



***APOA5* -1131T>C and *APOC3* -455T>C polymorphisms are associated with an increased risk of coronary heart disease**

Y. Sun, R.B. Zhou and D.M. Chen

Department of Emergency, The Military General Hospital of Beijing PLA, Beijing, China

Corresponding author: D.M. Chen
E-mail: chendongmei0109@126.com

Genet. Mol. Res. 14 (4): 18218-18228 (2015)
Received August 25, 2015
Accepted October 31, 2015
Published December 23, 2015
DOI <http://dx.doi.org/10.4238/2015.December.23.9>

ABSTRACT. The aim of this study was to investigate correlations between apolipoprotein A-V (*APOA5*) -1131T>C and apolipoprotein C-III (*APOC3*) -455T>C polymorphisms and coronary heart disease (CHD). PubMed, Ovid, Cochrane Library, Embase, China National Knowledge Infrastructure, and Wanfang databases were searched using combinations of keywords relating to these polymorphisms and CHD. Studies retrieved from database searches were screened using our stringent inclusion and exclusion criteria, and Comprehensive Meta-Analysis Version 2.0 software was used for statistical analyses. In total, 115 studies were initially retrieved and after further selection, 11 were included in the meta-analysis. These 11 articles comprised 4840 patients with CHD in the case group and 4913 healthy participants in the control group. Meta-analysis revealed that *APOA5* -1131T>C and *APOC3* -455T>C polymorphisms increased CHD risk. In addition, subgroup analysis by ethnicity showed that while the -1131T>C polymorphism elevated the risk of CHD in the Caucasian population under both allelic and dominant models, this increased risk was observed only under a dominant model in the Asian

population. The results of our meta-analysis point to a strong link between both *APOA5* -1131T>C and *APOC3* -455T>C polymorphisms and an increased risk of CHD. Thus, these polymorphisms constitute important predictive indicators of CHD susceptibility.

Key words: Coronary heart disease; Apolipoprotein A-V; Apolipoprotein C-III; Polymorphism; Single nucleotide polymorphisms; Triglycerides

INTRODUCTION

Coronary heart disease (CHD) resulting from atherosclerosis, also known as coronary artery disease, is a serious condition in which plaque builds up inside the coronary arteries. Plaques harden and, over time, narrow the coronary arteries that supply blood and oxygen to the heart, ultimately resulting in myocardial infarction and potentially death. CHD is the leading cause of mortality worldwide, accounting for nearly 7 million deaths annually (Chen et al., 2014). For individuals older than 18 years, the prevalence of CHD ranges from 2.9 to 6.6%; the prevalence varies by race and ethnicity, with American Indians and natives of Alaska having the highest prevalence and Asians having the lowest prevalence (Imes et al., 2013). Etiologically, both environmental and genetic factors contribute to the occurrence and development of CHD (Yu et al., 2011). The major risk factors are male gender, advancing age, elevated levels of plasma low-density lipoprotein cholesterol (LDL-C), low levels of high-density lipoprotein cholesterol (HDL-C), elevated blood pressure, obesity, and lifestyle factors such as smoking, a high-fat diet, and lack of exercise (Lettre et al., 2011). Elevated triglyceride (TG) and low HDL-C levels, irrespective of LDL-C levels, are typical of dyslipidemia, which puts individuals at high risk of CHD (Brautbar et al., 2011).

TGs are major components of plaque, and heightened TG levels correlate with an increased risk of CHD (Carey et al., 2010). Apolipoprotein A-V (*APOA5*) is a major determinant of plasma TG levels and is located next to sequences encoding apolipoproteins A-IV, C-III (*APOC3*), and A-I in a gene cluster on chromosome 11q23 (Soufi et al., 2012). *APOA5* encodes a protein of 366 amino acids, which is secreted into plasma to control plasma TG metabolism, and whose expression is restricted to human liver tissue (Ouatou et al., 2014). Variants of *APOA5* include -1131T>C and S19W (Yu et al., 2007). *APOC3*, another key regulator of plasma TG levels, is a glycoprotein consisting of 79 amino acids synthesized principally in the liver and, to a lesser extent, the intestine. This protein is an inhibitor of lipoprotein lipase (LPL) and a component of very low-density lipoprotein (VLDL). An excess of *APOC3* in plasma can result in elevated LDL levels and is positively associated with the progression of atherosclerosis and risk of CHD. Several polymorphisms have been found in the *APOC3* gene, including C-482T, T-455C, Sst I, and C1100T. Moreover, accumulating evidence suggests that *APOA5* -1131T>C and *APOC3* -455T>C polymorphisms play a major role in the development of CHD because of their association with increased plasma TGs (Zhang et al., 2011; Zhou et al., 2013; Cui et al., 2014). On the other hand, many studies have reached contradictory conclusions regarding the role of *APOC3* and *APOA5* variants in CHD (Martinelli et al., 2007; Maasz et al., 2008; Prochaska et al., 2010; Yu et al., 2011). We therefore employed a meta-analysis approach to investigate the relationship between these two important polymorphisms and CHD risk.

MATERIAL AND METHODS

Search strategy

PubMed, Ovid, Cochrane Library, Embase, China National Knowledge Infrastructure, and Wanfang databases were searched for relevant studies published up to October 2014. Additionally, potentially useful studies were obtained by manual searches. The following subject terms and key words were used to maximize search specificity and sensitivity: coronary heart disease, apolipoproteinA5, apolipoproteinC3, and genetic polymorphisms.

Study selection

The following inclusion criteria were applied to screen published articles for the present analysis: (a) use of a case-control study design; (b) a research focus consisting of an assessment of correlations between CHD susceptibility and single nucleotide polymorphisms (SNPs) of *APOA5* or *APOC3*; (c) subjects comprising patients with CHD in the case group and healthy individuals in the control group; (d) complete data relating to the first author, country, publication year, number, ethnicity, and sex of cases, genotyping method, and genotype distributions of -1131T>C and -455T>C; and (e) only the most recent studies or those with the largest sample sizes were considered when the extracted articles were published by the same authors, using the same case materials. The exclusion criteria were: (a) unclear diagnostic criteria regarding the included subjects; (b) only the latest complete study was considered when the extracted studies were published by the same authors; and (c) lack of data integrity.

Data extraction and methodological quality evaluation

Two investigators collected data independently using a standardized data extraction form. We retrieved information related to the first author, publication year, country, language, disease, number, age, and ethnicity of cases, genotyping method, and genotype distributions of -1131T>C and -455T>C polymorphisms. Any difference of opinion during data extraction was resolved through discussion among multiple researchers.

Statistical methods

All statistical analyses were conducted using Comprehensive Meta-Analysis Version 2.0 software (Biostat Inc., Englewood, NJ, USA). Correlations between *APOA5* and *APOC3* SNPs and risk of CHD were estimated by the calculation of odds ratios (ORs) and 95% confidence intervals (95% CIs). A Z-test was employed to detect the significance of overall effect size (Chen et al., 2012), and forest plots were generated to display OR values and 95% CIs between case and control groups. Heterogeneity among studies was evaluated using Cochran's Q-statistic ($P < 0.05$ was considered to signify evident heterogeneity) and the I^2 test, which measures the percentage of total variation across studies, ranging from 0 to 100% (Peters et al., 2006; Jackson et al., 2012). A fixed-effects model was employed unless significant heterogeneity was detected ($P < 0.05$ or $I^2 > 50\%$), in which case a random-effects model was applied (Zintzaras et al., 2005). Univariate and multivariate meta-regression analyses were used to estimate sources of heterogeneity, and Monte

Carlo simulation was performed to correct and verify results (Ferrenberg et al., 1988; Huizenga et al., 2011, Jackson et al., 2012). One-way sensitivity analysis was carried out to evaluate whether the removal of a single study would influence the overall outcome. Publication bias, an assessment of the reliability of the results, was evaluated by funnel plot, Egger test (Egger et al., 1997; Sterne et al., 2001), and classic fail-safe N (Wikstrom et al., 2009). All tests were two-sided, with $P < 0.05$ indicating a significant difference.

RESULTS

Study selection and baseline characteristics

Our search strategy retrieved 115 citations. In total, 64 studies remained after initially excluding 5 duplicates, 14 animal studies, 26 studies unrelated to the research topic, and 6 letters, reviews, or meta-analyses. Next, we excluded 14 cohort studies, 22 studies not relevant to *APOA5* and *APOC3*, 12 studies unrelated to CHD, and 5 studies containing insufficient information. Finally, 11 case-control studies (Bassi et al., 2003; Bi et al., 2004; Olivieri et al., 2005; Hsu et al., 2006; Zhu et al., 2007; Yu et al., 2007; Martinelli et al., 2007; Li et al., 2007; Jang et al., 2009; De Caterina et al., 2011; Bhaskar et al., 2011) published between 2003 and 2011 (containing in total 4840 CHD patients in the case group and 4913 healthy controls in the control group) were eventually selected for this meta-analysis. Of these, 7 studies involved Asian populations, with 5 conducted in China, 1 in Korea, and 1 in India. The other 4 studies comprised Caucasian populations in Italy. Sample sizes of included studies varied between 138 and 1864. The baseline characteristics of all included case-control studies are shown in Table 1.

Table 1. Baseline characteristics of studies included in this meta-analysis.

First author	Country	Ethnicity	Genotyping method	Age (years)		Gene	SNP	Case group	Control group
				Cases	Controls				
De Caterina (2011)	Italy	Caucasian	TaqMan array	-	-	<i>APOA5</i>	-1131T>C	1864	1864
Bhaskar (2011)	India	Asian	PCR-RFLP	-	-	<i>APOA5</i>	-1131T>C	250	120
Jang (2009)	Korea	Caucasian	PCR-RFLP	55.2 ± 0.32	55.2 ± 0.32	<i>APOA5</i>	-1131T>C	741	741
Zhu (2007)	China	Asian	PCR-RFLP	57.2 ± 12.1	58.3 ± 11.2	<i>APOA5</i>	-1131T>C	119	210
Yu (2007)	China	Asian	PCR-RFLP	52.1 ± 7.2	51.5 ± 8.7	<i>APOA5</i>	-1131T>C	140	156
Li (2007)	China	Asian	PCR-RFLP	62.80 ± 9.51	61.32 ± 9.43	<i>APOA5</i>	-1131T>C	186	268
Martinelli (2007)	Italy	Caucasian	PCR-RFLP	60.7 ± 9.3	58.7 ± 12.7	<i>APOA5</i>	-1131T>C/-455T>C	669	224
Hsu (2006)	China	Asian	PCR-RFLP	61.6 ± 8.9	55.1 ± 9.8	<i>APOA5</i>	-1131T>C	211	677
Olivieri (2005)	Italy	Caucasian	PCR-RFLP	60.5 ± 9.7	58.3 ± 12.8	<i>APOC3</i>	--455T > C	210	206
Bi (2004)	China	Asian	PCR-RFLP	60.22 ± 13.30	58.87 ± 14.27	<i>APOA5</i>	-1131T>C	312	317
Bassi (2003)	Italy	Caucasian	PCR-RFLP	30.3 ± 9.4	57.9 ± 12.4	<i>APOC3</i>	--455T > C	138	130

PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism; *APOA5* = apolipoprotein A-V; *APOC3* = apolipoprotein C-III; SNP = single nucleotide polymorphism.

Association between *APOA5* -1131T>C and CHD risk

Nine of the included studies investigated the correlation between the *APOA5* -1131T>C SNP and risk of CHD. As heterogeneity was detected across allelic and dominant models ($P < 0.05$), a random-effects model was employed. As presented in Figure 1 and Table 2, the results of our meta-analysis revealed that the -1131T>C polymorphism was associated with an increased risk of CHD (allelic model: OR = 0.64, 95%CI = 0.44-0.94, $P = 0.02$; dominant model: OR =

1.55, 95%CI = 1.17-2.06, P = 0.003). Subgroup analysis by ethnicity suggested that in Asian populations, this SNP might increase the risk of CHD under the dominant model (OR = 1.23, 95%CI = 1.10-1.36, P < 0.001), while no significant association was observed under the allelic model (OR = 0.58, 95%CI = 0.32-1.06, P = 0.077). On the other hand, in Caucasian populations, -1131T>C was associated with an increased risk of CHD using both models (allelic model: OR = 0.76, 95%CI = 0.68-0.84, P < 0.001; dominant model: OR = 1.39, 95%CI = 1.22-1.57, P < 0.001; Figure 2). In addition, we discovered a possible association between the -1131T>C allele and elevated plasma TG levels, while no significant relationship was observed between the *APOA5* polymorphism and plasma levels of LDL-C and HDL-C. Univariate and meta-regression analysis revealed that publication year, country, ethnicity, and detection methods were not the main sources of heterogeneity or the key factors influencing overall effect size (P > 0.05). Moreover, multivariate meta-regression analysis suggested that these factors were not sources of heterogeneity. Results of meta-regression analyses are displayed in Figure 3 and Table 3.

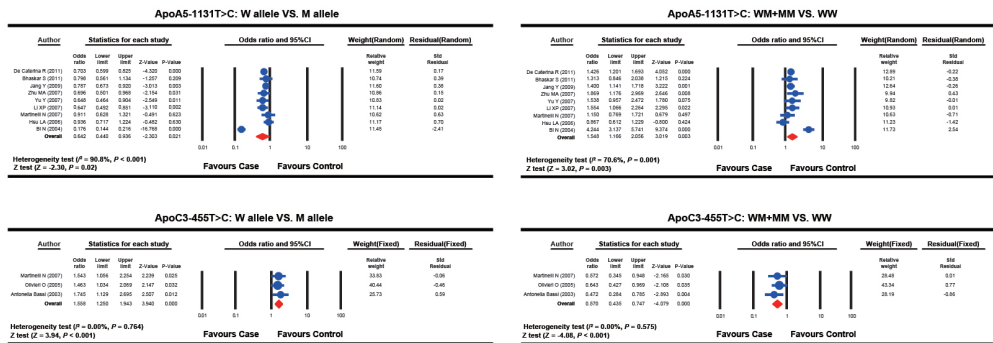


Figure 1. Forest plots of the relationship between apolipoprotein C-III-455T>C and apolipoprotein A-V-1131T>C polymorphisms and coronary heart disease. CI = confidence interval; Std = standard deviation.

Table 2. Meta-analysis results comparing genotype and allele frequencies between the case and control groups.

SNP	-1131T>C			-455T>C		
	OR	95%CI	P	OR	95%CI	P
Allelic model	0.64	0.44-0.94	0.02	1.56	1.25-1.94	<0.001
Dominant model	1.55	1.17-2.06	0.003	0.57	0.44-0.75	<0.001
Homozygous model	1.82	1.26-2.62	0.001	0.61	0.39-0.97	0.037
Heterozygous model	0.84	0.69-1.02	0.078	1.00	0.91-1.09	0.913
Recessive model	1.80	1.08-3.00	0.025	0.71	0.44-1.14	0.157

SNP = single nucleotide polymorphism; OR = odds ratio; CI = confidence interval.

Association between *APOC3* -455T>C and CHD risk

Three of the included studies investigated the correlation between the *APOC3* -455T>C SNP and risk of CHD. No heterogeneity was detected across allelic and dominant models, and thus a fixed-effects model was employed (P > 0.05). As presented in Figure 1, our meta-analysis showed that the -455T>C polymorphism increased the risk of CHD (allelic model: OR = 1.56, 95%CI = 1.25-1.94, P < 0.001; dominant model: OR = 0.57, 95%CI = 0.44-0.75, P < 0.001). In addition, we observed no significant correlation between *APOC3* -455T>C and plasma TG, LDL-C, or HDL-C levels.

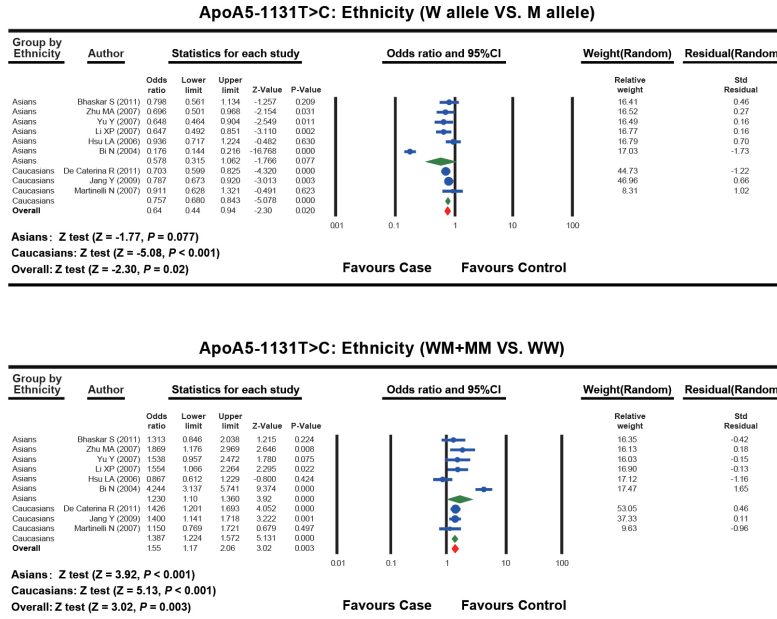


Figure 2. Subgroup analysis forest plots of the relationship between the apolipoprotein A-V-1131T>C polymorphism and coronary heart disease.

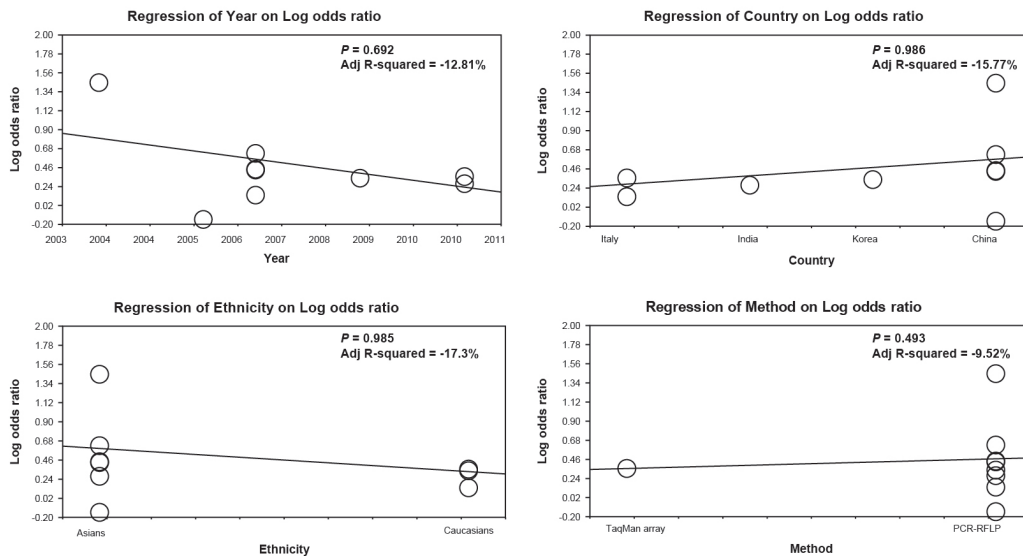


Figure 3. Meta-regression analyses assessing possible sources of heterogeneity and the impact of various factors on the observed relationship between the apolipoprotein A-V-1131T>C polymorphism and coronary heart disease. Adj = adjusted; PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism. A. Regression of year on log odds ratio. B. Regression of country on log odds ratio. C. Regression of ethnicity on log odds ratio. D. Regression of method on log odds ratio.

Table 3. Meta-regression analysis of potential sources of heterogeneity.

Heterogeneity factors	Coefficient	SEM	t	P (adjusted)	95%CI	
					LL	UL
Year	-0.03	0.045	-0.67	0.842	-0.156	0.095
Country	-0.002	0.108	-0.02	1.00	-0.303	0.298
Ethnicity	-0.031	0.219	-0.14	0.999	-0.639	0.577
Method	-0.267	0.279	-0.95	0.743	-1.042	0.509

SEM = standard error of mean; CI = confidence interval; LL = lower limit; UL = upper limit.

Sensitivity analysis and publication bias

Sensitivity analysis suggested that no single study affected the overall OR values of correlations between *APOA5* -1131T>C and *APOC3* -455T>C SNPs and the risk of CHD (Figure 4). Funnel plots for the -1131T>C polymorphism under allelic and dominant models and the -455T>C SNP under a dominant model were symmetrical, indicating no significant publication bias ($P > 0.05$; Figure 5). Classic fail-safe N and Egger tests further verified an absence of such bias ($P > 0.05$). However, asymmetrical funnel plots were observed regarding the -455T>C polymorphism under an allelic model, suggesting significant publication bias. Classic fail-safe N and Egger tests confirmed this.

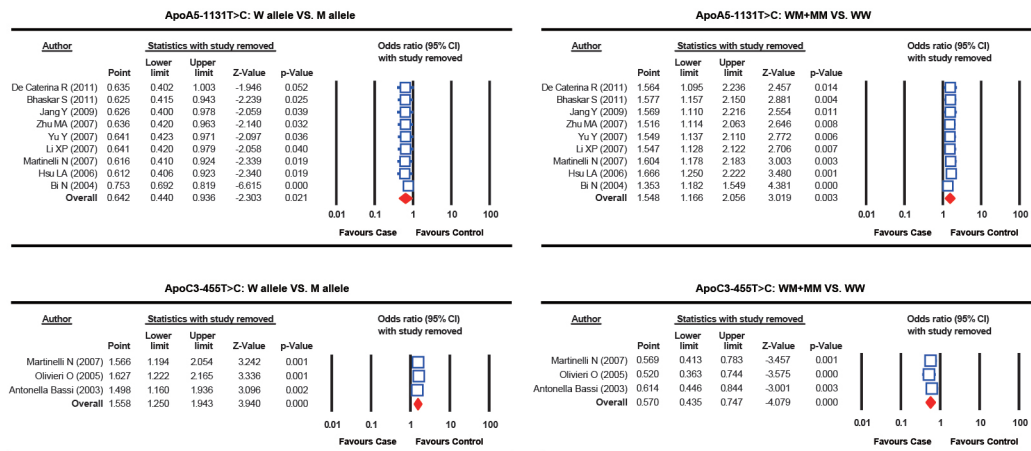


Figure 4. Sensitivity analysis testing the observed relationship between apolipoprotein C-III-455T>C and apolipoprotein A-V-1131T>C polymorphisms and coronary heart disease. CI = confidence interval.

DISCUSSION

HD, resulting from atherosclerosis, is a severe condition involving the build-up of plaque inside coronary arteries (Imes et al., 2013). Elevated TGs and low levels of HDL-C, irrespective of LDL-C levels, result in high CHD risk (Brautbar et al., 2011). *APOC3* and *APOA5* regulate TG levels and are associated with lipid metabolism, insulin resistance, and acute coronary syndrome (Ding et al., 2012; Garelnabi et al., 2013). To investigate the correlation between *APOA5* -1131T>C

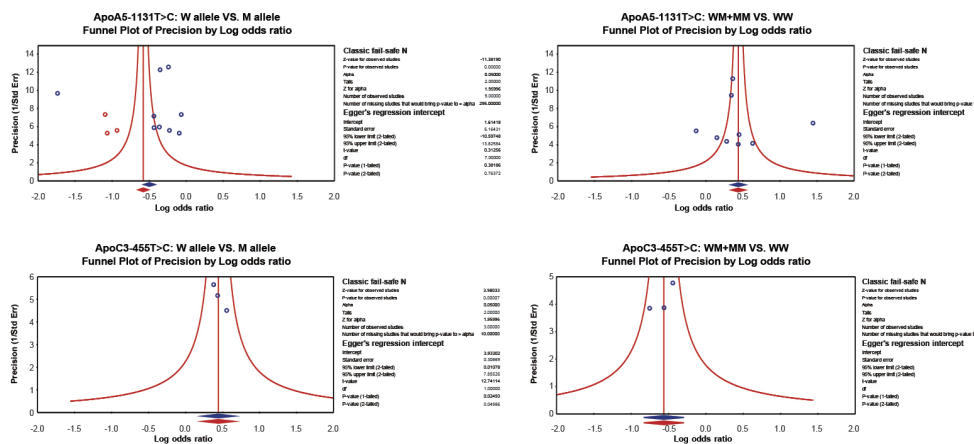


Figure 5. Assessments of publication bias relating to the observed relationship between apolipoprotein C-III-455T>C and apolipoprotein A-V-1131T>C polymorphisms and coronary heart disease. d.f. = degrees of freedom; SEM = standard error of the mean. (Red and blue represent the two-tailed test of our study; Circles stand for the number of enrolled study; Rhombuses represent effect value).

and APOC3 -455T>C SNPs and CHD, we conducted the present meta-analysis and found that both polymorphisms, under both allelic and dominant models, were positively associated with an increased risk of CHD. APOA5 encodes APOA5, a protein consisting of 366 amino acids that is exclusively expressed in human liver tissue and enhances LPL activity (Zhou et al., 2013). The loss of LPL activity interferes with the ability of APOA5 to interact with lipids and lipoproteins, including TGs, VLDLs, and HDLs (Dorfmeister et al., 2008; Johansen et al., 2011). Furthermore, the elevation of plasma TGs is a known CHD risk factor, and APOA5 status constitutes a major risk factor owing to its activation of TG hydrolysis in the blood (Carey et al., 2010). Genetic variations in the APOA5 gene have been shown to be associated with CHD. A correlation between the APOA5 gene region and CHD was established in a large meta-analysis in which the -1131T>C APOA5 promoter SNP was associated with both elevated TG levels and increased CHD events (Triglyceride Coronary Disease Genetics et al., 2010). However, it is unclear whether there is a causal relationship between this polymorphism and CHD. One potential mechanism involves a reduction in APOA5 expression caused by variation in the APOA5 promoter, leading to decreased TG hydrolysis in the blood, and thus elevated TG levels, which correlate with CHD susceptibility.

APOC3, a 79-amino acid glycoprotein synthesized mainly in the liver, and to a lesser extent in the intestine, functions as a key regulator of serum TG levels. Further, it acts as a constituent of triglyceride-rich lipoprotein particles, inhibiting their LPL-induced hydrolysis, and interferes with receptor-mediated lipoprotein uptake in liver (Yu et al., 2011). However, the -455T>C variant reduces the binding of transcription factors to its promoter elements, resulting in the dyslipidemia and abnormal glucose homeostasis associated with CHD risk (Miller et al., 2007). Interestingly, Yu et al. (2011) failed to find an association between the APOC3 -455T>C SNP and increased CHD risk in a Han Chinese population, although promoter variants did have a significant impact on plasma TG and APOC3 levels. Therefore, the results of epidemiological studies need to be supported by extensive experimental evidence, in order to thoroughly understand the underlying aberrations caused by polymorphisms and the mechanisms by which they lead to CHD.

Subgroup analysis based on ethnicity suggested that in Asian populations, *APOA5* -1131T>C might increase the risk of CHD under the dominant model. In Caucasian populations however, this SNP was associated with an increased risk of CHD under both allelic and dominant models. This difference may be attributed to different regional influences, ethnicities, and lifestyles.

Some limitations of this study should be noted. First, the number of CHD patients and healthy controls was relatively small in some of the included trials, which may reduce confidence in findings of the present meta-analysis. Second, this meta-analysis included data from Asian and Caucasian populations; however, no studies involving other ethnicities and mixed-race groups were included. Thus, our study may not be representative of all ethnicities. In addition, the present work was restricted to studies published in English or Chinese only, excluding investigations published in other languages, which may have led to selection bias.

In summary, our study revealed that *APOA5*-1131T>C and *APOC3*-455T>C polymorphisms, under both allelic and dominant models, were strongly associated with an increased risk of CHD, suggesting that they could be important indicators in predicting susceptibility to this disease.

Conflicts of interest

The authors declare no conflict of interest.

ACKNOWLEDGMENTS

We would like to thank our instructors for their valuable advice, for which we are grateful. We also appreciate the efforts of the reviewers of this paper for their valued comments.

REFERENCES

- Bhaskar S, Ganesan M, Chandak GR, Mani R, et al. (2011). Association of PON1 and APOA5 gene polymorphisms in a cohort of Indian patients having coronary artery disease with and without type 2 diabetes. *Genet. Test. Mol. Biomarkers* 15: 507-512.
- Bi N, Yan SK, Li GP, Yin ZN, et al. (2004). A single nucleotide polymorphism -1131T>C in the apolipoprotein A5 gene is associated with an increased risk of coronary artery disease and alters triglyceride metabolism in Chinese. *Mol. Genet. Metab.* 83: 280-286.
- Brautbar A, Covarrubias D, Belmont J, Lara-Garduno F, et al. (2011). Variants in the APOA5 gene region and the response to combination therapy with statins and fenofibric acid in a randomized clinical trial of individuals with mixed dyslipidemia. *Atherosclerosis* 219: 737-742.
- Carey VJ, Bishop L, Laranjo N, Harshfield BJ, et al. (2010). Contribution of high plasma triglycerides and low high-density lipoprotein cholesterol to residual risk of coronary heart disease after establishment of low-density lipoprotein cholesterol control. *Am. J. Cardiol.* 106: 757-763.
- Chen H, Manning AK and Dupuis J (2012). A method of moments estimator for random effect multivariate meta-analysis. *Biometrics* 68: 1278-1284.
- Chen S, Xie X, Wang Y, Gao Y, et al. (2014). Association between leukocyte mitochondrial DNA content and risk of coronary heart disease: a case-control study. *Atherosclerosis* 237: 220-226.
- Cui F, Li K, Li Y, Zhang X, et al. (2014). Apolipoprotein C3 genetic polymorphisms are associated with lipids and coronary artery disease in a Chinese population. *Lipids Health Dis.* 13: 170.
- De Caterina R, Talmud PJ, Merlini PA, Foco L, et al. (2011). Strong association of the APOA5-1131T>C gene variant and early-onset acute myocardial infarction. *Atherosclerosis* 214: 397-403.
- Ding Y, Zhu MA, Wang ZX, Zhu J, et al. (2012). Associations of polymorphisms in the apolipoprotein APOA1-C3-A5 gene cluster with acute coronary syndrome. *J. Biomed. Biotechnol.* 2012: 509420.
- Dorfmeister B, Zeng WW, Dichlberger A, Nilsson SK, et al. (2008). Effects of six APOA5 variants, identified in patients with severe hypertriglyceridemia, on *in vitro* lipoprotein lipase activity and receptor binding. *Arterioscler. Thromb. Vasc. Biol.* 28: 1866-1871.

- Egger M, Davey Smith G, Schneider M and Minder C (1997). Bias in meta-analysis detected by a simple, graphical test. *BMJ* 315: 629-634.
- Ferrenberg AM and Swendsen RH (1988). New Monte Carlo technique for studying phase transitions. *Phys. Rev. Lett.* 61: 2635-2638.
- Garelnabi M, Lor K, Jin J, Chai F, et al. (2013). The paradox of ApoA5 modulation of triglycerides: evidence from clinical and basic research. *Clin. Biochem.* 46: 12-19.
- Hsu LA, Ko YL, Chang CJ, Hu CF, et al. (2006). Genetic variations of apolipoprotein A5 gene is associated with the risk of coronary artery disease among Chinese in Taiwan. *Atherosclerosis* 185: 143-149.
- Huizenga HM, Visser I and Dolan CV (2011). Testing overall and moderator effects in random effects meta-regression. *Br. J. Math. Stat. Psychol.* 64: 1-19.
- Imes CC and Austin MA (2013). Low-density lipoprotein cholesterol, apolipoprotein B, and risk of coronary heart disease: from familial hyperlipidemia to genomics. *Biol. Res. Nurs.* 15: 292-308.
- Jackson D, White IR and Riley RD (2012). Quantifying the impact of between-study heterogeneity in multivariate meta-analyses. *Stat. Med.* 31: 3805-3820.
- Jang Y, Paik JK, Hyun YJ, Chae JS, et al. (2009). The apolipoprotein A5 -1131T>C promoter polymorphism in Koreans: association with plasma APOA5 and serum triglyceride concentrations, LDL particle size and coronary artery disease. *Clin. Chim. Acta* 402: 83-87.
- Johansen CT, Kathiresan S and Hegele RA (2011). Genetic determinants of plasma triglycerides. *J. Lipid Res.* 52: 189-206.
- Lette G, Palmer CD, Young T, Ejebe KG, et al. (2011). Genome-wide association study of coronary heart disease and its risk factors in 8,090 African Americans: the NHLBI CARE Project. *PLoS Genet.* 7: e1001300.
- Li XP, Zhao SP and Nie S (2007). Relationship between apolipoprotein A5-1131T> C polymorphism and coronary heart disease. *Chin. Circ. J.* 22: 4-8.
- Maasz A, Kisfali P, Szolnoki Z, Hadarits F, et al. (2008). Apolipoprotein A5 gene C56G variant confers risk for the development of large-vessel associated ischemic stroke. *J. Neurol.* 255: 649-654.
- Martinelli N, Trabetti E, Bassi A, Girelli D, et al. (2007). The -1131 T>C and S19W APOA5 gene polymorphisms are associated with high levels of triglycerides and apolipoprotein C-III, but not with coronary artery disease: an angiographic study. *Atherosclerosis* 191: 409-417.
- Miller M, Rhyne J, Chen H, Beach V, et al. (2007). APOC3 promoter polymorphisms C-482T and T-455C are associated with the metabolic syndrome. *Arch. Med. Res.* 38: 444-451.
- Olivieri O, Bassi A, Stranieri C, Trabetti E, et al. (2003). Apolipoprotein C-III, metabolic syndrome, and risk of coronary artery disease. *J. Lipid Res.* 44: 2374-2381.
- Olivieri O, Martinelli N, Sandri M, Bassi A, et al. (2005). Apolipoprotein C-III, n-3 polyunsaturated fatty acids, and "insulin-resistant" T-455C APOC3 gene polymorphism in heart disease patients: example of gene-diet interaction. *Clin. Chem.* 51: 360-367.
- Ouatou S, Ajjemami M, Charoute H, Sefri H, et al. (2014). Association of APOA5 rs662799 and rs3135506 polymorphisms with arterial hypertension in Moroccan patients. *Lipids Health Dis.* 13: 60.
- Peters JL, Sutton AJ, Jones DR, Abrams KR, et al. (2006). Comparison of two methods to detect publication bias in meta-analysis. *JAMA* 295: 676-680.
- Prochaska CL, Picheth G, Angheben-Oliveira MI, Costantini CO, et al. (2010). The polymorphisms -1131T>C and the S19W of the APOA5 gene are not associated with coronary artery disease in a Brazilian population. *Clin. Chem. Lab. Med.* 48: 419-422.
- Soufi M, Sattler AM, Kurt B and Schaefer JR (2012). Mutation screening of the APOA5 gene in subjects with coronary artery disease. *J. Investig. Med.* 60: 1015-1019.
- Sterne JA and Egger M (2001). Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. *J. Clin. Epidemiol.* 54: 1046-1055.
- Triglyceride Coronary Disease Genetics Consortium and Emerging Risk Factors Collaboration, Sarwar N, Sandhu MS, Ricketts SL, et al. (2010). Triglyceride-mediated pathways and coronary disease: collaborative analysis of 101 studies. *Lancet* 375: 1634-1639.
- Wikstrom EA, Naik S, Lodha N and Cauraugh JH (2009). Balance capabilities after lateral ankle trauma and intervention: a meta-analysis. *Med. Sci. Sports Exerc.* 41: 1287-1295.
- Yu Y, Xue L, Zhao CY, Li JP, et al. (2007). APOA5 gene polymorphisms in patients with coronary artery disease. *J. Peking Univ. (Health Sci.)* 39: 576-580.
- Yu J, Huang J, Liang Y, Qin B, et al. (2011). Lack of association between apolipoprotein C3 gene polymorphisms and risk of coronary heart disease in a Han population in East China. *Lipids Health Dis.* 10: 200.
- Zhang Z, Peng B, Gong RR, Gao LB, et al. (2011). Apolipoprotein A5 polymorphisms and risk of coronary artery disease: a meta-analysis. *Biosci. Trends* 5: 165-172.

- Zhou J, Xu L, Huang RS, Huang Y, et al. (2013). Apolipoprotein A5 gene variants and the risk of coronary heart disease: a case-control study and meta-analysis. *Mol. Med. Rep.* 8: 1175-1182.
- Zhu MA, Zhou YL, Ding Z and Mao DY (2007). The apolipoprotein A5 -1131T>C promoter polymorphism in patients with coronary artery disease. *Chin. J. Gerontol.* 1: 73-75.
- Zintzaras E and Ioannidis JP (2005). Heterogeneity testing in meta-analysis of genome searches. *Genet. Epidemiol.* 28: 123-137.