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RESEARCH ARTICLE

Association of *APOE* genotype with lipid profiles and type 2 diabetes mellitus in a Korean population

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Abstract

Background Type 2 diabetes mellitus (T2DM) is associated with chronic hyperglycemia and lipid metabolism. A previous genome-wide association study revealed the *TOMM40-APOE* region as novel locus for T2DM susceptibility.

Objective This association study was conducted to determine the genetic effects of *APOE* single nucleotide polymorphisms (SNPs) on T2DM susceptibility and lipid profiles in a Korean population.

Methods A total of 6 tagging SNPs, including *rs7412* and *rs429358*, were selected for ε genotype analysis and genotyped in 1436 subjects, consisting of 352 T2DM patients and 1084 unaffected controls.

Results Logistic regression analyses were conducted and there were no significant associations among the *APOE* 6 tagging SNPs, ε genotypes, and haplotypes with T2DM susceptibility. To investigate the association of the *APOE* tagging SNPs with the lipid profiles, a regression analysis was conducted. As a result, *rs7412* was significantly associated with the total cholesterol (TC) and low-density lipoprotein cholesterol (LDL) levels ($P_{corr} = 2.30 \times 10^{-5}$ and 3.39×10^{-13}, respectively) in the unaffected controls. The ε2 allele and ε3 allele were significantly associated with the TC ($P_{corr} = 4.46 \times 10^{-6}$ and 0.02, respectively) and LDL levels ($P_{corr} = 3.54 \times 10^{-14}$ and 0.0006, respectively) in the unaffected controls. Further analysis of only the unaffected controls was conducted. As a result, the *APOE* alleles ε2 and ε3 showed a significant association with the TC and LDL levels ($P < 0.05$).

Conclusion The results of this study may help in understanding *APOE* polymorphisms and ε alleles and lipid profiles, which have been highly linked to T2DM, in a Korean population.

Keywords Single nucleotide polymorphism (SNP) · *Apolipoprotein E* (*APOE*) · T2DM (type 2 diabetes mellitus) · Lipid profiles · Korean population

Introduction

Type 2 diabetes mellitus (T2DM) is a complicated metabolic disorder that is characterized by hyperglycemia, which results from defects in insulin secretion or insulin action (Diagnosis and Classification of Diabetes Mellitus 2009). Insulin resistance affects enzymes that are involved in lipid metabolism, such that dyslipidemia is one of the common characteristics of T2DM patients (Saydah et al. 2004; Vijayaraghavan 2010; Wu and Parhofer 2014). T2DM is known to be linked to interactions between environmental and genetic factors (Ali 2013; Hu 2003). Environmental factors, including a sedentary lifestyle, weight, and diet, play a major role in the cause of diabetes, but theses do not impact everyone in the same way. Several studies have revealed that some individuals are more susceptible to T2DM than others, even when comparing individuals in the same environment

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(Ali 2013; Florez et al. 2003; Poulsen et al. 1999). These results imply that genetic differences can explain the etiology of T2DM among different individuals. Recently, a multi-ethnic genome-wide association study (GWAS) identified that the *TOMM40-APOE* region *rs157582* showed a significant association with T2DM ($P = 2.8 \times 10^{-9}$) (Cook and Morris 2016). Furthermore, several studies have revealed that the *APOE* allele, especially ε4, is an independent risk factor for T2DM and coronary artery disease (Chaudhary et al. 2012; El-Lebedy et al. 2016).

Apolipoprotein E (ApoE) is one of the apolipoproteins that binds to lipids to form lipoproteins that are primarily synthesized in the liver (Baars et al. 2011). ApoE plays a role in the stability and solubility of lipoproteins during circulation and acts as a ligand for plasma lipoprotein receptors; therefore, it plays an important role in plasma lipid metabolism (Rall and Mahley 1992). The apolipoprotein E gene, *APOE*, is polymorphic with three alleles, ε2, ε3, and ε4, that are composed of two single nucleotide polymorphisms (SNPs), *rs429358* and *rs7412,* and 6 *APOE* ε genotypes can exist. The *APOE* ε alleles are known to be associated with diseases, such as ischemic stroke, Alzheimer's disease, and coronary artery disease (Afroze et al. 2016; Liu et al. 2014; Zhao et al. 2017). Additionally, the *APOE* ε alleles are known to be related to several lipid profiles. ε2 carriers have been associated with lower total cholesterol (TC) and low-density lipoprotein cholesterol (LDL) levels compared to ε3 or ε4 carriers (Horejsi and Ceska 2000; Jeenduang et al. 2015; Larifla et al. 2017), and ε4 carriers have been associated with higher levels of TC, LDL, and triglycerides (TG) (Alvim et al. 2010; Guang-da et al. 2004; Jeenduang et al. 2015; Kalina et al. 2002). Elevated levels of TC, TG, and LDL and a lower high-density lipoprotein cholesterol (HDL) level are known to be linked to T2DM (Ozder 2014; Raj et al. 2015).

The aim of this Korean population study was to investigate the genetic effects of *APOE* 6 tagging SNPs, including *rs7412* and *rs429358*, for ε allele and genotype analysis for T2DM susceptibility and their effects on lipid profiles, including TC, HDL, LDL, and TG, which have been highly linked to T2DM.

Materials and methods

Study subjects

A total of 1436 subjects (352 T2DM cases and 1084 unaffected controls) were received from Korea BioBank, the Center for Genome Science, the National Institute of Health and Korea Center for Disease Control and Prevention. This study was approved by the Public Institutional Bioethics Committee as designated by the Ministry of Health and Welfare (2015-0504-001). Details about the number of samples and gender ratio are shown in Table 1.

SNP genotyping

The candidate *APOE* SNPs were filtered to remove those sites with minor allele frequency (MAF) < 5% in Han Chinese from Beijing, Southern Han Chinese, and Japanese from Tokyo panels from the 1000 Genomes Project. Two SNPs (*rs7412* and *rs429358*) for *APOE* ε alleles were included. There was no genotyping error though *rs7412* and *rs429358* have deviated from HWE in the control group ($P < 0.05$) so that we included these SNPs in further analysis. The final six SNPs in *APOE* were selected based on high linkage disequilibrium (LD) between SNPs of interest ($r^2 > 0.98$). All loci were genotyped by the Fluidigm high-throughput platform and Fluidigm EP1 SNP Genotyping 192.24 Dynamic Array (Fluidigm Corp., South San Francisco, CA). The discrete genotype data were analyzed with the BioMark SNP Genotyping analysis software (version 4.3.2).

Statistical analysis

LD was obtained using Haploview v4.2 software downloaded from the Broad Institute (http://www.broadinstitute.org/mpg/haploview), with examination of Lewontin's D' ($|D'|$) and the LD coefficient r^2 between all pairs of

Table 1 Characteristics of study subjects

Characteristics	T2DM	Control	*P**
Number of Samples	352	1084	–
Gender ratio (male:female)	1.48: 1	1.53: 1	–
Age (mean ± SD)	59.81 ± 7.78	54.93 ± 9.52	–
TC[a] [mean ± SD (mg/mL)]	2.26 ± 0.09	2.29 ± 0.08	**< 0.0001**
HDL [mean ± SD (mg/mL)]	48.81 ± 11.94	52.27 ± 12.26	**< 0.0001**
TG[a] [mean ± SD (mg/mL)]	2.09 ± 0.26	2.04 ± 0.25	**< 0.01**
LDL [mean ± SD (mg/mL)]	107.10 ± 31.49	119.60 ± 31.27	**< 0.0001**
BMI [mean ± SD (mg/mL)]	24.41 ± 2.89	23.90 ± 2.68	**< 0.01**

T2DM, Type 2 Diabetes mellitus; SD, Standard deviation; TC, Total cholesterol; HDL, High-density lipoprotein cholesterol; TG, Triglyceride; LDL, Low-density lipoprotein cholesterol; BMI, Body Mass Index

**P*-value of t-test analysis

[a]log 10 transformed

bi-allelic loci (Barrett et al. 2005). Haplotypes were estimated using PHASE software (Stephens et al. 2001). Because total cholesterol (TC) and triglycerides (TG) levels had a skewed distribution, log10 transformation was applied. T-test was used to compare lipid profile means between T2DM patients and unaffected controls by using SAS, version 9.4 (SAS Inc., Cary, NC, USA). Logistic regression models were used to compare genotype distributions, including minor allele frequency (MAF) and Hardy–Weinberg equilibrium (HWE), among T2DM patients and unaffected controls, and to calculate odds ratios (ORs), 95% confidence intervals, and corresponding *P*-values adjusted for age (continuous value), sex (male = 0, female = 1) and body mass index (BMI) (continuous value) as covariates using Helixtree (Golden Helix Inc., Bozeman, MT, USA). In corrections for multiple comparisons, Bonferroni correction for multiple testing was applied. Regression model was used to compare *APOE* genetic polymorphisms or ε alleles with average values of lipid profiles among T2DM patients and unaffected controls, corresponding *P*-value adjusted for age, sex and BMI as covariates using SAS, version 9.4 (SAS Inc., Cary, NC, USA). One-way analysis of variance (ANOVA) and post hoc Scheffe test were used to compare TC and LDL mean levels according to *APOE* ε genotype or ε allele using SAS, version 9.4 (SAS Inc., Cary, NC, USA). To see the effect of each ε allele, all personnel were doubled and divided by ε alleles.

Results

Characteristics of the study subjects and *APOE* polymorphisms

A total of 1436 subjects, consisting of 352 type 2 diabetes mellitus (T2DM) patients and 1084 unaffected controls, were included in this study. A comparison of the mean values and standard deviations for several lipid profiles between the T2DM patients and unaffected controls is shown in Table 1. The T2DM patients showed higher mean values for the triglycerides (TG) and body mass index (BMI) ($P < 0.01$) and lower mean values for the total cholesterol (TC), high-density lipoprotein cholesterol (HDL), and low-density lipoprotein cholesterol (LDL) than the controls ($P < 0.0001$). The study subjects were divided according to their *APOE* ε genotype. Most of the study subjects exhibited the ε3/ε3 genotype (67% of the T2DM patients and 74.3% of the controls). Detailed information for the gender ratio, age, and mean values for several of the lipid profiles is shown in Table 1. The haplotypes and linkage disequilibrium (LD) for the *APOE* polymorphisms are shown in Supplementary Fig. 1.

Association analysis for the *APOE* 6 tagging SNPs, ε alleles (genotype) and haplotypes with the risk of T2DM

A logistic regression analysis under an additive model was conducted to investigate the association among the *APOE* polymorphisms, ε alleles (genotype), and haplotypes with T2DM susceptibility in a Korean population. For the case of the ε allele, all personnel were doubled. As a result, the *APOE* polymorphisms, ε alleles (genotype), and haplotypes were not significantly associated with the risk of T2DM (Table 2). Each SNPs position, alleles, heterozygosity, HWE *P*-values and minor allele frequencies, odds ratios (ORs) and *P*-values are shown in Table 2.

Association analysis for the *APOE* polymorphisms and ε alleles with several lipid profiles

To investigate the association between the *APOE* 6 tagging SNPs with the lipid profiles, a regression analysis under an additive model was conducted. As a result, *rs7412* was significantly associated with the TC level in the unaffected controls ($P = 2.56 \times 10^{-6}$) even after correcting for multiple test ($P_{corr} = 2.30 \times 10^{-5}$). Additionally, *rs7412* was significantly associated with the LDL level in the unaffected controls ($P_{corr} = 3.39 \times 10^{-13}$). *rs429358* was significantly associated with the TG level in the T2DM patients ($P_{corr} = 0.03$). According to the number of each ε allele, we divided into three groups, and a regression analysis under an additive model was conducted. The ε2 allele and ε3 allele were significantly associated with the TC ($P_{corr} = 4.46 \times 10^{-6}$ and 0.02, respectively) and LDL levels ($P_{corr} = 3.54 \times 10^{-14}$ and 0.0006, respectively) in the unaffected controls. The ε4 allele showed a significant association with the TG level in the T2DM patients ($P_{corr} = 0.05$) (Table 3). Especially, the controls who were *rs7412* homozygotes for the common allele, heterozygotes and homozygotes for the rare allele had the highest (122.3 ± 30.6 mg/dL), intermediate (101.0 ± 29.4 mg/dL), and lowest (90.4 ± 25.4 mg/dL) LDL levels, respectively. The controls who were −/− had the highest TC and LDL levels (199.2 ± 22.8 mg/dL and 122.2 ± 15.8 mg/dL, respectively); they were followed by the controls who were −/ε2 with intermediate TC and LDL levels (181.5 ± 33.6 mg/dL and 100.9 ± 29.5 mg/dL, respectively) and those who were ε2/ε2 with the lowest TC and LDL levels (178.3 ± 34.6 mg/dL and 84.5 ± 30.6 mg/dL, respectively). The controls who were−/−, −/ε3, and ε3/ε3 had the lowest (109.8 ± 28.9 mg/dL), intermediate (114.1 ± 33.3 mg/dL), and highest (121.8 ± 30.5 mg/dL) LDL levels, respectively.

Table 2 Association analysis of *APOE* genetic polymorphisms, ε alleles (genotype) and haplotypes with risk of T2DM in a Korean population

SNP	Chr:position	Position	Alleles	Heterozygosity	HWE *P*			MAF		OR (95% CI)	*P**
					Total (n = 1436)	Case (n = 352)	Control (n = 1084)	Case (n = 352)	Control (n = 1084)		
rs7259620	19:44904531	Promoter	G>A	0.401	0.068	0.145	0.199	0.268	0.281	1.00 (0.82–1.23)	0.98
rs405509	19:44905579	Promoter	A>C	0.403	0.032	0.072	0.148	0.276	0.281	1.04 (0.85–1.28)	0.69
rs440446	19:44905910	Intron	C>G	0.466	0.144	0.503	0.193	0.365	0.371	1.02 (0.85–1.23)	0.83
rs769450	19:44907187	Intron	G>A	0.318	0.221	0.089	0.643	0.192	0.200	1.00 (0.80–1.25)	0.99
rs429358	19:44908684	Missense	T>C	0.165	0.007	0.539	0.001	0.092	0.090	0.99 (0.73–1.33)	0.93
rs7412	19:44908822	Missense	C>T	0.120	0.001	0.629	0.0001	0.065	0.064	1.11 (0.78–1.57)	0.57
APOE ε											
ε2 (ε2/ε2, ε2/ε3)	–	–	ε2	0.270	–	–	–	–	–	–	0.67
ε3 (ε3/ε3)	–	–	ε3		–	–	–	–	–	–	
ε4 (ε3/ε4, ε4/ε4)	–	–	ε4		–	–	–	–	–	–	
ε2 < others[a]	–	–	ε2	–	–	–	–	0.062	0.064	-	0.37
ε3 < others[a]	–	–	ε3	–	–	–	–	0.849	0.844	-	0.55
ε4 < others[a]	–	–	ε4	–	–	–	–	0.089	0.092	-	0.98
ε genotype (ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4, ε4/ε4)					–	–	–	–	–	–	0.56
Haplotype											
Haplotype 1 (G-A-C-G-T-C)					–	–	–	0.396	0.400	1.04 (0.86–1.24)	0.71
Haplotype 2 (A-C-G-A-T-C)					–	–	–	0.185	0.184	1.06 (0.84–1.33)	0.62
Haplotype 3 (G-A-G-G-C-C)					–	–	–	0.095	0.089	1.02 (0.76–1.37)	0.88
Haplotype 4 (A-C-G-G-T-T)					–	–	–	0.068	0.061	1.21 (0.85–1.71)	0.30

T2DM, type 2 diabetes mellitus; SNP, single nucleotide polymorphism; HWE *P,* Hardy–Weinberg equilibrium p-value; MAF, minor allele frequency; OR, odds ratio; CI, confidence interval

**P*-value of logistic regression analysis under additive model by adjusting for sex, age and body mass index as covariates

[a]All personnel were doubled and divided by ε alleles to see the effect of each ε allele

Table 3 Association analysis of *APOE* genetic polymorphisms and ε alleles with level of lipid profiles (mg/dL)

Lipid profiles	SNP/ε allele	Control					T2DM				
		CC (mean ± SD)	CR (mean ± SD)	RR (mean ± SD)	*P**	P_{corr}**	CC (mean ± SD)	CR (mean ± SD)	RR (mean ± SD)	*P**	P_{corr}**
TC[a]	*rs7259620*	552 (198.7 ± 34.5)	455 (196.3 ± 35.3)	77 (192.2 ± 34.7)	0.13	ns	183 (185.4 ± 35.1)	149 (183.6 ± 38.8)	20 (184.6 ± 39.7)	0.31	ns
	rs405509	550 (198.4 ± 34.5)	457 (197.0 ± 35.2)	76 (189.8 ± 34.9)	0.10	ns	178 (184.4 ± 36.0)	154 (184.6 ± 37.9)	20 (186.4 ± 38.0)	0.71	ns
	rs440446	418 (197.8 ± 34.5)	525 (197.4 ± 35)	139 (194.9 ± 35.2)	0.34	ns	139 (185.8 ± 33.6)	169 (182.5 ± 38.3)	44 (188.8 ± 41.2)	0.73	ns
	rs769450	691 (195.5 ± 34.9)	352 (201.4 ± 34.4)	41 (190.5 ± 35.6)	0.19	ns	225 (182.5 ± 35.8)	119 (188.9 ± 38.4)	8 (179.1 ± 40.8)	0.92	ns
	rs429358	892 (196.7 ± 35.0)	157 (198.3 ± 34.4)	18 (204.8 ± 33.9)	0.58	ns	284 (184.5 ± 35.5)	60 (185.2 ± 43.9)	2 (189.5 ± 62.9)	0.85	ns
	rs7412	950 (199.3 ± 34.6)	114 (181.8 ± 33.6)	12 (182.8 ± 26.7)	**2.56×10^{-6}**	**2.30×10^{-5}**	305 (185.8 ± 37.1)	41 (177.2 ± 35.2)	2 (165.5 ± 41.7)	0.38	ns
	ε2 < Others	958 (199.2 ± 22.8)	113 (181.5 ± 33.6)	11 (178.3 ± 34.6)	**4.96×10^{-7}**	**4.46×10^{-6}**	309 (185.7 ± 41.7)	41 (177.2 ± 35.2)	2 (165.5 ± 37.0)	0.39	ns
	ε3 > Others	790 (199.2 ± 34.7)	257 (191.6 ± 35.2)	35 (192.6 ± 32.1)	**0.002**	**0.02**	250 (185.3 ± 35.5)	94 (184.5 ± 39.8)	8 (163.3 ± 41.4)	0.61	ns
	ε4 < Others	908 (196.8 ± 33.9)	156 (198.2 ± 34.5)	18 (204.8 ± 35)	0.63	ns	289 (184.5 ± 62.9)	61 (184.8 ± 43.6)	2 (189.5 ± 35.3)	0.93	ns
HDL	*rs7259620*	552 (52.5 ± 12.8)	455 (51.7 ± 11.6)	77 (54.0 ± 12.3)	1.00	ns	183 (48.7 ± 12.1)	149 (49.0 ± 11.9)	20 (48.6 ± 11.1)	0.85	ns
	rs405509	550 (52.5 ± 12.9)	457 (52.1 ± 11.5)	76 (51.9 ± 11.9)	0.41	ns	178 (48.8 ± 12.3)	154 (48.9 ± 11.8)	20 (48.3 ± 11.0)	0.93	ns
	rs440446	418 (52.9 ± 13.1)	525 (51.9 ± 11.6)	139 (51.5 ± 11.5)	0.07	ns	139 (50.5 ± 11.4)	169 (47.3 ± 12.4)	44 (49.2 ± 11.4)	0.13	ns
	rs769450	691 (52.2 ± 12.8)	352 (52.5 ± 11.3)	41 (50.8 ± 11.1)	0.93	ns	225 (48.8 ± 11.7)	119 (48.6 ± 12.2)	8 (51.9 ± 14.3)	0.99	ns
	rs429358	892 (52.6 ± 12.4)	157 (50.5 ± 11.9)	18 (50.6 ± 8.6)	**0.02**	ns	284 (49.4 ± 11.5)	60 (46.3 ± 12.9)	2 (46.5 ± 17.7)	0.06	ns
	rs7412	950 (52.1 ± 12.2)	114 (53.3 ± 12.3)	12 (52.8 ± 16.4)	0.63	ns	305 (48.9 ± 12.4)	41 (48.9 ± 9.1)	2 (40.5 ± 2.1)	0.90	ns
	ε2 < Others	958 (52.1 ± 16.5)	113 (53.3 ± 12.3)	11 (54.1 ± 12.2)	0.47	ns	309 (48.9 ± 2.1)	41 (48.9 ± 9.1)	2 (40.5 ± 12.3)	0.91	ns
	ε3 > Others	790 (52.4 ± 12.3)	257 (52.1 ± 12.3)	35 (50.5 ± 11.5)	0.18	ns	250 (185.3 ± 35.5)	94 (184.5 ± 39.8)	8 (163.3 ± 41.4)	0.11	ns
	ε4 < Others	908 (52.6 ± 8.6)	156 (50.6 ± 11.9)	18 (50.6 ± 12.4)	**0.02**	ns	289 (49.4 ± 17.7)	61 (46.3 ± 12.8)	2 (46.5 ± 11.7)	0.06	ns
TG[a]	*rs7259620*	552 (128.9 ± 87.6)	455 (137.0 ± 106.5)	77 (128.0 ± 97.1)	0.51	ns	183 (150.1 ± 122.2)	149 (151.9 ± 150.5)	20 (142.9 ± 76.5)	0.94	ns
	rs405509	550 (128.9 ± 87.6)	457 (134.3 ± 106.2)	76 (138.9 ± 104.4)	0.36	ns	178 (149.0 ± 122.8)	154 (152.1 ± 149.2)	20 (151.4 ± 74.2)	0.63	ns
	rs440446	418 (130.2 ± 89.9)	525 (132.8 ± 104.0)	139 (137.0 ± 95.0)	0.43	ns	139 (129.1 ± 80.5)	169 (162.0 ± 126.4)	44 (173.8 ± 240.7)	**0.01**	ns
	rs769450	691 (134.8 ± 104.9)	352 (128.0 ± 83.8)	41 (124.9 ± 75.3)	0.21	ns	225 (146.2 ± 114.8)	119 (161.0 ± 164.1)	8 (114.4 ± 60.6)	0.72	ns
	rs429358	892 (132.4 ± 100.1)	157 (129.5 ± 86.5)	18 (145.8 ± 88.8)	0.49	ns	284 (140.4 ± 93.4)	60 (200.2 ± 243.6)	2 (154.0 ± 17.0)	**0.003**	**0.03**
	rs7412	950 (129.8 ± 86.7)	114 (146.5 ± 155.3)	12 (212.3 ± 167.8)	**0.01**	ns	305 (152.6 ± 139.5)	41 (133.4 ± 76.6)	2 (210.0 ± 82.0)	0.85	ns
	ε2 < Others	958 (129.5 ± 175.9)	113 (145.6 ± 155.8)	11 (214.0 ± 86.5)	**0.02**	ns	309 (152.4 ± 82.0)	41 (133.4 ± 76.6)	2 (210.0 ± 138.6)	0.84	ns
	ε3 > Others	790 (129.6 ± 86.5)	257 (134.3 ± 122.1)	35 (170.9 ± 122.1)	**0.05**	ns	250 (140.4 ± 95.1)	94 (177.9 ± 202.3)	8 (142.5 ± 62.1)	**0.04**	ns
	ε4 < Others	908 (132.4 ± 88.8)	156 (128.6 ± 86.2)	18 (145.8 ± 99.6)	0.61	ns	289 (140.4 ± 17.0)	61 (198.0 ± 242.2)	2 (154.0 ± 93.0)	**0.005**	**0.05**

Table 3 (continued)

Lipid profiles	SNP/ε allele	Control					T2DM				
		CC (mean ± SD)	CR (mean ± SD)	RR (mean ± SD)	*P**	P_{corr}**	CC (mean ± SD)	CR (mean ± SD)	RR (mean ± SD)	*P**	P_{corr}**
LDL	*rs7259620*	552 (121.5 ± 29.8)	455 (118.4 ± 32.5)	77 (113.5 ± 33.3)	**0.03**	ns	183 (108.2 ± 30.6)	149 (105.7 ± 32)	20 (107.5 ± 36.9)	0.66	ns
	rs405509	550 (121.1 ± 29.8)	457 (119.2 ± 32.5)	76 (111.4 ± 33.3)	**0.04**	ns	178 (107.3 ± 31.4)	154 (106.8 ± 31.1)	20 (107.8 ± 36.6)	0.98	ns
	rs440446	418 (119.8 ± 29.5)	525 (120.2 ± 32.2)	139 (117.0 ± 33.1)	0.54	ns	139 (110.3 ± 29.2)	169 (104.6 ± 32.7)	44 (106.7 ± 33.8)	0.28	ns
	rs769450	691 (117.5 ± 30.9)	352 (124.3 ± 31.3)	41 (115.2 ± 33.2)	**0.02**	ns	225 (105.8 ± 31.3)	119 (109.8 ± 31.5)	8 (104.4 ± 38.6)	0.45	ns
	rs429358	892 (118.7 ± 31.2)	157 (123.2 ± 32.0)	18 (126.0 ± 25.6)	0.08	ns	284 (108.1 ± 31.2)	60 (102.2 ± 33.6)	2 (112.2 ± 48.6)	0.28	ns
	rs7412	950 (122.3 ± 30.6)	114 (101.0 ± 29.4)	12 (90.4 ± 25.4)	$\mathbf{3.77 \times 10^{-14}}$	$\mathbf{3.39 \times 10^{-13}}$	305 (107.9 ± 31.4)	41 (102.1 ± 31.4)	2 (83.0 ± 23.2)	0.21	ns
	ε2 < Others	958 (122.2 ± 15.8)	113 (100.9 ± 29.5)	11 (84.5 ± 30.6)	$\mathbf{3.93 \times 10^{-15}}$	$\mathbf{3.54 \times 10^{-14}}$	309 (107.9 ± 23.2)	41 (102.1 ± 31.4)	2 (83.0 ± 31.5)	0.22	ns
	ε3 > Others	790 (121.8 ± 30.5)	257 (114.1 ± 33.3)	35 (109.8 ± 28.9)	$\mathbf{7.18 \times 10^{-5}}$	**0.0006**	250 (108.7 ± 31.2)	94 (104.5 ± 31.3)	8 (86.4 ± 35.9)	0.08	ns
	ε4 < Others	908 (118.8 ± 25.6)	156 (123.2 ± 32.1)	18 (126.0 ± 31.2)	0.09	ns	289 (108.1 ± 48.6)	61 (102.3 ± 33.4)	2 (112.2 ± 31.0)	0.26	ns

Significant associations are shown in bold face ($P < 0.05$)

CC, CR, and RR represent homozygotes for the common allele and heterozygotes and homozygotes for the rare allele, respectively. (In case of ε alleles, ε2(CC): ε3/ε3, ε4/ε4, ε3/ε4, ε2(CR): ε2/ε3, ε2/ε4, ε2(RR): ε2/ε2, ε3(CC): ε3/ε3, ε3(CR): ε2/ε3, ε3/ε4, ε3(RR): ε2/ε2, ε4/ε4, ε2/ε4, ε4(CC): ε2/ε2, ε3/ε3, ε2/ε3, ε4(CR): ε2/ε4, ε3/ε4, ε4(RR): ε4/ε4)

SNP, single nucleotide polymorphism; SD, standard deviation; T2DM, type 2 diabetes mellitus; TC, Total cholesterol; HDL, High-density lipoprotein cholesterol; TG, Triglyceride; LDL, Low-density lipoprotein cholesterol; ns, not significant

**P*-value of regression analysis under additive model by adjusting for sex, age and body mass index as covariates

***P*-value after Bonferroni correction for multiple testing

[a]log10 transformed

Referent, co-dominant, dominant, and recessive regression analysis of the *APOE* ε allele with the TC and LDL for the control group

The lipid level of T2DM patients can be affected by their medicine intake. Therefore, we conducted further analyses only with the unaffected control samples. Based on the additive (co-dominant) analysis results shown in Table 3, the TC and LDL were selected. As a result, the −/ε2 genotype showed a significant association with the TC level, compared to the −/− genotype ($P = 5.38 \times 10^{-7}$). Among the three alternative analysis models, the ε2 allele showed significance in the co-dominant and dominant models ($P = 4.46 \times 10^{-6}$ and 1.56×10^{-7}, respectively). The ε3 allele showed a significant association with the TC in the co-dominant and dominant models ($P = 0.002$ and 0.0008, respectively). For the LDL level, the −/ε2 and ε2/ε2 genotypes showed significant associations ($P = 3.02 \times 10^{-13}$ and 9.27×10^{-5}, respectively) compared to the −/− genotype. The ε2 allele was significantly associated with the LDL level in all three of the alternative analysis models ($P = 3.93 \times 10^{-15}$, 9.72×10^{-15}, and 0.0004), and the ε3/ε3 genotype was significantly associated with the LDL level compared to the −/− genotype. The ε3 also showed a significant association in the co-dominant and dominant models ($P = 7.18 \times 10^{-5}$ and 7.45×10^{-5}, respectively). The ε4 allele showed no significance for either the TC or LDL level (Table 4).

Figure 1 shows the comparison of the mean TC and LDL levels according to the *APOE* ε genotype or ε allele. In Fig. 1a, b, there were significant differences in the TC and LDL levels according to the *APOE* ε genotype for the control group ($P = 5.47 \times 10^{-5}$ and 2.04×10^{-12}, respectively). According to the post hoc analysis, based on the Scheffe test, ε2/ε2, ε2/ε3, and ε2/ε4 were in the same group, and ε2/ε4, ε3/ε3, ε3/ε4, and ε4/ε4 were in another group based on the LDL levels. For the TC levels, there were no significant differences among the groups during the post hoc analysis. In Fig. 1c, d, there were significant differences in the TC and LDL levels according to the *APOE* ε allele for the control group ($P = 1.32 \times 10^{-6}$ and 6.66×10^{-16}, respectively). According to the Scheffe test, the ε3 allele and ε4 allele were in the same group for both the TC and LDL levels.

Discussion

T2DM is usually implicated in dyslipidemia, because insulin resistance affects the enzymes that are involved in lipid metabolism (Diagnosis and Classification of Diabetes Mellitus 2009; Saydah et al. 2004; Vijayaraghavan 2010; Wu and Parhofer 2014). In particular, diabetic dyslipidemia is

Table 4 Referent, co-dominant, dominant and recessive regression analysis of *APOE* ε allele with level of TC and LDL (mg/dL) in control group

Lipid profiles	ε allele		Control n (mean ± SD)	Referent analysis *P**	Co-dominant *P**	Dominant *P**	Recessive *P**
TC [a]	ε2	−/−	958 (199.2 ± 22.8)	–	**4.46×10^{-6}**	**1.56×10^{-7}**	0.17
		−/ε2	113 (181.5 ± 33.6)	**5.38×10^{-7}**			
		ε2/ε2	11 (178.3 ± 34.6)	0.1			
	ε3	−/−	35 (192.6 ± 32.1)	–	**0.002**	**0.0008**	0.53
		−/ε3	257 (191.6 ± 35.2)	0.65			
		ε3/ε3	790 (199.2 ± 34.7)	0.32			
	ε4	−/−	908 (196.8 ± 33.9)	–	0.63	0.73	0.54
		−/ε4	156 (198.2 ± 34.5)	0.87			
		ε4/ε4	18 (204.8 ± 35)	0.53			
LDL	ε2	−/−	958 (122.2 ± 15.8)	–	**3.93×10^{-15}**	**9.72×10^{-15}**	**0.0004**
		−/ε2	113 (100.9 ± 29.5)	**3.02×10^{-13}**			
		ε2/ε2	11 (84.5 ± 30.6)	**9.27×10^{-5}**			
	ε3	−/−	35 (109.8 ± 28.9)	–	**7.18×10^{-5}**	**7.45×10^{-5}**	0.07
		−/ε3	257 (114.1 ± 33.3)	0.57			
		ε3/ε3	790 (121.8 ± 30.5)	**0.02**			
	ε4	−/−	908 (118.8 ± 25.6)	–	0.09	0.10	0.42
		−/ε4	156 (123.2 ± 32.1)	0.14			
		ε4/ε4	18 (126.0 ± 31.2)	0.37			

n, number; SD, standard deviation; TC, Total cholesterol; LDL, Low-density lipoprotein cholesterol

Significant associations are shown in bold face ($P < 0.05$)

**P*-value of regression analysis by adjusting for sex, age and body mass index as covariates

[a]log10 transformed

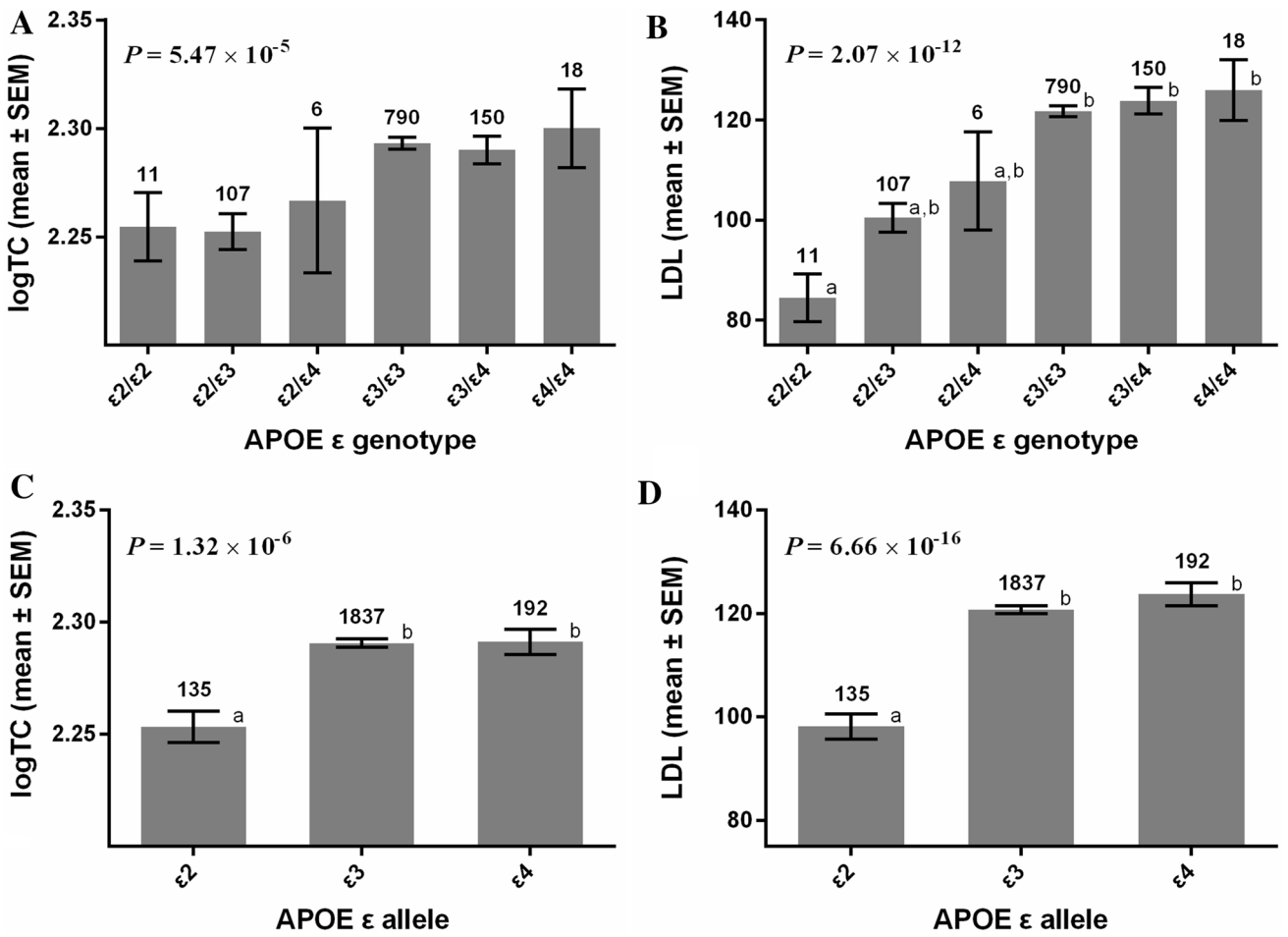

Fig. 1 Comparison of mean TC and LDL levels according to ε genotype/ε allele in control groups. Bar graph of **a** total cholesterol (TC) level (log10 transformed), **b** low-density lipoprotein cholesterol (LDL) level (mg/dL) according to *APOE* ε genotype with standard error of the mean (SEM). In **c** and **d**, All personnel were doubled and divided by ε alleles to see the effect of each ε allele. Bar graph of **c** total cholesterol (TC) level (log10 transformed), **d** low-density lipoprotein cholesterol (LDL) level (mg/dL) according to *APOE* ε allele with SEM. Each *P*-value represent results of one-way analysis of variance (ANOVA). Different lowercase letters refer to significant differences between post hoc analysis based on the Scheffe test ($P < 0.05$)

characterized by decreased HDL and increased TG and LDL levels (Daniel 2011). HDL is the so called "good cholesterol" because it removes excess cholesterol from peripheral tissues. For that reason, decreased HDL can induce increased TG and LDL levels (Haffner 2004; Inzucchi and Amatruda 2003).

A previous multi-ethnic GWAS identified that the *TOMM40-APOE* region is significantly associated with T2DM. Therefore, this association study was conducted using a Korean population to investigate the genetic effects of *APOE* polymorphisms and the ε genotype on T2DM susceptibility and lipid profiles, which has been linked to T2DM. Some studies have revealed that the *APOE* ε4 allele is an independent risk factor for T2DM and coronary artery disease (Chaudhary et al. 2012; El-Lebedy et al. 2016), and the ε2 and ε4 alleles have been associated with T2DM (Alharbi et al. 2014). Although genetic variants on *APOE*, especially ε4 allele is known to be associated with T2DM susceptibility in several populations, we could not find significant association in this study. Previous Korean studies (Kim et al. 1993; Lee et al. 2008) also showed no associations. Similarly, several negative association results have been also reported in Chile, Turkish, Northwest India populations (Duman et al. 2004; Leiva et al. 2005; Singh et al. 2006). Possible origins of inconsistence of genetic effects include small sample size, study heterogeneity, different ethnicity and so on.

ApoE is a plasma lipoprotein that has a significant role in cholesterol transport. The N-terminal of ApoE has an LDL receptor (LDLR) binding domain and a heparan sulfate proteoglycan (HSPG) binding domain, and the C-terminal has a domain for the initial binding of the protein to lipids (Getz and Reardon 2009). Through the LDLR and HSPG pathways, ApoE can be endocytosed and removed from

the plasma by the liver (Phillips 2014). The LDLR binding region, from position 135 to 150, is close to positions 112 and 158, which form an isoform of the *APOE* allele. The substitution Arg158Cys, the ε2 allele, produces a subtle conformational change that influences the binding to the LDLR, such that there is poor clearance of TG-rich lipoproteins from the plasma (Dong et al. 1996; Phillips 2014). The substitution Cys112Arg, the ε4 allele, can also induce a conformational change that can influence the binding of lipid profiles (Dong and Weisgraber 1996; Dong et al. 1994).

As a result of our analysis of the lipid profiles, *rs7412* was associated with the TC and LDL levels in the unaffected controls. The major homozygote of *rs7412* showed the highest TC level in this study, which is consistent with a previous study (Barbosa et al. 2012). The association between the *rs7412* minor allele and a lower LDL level was also consistent with previous studies (Bennet et al. 2010; Radwan et al. 2014; Zhen et al. 2017). In a Chinese study, there was no association between *rs429358* and the blood lipid levels (Zhao et al. 2017). Whereas, our study identified that *rs429358* was associated with the TG level in T2DM patients, although it was not associated with the risk of T2DM. No association was observed between the HDL level and the unaffected controls or T2DM patients.

Likewise, this study revealed that *rs7412* had an association with several lipid profiles in the unaffected controls, and this SNP is known to constitute *APOE* ε alleles. The *APOE* ε3 allele is the most common type of isoform, and the ε2 allele has cysteines at positions 112 and 158. The ε3 allele has a cysteine at position 112 and an arginine at position 158, and the ε4 allele has arginine at both positions 112 and 158 (Frieden 2015; Rall et al. 1982; Weisgraber et al. 1981). Several previous studies divided their samples into 3 groups, such as the ε2 carriers, ε3 carriers, and ε4 carriers, except those that exhibited the ε2/ε4 genotype. However, in this study, to see the effect of each ε allele on the lipid profile levels, we doubled all personnel and divided them into three types, according to the number of alleles in each allele, including the ε2/ε4 genotype. As a result, the TC and LDL levels were associated with the ε2 and ε3 alleles in the unaffected controls.

Table 5 shows the results from previous studies that identified that the ε2 allele is associated with lower TC and LDL levels; these results were consistent with our study (Bennet et al. 2007; Boerwinkle and Utermann 1988; Horejsi and Ceska 2000; Jeenduang et al. 2015; Larifla et al. 2017; Rasmussen 2016; Sing and Davignon 1985). In our study, the ε4 allele showed no association with the lipid profiles, but several previous studies have identified that ε4 carriers are associated with higher TC and LDL levels in healthy populations (Alvim et al. 2010; Guang-da et al. 2004; Jeenduang et al. 2015; Kalina et al. 2002; Larifla et al. 2017; Shin et al. 2005; Sing and Davignon 1985). This study showed different

Table 5 Effect of *APOE* ε genotypes on lipid profiles in previous studies

Study/reference number	Year	Country/race	Effect of *APOE* ε genotypes on lipid profiles	
			ε2	ε4
Jeenduang et al. (2015)	2015	Healthy Southern Thai population/Asians (n = 495)	↓TC ($P = 0.001$ and 0.01 in male and female, respectively) and/or LDL levels ($P < 0.001$ and 0.002 in male and female, respectively)	↑TC ($P = 0.001$ and 0.01 in male and female, respectively) and LDL levels ($P < 0.001$ and 0.002 in male and female, respectively)
Larifla et al. (2017)	2017	Afro-Caribbean population (non-CAD) (n = 492)	↓LDL and ↑TG levels ($P = 0.002$)	↑TC levels ($P = 0.016$)
Guang-da et al. (2004)	2004	Wuhan area/Chinese (T2DM) (n = 133)	–	↑TC and LDL levels (ε4/3 or ε4/4) ($P = 0.026$)
Kalina et al. (2002)	2002	Budapest (T2DM, n = 298/Control, n = 199)	↓TC and LDL levels (Control) ($P < 0.0001$ in elderly, $P < 0.01$ in young control)	↑TG levels (T2DM) ($P < 0.0001$)
Alvim et al. (2010)	2010	Urban population of the Vitória city, Brazil (n = 1493)	↓TC and LDL levels, TC/HDL ratio, LDL/HDL ratio, ↑HDL levels ($P < 0.001$, respectively)	↑TC and LDL levels, TC/HDL ratio, LDL/HDL ratio, ↓ HDL levels ($P < 0.001$, respectively)
Sing and Davignon (1985)	1985	Randomly selected cohort of healthy civil servants (n = 122)	↓TC and LDL levels ($P < 0.05$)	↑TC and LDL levels ($P < 0.05$)
Shin et al. (2005)	2005	Korean population (Namwon) (n = 1900)	↓TC and LDL levels (female) ($P < 0.05$)	↓HDL and ↑TG levels (female) ($P < 0.05$)
Seo et al. (this study)	2021	Korean population (non-T2DM, n = 1084)	↓TC ($P = 4.46 \times 10^{-6}$) and LDL levels ($P = 3.93 \times 10^{-15}$)	–

CAD, coronary artery disease; T2DM, type 2 diabetes mellitus; TC, Total cholesterol; HDL, High-density lipoprotein cholesterol; TG, Triglyceride; LDL, Low-density lipoprotein cholesterol

results for the ε4 allele compared to a previous Korean study. Shin et al. (Shin et al. 2005) showed that the ε4 allele was associated with lower HDL and higher TG levels in a female group that included T2DM patients, but we identified that there was no significant association with the lipid profile level for the ε4 allele in the unaffected controls. The lipid profiles of T2DM patients can be influenced by medicine intake. To elucidate the effect of only the ε allele on the lipid profile, we excluded the T2DM patients, which may be the reason for the different results compared to those from the previous Korean study.

In conclusion, this study was unable to find any association between the *APOE* 6 tagging SNPs and ε genotypes with T2DM susceptibility in the Korean population. However, *rs7412* was significantly associated with the TC and LDL levels in the unaffected controls. Moreover, the *APOE* ε2 and ε3 alleles showed a significant association with the TC and LDL levels in several models. Therefore, the results from this study may help in understanding *APOE* polymorphisms and lipid profiles in a Korean population.

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Compliance with ethical standards

Conflict of interest Jung Yeon Seo, Byeong Ju Youn, Hyun Sub Cheong and Hyoung Doo Shin declare that they have no conflict of interests with respect to the authorship or publication of this article.

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