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Original Article

Association of *APOA5* T1131C polymorphism and risk of coronary artery disease

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Abstract: Aims: Our research aimed to investigate the relationship between Apolipoprotein A5 (*APOA5*) T1131C polymorphism and the risk of coronary artery disease (CAD). Methods: We searched the relevant articles in databases and 25 ones were chosen. The association between *APOA5* T1131C polymorphism and CAD risk was evaluated using odds ratios (ORs) and 95% confidence intervals (95% CIs). The fixed-effect model or random-effect model was applied according to the heterogeneity analysis. Results: Overall, significant association between CAD risk and *APOA5* T1131C polymorphism was found (CC vs. TT: OR=1.47, 95% CI=1.22-1.78; CC+TC vs. TT: OR=1.13, 95% CI=1.07-1.20; CC vs. TT+TC: OR=1.37, 95% CI=1.13-1.66; allele C vs. allele T: OR=1.17, 95% CI=1.09-1.25; TC vs. TT: OR=1.12, 95% CI=1.06-1.20). In the ethnicity subgroup analysis, risk of CAD was observed in all genotypes among Asians (CC vs. TT: OR=1.40, 95% CI=1.17-1.68; CC+TC vs. TT: OR=1.13, 95% CI=1.06-1.20; CC vs. TT+TC: OR=1.30, 95% CI=1.08-1.56; allele C vs. allele T: OR=1.15, 95% CI=1.08-1.24; TC vs. TT: OR=1.13, 95% CI=1.06-1.21), While in Caucasians, the similar association was only found in several genotypes. In the subgroup analysis by source of control, we found that *APOA5* T1131C polymorphism could increase the risk of CAD in population-based (PB) genetic group (CC vs. TT: OR=1.54, 95% CI=1.29-1.84; CC+TC vs. TT: OR=1.15, 95% CI=1.08-1.23; CC vs. TT+TC: OR=1.45, 95% CI=1.19-1.76; allele C vs. allele T: OR=1.19, 95% CI=1.12-1.25; TC vs. TT: OR=1.14, 95% CI=1.06-1.22). There was no correlation found in hospital-based (HB) genetic group yet. Conclusion: *APOA5* T1131C polymorphism might be significantly associated with susceptibility to CAD.

Keywords: Apolipoprotein A5, polymorphism, coronary artery disease

Introduction

Coronary artery disease (CAD) is the most common cause of cancer-death and a major cause of hospital admissions in the world according to the statistics in 2012 [1-3]. Meanwhile, CAD is also a primary type of heart disease leading to heart attacks. The occurrence of CAD is affected by numbers of risk factors including smoking, obesity, family history, diabetes, stress and lack of exercise [4]. Among these factors, smoking accounts for about 54% of cases, obesity 20% and lack of exercise 7%-12% [5, 6]. The studies suggested that plasma triglycerides (TG) were also associated with CAD susceptibility [7, 8].

Various genetic and environmental factors may exert certain influence on the levels of TG, of which genetic factors have been regarded as important regulators for TG [9, 10]. A series of apolipoprotein genes, located on chromosome 11q23, such as *APOA1*, *APOC3*, *APOA4* and *APOA5*, have great effects on TG metabolism. Apolipoprotein A5 (*APOA5*) has been demonstrated to act vitally in mediating density of serum TG, high level of plasma *APOA5* gene resulting in lower level of TG [11].

In view of the significant relation of *APOA5* and TG, a number of single nucleotide polymorphisms (SNPs) of *APOA5* have been confirmed [12]. Among these SNPs, T1131C in *APOA5* promoter region has been identified to be in correlation with increased TG densities under different ethnic populations, including Caucasians, Chinese and Japanese [11, 13-17]. Epidemio logical studies found that the risk of CAD was correspondingly elevated along with the increasing level of TG [18, 19]. Therefore, the

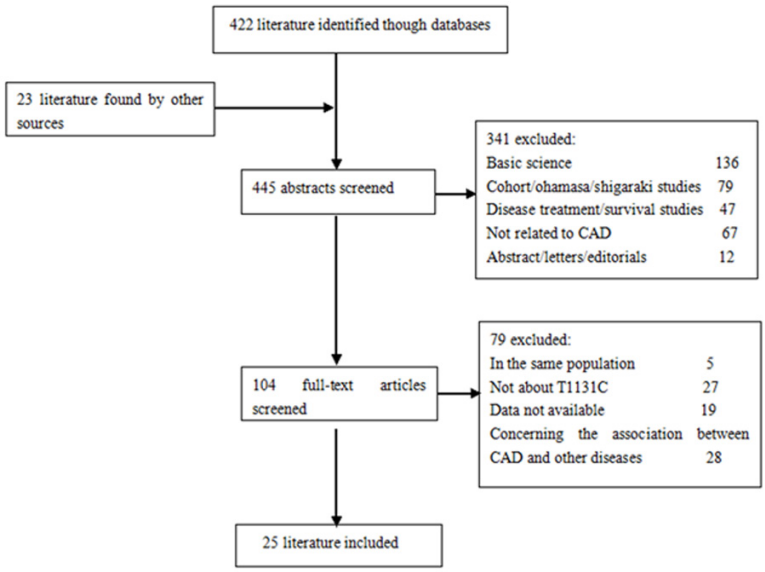

Figure 1. Flow diagram of included studies in the meta-analysis.

relation between *APOA5* T1131C polymorphism and risk of CAD has been extensively studied in recent years. Several studies have shown that *APOA5* T1131C polymorphism is involved in an elevated risk of CAD among different ethnic groups [20-23]. However, the specific relationship was not observed in any other studies [24-26]. Due to these divergent findings, we decided to further explore whether *APOA5* T1131C polymorphism was related to CAD risk.

Materials and methods

Search strategy

To identify all the studies concerning relation of *APOA5* T1131C polymorphism with CAD risk, we conducted computer searches on the databases of Medline, EMBASE, Elsevier and Springerlink with key words of "apolipoprotein A5" or "*APOA5*", "polymorphism" or "variant", "coronary artery disease" or "CAD". We also screened the reference lists of the selected publications to obtain other potential studies by hand search.

Selection criteria

All included studies in the meta-analysis should fulfill the following criteria: (1) case-control studies; (2) studies investigating the relationship of *APOA5* T1131C polymorphism with CAD susceptibility; (3) offering concrete genotype frequencies to efficiently calculate odds ratios (ORs) and 95% confidence intervals (95% CIs); (4) presenting clear sample sizes. The more comprehensive and larger one would be included if there were duplicated publications.

Data extraction

The following data was extracted individually by two researchers from the eligible studies: name of the first author, publication year, ethnicity, control source, genotyping method, and sample sizes of case and control groups, genotype frequencies and *P* value for Hardy-Weinberg equilibrium (HWE). Any discrepant opinions would be resolved by a third person to reach a consensus.

Statistical analysis

ORs and 95% CIs were used to assess whether the *APOA5* T1131C polymorphism was involved in the pathogenesis of CAD. The fixed-effect model or random-effect model was chosen to summarize pooled ORs according to the outcomes of heterogeneity among studies tested by a Chi-square-based Q-test. If $P>0.05$, we used the fixed-effect model; otherwise, we used the random-effect model. Pooled ORs were analyzed under the following genetic models: CC vs. TT, CC+TC vs. TT, CC vs. TT+TC, Allele C vs. Allele T and TC vs. TT. We checked the stability of the combined results with sensitivity analysis by omitting each single study one by one. Begg's funnel plot was used to evaluate publication bias and Egger's test was adopted to check funnel plot symmetry. The genotypes distribution in control group was checked by HWE with χ^2 test. Statistical analyses were conducted with STATA statistical software.

Results

Study characteristics

The process of study selection was presented in **Figure 1**. A total of 445 articles were screened by the search strategy, among which 136 studies were excluded for basic science,

Table 1. Characteristics of the investigated studies on the association between *APOA5* T1131C polymorphism and CAD risk

First author	Year	Country	Ethnicity	Genotyping method	Case	Control	HWE
Bi	2004	China	Asian	PCR-RFLP	312	317	0.20
Liu	2005	China	Asian	PCR-RFLP	483	502	0.86
Tang	2005	China	Asian	PCR	235	262	0.11
Hsu	2006	China	Asian	PCR-RFLP	211	317	0.01
Li	2007	China	Asian	PCR-RFLP	186	268	0.97
Yang	2007	China	Asian	PCR-RFLP	168	160	0.80
Yu	2007	China	Asian	PCR-RFLP-PAGE	140	156	0.28
Zhu	2007	China	Asian	PCR	119	210	0.01
Xu	2008	China	Asian	PCR-RFLP	195	181	0.46
Hubacek	2004	Czech	Caucasian	PCR-RFLP	435	2559	0.99
Szalai	2004	Hungary	Caucasian	PCR-RFLP	308	310	0.28
Yan	2005	China	Asian	PCR-RFLP	113	155	0.41
Martinelli	2007	Italy	Caucasian	PCR-RFLP	669	244	0.38
Jang	2009	Korea	Asian	SNP-IT	741	741	0.51
Ashkkumar	2009	India	Asian	NA	416	416	0.63
Prochaska	2010	Brazil	Caucasian	PCR-RFLP	180	170	0.86
Park	2010	Korea	Asian	SNP-IT	807	1123	0.44
Liu	2004	China	Asian	PCR-RFLP	268	340	0.90
Zhou	2013	China	Asian	PCR	290	331	0.04
Chen	2011	China	Asian	PCR-RFLP	249	176	0.23
Cheng	2007	China	Asian	PCR-RFLP	112	113	0.62
Yuan	2011	China	Asian	PCR-RFLP	344	408	0.44
Qiu	2007	China	Asian	PCR-RFLP	260	316	0.36
Zhang	2007	China	Asian	PCR-RFLP	141	129	0.35
Zhao	2008	China	Asian	PCR	155	145	0.05

PCR: polymerase chain reaction; PCR-RELP: PCR-restriction fragment length polymorphism; PCR-RFLP-PAGE: PCR-restriction fragment length polymorphism polyacrylamide gel electrophoresis; HWE: Hardy-Weinberg equilibrium.

79 for cohort/ohamasa/shigaraki, 47 for disease treatment/survival, 67 for not concerning CAD and 12 for abstract/letters/editorials. Finally 104 studies were screened in full-texts, in which 5 were excluded for searching the same population, 27 for not concerning T1131C, 19 for improper data, 28 for association between CAD and other diseases. Finally, 25 eligible studies with 7,537 cases and 10,049 controls were included in the meta-analysis [21, 23, 25-45]. As shown in **Table 1**, 21 were conducted in Asians, and 4 in Caucasians. Moreover, the source of control in 18 studies was population-based (PB), and 7 were hospital-based (HB).

Meta-analysis

Table 2 showed the relationship between *APOA5* T1131C polymorphism and CAD risk. In general, *APOA5* T1131C polymorphism was associated with increased risk of CAD (CC vs. TT: OR=1.47, 95% CI=1.22-1.78; CC+TC vs. TT: OR=1.13, 95% CI=1.07-1.20; CC vs. TT+TC: OR=1.37, 95% CI=1.13-1.66; allele C vs. allele T: OR=1.17, 95% CI=1.09-1.25; TC vs. TT: OR=1.12, 95% CI=1.06-1.20). In the subgroup analysis by ethnicity, similar overall pattern was observed among Asian populations (CC vs. TT: OR=1.40, 95% CI=1.17-1.68; CC+TC vs. TT: OR=1.13, 95% CI=1.06-1.20; CC vs. TT+TC: OR=1.30, 95% CI=1.08-1.56; allele C vs. allele T: OR=1.15, 95% CI=1.08-1.24; TC vs. TT: OR=1.13, 95% CI=1.06-1.21), whereas the association was found in Caucasians only under the following genetic models: CC vs. TT (OR=2.53, 95% CI=1.29-4.93), CC vs. TT+TC (OR=2.48, 95% CI=1.22-5.05) and allele C vs. allele T (OR=1.32, 95% CI=1.07-1.64) (**Figure 2**). In addition, in the subgroup analysis by source of control, increased risk of CAD was found to be related to all genotypes and alleles of T1131C in PB genetic group (CC vs. TT: OR=1.54, 95% CI=1.29-1.84; CC+TC vs. TT: OR=1.15, 95% CI=1.08-1.23; CC vs. TT+TC: OR=1.45, 95% CI=1.19-1.76; allele C vs. allele T: OR=1.19, 95% CI=1.12-1.25; TC vs. TT: OR=1.14, 95% CI=1.06-1.22), while the relationship of CAD risk with T1131C polymorphism was not discovered in HB genetic group (**Figure 3**).

Heterogeneity test

For *APOA5* T1131C polymorphism and its association with CAD risk, significant heterogeneity was observed under CC vs. TT, CC vs. TT+TC and allele C vs. allele T genetic models (P<0.05).

Table 2. Risk of CAD was associated with *APOA5* T1131C polymorphism

		CC vs. TT		CC+TC vs. TT		CC vs. TT+TC		Allele C vs. Allele T		TC vs. TT	
		OR (95% CI)	P_h	OR (95% CI)	P_h	OR (95% CI)	P_h	OR (95% CI)	P_h	OR (95% CI)	P_h
Ethnicity	Asian	1.40 (1.17, 1.68)	0.001	1.13 (1.06, 1.20)	0.750	1.30 (1.08, 1.56)	0.000	1.15 (1.08, 1.24)	0.009	1.13 (1.06, 1.21)	0.902
	Caucasian	2.53 (1.29, 4.93)	0.272	1.19 (0.99, 1.44)	0.200	2.48 (1.22, 5.05)	0.243	1.32 (1.07, 1.64)	0.236	1.07 (0.87, 1.31)	0.052
Control source	Population-based	1.54 (1.29, 1.84)	0.066	1.15 (1.08, 1.23)	0.878	1.45 (1.19, 1.76)	0.008	1.19 (1.12, 1.25)	0.506	1.14 (1.06, 1.22)	0.611
	Hospital-based	1.33 (0.82, 2.14)	0.000	1.08 (0.97, 1.20)	0.186	1.22 (0.78, 1.92)	0.000	1.13 (0.93, 1.37)	0.000	1.09 (0.96, 1.23)	0.521
Total		1.47 (1.22, 1.78)	0.000	1.13 (1.07, 1.20)	0.677	1.37 (1.13, 1.66)	0.000	1.17 (1.09, 1.25)	0.007	1.12 (1.06, 1.20)	0.679

P_h: *P*-value of heterogeneity test.

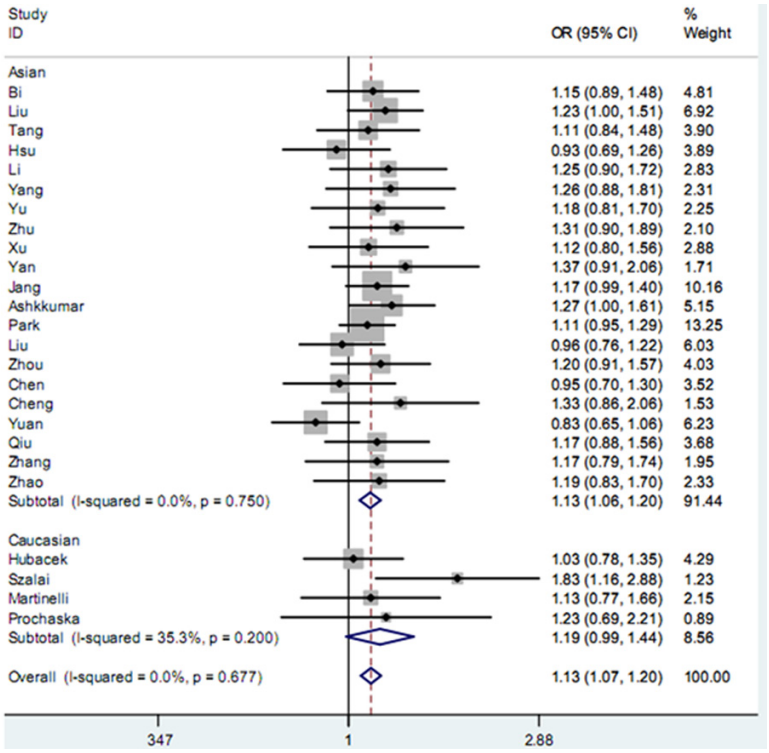

Figure 2. Forest plot of CAD risk is correlated with the *APOA5* T1131C polymorphism under CC+TC vs. TT genetic model by ethnicity. The squares and horizontal lines correspond to OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI.

Therefore, the random-effects model was used. Meanwhile, no significant heterogeneity was found in the genetic models of CC+TC vs. TT and TC vs. TT, so we used the fixed-effects model.

Sensitivity analysis

To check the stability of the combined results, sensitivity analysis was conducted. After deleting each study included in our meta-analysis once at a time, the overall result was not substantially changed, indicating that our results were stable and reliable.

Publication bias

The shapes of funnel plots under different genetic models indicated no obvious asymmetry (**Figure 4**). Statistical evidence was not found for bias with Egger's test (P=0.27). Therefore, there was no publication bias in the meta-analysis.

Discussion

To explore the association between *APOA5* T1131C polymorphism and risk of CAD, the meta-analysis was conducted based on published studies. The results implied that *APOA5* T1131C polymorphism was in relation with increasing risk of CAD.

As a well-known risk factor for cardiovascular disease, TG level is greatly affected by genetic factors. Apolipoprotein gene cluster *APOA1/APOC3/APOA4/APOA5*, located on chromosome 11q23, may play important roles in regulating the level of TG [10]. *APOA5*, expressed extensively in liver, has been identified to be a primary regulator for TG [46]. Recently, several investigations provided evidences that the *APOA5* gene may work as an activator of intravascular triglycerides hydrolysis process via lipoprotein lipase [47, 48].

So far, a total of 16 single nucleotide polymorphisms (SNPs) in the *APOA5* gene have been detected. Among these SNPs, T1131C, located in the proximal promoter of *APOA5* gene, has been reported to be associated with increased TG levels in various ethnicities, such as Africans, Caucasians, and Spaniards [11, 17, 22]. Additionally, T1131C polymorphism is regarded to be tightly related to CAD morbidity [23]. The studies conducted in Chinese population have observed a significant association between T1131C polymorphism and CAD risk [21, 27]. However, such association remains unclear in European population [49, 50]. The studies also provided evidence that carriers with T1131C polymorphism shows elevated TG levels and are more likely to suffer from CAD [28, 51]. Whereas Martinelli *et al*. found that variants of *APOA5* T1131C polymorphism predicting TG levels independently were not in relation with CAD risk [26]. These inconsistent observations for the association may be largely due to different ethnic backgrounds, limited samples, or

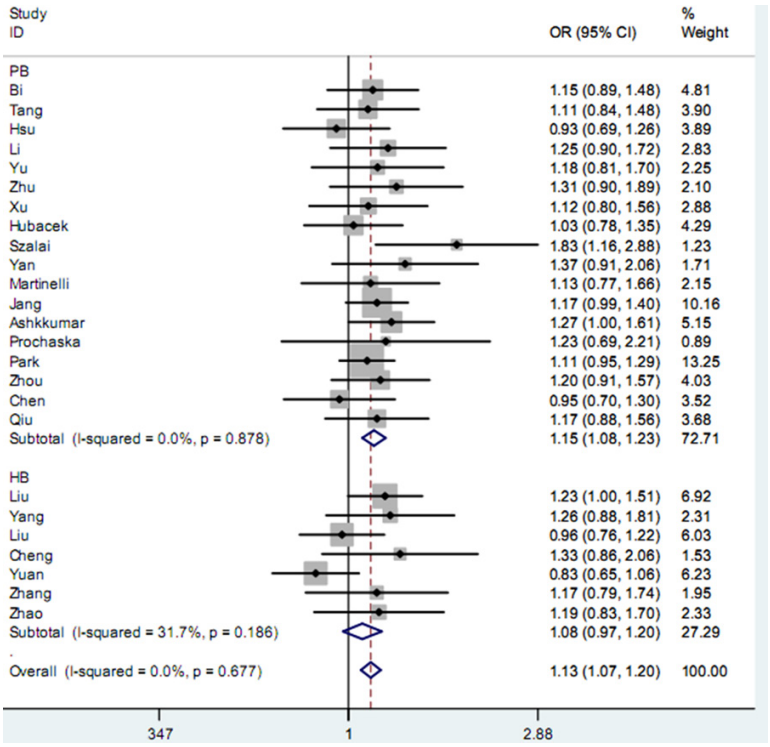

Figure 3. Forest plot of CAD risk is correlated with the *APOA5* T1131C polymorphism under CC+TC vs. TT genetic model by control source. The squares and horizontal lines correspond to OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI.

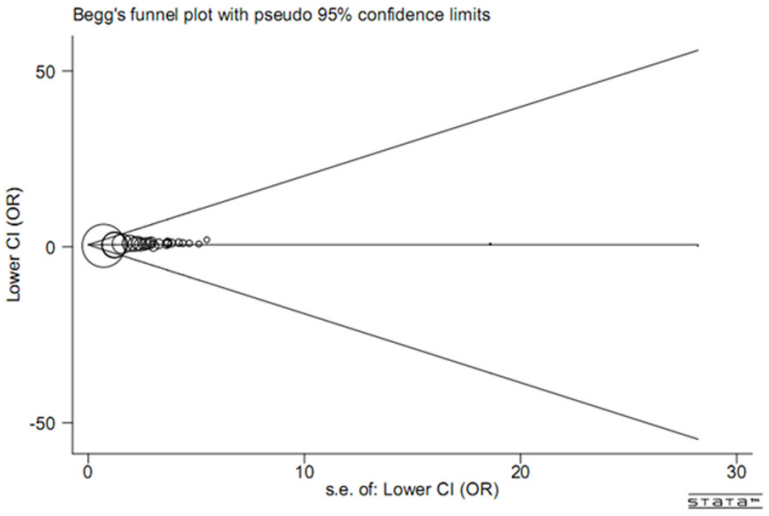

Figure 4. Begg's funnel plot of publication bias test. Each point represents an individual study for the association. Log (OR) means natural logarithm of OR. Horizontal line, the effect size.

absence of consideration of gene-environment and gene-gene interactions. Our present meta-analysis further explored the association and found *APOA5* T1131C polymorphism was in relation to increased CAD risk. Large sample sizes with 7,537 cases and 10,049 controls in both Asians and Caucasians made the results robust to a great extent.

Some limitations need to be discussed for the present meta-analysis. A limitation is that only one SNP loci of *APOA5* gene was studied, other potentially related genetic and environmental factors were not considered, which may introduce bias into the study. Another limitation is that the research covered relatively small number studies conducted in Caucasians compared Asians, which may decrease the statistical power of the analysis in this group.

In conclusion, we found that *APOA5* T1131C polymorphism was significantly associated with increased risk of CAD. More improved investigations with larger sample size are required to further explain this issue.

Disclosure of conflict of interest

None.

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