Laboratory Research

Effects of angiotensinogen gene polymorphisms on the risk of coronary heart disease in the Chinese population: a meta-analysis

Yan Pan1, Yu-Jing Wang2

1 Medical College of Yangtze University, Hangkong Road 8, Shashi District, Jingzhou 434000, Hubei Province, China
2 Cardiovascular Department, the First Affiliated Hospital of Yangtze University, Hangkong Road 8, Shashi District, Jingzhou 434000, Hubei Province, China.

Objective  Coronary heart disease (CHD) is a multifactorial disease. This meta-analysis was performed to evaluate the relationship between angiotensinogen gene polymorphisms and CHD in the Chinese population.

Methods  We searched literature in pubmed (1990-2010.8) and CNKI (1990-2010.8) for all the relevant studies on 2 angiotensinogen polymorphisms (M235T and T174M) and risk of CHD. The meta-analysis software Stata 10.0 was used for ascertaining heterogeneity among individual studies and for combining all the studies. Furthermore, Egger’s test and sensitivity analysis were performed to insure authenticity of the outcome.

Results  Ten associations studies on 2 angiotensinogen polymorphisms (M235T and T174M) were included in this meta-analysis. In a combined analysis, the summary per-allele odds ratio for CHD of the M235T polymorphism was 1.374 (95% confidence interval, 1.019 to 1.852) and T174M polymorphism was 4.089 (95% confidence interval, 1.697 to 9.851). Conclusions  The M235T polymorphism had weak but statistically significant association with CHD while the T174M polymorphism was more strongly associated with a CHD risk in Chinese population, but further confirmation studies are needed.

Key words  angiotensinogen; coronary heart disease; gene polymorphisms; meta-analysis

Introduction  Coronary heart disease (CHD) is a multifactorial disease and its pathogenesis is not yet fully understood. Evidence is accumulating that susceptibility to CHD is associated with angiotensinogen gene polymorphisms1-3. For Chinese population, the results of relevant studies were inconsistent. We performed a meta-analysis to evaluate the relationship between angiotensinogen gene polymorphisms (M235T and T174M) and CHD in the Chinese Han population.

Methods  Data retrieval  We searched for all published studies that assessed the relationship between angiotensinogen polymorphisms (M235T and T174M) and CHD in the Chinese Han population through CNKI, Chinese Journal Full Text Special Database and PUBMED. Keywords relating to retrieval were: "angiotensinogen, AGT, CHD, coronary heart disease, coronary artery disease, myocardial infarction, ischemic heart disease and polymorphism" and the time restricted was from 1990 to August 2010.

Data extraction  The following data were extracted independently by 2 investigators, when encountering data disputed, adjudicated by a third reviewer. The inclusion criteria in the meta-analysis were: study subjects limited to Han nationality of the Chinese population; paper languages restrict to English and Chinese; accessed literature must be the full text and come from case-control studies; diagnosis of coronary stenosis (defined as at least 50% stenosis of 1 or more major coronary arteries) or myocardial infarction (defined according to the World Health Organization criteria) was provided. Literature was excluded when the implementation and published time of the study was unclear or those contained duplicate data. Where significant ambiguities remained or when data could not be extracted for inclusion in the meta-analysis, the investigators were contacted via e-mail.

Meta analysis  Deviance from Hardy-Weinberg equilibrium was assessed of the contro1 group of each study using χ2 tests. We included studies irrespective of any departure from Hardy-Weinberg equilibrium. Heterogeneity was assessed with the Q test and F test, which describes the percentage of total
variation in point estimates attributable to genuine differences rather than to random error. If the results of the Q and I² test had no significant heterogeneity, the fixed effect model was used for the combination of data; If the results of the Q test had significant heterogeneity, the Galbraith plot was used to find those studies resulting in the heterogeneity. We evaluated the publication bias via Egger's test, sensitivity analysis was performed through random effect model values compared to the fixed effect. All probability values were 2-sided, and values of P≤0.05 were considered statistically significant. All statistical analyses were carried out with the Stata software version 10.0 (Stata Corporation, College Station, Tex), with meta-analyses performed using the `metan` subroutine.

Results

Study selection and subject characteristics

The search generated 47 association studies, of which 10 met the selection criteria. The flowchart of literature screening is presented in Figure 1 and the characteristics of the selected studies included in this meta-analysis is provided in Table 1. Both M235T and T174M polymorphisms were found to occur in frequencies consistent with Hardy-Weinberg equilibrium in the control populations of the vast majority of the published studies.

Association of the M 235T variant with CHD

Homogeneity was tested among the 8 studies of the M235T polymorphism (Q=16.2, I²=56.8%; P=0.023). Because of the significant heterogeneity, we used Galbraith plot to analyze the reason (Figure 2) and two reports were excluded. Afterwards we investigated the association of included studies using the fixed effect and the per-allele OR of the 235T variant for CHD was 1.12 (95% CI, 0.91 to 1.39; Figure 3). Publication bias was analyzed by Egger’s test (t=0.79, P=0.473), and the result showed no publication bias of the Meta-analysis. We further used random effect model to perform a sensitivity analysis and the OR was 1.123 (95% CI, 0.909 to 1.388), which indicated the previous data was actual and authentic.

Association of T174M variant with CHD

Heterogeneity among the 4 available studies of the T174M variant and CHD existed (Q=2.79, I²=28.3%; P=0.248). Overall, the per-allele OR of the T174M variant for CHD was 4.089 (95% CI, 1.697 to 9.851; Figure 4), Egger's test did not indicate the presence of publication bias in these studies (t=-0.34, P=0.703). Sensitivity analysis using random effect model and the OR was 3.799 (95% CI, 1.215 to 11.879), which revealed the previous value was credible and true.

Discussion

The renin angiotensin system plays a core role in promoting vascular growth and regulating blood pressure. Two variations of angiotensinogen gene loci, substitutions of methionine to threonine at residue 235 (M235T) and threonine to methionine at 174 (T174M), have been linked to elevated blood pressure previously.14,15 Ishigami, et al16 were the first to report that M235T variation remarkably increased risk of CHD using case-control study. Thereafter several studies drew the similar conclusion17 while others reported different results.18 In order to clarify the inconsistent findings, we performed this meta-analysis which showed an weak but statistically significant association between the M235T polymorphism and CHD risk in Chinese population, similar to the previous meta-analysis.18 Owing to the limitation of literature quality, we can not use both meta-regression and subgroup analysis to investigate the reason of heterogeneity of the M235T studies informed, instead, we use Galbraith plot to exclude the literatures lead-

<table>
<thead>
<tr>
<th>Study included</th>
<th>Area</th>
<th>Number of cases</th>
<th>Number of cases</th>
<th>Genotypes for cases</th>
<th>Genotypes for controls</th>
<th>Frequency of T allele</th>
<th>Test for HWE</th>
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<tbody>
<tr>
<td>M235T</td>
<td></td>
<td></td>
<td></td>
<td>MM MT TT</td>
<td>MM MT TT</td>
<td>x²</td>
<td>P</td>
</tr>
<tr>
<td>Ko et al⁶</td>
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<td>268</td>
<td>338</td>
<td>6 36 225</td>
<td>4 54 279</td>
<td>0.908</td>
<td>0.561 0.454</td>
</tr>
<tr>
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<td>13 31 32</td>
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<td>1.281 0.258</td>
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<td>1 37 107</td>
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<td>1.340 0.247</td>
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<tr>
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<tr>
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<td>2 21 105</td>
<td>0.902</td>
<td>0.611 0.434</td>
</tr>
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</table>
**Figure 1** The flowchart of literature screening

47 Abstracts imported from PUBMED and CNKI

- 16 Potentially relevant articles identified and reviewed
- Articles excluded: 32 Non-associative outcome
- 5 Excluded: 2 Review, 3 Repeat reported literature
- 11 relevant studies included
- 1 Unable to get the original data
- 10 studies adopted in meta-analysis

**Figure 2** Galbraith plot of studies of the M235T polymorphism and CHD
ing to heterogeneity, so further relevant studies are needed. In our study, the T174M was strongly associated with CHD risk in the Chinese population, which was in consistent with previously results.\(^\text{20}\)

The meta-analysis also had its own limitations. Test technologies were not identical between different laboratories, which may result in bias. In addition, the quality of the meta-analysis depends on that of individual studies, and we use Galbraith plot and Egger's test to control the bias. Furthermore, the relatively poor quality of the literature we included in the present meta-analysis may limit the reliability of the summarized values, so further confirmation studies are needed.

In summary, this study evaluated the effect of angiotensinogen gene polymorphisms on the risk of coronary heart disease in the Chinese population. Our study suggested that M235T had a weak but statistically significant association with CHD, while T174M polymorphism was more strongly associated with an increased risk of CHD in the Chinese population.

**References**


