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Original Article

# Lipoprotein Lipase Polymorphism *rs10503669* is Associated with High-density Lipoprotein Cholesterol Levels in Korean Population

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High-density lipoprotein (HDL) cholesterol levels are associated with decreased risk of coronary artery disease. Several genome-wide association studies (GWAS) for HDL cholesterol levels have implicated Lipoprotein lipase (LPL) as possibly being causal. Herein, the association between single nucleotide polymorphism (SNP) rs10503669 in the *LPL* gene and HDL cholesterol levels and triglyceride levels was tested in the Korean population. A total of 994 subjects from Seoul City were included in a replication study with LPL SNP rs10503669. SNP rs10503669 in the LPL gene was associated with mean HDL cholesterol levels (effect per allele 3.13 mg/dL, $P<0.0001$) and triglyceride levels (effect per allele -18.0 mg/dL, $P=0.0026$). Subjects with the CA/AA genotype had a 0.42-fold (range 0.23~0.77-fold) lower risk of having abnormal HDL cholesterol levels (<40 mg/dL) than subjects with the CC genotype. When analyzed by gender, the association of LPL was stronger in men than in women. This study clearly demonstrates that genetic variants in *LPL* influence HDL cholesterol levels and triglyceride levels in Korean adults.

**Key Words:** HDL-cholesterol, *LPL*, Polymorphisms

## INTRODUCTION

High-density lipoprotein (HDL) cholesterol levels are associated with decreased risk of cardiovascular disease (Pekkanen et al., 1990; Assmann and Gotto, 2004; Teramoto et al., 2008). Several genome-wide association studies (GWAS) for HDL cholesterol levels have reported that Lipoprotein lipase (LPL) (MIM 609708) gene is one of candidate genes (Kathiresan et al., 2008; Kooner et al. 2008; Willer et al., 2008; Aulchenko et al., 2009; Sabatti et al., 2009; Teslovich et al., 2010). Continental Asian populations tend to have lower levels of serum cholesterol than Europeans (Jee et al., 1999; Suh et al., 2001). Recent GWAS studies in Asian populations reported that SNPs in LPL showed strong evidence of association with HDL cholesterol levels as well as triglyceride levels. Kim et al. identified an SNP on chromosome 8p21.3, rs10503669, as having significant association with triglyceride and HDL cholesterol levels (Kim et al., 2011). However, they did not analyze the association of rs10503660 with HDL cholesterol by other risk factors like smoking status and body mass index.

*Lipoprotein lipase (LPL)* is a key enzyme in the metabolism of lipoproteins. It hydrolyzes plasma lipoprotein triglycerides (TG) into free fatty acids and glycerol (Goldberg,

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1996). In this study, the association of HDL cholesterol levels and triglyceride levels with LPL SNP rs10503669 was analyzed on a sample of volunteers from the Korean Metabolic Syndrome Research Initiative Study in Seoul. The association was also analyzed by body mass index level and smoking status.

## MATERIALS AND METHODS

### Study population

Subjects for the GWAS were recruited from the Korean Metabolic Syndrome Research Initiative study in Seoul city, which was initiated in December 2005. A total of 9,128 individuals were recruited in 2006 and an additional 17,569 individuals were recruited in 2007, for a total cohort of 26,697 volunteers (Yoon et al., 2008; Sull et al., 2009; Jee et al., 2010). Volunteers from the first round underwent routine health examinations at health promotion centers in university hospitals between January 2006 and December 2007. From this group, 6,563 individuals were randomly selected for measurement of adiponectin levels. The subject characteristics were described in a previous study (Jee et al., 2010). In brief, of the 6,563 individuals whose adiponectin was measured, 1,004 individuals were genotyped. The 1,004 subjects were all healthy individuals who were not undergoing any type of lipid-lowering therapy. The protocols of this study were approved by the Institutional Review Board of Human Research at Yonsei University, and written informed consent was obtained from all subjects prior to enrollment.

### Data collection

Participants were interviewed using a structured questionnaire to collect personal histories of cigarette smoking (never smoked, ex-smoker, or current smoker), and demographic characteristics (age, gender, etc.). Waist circumference was measured midway between the lower rib and iliac crest. For measurements of weight and height, light clothing was worn. Body mass indices were calculated as the subject's weight (kg) divided by the square of the subject's height ($m^2$).

For clinical chemistry assays, serum was separated from peripheral venous blood samples obtained from each participant after 12-hour fast and stored at -70℃ until use. Biomarkers of metabolic syndrome, including fasting blood glucose, total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C) were measured with a Hitachi-7600 analyzer (Hitachi, Ltd., Tokyo, Japan). Quality control of the data was conducted in accordance with the procedures recommended by the Korean Association of participant Laboratory Quality Control.

### Genotyping assays

Samples from the Seoul city cohort were genotyped on the Affymetrix Genome-Wide Human SNP (array 5.0) at DNALink. Internal quality control (QC) measures were used for the data obtained: the QC call rate (Dynamic Model algorithm) always exceeded 86%. Genotype calling was carried out using the Birdseed (v2) algorithm. A total of 1,004 individuals were genotyped using this platform. Ten of the 1,004 individuals were removed due to low genotyping call rates (< 95%), leaving a total of 994 individuals for the genome-wide analysis.

### Statistical analysis

LPL gene SNP rs10503669 was tested for possible effects on HDL cholesterol levels under an additive model in PLINK. Multivariate linear regression models used herein incorporated covariates (age and sex). Multiple logistic regression analysis was also performed. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to examine the association of the *LPL* SNP with abnormal HDL cholesterol levels (<40 mg/dL for males and <50 mg/dL for females) (NCEP ATP III). The analyses were also conducted using SAS statistical software, version 9.2 (SAS Institute, Cary, NC). All statistical tests were two-sided, and the statistical significance was determined as $P<0.05$.

## RESULTS

Mean age was 41.9 for male subjects and 41.1 for female subjects (Table 1). On average, this sample of Korean volunteers had low HDL cholesterol levels. Mean levels of HDL cholesterol in the dataset were lower in males (49.8

mg/dL) than in females (59.9 mg/dL). About 10.6% of the individuals had abnormal HDL cholesterol levels (<40 mg/dL). Of the sample dataset, 46.5% of men and 3.9% of women were current smokers.

Table 2 shows the *P* values from a linear regression model for HDL cholesterol levels in the cohort sample when age and sex were included as covariates. SNP rs10503669 in the LPL gene was found to be associated with mean HDL cholesterol levels (effect per allele 3.13 mg/dL, $P<0.0001$) and triglyceride levels (effect per allele -18.0 mg/dL, $P=0.0026$).

The association of *LPL* gene SNP rs10503669 with abnormal HDL cholesterol levels was also examined (Table 3). Subjects with the CA/AA genotype had a 0.42 -fold (range 0.23~0.77-fold) lower risk of having abnormal HDL cholesterol levels (<40 mg/dL) than subjects with the CC genotype. When analyzed by gender, the association of LPL was stronger in men than in women. Analysis by BMI median level and smoking status in male subjects is presented in Table 4. The association of LPL was a bit stronger in subjects with BMI≥24.3 than in subjects with BMI<24.3, but they showed similar trends. The association of LPL was stronger in heavy smokers (≥11/day) ($P=0.0370$) than non or light smokers (1~10/day) ($P=0.0963$).

**Table 1.** General characteristics of study population

| Subjects | | Seoul City |
|---|---|---|
| N | | 994 |
| Male gender (%) | | 56.4 |
| | | Mean ± SD |
| Age, year | | 41.5 ± 8.5 |
| Waist circumference, cm | | 81.1 ± 9.7 |
| Body mass index, kg/m$^2$ | | 23.7 ± 3.1 |
| Fasting blood sugar, mg/Dl | | 93.8 ± 16.4 |
| Systolic blood pressure, mmHg | | 120.9 ± 13.8 |
| Diastolic blood pressure, mmHg | | 73.9 ± 10.4 |
| HDL cholesterol, mg/dL | | 54.2 ± 12.9 |
| LDL cholesterol, mg/Dl | | 108.7 ± 29.2 |
| Triglyceride, mg/dL | | 118.1 ± 93.4 |
| | | N (%) |
| Smoking status | Non | 550 (55.3) |
| | Ex | 166 (16.7) |
| | Current | 278 (28.0) |
| HDL cholesterol | Normal (≥40 mg/dL) | 889 (89.4) |
| | Abnormal (<40 mg/dL) | 105 (10.6) |

SD: standard deviation

## DISCUSSION

In a cohort of 994 subjects, SNP rs10503669 near LPL was associated with increased HDL, consistent with previous studies. Recently, in a GWAS by the Korea Association Resource (KARE) consortium, SNP rs10503669 in *LPL* showed strong evidence of association with HDL cholesterol level ($P=8.4 \times 10^{-43}$) and triglyceride levels ($P=6.84 \times 10^{-39}$) (Kim et al., 2011). However, a more moderate association of the SNP was observed herein. One possible reason for the difference in result is that the subjects included in this study were almost 10 years younger on average than the KARE study subjects. The mean HDL cholesterol levels in the present study were also much higher than in the KARE subjects. Another recent Korean study also reported similar results for rs10503669 with HDL cholesterol in replication data ($P=8.48 \times 10^{-3}$) (Go et al.,

**Table 2.** Association of *LPL* gene SNP rs10503669 with Lipid levels based on linear regression model

| Phenotypes | Genotypes | | | Effect (mg/dL) | *P*-value* |
|---|---|---|---|---|---|
| | CC (N=769) | CA (N=208) | AA (N=17) | | |
| | Mean ± SD | Mean ± SD | Mean ± SD | | |
| HDL cholesterol, mg/dL | 53.4 ± 12.8 | 56.5 ± 13.0 | 59.5 ± 10.9 | 3.13 | <0.0001 |
| Triglyceride, mg/dL | 122.1 ± 100.1 | 107.0 ± 65.6 | 71.6 ± 23.7 | -18.0 | 0.0026 |
| LDL cholesterol, mg/dL | 109.1 ± 29.2 | 108.1 ± 29.9 | 98.1 ± 18.9 | -2.43 | 0.2087 |

Estimated effect size (β) and *P*-value in multiple linear regression model, considering age and sex under an additive model.

**Table 3.** Odds ratio (OR) of polymorphic genotypes of LPL rs10503669 on HDL cholesterol levels[a] in Severance data (N=994)

| Subjects | Genotype | Normal (≥40 mg/dL) | Abnormal (<40 mg/dL)* | | |
|---|---|---|---|---|---|
| | | *N* (%) | *N* (%) | OR (95% CI[b]) | *P*-value |
| All | CC | 677 (76.2) | 92 (87.6) | 1.00 (reference) | |
| | CA /AA | 212 (23.8) | 13 (12.4) | 0.42 (0.23~0.77) | 0.0051 |
| Men | CC | 350 (74.8) | 82 (88.2) | 1.00 (reference) | |
| | CA/AA | 118 (25.2) | 11 (11.8) | 0.38 (0.20~0.75) | 0.0047 |
| Women | CC | 260 (77.4) | 77 (79.4) | 1.00 (reference) | |
| | CA/AA | 76 (22.6) | 20 (20.6) | 0.90 (0.51~1.56) | 0.6989 |

[a]Adjusted for age and sex [b]CI: Confidence interval
*Abnormal HDL cholesterol levels were defined as <50 mg/dL for women

**Table 4.** Odds ratio (OR) of polymorphic genotypes of LPL rs10503669 on HDL cholesterol levels[a] in Korean Men (N=561)

| Subjects | Genotype | Normal (≥40 mg/dL) | Abnormal (<40 mg/dL) | | |
|---|---|---|---|---|---|
| | | *N* (%) | *N* (%) | OR (95% CI[b]) | *P*-value |
| BMI<24.3 | CC | 185 (72.8) | 22 (84.6) | 1.00 (reference) | |
| | CA/AA | 69 (27.2) | 4 (15.4) | 0.44 (0.15~1.35) | 0.1522 |
| BMI≥24.3 | CC | 165 (77.1) | 60 (89.6) | 1.00 (reference) | |
| | CA/AA | 49 (22.9) | 7 (10.4) | 0.39 (0.17~0.90) | 0.0275 |
| Non or light smokers (1~10/day) | CC | 167 (80.7) | 36 (92.3) | 1.00 (reference) | |
| | CA/AA | 40 (19.3) | 3 (7.7) | 0.35 (0.10~1.21) | 0.0963 |
| Ex smokers | CC | 88 (69.3) | 21 (80.8) | 1.00 (reference) | |
| | CA/AA | 39 (30.7) | 5 (19.2) | 0.54 (0.19~1.52) | 0.2411 |
| Heavy smokers (≥11/day) | CC | 92 (71.3) | 24 (88.9) | 1.00 (reference) | |
| | CA/AA | 37 (28.7) | 3 (11.1) | 0.25 (0.07~0.69) | 0.0370 |

[a]Adjusted for age [b]CI: Confidence interval

2012).

The associations between genotypes and phenotypes can be modified by gene-environment interactions. Effect modification of the associations between LPL SNPs and serum lipid concentrations by interactions with cigarette smoking has been reported (Lee et al., 2004; Kathiresan et al., 2008; Kooner et al., 2008; Pyun et al., 2012; Mo et al., 2013). In the present study, association of the LPL SNP with HDL cholesterol by smoking status was also examined. The association was a little stronger in current heavy smokers than non or light smokers. The association by body mass index median value was also examined, but the association was similar. In a cohort study of 22,939 healthy US women of European ancestry, the effects of common variants in the LPL gene on HDL-C levels were modified by physical activity (Ahmad et al., 2011).

The LPL gene is comprised of 10 exons spanning about 30 kb, with exon 10 specifying the entire 3-prime untranslated sequence (Deeb and Peng, 1989; Monsalve et al., 1990). Differences in the frequency of rs10503669 have been found between different populations. The A allele frequency was 11.5% in Europeans, while being much lower in sub-saharan Africans (4%) and Mexican Americans (6%). The frequency in East Asians was 8.1% in CHB (Han Chinese in Beijing), and 11.6% in Japanese according to HapMap data. In the present study, the frequency was 12.0% (NCBI website).

The lack of association between the previously reported loci and HDL cholesterol levels in our study may be attributable to the insufficient statistical power of the cohort data. Genetic studies of lipid levels in Asian populations may not necessarily identify the same set of susceptibility genes as those in European-derived populations. However,

this Korean cohort showed evidence that the LPL gene on chromosome 8 is associated with serum HDL cholesterol levels as well as triglycerides levels.

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