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Original Article

Effects of Obesity and Family History of Diabetes on the Association of *CETP* rs6499861 with HDL-C Level in Korean Populations

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ABSTRACT

Objectives: The aim of this study was to examine the associations of cholesterol ester transfer protein (*CETP*) rs6499861 and rs12708980 with high-density lipoprotein cholesterol (HDL-C) considering obesity and family history of diabetes (FHD) in Korean men and women.
Methods: We analyzed the association of *CETP* single nucleotide polymorphisms (SNPs) with HDL-C among individuals selected from a hospital (n=4 294) and the Bundang-gu area in Korea (n=2 304).
Results: We found that the *CETP* SNP rs6499861 was associated with a lower HDL-C level (effect per allele: −2.044 mg/dL, $p<0.0001$). Individuals with a rs6499861 CG/GG genotype had a 1.45-fold higher risk of an abnormal level of HDL-C (<40 mg/dL) than those with a CC genotype. This genotype-HDL-C association was stronger in women (odds ratio [OR], 1.99; 95% confidence interval [CI], 1.39–2.85) compared with men (OR, 1.33; 95% CI, 1.10–1.61) and in women with a FHD (OR, 4.82; 95% CI, 1.86–12.5; $p=0.0012$) compared with women without a family history. Relative to individuals with a CC genotype and body mass index (BMI) <25.69 kg/m^2, individuals with a CG/GG genotype and BMI ≥25.69 kg/m^2 had an OR (95% CI) of 2.61 (1.97–3.47).
Conclusions: These findings indicate that *CETP* variants are linked to HDL-C level in Koreans and that this link is stronger in obese men and in women who have a FHD.

Keywords: Cholesterol ester transfer proteins; HDL cholesterol; Physical activity; Genetic polymorphisms

INTRODUCTION

The level of high-density lipoprotein cholesterol (HDL-C) independently predicts cardiovascular disease.[1-3] Previous genome-wide association studies elucidated genes that may directly influence the level of HDL-C, including the gene for cholesterol ester transfer protein (*CETP*, MIM 118470).[4-10] Specifically, previous Swiss and Korean studies show that *CETP* single nucleotide polymorphisms (SNPs) rs6499861, rs6499863, and rs12708980 are

Conflict of Interest
The authors have no conflicts of interest to declare.

Author Contributions
Conceptualization: Sull JW, Kim S, Jee SH. Data curation: Sull JW. Formal analysis: Sull JW, Jee SH. Funding acquisition: Sull JW. Methodology: Sull JW. Supervision: Jee SH. Validation: Kim S, Jee SH. Writing - original draft: Sull JW. Writing - review & editing: Sull JW, Jee SH.

associated with HDL-C level.[9,11] Another recent study reported that SNP rs6499863 was related to type 2 diabetes and HDL-C.[12] Some studies analyzed the association between CETP gene SNP and HDL-C in subjects with other risk factors like obesity.[13,14] Family history of diabetes (FHD) is also related to lipid levels.[15,16] In this study, we hypothesized that *CETP* variants would be linked to HDL-C level in Korean populations. To test this hypothesis, we evaluated the association between HDL-C level and the rs6499861 and rs12708980 *CETP* gene SNPs in Korean men and women. The relation was also analyzed considering obesity and FHD.

MATERIALS AND METHODS

1. Study population

Individuals were selected from Severance Hospital in Seoul, South Korea from 1994 to 2012 (n=4,294).[10,17] Among 4,294 participants, 137 participants with lipid-lowering therapy were eliminated, and other subjects were eliminated due to missing data for rs6499861 SNP. Thus, the final subjects included 4,123 individuals. Among 4,123 subjects, 1,715 subjects were cardiovascular disease (CVD) patients identified by the health insurance reimbursement data from the National Health Insurance Corporation.[17] Other 2408 subjects were the healthy subjects.

Other 2,304 participants were chosen in 2008 from the Bundang-gu area in Gyeonggi Province in Korea.[10] Among them, 27 subjects with lipid-lowering therapy were eliminated, and other individuals were eliminated because of missing data for rs6499861 SNP. Thus, the final subjects involved 2,263 individuals.

The Institutional Review Board of Human Research at Eulji University approved the protocols for this study (IRB No: EURIB2018-74), and written informed consent was acquired from all participants prior to participation.

2. Data collection

Demographic characteristics and cigarette smoking status (current smoker, ex-smoker, or never smoked) were obtained using a structured questionnaire.[17] Body mass index (BMI) was calculated as an individual's weight divided by height squared (kg/m^2). Serum was isolated from samples of peripheral venous blood after 12 hours of fasting, stored at −70°C, and analyzed for metabolic biomarkers using a Hitachi 7600 analyzer (Hitachi, Ltd., Tokyo, Japan).

3. Genotyping assays

CETP rs6499861 and rs12708980 genotypes that our previous study reported were obtained using TaqMan probes.[10,18] For quality control, duplicate genotyping was performed for 1%–2.5% of samples.

4. Statistical analysis

Data were expressed as mean±standard deviation. SNPs were examined for possible effects on HDL-C levels under an additive model in PLINK. Multivariate linear regression models and multiple logistic regression analyses were performed using SAS statistical software, version 9.2 (SAS Institute, Cary, NC, USA). Odds ratios (ORs) were calculated to test the relation between the *CETP* SNP and abnormal HDL-C levels (<40 mg/dL). The joint effect of obesity on the association of *CETP* SNP with HDL-C levels was also tested. All statistical examinations were two-sided, and the statistical significance was decided as $p<0.05$.

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RESULTS

Most individuals were middle-aged (**Table 1**), 13.8% had a positive FHD, and 38.8% of men and 3.2% of women were current smokers (data not shown).

A linear regression model adjusted for age and gender showed that *CETP* rs6499861 and rs12708980 were related to HDL-C level in the Severance dataset but that only rs6499861 was related to HDL-C level in the Bungdang-gu dataset (**Table 2**).

Individuals with the CG/GG genotype of *CETP* rs6499861 were more at risk of having an abnormal HDL-C level than individuals with the CC genotype. This association between genotype and HDL-C was stronger in women compared with men (**Table 3**), in men with a

Table 1. General characteristics of study population

Individuals	Severance	Bundang-gu
No. of patients	4,123	2,263
Men (%)	68.0	54.8
Age (yr)	52.1±10.2	42.8±7.8
Waist circumference (cm)	84.0±9.0	80.0±9.5
BMI (kg/m^2)	24.4±2.9	23.4±3.0
Fasting blood sugar (mg/dL)	97.0±22.7	93.6±16.7
Systolic blood pressure (mmHg)	121.9±14.6	117.8±14.2
Diastolic blood pressure (mmHg)	78.4±10.8	76.7±11.9
HDL-C (mg/dL)	50.9±11.6	52.1±12.7
LDL-C (mg/dL)	117.1±31.7	118.1±30.6
Triglycerides (mg/dL)	143.6±97.1	124.3±81.7
Smoking status		
Ex-smoker	1,075 (27.9)	490 (21.7)
Current smoker	1,056 (27.4)	528 (23.3)
HDL-C		
Normal (≥40 mg/dL)	3,445 (83.6)	1,919 (84.8)
Abnormal (<40 mg/dL)	678 (16.4)	344 (15.2)
FHD		
Negative	3,527 (85.5)	1,970 (87.1)
Positive	596 (14.5)	293 (13.2)

Values are expressed as mean±standard deviation or number (%) not otherwise specified.
BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FHD, family history of diabetes.

Table 2. Association between *CETP* SNPs and HDL-C level adjusted for age and gender

SNP	Position	Severance			Bungdang-gu*		
		MAF	β (mg/dL)	*p*	MAF	β (mg/dL)	*p*
rs6499861	55548996	0.096	−2.044	7.23×10^{-7}	0.096	−1.568	8.91×10^{-3}
rs12708980	55569880	0.096	−2.465	1.54×10^{-9}	0.103	−0.839	0.143

CETP, cholesterol ester transfer protein; SNP, single nucleotide polymorphism; HDL-C, high-density lipoprotein cholesterol; MAF, minor allele frequency.
*Bundang-gu data were previously reported in Sull et al. (2012).[10]

Table 3. Age-adjusted ORs of low HDL-C* in the association with the genotypes of *CETP* SNP rs6499861 in the merged dataset (Severance and Bundang-gu, n=6 386)

Individuals	Genotype	Normal (≥40 mg/dL) No. (%)	Abnormal (<40 mg/dL)		
			No. (%)	OR (95% CI)	*p*
All	CC	4,425 (82.5)	781 (76.4)	1.00 (reference)	
	CG/GG	939 (17.5)	241 (23.6)	1.45 (1.22–1.71)	<0.0001
Men	CC	2,632 (82.3)	659 (77.6)	1.00 (reference)	
	CG/GG	565 (17.7)	190 (22.4)	1.33 (1.10–1.61)	0.0029
Women	CC	1,793 (82.7)	122 (70.5)	1.00 (reference)	
	CG/GG	374 (17.3)	51 (29.5)	1.99 (1.39–2.85)	0.0002

OR, odds ratio; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; CETP, cholesterol ester transfer protein; SNP, single nucleotide polymorphism.
*Adjusted for age, gender, and BMI.

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Table 4. Age-adjusted ORs of low HDL-C in the association with the genotypes of *CETP* SNP rs6499861 stratified by gender, BMI, and FHD in the merged dataset (Bundang-gu and Severance, n=6,386)

Individual	Genotype	Normal (≥40 mg/dL) No. (%)	Abnormal (<40 mg/dL)		
			No. (%)	OR (95% CI)	*p*
Men					
BMI<23.55	CC	952 (81.2)	131 (76.2)	1.00 (reference)	
	CG/GG	220 (18.8)	41 (23.8)	1.34 (0.92–1.97)	0.1246
23.55<BMI≤25.69	CC	864 (82.7)	242 (80.9)	1.00 (reference)	
	CG/GG	181 (17.3)	57 (19.1)	1.12 (0.81–1.56)	0.4936
BMI≥25.69	CC	816 (83.4)	282 (76.4)	1.00 (reference)	
	CG/GG	162 (16.6)	87 (23.6)	1.55 (1.15–2.07)	0.0037
Negative FHD	CC	2,286 (82.4)	562 (78.4)	1.00 (reference)	
	CG/GG	490 (17.6)	155 (21.6)	1.29 (1.05–1.58)	0.0153
Positive FHD	CC	346 (82.2)	97 (73.5)	1.00 (reference)	
	CG/GG	75 (17.8)	35 (26.5)	1.66 (1.05–2.64)	0.0301
Women					
BMI<21.34	CC	637 (84.2)	17 (85.0)	1.00 (reference)	
	CG/GG	120 (15.8)	3 (15.0)	0.98 (0.28–3.42)	0.9752
21.34<BMI≤23.82	CC	585 (81.5)	37 (60.7)	1.00 (reference)	
	CG/GG	133 (18.5)	24 (39.3)	2.89 (1.66–5.02)	0.0002
BMI≥23.82	CC	571 (82.5)	63 (75.0)	1.00 (reference)	
	CG/GG	121 (17.5)	21 (25.0)	1.59 (0.93–2.70)	0.0903
Negative FHD	CC	1,535 (82.9)	112 (73.2)	1.00 (reference)	
	CG/GG	316 (17.1)	41 (26.8)	1.78 (1.22–2.61)	0.0030
Positive FHD	CC	258 (81.7)	10 (50.0)	1.00 (reference)	
	CG/GG	58 (18.3)	10 (50.0)	4.82 (1.86–12.5)	0.0012

OR, odds ratio; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; CETP, cholesterol ester transfer protein; SNP, single nucleotide polymorphism; BMI, body mass index; FHD, family history of diabetes.

Table 5. Age-adjusted ORs for HDL-C depending on *CETP* rs6499861 genotype and BMI in men in the merged dataset (n=4,046)

Individuals	Number by genotype	OR (95% CI)		
		CC	CG/GG	*p* for interaction
BMI (kg/m^2)				
<25.69	2,203/508	1.00 (reference)	1.19 (0.93–1.52)	0.1781
≥25.69	1,088/247	1.69 (1.41–2.01)	2.61 (1.97–3.47)	

OR, odds ratio; HDL-C, high-density lipoprotein cholesterol; CETP, cholesterol ester transfer protein; BMI, body mass index.

BMI ≥25.69 kg/m^2 compared with those with a BMI <25.69 kg/m^2 (**Table 4**), and in women with a positive FHD compared with those with a negative FHD (**Table 4**). Individuals with the CG/GG genotype and a BMI ≥25.69 kg/m^2 were more at risk of having an abnormal HDL-C level than those with the CC genotype or a BMI <25.69 kg/m^2 although the interaction effect was not significant (**Table 5**).

DISCUSSION

In this study of 6,386 Korean individuals, we found that *CETP* rs6499861 and rs12708980 were associated with a lower HDL-C level and that rs6499861 was more strongly associated with HDL-C level in women than in men. In several previous studies, a *CETP* SNP was associated with HDL-C in women but not in men, and *CETP* SNPs related to HDL-C were linked to type 2 diabetes in women only.[5,12] However, another study reports associations between *CETP* SNP genotypes and low HDL-C in both women (p<0.0001) and men (p=0.0368).[19]

We also found that *CETP* rs6499861 was associated with a higher HDL-C level in obese individuals. Likewise, a previous study reports that a G mutation at the CETP442 locus

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is related to a higher HDL-C level in obese Chinese individuals.[13] Another study reports a significant interaction between obese vs. lean status and genetic risk score on HDL-C.[14] Although we found a combined effect of BMI and *CETP* SNP genotype on abnormal HDL-C level, the interaction was not statistically significant in the multivariate analysis.

In this study, we also found that *CETP* SNP had a stronger association with HDL-C levels in women subjects with positive FHD than that in women subjects with negative FHD. In a South East Asian study, subjects with a positive FHD had higher HDL-C concentration as compared to subjects with no family history.[16] In a Japanese study, low-density lipoprotein cholesterol (LDL-C)/HDL-C ratio was independently associated with maternal family history of type 2 diabetes.[15] A study found that a high polyunsaturated fatty acid/saturated fatty acid ratio was related to lower insulin sensitivity and the protective effect of PPARG2 Pro12Ala allele was obvious in subjects with family history of type 2 diabetes.[20]

In the present study, the association between the SNPs and HDL-C were inconsistent in the Severance data and Bundang-gu data. One of the possible reasons is that the mean age in the Severance data is much higher than the Bundang-gu data. In this study, CETP gene SNP had stronger relation to HDL-C levels in women than in men. It may be due to the different smoking prevalence between men and women. In our study, 38.8% of men participants and 3.2% of women participants were current smokers like the report of Korean national data.[21]

A limitation of the present study is that we did not categorize type of diabetes. However, type 2 diabetes is more common in Korea, whereas the incidence of type 1 diabetes is very low.[22,23] In conclusion, although the genetic associations of lipid levels in Asian people may not be comparable to those in European people, we found that *CETP* SNPs are associated with serum HDL-C level in Korean individuals and that this relationship is most pronounced in obese men and in women with a FHD.

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