

Oily Fish Consumption Modifies the Association between CD36 rs6969989 Polymorphism and Lipid Profiles in Korean Women.

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ABSTRACT: The aim of this study was to investigate the association of CD36, a class B scavenger receptor, rs6969989 polymorphism with the serum lipid profiles in Korean women, together with their modulation by oily fish consumption. Subjects were participants from the Korean Genome Epidemiology Study (KoGES), which was initiated in 2001 as a large-scale. A total of 4,210 women aged 39 to 70 were included in this study. Data were collected using self-administered questionnaires, anthropometric measurements, and blood chemical analysis. Dietary intake was analyzed using a semi-quantitative food frequency questionnaire. The minor allele frequency for rs6969989 was found in 12% of this population. Homozygotes minor G allele at the rs6868989 exhibited significantly higher high density lipoprotein cholesterol (HDL-C) concentrations (P -trend=0.043) and lower fasting glucose (P -trend=0.013) than major allele A carriers. The risk of low HDL-C was significantly lower in homozygotes for the G allele than the A allele carriers (P -trend=0.032). Gene-diet interaction effects between rs6969989 and oily fish intake were significantly associated with the risk of dyslipidemia (P -interaction=0.004). Subjects with homozygotes minor G allele and high oily fish intake generally had a lower risk of dyslipidemia than did those with major allele homozygotes and low oily fish intake. These findings supported that oily fish consumption may modulate the contributions of CD36 rs6969989 on genetic predisposition to the risk of dyslipidemia.

Keywords: CD36, rs6969989, single nucleotide polymorphism, lipid profile, oily fish consumption

INTRODUCTION

Dyslipidemia is a lipid profile known to increase the risk of coronary heart disease (CHD), including elevated total cholesterol (TC), decreased high density lipoprotein cholesterol (HDL-C), elevated low density lipoprotein cholesterol (LDL-C), and elevated triglycerides (TGs) (1). Epidemiological studies have revealed that each increase of 10 mg/dL in TC was associated with an increase of 5% in total mortality and 9% in cardiovascular mortality (2). Given its asymptomatic nature and slow progression, the prevention strategies of CHD have focused on adequate control of lipid concentrations, and this is recognized as a critical public health goal.

It has been suggested by epidemiological and intervention researches that fish oil consumption can help reduce cardiovascular risk factors (3,4). Oily fish and fish oil are protective against adverse cardiac events due to the n-3 fatty acids (FAs) that are specific to fish lipids (5).

CD36 gene is a class B scavenger receptor related to angiogenesis, atherosclerosis, and lipid metabolism (7). It is expressed on various cell types such as macrophages,

platelets, adipocytes, myocytes, and vascular epithelial cells (8). CD36 functions in the uptake of FAs and oxidized LDL. CD36 null rodents have been reported to exhibit high blood TGs and FAs due to slow lipid clearance (8-10). Also, in humans, CD36 deficient individuals had defective myocardial uptake of long chain FAs (11) and oxidized LDL (12). Although regulation of lipid metabolism in rodents and humans is slightly different, these findings suggest that CD36 absence is related to high plasma lipids and poor metabolic profiles.

Recent single nucleotide polymorphism (SNP) association studies have suggested an association of CD36 variants with lipid profiles as CHD risk factors in various populations. One such a study by Chien et al. (13) has demonstrated that CD36 gene polymorphisms were significantly related to TGs and HDL-C concentrations among ethnic Chinese in Taiwan. The authors reported that individuals with rs3211848 homozygote had higher TG levels and individuals with rs1054516 heterozygous and homozygous genotypes had a significantly lower HDL-C compared with non-carriers. In a Mexican young population, 5 polymorphisms (rs1984112, rs1761667, rs

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2151916, rs3840546, and rs1049673) of the CD36 gene in haplotypes combinations were associated with high LDL-C and TC levels (14). However, in the Korean population, the association of polymorphism of the CD36 gene with lipid profiles has yet to be investigated.

Therefore, the aims of present study were to evaluate the association between CD36 polymorphism and serum lipid profiles in a population-based cohort study composed of Korean adults. Additionally, we examined whether the combined effect of intake of oily fish and CD36 polymorphism modify the risk of dyslipidemia.

SUBJECTS AND METHODS

Subjects

The study subjects were participants in the Anseong and Ansan Cohort Study, which was a part of the Korean Genome and Epidemiology Study (KoGES) in 2001 (15). The population was collected in 2 different communities in South Korea: the Ansan cohort representing an urban community, and the Ansong cohort representing a rural community. The KoGES was performed to investigate the relationship between the genetic and environmental factors associated with major diseases such as diabetes mellitus, hypertension, obesity, and metabolic syndrome in Korean adults aged 39~70 years old. The initial cohort included 10,038 participants, and 8,842 (4,183 men and 4,659 women) data were released in public after performing genotype calling and quality control processes. The present analysis was restricted to women who completed the survey ($n=4,659$). Subjects who had received treatment of dyslipidemia ($n=28$) or who did not respond to related question ($n=265$) were excluded in this study because of the possibility of serum lipid profile changes after medication. Also, the records with extremely low or high energy intake (<500 or $>5,000$ kcal) were excluded ($n=156$). Finally, 4,210 subjects were included for the analysis of this study. This study was approved by the institutional review board of Ewha Womans University (57-5, July 2013), and the procedures followed were in accordance with the Helsinki Declaration of 1975, as revised in 2008.

General characteristics, anthropometric measurements, and biochemical variables

Information on age, gender, smoking status (current smoker or non-current smoker), alcohol intake (g/d), exercise (metabolic equivalent task h/d), and education (less than high school, high school, or greater) was collected using an interview-administered questionnaire.

Body weight, height, and waist circumference were measured using a standardized procedure. Weight in light clothes with no shoes was measured with a metric scale,

and height was measured with a stadiometer. Waist circumference over the unclothed abdomen at a minimal diameter was measured by non-stretchable standard tape. Systolic and diastolic blood pressures were measured with the subjects in a lying position after 5 min of rest.

Blood samples were collected after an overnight fast, and concentrations of TC, HDL-C, TG, haemoglobin A1c (HbA1c), fasting glucose, and fasting insulin were measured using biochemical assays performed by a central laboratory (Seoul Clinical Laboratories, Seoul, Korea). LDL-C levels were calculated by the following equations described by Friedewald for subjects with TG concentrations <400 mg/dL (16):

$$\text{LDL-C} = \text{TC} - \left(\text{HDL-C} + \frac{\text{TGs}}{5} \right)$$

Definition of lipid abnormalities

According to the criteria of the Korean Society of Lipidology and Atherosclerosis (17), lipid abnormalities are defined as follow: TC levels over 230 mg/dL in the blood test results were defined as high TC, HDL-C levels under 40 mg/dL were defined as low HDL-C, LDL-C levels over 150 mg/dL were defined as high LDL-C, and TG levels over 200 mg/dL were defined as high TG.

Dietary measurements

Dietary intake was estimated using a semi-quantitative food frequency questionnaire that had been developed and validated for the KoGES (18,19). It consisted of questions on 103 food items, which were combined into the 23 nutrients used in the Korean food composition table (20), and then calculated to the average daily dietary intake. Oily fish on the questionnaire included mackerel, Spanish mackerel, and saury, which are the most frequently consumed oily fish in Korea. Low oily fish intake was defined as <12.5 g/d (the median level of oily fish intake in this population), whereas high oily fish intake was defined as ≥ 12.5 g/d. Daily fish and nutrient intakes were estimated using a weighted frequency per day and a portion size per unit that was provided by KoGES (18).

Genotyping and SNP selection

Genomic DNA samples were extracted from peripheral blood and genotyped on an Affymetrix Genome-Wide Human SNP array 5.0 (Affymetrix, Inc., Santa Clara, CA, USA). Bayesian robust linear modeling using the Mahalanobis distance genotyping algorithm was used for genotype calling. The genotype calling and quality-control processes were described in a previous study (21). The minor allele frequency (MAF) of CD36 rs6969989 polymorphism was greater than 5%, and the genotype distribution of rs6969989 was in Hardy-Weinberg equilibrium (HWE) ($P=0.22$).

Statistical analysis

The CD36 rs6969989 polymorphism was in HWE ($P > 0.05$) according to the chi-squared test. Data was expressed as the mean \pm standard deviation (SD) for continuous variables and as percentages for categorical variables. We used a linear regression model and the Cochran-Mantel-Haenszel analysis to test for trend across CD36 genotypes, assuming an additive genetic model. The association between CD36 rs6969989 polymorphism and the risk of lipid abnormalities were examined using logistic regression. Odds ratio (OR) and 95% confidence interval (CI) were calculated. Daily fish consumption were dichotomized (based on less than and equal or greater than median intakes), and the interaction between the rs6969989 and the risk of lipid abnormalities was detected with logistic regression. All statistical analyses were performed using SAS v9.3 (SAS Institute Inc., Cary, NC, USA), and a P -value of 0.05 was considered to be statistically significant.

RESULTS

Subjects' characteristics sorted by CD36 rs6969989 genotypes are listed in Table 1. Homozygous minor G allele

subjects had a significantly higher levels of HDL-C (P -trend=0.043) and lower levels of fasting glucose (P -trend=0.013) than those with homozygous major A allele. There were no significant differences in age, height, weight, waist, BMI, blood pressure, smoke status, alcohol intake, exercise, education level, TC, LDL-C, TG, Hba1c, and fasting insulin among the three groups. Also, the intake of daily nutrients, such as energy, carbohydrate, fat, and protein showed no differences according to genotypes of CD36 rs6969989. The MAF of CD36 rs6969989 was 0.12 in all of the participants, and the genotype distributions did not deviate from HWE ($P > 0.05$).

The prevalence and ORs of dyslipidemia according to the CD36 rs6969989 genotype are shown in Table 2. Among the phenotypes of dyslipidemia, the risk of low HDL-C was significantly lower in homozygotes for the G allele than for the A allele carriers (P -trend=0.032). There was no significant trend association for the risks of dyslipidemia, high TC, high LDL-C, and high TG across rs6969989 genotypes.

As shown in Table 3, the gene-diet interaction effects between CD36 rs6969989 and oily fish intake were significantly associated with the risk of dyslipidemia (P -interaction=0.004). Significant interaction effects between

Table 1. General characteristics of participants by CD36 rs6969989 genotype

	AA (n=1,760)	AG (n=1,952)	GG (n=498)	P -trend
Age (yr)	52.5 \pm 9.0	52.4 \pm 9.0	52.6 \pm 9.0	0.806
Height (cm)	153.7 \pm 5.6	153.9 \pm 5.5	154.1 \pm 5.3	0.503
Weight (kg)	59.0 \pm 8.3	59.1 \pm 8.7	59.0 \pm 8.5	0.732
Waist (cm)	81.5 \pm 9.4	81.5 \pm 9.7	81.7 \pm 10.2	0.981
BMI (kg/m ²)	24.9 \pm 3.2	24.9 \pm 3.3	24.8 \pm 3.4	0.806
Blood pressure (mmHg)				
Systolic	116.8 \pm 19.9	117.3 \pm 19.4	116.6 \pm 19.2	0.589
Diastolic	73.8 \pm 12.4	73.7 \pm 11.9	73.5 \pm 11.7	0.799
Current smokers (%)	3.7	3.6	2.4	0.259
Alcohol intake (g/d)	1.4 \pm 5.7	1.0 \pm 4.0	1.5 \pm 6.7	0.334
Exercise (MET-h/d)	0.8 \pm 1.4	0.8 \pm 1.4	0.9 \pm 1.5	0.593
High school education (%)	32.2	33.1	33.6	0.490
Hba1c (%)	5.8 \pm 0.9	5.8 \pm 1.0	5.8 \pm 0.9	0.992
Fasting glucose (mg/dL)	85.2 \pm 20.4	85.7 \pm 20.7	83.3 \pm 15.4	0.013
Fasting insulin (μ IU/mL)	7.9 \pm 4.6	8.2 \pm 5.3	7.9 \pm 5.6	0.263
TC (mg/dL)	191.4 \pm 35.8	191.7 \pm 35.7	191.8 \pm 35.0	0.979
HDL-C (mg/dL)	45.7 \pm 10.0	45.4 \pm 10.1	46.6 \pm 10.7	0.043
LDL-C (mg/dL)	116.5 \pm 32.4	116.5 \pm 31.6	115.4 \pm 31.8	0.735
TG (mg/dL)	146.0 \pm 81.5	149.1 \pm 93.6	149.0 \pm 88.0	0.540
Dietary intake				
Energy (kcal)	1,822.8 \pm 607.5	1,827.2 \pm 612.1	1,788.3 \pm 588.3	0.358
Carbohydrate (%E)	72.1 \pm 6.8	71.6 \pm 6.8	71.6 \pm 6.8	0.077
Protein (%E)	13.4 \pm 2.4	13.5 \pm 2.5	13.5 \pm 2.3	0.146
Fat (%E)	13.3 \pm 5.3	13.6 \pm 5.3	13.7 \pm 5.3	0.125
CD36 rs6969989 G>A (MAF/HWE)				0.12/0.22

Values are presented as mean \pm SD or percentage.

P -trend obtained in linear regression model and Cochran-Mantel-Haenszel analysis.

BMI, body mass index; MET, metabolic equivalent task; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; MAF, minor allele frequency; HWE, Hardy-Weinberg equilibrium.

Table 2. Association between CD36 rs6969989 genotype and risk of dyslipidemia

	AA (n=1,760)	AG (n=1,952)	GG (n=498)	<i>P</i> -trend
Dyslipidemia				
Prevalence (%)	45.7	47.3	44.6	0.932
OR (95% CI)	1.00	1.07 (0.94~1.21)	0.95 (0.78~1.17)	0.437
High TC				
Prevalence (%)	13.8	13.5	15.7	0.461
OR (95% CI)	1.00	0.98 (0.81~1.18)	1.17 (0.88~1.54)	0.459
Low HDL-C				
Prevalence (%)	27.6	29.8	24.1	0.627
OR (95% CI)	1.00	1.11 (0.97~1.29)	0.84 (0.66~1.05)	0.032
High LDL-C				
Prevalence (%)	14.3	13.9	12.7	0.374
OR (95% CI)	1.00	0.97 (0.80~1.16)	0.87 (0.65~1.17)	0.636
High TG				
Prevalence (%)	16.9	17.5	16.5	0.979
OR (95% CI)	1.00	1.04 (0.88~1.24)	0.97 (0.74~1.26)	0.814

Values are presented as percentage or OR (odds ratio) [95% CI (confidence interval)].

P-trend obtained in Cochran-Mantel-Haenszel analysis and logistic regression analysis.

TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride.

Table 3. Interactions between CD36 rs6969989 genotype and oily fish intake for the risk of dyslipidemia

	AA (n=1,760)	AG (n=1,952)	GG (n=498)	<i>P</i> -interaction
Dyslipidemia				0.004
Low oily fish intake	1.00	1.00 (0.83~1.20)	0.89 (0.67~1.18)	
High oily fish intake	0.73 (0.61~0.88)	0.83 (0.69~1.00)	0.75 (0.56~0.99)	
High TC				0.442
Low oily fish intake	1.00	1.13 (0.87~1.48)	1.39 (0.95~2.05)	
High oily fish intake	1.14 (0.87~1.49)	0.97 (0.73~1.27)	1.11 (0.74~1.66)	
Low HDL-C				0.0001
Low oily fish intake	1.00	0.92 (0.75~1.12)	0.70 (0.51~0.97)	
High oily fish intake	0.63 (0.51~0.78)	0.87 (0.71~1.06)	0.64 (0.46~0.88)	
High LDL-C				0.350
Low oily fish intake	1.00	1.09 (0.83~1.43)	0.90 (0.58~1.40)	
High oily fish intake	1.31 (1.00~1.72)	1.14 (0.87~1.49)	1.11 (0.73~1.67)	
High TG				<0.0001
Low oily fish intake	1.00	0.98 (0.78~1.23)	0.83 (0.58~1.19)	
High oily fish intake	0.57 (0.44~0.73)	0.64 (0.50~0.81)	0.66 (0.45~0.97)	

Values are presented as OR (odds ratio) (95% confidence interval). *P*-trend obtained in logistic regression analysis.

Low oily fish intake, <median (12.5 g/d); high oily fish intake, ≥median (12.5 g/d).

TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride.

rs6969989 and oily fish intake were found with low HDL-C (*P*-interaction=0.0001) and high TG (*P*-interaction<0.0001). The groups with minor allele homozygotes and high oily fish intake had the lowest risk of dyslipidemia compared to the groups with major allele homozygotes and low fish intake.

DISCUSSION

In this study, we demonstrated that the interaction between CD36 rs6969989 polymorphism and oily fish intake in relation to the lipid profiles in Korean women. Homozygotes minor G allele at the rs6868989 had a significantly higher level of HDL-C and a lower level of fas-

ting glucose than those with homozygous major A allele. Dietary intakes of energy, carbohydrate, fat, and protein showed no differences according to genotypes of rs 6969989. Among the phenotypes of dyslipidemia, the risk of low HDL-C was significantly lower in homozygotes for the G allele than for the A allele carriers. Moreover, the gene-diet interaction effects between rs6969989 and oily fish intake showed a strong association with the risks of dyslipidemia, low HDL-C, and high TGs. Subjects with minor allele homozygotes and high oily fish intake (≥12.5 g/d) showed the lowest risk of dyslipidemia compared with those with major allele homozygotes and low oily fish intake (<12.5 g/d). These findings suggest that dietary oily fish intake may modulate the contributions of CD36 polymorphisms on genetic predisposition to risk

of dyslipidemia.

The CD36 rs6969989 polymorphism is the consequence of an A to G transversion in the intron region of NM_001001547. In the present study, the MAF for the rs6969989 in the Korean population was found to be 12%. This MAF is lower than those in other Asian (Japanese: 30.8%, Chinese: 29.8%) and in an African-American (40.8%) populations, which was obtained from HapMap data. Further studies have reported that CD36 deficiency is about 10 times more in Asians and African-Americans (3~6%) than in Caucasians (<0.3%) (22,23). Polymorphisms in CD36 gene are also more prevalent in Asian and African-American populations than in Caucasians, perhaps reflecting the influence of natural selection (24, 25).

Our results show that homozygous minor G allele of rs6868989 subjects had a less risk of low HDL-C, among the phenotypes of dyslipidemia. Previous studies have shown the association of CD36 variants with HDL-C levels in different populations. Love-Gregory et al. (26) reported that the CD36 polymorphisms (rs1358337, rs10499859, and rs109654) might contribute to an increase in HDL-C in African-Americans. On the other hand, Chien et al. (13) demonstrated that subjects carrying the minor allele of rs1054516 had a significantly lower HDL-C compared with non-carriers among ethnic Chinese in Taiwan. Also, in a Mexican population, subjects with CD36 promoter rs2151916 polymorphism were associated with lower concentration of HDL-C than non-carriers (14). Consistent with these results, we showed that the CD36 rs6969989 variant is associated with a low risk of low HDL-C in Korean women.

To support this lipid lowering effect of the CD36 variant, we focused on dietary factors associated with lipid health. Oily fish consumption is known to increase HDL-C levels due to its n-3 FAs content (5). Elevated levels of n-3 polyunsaturated fatty acids (PUFA) would enhance the fluidity of the HDL surface monolayer and thereby improve its ability to uptake cholesterol. An animal study reported that a high n-3 PUFA diet promoted HDL-C levels, partially through increasing the activity of lecithin-cholesterol acyltransferase that is essential for HDL remodeling (27). Human studies also showed a positive association between n-3 PUFA and HDL-C levels (28,29). These results suggest that fish-specific n-3 FAs may improve lipid profiles.

This study analyzed that the interactive effect between oily fish consumption and CD36 rs6969989 to modify the risk of dyslipidemia. We found that carriers of homozygous minor G allele and high oily fish intake (≥ 12.5 g/d) generally had lower risks of dyslipidemia, low HDL-C, and high TGs than did those with major allele homozygotes and low oily fish intake (<12.5 g/d). An intervention study by Madden et al. (30) reported that a daily sup-

plement of 6 g fish oil, during 12 weeks, raised HDL-C in subjects with CD36 rs1761667 (AA, AG, and GG), rs1984112 (AA), rs1527483 (GG), and rs1049673 (CC and GG) genotypes in healthy Caucasian men. Also, fasting TGs decreased in subjects with the GG variant of the 4 SNPs examined. The authors assumed that the modulatory influence of CD36 SNPs, on the effects of fish oil on TG concentration, may be due to changes in CD36 activity that is connected by the link between the CD36 variants and a decline in TG concentration (30). But, fish oil brings about the lipid-lowering effects by n-3 FA via multiple pathways. Therefore, future biochemical studies are needed to clarify the genomic sensitivity of individuals to lipid-lowering properties of fish oil.

This study had some limitations. Because the association between genetic variants and the risk of dyslipidemia was analyzed with a cross-sectional study design, it was not possible to establish a cause-effect relation. Another limitation is that dietary intake was measured by semi-quantitative food frequency questionnaires and may be inaccurate quantifications of real consumption. Despite these limitations, we were able to check into several important confounding variables in CHD, such as alcohol intake, smoking status, exercise, and nutrient intakes (31).

In summary, this study suggested that CD36 rs6969989 is associated with a decreased risk of low HDL-C in Korean women. In particular, the beneficial association of rs6969989 with lipid profiles was observed in subjects with high intakes of oily fish. Although future studies are needed, our findings may lead to a useful approach for reducing the risk of lipid abnormalities through dietary modification on the basis of genetic variants.

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AUTHOR DISCLOSURE STATEMENT

The authors declare no conflict of interest.

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