Original Article

S447X Polymorphism in the Lipoprotein Lipase Gene and the Adiponectin Level in the General Population: Results from the Mima Study

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Aim: Lipoprotein lipase (LPL) plays an important role in lipid metabolism. There is an association between the common S447X polymorphism in the LPL gene and high-density lipoprotein cholesterol (HDL-C) levels, and some association between circulating HDL-C and adiponectin levels has been suggested; however, it is not known whether there is any association between the S447X polymorphism and adiponectin levels. The aim of this study was to investigate whether the LPL S447X polymorphism was associated with adiponectin in the general population.

Methods: LPL S447X was analyzed in 277 community-dwelling subjects (123 men and 154 women, mean age; 65 ± 13 years) in the Mima study. Whole samples were genotyped using a fluorescent allele-specific DNA primer assay system. The allele frequencies and any associations with serum lipid and adiponectin levels were investigated.

Results: The allele frequencies were $S=0.875$ and $X=0.125$ for the LPL S447X polymorphism. The carriers of the X allele had significantly higher levels of adiponectin and HDL-C than non-carriers. The presence of the X allele was significantly associated with higher adiponectin levels, independent of age, sex, body mass index, smoking and HDL-C in multiple regression analyses.

Conclusion: The LPL S447X polymorphism might therefore be significantly associated with higher adiponectin levels, independent of HDL-C.

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Key words; Lipid metabolism, Adipocytokine, HDL-cholesterol, Association study

Introduction

Lipoprotein lipase (LPL) is an enzyme that catalyzes the hydrolysis of triglycerides in chylomicrons and very low density lipoproteins¹. A decline in LPL activity can influence blood lipid levels, thus causing various degrees of hypertriglyceridemia in association with hypercholesterolemia². Hypertriglyceridemia is

often accompanied by low levels of high-density lipoprotein cholesterol (HDL-C)^{3,4}.

HDL-C has been established as an inverse predictor of cardiovascular disease (CVD) and in recent years, investigations have focused on the genetic regulation of HDL-C⁵⁻⁷. The common S447X polymorphism in exon 9 of the LPL gene, where cytosine is replaced by guanine at position 1595⁸, is thought to be a genetic factor associated with the metabolism of HDL-C. This polymorphism results in the exchange of a serine for a terminal codon and the suppression of the last two amino acids, serine and glycine, at position 447 of the protein⁹. In fact, according to a review article by Rip J *et al.* based on thirty previous studies, despite some conflicting results, fourteen studies have

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Table 1. Characteristics

	All (n=277)	Men (n=123)	Women (n=154)	p-value
Age (years)	65.2 ± 12.8	63.7 ± 15.1	66.4 ± 10.6	0.088
Smoking (%)	24.5	52.8	1.9	<0.001
Body mass index (kg/m ²)	24.0 ± 3.1	23.7 ± 2.8	24.2 ± 3.2	0.198
Systolic blood pressure (mmHg)	137.9 ± 19.4	136.4 ± 20.6	139.1 ± 18.5	0.263
Diastolic blood pressure (mmHg)	76.8 ± 11.6	76.0 ± 11.4	77.5 ± 11.7	0.275
Fasting blood glucose (mg/dL)	99.8 ± 28.7	103.0 ± 29.5	97.1 ± 27.8	0.091
HbA _{1c} (%)	5.6 ± 1.1	5.6 ± 1.2	5.6 ± 1.1	0.763
BUN (mg/dL)	16.8 ± 5.3	17.7 ± 6.1	16.1 ± 4.5	0.016
Cr (mg/dL)	0.76 ± 0.21	0.89 ± 0.24	0.66 ± 0.12	<0.001
Total cholesterol (mg/dL)	186.4 ± 35.2	177.6 ± 37.3	193.4 ± 31.9	<0.001
HDL-C (mg/dL)	53.9 ± 14.6	49.7 ± 14.8	57.3 ± 13.6	<0.001
Triglycerides (mg/dL)	100.7 ± 51.8	108.7 ± 63.1	94.2 ± 39.6	0.075
Adiponectin (μg/mL)	8.4 ± 5.8	6.6 ± 5.3	9.8 ± 5.7	<0.001

BUN, blood urea nitrogen. Cr, serum creatinine.

HDL-C, high-density lipoprotein cholesterol

Data are means ± SD or percentages.

P-value was calculated for comparison between men and women. Because of a skewed distribution, BUN, Cr, HDL-C, triglycerides, and adiponectin values were log-transformed in these analyses.

reported significantly higher circulating HDL-C levels in carriers of the S447X X allele than in non-carriers¹⁰.

In addition to HDL-C, the anti-CVD-related adiponectin, secreted by adipose tissue, has drawn much attention¹¹⁻¹⁴. Furthermore, circulating adiponectin levels may be partially modulated by genetic factors¹⁵. The LPL activity is associated with levels of HDL-C^{16, 17} and adiponectin^{18, 19} and HDL-C and adiponectin levels may be associated with each other¹⁸⁻²²; however, it is unclear whether the S447X polymorphism affects adiponectin levels in an analysis of lipid parameters. Therefore, the aim of the present cross-sectional study was to investigate the effects of this common polymorphism in LPL on serum lipid and adiponectin levels in the general population.

Subjects and Methods

A total of 277 Japanese community-dwelling subjects (123 men and 154 women, mean age: 65 ± 13 SD) years, range; 24-88 years) in the Koyadaira area of Mima city were enrolled in this study (Table 1), which was approved by the Ethics Committee of Kyoto Medical Center²³. All subjects gave their written informed consent and were recruited during general health check-ups. Eligible subjects had no clinical features of renal failure, ischemic heart disease, or stroke, no clinical diagnosis of diabetes, and were not currently taking medication. Blood pressure was mea-

sured in seated subjects using a standard sphygmomanometer. The overnight fasting blood glucose, serum total cholesterol, triglyceride and creatinine (Cr) levels were determined enzymatically and blood urea nitrogen (BUN) was determined by the urease method. HDL-C was determined by the homogeneous method. Serum adiponectin levels were measured by an enzyme-linked immunosorbent assay (Otsuka Pharmaceutical Co. Ltd., Tokyo, Japan). Subjects with a history of smoking were defined as smokers.

A noninvasive method was implemented for collecting buccal mucosa cells using cytobrushes. After the phenol-extraction procedure, 0.2-2 μg of DNA per subject was obtained. The genotypes were determined with a fluorescence-based allele-specific DNA primer assay system (Toyobo Gene Analysis, Tsuruga, Japan). The polymorphic region of LPL was amplified using the polymerase chain reaction with allele-specific sense primers labeled at the 5' end with either fluorescein isothiocyanate (5'-TTT GTG CAG CGA TTT CTG ATT GAC-3') or Texas red (5'-AGG AGT GGC AGC AAG TTC TGA ATG-3') and with an antisense primer labeled at the 5' end with biotin (5'-AAA TGC ACT CGA TCA AAC TGT-3'). The reaction mixture (25 μL) contained 20 ng DNA, 5 pmol of each primer, 0.2 mmol/L of each deoxynucleoside triphosphate, 3.5 mmol/L MgCl₂ and 1 U rTaq DNA polymerase (Toyobo, Osaka, Japan) in polymerase buffer. The amplification protocol was initial denaturation at 95°C for 5 min, 35 cycles of denatur-

Table 2. Physical and clinical parameters, lipoprotein profiles, and adiponectin levels of subjects according to genotype of the lipoprotein lipase gene

	All			Men			Women		
	Wild (<i>n</i> =213)	S447X (<i>n</i> =64)	<i>p</i> value	Wild (<i>n</i> =92)	S447X (<i>n</i> =31)	<i>p</i> value	Wild (<i>n</i> =121)	S447X (<i>n</i> =33)	<i>p</i> value
Age (years)	64.9 ± 12.7	66.4 ± 13.3	0.407	63.1 ± 14.9	65.3 ± 15.8	0.489	66.2 ± 10.6	67.4 ± 10.7	0.562
Sex (male/female)	92/121	31/33	0.461	—	—		—	—	
Smoking (%)	24.4	25.0	0.924	53.3	51.6	0.875	2.5	0.0	0.364
Body mass index (kg/m ²)	24.1 ± 3.0	23.7 ± 3.3	0.430	23.7 ± 2.7	23.9 ± 3.0	0.666	24.4 ± 3.1	23.5 ± 3.6	0.191
Systolic blood pressure (mmHg)	137.3 ± 19.8	139.9 ± 18.3	0.348	136.4 ± 21.0	136.5 ± 19.4	0.997	138.0 ± 18.8	143.2 ± 16.9	0.153
Diastolic blood pressure (mmHg)	76.6 ± 11.8	77.5 ± 10.9	0.582	76.0 ± 11.1	75.7 ± 12.3	0.906	77.0 ± 12.3	79.2 ± 9.3	0.282
Fasting blood glucose (mg/dL)	99.7 ± 28.4	99.8 ± 30.0	0.978	104.1 ± 31.3	99.8 ± 23.6	0.479	96.4 ± 25.5	99.9 ± 35.3	0.520
HbA _{1c} (%)	5.6 ± 1.2	5.5 ± 0.9	0.558	5.7 ± 1.3	5.5 ± 0.8	0.342	5.6 ± 1.1	5.6 ± 1.0	0.884
BUN (mg/dL)	16.7 ± 5.5	17.2 ± 4.7	0.377	17.6 ± 6.4	18.0 ± 5.1	0.559	16.1 ± 4.7	16.4 ± 4.1	0.603
Cr (mg/dL)	0.76 ± 0.22	0.77 ± 0.18	0.666	0.89 ± 0.26	0.88 ± 0.17	0.923	0.66 ± 0.12	0.67 ± 0.11	0.923
Total cholesterol (mg/dL)	184.7 ± 35.4	192.1 ± 34.5	0.138	175.4 ± 38.0	184.3 ± 34.9	0.251	191.7 ± 31.6	199.5 ± 32.9	0.218
HDL-C (mg/dL)	52.9 ± 14.9	57.1 ± 13.2	0.030	48.6 ± 15.1	52.8 ± 13.7	0.130	56.2 ± 14.0	61.2 ± 11.5	0.044
Triglycerides (mg/dL)	101.9 ± 54.8	96.5 ± 40.3	0.594	109.9 ± 69.3	105.4 ± 40.6	0.778	95.9 ± 39.8	88.3 ± 38.9	0.190
Adiponectin (μg/mL)	7.9 ± 5.3	9.9 ± 6.8	0.029	6.3 ± 4.9	7.6 ± 6.5	0.232	9.1 ± 5.4	12.1 ± 6.4	0.011

BUN, blood urea nitrogen. Cr, serum creatinine.

HDL-C, high-density lipoprotein cholesterol

Data are means ± SD or percentages.

Because of a skewed distribution, BUN, Cr, HDL-C, triglycerides, and adiponectin values were log-transformed in these analyses.

ation at 95°C for 30 s, annealing at 60°C for 30 s and extension at 68°C for 30 s, and a final extension at 68°C for 2 min. The amplified DNA was incubated in a solution containing streptavidin-conjugated magnetic beads in the wells of a 96-well plate at room temperature. The plate was then placed on a magnetic stand and the supernatants from each well were transferred to the wells of a 96-well plate containing 0.01 mol/L NaOH and measured for fluorescence with a microplate reader (Fluoroscan Ascent; Dainippon Pharmaceutical, Osaka, Japan) at excitation and emission wavelengths of 485 nm and 538 nm, respectively, for fluorescein isothiocyanate and of 584 nm and 612 nm, respectively, for Texas red.

Statistical analyses were conducted using SPSS II for Windows (version 11.01J; Chicago, IL, USA). All data are shown as the means ± SD. The chi-squared test was performed to test for any deviation from the Hardy-Weinberg equilibrium. Data were analyzed with the unpaired *t*-test and multiple regression analysis controlling for age, sex, cigarette smoking, body mass index and HDL-C (explanatory variables, which could affect adiponectin) was performed to evaluate the influence of the S447X polymorphism (explanatory variable) on adiponectin (response variable). Correlations between adiponectin and HDL-C or the body mass index were assessed using Pearson's correlation

coefficient test. Because of a skewed distribution, adiponectin, HDL-C, triglyceride, BUN and Cr values were log-transformed in these analyses. *P* < 0.05 was used as the determinant of statistical significance for all analyses.

Results

Overall, the allele frequencies were *S* = 0.875 and *X* = 0.125 for the LPL S447X polymorphism. Genotype frequencies were thus found to be in accordance with the Hardy-Weinberg equilibrium. subjects' characteristics are shown in **Table 1**. Smoking prevalence and Cr levels were higher in men, whereas total cholesterol, HDL-C and adiponectin levels were higher in women. In a simple comparison of genotypes in all subjects and women, the group of X-allele carriers had significantly higher levels of adiponectin and HDL-C, respectively, than non-carriers (**Table 2**). There was no difference in age, sex, blood pressure, fasting blood glucose, BUN, Cr, or triglyceride between the two genotypes.

Multiple regression analysis showed that the X allele was significantly associated with higher adiponectin levels, independent of age, sex, smoking, body mass index and HDL-C (**Table 3**). In multiple regression analysis by sex, this association between the X

allele and adiponectin tended to be observed in women not men, ($R^2=0.23$, regression coefficient=0.106, $p=0.068$).

The relationship between adiponectin and HDL-C in the subgroup by genotype is illustrated in **Fig. 1**. Although the positive correlation reached statistical significance in the group of non-carriers of the X allele only, the correlation coefficient in the group of X allele-carriers was higher than that of the non-carriers.

As illustrated in **Fig. 2**, there were significant negative correlations between adiponectin and the body mass index in both subgroups. The correlation coefficient in the group of X-allele carriers was lower than that of non-carriers.

Table 3. Multiple regression analysis of adiponectin levels with clinical parameters and the S447X allele

Parameters	Adiponectin	
	regression coefficient	p-value
Age	0.020	<0.001
Sex	0.412	<0.001
Smoking	-0.009	0.923
Body mass index	-0.048	<0.001
HDL-C	0.192	0.142
S447X allele	0.168	0.034

HDL-C, high-density lipoprotein cholesterol
Because of a skewed distribution, adiponectin and HDL-C values were log-transformed in this analysis.
 R^2 value in this model=0.37

Fig. 1. The relationship between adiponectin and HDL-C in the subgroup by genotype.

(A) Non-carriers, (B) S447X X-allele carriers

Fig. 2. The relationship between adiponectin and the body mass index in the subgroup by genotype.

(A) Non-carriers, (B) S447X X-allele carriers

Discussion

The allele frequency of the S447X polymorphism in this population was 12.5%, similar to the frequency previously reported in Caucasian populations in Europe, Australia, North America and Japan^{4, 24-27}. This study represents the first description that the S447X polymorphism was significantly associated with increased adiponectin levels, independent of HDL-C.

There is evidence of an association between LPL and adiponectin^{18, 19}. Adipocyte-derived adiponectin modulates insulin sensitivity²⁸. LPL expression and production mainly in adipocytes is also controlled by insulin^{29, 30}. Adiponectin is thus associated with LPL levels via the action of insulin. The LPL S447X polymorphism is reported to be associated with circulating LPL levels¹⁰, while it was unfortunately not measured in the present study. LPL polymorphisms could also be related to insulin metabolism by an unknown pathway³¹. With respect to the relationships between adiponectin and HDL-C or body mass index (which is a representative marker of insulin resistance) in the current study, the higher correlation level in the group of X-allele carriers than non-carriers may be reflective of the adiponectin-insulin-LPL correlation by the S447X polymorphism.

On the other hand, Kobayashi *et al.* noted that insulin sensitivity determines circulating LPL activity and adiponectin levels 'independently'³², thus suggesting that various potential factors affect the adiponectin-insulin-LPL correlation. The current findings of a significant association between the S447X polymorphism and circulating adiponectin levels, independent of HDL-C and body mass index, may imply that the polymorphism is one of the potential factors affecting the adiponectin level in association with LPL and insulin metabolism.

The current study had several limitations. A cross-sectional study design does not consider cause and effect, and a prospective design and a longer follow-up study are therefore needed. The present study also had a relatively small sample size. Sex differences are generally known to exist regarding HDL-C and adiponectin levels. The association between the polymorphism and adiponectin tended to be found especially in women. Also, in subgroup analysis by genotype, the correlation between adiponectin and HDL-C in the group of X-allele carriers did not reach significance, despite a higher correlation coefficient in the group of X-allele carriers rather than non-carriers. These results might have been partly influenced by the sample size; therefore, future studies with a larger number of subjects are necessary.

In summary, the presence of the LPL S447X polymorphism was significantly associated with increases in adiponectin levels, independent of HDL-C in the general Japanese population. Both adiponectin and HDL-C are now considered an inverse predictor of CVD, so LPL S447X may become an important polymorphic site in anti-CVD management.

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