Association of genetic variants with dyslipidemia

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Abstract. Although genetic variants, which regulate lipid metabolism, have been extensively investigated in Caucasian populations, the genes, which confer susceptibility to dyslipidemia in Japanese individuals, remain to be elucidated. The aim of the present study was to examine a possible association among hypertriglyceridemia, hypo-high density lipoprotein (HDL)-cholesterolemia or hyper-low density lipoprotein (LDL)-cholesterolemia in Japanese individuals with 29 polymorphisms observed to confer susceptibility for coronary heart disease. This was performed through meta-analyses of genome-wide association studies in Caucasian populations. The study population comprised 2,354 individuals with dyslipidemia (hypertriglyceridemia, hypo-HDL-cholesterolemia or hyper-LDL-cholesterolemia) and 3,106 control individuals. To compensate for multiple comparisons of genotypes, a false discovery rate (FDR) of <0.05 was adopted to determine the statistical significance of the associations. Comparisons of allele frequencies using the χ^2 test revealed that rs964184 of zinc finger gene (*ZPR1*; FDR=2.1x10^{-7}), rs4845625 of interleukin 6 receptor (IL6R; FDR=0.032), rs46522 of ubiquitin-conjugating enzyme E2Z gene (UBE2Z; FDR=0.032) and rs17514846 of furin (FDR=0.041) were significantly associated with hypertriglyceridemia. The χ^2 test revealed that rs599839 of proline/serine-rich coiled-coil 1 *(PSRC1;* FDR=0.004) and rs2075650 of translocase of outer mitochondrial membrane 40 homolog *(TOMM40*; FDR=0.004) were significantly associated with hyper-LDL-cholesterolemia. Multivariate logistic regression analysis with adjustment for age, gender and body mass index revealed that rs964184 of *ZPR1* (P=5.1x10^{-7}; odds ratio, 1.37; dominant model), rs4845625 of *IL6R* (P=0.0019, odds ratio, 1.25; dominant model) and rs46522 of *UBE2Z* (P=0.0039, odds ratio, 1.19; dominant model) were significantly associated with hypertriglyceridemia, and that rs599839 of *PSRC1* (P=0.0004, odds ratio, 0.70; dominant model) and rs2075650 of *TOMM40* (P=0.0004, odds ratio, 1.43; dominant model) were significantly associated with hyper-LDL-cholesterolemia. Therefore, *ZPR1*, *IL6R*, and *UBE2Z* may be susceptibility loci for hypertriglyceridemia, whereas *PSRC1* and *TOMM40* may be such loci for hyper-LDL-cholesterolemia in Japanese individuals.

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Introduction

Dyslipidemia is a complex and multifactorial disease caused by an interaction between genetic and environmental factors, the latter including a high-fat and high-calorie diet and physical inactivity. In conjunction with lifestyle and environmental factors, a genetic factor has been revealed to contribute to the development of this metabolic disorder (1,2). Accordingly, recognizing the genetic susceptibility for dyslipidemia has become crucial to promote an improved assessment of disease prediction and allow an earlier preventive strategy to be implicated.

Genetic variants, which regulate lipid metabolism, have been extensively investigated and 157 loci associated with plasma lipid levels have been identified, including 62 loci, which have not been previously reported (3). At present, >400 genes have been postulated as potential candidates for dyslipidemia (4). It was previously identified that rs6929846 (C→T) of the butyrophilin, subfamily 2, member A1 gene (5-7) was a susceptibility locus for dyslipidemia in Japanese individuals. However, the genetic variants, which confer susceptibility to dyslipidemia in Japanese individuals, remain to be elucidated.

Various loci and genes, which confer susceptibility to coronary heart disease (CHD), have been identified in Caucasian

populations by meta-analyses of genome-wide association studies (GWAS) (8,9). Considering that dyslipidemia is a major risk factor for CHD, it was hypothesized that certain polymorphisms may contribute to the genetic susceptibility to CHD through their effects on the susceptibility to dyslipidemia.

The aim of the present study was to examine a possible association of hypertriglyceridemia, hypo-high density lipoprotein (HDL)-cholesterolemia or hyper-low density lipoprotein (LDL)-cholesterolemia in Japanese individuals. This was performed with 29 polymorphisms identified as susceptibility loci for CHD by meta-analyses of GWAS in Caucasian populations (8,9).

Patients and methods

Study population. The study population comprised 5,460 Japanese individuals who either visited outpatient clinics or were admitted to the participating hospitals (Gifu Prefectural General Medical Center, Gifu, Japan; Gifu Prefectural Tajimi Hospital, Tajimi, Japan; Japanese Red Cross Nagoya First Hospital, Nagoya, Japan; Inabe General Hospital, Inabe, Japan; Hirosaki University Hospital and Hirosaki Stroke Center, Hirosaki, Japan) between 2002 and 2012, as a result of various symptoms or for an annual health checkup. Venous blood was collected from the patients in the early morning following fasting overnight. Blood samples were centrifuged at 1,600 x g for 15 min at 4˚C, and the serum was separated and stored at -30˚C prior to analysis. Serum concentrations of triglycerides, HDL-cholesterol and LDL-cholesterol were measured using an automatic biochemical analyzer at a clinical laboratory in each hospital.

Hypertriglyceridemia was defined as a serum concentration of triglycerides of >1.65 mmol/l (150 mg/dl), hypo-HDL-cholesterolemia as a serum concentration of HDL-cholesterol of <1.04 mmol/l (40 mg/dl) and hyper-LDL-cholesterolemia as a serum concentration of LDL-cholesterol of >3.63 mmol/l (140 mg/dl). Individuals with dyslipidemia either exhibited hypertriglyceridemia, hypo-HDL-cholesterolemia or hyper-LDL-cholesterolemia. The corresponding controls exhibited a serum triglyceride level of <1.65 mmol/l, a serum HDL-cholesterol of ≥1.04 mmol/l or a serum LDL-cholesterol of <3.64 mmol/l in investigations of hypertriglyceridemia, hypo-HDL-cholesterolemia or hyper-LDL-cholesterolemia, respectively, and no history of taking antidyslipidemic medications.

The study protocol complied with the Helsinki Declaration of 1975 (as revised in 1983) and was approved by the Ethics Committees of each participating hospital. Written informed consent was obtained from all individuals involved in the present study.

Selection and genotyping of polymorphisms. Single nucleotide polymorphisms (SNPs), which have been revealed to be significantly associated with CHD or myocardial infarction in Caucasian populations in meta-analyses of GWAS data were searched (8,9). The identified SNPs were examined using the SNP database (dbSNP; National Center for Biotechnology Information, Bethesda, MD, USA; http://www.ncbi.nlm.nih.gov/SNP) to identify SNPs with a minor allele frequency of ≥0.015 in a Japanese population. A total of 29 SNPs were selected (data not shown) and the possible association with hypertriglyceridemia, hypo-HDL-cholesterolemia or hyper-LDL-cholesterolemia was investigated. Wild-type (ancestral allele) and variant alleles of the SNPs were determined from the original sources.

Venous blood (7 ml) was collected into tubes, containing 50 mmol/l ethylenediaminetetraacetic acid (disodium salt) and the peripheral blood leukocytes were isolated. The genomic DNA was subsequently extracted from these cells using a DNA extraction kit (Genomix; Talent Srl, Trieste, Italy). The genotypes of the 29 polymorphisms were determined at G&G Science Co., Ltd. (Fukushima, Japan) using a method, which combines polymerase chain reaction and sequence-specific oligonucleotide probes with suspension array technology (Luminex Corporation, Austin, TX, USA). The overall call rate of genotyping of 29 SNPs was 99%. Detailed genotyping methodology was as described previously (10).

Statistical analysis. The χ^2 test was used to compare categorical variables and the Mann-Whitney *U* test was used for the analysis of quantitative data. The allele frequencies of each SNP were compared between the patients with hypertriglyceridemia, hypo-HDL-cholesterolemia or hyper-LDL-cholesterolemia, and the controls, using the χ^2 test. To compensate for multiple comparisons of genotypes, a false discovery rate (FDR) was calculated from the distribution of P-values for the allele frequencies of 29 SNPs, and an FDR of <0.05 was considered to be statistically significant for the association. The statistical power of each SNP was calculated using an Online Sample Size Estimator (http://osse.bii.a-star.edu.sg/index.php). Multivariable logistic regression analysis was performed with hypertriglyceridemia, hypo-HDL-cholesterolemia or hyper-LDL-cholesterolemia as a dependent variable, and independent variables, including age, gender (0, female; 1, male), body mass index (BMI) and the genotype of each SNP. Each SNP was assessed, according to dominant (the combined group of heterozygotes and variant homozygotes versus wild-type homozygotes), recessive (variant homozygotes versus the combined group of wild-type homozygotes and heterozygotes) and two additive [additive 1 (heterozygotes versus wild-type homozygotes) and additive 2 (variant homozygotes versus wild-type homozygotes)] genetic models. Considering that the serum concentrations of triglycerides, HDL-cholesterol, or LDL-cholesterol were not normally distributed (P<0.01, according to the Kolmogorov-Smirnov and Lilliefors test), these parameters were compared among genotypes using the non-parametric Kruskal-Wallis test. Statistical analyses were performed with JMP version 11 and JMP Genomics version 6 software (SAS Institute Inc., Cary, NC, USA).

Results

Characteristics of the patients. The clinical characteristics of patients with hypertriglyceridemia, hypo-HDL-cholesterolemia or hyper-LDL-cholesterolemia, and the corresponding controls are presented in Tables I-III. In the investigation of hypertriglyceridemia, the frequency of males, BMI, the prevalence of smoking, diabetes mellitus, hypertension, the

Table I. Characteristics of patients with hypertriglyceridemia and the corresponding controls.

Characteristic	Hypertriglyceridemia	Controls	P-value
No. of patients	1,612	3,005	
Age (years)	63.6±10.3	64.7±11.2	0.0004
Gender (male/female, %)	69.6/30.4	60.0/40.0	<0.0001
Body mass index (kg/m^2)	24.7±3.5	23.4±3.4	<0.0001
Current or former smoker (%)	31.5	25.8	<0.0001
Diabetes mellitus (%)	47.4	34.4	<0.0001
Hypertension (%)	72.6	61.9	<0.0001
Serum triglycerides (mmol/l)	2.63±1.31	1.03±0.34	<0.0001
Serum HDL-cholesterol (mmol/l)	1.19±0.35	1.40±0.42	<0.0001
Serum LDL-cholesterol (mmol/l)	3.21±1.02	3.09±0.86	<0.0001
Serum creatinine (μmol/l)	92.9±101.7	86.7±103.5	<0.0001
eGFR (ml min^{-1} 1.73 m^{-2})	66.1±25.2	70.1±23.6	<0.0001
Fasting plasma glucose (mmol/l)	7.52±3.75	6.63±3.00	<0.0001

Quantitative data are presented as the mean ± standard deviation. HDL, high density lipoprotein; LDL, low density lipoprotein; eGFR, estimated glomerular filtration rate (ml min^{-1} 1.73 m-2)=194 x [age (years)]$^{-0.287}$ x [serum creatinine (mg/dl)]$^{-1.094}$ x [0.739 if female].

Table II. Characteristics of patients with hypo-HDL-cholesterolemia and the corresponding controls.

Characteristic	Hypo-HDL-cholresterolemia	Controls	P-value
No. of patients	1,100	3,521	
Age (years)	64.1±10.8	64.3±11.0	0.5742
Gender (male/female, %)	81.9/18.1	57.2/42.8	<0.0001
Body mass index (kg/m^2)	24.4±3.5	23.6±3.4	<0.0001
Current or former smoker (%)	37.4	24.2	<0.0001
Diabetes mellitus (%)	47.3	35.4	<0.0001
Hypertension (%)	71.6	63.5	<0.0001
Serum triglycerides (mmol/l)	1.89±1.42	1.49±0.97	<0.0001
Serum HDL-cholesterol (mmol/l)	0.88±0.12	1.46±0.36	<0.0001
Serum LDL-cholesterol (mmol/l)	3.06±0.95	3.15±0.91	<0.0001
Serum creatinine (μmol/l)	99.9±126.5	84.9±94.6	<0.0001
eGFR (ml min^{-1} 1.73 m^{-2})	67.1±28.3	69.2±22.7	0.0008
Fasting plasma glucose (mmol/l)	7.46±3.41	6.77±3.27	<0.0001

Quantitative data are presented as the mean ± standard deviation. HDL, high density lipoprotein; LDL, low density lipoprotein; eGFR, estimated glomerular filtration rate.

serum concentrations of triglycerides, LDL-cholesterol and creatinine, and the fasting plasma glucose level were greater, whereas age, the serum concentrations of HDL-cholesterol and the estimated glomerular filtration rate (eGFR) were lower, in patients with hypertriglyceridemia compared with the controls (Table I). In the study of hypo-HDL-cholesterolemia, the frequency of males, BMI, the prevalence of smoking, diabetes mellitus, hypertension, the serum concentrations of triglycerides and creatinine, and the fasting plasma glucose level were greater, whereas the serum concentrations of LDL-cholesterol, HDL-cholesterol and eGFR were lower, in patients with hypo-HDL-cholesterolemia compared with the controls (Tables II). In the study of hyper-LDL-cholesterolemia, BMI, the serum concentrations of triglycerides and LDL-cholesterol, and the fasting plasma glucose level were greater, whereas age, the frequency of males and the serum concentrations of creatinine were lower, in patients with hyper-LDL-cholesterolemia compared with the controls (Table III).

Association of SNPs with hypertriglyceridemia, hypo-HDL-cholesterolemia or hyper-LDL-cholesterolemia. The allele frequencies were compared between the patients with hypertriglyceridemia, hypo-HDL-cholesterolemia (data not shown) or hyper-LDL-cholesterolemia and the corresponding controls using the χ^2 test, and SNPs with an FDR of <0.05 are demonstrated in Table IV. The analysis revealed that rs964184 of zinc finger protein (*ZPR1*), rs4845625 of interleukin 6 receptor (*IL6R*), rs46522 of the ubiquitin-conjugating

Table III. Characteristics of patients with hyper-LDL-cholesterolemia and the corresponding controls.

Characteristic	Hyper-LDL-cholesterolemia	Controls	P-value
No. of patients	1,174	3,296	
Age (years)	63.7±10.7	64.5±11.0	0.0135
Gender (male/female, %)	57.4/42.6	65.1/34.9	<0.0001
Body mass index (kg/m^2)	24.1±3.5	23.7±3.5	0.0018
Current or former smoker (%)	26.4	28.4	0.1850
Diabetes mellitus (%)	40.0	38.0	0.2087
Hypertension (%)	67.3	64.8	0.1287
Serum triglycerides (mmol/l)	1.55±0.82	1.50±0.91	<0.0001
Serum HDL-cholesterol (mmol/l)	1.31±0.36	1.33±0.41	0.3301
Serum LDL-cholesterol (mmol/l)	4.28±0.68	2.72±0.59	<0.0001
Serum creatinine (μmol/l)	82.3±84.0	92.0±110.6	0.0026
eGFR (ml min^{-1} 1.73 m^{-2})	69.6±23.4	68.2±24.6	0.2490
Fasting plasma glucose (mmol/l)	7.08±3.43	6.81±3.17	0.0036

Quantitative data are presented as the mean ± standard deviation. HDL, high density lipoprotein; LDL, low density lipoprotein; eGFR, estimated glomerular filtration rate.

enzyme E2Z (*UBE2Z*) and rs17514846 of furin (*FURIN*) were significantly associated with hypertriglyceridemia (FDR<0.05). Similar analysis revealed that rs599839 of proline/serine-rich coiled-coil 1 (*PSRC1*) and rs2075650 of translocase of outer mitochondrial membrane 40 homolog (*TOMM40*) were significantly associated with hyper-LDL-cholesterolemia. The statistical power of each SNP was calculated with the sample sizes and minor allele frequencies of cases and controls, and the significance level (α=0.05) was between 50.4 and 98.1%. No SNPs significantly associated with hypo-HDL-cholesterolemia were identified (data not shown). The genotype distributions of six SNPs were in Hardy-Weinberg equilibrium (FDR >0.05) among patients with hypertriglyceridemia or hyper-LDL-cholesterolemia, and the controls.

Multivariable logistic regression analysis with adjustment for age, gender and BMI revealed that rs964184 of *ZPR1* (dominant, recessive, and additive 1 and 2 models), rs4845625 of *IL6R* (dominant and additive 1 and 2 models) and rs46522 of *UBE2Z* (dominant and additive 1 models), however, not rs17514846 of *FURIN*, were significantly associated with hypertriglyceridemia (Table V). A similar analysis revealed that rs599839 of *PSRC1* (dominant and additive 1 models) and rs2075650 of *TOMM40* (dominant and additive 1 and 2 models) were significantly associated with hyper-LDL-cholesterolemia.

Association of SNPs with serum concentrations of triglycerides or LDL-cholesterol. Finally, the association of the genotypes of each SNP with the serum concentrations of triglycerides or LDL-cholesterol were examined using the Kruskal-Wallis test (Table VI). The serum concentrations of triglycerides significantly differed among the genotypes of rs964184 of *ZPR1*, rs485625 of *IL6R* and rs46522 of *UBE2Z*, with the minor G, C and C alleles, respectively, being associated with increased serum triglycerides. The rs17514846 of *FURIN* was also significantly associated with serum concentrations of triglycerides with the minor A allele being associated with reduced serum triglycerides. Serum concentrations of LDL-cholesterol also differed significantly among the genotypes of rs599839 of *PSRC1* and rs2075650 of *TOMM40*. The minor G allele of rs599839 or the G allele of rs2075650 was associated with a reduced or increased concentration of serum LDL-cholesterol, respectively.

Discussion

The association between 29 SNPs and dyslipidemia was examined and it was observed that rs964184 of *ZPR1*, rs485625 of *IL6R* and rs46522 of *UBE2Z* were significantly associated with hypertriglyceridemia and that rs599839 of *PSRC1* and rs2075650 of *TOMM40* were associated with hyper-LDL-cholesterolemia.

The previous GWAS revealed that the G allele of rs964184 of *ZPR1* was significantly associated with increased serum triglycerides and LDL-cholesterol, and with decreased serum HDL-cholesterol in European populations (11-14). The present study replicated the association of rs964184 with hypertriglyceridemia, however, not with hyper-LDL-cholesterolemia or hypo-HDL-cholesterolemia. The rs964184 of *ZPR1* is located in close proximity to the *APOA5-A4-C3-A1* locus, which was revealed to be associated with plasma triglycerides in several previous studies with diverse populations, including Caucasian individuals (15,16), Chinese individuals (17), individuals of Caucasian and African descent in the United States (18), and Middle Eastern populations (19). The expression of *APOA5* is an efficient regulator of plasma triglycerides through its enhancement of the catabolism of triglyceride-rich lipoprotein (20) and prohibiting the transportation of triglycerides (21). The present results supported the findings of the previous investigations (11-19), that the genetic variant of *ZPR1* is important in the development of hypertriglyceridemia.

Consistent with previous GWAS investigating other ethnic groups (22,23), an association between rs4845625 of *IL6R* with hypertriglyceridemia in Japanese individuals was observed.

Table IV. Comparison of allele frequencies of SNPs (FDR<0.05) using the χ^2 test between patients with hypertriglyceridemia or hyper-LDL-cholesterolemia and controls.

A, Hypertriglyceridemia allele frequencies

SNP	Hypertriglyceridemia[a]	Controls[a]	P (allele)	FDR (allele)	Statistical power (%)
rs964184			$7.1x10^{-9}$	$2.1x10^{-7}$	98.1
CC	773 (48.3)	1,659 (55.8)			
CG	672 (42.0)	1,136 (38.2)			
GG	156 (9.7)	178 (6.0)			
G allele frequency	0.31	0.25			
Hardy-Weinberg P	0.5727	0.3699			
rs4845625			0.003	0.032	54.2
TT	379 (23.7)	828 (27.8)			
TC	820 (51.2)	1,475 (49.5)			
CC	402 (25.1)	679 (22.8)			
C allele frequency	0.51	0.48			
Hardy-Weinberg P	0.3255	0.6521			
rs46522			0.001	0.032	57.1
TT	850 (53.1)	1,729 (58.2)			
TC	631 (39.4)	1,043 (35.1)			
CC	119 (7.4)	200 (6.7)			
C allele frequency	0.27	0.24			
Hardy-Weinberg P	0.8988	0.0132			
rs17514846			0.006	0.041	50.4
CC	1,175 (73.8)	2,067 (70.2)			
CA	387 (24.3)	796 (27.0)			
AA	31 (2.0)	82 (2.8)			
A allele frequency	0.14	0.16			
Hardy-Weinberg P	0.8949	0.6110			

B, Hyper-LDL-cholesterolemia allele frequencies

SNP	Hyper-LDL-cholesterolemia[a]	Controls[a]	P (allele)	FDR (allele)	Statistical power (%)
rs599839			0.0003	0.004	77.4
AA	1,023 (88.4)	2,729 (84.1)			
AG	129 (11.2)	487 (15.0)			
GG	5 (0.4)	29 (0.9)			
G allele frequency	0.06	0.08			
Hardy-Weinberg P	0.6674	0.1627			
rs2075650			0.0003	0.004	72.0
AA	763 (65.8)	2,321 (71.2)			
AG	351 (30.3)	848 (26.0)			
GG	46 (4.0)	92 (2.8)			
G allele frequency	0.19	0.16			
Hardy-Weinberg P	0.4813	0.1735			

[a]Numbers in parentheses are percentages. Allele frequencies of each SNP were compared between subjects with (A) hypertriglyceridemia or with (B) hyper-LDL-cholesterolemia and corresponding controls by the χ^2 test and an FDR<0.05 was considered statistically significant. Call rate of genotyping was (A) 99.1% for rs964184, 99.3% for rs4845625, 99.0% for 46522, 98.3% for 17514846, (B) 98.5% for 599839, or 98.9% for rs2075650. LDL, low density lipoprotein; FDR, false discovery rate; SNP, single nucleotide polymorphism.

IL6 binds to its receptor, initiating the intracellular cascade of the inflammatory response. In addition, IL6 has been reported to inhibit lipoprotein lipase activity and stimulate lipolysis, which lead to increased concentrations of serum triglycer-

Table V. Multivariable logistic regression analysis regarding the association of SNP (false discovery rate <0.05) to hypertriglyceridemia or hyper-LDL-cholesterolemia.

	Dominant		Recessive		Additive 1		Additive 2	
SNP	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)
Hypertriglyceridemia								
rs964184 (C→G)	**$5.1x10^{-7}$**	1.37 (1.20-1.56)	**$4.1x10^{-6}$**	1.73 (1.37-2.17)	**$1.3x10^{-4}$**	1.29 (1.14-1.47)	**$7.8x10^{-8}$**	1.92 (1.52-2.44)
rs4845625 (T→C)	**0.0019**	1.25 (1.09-1.45)	0.0604	1.15 (0.99-1.33)	**0.0084**	1.23 (1.05-1.43)	**0.0024**	1.31 (1.10-1.56)
rs46522 (T→C)	**0.0039**	1.19 (1.06-1.37)	0.3199	1.13 (0.88-1.43)	**0.0067**	1.20 (1.05-1.37)	0.1226	1.22 (0.94-1.56)
rs17514846 (C→A)	0.2270	0.91 (0.77-1.06)	0.5499	1.20 (0.63-2.17)	0.1793	0.90 (0.76-1.05)	0.6125	1.18 (0.62-2.13)
Hyper-LDL-cholesterolemia								
rs599839 (A→G)	**0.0004**	0.70 (0.57-0.85)	0.3955	0.66 (0.22-1.64)	**0.0006**	0.70 (0.57-0.86)	0.3425	0.63 (0.21-1.56)
rs2075650 (A→G)	**0.0004**	1.43 (1.12-1.49)	0.0799	1.39 (0.96-2.00)	**0.0016**	1.28 (1.10-1.47)	**0.0360**	1.49 (1.03-2.13)

Multivariable logistic regression analysis was performed with adjustment for age, gender and body mass index. Bold indicates P<0.05. SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval; LDL, low density lipoprotein.

Table VI. Association between genotypes of SNPs and fasting serum concentrations of triglycerides or LDL-cholesterol as determined using the Kruskal-Wallis test.

A, Triglycerides

Genotype of SNP	Serum concentration (mmol/l)	P-value
rs964184 (C→G)		
CC	1.49±1.03	
CG	1.66±1.19[a]	
GG	1.93±1.32[a]	$1.37x10^{-12}$
rs4845625 (T→C)		
TT	1.52±1.02	
TC	1.61±1.18[a]	
CC	1.61±1.10[a]	0.0273
rs46522 (T→C)		
TT	1.53±1.02	
TC	1.68±1.27[a]	
CC	1.61±1.06	0.0025
rs17514846 (C→A)		
CC	1.61±1.16	
CA	1.56±1.08	
AA	1.37±0.77[a]	0.0455

B, LDL-cholesterol

Genotype of SNP	Serum concentration (mmol/l)	P-value
rs599839 (A→G)		
AA	3.15±0.93	
AG	3.01±0.87[a]	
GG	2.93±0.86	0.0042
rs2075650 (A→G)		
AA	3.09±0.90	
AG	3.20±0.97[a]	
GG	3.24±0.87[a]	0.0005

[a]P-value of <0.05 vs. corresponding wild-type homozygotes. SNP, single nucleotide polymorphism; LDL, low density lipoprotein.

ides (24), suggesting that the IL6-IL6R cascades are crucial in the metabolism of triglycerides. Observations from previous studies (22,23,25,26) and the present observations, therefore, demonstrated that rs4845625 of *IL6R* is a susceptibility locus for increased serum triglycerides levels.

The rs46522 of *UBE2Z* was significantly associated with hypertriglyceridemia. *UBE2Z* is located at position q21.32 on chromosome 17 and encodes an enzyme, which ubiquitinates proteins involved in signaling pathways and apoptosis (27). Although the biological mechanism by which rs46522 of *UBE2Z* modifies the serum triglyceride level remains to be elucidated, one possibility is the effect mediated by a

polymorphism of the gastric inhibitory polypeptide gene, which is in linkage disequilibrium with the rs46522 (8) and was observed to affect plasma glucose and serum triglycerides levels (28).

The *FURIN* locus has been reported to be associated with hypertension (29) and formation of atherosclerotic plaques (30), however, not with hypertriglyceridemia. In the present study, logistic regression analysis with adjustment for covariates revealed no significant association between rs17514846 and hypertriglyceridemia. Although serum concentrations of triglycerides differed among genotypes of rs17514846 with a borderline significance, this SNP may not be a significant factor affecting the serum triglyceride levels.

Previous studies have demonstrated that rs599839 of *PSRC1* is significantly associated with serum LDL-cholesterol levels, wherein the minor G allele is associated with decreased serum LDL-cholesterol (31-35). The association of rs599839 with hyper-LDL-cholesterolemia with the G allele and its association with reduced LDL-cholesterol levels in a Japanese population was also assessed. The rs599839 of *PSRC1* is located in the cadherin EGF LAG seven-pass G-type receptor 2 (*CELSR2*)-*PSRC1*-sortilin 1 (*SORT1*) gene cluster in position p13.3 on chromosome 1. The primary role of *CELSR2* or *PSRC1* is contact-mediated cell adhesion (36) or microtubule destabilization (37), respectively, while *SORT1* is important in lipid metabolism (38). SORT1, the higher expression of which is associated with the *G* allele of rs599839, is a multi-ligand transmembrane receptor protein, which binds to a variety of ligands, including LDL-receptor-associated protein (39), lipoprotein lipase (40) and apolipoprotein A-V (41), and enhances the endocytosis and intracellular degradation of LDL-cholesterol. Considering that rs599839 is located in the 3'-untranslated region of *PSCR1,* which is downstream of *SORT1*, the effect of rs599839 on LDL-cholesterol may be mediated by an interaction with *SORT1* (42).

The rs2075650 of *TOMM40* was also associated with serum concentrations of LDL-cholesterol. TOMM40 protein is localized to the mitochondrial outer membrane and is essential for the import and trafficking of proteins into the mitochondria (43). A genetic variant of *TOMM40* was observed to be a risk factor for Alzheimer's disease through the increased deposition of β-amyloid (44). However, the underlying mechanism by which *TOMM40* affects serum LDL-cholesterol levels remains to be elucidated. The rs2075650 is located in close proximity to the apolipoprotein E (*APOE)* locus. The SNPs of *TOMM40* are in strong linkage disequilibrium with the C allele of rs429358 of *APOE*, which increases the plasma LDL-cholesterol levels (45,46). Therefore, the effect of rs2075650 on LDL-cholesterol may be attributable to linkage disequilibrium with the polymorphism of *APOE* (47,48).

In conclusion, the present study indicated that rs964184 of *ZPR1*, rs4845625 of *IL6R* and rs46522 of *UBE2Z* were susceptibility loci for hypertriglyceridemia, and that rs599839 of *PSRC1* and rs2075650 of *TOMM40* were such loci for hyper-LDL-cholesterolemia in Japanese individuals. Further studies are required to confirm the present findings in other ethnic groups and to elucidate the functional relevance of these genes or SNPs to the pathogenesis of dyslipidemia.

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