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Original Article

Association of lipoprotein lipase gene polymorphisms with coronary artery disease among Filipinos

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Abstract: Studies have shown association of lipoprotein lipase (LPL) polymorphisms with coronary artery disease (CAD); however, limited studies on the genetics of CAD have been done in the Philippines. Because of their effects on high-density lipoprotein and triglyceride metabolism, the G-allele of the Ser447X variant of LPL gene has been shown to be atheroprotective, while *Hind*III polymorphism has been shown to be pro-atherogenic. We assessed 1301 patients undergoing coronary angiography to determine the prevalence of *Hind*III and Ser447X polymorphisms and their association with angiographically significant CAD. Genotyping for *Hind*III and Ser447X variants were analyzed by real-time PCR. Multivariate analyses were performed to determine the interaction between LPL polymorphisms and risk factors of CAD. CAD+ group (72%) was predominantly male (76%) with a mean age of 60.17 ± 11.01 with hypertension (89%), dyslipidemia (84%) and smoking (54%) as the most common risk factors. *Hind*III carriage frequency among the CAD+ group was 20.3% with a genotypic distribution of 78.71% (T/T), 19.83% (T/G) and 1.46% (G/G). Ser447X carriage frequency among the CAD+ group was 8.0% with a genotypic distribution of 91.39% (C/C), 8.38% (C/G) and 0.23% (G/G). *Hind*III and Ser447X polymorphisms were both not significantly associated with CAD. LPL polymorphic allele *Hind*III was common, while Ser447X was rare. Present study did not show association of LPL polymorphisms with the development of CAD. However, among patients with dyslipidemia, presence of Ser447X allele is associated with an increased risk (OR 2.6; 95% CI 2.1-3.7; p value < 0.001) of developing CAD than those without LPL polymorphisms.

Keywords: Coronary artery disease, *Hind*III, lipoprotein lipase, polymorphisms, Ser447X

Introduction

Coronary artery disease (CAD) remains the leading cause of mortality worldwide despite the advances in treatment and prevention strategies [1, 2]. Because of its high disease burden, control of risk factors prior to development is therefore imperative.

One of the established major risk factors for CAD is dyslipidemia, which usually occurs early in life, even before the development of other risk factors [3]. Despite advances in medications in the treatment of dyslipidemia and risk factor control, the prevalence of CAD remains high.

Polymorphisms affecting cholesterol metabolism play certain roles in CAD development, whether acting alone or through its interaction with other risk factors such as smoking, diabetes mellitus (DM) and hypertension. Genetic polymorphisms may partly explain CAD preponderance in certain subsets of the population [4, 5].

Studies investigating dyslipidemia as a risk factor for CAD have investigated the role of polymorphisms of the lipoprotein lipase (LPL) gene. The LPL plays a pivotal role in lipid metabolism; it hydrolyzes triglycerides and initiates chylomicron catabolism by enhancing apolipoprotein E binding with its receptors [6]. Gene alterations

in LPL such as those causing reduction in levels of LPL are associated with increased risk for CAD [7].

Two common polymorphisms in the LPL gene are the *Hind*III and Ser447X which have influence on the blood cholesterol levels. The *Hind*III polymorphism of the LPL gene has been associated with unfavorable lipid levels in certain populations [8, 9]. For instance, the H+/H+ genotype of this polymorphism has been associated with increased triglyceride and decreased high-density lipoprotein-C (HDL-C) levels among Chinese patients diagnosed with type II DM [9]; the same genotype has also been associated with CAD and its disease severity among young patients with myocardial infarction among Italians [10]. However, a study on the Saudi Arabian population showed no association between *Hind*III polymorphism and CAD [11]. The wild type allele of the *Hind*III polymorphism carries a more protective effect through its association with an increased HDL-C and decreased triglyceride level among Brazilians of European decent [12, 13]. The *Hind*III polymorphism with its associated increase in triglycerides and decrease in HDL-C levels has also been associated with CAD progression and macrovascular events among patients with DM in certain populations including Japanese, Brazilians and Indians [13-16].

On the other hand, Ser447X polymorphism is associated with increased HDL-C and decreased triglyceride levels in certain populations and thus, may be associated with protective effects in atherogenesis via its favorable lipoprotein profile [17]. A study done among Italian patients showed that carriers of the Ser447X polymorphism presented with higher HDL-C concentration as well as significantly reduced risk of high triglyceride/low HDL-C dyslipidemia [18]. A study of a homogenous Caucasian population likewise showed significantly lower levels of triglyceride levels among those with Ser447X polymorphism [19]. A meta-analysis in China supported the idea of the polymorphism having a protective effect on the development of hypertension which is a symptom of CAD [20].

Given the high burden of CAD and the potential association of LPL polymorphisms with CAD risk, we assessed a relatively large, well-defined Filipino population who underwent coronary angiography to determine whether *Hind*III and Ser447X polymorphisms were associated with angiographically significant CAD.

Materials and methods

Samples and patients

This is a single-center study conducted among patients who presented for coronary angiography in a tertiary hospital in the Philippines from February 2007 to December 2011. There were 899 (69%) males and 402 (31%) females with ages ranging from 18 to 89 years old. Participants of purely Chinese, European and American descent were excluded. Patients were designated as having CAD if they have more than or equal to 50% stenosis in at least one coronary artery or major branch. Participants with angiographically normal findings and those with less than 50% stenosis in all the major vessels were designated as controls.

Laboratory results, clinical and demographic characteristics were recorded using standardized data acquisition forms and were encoded electronically into the Cardiovascular Disease Information System (CVDIS) of the Dr. HB Calleja Vascular and Heart Institute. Angiographic data were recorded using visual estimates by experienced angiographers, who were blinded to the results of the genomic studies. Written informed consent was obtained from all the participants included in the study. The study was approved by the St. Luke's Institutional Ethics Review Committee.

DNA extraction

The nucleic acid was extracted from peripheral blood using the GenElute™ Blood Genomic kit (Sigma-Aldrich) according to manufacturer's instructions. All samples were stored at -80°C until use.

Genotyping by real-time PCR

LPL genotyping assay was carried out using the Applied Biosystems 7500 Fast Real-Time PCR. Cycling conditions include the following: (1) pre-PCR [60°C for 30 sec]; (2) DNA polymerase activation [95°C for 20 sec]; (3) denaturation [95°C for 3 sec]; (4) annealing/extension [60°C for 30 sec] and (5) post-PCR [60°C for 30 sec]. Steps 3 and 4 were repeated for 40 cycles. Negative and no template controls were included for every run to ensure the quality of genotyping results. The single nucleotide polymor-

Table 1. Baseline characteristics of patients

Characteristics	CAD patients N (%)	Controls N (%)	*p*-value
Age in years (mean ± SD)	60.17 ± 11.01	54.41 ± 11.46	< 0.001
Range	23 to 89	18 to 83	
Sex			
Female	221 (24)	181 (50)	< 0.001
Male	717 (76)	182 (50)	
Smoking	504 (54)	122 (34)	< 0.001
Dyslipidemia	789 (84)	237 (65)	< 0.001
Diabetes mellitus	431 (46)	108 (30)	< 0.001
Sedentary lifestyle	311 (33)	90 (25)	0.003
Obese	236 (25)	85 (23)	NS
With hypertension	832 (89)	284 (79)	< 0.001

NS = not significant; SD = standard deviation.

phisms that were used for this study were *Hind*III (rs320) and Ser447X (rs328). Genotypes were recorded by an experienced reader blinded to the clinical, demographic and angiographic results.

Statistical analysis

Descriptive statistics were computed to describe the demographic, clinical and angiographic profile of the study participant. Mean and standard deviation were computed for quantitative variables, while frequencies and proportions were computed for qualitative variables. The proportions and the 95% confidence intervals for the allelic and genotypic frequencies were determined. Pearson chi-square analysis was used to compare the allelic and genotypic frequencies that were calculated and was used to assess the Hardy-Weinberg equilibrium. Other group comparisons were compared using t-test for independent samples with unequal variances for quantitative variables and using Pearson chi-square test or Fisher's exact test for nominal variables. Associations were determined using logistic regression. Univariate logistic regression was done to compute for unadjusted odds ratios and 95% confidence intervals. Determination of significant difference between odds ratios of different subgroups were done using Mantel-Haenszel test of homogeneity. Multivariable logistic regression was done to determine the odds ratios and 95% confidence intervals with control for significant confounders and interactions. A two-sided *p*-value of less than 0.05 was considered statistically significant. The odds of carrying a specific allele is defined as the frequency of subjects in whom it occurs divided by the frequency of subjects in whom it does not occur. The odds of ratio for CAD are the odds of allelic carriage in the diseased CAD group divided by the no-CAD group. The statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) Version 20.

Results

A total of 1301 patients were included in the study, 938 of whom (72%) had significant CAD assessed angiographically and 269 (20%) had a previous history of myocardial infarction. The CAD+ group was predominantly male (76%) with a mean age of 60.17 ± 11.01 years and had a higher proportion of patients with hypertension (89%), dyslipidemia (84%) and smoking history (54%). The baseline characteristics of the patients are summarized in **Table 1**. The distribution of the *Hind*III and Ser447X genotypes both satisfy Hardy-Weinberg equilibrium as shown in **Table 2**.

HindIII polymorphism and CAD

The *Hind*III allelic frequency among the CAD+ group was 11% with a genotypic distribution of 80%, 19% and 1% for the T/T, T/G and G/G genotypes, respectively (**Table 3**). The frequency of *Hind*III carriage among the CAD patients did not differ significantly compared to the non-CAD patients with a computed odds ratio of 0.81 (95% CI 0.60 - 1.08) (**Table 4**).

Ser447X polymorphism and CAD

Among CAD patients, the Ser447X allelic frequency was 4% with a genotypic distribution of 92% and 8% for the C/C and C/G, respectively (**Table 3**). Overall, the genotypic distributions between the CAD and control subjects did not differ significantly with a computed odds ratio of 0.77 (95% CI 0.51 - 1.16) (**Table 4**).

Associations between LPL polymorphisms and CAD in pre-specified subgroups

Subgroup analyses based on significant risk factors (**Table 5**) have shown that only dyslipid-

Table 2. Hardy-Weinberg equilibrium test of *Hind*III and Ser447X of lipoprotein lipase gene

Genotype	Observed	Expected	Genotype frequency (%)	Allele	Observed	Allele frequencies (%)	X^2	*p*-value
*Hind*III								
Wild type (T/T)	1024	1021.84	78.71	T	2306	88.62	0.35	NS
Heterozygote (T/G)	258	262.33	19.83	G	296	11.38		
Variant (G/G)	19	16.84	1.46					
Total	1301	1301	100		2602	100		
Ser447X								
Wild type (C/C)	1189	1188.54	91.39	C	2487	95.58	0.09	NS
Heterozygote (C/G)	109	109.92	8.38	G	115	4.42		
Variant (G/G)	3	2.54	0.23					
Total	1301	1031	100		2602	100		

NS = not significant.

Table 3. Allelic and genotypic frequency distribution of *Hind*III and Ser447X among CAD patients and controls

Genotype	CAD N (%)	Controls N (%)	*p*-value	Allele	CAD N (%)	Controls N (%)	*p*-value
*Hind*III							
Wild type (T/T)	748 (80)	276 (76)	NS	T	1673 (89)	633 (87)	NS
Heterozygote (T/G)	177 (19)	81 (22)		G	203 (11)	93 (13)	
Variant (G/G)	13 (1)	6 (2)					
Ser447X							
Wild type (C/C)	863 (92)	326 (90)	NS	C	1800 (96)	687 (95)	NS
Heterozygote (C/G)	74 (8)	35 (10)		G	76 (4)	39 (5)	
Variant (G/G)	1 (0)	2 (0)					

NS = not significant.

Table 4. Association of *Hind*III and Ser447X polymorphisms with CAD

Polymorphism	CAD patients N (%)	Controls N (%)	Unadjusted OR (95% CI)	*p*-value
*Hind*III				
Wild type	748	276	0.81 (0.60-1.08)	NS
Heterozygote + variant	190	87		
Ser447X				
Wild type	863	326	0.77 (0.51-1.16)	NS
Heterozygote + variant	75	37		

NS = not significant.

Table 5. Risk factors of CAD

Risk factors	Unadjusted odds ratio (95% CI)	*p*-value
Age	1.05 (1.04-1.06)	< 0.001
Male	3.23 (2.50-4.16)	< 0.001
Smoking	2.29 (1.78-2.95)	< 0.001
Dyslipidemia	2.82 (2.13-3.72)	< 0.001
Diabetes mellitus	2.00 (1.55-2.60)	< 0.001
Sedentary lifestyle	1.51 (1.14-1.98)	0.004
Obesity	1.10 (0.83-1.46)	NS
Hypertension	2.18 (1.58-3.01)	< 0.001

NS = not significant.

emia have a significant interaction with both polymorphisms (**Tables 6** and **7**). However, among patients with dyslipidemia, the presence of Ser447X allele is associated with an increased risk (OR 2.6; 95% CI 2.1-3.7; *p*-value < 0.001) of developing CAD than those without the LPL polymorphisms using multivariate analyses (table not shown).

Discussion

Coronary artery disease remains the number one cause of death worldwide accounting for 16.6% in 2016 [21]. The same trend has been seen in the local setting by the Philippine Statistics Authority wherein the 71% deaths caused by

Table 6. Association of *HindIII* polymorphism and risk factors with CAD

Risk factors	Subgroups	Subgroup odds ratio (95% CI)	Test of homogeneity *p*-value
Sex	Female	0.59 (0.37-0.96)	0.12
	Male	0.98 (0.66-1.46)	
Smoking	Non-smoker	0.66 (0.45-0.97)	0.18
	Smoker	1.01 (0.62-1.62)	
Dyslipidemia	Without	0.97 (0.68-1.38)	0.02
	With	0.43 (0.23-0.78)	
Diabetes mellitus	Without	1.05 (0.63-1.75)	0.19
	With	0.69 (0.48-0.99)	
Sedentary lifestyle	Without	0.68 (0.39-1.18)	0.48
	With	0.86 (0.61-1.21)	
Obesity	Normal	0.74 (0.53-1.04)	0.394
	Obese	0.99 (0.56-1.77)	
Hypertension	Normotensive	0.84 (0.41-1.70)	0.894
	Hypertensive	0.79 (0.58-1.09)	

Table 7. Association of *Ser447X* polymorphism and risk factors with CAD

Risk factors	Subgroups	Subgroup odds ratio (95% CI)	Test of homogeneity *p*-value
Sex	Female	0.64 (0.32-1.24)	0.42
	Male	0.91 (0.51-1.63)	
Smoking	Non-smoker	0.67 (0.38-1.18)	0.65
	Smoker	0.82 (0.43-1.58)	
Dyslipidemia	Without	0.26 (0.09-0.73)	0.02
	With	0.95 (0.58-1.57)	
Diabetes mellitus	Without	0.67 (0.40-1.11)	0.29
	With	1.11 (0.50-2.46)	
Sedentary lifestyle	Without	0.75 (0.46-1.24)	0.97
	With	0.74 (0.35-1.54)	
Obesity	Normal	0.88 (0.54-1.44)	0.28
	Obese	0.53 (0.25-1.15)	
Hypertension	Normotensive	0.79 (0.33-1.89)	0.95
	Hypertensive	0.81 (0.50-1.31)	

the top ten leading causes 12.7% of these are from ischemic heart disease [22].

This study found no association between the presence of *Hind*III and Ser447X polymorphisms and angiographically significant CAD. *Hind*III genotypic carriage which is postulated to be pro-atherogenic as seen in other ethnicities was not significantly associated with increased presence of CAD among Filipinos [23, 24]. Ser447X genotypic carriage which in some ethnicities have been shown to be athero-protective was likewise not associated to have lower frequencies of CAD [24-30].

The group with angiographically-proven CAD had expectantly higher frequencies of major risk factors for CAD such as increased age, male, smoking, dyslipidemia, DM, sedentarism and hypertension. Because CAD is known to be a multifactorial disorder resulting from interactions between the genetic and environmental factors, the authors postulated a possible gene-environmental interaction between the LPL polymorphisms and the different proven risk factors for CAD [31]. We found no significant associations between the LPL polymorphisms and CAD after stratification for presence or absence of the following risk factors: smoking, DM, sedentary lifestyle, obesity and hypertension.

Among those with dyslipidemia, the presence of Ser447X allele carriage significantly increased the risk (OR 2.6; 95% CI 2.1-3.7; *p*-value < 0.001) of developing CAD by 2-fold. Although we found statistically significant associations for these subsets of patients, the confidence intervals were moderately broad, and the power was low for definitive conclusions.

The carrier frequency of the *Hind*III genotype in the CAD study population was 20.3%. This contrasts with those found in other ethnic groups, including Northern Europeans, Russians and Saudi Arabians with higher frequencies of the variant genotypes in the ranges of 45.1% to 53.6%. All these previous studies found significant associations of the *Hind*III polymorphism for CAD susceptibility [23, 32, 33]. A meta-analysis showed CAD susceptibility for *Hind*III poly-

morphisms for Caucasians but not for other ethnicities [24].

Compared to *Hind*III carriage frequency, Ser447X carriage among the Filipino CAD group was uncommon at 8.0%. This is similar to those reported in other CAD populations of different ethnicities ranging from 7.4% to 20% [26, 34, 35]. Other studies demonstrated a protective role for Ser447X polymorphisms for CAD. The protective role in CAD is postulated to be related to the favorable effects on the cholesterol levels, demonstrating reduced triglycerides and increased HDL-C for those with Ser447X polymorphisms [19, 26-30]. This contrasts with our findings, where we found a higher risk for CAD for those with dyslipidemia and Ser447X polymorphism. Possibly, the polymorphism in Ser447X affects the study population in a different protein function, which increases CAD risk instead of having athero-protective effects.

Various pathways by which LPL Ser447X may exert beneficial effects include increased lipolytic activity and concentration in the circulation; increased stability of LPL binding to heparan sulfate containing proteoglycans and lipoproteins; promotion of hepatic uptake of lipoproteins and; reduced LPL-mediated uptake of lipoproteins by macrophages [36].

Our study is relevant as it highlights the presence of global ethnic differences in terms of atherosclerotic risk factors at a genetic level. Since there are some ethnic variations in the prevalence of LPL polymorphism and its associations with CAD, it is possible that there could also be ethnic differences in other CAD risks at a genetic level and differences in gene-environment interactions. Future research may be needed to determine whether local guidelines for lipids and coronary artery disease should be adjusted according to ethnicity.

This study also adds substantially to the current limited body of data of LPL polymorphisms among Filipinos with or without CAD, with its strength primarily in terms of having a large population size, and thus a high statistical power; as well as having certainty in the diagnosis of CAD.

Our study comes with some limitations. First, the included subjects were deemed by their clinicians as having the need for coronary angiography. They may possibly be subset of patients who have confounding risk factors that predispose them to have a high atherogenic profile. Thus, the results of the study may not be generalizable to a healthy population. Second, lipid profile of patients was not part of the analysis, which may be integral in the determination of the association of LPL polymorphisms with atherosclerosis. It would be interesting to determine in future studies if there is a specific lipid profile pattern for Filipino patients having certain LPL polymorphisms. Finally, this study was done in a single center only. Thus, the results may not be generalizable to the whole Filipino population. Future studies which include multiple centers are recommended. Given the finding of possible association of LPL polymorphisms and CAD among dyslipidemic patients, focused studies that look at interactions of the different major risk factors of CAD with the LPL polymorphisms are also recommended.

In conclusion, among Filipino CAD patients, LPL polymorphic allele *Hind*III was common while S447X was rare. Unlike previously reported in other ethnicities, our study did not show any association of both polymorphisms either as an independent risk factor or protective of CAD.

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Disclosure of conflict of interest

None.

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