Review Article

Meta-analysis of the association between Apo-A1 rs670, rs5069 polymorphisms and coronary artery diseases

Li-Ping Dong¹,², Da Huang¹, Wei-Jun Cai³

¹Department of Histology and Embryology, School of Basic Medicine, Central South University, Changsha 410013, China; ²Department of Anatomy, Histology and Embryology, Institute of Neuroscience, Changsha Medical University, Changsha 410219, China

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Abstract: Coronary artery disease (CAD) is a major cause of mortality and morbidity around the whole world. The polymorphisms of Apolipoprotein A-I (Apo-A1), including rs670 (-75 G/A) and rs5069 (+83 C/T), have been found to be probably associated with the risk of CAD. However, the results were inconsistent. To determine the association between Apo-A1 rs670 and rs5069 polymorphisms with CAD, we conducted the meta-analysis of all available studies cited in Pubmed, Embase, CBM and CNKI before 11 Mar 2017. A total of 6 studies, including 1358 cases and 863 controls, were identified for the meta-analysis. The results showed that rs670 and rs5069 had no significant associations with risk of CAD in the overall analysis. But in subgroup analysis by ethnicity, the GG of rs670 was associated with a significantly lower risk of CAD in allelic model (OR = 0.61, 95% CI = 0.61 [0.38, 0.96], p = 0.03) and homozygous model (OR = 0.25, 95% CI = 0.25 [0.15, 0.44], p<0.00001) in Caucasians, the GG of rs670 was associated with a significantly higher risk of CAD in homozygous model (OR = 2.12, 95% CI = 2.12 [1.27, 3.53], p = 0.004) in Asian, and a lower risk of CAD for the CC genotype and C allele of rs5069 in allelic model (OR = 0.21, 95% CI = 0.21 [0.06, 0.72], p = 0.01) and homozygous model (OR = 0.11, 95% CI = 0.11 [0.04, 0.32], p<0.00001) in Caucasians. In conclusion, this study suggested that Apo-A1 rs670 and rs5069 had no significant associations with risk of CAD in the overall analysis. However, the results of this meta-analysis are hypothesis-generating results which should be interpreted with caution because of the heterogeneity and publication bias among study designs.

Keywords: Apo-A1, rs670, rs5069, polymorphism, coronary artery disease

Introduction

Cardiovascular Diseases (CVDs) is the major cause of death around the world. According to the World Health Organization (WHO) report in 2014, more than 17.5 million individuals died from cardiovascular disease in 2012, accounting for 46.2% of noncommunicable diseases death [1]. Coronary artery disease (CAD), one of the CVDs, has a complex pathogenesis generated by interactions between genetic and environmental risk factors. Besides the environmental risk factors, many studies discussed an association of gene polymorphisms with the risk of CAD.

Apo-A1 is the main protein component of high density lipoprotein (HDL) which provides protection against atherosclerosis. The human Apo-A1 gene is located in chromosome 11q23 [2]. The polymorphisms in Apo-A1 have been found to be probably associated with the risk of CAD. However, the results were controversial results. Some studies have showed that the Apo-A1 polymorphisms, including rs760 and rs5069, were related to the risk of CAD [3-7], while others considered they were not [8]. Thus, in this study, we included 6 studies (1358 cases and 863 controls) to obtain a more accurate and comprehensive estimation of the association between these polymorphisms and CAD.

Experimental section

Publication search strategy

We used the following electronic databases to search studies: Pubmed, Embase, Chinese
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National Knowledge Infrastructure (CNKI), and Chinese Biomedical Literature Database (CBM). The search terms and key words were (“Coronary artery disease”, or “CAD”), (“Apo-A1”), and (“polymorphism” or “mutation” or “SNP” or “single nucleotide polymorphism”), without restrictions to language. The deadline for publication was 11 Mar 2017. All the results from the databases were read. First, we read the title. If the titles met our criteria, we then read the abstract. We read the full text if the abstract also met our criteria to determine eligible studies.

Inclusion criteria and exclusion criteria

Inclusion criteria: (1) case-control design; (2) the association of Apo-A1 rs670 or rs5069 polymorphisms with CAD risks should be evaluated; (3) sufficient data should be provided for this estimation.

Exclusion criteria: (1) abstracts, letters, reviews and master degree thesis; (2) repeat publications; (3) studies not satisfying all of the inclusion criteria.

Data extraction

We extracted information from each included study by two investigators independently. Any discrepancy between the reviewers was resolved by consensus or a third investigator. For each study, we gathered the first authors’ name, publishing year, country, ethnicity, genotyping method, age and sex match, genotype numbers and source of cases and controls.

Statistical methods

We evaluate the HWE of the control group polymorphism by \( \chi^2 \)-test. If \( p < 0.05 \), it was considered to be deviated from HWE.

We used the odds ratio (OR) with 95% confidence interval (CI) to assessed the association between Apo-A1 polymorphisms and CAD risk. The pooled ORs were calculated in homozygous, heterozygous, dominant, and allelic genetic model. The statistical significance was evaluated by the Z-test, \( p < 0.05 \) was considered to be statistically significant.

Heterogeneity between studies was evaluated by an \( I^2 \) statistical test, which was not dependent on the number of studies in the present study [10]. \( I^2 > 50\% \) was considered an obvious heterogeneity among the studies, the random-effects model was used for the meta-analysis [11]. Otherwise, the fixed-effect model was used [12]. Subgroup analysis was conducted to identify the heterogeneity.

Sensitivity analysis was conducted to detect the effect of each study on pooled results and the stability of results.

To detect publication bias, we used Begg’s funnel plot and Egger’s linear regression method, and \( p < 0.05 \) was regarded as statistically significant [13].

All statistical analysis was performed using the STATA 12.0 software and Revman 5.3.

Quality assessment

We evaluated the quality of the included studies according to the predefined scale for quality assessment [9]. The score scale includes total sample size, source of cases, source of controls, specimens used for determining genotypes, and evidence of Hardy-Weinberg equilibrium (HWE). The quality scores range from 0-15, higher scores indicating better quality. Generally considered publications scoring ≥10 were “high quality”, and those <10 were “low quality”.

Figure 1. PRISMA flowchart of study inclusion and exclusion.
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### Table 1. Characteristics of eligible studies included in the meta-analysis

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Ethnicity</th>
<th>Genotype method</th>
<th>Sex/age match</th>
<th>Quality score</th>
<th>Sample size (case/control)</th>
<th>Case Control</th>
<th>HWE of control</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. Chhabra [3]</td>
<td>2005</td>
<td>India</td>
<td>Caucasians</td>
<td>PCR</td>
<td>match</td>
<td>10</td>
<td>164/36</td>
<td>102 51 11 29 7 0</td>
<td>0.518</td>
</tr>
<tr>
<td>Himanshu Rai [8]</td>
<td>2016</td>
<td>India</td>
<td>Caucasians</td>
<td>PCR-RFLP</td>
<td>match</td>
<td>10</td>
<td>200/200</td>
<td>117 71 12 118 75 7</td>
<td>0.236</td>
</tr>
<tr>
<td>BiHong Liao [4]</td>
<td>2015</td>
<td>China</td>
<td>Asian</td>
<td>PCR-RFLP</td>
<td>match</td>
<td>8</td>
<td>300/300</td>
<td>175 104 21 161 100 39</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Zou Yangchun [5]</td>
<td>2003</td>
<td>China</td>
<td>Asian</td>
<td>PCR</td>
<td>match</td>
<td>9</td>
<td>92/45</td>
<td>78 8 6 26 12 7</td>
<td>0.019</td>
</tr>
<tr>
<td>Taranjit Singh Rai [7]</td>
<td>2008</td>
<td>India</td>
<td>Caucasians</td>
<td>PCR</td>
<td>match</td>
<td>9</td>
<td>140/100</td>
<td>45 44 51 51 39 10</td>
<td>0.533</td>
</tr>
</tbody>
</table>

### Table 2. Pooled ORs and 95% CIs of the association between Apo-A1 rs670, rs5069, and CAD risks

#### Apo-A1 rs670 and CAD

<table>
<thead>
<tr>
<th>Genetic model</th>
<th>Model</th>
<th>N</th>
<th>OR (95% CI)</th>
<th>P</th>
<th>(\hat{I}^2) (%)</th>
<th>Model</th>
<th>N</th>
<th>OR (95% CI)</th>
<th>P</th>
<th>(\hat{I}^2) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GG vs. AA</td>
<td>Overall</td>
<td>6</td>
<td>0.59 [0.19, 1.76]</td>
<td>0.34</td>
<td>85</td>
<td>R</td>
<td>GG vs. GA</td>
<td>Overall</td>
<td>6</td>
<td>1.04 [0.75, 1.44]</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
<td>2</td>
<td>2.12 [1.27, 3.53]</td>
<td>0.004</td>
<td>0</td>
<td>F</td>
<td>Asian</td>
<td>2</td>
<td>2.01 [0.48, 8.32]</td>
<td>0.34</td>
</tr>
<tr>
<td></td>
<td>Caucasians</td>
<td>4</td>
<td>0.25 [0.15, 0.44]</td>
<td>&lt;0.00001</td>
<td>23</td>
<td>F</td>
<td>Caucasians</td>
<td>4</td>
<td>0.92 [0.72, 1.17]</td>
<td>0.51</td>
</tr>
<tr>
<td>GG vs. AA/GA</td>
<td>Overall</td>
<td>6</td>
<td>0.95 [0.61, 1.48]</td>
<td>0.82</td>
<td>80</td>
<td>R</td>
<td>G vs. A</td>
<td>Overall</td>
<td>6</td>
<td>0.89 [0.54, 1.45]</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
<td>2</td>
<td>2.09 [0.64, 6.82]</td>
<td>0.22</td>
<td>86</td>
<td>R</td>
<td>Asian</td>
<td>2</td>
<td>1.99 [0.80, 4.93]</td>
<td>0.14</td>
</tr>
<tr>
<td></td>
<td>Caucasians</td>
<td>4</td>
<td>0.69 [0.46, 1.04]</td>
<td>0.08</td>
<td>63</td>
<td>R</td>
<td>Caucasians</td>
<td>4</td>
<td>0.61 [0.38, 0.96]</td>
<td>0.03</td>
</tr>
</tbody>
</table>

#### Apo-A1 rs5069 and CAD

<table>
<thead>
<tr>
<th>Genetic model</th>
<th>Model</th>
<th>N</th>
<th>OR (95% CI)</th>
<th>P</th>
<th>(\hat{I}^2) (%)</th>
<th>Model</th>
<th>N</th>
<th>OR (95% CI)</th>
<th>P</th>
<th>(\hat{I}^2) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC vs. TT</td>
<td>Overall</td>
<td>4</td>
<td>0.78 [0.14, 4.44]</td>
<td>0.78</td>
<td>91</td>
<td>R</td>
<td>CC vs. CT</td>
<td>Overall</td>
<td>4</td>
<td>0.39 [0.10, 1.58]</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
<td>2</td>
<td>1.80 [0.63, 5.13]</td>
<td>0.27</td>
<td>61</td>
<td>R</td>
<td>Asian</td>
<td>2</td>
<td>1.08 [0.38, 3.07]</td>
<td>0.89</td>
</tr>
<tr>
<td></td>
<td>Caucasians</td>
<td>2</td>
<td>0.11 [0.04, 0.32]</td>
<td>&lt;0.00001</td>
<td>-</td>
<td>F</td>
<td>Caucasians</td>
<td>2</td>
<td>0.13 [0.01, 1.22]</td>
<td>0.07</td>
</tr>
<tr>
<td>CC vs. TT/CT</td>
<td>Overall</td>
<td>4</td>
<td>0.47 [0.11, 1.98]</td>
<td>0.30</td>
<td>95</td>
<td>R</td>
<td>C vs. T</td>
<td>Overall</td>
<td>4</td>
<td>0.60 [0.18, 2.03]</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
<td>2</td>
<td>1.38 [0.47, 4.05]</td>
<td>0.55</td>
<td>82</td>
<td>R</td>
<td>Asian</td>
<td>2</td>
<td>1.53 [0.57, 4.10]</td>
<td>0.40</td>
</tr>
<tr>
<td></td>
<td>Caucasians</td>
<td>2</td>
<td>0.15 [0.02, 1.01]</td>
<td>0.05</td>
<td>92</td>
<td>R</td>
<td>Caucasians</td>
<td>2</td>
<td>0.21 [0.06, 0.72]</td>
<td>0.01</td>
</tr>
</tbody>
</table>

R: Random model; F: Fixed model.
Results

Characteristics of eligible studies

A total of 294 studies were found from the literature search after duplicates were removed. Among them, 243 studies were excluded for irrelevance and reviews, 15 were master’s degree theses, and 30 full text articles excluded according to inclusion and exclusion criteria. Finally, 6 studies met the criteria, including 1358 cases and 863 controls [4-10]. Among
them, 6 studies described the associations between Apo-A1 rs670 and CAD, and 4 studies described the associations between Apo-A1 rs5069 and CAD. The PRISMA flowchart is shown in Figure 1 and the information for included studies is presented in Table 1.

Results of meta-analysis

The results of the meta-analysis for the associations between Apo-A1 rs670, rs5069 and CAD risks were shown in Table 2 and Figures 2, 3.

Apo-A1 rs670 and CAD

Six studies, with 1358 cases and 863 controls, were included in this study. No significant associations were found between Apo-A1 rs670 and CAD susceptibility in overall analysis for all genetic models. But in subgroup analysis by ethnicity, the rs670 was associated with a significantly lower risk of CAD in allelic model (G vs. A, OR = 0.61, 95% CI = 0.61 [0.38, 0.96], p = 0.03) and homozygous model (GG vs. AA, OR = 0.39 [0.10, 1.58], p = 0.39)
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Table 3. Egger’s and Begg’s test for the publication bias of rs670

<table>
<thead>
<tr>
<th>Genetic model</th>
<th>Egger’s test p Value</th>
<th>Begg’s Test p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GG vs. AA</td>
<td>0.477</td>
<td>0.707</td>
</tr>
<tr>
<td>GG vs. GA</td>
<td>0.733</td>
<td>0.707</td>
</tr>
<tr>
<td>GG vs. AA/GA</td>
<td>0.896</td>
<td>0.707</td>
</tr>
<tr>
<td>G vs. A</td>
<td>0.957</td>
<td>0.707</td>
</tr>
</tbody>
</table>

Table 4. Egger’s and Begg’s test for the publication bias of rs5069

<table>
<thead>
<tr>
<th>Genetic model</th>
<th>Egger’s test p Value</th>
<th>Begg’s Test p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC vs. TT</td>
<td>0.828</td>
<td>1.000</td>
</tr>
<tr>
<td>CC vs. CT</td>
<td>0.690</td>
<td>1.000</td>
</tr>
<tr>
<td>CC vs. TT/CT</td>
<td>0.726</td>
<td>0.734</td>
</tr>
<tr>
<td>C vs. T</td>
<td>0.769</td>
<td>1.000</td>
</tr>
</tbody>
</table>

= 0.25, 95% CI = 0.25 [0.15, 0.44], p<0.00001) in Caucasians, and associated with a significantly higher risk of CAD in homozygous model (GG vs. AA, OR = 2.12, 95% CI = 2.12 [1.27, 3.53], p = 0.004) in Asian.

Apo-A1 rs5069 and CAD

Four studies, with 994 cases and 622 controls, were included in this study. No significant associations were found between Apo-A1 rs5069 and CAD susceptibility in overall analysis for all genetic models. But subgroup analysis by ethnicity discovered CC genotype of rs5069 was associated with a significantly lower risk of CAD in allelic model (C vs. T, OR = 0.21, 95% CI = 0.21 [0.06, 0.72], p = 0.01) and homozygous model (CC vs. TT, OR = 0.11, 95% CI = 0.11 [0.04, 0.32], p<0.00001) in Caucasians.

Test of heterogeneity

For Apo-A1 rs670 polymorphism, there was significant heterogeneity between studies in all comparison models. However, in the subgroup analysis of ethnicity, heterogeneity decreased or even disappeared in homozygous and heterozygous model. But the heterogeneity still existed in allelic and dominant model. In addition, for rs5069, significant heterogeneity existed in all genetic models. Although we also performed subgroup analysis, we failed to explain the source of the heterogeneity.

Sensitivity analysis

The influence of each study on the pooled OR and 95% CI was evaluated by excluding one single study at a time using STATA 12.0 software. The analysis showed that no single individual study significantly affected the pool OR in all genetic models for rs670 and rs5069 (only the heterozygous model of rs670 results are shown in Figure 4).

Publication bias

To assess the publication bias, the Begg’s and Egger’s test were performed. The p values for Begg’s and Egger’s tests are shown in Tables 3, 4. These results showed that there was no evidence of publication bias in all comparison models. These results were also demonstrated by the shape of the funnel plot (the homozygous model of rs670 and the allelic model of rs5069 results are shown in Figures 5, 6).

Discussion

Previous studies have reported the importance of inflammation in the risk of atherosclerosis...
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HDL is involved in reverse cholesterol transport and has important anti-inflammatory and anti-oxidant properties [15]. Apo-A1, which is the major protein of HDL, is a major participant in the regulation of reverse cholesterol transport [16]. The variation in the Apo-A1 gene was associated with Apo-A1 serum concentrations [17-19], and serum levels of Apo-A1 may influence the risk of CAD [18, 20, 21], diabetic retinopathy [22].

Recently, several SNPs in Apo-A1 have been studied to investigate their relations with CAD risk. Rs670 has gained the greatest attention in these involved studies, some of which found a significant association between rs670 and CAD, while others denied it.

In the present meta-analysis of 6 studies including 1358 cases and 863 controls, we found that Apo-A1 rs670 and rs5069 had no significant associations with risk of CAD in the overall analysis. But in subgroup analysis by ethnicity, the GG of rs670 was associated with a significantly lower risk of CAD in allelic model (OR = 0.61) and homozygous model (OR = 0.25) in Caucasians, the GG of rs670 was associated with a significantly higher risk of CAD in homozygous model (OR = 2.12) in Asian, and a lower risk of CAD for the CC genotype and C allele of rs5069 in allelic model (OR = 0.21) and homozygous model (OR = 0.11) in Caucasians. In the subgroup analysis of ethnicity, we found that the opposite directions of the observed association among Caucasians and Asians, which may be related to the difference in race.

We found that significant deviation from HWE (p<0.05) in one of the rs670 studies and three of the rs5069 studies, which may be due to the small sample size. Therefore, further studies need larger sample size to confirm the results.

Significant heterogeneity was found in this study for rs670 and rs5069. Thus, we conducted subgroup analysis by ethnicity and found that it was in part sources of the heterogeneity for rs670 and rs5069. Thus, further studies are needed to confirm these results. In the sensitivity analysis, no significant changes were found when omitting each study one at a time, showing the relative stability and credibility of the results of this study.
Since no significant p-values for rs670 and rs5069 through Begg’s and Egger’s test were found in this study, we think that several limitations should be considered. Firstly, only 6 studies were included and all studies were small sample sizes in this study. There are not large-scale studies available. Secondly, heterogeneity may have distorted the meta-analysis. Furthermore, studies only in English or Chinese have been searched. There might be studies in other languages which are not included. Thus, the conclusion in the present meta-analysis might be only of generalizability for Asians. The last limitation is that CAD is a multifactorial disease influenced by both genetic and environmental factors, but most studies lack the information on multiple SNPs in haplotypes and environmental exposure.

Conclusions

In conclusion, this study suggested that Apo-A1 rs670 and rs5069 had no significant associations with risk of CAD in the overall analysis. But the GG of rs670 was associated with a significantly lower risk of CAD in allelic model (OR = 0.61) and homozygous model (OR = 0.25) in Caucasians and the GG of rs670 was associated with a significantly higher risk of CAD in homozygous model (OR = 2.12) in Asian. In addition, the CC genotype and C allele of rs5069 was associated with a significantly lower risk of CAD for in allelic model (OR = 0.21) and homozygous model (OR = 0.11) in Caucasians. However, the results of this meta-analysis are hypothesis-generating results which should be interpreted with caution because of the heterogeneity and publication bias among study designs. Further studies are required to evaluate the association between Apo-A1 polymorphisms and CAD in various ethnic groups.

Acknowledgements

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Disclosure of conflict of interest

None.

Address correspondence to: Wei-Jun Cai, Department of Histology and Embryology, School of Basic Medicine, Central South University, Changsha 410013, China. Tel: +86-731-8578-9635; Fax: +86-731-8578-9635; E-mail: caiweijun@csu.edu.cn

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