------------------------------|
| M vs T (allele model)              | Overall | 6   | 1.26 | 0.91–1.75 | $\leq .001$              | Random | .16 | .405                        |
| MM + MT vs TT (dominant model)     | Overall | 6   | 1.20 | 0.87–1.65 | $\leq .001$              | Random | .27 | .121                        |
| MM vs MT + TT (recessive model)    | Overall | 6   | 2.28 | 1.48–3.53 | .26                      | Fixed  | $\leq .001$ | .375                         |
| MM vs MT (homozygote model)        | Overall | 6   | 2.37 | 1.53–3.66 | .24                      | Fixed  | $\leq .001$ | .211                         |
| MT vs TT (heterozygote model)      | Overall | 6   | 0.98 | 0.84–1.14 | 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 model. CAD = coronary artery disease, 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. Paranginal 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. 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. 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. 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. Wen found that there was no significantly increased risk of developing CAD in Asians. 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.

References

[1] Roth GA, Huffman MD, Moran AE, et al. Global and regional patterns in cardiovascular mortality from 1990 to 2013. Circulation. 2015;132:1667–78.
[2] Svendsen K, Krøll HW, Iglanova J, et al. 2.5-fold increased risk of recurrent acute myocardial infarction with familial hypercholesterolemia. Atherosclerosis. 2021;319:28–34.
[3] Warrington NM, Beaumont RN, Horikoshi M, et al. Maternal and fetal genetic effects on birth weight and their relevance to cardio-metabolic risk factors. Nat Genet. 2019;51:804–14.
[4] Kaphan R, Tyhjæng-Hansen A. Genetics of coronary artery disease. Circ Res. 2016;118:564–78.
[5] Yuepeng J, Zhao X, Zhao Y, et al. Gene polymorphism associated with TNF-α (G308A) IL-6 (C174G) and susceptibility to coronary atherosclerotic heart disease: a meta-analysis. Medicine (Baltim). 2019;98:e13813.
[6] Ryu SK, Cho EY, Park HY, et al. Renin-angiotensin-aldosterone system (RAAS) gene polymorphism as a risk factor of coronary in-stent restenosis. Yonsei Med J. 2002;43:461–72.
[7] Darcy A, Clarke A, Oliver D, et al. Renin-angiotensin aldosterone profile before and after angiotensin-converting enzyme-inhibitor administration in dogs with angiotensin-converting enzyme gene polymorphism. J Vet Intern Med. 2020;34:600–6.
[8] Wang JG, Staessen JA. Genetic polymorphisms in the renin-angiotensin system: relevance for susceptibility to cardiovascular disease. Eur J Pharmacol. 2000;410:289–302.
[9] Koh KK, Han SH, Oh PC, et al. Combination therapy for treatment or prevention of atherosclerosis: focus on the lipid-RAAS interaction. Atherosclerosis. 2010;209:307–13.
[10] Zhao H, Zhao R, Hu S, et al. Gene polymorphism associated with angiotensinogen (M235T), endothelial lipase (584C/T) and susceptibility to coronary artery disease: a meta-analysis. Biosci Rep. 2020;40:e20201414.
[11] Lanz JR, Pereira AC, Lemos PA, et al. Angiotensinogen M235T polymorphism is associated with coronary artery disease severity. Clin Chim Acta. 2005;362:176–81.
[12] Raggan F, Karimian M, Rezaeian A, et al. Angiotensinogen-M235T as a risk factor for myocardial infarction in Asian populations: a genetic association study and a bioinformatics approach. Croat Med J. 2016;57:351–62.
[13] Isordia-Salas I, Alvarado-Moreno JA, Jiménez-Alvarado RM, et al. Association of renin-angiotensin system genes polymorphisms and risk of premature ST elevation myocardial infarction in young Mexican population. Blood Coagul Fibrinolysis. 2018;29:267–74.
[14] Li X, Li Q, Wang Y, et al. AGT gene polymorphisms (M235T, T174M) are associated with coronary heart disease in a Chinese population. J Renin Angiotensin Aldosterone Syst. 2013;14:354–9.
[15] Remmer W, Nauck M, Winkelmann BR, et al. Association of angiotensinogen haplotypes with angiotensinogen levels but not with blood pressure or coronary artery disease: the Ludwigshafen Risk and Cardiovascular Health Study. J Mol Med (Berl). 2005;83:235–9.
[16] Khutami M, Heidari MM, Hadiadzadeh M, et al. Simultaneous genotyping of the rs4762 and rs699 polymorphisms in angiotensinogen gene and correlation with Iranian CAD patients with novel Hexa-primer ARMS-PCR. Iran J Public Health. 2017;46:811–9.
[17] Min Z, Jiangbo L, Chen W, et al. The relationship among angiotensinogen genes polymorphisms and hs-CRP and coronary artery disease. J Clin Lab Anal. 2019;33:e22881.

[18] Tiet L, Ricard S, Poirier O, et al. Genetic variation at the angiotensinogen locus in relation to high blood pressure and myocardial infarction: the ECTIM Study. J Hypertens. 1995;13:311–7.

[19] Nesrine A, Lakhder G, Belhassen K, et al. Evaluation of the contribution of renin angiotensin system polymorphisms to the risk of coronary artery disease among Tunisians. Genet Test Mol Biomarkers. 2010;14:661–6.

[20] Kamitani A, Rakugi H, Higaki J, et al. Enhanced predictability of myocardial infarction in Japanese by combined genotype analysis. Hypertension. 1995;25:950–3.

[21] Ichihara S, Yokota M, Fujimura T, et al. Lack of association between variants of the angiotensinogen gene and the risk of coronary artery disease in middle-aged Japanese men. Am Heart J. 1997;134:260–5.

[22] Ko YL, Ko YS, Wang SM, et al. Angiotensinogen and angiotensin-I converting enzyme gene polymorphisms and the risk of coronary artery disease in Chinese. Hum Genet. 1997;100:210–4.

[23] Cong ND, Hamaguchi K, Saikawa T, et al. A polymorphism of angiotensinogen gene codon 174 and coronary artery disease in Japanese subjects. Am J Med Sci. 1998;316:339–44.

[24] Sheu WH, Lee WJ, Jeng CY, et al. Angiotensinogen gene polymorphism is associated with insulin resistance in nondiabetic men with or without coronary heart disease. Am Heart J. 1998;136:125–31.

[25] Chi-Ti T, Juey-Jen H, Marylyn DR, et al. Renin–angiotensin system gene polymorphisms and coronary artery disease in a large angiographic cohort: detection of high order gene–gene interaction. Atherosclerosis. 2007;195:172–80.

[26] Tianhua N, Xiu C, Xiping X. Angiotensin converting enzyme gene insertion/deletion polymorphism and cardiovascular disease: therapeutic implications. Drugs. 2002;62:977–93.

[27] Peters J. Molecular basis of human hypertension: role of angiotensin. Baillieres Clin Endocrinol Metab. 1995;9:657–78.

[28] Xingsheng L, Qiao L, Yongming W, et al. AGT gene polymorphisms (M235T, T174M) are associated with coronary heart disease in a Chinese population. J Renin Angiotensin Aldosterone Syst. 2013;14:354–9.

[29] Xizhong S, Changqing G. The angiotensinogen gene M235T polymorphism and acute myocardial infarction risk: a meta-analysis of 22 studies. Mol Biol Rep. 2013;40:4439–45.

[30] Wen Zhu W. Association between T174M polymorphism in the angiotensinogen gene and risk of coronary artery disease: a meta-analysis. J Geriatr Cardiol. 2013;10:59–65.