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Original Article

Associations between Lectin-like, oxidized low-density lipoprotein receptor-1 G501C and 3'-UTR-C188T polymorphisms with coronary artery disease: a meta-analysis

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Abstract: The background and purpose: Published data on the association between LOX-1 3'UTR C188T and G501C polymorphisms with coronary artery disease (CAD) risk are inconclusive. In order to derive a more precise estimation of the relationship, a meta-analysis was conducted. Methods and subjects: Crude ORs with 95% CIs were used to assess the strength of association between these polymorphisms and CAD risk. The pooled ORs were performed for homozygous model, heterozygous model, dominant model, and recessive model, respectively. Results: A total of seventeen studies were involved in the meta-analysis with 5006 cases and 15053 controls for LOX-1 3'UTR C188T polymorphism and with 5905 cases and 15050 controls for G501C polymorphism. For LOX-1 3'UTR C188T polymorphism, significantly elevated CAD risk was associated with variant genotype when all studies were pooled into the meta-analysis (TT vs. CC: OR = 1.35, 95% CI 1.08-1.69; dominant model: OR = 1.17, 95% CI 1.02-1.34; and recessive model: OR = 1.23, 95% CI 1.03-1.47). For LOX-1 G501C polymorphism, significantly increased CAD risk was also associated with variant genotype (GG vs. CC: OR = 1.42, 95% CI 1.07-1.87; CG vs. CC: OR = 1.28, 95% CI 1.04-1.56; and dominant model: OR = 1.30, 95% CI 1.07-1.58). Conclusion: This meta-analysis suggests that the variant G allele of LOX1 3'UTR C188T and the variant C allele of G501C polymorphisms are low penetrant risk factors for developing CAD.

Keywords: SNP, polymorphism, coronary artery disease, Lectin-like, oxidized low-density lipoprotein receptor-1, meta-analysis

Introduction

Coronary artery disease (CAD) is the most common substrate for heart failure in industrialized nations [1]. Over the past 150 years, there have been numerous efforts to explain the complex events associated with the development of CAD. Traditional risk factors of CAD such as hypertension, diabetes mellitus, dyslipidemia and smoking can only explain approximately two-thirds of the observed clinical events, and genetic factors that might contribute to the underlying pathophysiology of CAD [2]. Identification of susceptibility genes of CAD can highlight the links among CAD and inflammation and immunity, and highlight the biological insights to be gained from a genetic understanding of CAD.

Atherosclerosis of coronary artery is the pathogenetic basis of CAD. Oxidized low-density lipoprotein (ox-LDL) plays a key role in the initiation and progression of atherosclerosis [3]. Lectin-like, oxidized low-density lipoprotein receptor-1 (LOX1) is the main receptor of ox-LDL and is highly expressed in atherosclerotic lesions. The binding of ox-LDL to LOX1 (also known as OLR1) induces several cellular events in endothelial cells such as activation of transcription factor NF-kB, upregulation of monocyte chemoattractant protein-1, and reduction in intracellular nitric oxide,9 which may trigger the onset of cardiovascular events or accelerate the development of atherosclerosis [4]. Several functional variations have been found in LOX1. Several studies have reported the role of 3'untranslated region (3'UTR) 188CT and G501C polymor-

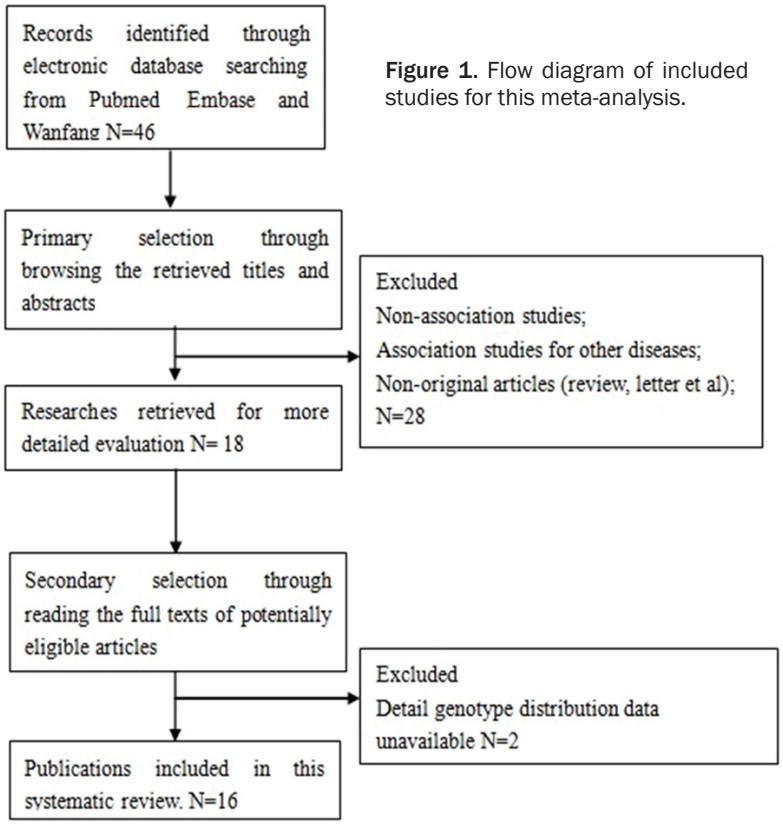

Figure 1. Flow diagram of included studies for this meta-analysis.

phisms of LOX-1 gene in CAD [5-7], but the results are inconclusive, partially because of the possible small effect of the polymorphism on CAD risk and the relatively small sample size in each of published studies. Therefore, we performed this meta-analysis to derive a more precise estimation of the associations.

Materials and methods

Publication search

PubMed, Embase, and Wanfang database were searched (last search was updated on 10 June 2013, using the search terms: "Lectin-like, oxidizedlow-densitylipoproteinreceptor-1","Oxidized-lipoprotein receptor 1", "LOX1", "OLR1", "coronary heart disease", "unstable angina", "acute coronary syndrome" and "polymorphism". All searched studies were retrieved, and their bibliographies were checked for other relevant publications. Review articles and bibliographies of other relevant studies identified were hand-searched to find additional eligible studies. Only published studies with full text articles were included. When more than one of the same patient population was included in several publications, only the most recent or complete study was used in this meta-analysis.

Inclusion criteria

The inclusion criteria were: (a) evaluation of the LOX1 3'UTR C188T or G501C polymorphism and CAD risk, (b) case-control studies, and (c) sufficient published data for estimating an odds ratio (OR) with 95% confidence interval (CI).

Data extraction

Information was carefully extracted from all eligible publications independently by two of the authors according to the inclusion criteria listed above. Disagreement was resolved by discussion between the two authors. If these two authors could not reach a consensus, another author was consulted to resolve the dispute and a final decision was made by the majority of the votes. The following data were collected from each study: first author's name, publication date, ethnicity, study design, total number of cases and controls, respectively. Different ethnicities were categorized as Caucasian and Asian. We did not define any minimum number of patients to include in our meta-analysis.

Statistical methods

Crude ORs with 95% CIs were used to assess the strength of association between the LOX-1 (3'UTR C188T or G501C) polymorphism and CAD risk. For LOX-1 3'UTR C188T, the pooled ORs were performed for co-dominant model (TT vs. CC, TC vs. CC), dominant model (TC+TT vs. CC), and recessive model (TT vs. TC+CC). For LOX-1 G501C, the pooled ORs were performed for co-dominant model (GG vs. CC, CG vs. CC), dominant model (CG+GG vs. CC), and recessive model (GG vs. CG+CC). Heterogeneity assumption was checked by the Chi-square-based Q test [8]. *P* value greater than 0.10 for the Q test indicates a lack of heterogeneity across studies, so the pooled OR estimate of the each study was calculated by the fixed-effects model (the Mantel-Haenszel method) [9]. Otherwise, the random-effect model (the

Table 1. Characteristics of studies on the association between G501C and 3-UTR-C188T polymorphisms and CAD in the meta-analysis

study	year	country	Ethnicity	Source of the control	G501C		3'-UTR-C188T	
					case	control	case	control
Chen [17]	2003	USA	Caucasian	hospital based	247	269	\	\
Mango [5]	2003	Italy	Caucasian	hospital based	205	120	150	103
Tatsuguchi [6]	2003	Japan	Asian	hospital based	\	\	102	102
Ohmori [7]	2004	Japan	Asian	hospital based	\	\	419	128
Trabetti [13]	2006	Italy	Caucasian	hospital based	350	637	350	637
Novelli [18]	2007	Italy	Caucasian	hospital based	381	115	\	\
Shan [20]	2007	China	Asian	hospital based	202	161	161	202
Morgan [19]	2007	USA	Caucasian	hospital based	\	\	803	649
Qiang [25]	2007	China	Asian	hospital based	101	54	\	\
Knowles (ADVANCE study) [15]	2008	USA	Caucasian	population based	1797	1725	1808	1731
Knowles (ARIC study) [15]	2008	USA	Caucasian	population based	1470	11733	1470	11215
Kurnaz [16]	2009	Turkey	Caucasian	hospital based	\	\	91	72
Predazzi [14]	2010	Italy	Caucasian	hospital based	\	\	265	67
Su [24]	2011	China	Asian	hospital based	\	\	127	38
Zhou [22]	2012	China	Asian	hospital based	\	\	159	106
Dou [23]	2012	China	Asian	hospital based	170	140	\	\
Kurnaz [21]	2012	Turkey	Caucasian	hospital based	83	99	\	\

Table 2. Meta-analysis of the association between LOX-1 3'UTR C188T polymorphisms and CAD risk

3'-UTR-C188T	studies	OR (95% CI)	P_{OR}	Model	I^2 (%)	P_H
Total studies						
Homozygous	11	1.35 (1.08-1.69)	0.009	Random	62.6	0.003
Heterozygous	11	1.07 (0.98-1.15)	0.123	Fixed	14.3	0.308
Recessive	11	1.23 (1.03-1.47)	0.021	Random	53.8	0.017
Dominant	11	1.17 (1.02-1.34)	0.028	Random	48.2	0.037
Caucasians						
Homozygous	7	1.44 (1.08-1.92)	0.012	Random	77.3	0
Heterozygous	7	1.07 (0.98-1.16)	0.136	Fixed	41.1	0.117
Recessive	7	1.28 (1.02-1.59)	0.03	Random	72	0.002
Dominant	7	1.22 (1.02-1.46)	0.034	Random	66.4	0.007
Asian						
Homozygous	4	1.14 (0.78-1.67)	0.505	Fixed	0	0.976
Heterozygous	4	1.05 (0.82-1.35)	0.679	Fixed	0	0.689
Recessive	4	1.11 (0.77-1.58)	0.584	Fixed	0	0.987
Dominant	4	1.07 (0.85-1.35)	0.557	Fixed	0	0.705

DerSimonian and Laird method) was used [10]. Sensitivity analysis was performed to assess the stability of the results. A single study involved in the meta-analysis was deleted each time to reflect the influence of the individual data-set to the pooled Ors [11]. An estimate of potential publication bias was carried out by the funnel plot, in which the standard error of log (OR) of each study was plotted against its log (OR). An asymmetric plot suggests a possible publication bias. Funnel plot asymmetry was assessed by the method of Egger's linear regression test, a linear regression approach to measure funnel plot asymmetry on the natural logarithm scale of the OR. The significance of the intercept was determined by the t test suggested by Egger ($P<0.05$ was considered representative of statistically significant publication bias) [12]. All the statistical tests were performed with STATA version 10.0 (Stata Corporation, College Station, TX).

Results

Study characteristics

After the literature searching and the subsequent screening, we came up with 16 research papers concerning the association of LOX1 3'UTR C188T and G501C polymorphisms with CAD (**Figure 1**) [5-7, 13-25]. In the study of

Table 3. Meta-analysis of the association between LOX-1 G501C polymorphisms and CAD risk

G501C	studies	OR (95% CI)	P_{OR}	Model	I^2 (%)	P_H
Total studies						
Homozygous	10	1.42 (1.07-1.87)	0.014	Fixed	0	0.606
Heterozygous	10	1.28 (1.04-1.56)	0.017	Fixed	0	0.873
Recessive	10	0.99 (0.73-1.33)	0.926	Random	85.5	0
Dominant	10	1.30 (1.07-1.58)	0.009	Fixed	0	0.809
Caucasians						
Homozygous	6	1.44 (1.05-1.97)	0.024	Fixed	0	0.429
Heterozygous	6	1.28 (1.04-1.59)	0.022	Fixed	0	0.689
Recessive	6	1.10 (0.76-1.60)	0.607	Random	87.5	0
Dominant	6	1.30 (1.06-1.60)	0.014	Fixed	0	0.579
Asian						
Homozygous	4	1.34 (0.75-2.39)	0.319	Fixed	0	0.501
Heterozygous	4	1.22 (0.67-2.20)	0.516	Fixed	0	0.699
Recessive	4	0.81 (0.43-1.51)	0.5	Random	85	0
Dominant	4	1.27 (0.72-2.24)	0.408	Fixed	0	0.687

Knowles et al., the ORs were presented separately according to the different subgroup [15]. Therefore, each study in the publication was considered separately for analysis. Thus, a total of 17 studies were involved in the meta-analysis with 5006 cases and 15053 controls for LOX1 3'UTR C188T polymorphism and with 5905 cases and 15050 controls for LOX1 G501C polymorphism. **Table 1** lists the studies identified. Controls were mainly healthy populations and matched for age. Genotypes distribution in the controls of each study was in agreement with Hardy-Weinberg equilibrium (**Table 1**).

Main results

Tables 2, **3** lists the main results of this meta-analysis. For LOX1 3'UTR C188T polymorphism, significantly elevated CAD risk was associated with variant genotype (TT vs. CC: OR = 1.35, 95% CI 1.08-1.69; dominant model: OR = 1.17, 95% CI 1.02-1.34; and recessive model: OR = 1.23, 95% CI 1.03-1.47). In the subgroup analysis by ethnicity, significantly increased risks were found for Caucasians (TT vs. CC: OR = 1.44, 95% CI 1.08-1.92; dominant model: OR = 1.22, 95% CI 1.02-1.46; and recessive model: OR = 1.28, 95% CI 1.02-1.59), but not for Asians (TT vs. CC: OR = 1.14, 95% CI 0.78-1.67; TC vs. CC: OR = 1.05, 95% CI 0.82-1.35; dominant model: OR = 1.07, 95% CI 0.85-1.35; and recessive model: OR = 1.11, 95% CI 0.77-1.58) (**Figure 2**).

For LOX1 G501C polymorphism, significantly elevated CAD risk was associated with variant genotype (GG vs. CC: OR = 1.42, 95% CI 1.07-1.87; CG vs. CC: OR = 1.28, 95% CI 1.04-1.56; and dominant model: OR = 1.30, 95% CI 1.07-1.58). In the subgroup analysis by ethnicity, significantly increased risks were found for Caucasians (GG vs. CC: OR = 1.44, 95% CI 1.05-1.97; CG vs. CC: OR = 1.28, 95% CI 1.04-1.59; and dominant model: OR = 1.30, 95% CI 1.06-1.60), but not for Asians (GG vs. CC: OR = 1.34, 95% CI 0.75-2.39; CG vs. CC: OR = 1.22, 95% CI 0.67-2.20; dominant model: OR = 1.27, 95% CI 0.72-2.24; and recessive model: OR = 0.81, 95% CI 0.43-1.51) (**Figure 3**).

Sensitivity analysis

A single study involved in the meta-analysis was deleted each time to reflect the influence of the individual data-set to the pooled ORs, and the corresponding pooled ORs were not materially altered (data not shown), indicating that our results were statistically robust.

Publication bias

Begg's funnel plot and Egger's test were performed to assess the publication bias. The shapes of the funnel plots did not reveal any evidence of obvious asymmetry in all comparison models. The Egger's test was further used to provide statistical evidence of funnel plot asymmetry, and the results still did not show any evidence of publication bias (for LOX1 3'UTR C188T: TT vs. CC, P = 0.815; for TC vs. CC, P = 0.484; dominant model, P = 0.938; recessive model, P = 0.938; for LOX1 G501C: GG vs. CC: P = 0.186; CG vs. CC, P = 0.102; dominant model, P = 0.244 and recessive model, P = 0.938).

Discussion

Ox-LDL plays a central role in the development and progression of atherosclerotic lesions. LOX-1 is considered a critical molecule responsible for the binding, internalization and degra-

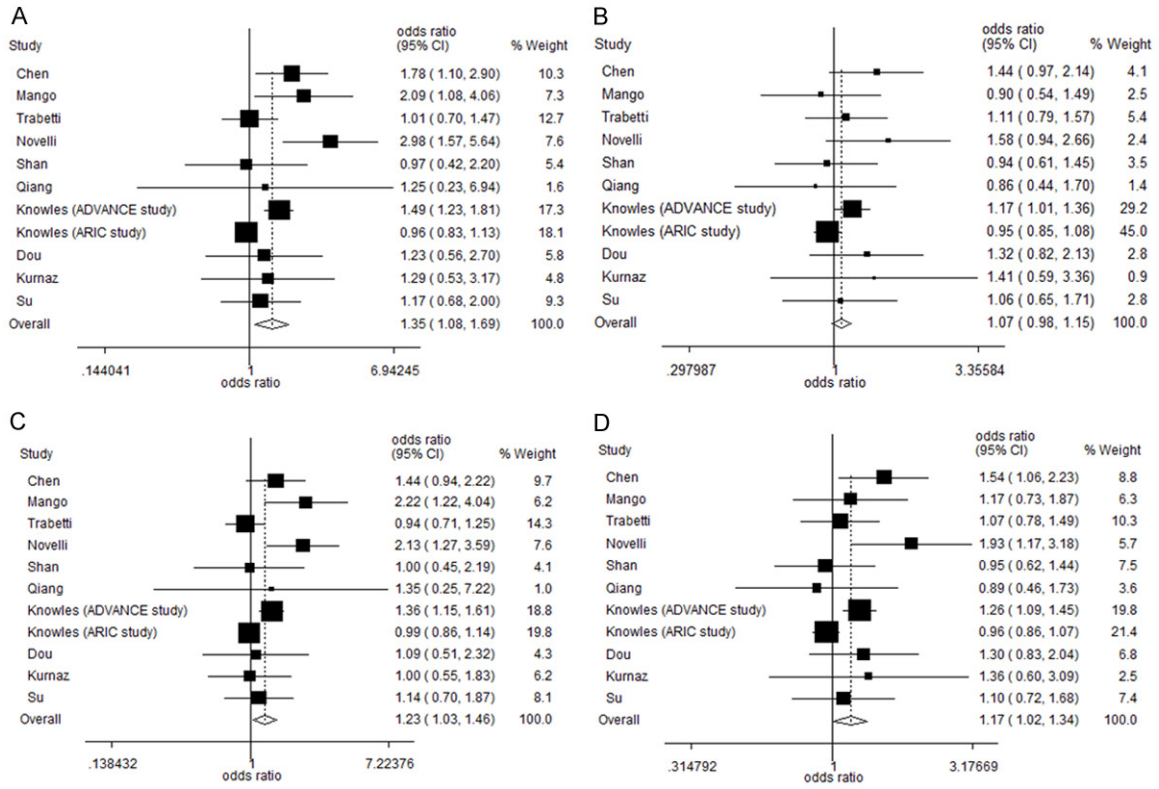

Figure 2. Meta-analysis for LOX-1 3'UTR C188T polymorphism in CAD. (A) Homozygous (B) Heterozygous (C) recessive (D) dominant.

dation of ox-LDL in endothelial cells and does not interact with modified LDL [25]. Recently, upregulation of LOX1 has been shown in ischaemia reperfusion injury in the rat [26]. LOX1 acts as a mediator of "endothelial dysfunction" favouring superoxide generation, inhibiting nitric oxide production, and enhancing endothelial adhesiveness for monocytes .Deletion of the LOX1 gene attenuates the progression of atherosclerosis [27]. Therefore, it seems that the LOX1 gene makes a useful contribution to atherosclerosis.

The present meta-analysis analysis explored the association between the LOX1 3'UTR C188T and G501C polymorphisms with CAD risk. The results indicated that the variant G allele of LOX1 3UTR C188T and the variant C allele of G501C polymorphisms are low penetrant risk factors for developing CAD. Moreover, significant associations were found in Caucasians but not for Asians, suggesting a possible role of ethnic differences in genetic backgrounds and the environment they lived in [28-30]. In addition, there is no reported study using African population for this polymorphism. So it is also likely that the observed ethnic differences may be attributable to chance because studies with small sample size may have insufficient statistical power to detect a slight effect. Therefore, additional studies are warranted to further validate ethnic difference in the effect of this polymorphism on CAD risk, especially in Africans.

Heterogeneity is a potential problem when interpreting the results of the present meta-analysis. In overall analysis and subgroup analysis for LOX1 G501C, the heterogeneity was not obvious under all four genetic models. In overall analysis and subgroup analysis for LOX1 3'UTR C188T, significant between-study heterogeneity existed in homozygous model, recessive model and dominant model comparisons. After subgroup analyses by ethnicity, the heterogeneity was effectively removed in Asians. There are some factors that could have contributed toward the high heterogeneity. First, there is likely to be considerable genetic heterogeneity between the samples that were drawn from

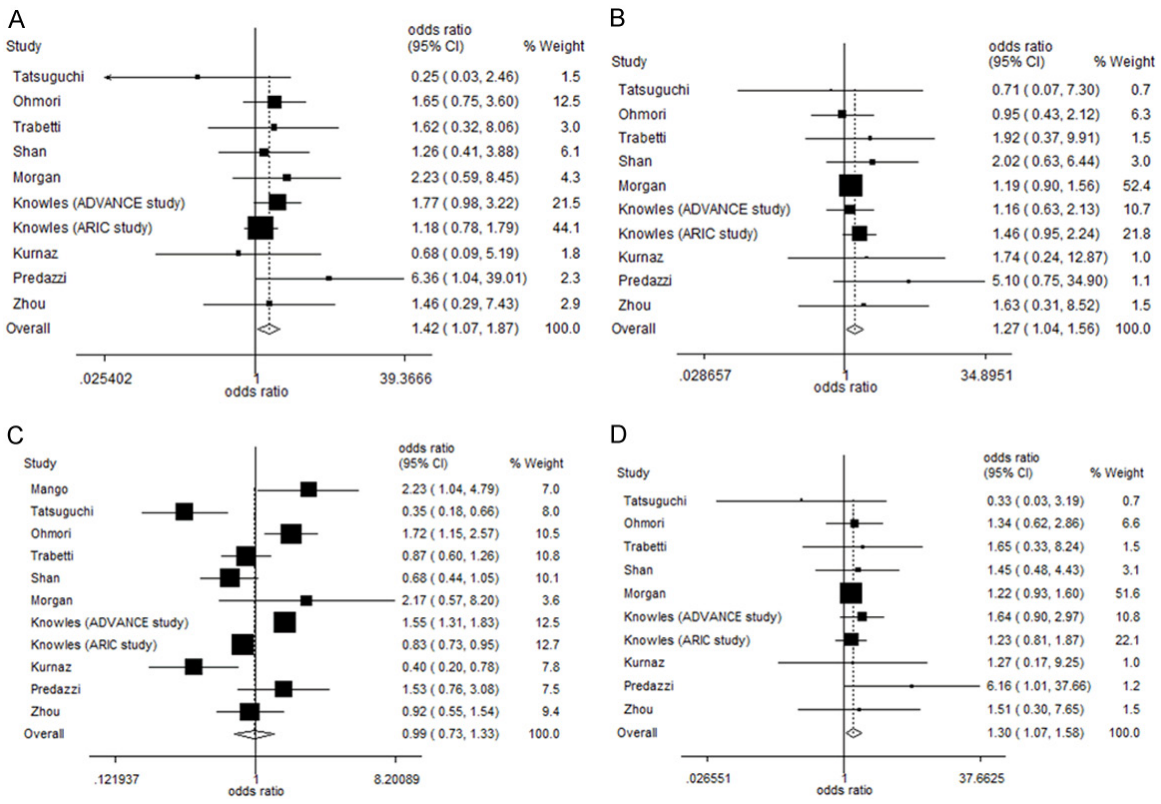

Figure 3. Meta-analysis for LOX-1 G501C polymorphism in CAD. (A) Homozygous (B) Heterozygous (C) recessive (D) dominant.

geographically diverse populations. It is known that genotype distributions differ across populations, and genotype-phenotype associations may also depend on population stratification [29]. Second, definition of control group is different in different studies, the definition differences of the controls could have contributed to the high heterogeneity observed in our meta-analysis. Third, we attempted to determine if the high heterogeneity might also be explained by other variables such as gender, age, smoking status, and environmental factors included in the different studies, but are unable to provide a reliable answer to this question because we did not have access to individual level data for these variables.

However, some limitations of this meta-analysis should be acknowledged when explaining our results. Firstly, only published studies that were included by the selected electronic databases were identified in this study, and it is possible that some relevant published studies or unpublished studies that had null results were missed, which might bias the results, while our statistical test may not have totally shown it. Second, all case-controls were from Asians and Caucasians; thus, our results may be applicable to these two ethnic groups only. Thirdly, some of the individual studies have a small number of cases, this may affect statistical power of the publication bias, thus, it should be caution when explained our results. In spite of these, our meta-analysis also had some advantages. First, substantial numbers of cases and controls were pooled from different studies, which significantly increased the statistical power of the analysis. Second, no publication biases were detected, indicating that the whole pooled result may be unbiased.

In conclusion, our meta-analysis suggests that the LOX1 3'UTR C188T and G501C polymorphisms may contribute to genetic susceptibility of CAD. However, large studies using standardized unbiased methods, enrolling precisely defined CAD patients and well-matched controls, with more detailed individual data are needed. Furthermore, more and larger studies, especially studies stratified for gene-environ-

mental interaction, should be performed to clarify the possible roles of the LOX1 polymorphisms in the genetic aetiology of CAD.

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Disclosure of conflict of interest

None.

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