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Review Article

The association of the D9N and N291S polymorphisms in LPL gene with coronary disease: a meta-analysis

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Abstract: The current study aimed to evaluate the relationships between the D9N and N291S polymorphisms and coronary disease risk. We searched the PUBMED, EMBASE, and ISI web of science databases to identify eligible published studies without language restrictions up to May 2016. Summary odds ratios (ORs) and 95% confidence intervals (CIs) were estimated under different genetic models using meta-analytic methods. Stratified analysis and sensitivity analysis were performed to explore potential sources of heterogeneity. A total of eligible 12 articles were included in this meta-analysis. The carriers of the D9N genotype experienced a 1.57-fold increased risk of coronary disease when compared to non-carriers with the AA genotype (OR=1.57, 95% CI: 1.32-1.81). The significant relationships between the D9N polymorphism and coronary disease were also observed in other genetic models (all $P < 0.05$). Stratified analysis based on ethnicity found that the D9N polymorphism had a significant association with the increased risk of the disease in the White population (OR=1.62, 95% CI: 1.36-1.88), but not in the Black and Asian populations (Black: OR=1.48, 95% CI, 0.61-2.36; Asian: OR=0.33, 95% CI, 0.04-2.83). There were no significant associations of the N291S polymorphism with coronary disease in all genetic models (all $P > 0.05$). The present meta-analysis indicated that the LPL D9N polymorphism could significantly increase the susceptibility to coronary disease, especially in the White population. No significant association between the LPL N291S polymorphism with this disease was observed in diverse populations.

Keywords: Coronary disease, D9N, N291S, polymorphism, meta-analysis

Introduction

Coronary disease is greatly harmful to people's health, which is one of major causes of morbidity and mortality annually all over the world. Coronary disease is caused by the complicated interaction of environment and inheritance, and the lipid metabolism disorder plays an important role in the pathogenesis [1, 2]. In prospective studies, the higher level of very low density lipoprotein (VLDL) and low density lipoprotein (LDL) have a positive correlation with risk of CAD, however high density lipoprotein (HDL) is inverse. During the process of lipid metabolism, Lipoprotein lipase (LPL) plays a key role, which can hydrolyze core TG from circulating chylomicron and VLDL, in transferring phospholipids and apolipoproteins to HDL, which will result in low TG and high HDL [3].

The LPL gene is located on chromosome 8p22, spans 30 kb, composed of 10 exons [4], and has a trait of polymorphism. Several mutations of LPL have been deserved to be associated with LPL activity, and the activity partly accounts for the risk of coronary disease through mediating lipid metabolism [5]. In addition to these rare mutations, the D9N and N291S polymorphisms in the LPL gene have been identified to have a more modest effect on LPL catalytic function. These two common structural variants have been shown to reduce LPL lipolytic activity in the in vitro expression of LPL by COS cells, indicating that they may play a key role in increasing risk of coronary disease. Recently, many studies have investigated the associations of the D9N and N291S polymorphisms with the coronary disease risk; however, the results from previous studies have been inconsistent. In addition, whether or not the associations of two polymorphisms were controversial for different populations remained unclear.

Therefore, we conducted a meta-analysis to evaluate the relationships between the D9N

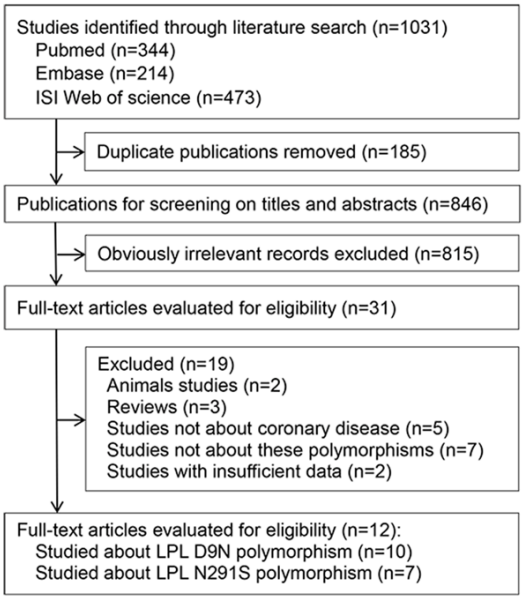

Figure 1. Flowchart for the selection of eligible studies.

and N291S polymorphisms and risk of coronary disease. Furthermore, stratified analyses were also conducted to explore associations with differentiation in ethnicity.

Materials and methods

Search strategy

The present methods recommendations were followed and a prospective protocol was used to enable compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

We searched PubMed, Web of science and EMBASE, updated on May, 2016, without language restrictions with the following search terms: "Asp9Asn", "N291S", "G280A", "Asrs268-er", "D9N", or "A1127G" and combined with "coronary disease", "coronary heart disease", "coronary artery disease (CAD)" or "myocardial infarction (MI)". We also searched the reference lists of retrieved articles. Corresponding authors were contacted, in most cases successfully, for methodological clarifications and retrieval of missing data.

Study selection criteria

The included studies fulfilled the following inclusion criteria: (1) using cross-sectional, case-control, or cohort design; (2) an original report evaluating the association of any of the D9N or N291S with the risk of coronary disease; (3) providing an odds ratio (OR) with 95% confidence interval (CI) under any genetic models or sufficient data to estimate them. Studies would be excluded if they did not fulfill the following criteria: (1) studies not about coronary disease; (2) studies not about D9N or N291S polymorphisms; (3) studies with insufficient data. When multiple publications reported the same or overlapping data, the study with the largest sample size or the latest study was included in the meta-analysis. According to these criteria, the studies were selected by two independent investigators (F.J and H.Z), and any disagreement was resolved by discussion with a senior author (JF.Z) for adjudication.

Data extraction and quality assessment

Two investigators (F.J and H.Z) checked study eligibility. Disagreements were resolved through discussion or referral to a senior investigator (JF.Z). The following information was extracted from each study: authors, year of publication, study design, ethnicity, mean age, the number of cases and controls, genotyping method, diagnosis method of disease, frequencies of genotypes in cases and controls for each of the genotypes/polymorphisms, whether or not the genotype distributions among controls were in accordance with Hardy-Weinberg equilibrium (HWE). The results were compared, and disagreements were discussed among all authors and resolved with consensus.

The quality of the included studies was independently appraised with the Newcastle-Ottawa Scale (NOS), which used a 'star' rating system to evaluate the quality of observational studies [6]. The NOS criteria include three broad perspectives-the selection, comparability and exposure-and the scores range from zero (worst) up to nine stars (best). A score of 5 or greater was considered high quality, whereas the scores less than 5 were considered low quality [7, 8].

Statistical analysis

HWE was assessed via the chi-square test for genotypes ($P < 0.05$ was considered significant deviation from HWE). The associations between LPL the D9N or N291S polymorphisms

Table 1. Characteristics of studies included in this meta-analysis

Surname	Ethnicity	Study design	Sample size (Cases/Controls)	Mean Age, y (Case/Control)	Genotyping Method	HWE	Study quality*
D9N polymorphism							
Hamid et al, 2015	Black	Case-control	54/59	NA/NA	PCR-RFLP	NP	4
Rebhi et al, 2012	Black	Case-control	212/104	60.6/59.4	PCR-RFLP	YES	7
Bhanushali et al, 2010	Asian	Case-control	90/150	NA/NA	PCR	YES	6
Izar et al, 2009	White	Case-control	386/604	62/59	PCR-RFLP	YES	7
Schmidt et al, 2007	White	Cohort	916/7540	52.5/44.9	PCR	YES	7
Bockxmeer et al, 2000	White	Case-control	721/691	43.3/39.9	PCR	YES	7
Talmud et al, 2000	White	Case-control	134/2574	56.7/56.0	PCR	YES	7
Kastelein et al, 1999	White	Case-control	1997/5171	NA/NA	PCR	YES	6
Mailly et al, 1996	White	Case-control	641/806	NA/NA	PCR	YES	6
Zhang et al, 1995	White	Case-control	238/85	NA/NA	PCR-RFLP	YES	6
N291S polymorphism							
Hamid et al, 2015	Black	Case-control	54/59	NA/NA	PCR-RFLP	NP	4
Rebhi et al, 2012	Black	Case-control	212/104	60.6/59.4	PCR-RFLP	YES	7
Franceschini et al, 2011	White	Cohort	8404/4004	63.4/61.7	Taqman assays	YES	7
Schmidt et al, 2007	White	Cohort	916/7540	52.5/44.9	PCR	YES	7
Ferencak et al, 2003	White	Case-control	479/200	59.3/55.1	Multilocus genotyping assay	YES	6
Talmud et al, 2000	White	Case-control	134/2574	56.7/56.0	PCR	YES	7
Kastelein et al, 1999	White	Case-control	54/59	NA/NA	PCR	YES	6

NP, not reported; HWE, Hardy-Weinberg equilibrium. *Study score was judged based on Newcastle-Ottawa Scale.

Table 2. Results of meta-analysis of the associations between the D9N or N291S polymorphisms and risk of coronary disease using different genetic models

Genotype contrast	N	OR	95% CI	Heterogeneity	
				I^2	P
D9N polymorphism					
GC+GG versus CC	10	1.56	1.31 to 1.80	0	0.82
G versus C	4	1.45	1.12 to 1.76	18.90%	0.30
GC versus CC	3	1.40	1.08 to 2.01	33.60%	0.22
GG versus CC	1	1.62	0.43 to 6.13		
N291S polymorphism					
GC+GG versus CC	6	1.19	0.53 to 1.85	83.50%	< 0.001
G versus C	3	0.36	0.13 to 1.001	91.20%	< 0.001
GC versus CC	2	1.36	0.27 to 1.79	0	0.95
GG versus CC	1	0.36	0.13 to 1.00		

CI, confidence interval; MI, myocardial infarction; OR, odds ratio.

and risk of coronary disease were estimated by calculating pooled ORs and 95% CI under the dominant, heterozygous, homozygous and allelic genetic models respectively. Random-effects model or fixed-effects model by using Mantel-Haentzel statistics will be chosen according to degree of heterogeneity. Heterogeneity across individual studies was evaluated by calculating the Cochran's Q statistic and the I^2 test (P < 0.10 indicates the evidence of heterogeneity and I^2 > 50% indicated a statistical significance). In addition, the stratified analyses were conducted to investigate potential sources of heterogeneity. Moreover, sensitivity analyses are performed to assess the stability of the pooled results by sequentially removing one study at a time. Potential publication bias was analyzed by the Begg's funnel plot and Egger's regression test. STATA version 11.0 (Stata Corp LP, College Station, TX, USA) was used for all statistical analyses. P value of < 0.05 was considered statistically significant.

Results

Study characteristics

Based on our search strategy, a total of 1031 potentially eligible articles were identified. After the removal of duplicate publications, 846 studies were considered of potential relevance (**Figure 1**). The remaining studies were retrieved for full-text review, and twelve articles concerning the D9N or N291S polymorphisms and risk of coronary disease were included in the final meta-analysis [9-20]. Main characteristics of the included studies were presented in **Table 1**. Ten studies assessed the association between the rs1801177 polymorphism and coronary

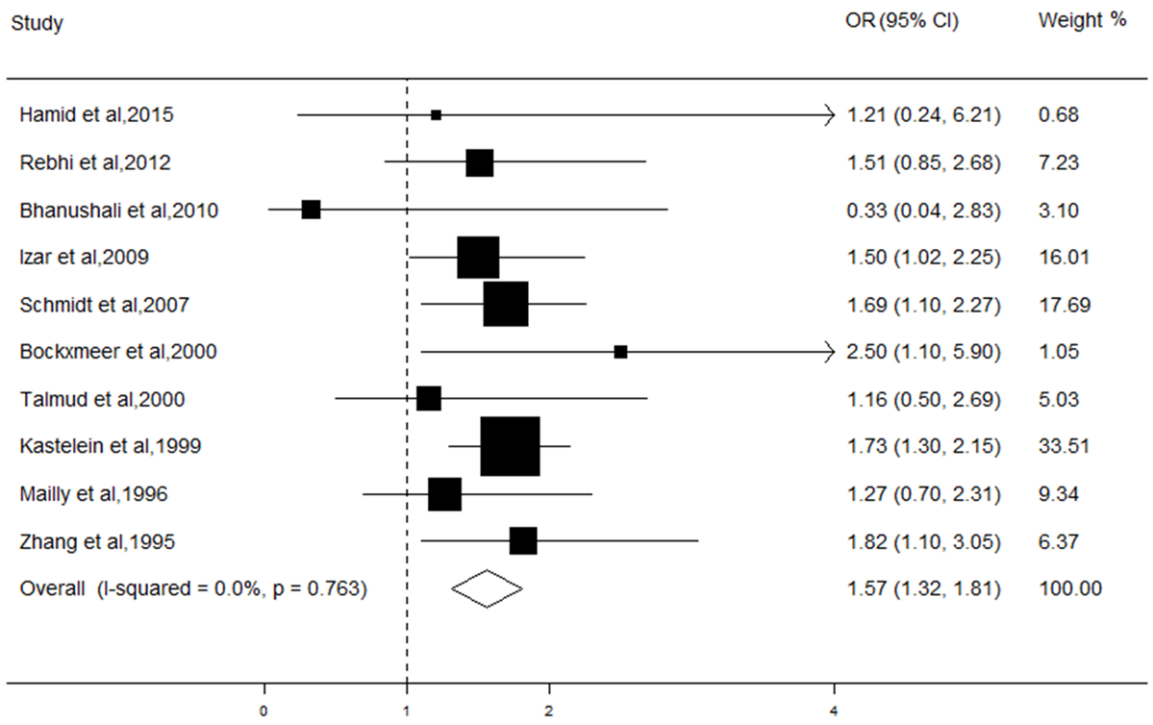

Figure 2. Forest plot on the association between the D9N polymorphism and coronary disease under the dominant genetic model. The boxes and lines indicate the odds ratios (ORs) and their 95% confidence intervals (CIs) on a log scale for each study. The pooled odds ratio is represented by a diamond. The size of the black squares indicates the relative weight of each estimate.

disease. Except for one cohort study, all the other included studies had case-control design.

Among these, seven studies were conducted on White, two on Black, and one on Asian. The average age ranged from 43.3 to 62.0 years in case group and 39.9 to 59.4 years in control group. Nine studies were considered high quality and one study was under low quality. The genotype frequency was in HWE in the controls for all included studies ($P > 0.05$ for all), except for one studies that did not report the available data. Among the seven included studies of the rs268 polymorphism, five had case-control designs, and two had cohort designs. Of them, five studies were carried out in White, and two were performed in Black. Six studies were considered high quality and one study was under low quality. Except one study that did not reported HWE, the genotypes of control group in other studies were in agreement with HWE ($P > 0.05$).

The D9N polymorphism and the risk of coronary disease

The relation between the D9N polymorphism and coronary disease was evaluated in ten studies. In the dominant genetic model, five studies showed no association between the D9N polymorphism and coronary disease, and five studies showed a significantly increased risk of this disease. The results of the present meta-analysis showed that the carriers of the D9N genotype experienced a 1.57-fold increased risk of coronary disease when compared to non-carriers with the AA genotype (OR=1.57, 95% CI: 1.32-1.81; fixed effects, $I^2=0$, $P=0.76$) (**Table 2**; **Figure 2**). The significant relationships between this variant and coronary disease were also observed in other genetic models (G versus C: OR=1.45, 95% CI, 1.12-1.76; GA versus AA: OR=1.40, 95% CI, 1.08-2.01; **Table 2**). The results of the stratified analysis based on study design showed that it did not significantly alter the shape of association between the D9N polymorphism and the risk of coronary disease (**Table 3**). However, the results for race found that theD9N polymorphism had a significant association with the increased risk of the disease in the White population (OR=1.62, 95% CI: 1.36-1.88), but not in the Black and Asian populations (Black: OR=1.48, 95% CI, 0.61-2.36; Asian: OR=0.33, 95% CI, 0.04-2.83; **Table 3**). Moreover, we performed the sensitiv-

Table 3. Stratified analysis of the association between the D9N or N291S polymorphisms and risk of coronary disease in the dominant genetic model

Subgroup	N	OR	95% CI	P	
				Heterogeneity	Meta-regression
D9N polymorphism	10	1.57	1.32 to 1.81	0.76	
Study design					0.43
Cohort	1	1.69	1.10 to 2.27		
Case-control	9	1.54	1.27 to 1.81	0.70	
Race					0.85
White	7	1.62	1.36 to 1.88	0.86	
Black	2	1.48	0.61 to 2.36	0.85	
Asian	1	0.33	0.04 to 2.83		
Study quality					0.16
High	9	1.57	1.32 to 1.82	0.68	
Low	1	1.21	0.24 to 6.21		
N291S polymorphism	6	1.19	0.53 to 1.85	< 0.001	
Study design					0.77
Cohort	1	1.01	0.72 to 1.30		
Case-control	5	1.29	0.28 to 2.32	< 0.001	
Race					0.85
White	4	1.29	0.47 to 2.11	< 0.001	
Black	2	0.92	0.15 to 1.70	0.83	
Study quality					0.16
High	5	1.26	0.47 to 2.05	< 0.001	
Low	1	0.94	0.16 to 1.73		

CI, confidence interval; OR, odds ratio.

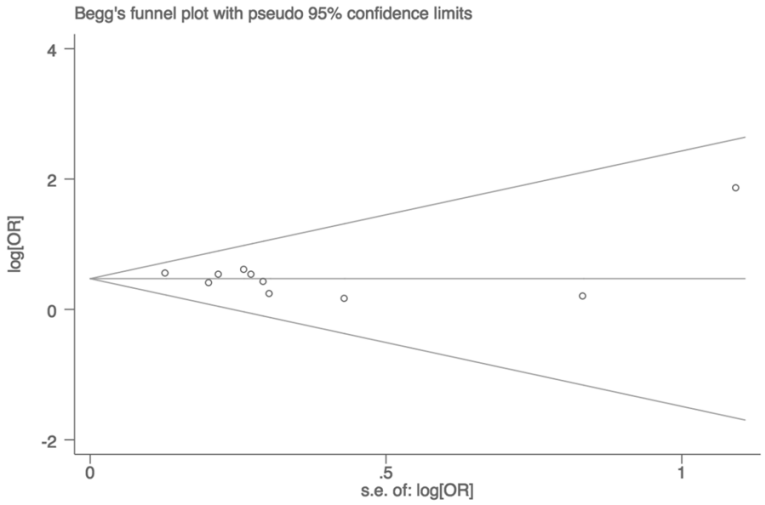

Figure 3. Funnel plots for D9N polymorphism and coronary disease risk.

ity analyses by omitting each study. The pooled ORs were not materially altered for all comparisons, thereby indicating that our results were statistically robust. We assessed possible publication bias with a funnel plot and no publication bias was detected under the dominant model (**Figure 3**).

The N291S polymorphism and the risk of coronary disease

We subsequently evaluated the association of the N291S polymorphism and the risk of coronary disease in seven studies. Six studies assessed the associations of the N291S polymorphism and the risk of this disease in the dominant genetic model; and three studies were in the all elicgenetic model, two in heterozygous genetic model and one in homozygous genetic model. In the all genetic models, there were no significant associations between N291S polymorphism and the risk of coronary disease [(GG+GA) versus AA: OR=0.19, 95% CI, 0.53-1.85; GA versus AA: OR=1.36, 95% CI, 0.27-1.79; G versus A: OR=0.36, 95% CI, 0.13-1.001; GG versus AA: OR=0.36, 95% CI, 0.13-1.00; **Table 2**; **Figure 4**]. The results of the stratified analysis based on the characteristics were presented consistent in the same directions of effect (**Table 3**). In addition, the sensitivity analysis by removing each study one at a time showed that the pooled RRs remained stable. There was no evidence for publication bias (**Figure 5**).

Discussion

Our meta-analysis found that the LPL D9N polymorphism was significantly associated with an increased risk of coronary disease; however, there was no apparent association between the LPL

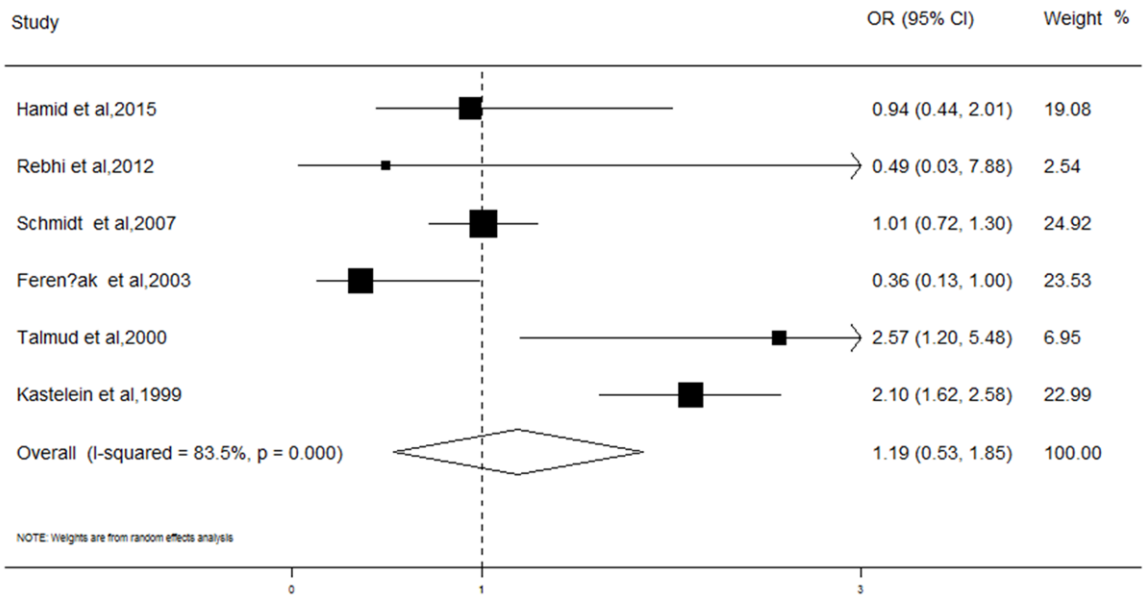

Figure 4. Forest plot on the association between the N291S polymorphism and coronary disease under the dominant genetic model. The boxes and lines indicate the odds ratios (ORs) and their 95% confidence intervals (CIs) on a log scale for each study. The pooled odds ratio is represented by a diamond. The size of the black squares indicates the relative weight of each estimate.

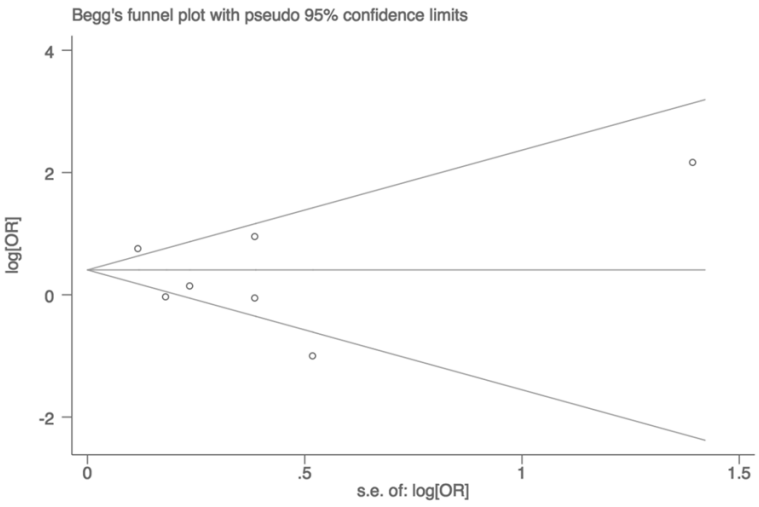

Figure 5. Funnel plots for N291S polymorphism and coronary disease risk.

N291S polymorphism and coronary disease. The stratified analysis based on ethnicity showed that the D9N polymorphism might be significantly risky in the White population. For the previous individual studies, a lack of power might result in the failure to demonstrate a significant relationship. Therefore, this prevent meta-analysis was conducted to focus on the association in the currently published literatures, and our finding also demonstrated that LPL D9N polymorphism might be a genetic risky factor for coronary disease, which also was in agreement with the result of the previous relative large cohort study [11].

The numerous of studies had shown that plasma lipoprotein levels are significant predictors of coronary disease risk. Therefore, genes with key effects on in lipoprotein metabolism are excellent candidates for individual variation in susceptibility to coronary diseases. As a major variant, impairing enzymatic function of lipid metabolism, the LPL D9N mutation was associated with adverse effects on lipid homeostasis, increased lipolytic function and an anti-atherogenic lipid profile [21-23]. In the different pathways, LPL D9N mutation could decrease lipolytic activity and concentration in the circulation; and it would damage stability of LPL dimers binding to heparin sulfate containing proteoglycans and lipoproteins; and it would decrease the uptake and clearance of atherogenic lipopro-

teins by the liver via the LDL receptors and very LDL through acting as a ligand and a molecular bridge; and it might increase expression of by reduced uptake of modified LDL in sub endothelial macrophages [24-28]. Ultimately, these beneficial effects would decrease LPL activity, and cause higher plasma triglyceride levels and lower HDL cholesterol levels, which would result in the formation of intermediate-density lipoprotein and chylomicrons remnants, and development of the coronary disease. Therefore, the LPL D9N mutation could decrease the concentrations of HDL through the retarding LPL activity, accelerate cholesterol deposition, and promote the atherosclerosis process and eventually increase the coronary disease risk. Moreover, the LPL D9N mutation would decrease the LPL mRNA translation. The inclusion of the SNP would avoid a blunted response to the epinephrine treated adipocyte extract, and the epinephrine by an RNA-protein complex, consisting of PKA subunits and an A kinase anchoring protein (AKAP) would regulated the LPL translation [29-31]. Therefore, due to the lower mRNA translation, a blunted response would promote inhibitory influences of PKA activation and LPL activity would be decreased, and this lipoprotein metabolism increase could result in a decrease in HDL, and an increase in triglycerides, and a subsequent accelerate the progress of coronary disease [10], indicating the association between the LPL D9N variant and the increased risk of coronary disease.

The results of the present meta-analysis found that the effect of the LPL D9N polymorphism on coronary disease might differ in various ethnic populations. In White population, we observed a strong association between the D9N polymorphism and coronary disease, but not in Black and Asian populations. The previous studies showed that G-allele frequency was different in these populations [9, 10, 32]; and the possible higher G-allele frequency observed in White population could explain the more significant association [33]. In addition, from the heterozygous model to the homozygous model, an additional copy of the minor allele could increase the coronary disease risk which would also support the latter hypothesis.

It should be noted that some potential limitations of the present meta-analysis should also deserve consideration in interpreting the results from this study. First, only two cohort studies were found, the meta-analysis was primarily performed with case-control studies, and this type of study design might have the problems of potential bias and confounding effects associated with such studies. However, the insignificant heterogeneity, the accurate diagnostic criteria, and the high quality of most of the included studies could add to the strength of our analysis. Second, coronary disease was a complex multifactorial disease caused by synergistic effects of genetic and the environmental factors such as age, family history, body mass index, smoking habits, and other environmental influences, which might also partly confuse our results. Our outcome was based on primarily unadjusted estimates and data provided from the original literature; and these confounding factors did not be controlled or sufficient data was extracted to analyze the association between environmental and genetic factors. Thus, further large detailed research studies were necessary to be conducted that allow for adjusting for different genes and environmental factors. Finally, there was also a need to concern potential publication bias. Although any apparent evidence of publication bias was not observed according to the Egger test, Begg test and the funnel plot, these analyses could not exclude its possibility. Moreover, it was still difficult to fully rule out this problem because there was not an enough quantity of studies to detect it adequately.

In conclusion, our analysis provided substantial evidence that the LPL D9N polymorphism could significantly increase the susceptibility to coronary disease, especially in the White population. No significant association between the LPL N291S polymorphism with this disease was observed in diverse populations. To reach a more definitive conclusion, future carefully designed trials with large interethnic study populations are warranted to evaluate the association with coronary disease.

Disclosure of conflict of interest

None.

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