Original Article
Rs5498 polymorphism may be a risk factor for coronary heart disease in Chinese population: evidence from a meta-analysis involving 5537 subjects

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Abstract: Despite large numbers of studies from Chinese population related to the association between rs5498 polymorphism and coronary heart disease (CHD) risk, the results are inconsistent probably due to the difference in the nationalities. To further evaluate the impact of the rs5498 polymorphism on CHD risk of different nationalities population, we performed this meta-analysis. We comprehensively searched the eligible studies for the present meta-analysis through China National Knowledge Infrastructure (CNKI), PubMed, EMBASE databases. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were obtained to evaluate the strength of the association between rs5498 polymorphism and CHD risk. Finally, a total of 18 studies including 5537 subjects met the inclusion criteria. The pooled result showed that the rs5498 polymorphism was significantly associated with an increased risk of CHD in allele comparison model (OR=1.43, 95% CI=1.17-1.73, P=0.000), homozygote model (OR=1.23, 95% CI=1.03-1.46, P=0.000), heterozygote model (OR=1.23, 95% CI=1.03-1.46, P=0.018), dominant model (OR=1.45, 95% CI=1.21-1.74, P=0.000) and recessive model (OR=2.17, 95% CI=1.70-2.77, P=0.000). But subgroup analysis only supported the results from data of Han and Zhuang population in South China and North China. We did not find any evidences revealing some relationship between them in the Uygur population of Northwest China. Totally, the results of our meta-analysis indicate that the rs5498 polymorphism may be associated with coronary heart disease in Han and Zhuang population but not in Uyghur population. A large number of well-designed and multiracial studies should be conducted to re-evaluate the relationship.

Keywords: Coronary heart disease, rs5498, meta-analysis, polymorphism

Introduction
Coronary artery disease (CAD) is a complex multifactorial disease characterized by remodeling and narrowing the coronary arteries, which supply oxygen to the heart. It is likewise the primary cause of death around the world and the prevalence is still increasing [1]. Although the explicit pathogenic mechanisms leading to CAD are still unclear, it is generally believed that obesity [2], smoking [3], physical activity, environmental factors contribute to its development. Beyond that, the outcome of many studies over the past decades has shown that numerous genes play a critical role in CAD, for example, PAI-1, AMPD1, HPA-3 and ICAM-1 [4].

Intercellular adhesion molecule-1 (ICAM-1), located at chromosome 19p13.3 to 13.2, is one of the most widely studied candidate genes for predisposition to CAD [5]. As a famous member of the immunoglobulin superfamily of adhesion molecules, it acts as a significant role in adhering leukocytes to the blood vessel wall and transendothelial migration to the vascular
Association between rs5498 polymorphism coronary heart disease

intima [6]. However, one single nucleotide G to A polymorphism, namely rs5498 polymorphism, was found to result in the glutamic acid being supplanted by lysine, suggesting that it may affect mRNA splicing patterns [7].

Up to now, several studies investigated the role of the rs5498 polymorphism on the risk of CAD from data of the Chinese population. It was reported that some were considered to be associated with increased CAD risk, however, some others did not observe a similar relationship. Thus, the results were often inconsistent and ambiguous. China is a multinational country, but for all we know, there was only one meta-analysis once studied the influence of this location on CAD in China. In addition, they had some limitations: First, the meta-analysis only included limited papers and subjects; Second, the subgroup analysis of the meta-analysis was merely performed and stratified by the ratio of the number of CAD patients and controls (RR), and they did not research the diversity of rs5498 polymorphism in different regions and nationalities which are of crucial importance in gene analysis.

Considering the reasons above, we decided to add the latest data and made subgroup analysis by region and nationality with the aim of providing a clearer and correct understanding of the relationship between the rs5498 polymorphism and CAD.

Methods

Search strategies

Relevant epidemiologic studies were searched to investigate the association of rs5498 polymorphism with coronary heart disease. Two authors retrieved China National Knowledge Infrastructure (CNKI), EMBASE and PubMed databases independently to identify valuable papers published up to July 2015. The following key words and combinations of them were utilized: “coronary,” “heart,” “intercellular adhesion molecule-1, ICAM-1” “polymorphism, variation, variant, mutation,” “genetic,” “rs5498, K469E”. In addition to that, we also manually screened the reference lists of all cited articles and relevant reviews and meta-analysis to confirm other potentially available studies.

Inclusion and exclusion criteria

For the meta-analysis, the following criteria for inclusion were defined: (1) evaluating the associations between rs5498 polymorphism and the risk of CHD; (2) case-control studies that had original data to assess the association; (2) cases and controls were eligible regardless of country, region, ethnicity and age; (3) providing sufficient data for calculation of odds ratio (OR) and 95% confidence interval (CI).

While for the exclusion criteria, the following were used: (1) not for rs5498 polymorphism research; (2) studies containing repeat or overlapping studies; (3) not case-control study; (4) studies that investigated rs5498 variants as makers for response to therapy; (6) studies in which the number of genotypes or alleles were not offered.

Data extraction

Two investigators strictly extracted relevant information from all definite papers according to the inclusion and exclusion criteria. Discrepancy was resolved by consensus. The following parameters were extracted from each study: first author’s surname, year of publication, nationality, province, region, the number of cases and controls and genotype frequency information. The accuracy of information was verified by comparing data drawn from papers. If different studies include the same population, we only included the most valuable study in this meta-analysis.

Statistical analysis

The data from these researches were used to investigate the association between rs5498 polymorphism and CHD. The strength of the association was evaluated by calculating the odds ratios (ORs) and 95% confidence intervals (CIs). The statistical significance of the pooled OR was evaluated by the Z test. Hardy-Weinberg equilibrium (HWE) in the control group for each included studies was estimated by a goodness of fit χ² test; P>0.05 was considered disequilibrium. We calculated the pooled ORs for allele comparison model (E vs. K), homozygote model (EE vs. KK), heterozygote model (EK vs. KK), dominant model [(EK+EE) vs. KK] and recessive model [EE vs. (KK+EK)], respectively. Heterogeneity was evaluated with the chi-square-based Q test. In addition to that, heterogeneity was also assessed by the I² statistic (I²=0-25%: no heterogeneity; I²=25-50%: moderate heterogeneity; I²=50-75%: large heterogeneity; I²=75-100%: extreme heterogeneity [8]. When the heterogeneity was obvious, we will use the ran-
Association between rs5498 polymorphism coronary heart disease

dom-effect model to calculate the pooled OR [9], otherwise the fix-effect model was used [10]. Moreover, we also performed the stratified analysis by nationality, region, province and sample size. In order to assess the stability of the results, sensitivity analyses were performed by deleting one study successively at a time to evaluate it. We performed funnel plots to assess the potential publication bias. And the publication bias was also explored using Begg's [11] and Egger's [12] tests (P<0.05 indicates a significant publication bias). All analyses for this meta-analysis were performed with STATA Version 12.0 (Stata Corporation, College Station, TX).

Results

Characteristics of included studies

The flow diagram in Figure 1 summarizes the selection process of this literature. 374 pub-
## Association between rs5498 polymorphism coronary heart disease

Table 2. Overall and subgroup meta-analysis of the association between rs2228570 polymorphism and degenerative disc disease under genetic models

<table>
<thead>
<tr>
<th>Groups</th>
<th>N</th>
<th>Allelic OR (95% CI)</th>
<th>P</th>
<th>Homozygous OR (95% CI)</th>
<th>P</th>
<th>Heterozygous OR (95% CI)</th>
<th>P</th>
<th>Dominant OR (95% CI)</th>
<th>P</th>
<th>Recessive OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>18</td>
<td>1.43 (1.17, 1.73)</td>
<td>0.000</td>
<td>1.90 (1.37, 2.64)</td>
<td>0.000</td>
<td>1.23 (1.03, 1.46)</td>
<td>0.018</td>
<td>1.45 (1.21, 1.74)</td>
<td>0.001</td>
<td>2.17 (1.70, 2.77)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Nationality</strong></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Han</td>
<td>14</td>
<td>1.54 (1.22, 1.94)</td>
<td>0.000</td>
<td>2.13 (1.44, 3.15)</td>
<td>0.000</td>
<td>0.94 (0.64, 1.36)</td>
<td>0.000</td>
<td>1.45 (1.15, 1.84)</td>
<td>0.000</td>
<td>2.36 (1.79, 3.12)</td>
<td>0.004</td>
</tr>
<tr>
<td>Uygur</td>
<td>3</td>
<td>0.97 (0.78, 0.21)</td>
<td>0.534</td>
<td>1.03 (0.52, 2.04)</td>
<td>0.073</td>
<td>1.45 (1.08, 1.95)</td>
<td>0.051</td>
<td>1.39 (1.05, 1.84)</td>
<td>0.105</td>
<td>1.32 (0.88, 2.00)</td>
<td>0.431</td>
</tr>
<tr>
<td>Zhuang</td>
<td>1</td>
<td>1.55 (1.21, 1.99)</td>
<td>NA</td>
<td>2.12 (1.18, 3.79)</td>
<td>NA</td>
<td>1.69 (1.20, 2.36)</td>
<td>NA</td>
<td>1.76 (1.28, 2.42)</td>
<td>NA</td>
<td>2.61 (1.48, 4.60)</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Province</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Hubei</td>
<td>5</td>
<td>1.44 (0.96, 2.17)</td>
<td>0.000</td>
<td>1.89 (0.98, 3.66)</td>
<td>0.000</td>
<td>0.98 (0.64, 1.50)</td>
<td>0.005</td>
<td>1.31 (0.88, 1.95)</td>
<td>0.002</td>
<td>2.62 (1.71, 4.01)</td>
<td>0.060</td>
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<tr>
<td>Shandong</td>
<td>4</td>
<td>1.79 (1.49, 2.15)</td>
<td>0.922</td>
<td>2.75 (1.95, 3.88)</td>
<td>0.928</td>
<td>1.81 (1.07, 3.05)</td>
<td>0.870</td>
<td>1.75 (1.33, 2.31)</td>
<td>0.868</td>
<td>2.07 (1.53, 2.79)</td>
<td>0.999</td>
</tr>
<tr>
<td>Guangxi</td>
<td>2</td>
<td>1.50 (1.24, 1.81)</td>
<td>0.669</td>
<td>2.01 (1.30, 3.11)</td>
<td>0.791</td>
<td>1.61 (1.25, 2.07)</td>
<td>0.665</td>
<td>1.67 (1.31, 2.13)</td>
<td>0.647</td>
<td>2.54 (1.66, 3.90)</td>
<td>0.900</td>
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<tr>
<td>Zhejiang</td>
<td>1</td>
<td>1.64 (1.14, 2.36)</td>
<td>NA</td>
<td>2.09 (0.87, 5.03)</td>
<td>NA</td>
<td>1.83 (1.13, 2.95)</td>
<td>NA</td>
<td>1.87 (1.19, 2.94)</td>
<td>NA</td>
<td>2.94 (1.23, 7.02)</td>
<td>NA</td>
</tr>
<tr>
<td>Shanghai</td>
<td>1</td>
<td>4.79 (2.93, 7.84)</td>
<td>NA</td>
<td>12.34 (4.93, 30.89)</td>
<td>NA</td>
<td>1.45 (0.60, 3.50)</td>
<td>NA</td>
<td>3.80 (1.84, 7.86)</td>
<td>NA</td>
<td>6.55 (2.98, 14.40)</td>
<td>NA</td>
</tr>
<tr>
<td>Xinjiang</td>
<td>3</td>
<td>0.97 (0.78, 1.21)</td>
<td>0.927</td>
<td>1.03 (0.52, 2.04)</td>
<td>0.232</td>
<td>1.45 (1.08, 1.95)</td>
<td>0.801</td>
<td>1.39 (1.05, 1.84)</td>
<td>0.561</td>
<td>1.32 (0.88, 2.00)</td>
<td>0.431</td>
</tr>
<tr>
<td>Guangdong</td>
<td>1</td>
<td>0.48 (0.27, 0.83)</td>
<td>NA</td>
<td>0.29 (0.11, 0.80)</td>
<td>NA</td>
<td>0.43 (0.16, 1.17)</td>
<td>NA</td>
<td>0.35 (0.14, 0.85)</td>
<td>NA</td>
<td>0.51 (0.22, 1.16)</td>
<td>NA</td>
</tr>
<tr>
<td>Hebei</td>
<td>1</td>
<td>1.11 (0.72, 1.72)</td>
<td>NA</td>
<td>1.68 (0.62, 4.56)</td>
<td>NA</td>
<td>0.83 (0.46, 1.52)</td>
<td>NA</td>
<td>0.96 (0.55, 1.69)</td>
<td>NA</td>
<td>3.26 (1.22, 8.72)</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Sample</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>&gt;300</td>
<td>9</td>
<td>1.35 (1.12, 1.63)</td>
<td>0.001</td>
<td>1.77 (1.33, 2.35)</td>
<td>0.077</td>
<td>1.36 (1.09, 1.69)</td>
<td>0.018</td>
<td>1.47 (1.19, 1.81)</td>
<td>0.010</td>
<td>2.10 (1.73, 2.56)</td>
<td>0.624</td>
</tr>
<tr>
<td>&lt;300</td>
<td>9</td>
<td>1.50 (1.00, 2.24)</td>
<td>0.000</td>
<td>1.93 (0.98, 3.82)</td>
<td>0.000</td>
<td>1.03 (0.81, 1.30)</td>
<td>0.442</td>
<td>1.40 (0.98, 2.01)</td>
<td>0.004</td>
<td>2.02 (1.19, 3.43)</td>
<td>0.000</td>
</tr>
</tbody>
</table>

N: total number of studies involved in the analysis; NA: the data were not available.
Association between rs5498 polymorphism coronary heart disease

Published papers were included and screened. Eventually, a total of 18 eligible studies involving 2,730 cases and 2,807 controls completely met the inclusion criteria were enrolled in our meta-analysis [13-30]. Of the 18 papers, there were 14 studies performed in Han population

Figure 2. Meta-analysis for the association between rs5498 polymorphism and CHD.

Figure 3. Meta-analysis for the association between rs5498 polymorphism and CHD.
Association between rs5498 polymorphism and coronary heart disease

Quantitative synthesis

The total results of the present study concerning the association between rs5498 polymorphism and coronary heart disease were listed in Table 2. Overall, significant association was found in allele comparison model (OR=1.43, 95% CI=1.17-1.73, P=0.000), homozygote model (OR=1.23, 95% CI=1.03-1.46, P=0.000), heterozygote model (OR=1.23, 95% CI=1.03-1.46, P=0.018), dominant model (OR=1.45, 95% CI=1.21-1.74, P=0.001) and recessive model (OR=2.17, 95% CI=1.70-2.77, P=0.002), suggesting that rs5498 polymorphism may be a risk factor for CHD susceptibility (Figure 2).

But large heterogeneity was found in all genetic model of our current meta-analysis. To explore the source of heterogeneity, stratified analyses by nationality, region, province and sample size were performed. It was found that the K allele was associated with increased CHD in Han allele comparison model (OR=1.54, 95% CI=1.22-1.94, P=0.000) and Zhuang population allele comparison model (OR=1.55, 95% CI=1.21-1.99), but not the Uygur (allele comparison model (OR=0.97, 95% CI=0.78-0.21, P=0.534) (Figure 3). We also found significant association between rs5498 polymorphism and CHD in South and North China. In addition to that, the polymorphism may play a crucial role in population living in Hubei, Shandong, Guangxi, Zhejiang and Shanghai. Sample size above 300 also got a significant association. Above all, the data from Han population of Hubei located in South China were the main source of heterogeneity. The detailed data were listed in Table 2.

Sensitivity analysis and publication bias

To evaluate the stability of the pooled results of our meta-analysis, sensitivity analysis was conducted by sequentially omitting each study. In Figure 4. One-way sensitivity analysis of the pooled ORs and 95% CI for the rs5498 polymorphism and CHD risk.

Figure 5. Begg’s test was held to detect potential publication bias.
consideration of the data homogeneity in the Uygur and Zhuang, we merely analyzed the main origin of heterogeneity in Han population. As shown in Figure 4, sensitivity analyses indicate that the papers published by Zhou [22], Xu [23] and Mo [27] were the primary source of the heterogeneity (OR=1.65, 95% CI=1.44-1.88, I²=39.8%, P=0.083). And though excluding the papers which were not in conformity with Hardy-Weinberg equilibrium, the result was still stable.

Both Begg’s and Egger’s test were adopted in order to evaluate the publication bias of the literatures for the association between rs5498 polymorphism and coronary heart disease. The shape of funnel plots seemed symmetrical. Our statistical data also did not show any evidences of publication bias (Begg’s test P=0.940; Egger’s test P=0.767) (Figures 5, 6).

Discussion

Coronary artery disease is a common disease which has threatened the people’s life around the world. In the past decades, scientists dedicated to researching its mechanism of the onset and progress. However, until now, its etiology and pathogenesis are still unknown. Coronary atherosclerosis is generally treated as the primary reason for coronary heart disease. Atherosclerotic lesions can contribute to the dysfunction of artery wall metabolism, which results from a variety of factors, genetic and non-genetic.

In recent years, a growing number of people have already focused on the role of inflammation in the pathogenesis of coronary heart disease [31]. They thought that atherosclerosis was a chronic inflammation process, in which inflammatory cells adhered to endothelial cells and traversed the endothelium in the early stage of CAD onset [32]. As an important inflammatory protein, belonging to a large immunoglobulin superfamily [33], intercellular adhesion molecule-1 plays a crucial role in recruiting leukocytes at sites of inflammation and the adhesion of circulating leukocytes to vascular intima [34]. This suggested that ICAM-1 may work in the development of the inflammatory reaction, atherosclerosis, and thrombosis.

As research continues, it was found that rs5498 polymorphism at position 1,548 of the 6th exon of the intercellular adhesion molecule-1 gene could result in the glutamate (E) being substituted by lysine (K). It was pointed out that this polymorphism might influence the serum level and activity of ICAM-1 [35] and have a possible function in the pathogenesis of atherosclerosis [36]. Thus, a large number of studies have tried to illuminate the association between rs5498 polymorphism and CHD, but the results were controversial, especially in China. For instance, Shang [16] reported that the KK and EK genotypes of the rs5498 polymorphism was possibly related to coronary heart disease (CHD) susceptibility and similar results were found in several studies in other different Chinese population [14, 19, 21, 24]. However, Zhou [22] and Mo [27] both suggested that the E allele might be a genetic risk factor for CHD. Therefore, to address this argument, we performed the most comprehensive review on the association between rs5498 polymorphism with coronary heart disease.

This meta-analysis included 2,730 cases and 2,807 controls from 18 case-control studies and is the largest scale meta-analysis up to now. In summary, our results suggested that the rs5498 polymorphism may be associated...
Association between rs5498 polymorphism coronary heart disease

with the increasing of coronary heart disease. But in stratified analyses by nationality, we got a completely different result. It showed that the K allele was associated with increased CHD in Han and Zhuang population, but not the Uygur. It suggested that the rs5498 polymorphism may not be a risk gene for CHD in the Uygur. This phenomenon may result from the impact of diverse nationalities. Then we explored the heterogeneity of our study, finding large heterogeneity in all genetic model. To explore the origin of heterogeneity, stratified analyses by nationality, region, province and sample size were performed. We found a significant association between rs5498 polymorphism and CHD in South and North China. In addition to that, the polymorphism may play a critical role in population living in Hubei, Shandong, Guangxi, Zhejiang and Shanghai. Sample size above 300 also got a meaningful association. According to the detailed data, the Han population of Hubei located in South China may be the main source of heterogeneity. Although high heterogeneity for this polymorphism was detected in all models, results from one-way sensitivity analysis revealed high stability and reliability of our results. In addition to that, we also conducted Begg's and Egger's test which manifested that there was no obvious publication bias in our meta-analysis.

Regardless of the fact that meta-analyses have been made to resolve the matter, several limitations should be taken into account when interpreting our research. First, the sample size of the published studies was not sufficient to do a large-scale research on the relationship between rs5498 polymorphism and coronary heart disease. Second, some papers were not included in our meta-analysis because of insufficient data, which may result in bias. Third, the studies were limited to Han, Zhuang and Uyghur population so that we cannot make precise conclusions and this may increase the risk of false-negative findings in all population levels. Thus, the information from other nationalities still need to be investigated. Fourth, our result was based on unadjusted estimates, while a more precise analysis should be conducted adjusted by other factors like gender, BMI, smoking, etc.

In conclusion, the results of our meta-analysis indicate that the rs5498 polymorphism may be associated with coronary heart disease in Han and Zhuang population but not in the Uygur population. A large number of well-designed and multiracial studies should be done to re-evaluate the relationship.

Disclosure of conflict of interest

None.

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Association between rs5498 polymorphism coronary heart disease


Association between rs5498 polymorphism coronary heart disease


