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Identification of 12 novel loci that confer susceptibility to early-onset dyslipidemia

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Abstract. The circulating concentrations of triglycerides, high density lipoprotein (HDL)-cholesterol, and low density lipoprotein (LDL)-cholesterol have a substantial genetic component, and the heritability of early-onset dyslipidemia might be expected to be higher compared with late-onset forms. In the present study, exome-wide association studies (EWASs) were performed for early-onset hypertriglyceridemia, hypo-HDL-cholesterolemia, and hyper-LDL-cholesterolemia, with the aim to identify genetic variants that confer susceptibility to these conditions in the Japanese population. A total of 8,073 individuals aged ≤ 65 years were enrolled in the study. The EWASs for hypertriglyceridemia (2,664 cases and 5,294 controls), hypo-HDL-cholesterolemia (974 cases and 7,085 controls), and hyper-LDL-cholesterolemia (2,911 cases and 5,111 controls) were performed with Illumina Human Exome-12 v1.2 DNA Analysis BeadChip or Infinium Exome-24 v1.0 BeadChip arrays. The association of allele frequencies for 31,198, 31,133, or 31,175 single nucleotide polymorphisms (SNPs) to hypertriglyceridemia, hypo-HDL-cholesterolemia, or hyper-LDL-cholesterolemia, respectively, was examined with Fisher's exact test. To compensate for multiple comparisons of genotypes with each of the three conditions, Bonferroni's correction was applied

for statistical significance of association. The results demonstrated that 25, 28 and 65 SNPs were significantly associated with hypertriglyceridemia, hypo-HDL-cholesterolemia and hyper-LDL-cholesterolemia, respectively. Multivariable logistic regression analysis with adjustment for age and sex revealed that all 25, 28 and 65 of these SNPs were significantly associated with hypertriglyceridemia, hypo-HDL-cholesterolemia and hyper-LDL-cholesterolemia, respectively. Following examination of the association of the identified SNPs to serum concentrations of triglycerides, HDL-cholesterol, or LDL-cholesterol, linkage disequilibrium of the SNPs, and results of previous genome-wide association studies, we newly identified chromosomal region 19p12 as a susceptibility locus for hypertriglyceridemia, eight loci (*MOB3C-TMOD4*, *LPGAT1*, *EHD3*, *COL6A3*, *ZNF860-CACNA1D*, *COL6A5*, *DCLRE1C*, *ZNF77*) for hypo-HDL-cholesterolemia, and three loci (*KIAA0319-FAM65B*, *UBD*, *LOC105375015*) for hyper-LDL-cholesterolemia. The present study thus identified 12 novel loci that may confer susceptibility to early-onset dyslipidemia. Determination of genotypes for the SNPs at these loci may prove informative for assessment of genetic risk for hypertriglyceridemia, hypo-HDL-cholesterolemia, or hyper-LDL-cholesterolemia in the Japanese population.

Introduction

Dyslipidemia, including hypertriglyceridemia, hypo-high density lipoprotein (HDL)-cholesterolemia and hyper-low density lipoprotein (LDL)-cholesterolemia, has a substantial genetic component (1-3). Familial hypercholesterolemia is an autosomal dominant disorder characterized by pronounced increases in the circulating concentrations of total cholesterol and LDL-cholesterol (1,2). One of the underlying causes of familial hypercholesterolemia is a defect in the LDL receptor that is responsible for the uptake of most circulating LDL-cholesterol by the liver (2,4). In addition to mutations

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of the LDL receptor gene (*LDLR*), familial hypercholesterolemia can be caused by mutations in the apolipoprotein B gene (*APOB*), proprotein convertase subtilisin/kexin type 9 gene (*PCSK9*), cytochrome P450 family 7 subfamily A member 1 gene (*CYP7A1*), and LDL receptor adaptor protein 1 gene (*LDLRAP1*) (2,4). Common forms of dyslipidemia are multifactorial and polygenic disorders, that result from an interaction between genetic background and both lifestyle and environmental factors, such as consumption of high-fat or high-calorie diets and physical inactivity (1,5). The heritability of plasma concentrations of triglycerides, HDL-cholesterol, or LDL-cholesterol was demonstrated to be 33-43, 40-74, and 41-59%, respectively (6-8). Given that dyslipidemia is a key risk factor for coronary artery disease and ischemic stroke (9,10), as well as for colorectal cancer (11,12), personalized prevention is an important public health goal.

Genome-wide association studies (GWASs) and gene-centric meta-analyses have implicated various genes and loci as determinants of blood lipid levels or of predisposition to dyslipidemia in European-ancestry populations (13-17). Genetic variants associated with lipid profiles have been extensively investigated, with one recent study having identified 157 such loci, including 62 variants not previously reported (18). Recent GWASs (19,20) or studies based on whole-exome (21) or whole-genome (22) sequencing in European-ancestry populations have also identified low-frequency or rare variants associated with circulating lipid levels. A more recent exome-wide association study (EWAS) identified 444 independent variants at 250 loci as being significantly associated with plasma levels of total cholesterol, LDL-cholesterol, HDL-cholesterol, or triglycerides (23). An electronic health record-based study reported that genetic risk scores for circulating LDL-cholesterol and triglyceride levels based on 477 single nucleotide polymorphisms (SNPs) were predictive of age at initiation of treatment with lipid-lowering medication (24). Although various SNPs have been demonstrated to be associated with blood lipid profiles in East Asian (25,26) or Japanese (27) populations, genetic variants that contribute to susceptibility to dyslipidemia in Japanese remain to be identified definitively.

Given the substantial genetic component of the circulating concentrations of triglycerides, HDL-cholesterol, and LDL-cholesterol (6-8), the genetic contribution to early-onset forms of hypertriglyceridemia, hypo-HDL-cholesterolemia, and hyper-LDL-cholesterolemia may be greater compared with late-onset forms (2,3). The statistical power of genetic association studies may thus be increased by focusing on subjects with early-onset forms of these disorders.

The present study performed EWASs for early-onset forms of hypertriglyceridemia, hypo-HDL-cholesterolemia, and hyper-LDL-cholesterolemia with the use of human exome array-based genotyping methods. The aim was to identify genetic variants that confer susceptibility to these conditions in the Japanese population.

Materials and methods

Study subjects. In our previous studies, the median age of subjects with hypertriglyceridemia, hypo-HDL-cholesterolemia or hyper-LDL-cholesterolemia was 64, 68 or 62 years,

respectively (28). Therefore, in the present study, early-onset dyslipidemia was defined as that occurring at an age of ≤ 65 years. A total of 8,073 individuals aged ≤ 65 years were examined. Recruited subjects either visited outpatient clinics or were admitted to participating hospitals in Japan (Gifu Prefectural Tajimi Hospital, Tajimi; Gifu Prefectural General Medical Center, Gifu; Japanese Red Cross Nagoya First Hospital, Nagoya; Northern Mie Medical Center Inabe General Hospital, Inabe; Hirosaki University Hospital and Hirosaki Stroke and Rehabilitation Center, Hirosaki) because of various symptoms or for an annual health checkup between 2002 and 2014, or were community-dwelling individuals recruited to a population-based cohort study in Inabe between 2010 and 2014 (29).

Venous blood was collected in the early morning after subjects had fasted overnight. The blood samples were centrifuged at 1,600 x g for 15 min at 4°C, and serum was separated for subsequent analysis. Serum concentrations of triglycerides, HDL-cholesterol, and LDL-cholesterol were measured in the clinical laboratory of each hospital. The 2,664 subjects with hypertriglyceridemia and 5,294 controls had serum triglyceride concentrations of ≥ 1.69 mmol/l (150 mg/dl) and < 1.69 mmol/l, respectively. The 974 subjects with hypo-HDL-cholesterolemia and 7,085 controls had serum HDL-cholesterol concentrations of < 1.03 mmol/l (40 mg/dl) and ≥ 1.03 mmol/l, respectively. The 2,911 subjects with hyper-LDL-cholesterolemia and 5,111 controls had serum LDL-cholesterol concentrations of ≥ 3.62 mmol/l (140 mg/dl) and < 3.62 mmol/l, respectively. The 562 subjects with both hypertriglyceridemia and hypo-HDL-cholesterolemia, and the 4,907 controls, overlapped between the corresponding studies, as did the 1,312 subjects with both hypertriglyceridemia and hyper-LDL-cholesterolemia and 3,723 controls, as well as the 317 subjects with both hypo-HDL-cholesterolemia and hyper-LDL-cholesterolemia and 4,484 controls. Individuals with single-gene disorders, such as familial hypercholesterolemia, or with endocrinologic or metabolic diseases that cause dyslipidemia were excluded from the study. Those taking medications that may cause secondary dyslipidemia were also excluded.

EWAS. Venous blood was collected into tubes containing 50 mmol/l EDTA (disodium salt), peripheral blood leukocytes were isolated, and genomic DNA was extracted from these cells with the use of a kit (Genomix, Talent Srl, Trieste, Italy; or SMITEST EX-R&D, Medical & Biological Laboratories, Co., Ltd., Nagoya, Japan). EWASs for hypertriglyceridemia (2,664 cases and 5,294 controls), hypo-HDL-cholesterolemia (974 cases and 7,085 controls), and hyper-LDL-cholesterolemia (2,911 cases and 5,111 controls) were performed with Human Exome-12 v1.2 DNA Analysis BeadChip or Infinium Exome-24 v1.0 BeadChip arrays (Illumina, San Diego, CA, USA). These exome arrays include putative functional exonic variants selected from $\sim 12,000$ individual exome and whole-genome sequences. The exonic content consists of $\sim 244,000$ SNPs from diverse populations, including European, African, Chinese, and Hispanic individuals (30). SNPs contained in only one of the arrays ($\sim 2.6\%$ of all SNPs) were excluded from analysis. Quality control was performed, as previously described (31). Briefly, genotyping data with a call rate of $< 97\%$ were discarded, with the mean call rate for

Table I. Characteristics of subjects with hypertriglyceridemia and control individuals.

Characteristic	Control	Hypertriglyceridemia	P-value
Number of subjects	5,294	2,664	
Age (years)	51.3±10.2	53.3±8.8	<0.0001
Sex (men/women, %)	50.2/49.8	75.6/24.4	<0.0001
Smoking (%)	35.9	54.0	<0.0001
Obesity (%)	22.9	42.6	<0.0001
Body mass index (kg/m ²)	22.7±3.4	24.8±3.6	<0.0001
Hypertension (%)	35.3	57.2	<0.0001
Systolic BP (mmHg)	125±23	132±23	<0.0001
Diastolic BP (mmHg)	75±14	80±13	<0.0001
Diabetes mellitus (%)	17.5	33.8	<0.0001
Fasting plasma glucose (mmol/l)	5.83±2.04	6.55±2.81	<0.0001
Blood hemoglobin A _{1c} (%)	5.83±1.08	6.26±1.50	<0.0001
Serum triglycerides (mmol/l)	0.94±0.34	2.40±1.37	<0.0001
Serum HDL-cholesterol (mmol/l)	1.66±0.47	1.30±0.36	<0.0001
Serum LDL-cholesterol (mmol/l)	3.06±0.80	3.35±0.95	0.8593
Chronic kidney disease (%)	12.3	19.9	<0.0001
Serum creatinine (μmol/l)	71.9±69.8	82.1±85.2	<0.0001
eGFR (ml min ⁻¹ 1.73 m ⁻²)	78.5±19.4	74.1±21.6	<0.0001
Hyperuricemia (%)	11.7	28.4	<0.0001
Serum uric acid (μmol/l)	308±90	362±91	<0.0001

Quantitative data are presented as mean ± standard deviation and were compared between subjects with hypertriglyceridemia and controls with the unpaired Student's t-test. Categorical data were compared between the two groups with Pearson's Chi-square test. Based on Bonferroni's correction, P<0.0026 (0.05/19) was considered statistically significant. BP, blood pressure; HDL, high density lipoprotein; LDL, low density lipoprotein; eGFR, estimated glomerular filtration rate.

the remaining data being 99.9%. Gender specification was checked for all samples, and those for which gender phenotype in the clinical records was inconsistent with genetic sex were discarded. Duplicated samples and cryptic relatedness were checked by calculation of identity by descent; all pairs with a value of >0.1875 were inspected and one sample from each pair was excluded. Heterozygosity of SNPs was calculated for all samples, and those with extremely low or high heterozygosity (>3 standard deviations from the mean) were discarded. SNPs in sex chromosomes or mitochondrial DNA were excluded from analysis, as were non-polymorphic SNPs or SNPs with a minor allele frequency of <1.0%. SNPs whose genotype distributions deviated significantly (P<0.01) from Hardy-Weinberg equilibrium in control individuals were discarded. Finally, genotype data for each EWAS were examined for population stratification by principal components analysis (32), and population outliers were excluded from further study. A total of 31,198, 31,133, and 31,175 SNPs passed quality control in the EWASs for hypertriglyceridemia, hypo-HDL-cholesterolemia and hyper-LDL-cholesterolemia, respectively, and were subjected to further analyses.

Statistical analysis. For analysis of characteristics of the study subjects, quantitative and categorical data were compared between cases and controls with the unpaired Student's t-test and Pearson's Chi-square test, respectively. Allele frequencies were estimated by the gene counting method, and depar-

ture from Hardy-Weinberg equilibrium was identified with Fisher's exact test. The association of allele frequencies of SNPs to hypertriglyceridemia, hypo-HDL-cholesterolemia or hyper-LDL-cholesterolemia in the EWASs was examined with Fisher's exact test. To compensate for multiple comparisons of allele frequencies with hypertriglyceridemia, hypo-HDL-cholesterolemia, or hyper-LDL-cholesterolemia, Bonferroni's correction was applied for statistical significance of association. Given that 31,198, 31,133 or 31,175 SNPs were analyzed, a P-value of <1.60×10⁻⁶ [0.05/(31,198 or 31,175)] for hypertriglyceridemia and hyper-LDL-cholesterolemia and a P-value of <1.61×10⁻⁶ (0.05/31,133) for hypo-HDL-cholesterolemia was considered statistically significant for association. The inflation factor (λ) was 1.07 for hypertriglyceridemia, 1.05 for hypo-HDL-cholesterolemia, and 1.00 for hyper-LDL-cholesterolemia. Multivariable logistic regression analysis was performed with hypertriglyceridemia, hypo-HDL-cholesterolemia, or hyper-LDL-cholesterolemia as a dependent variable and independent variables including age, sex (0, woman; 1, man), and genotype of each SNP. Genotypes of SNPs were assessed according to dominant [0, AA; 1, AB + BB (A, major allele; B, minor allele)], recessive (0, AA + AB; 1, BB), and additive genetic models, and the P-value, odds ratio, and 95% confidence interval were calculated. Additive models comprised additive 1 (0, AA; 1, AB; 0, BB) and additive 2 (0, AA; 0, AB; 1, BB) scenarios, which were analyzed simultaneously with a single statistical model. Associations

Table II. Characteristics of subjects with hypo-HDL-cholesterolemia and control individuals.

Characteristic	Control	Hypo-HDL-cholesterolemia	P-value
Number of subjects	7,085	974	
Age (years)	51.7±9.9	54.3±8.7	<0.0001
Sex (men/women, %)	55.1/44.9	85.3/14.7	<0.0001
Smoking (%)	40.5	54.6	<0.0001
Obesity (%)	27.0	48.2	<0.0001
Body mass index (kg/m ²)	23.2±3.5	25.1±3.9	<0.0001
Hypertension (%)	39.6	64.8	<0.0001
Systolic BP (mmHg)	126±23	137±27	<0.0001
Diastolic BP (mmHg)	76±14	80±16	<0.0001
Diabetes mellitus (%)	19.5	48.2	<0.0001
Fasting plasma glucose (mmol/l)	5.93±2.16	7.16±3.26	<0.0001
Blood hemoglobin A _{1c} (%)	5.89±1.17	6.59±1.60	<0.0001
Serum triglycerides (mmol/l)	1.35±0.96	2.12±1.62	<0.0001
Serum HDL-cholesterol (mmol/l)	1.63±0.42	0.88±0.12	<0.0001
Serum LDL-cholesterol (mmol/l)	3.16±0.84	3.13±0.99	0.2860
Chronic kidney disease (%)	13.4	26.2	<0.0001
Serum creatinine (μmol/l)	72.6±66.6	96.0±122.7	<0.0001
eGFR (ml min ⁻¹ 1.73 m ⁻²)	77.5±18.5	73.3±29.8	<0.0001
Hyperuricemia (%)	15.9	27.2	<0.0001
Serum uric acid (μmol/l)	323±91	361±0.3	<0.0001

Quantitative data are presented as mean ± standard deviation and were compared between subjects with hypo-HDL-cholesterolemia and controls with the unpaired Student's t-test. Categorical data were compared between the two groups with Pearson's Chi-square test. Based on Bonferroni's correction, $P < 0.0026$ ($0.05/19$) was considered statistically significant. BP, blood pressure; HDL, high density lipoprotein; LDL, low density lipoprotein; eGFR, estimated glomerular filtration rate.

of genotypes of identified SNPs to serum concentrations of triglycerides, HDL-cholesterol, or LDL-cholesterol were examined by one-way analysis of variance. Bonferroni's correction was also applied to other statistical analysis as indicated. Statistical tests were performed with JMP Genomics version 9.0 software (SAS Institute, Cary, NC, USA).

Results

Characteristics of subjects. The characteristics of the 7,958 subjects enrolled in the hypertriglyceridemia study are listed in Table I. Age, the frequency of men, and the prevalence of smoking, obesity, hypertension, diabetes mellitus, chronic kidney disease, and hyperuricemia as well as body mass index (BMI), systolic and diastolic blood pressure (BP), fasting plasma glucose (FPG) level, blood glycosylated hemoglobin (hemoglobin A_{1c}) content, and serum concentrations of creatinine and uric acid were greater, whereas the serum concentration of HDL-cholesterol and estimated glomerular filtration rate (eGFR) were lower, in subjects with hypertriglyceridemia compared with controls.

The characteristics of the 8,059 subjects enrolled in the hypo-HDL-cholesterolemia study are listed in Table II. Age, the frequency of men, and the prevalence of smoking, obesity, hypertension, diabetes mellitus, chronic kidney disease, and hyperuricemia as well as BMI, systolic and diastolic BP, FPG level, blood hemoglobin A_{1c} content, and serum concentrations

of triglycerides, creatinine, and uric acid were greater, whereas eGFR was lower, in subjects with hypo-HDL-cholesterolemia compared with controls.

The characteristics of the 8,022 subjects enrolled in the hyper-LDL-cholesterolemia study are listed in Table III. Age, the prevalence of obesity, BMI, diastolic BP, and serum concentrations of triglycerides and uric acid were greater, whereas systolic BP and serum concentrations of HDL-cholesterol and creatinine were lower, in subjects with hyper-LDL-cholesterolemia compared with controls.

EWASs for hypertriglyceridemia, hypo-HDL-cholesterolemia, and hyper-LDL-cholesterolemia. The association of allele frequencies for 31,198 SNPs that passed quality control to hypertriglyceridemia was examined with the use of Fisher's exact test. Following Bonferroni's correction, 25 SNPs were significantly associated with hypertriglyceridemia ($P < 1.60 \times 10^{-6}$; Table IV). Similar analysis of the association of allele frequencies for 31,133 SNPs to hypo-HDL-cholesterolemia or of those for 31,175 SNPs to hyper-LDL-cholesterolemia revealed that 28 SNPs were significantly associated with hypo-HDL-cholesterolemia ($P < 1.61 \times 10^{-6}$; Table V) and 65 SNPs with hyper-LDL-cholesterolemia ($P < 1.60 \times 10^{-6}$; Table VI).

Multivariable logistic regression analysis of the association of SNPs to hypertriglyceridemia, hypo-HDL-cholesterolemia or hyper-LDL-cholesterolemia. The association of the

Table III. Characteristics of subjects with hyper-LDL-cholesterolemia and control individuals.

Characteristic	Control	Hyper-LDL-cholesterolemia	P-value
Number of subjects	5,111	2,911	
Age (years)	51.3±10.3	53.2±8.9	<0.0001
Sex (men/women, %)	59.0/41.0	58.2/41.8	0.4936
Smoking (%)	40.9	44.3	0.0034
Obesity (%)	27.7	32.6	<0.0001
Body mass index (kg/m ²)	23.2±3.6	23.9±3.5	<0.0001
Hypertension (%)	42.5	42.6	0.8966
Systolic BP (mmHg)	128±25	126±21	0.0025
Diastolic BP (mmHg)	76±14	77±13	0.0004
Diabetes mellitus (%)	23.2	22.0	0.2593
Fasting plasma glucose (mmol/l)	6.11±2.49	6.02±2.12	0.0831
Blood hemoglobin A _{1c} (%)	5.96±1.25	5.99±1.26	0.4573
Serum triglycerides (mmol/l)	1.40±1.19	1.52±0.91	<0.0001
Serum HDL-cholesterol (mmol/l)	1.56±0.49	1.51±0.42	<0.0001
Serum LDL-cholesterol (mmol/l)	2.70±0.56	3.90±0.74	<0.0001
Chronic kidney disease (%)	15.3	14.3	0.2118
Serum creatinine (μmol/l)	78.3±88.7	71.7±58.9	0.0001
eGFR (ml min ⁻¹ 1.73 m ⁻²)	77.0±21.7	76.8±17.8	0.7007
Hyperuricemia (%)	16.3	18.9	0.0028
Serum uric acid (μmol/l)	323±97	334±87	<0.0001

Quantitative data are presented as mean ± standard deviation and were compared between subjects with hyper-LDL-cholesterolemia and controls with the unpaired Student's t-test. Categorical data were compared between the two groups with Pearson's Chi-square test. Based on Bonferroni's correction, $P < 0.0026$ (0.05/19) was considered statistically significant. BP, blood pressure; HDL, high density lipoprotein; LDL, low density lipoprotein; eGFR, estimated glomerular filtration rate.

25 SNPs identified in the EWAS for hypertriglyceridemia to this condition was further examined by multivariable logistic regression analysis, following adjustment for age and sex. All 25 SNPs were significantly [$P < 0.0005$ (0.05/100) in at least one genetic model] associated with hypertriglyceridemia (Table VII). Similar analysis revealed that all 28 SNPs identified in the EWAS for hypo-HDL-cholesterolemia [$P < 0.0004$ (0.05/112); Table VIII] and all 65 SNPs identified in the EWAS for hyper-LDL-cholesterolemia [$P < 0.0002$ (0.05/260); Table IX] were significantly associated with the respective conditions.

Association of identified SNPs to serum concentrations of triglycerides, HDL-cholesterol or LDL-cholesterol. The association of the genotypes of identified SNPs to serum concentrations of triglycerides, HDL-cholesterol, or LDL-cholesterol was examined by one-way analysis of variance. The 25 SNPs identified in the EWAS for hypertriglyceridemia were all significantly associated with serum triglyceride concentration [$P < 0.0020$ (0.05/25); Table X]. Among the 28 SNPs identified in the EWAS for hypo-HDL-cholesterolemia, 27 polymorphisms were significantly associated with the serum HDL-cholesterol level [$P < 0.0018$ (0.05/28)], whereas rs114501427 of *SPOPL* was not related to this parameter (Table XI). Among the 65 SNPs identified in the EWAS for hyper-LDL-cholesterolemia, 37 SNPs were significantly associated with serum LDL-cholesterol

concentration [$P < 0.0008$ (0.05/65); Table XII]. It is possible that the lack of significant correlation between the remaining 28 SNPs and the serum LDL-cholesterol levels may be due to effects of medical treatment.

Linkage disequilibrium analysis. The linkage disequilibrium (LD) was assessed among SNPs associated with hypertriglyceridemia, hypo-HDL-cholesterolemia, or hyper-LDL-cholesterolemia. For the hypertriglyceridemia study, strong LD was apparent among rs1260326 and rs780093 of *GCKR* and rs1260333 at chromosome 2p23 [square of the correlation coefficient (r^2), 0.876–0.983]. An LD plot for the 12 SNPs located at chromosomal region 8p21.3 is illustrated in Fig. 1. Strong LD was observed among rs301, rs326, rs13702, and rs15285 of *LPL*, rs2083637 and rs1441756 (r^2 , 0.942–0.988), as well as among rs328 of *LPL*, rs10096633, rs17482753, rs12678919, rs10503669 and rs7016880 (r^2 , 0.910–0.999). An LD plot for the eight SNPs located at chromosomal region 11q23.3 is illustrated in Fig. 2. Significant LD was apparent among rs10790162 of *BUDI3*, rs7350481, rs9326246, both rs964184 and rs2075290 of *ZPFI*, and rs2266788 of *APOA5* (r^2 , 0.687–0.990).

For the hypo-HDL-cholesterolemia study, significant LD was apparent between rs139537100 of *MOB3C* and rs115287176 of *TMOD4* (r^2 , 0.984); between rs116417209 of *EHD3* and rs114501427 of *SPOPL* (r^2 , 0.703); between rs140232911 of *ZNF860* and rs35874056 of *CACNAID*

Table IV. The 25 SNPs significantly associated with hypertriglyceridemia in the exome-wide association study.

Gene	SNP	Nucleotide substitution ^a	Amino acid substitution	Chromosome	Position	MAF (%)	Allele OR	Allele frequency (P-value)
<i>APOA5</i>	rs2075291	G/T	G185C	11	116790676	7.3	1.89	2.83x10 ⁻²⁴
<i>BUD13</i>	rs10790162	G/A		11	116639104	26.3	1.47	3.58x10 ⁻²⁴
<i>ZPR1</i>	rs964184	C/G		11	116778201	26.3	1.46	8.82x10 ⁻²⁴
<i>APOA5</i>	rs2266788	T/C		11	116789970	26.2	1.47	1.27x10 ⁻²³
	rs7350481	C/T		11	116715567	27.7	1.44	7.94x10 ⁻²³
	rs9326246	G/C		11	116741017	26.5	1.45	1.36x10 ⁻²²
<i>ZPR1</i>	rs2075290	T/C		11	116782580	26.7	1.43	1.58x10 ⁻²¹
	rs12678919	A/G		8	19986711	12.6	0.71	6.07x10 ⁻¹¹
	rs10503669	C/A		8	19990179	12.6	0.71	8.32x10 ⁻¹¹
	rs17482753	G/T		8	19975135	12.6	0.72	2.04x10 ⁻¹⁰
	rs10096633	C/T		8	19973410	12.7	0.72	2.50x10 ⁻¹⁰
<i>LPL</i>	rs328	C/G	S474*	8	19962213	12.9	0.72	2.72x10 ⁻¹⁰
<i>APOA4</i>	rs5104	A/G	N147S	11	116821618	35.7	1.25	2.78x10 ⁻¹⁰
	rs7016880	G/C		8	20019235	12.0	0.72	1.72x10 ⁻⁹
<i>GCKR</i>	rs1260326	T/C	L446P	2	27508073	43.6	0.82	6.27x10 ⁻⁹
<i>GCKR</i>	rs780093	A/G		2	27519736	43.0	0.83	2.18x10 ⁻⁸
	rs1260333	T/C		2	27525757	42.9	0.83	4.38x10 ⁻⁸
	rs11085421	A/C		19	20985948	19.1	0.79	1.59x10 ⁻⁷
	rs1441756	T/G		8	20010875	19.0	0.80	5.61x10 ⁻⁷
	rs2083637	T/C		8	20007664	19.0	0.81	6.24x10 ⁻⁷
<i>LPL</i>	rs301	T/C		8	19959423	19.3	0.81	7.70x10 ⁻⁷
<i>LPL</i>	rs13702	A/G		8	19966981	19.2	0.81	9.15x10 ⁻⁷
<i>LPL</i>	rs15285	G/A		8	19967156	19.2	0.81	1.02x10 ⁻⁶
	rs2954033	G/A		8	125481504	33.3	1.19	1.02x10 ⁻⁶
<i>LPL</i>	rs326	A/G		8	19961928	19.4	0.81	1.24x10 ⁻⁶

Allele frequencies were analyzed with Fisher's exact test. $P < 1.60 \times 10^{-6}$ was considered statistically significant. ^aMajor allele/minor allele. SNP, single nucleotide polymorphism; MAF, minor allele frequency; OR, odds ratio.

(r^2 , 1.00); among rs192210727 of *ADGRL3*, rs188378669 of *CXCL8*, and rs61734696 of *MARCH1* (r^2 , 0.901 to 0.972); between rs199921354 of *VPS33B* and rs141569282 of *OR4F6* (r^2 , 0.994); and between rs247616 and rs3764261 at chromosome 16q13 (r^2 , 0.992). An LD plot for the five SNPs located at chromosomal region 12q24.12 to 12q24.13 is illustrated in Fig. 3. Significant LD was detected among rs3782886 of *BRAP*, rs11066015 of *ACAD10*, rs671 of *ALDH2*, and rs2074356 and rs11066280 of *HECTD4* (r^2 , 0.813-0.995).

For the hyper-LDL-cholesterolemia study, significant LD was apparent among rs147284320 of *PTCH2*, rs139537100 of *MOB3C* and rs115287176 of *TMOD4* (r^2 , 0.828-0.984); among rs192210727 of *ADGRL3*, rs188378669 of *CXCL8*, and rs61734696 of *MARCH1* (r^2 , 0.901-0.972); and between rs200787930 of *PLCB2* and rs199921354 of *VPS33B* (r^2 , 0.994). An LD plot for the 47 SNPs located at chromosomal region 6p22.3 to 6p21.3 is illustrated in Fig. 4. There were two major LD blocks. The first LD block (r^2 , 0.571-1.000) comprised rs7749235, rs2285321, and rs6937357 of *DHX16*; rs9468805, rs6457254, and rs2394392 of *PPP1R18*; rs3130663 at 6p21.3; rs2269702, rs28986465, rs2075015, and rs6924270 of *MDC1*; and rs3132584, rs25527, and rs9500864 of

TUBB. The second LD block (r^2 , 0.762-1.000) comprised rs147733073 of *CCHCR1*; rs2596574 at 6p21.3; rs11538264 of *PRRC2A*; rs9267546, rs17200983, and rs9267547 of *LY6G6F*; rs117894946 of *LY6G6C*; rs11754464 of *MSH5*; rs5030798 and rs11751198 of *VARS*; rs6457452 of *HSPA1B*; rs11968400 of *C6orf48*; rs12210887 at 6p21.3; rs13118 of *NEU1*; rs117127493 of *SLC44A4*; rs492899 of *SKIV2L*; rs140770834 and rs11751545 of *TNXB*; and rs204999 at 6p21.3. Significant LD was also observed between rs4576240 of *KIAA0319* and rs150142878 of *FAM65B* (r^2 , 0.893); among rs34902660 of *SLC17A3*, rs76463649 of *ZSCAN26*, rs6922302 of *ZSCAN31*, rs29243 of *GABBRI*, and rs2523995 of *TRIM40* (r^2 , 0.601-0.995); between rs64036 of *UBD* and rs2524272 at 6p22.1 (r^2 , 0.753); and among rs6933400 and rs11970154 of *DPCR1*, rs2508015 at 6p21.3, and rs147733073 of *CCHCR1* (r^2 , 0.596-0.987).

Relation of SNPs identified in the present study to dyslipidemia-related phenotypes examined in previous GWASs. The relation of genes, chromosomal loci and SNPs identified in the present study was further analyzed against phenotypes previously examined by GWASs available in the

Table V. The 28 SNPs significantly associated with hypo-HDL-cholesterolemia in the exome-wide association study.

Gene	SNP	Nucleotide substitution ^a	Amino acid substitution	Chromosome	Position	MAF (%)	Allele OR	Allele frequency (P-value)
<i>LPGAT1</i>	rs150552771	T/C	K200E	1	211783358	5.0	16.67	1.09x10 ⁻¹²
<i>APOA5</i>	rs2075291	G/T	G185C	11	116790676	7.3	1.79	4.10x10 ⁻¹²
<i>COL6A5</i>	rs200982668	G/A	E2501K	3	130470894	1.3	0.18	4.51x10 ⁻¹¹
<i>ZNF860</i>	rs140232911	C/T	S161L	3	31989561	10.4	4.39	5.21x10 ⁻¹¹
	rs9261800	C/G		6	30408822	2.8	19.65	6.69x10 ⁻¹¹
<i>VPS33B</i>	rs199921354	C/T	R80Q	15	91013841	1.2	0.17	1.03x10 ⁻¹⁰
<i>ADGRL3</i>	rs192210727	G/T	R580I	4	61909615	1.3	0.19	1.33x10 ⁻¹⁰
<i>TMOD4</i>	rs115287176	G/A	R277W	1	151170961	1.2	0.18	1.46x10 ⁻¹⁰
<i>COL6A3</i>	rs146092501	C/T	E1386K	2	237371861	1.2	0.18	2.10x10 ⁻¹⁰
<i>MARCH1</i>	rs61734696	G/T	Q137K	4	164197303	1.2	0.19	2.74x10 ⁻¹⁰
<i>PLCB2</i>	rs200787930	C/T	E1106K	15	40289298	1.2	0.19	2.79x10 ⁻¹⁰
<i>MOB3C</i>	rs139537100	C/T	R24Q	1	46615006	1.2	0.19	2.87x10 ⁻¹⁰
<i>CXCL8</i>	rs188378669	G/T	E31*	4	73741568	1.2	0.19	3.94x10 ⁻¹⁰
<i>EHD3</i>	rs116417209	G/A	V151I	2	31249417	3.5	12.5	5.66x10 ⁻¹⁰
<i>ZNF77</i>	rs146879198	G/A	R340*	19	2934109	1.2	0.20	1.17x10 ⁻⁹
<i>OR4F6</i>	rs141569282	G/A	A117T	15	101806068	1.7	0.23	2.31x10 ⁻⁹
<i>ACAD10</i>	rs11066015	G/A		12	111730205	27.5	1.37	2.61x10 ⁻⁹
<i>CACNA1D</i>	rs35874056	G/A	G460S	3	53702798	2.0	100.00	2.95x10 ⁻⁹
<i>ALDH2</i>	rs671	G/A	E504K	12	111803962	27.6	1.35	4.23x10 ⁻⁹
	rs3764261	G/T		16	56959412	19.8	0.69	7.90x10 ⁻⁹
	rs247616	C/T		16	56955678	19.7	0.69	9.31x10 ⁻⁹
<i>BRAP</i>	rs3782886	A/G		12	111672685	29.3	1.34	1.19x10 ⁻⁸
<i>CETP</i>	rs1532624	G/T		16	56971567	29.6	0.74	2.63x10 ⁻⁸
<i>HECTD4</i>	rs11066280	T/A		12	112379979	29.0	1.33	3.54x10 ⁻⁸
<i>HECTD4</i>	rs2074356	C/T		12	112207597	25.4	1.32	1.43x10 ⁻⁷
<i>LILRB2</i>	rs73055442	C/T	R103H	19	54279838	1.6	34.09	1.80x10 ⁻⁷
<i>DCLRE1C</i>	rs150854849	C/T	R179Q	10	14934704	2.4	59.56	3.16x10 ⁻⁷
<i>SPOPL</i>	rs114501427	G/A	D349N	2	138568946	8.8	3.23	4.01x10 ⁻⁷

Allele frequencies were analyzed with Fisher's exact test. $P < 1.61 \times 10^{-6}$ was considered statistically significant. ^aMajor allele/minor allele. SNP, single nucleotide polymorphism; MAF, minor allele frequency; OR, odds ratio.

Genome-Wide Repository of Associations Between SNPs and Phenotypes (GRASP) Search v.2.0.0.0 (<https://grasp.nihbi.nih.gov/Search.aspx>) developed by the Information Technology and Applications Center, National Center for Biotechnology Information, National Heart, Lung, and Blood Institute, National Institutes of Health (Bethesda, MD, USA) (33,34).

In the hypertriglyceridemia study, *GCKR*, chromosomal region 2p23, *LPL*, region 8p21.3, region 8q24.2, *BUD13*, region 11q23.3, *ZP1*, *APOA5*, and *APOA4* have been previously reported to be associated with circulating triglyceride concentrations, whereas chromosome 19p12 had not been related to triglyceride levels or other dyslipidemia-related traits (Table XIII).

In the study of hypo-HDL-cholesterolemia, *APOA5*, *BRAP*, *ALDH2*, *HECTD4*, chromosome 16q13, *CETP*, and *LILRB2* were previously reported to be associated with circulating HDL-cholesterol levels, whereas *CXCL8*, *ACAD10*,

and *PLCB2* were associated with circulating levels of total cholesterol, LDL-cholesterol, and triglycerides, respectively (Table XIV). *MARCH1*, chromosome 6p22.1, and *VPS33B* were also associated with adiponectin concentrations, type 1 diabetes mellitus, and type 2 diabetes mellitus, respectively. The remaining 13 genes (*MOB3C*, *TMOD4*, *LPGAT1*, *EHD3*, *SPOPL*, *COL6A3*, *ZNF860*, *CACNA1D*, *COL6A5*, *ADGRL3*, *DCLRE1C*, *OR4F6*, *ZNF77*) had not been related to circulating HDL-cholesterol or other dyslipidemia-related phenotypes.

In the study of hyper-LDL-cholesterolemia, *PCSK9*, *APOB*, chromosome 6p21.3, *SKIV2L*, *HECTD4*, *APOE*, and *APOC1* were previously reported to be associated with circulating LDL-cholesterol levels, whereas *CXCL8*, 6p21.3, *CCHCR1*, *PRRC2A*, *LY6G6F*, *MSH5*, *C6orf48*, *SLC44A4*, *TNXB*, and *PLCB2* were associated with circulating concentrations of total cholesterol or triglycerides (Table XV). *MARCH1*, *SLC17A3*, *ZSCAN31*, *GABBR1*, 6p22.1, *TRIM40*, *PPP1R18*, 6p21.3, *MDC1*, *TUBB*, *DPCRI*, *LY6G6C*, *VAR5*, *HSPA1B*, and *VPS33B*

Table VI. The 65 SNPs significantly associated with hyper-LDL-cholesterolemia in the exome-wide association study.

Gene	SNP	Nucleotide substitution ^a	Amino acid substitution	Chromosome	Position	MAF (%)	Allele OR	Allele frequency (P-value)
<i>APOE</i>	rs7412	C/T	R176C	19	44908822	4.3	0.42	6.62x10 ⁻²²
<i>COL6A3</i>	rs146092501	C/T	E1386K	2	237371861	1.2	2.14	1.42x10 ⁻¹¹
<i>TMOD4</i>	rs115287176	G/A	R277W	1	151170961	1.2	2.13	1.83x10 ⁻¹¹
<i>CXCL8</i>	rs188378669	G/T	E31*	4	73741568	1.2	2.10	1.95x10 ⁻¹¹
<i>VPS33B</i>	rs199921354	C/T	R80Q	15	91013841	1.2	2.11	2.32x10 ⁻¹¹
<i>ZNF77</i>	rs146879198	G/A	R340*	19	2934109	1.2	2.08	4.91x10 ⁻¹¹
<i>MOB3C</i>	rs139537100	C/T	R24Q	1	46615006	1.2	2.06	5.58x10 ⁻¹¹
<i>PLCB2</i>	rs200787930	C/T	E1106K	15	40289298	1.2	2.03	1.70x10 ⁻¹⁰
<i>MUC17</i>	rs78010183	A/T	T1305S	7	101035329	1.8	1.81	2.30x10 ⁻¹⁰
<i>MARCH1</i>	rs61734696	G/T	Q137K	4	164197303	1.2	2.01	3.49x10 ⁻¹⁰
<i>APOB</i>	rs13306206	G/A	P955S	2	21019859	3.2	1.75	7.32x10 ⁻¹⁰
<i>COL6A5</i>	rs200982668	G/A	E2501K	3	130470894	1.3	1.92	9.85x10 ⁻¹⁰
<i>PTCH2</i>	rs147284320	C/T	V503I	1	44828589	2.0	1.86	1.23x10 ⁻⁹
<i>ADGRL3</i>	rs192210727	G/T	R580I	4	61909615	1.3	1.94	1.49x10 ⁻⁹
<i>APOC1</i>	rs445925	C/T		19	44912383	6.6	0.66	3.62x10 ⁻⁹
<i>HSPA1B</i>	rs6457452	C/T		6	31827773	9.7	1.33	2.97x10 ⁻⁸
<i>C6orf48</i>	rs11968400	C/T		6	31836952	9.7	1.33	3.96x10 ⁻⁸
	rs12210887	G/T		6	31847946	9.7	1.33	5.26x10 ⁻⁸
<i>UBD</i>	rs64036	C/A		6	29559490	22.5	1.23	7.55x10 ⁻⁸
<i>CCHCR1</i>	rs147733073	C/G	H539Q	6	31145462	10.2	1.32	8.01x10 ⁻⁸
<i>VARS</i>	rs11751198	G/A		6	31785749	9.5	1.33	8.12x10 ⁻⁸
	rs2596574	G/A		6	31366397	9.7	1.32	8.83x10 ⁻⁸
<i>LY6G6F</i>	rs9267547	G/A	A107T	6	31707724	10.0	1.32	9.72x10 ⁻⁸
<i>NEU1</i>	rs13118	T/A		6	31859509	9.7	1.32	1.01x10 ⁻⁷
<i>SLC17A3</i>	rs34902660	C/A	G239V	6	25850874	8.4	1.35	1.04x10 ⁻⁷
<i>FAM65B</i>	rs150142878	C/T	R371Q	6	24847657	5.6	1.42	1.18x10 ⁻⁷
<i>TUBB</i>	rs9500864	G/A		6	30725455	20.4	1.23	1.19x10 ⁻⁷
	rs204999	A/G		6	32142202	9.1	1.33	1.34x10 ⁻⁷
	rs3130663	A/G		6	30698817	10.7	1.28	1.38x10 ⁻⁷
<i>VARS</i>	rs5030798	G/A	V1055I	6	31779733	9.5	1.32	1.43x10 ⁻⁷
<i>LY6G6F</i>	rs9267546	G/A		6	31705659	9.8	1.32	1.44x10 ⁻⁷
<i>PRRC2A</i>	rs11538264	G/A	V1774M	6	31635412	9.5	1.32	1.55x10 ⁻⁷
<i>DPCR1</i>	rs11970154	G/C	G1213R	6	30952101	13.3	1.28	1.60x10 ⁻⁷
<i>MSH5</i>	rs11754464	C/T		6	31755958	9.5	1.32	1.73x10 ⁻⁷
<i>PCSK9</i>	rs151193009	C/T	R93C	1	55043912	1.1	0.42	1.85x10 ⁻⁷
<i>GABBR1</i>	rs29243	C/T		6	29631325	10.6	1.30	1.94x10 ⁻⁷
<i>KIAA0319</i>	rs4576240	G/T	P133T	6	24596250	5.5	1.41	2.10x10 ⁻⁷
<i>LY6G6F</i>	rs17200983	C/A	P34Q	6	31707506	9.5	1.32	2.38x10 ⁻⁷
<i>TNXB</i>	rs140770834	C/G	L2271V	6	32064851	8.8	1.32	2.42x10 ⁻⁷
<i>TNXB</i>	rs11751545	A/C		6	32073266	8.8	1.32	2.42x10 ⁻⁷
<i>DPCR1</i>	rs6933400	C/T		6	30939399	13.2	1.27	2.43x10 ⁻⁷
<i>LY6G6C</i>	rs117894946	G/C	G75A	6	31719250	9.5	1.32	2.66x10 ⁻⁷
<i>SLC44A4</i>	rs117127493	G/C	E344Q	6	31869232	8.9	1.32	3.22x10 ⁻⁷
<i>ZSCAN26</i>	rs76463649	A/G	N15S	6	28271963	9.6	1.30	4.26x10 ⁻⁷
<i>DHX16</i>	rs7749235	T/C		6	30667816	17.8	1.23	4.67x10 ⁻⁷
<i>LOC105-375015</i>	rs9264942	T/C		6	31306603	40.1	1.18	4.82x10 ⁻⁷
<i>ZSCAN31</i>	rs6922302	C/G	P128A	6	28327533	9.6	1.30	5.06x10 ⁻⁷
<i>MDC1</i>	rs2269702	A/G		6	30707358	17.7	1.23	5.13x10 ⁻⁷
<i>MDC1</i>	rs28986465	C/T	P386L	6	30712785	17.7	1.23	5.17x10 ⁻⁷

Table VI. Continued.

Gene	SNP	Nucleotide substitution ^a	Amino acid substitution	Chromosome	Position	MAF (%)	Allele OR	Allele frequency (P-value)
<i>MDC1</i>	rs2075015	G/A	E371K	6	30712831	17.7	1.23	5.17x10 ⁻⁷
<i>DHX16</i>	rs2285321	T/C		6	30670221	17.8	1.23	5.18x10 ⁻⁷
<i>SKIV2L</i>	rs492899	A/G		6	31965741	9.1	1.31	5.33x10 ⁻⁷
<i>MDC1</i>	rs6924270	A/G		6	30714203	17.8	1.23	5.81x10 ⁻⁷
	rs2508015	C/T		6	31042423	11.7	1.27	6.07x10 ⁻⁷
<i>TUBB</i>	rs25527	C/T		6	30723161	21.0	1.22	6.08x10 ⁻⁷
<i>PPP1R18</i>	rs9468805	G/A		6	30675932	17.7	1.23	7.07x10 ⁻⁷
<i>DHX16</i>	rs6937357	T/C		6	30672547	17.8	1.23	7.07x10 ⁻⁷
<i>HECTD4</i>	rs11066280	T/A		12	112379979	29.0	1.19	7.09x10 ⁻⁷
<i>TRIM40</i>	rs2523995	G/A		6	30134407	10.6	1.28	7.88x10 ⁻⁷
<i>PPP1R18</i>	rs6457254	C/T		6	30681357	17.9	1.22	1.20x10 ⁻⁶
<i>TUBB</i>	rs3132584	C/A		6	30720650	21.2	1.20	1.22x10 ⁻⁶
	rs3130685	T/C		6	31238429	41.6	0.85	1.43x10 ⁻⁶
<i>GIT2</i>	rs2292354	C/T		12	109930396	26.2	0.83	1.45x10 ⁻⁶
<i>PPP1R18</i>	rs2394392	T/G		6	30682541	18.0	1.22	1.50x10 ⁻⁶
	rs2524272	T/C		6	29714623	26.8	1.19	1.55x10 ⁻⁶

Allele frequencies were analyzed with Fisher's exact test. $P < 1.60 \times 10^{-6}$ was considered statistically significant. ^aMajor allele/minor allele. SNP, single nucleotide polymorphism; MAF, minor allele frequency; OR, odds ratio.

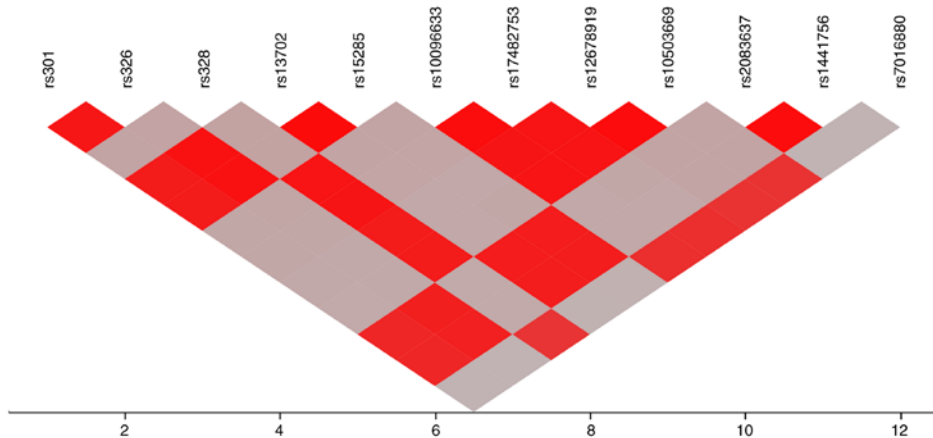


Figure 1. LD map for 12 SNPs at chromosomal region 8p21.3 associated with hypertriglyceridemia. LD was calculated as the square of the correlation coefficient (r^2), with the extent of LD increasing according to the color order of gray to red. LD, linkage disequilibrium; SNP, single nucleotide polymorphism.

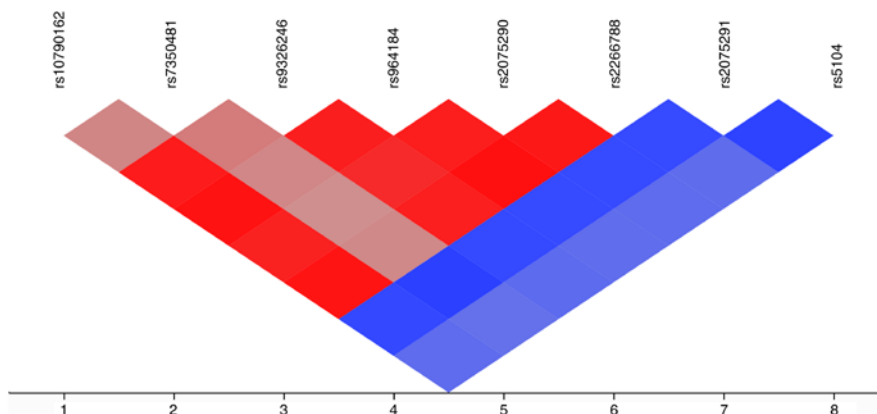


Figure 2. LD map for eight SNPs at chromosomal region 11q23.3 associated with hypertriglyceridemia. LD was calculated as the square of the correlation coefficient (r^2), with the extent of LD increasing according to the color order of blue to gray to red. LD, linkage disequilibrium; SNP, single nucleotide polymorphism.

Table VII. Association of SNPs to hypertriglyceridemia as determined by multivariable logistic regression analysis.

Gene	SNP	Dominant			Recessive			Additive 1			Additive 2		
		P-value	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI
<i>APOA5</i>	rs2075291	<0.0001	1.99	1.74-2.28	<0.0001	3.19	1.79-5.66	<0.0001	1.93	1.68-2.22	<0.0001	3.50	1.97-6.22
<i>BUDJ3</i>	rs10790162	<0.0001	1.66	1.51-1.83	<0.0001	1.80	1.50-2.15	<0.0001	1.58	1.42-1.75	<0.0001	2.17	1.81-2.62
<i>ZPR1</i>	rs964184	<0.0001	1.67	1.51-1.84	<0.0001	1.74	1.46-2.09	<0.0001	1.59	1.44-1.76	<0.0001	2.12	1.76-2.56
<i>APOA5</i>	rs2266788	<0.0001	1.67	1.51-1.84	<0.0001	1.74	1.45-2.09	<0.0001	1.59	1.44-1.76	<0.0001	2.11	1.75-2.55
	rs7350481	<0.0001	1.65	1.50-1.82	<0.0001	1.68	1.41-2.00	<0.0001	1.58	1.42-1.75	<0.0001	2.06	1.72-2.47
	rs9326246	<0.0001	1.64	1.49-1.81	<0.0001	1.75	1.46-2.09	<0.0001	1.56	1.41-1.73	<0.0001	2.11	1.75-2.54
<i>ZPR1</i>	rs2075290	<0.0001	1.62	1.47-1.78	<0.0001	1.70	1.42-2.04	<0.0001	1.54	1.39-1.71	<0.0001	2.05	1.70-2.46
	rs12678919	<0.0001	0.70	0.62-0.79	0.0362	0.62	0.39-0.97	<0.0001	0.71	0.63-0.80	0.0163	0.57	0.36-0.90
	rs10503669	<0.0001	0.70	0.62-0.79	0.0434	0.63	0.40-0.99	<0.0001	0.71	0.63-0.80	0.0199	0.58	0.37-0.92
	rs17482753	<0.0001	0.71	0.63-0.80	0.0357	0.62	0.40-0.97	<0.0001	0.72	0.64-0.82	0.0163	0.58	0.37-0.90
	rs10096633	<0.0001	0.71	0.64-0.80	0.0306	0.61	0.39-0.96	<0.0001	0.72	0.64-0.82	0.0138	0.57	0.37-0.89
<i>LPL</i>	rs328	<0.0001	0.72	0.64-0.81	0.0253	0.61	0.39-0.94	<0.0001	0.73	0.64-0.82	0.0110	0.57	0.37-0.88
<i>APOA4</i>	rs5104	<0.0001	1.38	1.25-1.52	<0.0001	1.37	1.19-1.58	<0.0001	1.32	1.19-1.47	<0.0001	1.60	1.37-1.86
	rs7016880	<0.0001	0.72	0.64-0.82	0.0548	0.73	0.65-0.83	<0.0001	0.73	0.65-0.83	0.0327	0.61	0.39-0.96
<i>GCKR</i>	rs1260326	<0.0001	0.75	0.68-0.83	<0.0001	0.77	0.68-0.88	<0.0001	0.78	0.70-0.87	<0.0001	0.67	0.58-0.77
<i>GCKR</i>	rs780093	<0.0001	0.77	0.69-0.85	<0.0001	0.77	0.68-0.88	<0.0001	0.80	0.72-0.89	<0.0001	0.68	0.59-0.78
	rs1260333	<0.0001	0.77	0.70-0.86	<0.0001	0.77	0.68-0.88	0.0001	0.81	0.73-0.90	<0.0001	0.68	0.59-0.78
	rs11085421	<0.0001	0.78	0.70-0.86	0.0032	0.66	0.49-0.87	<0.0001	0.80	0.72-0.89	0.0007	0.61	0.46-0.81
	rs1441756	<0.0001	0.79	0.71-0.88	0.0125	0.70	0.53-0.93	<0.0001	0.81	0.72-0.90	0.0032	0.66	0.49-0.87
	rs2083637	<0.0001	0.79	0.71-0.88	0.0166	0.71	0.54-0.94	<0.0001	0.81	0.72-0.90	0.0044	0.66	0.50-0.88
<i>LPL</i>	rs301	<0.0001	0.79	0.72-0.88	0.0107	0.70	0.53-0.92	0.0001	0.81	0.73-0.90	0.0027	0.66	0.50-0.86
<i>LPL</i>	rs13702	<0.0001	0.80	0.72-0.88	0.0130	0.71	0.54-0.93	0.0001	0.81	0.73-0.90	0.0034	0.66	0.50-0.87
<i>LPL</i>	rs15285	<0.0001	0.80	0.72-0.88	0.0149	0.71	0.54-0.94	0.0001	0.81	0.73-0.91	0.0040	0.67	0.51-0.88
	rs2954033	<0.0001	1.26	1.14-1.39	0.0011	1.28	1.10-1.49	0.0001	1.22	1.10-1.35	<0.0001	1.42	1.21-1.67
<i>LPL</i>	rs326	<0.0001	0.80	0.72-0.88	0.0233	0.73	0.56-0.96	0.0001	0.81	0.73-0.90	0.0062	0.69	0.52-0.90

Multivariable logistic regression analysis was performed with adjustment for age and sex. Based on Bonferroni's correction, $P < 0.0005$ (0.05/100) was considered statistically significant. SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval.

Table VIII. Association of SNPs to hypo-HDL-cholesterolemia as determined by multivariable logistic regression analysis.

Gene	SNP	T/C	Dominant			Recessive			Additive 1			Additive 2		
			P-value	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI
<i>LPGAT1</i>	rs150552771	T/C	<0.0001	19.16	8.16-45.01	<0.0001	19.16	8.16-45.01	<0.0001	19.16	8.16-45.01	<0.0001	19.16	8.16-45.01
<i>APOA5</i>	rs2075291	G/T	<0.0001	1.85	1.55-2.20	0.0031	2.66	1.39-5.07	<0.0001	1.80	1.50-2.16	<0.0001	1.80	1.50-2.16
<i>COL6A5</i>	rs200982668	G/A	<0.0001	0.18	0.09-0.35				<0.0001	0.18	0.09-0.35	<0.0001	0.18	0.09-0.35
<i>ZNF860</i>	rs140232911	C/T	<0.0001	4.88	3.12-7.63				<0.0001	4.88	3.12-7.63	<0.0001	4.88	3.12-7.63
	rs9261800	C/G	<0.0001	28.11	10.15-77.87				<0.0001	28.11	10.15-77.87	<0.0001	28.11	10.15-77.87
<i>VPS33B</i>	rs199921354	C/T	<0.0001	0.17	0.08-0.34				<0.0001	0.17	0.08-0.34	<0.0001	0.17	0.08-0.34
<i>ADGRL3</i>	rs192210727	G/T	<0.0001	0.19	0.10-0.37	0.2341			<0.0001	0.19	0.10-0.38	<0.0001	0.19	0.10-0.38
<i>TMOD4</i>	rs115287176	G/A	<0.0001	0.17	0.08-0.35				<0.0001	0.17	0.08-0.35	<0.0001	0.17	0.08-0.35
<i>COL6A3</i>	rs146092501	C/T	<0.0001	0.17	0.08-0.35				<0.0001	0.17	0.08-0.35	<0.0001	0.17	0.08-0.35
<i>MARCH1</i>	rs61734696	G/T	<0.0001	0.19	0.10-0.37				<0.0001	0.19	0.10-0.37	<0.0001	0.19	0.10-0.37
<i>PLCB2</i>	rs200787930	C/T	<0.0001	0.19	0.10-0.36				<0.0001	0.19	0.10-0.36	<0.0001	0.19	0.10-0.36
<i>MOB3C</i>	rs139537100	C/T	<0.0001	0.19	0.10-0.37				<0.0001	0.19	0.10-0.37	<0.0001	0.19	0.10-0.37
<i>CXCL8</i>	rs188378669	G/T	<0.0001	0.19	0.10-0.36				<0.0001	0.19	0.10-0.36	<0.0001	0.19	0.10-0.36
<i>EHD3</i>	rs116417209	G/A	<0.0001	14.34	6.16-33.35				<0.0001	14.34	6.16-33.35	<0.0001	14.34	6.16-33.35
<i>ZNF77</i>	rs146879198	G/A	<0.0001	0.19	0.10-0.38				<0.0001	0.19	0.10-0.38	<0.0001	0.19	0.10-0.38
<i>OR4F6</i>	rs141569282	G/A	<0.0001	0.25	0.13-0.46				<0.0001	0.25	0.13-0.46	<0.0001	0.25	0.13-0.46
<i>ACAD10</i>	rs11066015	G/A	<0.0001	1.40	1.22-1.60	<0.0001	1.56	1.26-1.93	0.0003	1.32	1.14-1.52	<0.0001	1.77	1.42-2.22
<i>CACNA1D</i>	rs35874056	G/A	<0.0001	92.59	11.37-753.91				<0.0001	92.59	11.37-753.91	<0.0001	92.59	11.37-753.91
<i>ALDH2</i>	rs671	G/A	<0.0001	1.39	1.21-1.60	<0.0001	1.55	1.25-1.92	0.0003	1.31	1.13-1.52	<0.0001	1.76	1.40-2.20
	rs3764261	G/T	<0.0001	0.68	0.58-0.79	0.0004	0.39	0.23-0.66	<0.0001	0.72	0.61-0.84	0.0001	0.35	0.21-0.60
	rs247616	C/T	<0.0001	0.68	0.58-0.79	0.0009	0.43	0.26-0.71	<0.0001	0.71	0.61-0.83	0.0002	0.39	0.24-0.64
<i>BRAP</i>	rs3782886	A/G	<0.0001	1.39	1.21-1.60	<0.0001	1.52	1.24-1.87	0.0003	1.31	1.13-1.52	<0.0001	1.74	1.40-2.17
<i>CETP</i>	rs1532624	G/T	<0.0001	0.73	0.64-0.84	<0.0001	0.50	0.37-0.67	0.0021	0.80	0.69-0.92	<0.0001	0.45	0.33-0.61
<i>HECTD4</i>	rs11066280	T/A	<0.0001	1.42	1.23-1.63	0.0010	1.43	1.15-1.76	<0.0001	1.36	1.17-1.58	<0.0001	1.66	1.32-2.08
<i>HECTD4</i>	rs2074356	C/T	<0.0001	1.37	1.19-1.57	0.0016	1.45	1.15-1.83	0.0002	1.32	1.14-1.52	<0.0001	1.64	1.29-2.09
<i>LILRB2</i>	rs73055442	C/T	<0.0001	51.91	10.66-252.93				<0.0001	51.91	10.66-252.93	<0.0001	51.91	10.66-252.93
<i>DCLRE1C</i>	rs150854849	C/T	<0.0001	78.09	9.17-665.03				<0.0001	78.09	9.17-665.03	<0.0001	78.09	9.17-665.03
<i>SPOPL</i>	rs114501427	G/A	<0.0001	3.54	2.24-5.61				<0.0001	3.54	2.24-5.61	<0.0001	3.54	2.24-5.61

Multivariable logistic regression analysis was performed with adjustment for age and sex. Based on Bonferroni's correction, $P < 0.0004$ (0.05/112) was considered statistically significant. SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval.

Table IX. Association of SNPs to hyper-LDL-cholesterolemia as determined by multivariable logistic regression analysis.

Gene	SNP		Dominant			Recessive			Additive 1			Additive 2		
			P-value	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI
<i>APOE</i>	rs7412	C/T	<0.0001	0.40	0.33-0.48	0.0738			<0.0001	0.40	0.33-0.49	0.0984		
<i>COL6A3</i>	rs146092501	C/T	<0.0001	2.34	1.87-2.93			<0.0001	2.34	1.87-2.93				
<i>TMOD4</i>	rs115287176	G/A	<0.0001	2.33	1.86-2.91			<0.0001	2.33	1.86-2.91				
<i>CXCL8</i>	rs188378669	G/T	<0.0001	2.30	1.85-2.87			<0.0001	2.30	1.85-2.87				
<i>VPS33B</i>	rs199921354	C/T	<0.0001	2.31	1.85-2.89			<0.0001	2.31	1.85-2.89				
<i>ZNF77</i>	rs146879198	G/A	<0.0001	2.30	1.84-2.87			<0.0001	2.30	1.84-2.87				
<i>MOB3C</i>	rs139537100	C/T	<0.0001	2.27	1.82-2.83			<0.0001	2.27	1.82-2.83				
<i>PLCB2</i>	rs200787930	C/T	<0.0001	2.22	1.78-2.77			<0.0001	2.22	1.78-2.77				
<i>MUC17</i>	rs78010183	A/T	<0.0001	1.99	1.65-2.40			<0.0001	1.99	1.65-2.40				
<i>MARCH1</i>	rs61734696	G/T	<0.0001	2.20	1.77-2.74			<0.0001	2.20	1.77-2.74				
<i>APOB</i>	rs13306206	G/A	<0.0001	1.69	1.41-2.03	0.0145	5.13	1.38-19.03	<0.0001	1.65	1.37-1.98	0.0127	5.30	1.43-19.67
<i>COL6A5</i>	rs200982668	G/A	<0.0001	2.12	1.71-2.63			<0.0001	2.12	1.71-2.63				
<i>PTCH2</i>	rs147284320	C/T	<0.0001	2.02	1.65-2.49			<0.0001	2.02	1.65-2.49				
<i>ADGRL3</i>	rs192210727	G/T	<0.0001	2.14	1.72-2.66	0.8431			<0.0001	2.17	1.74-2.71	0.8732		
<i>APOC1</i>	rs445925	C/T	<0.0001	0.63	0.55-0.73	0.8258			<0.0001	0.63	0.54-0.73	0.7212		
<i>HSPA1B</i>	rs6457452	C/T	<0.0001	1.37	1.22-1.53	0.0284	1.51	1.04-2.20	<0.0001	1.35	1.20-1.52	0.0125	1.61	1.11-2.33
<i>C6orf48</i>	rs11968400	C/T	<0.0001	1.37	1.22-1.53	0.0425	1.48	1.01-2.15	<0.0001	1.36	1.21-1.52	0.0195	1.57	1.07-2.29
	rs12210887	G/T	<0.0001	1.37	1.22-1.53	0.0590			<0.0001	1.36	1.21-1.52	0.0272	1.53	1.05-2.24
<i>UBD</i>	rs64036	C/A	<0.0001	1.28	1.17-1.40	0.0043	1.30	1.09-1.56	<0.0001	1.26	1.14-1.38	0.0002	1.42	1.18-1.71
<i>CCHCR1</i>	rs147733073	C/G	<0.0001	1.37	1.22-1.53	0.1210			<0.0001	1.36	1.21-1.53	0.0592		
<i>VARS</i>	rs11751198	G/A	<0.0001	1.36	1.22-1.52	0.0505			<0.0001	1.35	1.20-1.51	0.0238	1.56	1.06-2.29
	rs2596574	G/A	<0.0001	1.36	1.22-1.53	0.0807			<0.0001	1.35	1.21-1.52	0.0377	1.48	1.02-2.14
<i>LY6G6F</i>	rs9267547	G/A	<0.0001	1.35	1.21-1.51	0.0797			<0.0001	1.34	1.20-1.51	0.0370	1.47	1.02-2.11
<i>NEU1</i>	rs13118	T/A	<0.0001	1.36	1.21-1.52	0.0450	1.47	1.01-2.16	<0.0001	1.34	1.20-1.51	0.0217	1.56	1.07-2.29
<i>SLC17A3</i>	rs34902660	C/A	<0.0001	1.40	1.24-1.57	0.2131			<0.0001	1.40	1.24-1.57	0.1319		
<i>FAM65B</i>	rs150142878	C/T	<0.0001	1.48	1.29-1.70	0.5456			<0.0001	1.49	1.30-1.71	0.4556		
<i>TUBB</i>	rs9500864	G/A	<0.0001	1.28	1.16-1.40	0.0025	1.36	1.11-1.66	<0.0001	1.25	1.13-1.38	0.0002	1.47	1.20-1.81
	rs204999	A/G	<0.0001	1.37	1.22-1.53	0.1767			<0.0001	1.37	1.22-1.54	0.1002		
	rs3130663	A/G	<0.0001	1.35	1.21-1.49	0.1104			<0.0001	1.34	1.21-1.50	0.0388	1.39	1.02-1.90
<i>VARS</i>	rs5030798	G/A	<0.0001	1.35	1.21-1.52	0.0609			<0.0001	1.34	1.19-1.51	0.0296	1.53	1.04-2.24
<i>LY6G6F</i>	rs9267546	G/A	<0.0001	1.35	1.21-1.51	0.1053			<0.0001	1.35	1.20-1.51	0.0525		
<i>PRRC2A</i>	rs11538264	G/A	<0.0001	1.36	1.21-1.52	0.0873			<0.0001	1.35	1.20-1.51	0.0437	1.48	1.01-2.16
<i>DPCR1</i>	rs11970154	G/C	<0.0001	1.33	1.20-1.47	0.1235			<0.0001	1.33	1.19-1.47	0.0445	1.37	1.01-1.86
<i>MSH5</i>	rs11754464	C/T	<0.0001	1.35	1.21-1.51	0.0735			<0.0001	1.34	1.19-1.51	0.0365	1.50	1.03-2.20

Table IX. Continued.

Gene	SNP	Dominant			Recessive			Additive 1			Additive 2		
		P-value	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI
<i>PCSK9</i>	rs151193009	<0.0001	0.41	0.29-0.59	0.4126			<0.0001	0.42	0.29-0.59	0.9943		
<i>GABBR1</i>	rs29243	<0.0001	1.34	1.20-1.50	0.0562			<0.0001	1.33	1.19-1.49	0.244	1.50	1.05-2.13
<i>KIAA0319</i>	rs4576240	<0.0001	1.47	1.29-1.69	0.7773			<0.0001	1.49	1.29-1.71	0.6763		
<i>LY6G6F</i>	rs17200983	<0.0001	1.35	1.20-1.51	0.0873			<0.0001	1.34	1.19-1.50	0.0444	1.48	1.01-2.16
<i>TNXB</i>	rs140770834	<0.0001	1.36	1.21-1.53	0.1723			<0.0001	1.36	1.21-1.53	0.1013		
<i>TNXB</i>	rs11751545	<0.0001	1.36	1.21-1.53	0.1723			<0.0001	1.36	1.21-1.53	0.1013		
<i>DPCR1</i>	rs6933400	<0.0001	1.32	1.20-1.47	0.1222			<0.0001	1.32	1.19-1.47	0.0456	1.37	1.01-1.87
<i>LY6G6C</i>	rs117894946	<0.0001	1.35	1.20-1.51	0.0871			<0.0001	1.34	1.19-1.50	0.0445	1.48	1.01-2.16
<i>SLC44A4</i>	rs117127493	<0.0001	1.36	1.21-1.52	0.2033			<0.0001	1.36	1.20-1.53	0.1218		
<i>ZSCAN26</i>	rs76463649	<0.0001	1.36	1.21-1.52	0.3394			<0.0001	1.36	1.21-1.53	0.2111		
<i>DHX16</i>	rs7749235	<0.0001	1.28	1.16-1.40	0.0064	1.37	1.09-1.72	<0.0001	1.25	1.13-1.38	0.0010	1.47	1.17-1.86
<i>LOC105-375015</i>	rs9264942	<0.0001	1.26	1.14-1.39	0.0004	1.24	1.10-1.39	0.0002	1.21	1.09-1.35	<0.0001	1.38	1.21-1.58
<i>ZSCAN31</i>	rs6922302	<0.0001	1.36	1.21-1.52	0.3391			<0.0001	1.36	1.21-1.53	0.2111		
<i>MDC1</i>	rs2269702	<0.0001	1.27	1.16-1.40	0.0048	1.39	1.11-1.75	<0.0001	1.25	1.13-1.38	0.0007	1.49	1.18-1.88
<i>MDC1</i>	rs28986465	<0.0001	1.27	1.16-1.40	0.0048	1.39	1.11-1.75	<0.0001	1.24	1.13-1.38	0.0007	1.49	1.18-1.88
<i>MDC1</i>	rs2075015	<0.0001	1.27	1.16-1.40	0.0048	1.39	1.11-1.75	<0.0001	1.24	1.13-1.38	0.0007	1.49	1.18-1.88
<i>DHX16</i>	rs2285321	<0.0001	1.27	1.16-1.40	0.0056	1.38	1.10-1.73	<0.0001	1.25	1.13-1.38	0.0008	1.48	1.18-1.87
<i>SKIV2L</i>	rs492899	<0.0001	1.34	1.20-1.51	0.1465			<0.0001	1.34	1.19-1.51	0.0843		
<i>MDC1</i>	rs6924270	<0.0001	1.27	1.16-1.40	0.0055	1.38	1.10-1.74	<0.0001	1.25	1.13-1.38	0.0008	1.48	1.18-1.87
<i>TUBB</i>	rs2508015	<0.0001	1.30	1.17-1.45	0.0409	1.39	1.01-1.91	<0.0001	1.29	1.16-1.44	0.0166	1.47	1.07-2.02
<i>PPP1R18</i>	rs25527	<0.0001	1.26	1.14-1.38	0.0028	1.35	1.11-1.64	<0.0001	1.23	1.11-1.35	0.0002	1.45	1.19-1.78
<i>DHX16</i>	rs9468805	<0.0001	1.27	1.15-1.39	0.0048	1.39	1.11-1.75	<0.0001	1.24	1.12-1.37	0.0007	1.49	1.18-1.87
<i>HECTD4</i>	rs6937357	<0.0001	1.27	1.15-1.39	0.0048	1.39	1.11-1.75	<0.0001	1.24	1.12-1.37	0.0007	1.49	1.18-1.87
<i>TRIM40</i>	rs11066280	<0.0001	1.26	1.15-1.38	0.0083	1.23	1.05-1.43	<0.0001	1.24	1.13-1.37	0.0002	1.36	1.16-1.59
<i>PPP1R18</i>	rs2523995	<0.0001	1.34	1.20-1.49	0.2147			<0.0001	1.34	1.20-1.50	0.1152		
<i>TUBB</i>	rs6457254	<0.0001	1.26	1.15-1.39	0.0063	1.37	1.09-1.72	<0.0001	1.24	1.12-1.37	0.0010	1.47	1.17-1.85
	rs3132584	<0.0001	1.25	1.14-1.37	0.0035	1.34	1.10-1.63	<0.0001	1.22	1.11-1.35	0.0003	1.44	1.18-1.76
	rs3130685	0.0005	0.80	0.71-0.91	<0.0001	0.82	0.74-0.90	0.0264	0.86	0.75-0.98	<0.0001	0.73	0.64-0.84
<i>GIT2</i>	rs2292354	0.0001	0.83	0.76-0.91	<0.0001	0.68	0.56-0.82	0.0050	0.87	0.79-0.96	<0.0001	0.64	0.52-0.78
<i>PPP1R18</i>	rs2394392	<0.0001	1.26	1.15-1.39	0.0074	1.36	1.09-1.71	<0.0001	1.24	1.12-1.37	0.0012	1.46	1.16-1.84
	rs2524272	<0.0001	1.22	1.11-1.34	0.0010	1.30	1.11-1.52	0.0007	1.18	1.07-1.30	<0.0001	1.40	1.19-1.65

Multivariable logistic regression analysis was performed with adjustment for age and sex. Based on Bonferroni's correction, $P < 0.0002$ (0.05/260) was considered statistically significant. SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval.

Table X. Association of SNPs identified in the present study to serum triglyceride concentration.

Gene	SNP		Serum triglycerides (mmol/l)			P-value
<i>APOA5</i>	rs2075291	G/T	GG	GT	TT	<0.0001
			1.39±0.98	1.83±1.55	2.56±2.27	
<i>BUD13</i>	rs10790162	G/A	GG	GA	AA	<0.0001
			1.35±1.00	1.54±1.18	1.77±1.31	
<i>ZPR1</i>	rs964184	C/G	CC	CG	GG	<0.0001
			1.35±1.00	1.55±1.18	1.75±1.30	
<i>APOA5</i>	rs2266788	T/C	TT	TC	CC	<0.0001
			1.35±1.00	1.54±1.17	1.76±1.30	
			rs7350481	C/T	CC	
rs9326246	G/C	GG	GC	CC	<0.0001	
<i>ZPR1</i>	rs2075290	T/C	TT	TC	CC	<0.0001
			1.36±1.01	1.54±1.17	1.74±1.29	
	rs12678919	A/G	AA	AG	GG	<0.0001
			1.49±1.11	1.33±1.03	1.32±1.37	
	rs10503669	C/A	CC	CA	AA	<0.0001
			1.49±1.11	1.33±1.03	1.32±1.38	
rs17482753	G/T	GG	GT	TT	<0.0001	
		1.49±1.11	1.33±1.02	1.31±1.35		
rs10096633	C/T	CC	CT	TT	<0.0001	
		1.49±1.11	1.33±1.03	1.31±1.34		
<i>LPL</i>	rs328	C/G	CC	CG	GG	<0.0001
			1.49±1.11	1.33±1.02	1.33±1.33	
<i>APOA4</i>	rs5104	A/G	AA	AG	GG	<0.0001
			1.37±1.00	1.49±1.12	1.57±1.28	
rs7016880	G/C	GG	GC	CC	<0.0001	
		1.49±1.11	1.33±1.04	1.30±1.35		
<i>GCKR</i>	rs1260326	T/C	TT	TC	CC	<0.0001
			1.54±1.14	1.44±1.14	1.33±0.89	
<i>GCKR</i>	rs780093	A/G	AA	AG	GG	<0.0001
			1.53±1.12	1.45±1.16	1.33±0.87	
			rs1260333	T/C	TT	
rs11085421	A/C	AA	AC	CC	<0.0001	
rs1441756	T/G	TT	TG	GG	<0.0001	
		1.49±1.12	1.38±1.04	1.34±1.16		
rs2083637	T/C	TT	TC	CC	<0.0001	
		1.49±1.12	1.38±1.05	1.34±1.16		
<i>LPL</i>	rs301	T/C	TT	TC	CC	<0.0001
			1.49±1.11	1.38±1.08	1.34±1.14	
<i>LPL</i>	rs13702	A/G	AA	AG	GG	<0.0001
			1.50±1.12	1.38±1.04	1.34±1.15	
<i>LPL</i>	rs15285	G/A	GG	GA	AA	<0.0001
			1.50±1.12	1.38±1.04	1.34±1.15	
rs2954033	G/A	GG	GA	AA	0.0007	
		1.41±1.02	1.47±1.16	1.55±1.18		
<i>LPL</i>	rs326	A/G	AA	AG	GG	<0.0001
			1.49±1.11	1.38±1.07	1.35±1.14	

Data are presented as mean ± standard deviation and were compared among genotypes by one-way analysis of variance. Based on Bonferroni's correction, $P < 0.0020$ ($0.05/25$) was considered statistically significant. SNP, single nucleotide polymorphism.

Table XI. Association of SNPs identified in the present study to serum HDL-cholesterol concentration.

Gene	SNP		Serum HDL-cholesterol (mmol/l)			P-value
<i>LPGAT1</i>	rs150552771	T/C	TT	TC		<0.0001
			1.54±0.47	1.11±0.63		
<i>APOA5</i>	rs2075291	G/T	GG	GT	TT	<0.0001
			1.56±0.47	1.42±0.45	1.29±0.40	
<i>COL6A5</i>	rs200982668	G/A	GG	GA		<0.0001
			1.53±0.47	1.69±0.44		
<i>ZNF860</i>	rs140232911	C/T	CC	CT		0.0003
			1.54±0.47	1.37±0.59		
	rs9261800	C/G	CC	CG		<0.0001
			1.54±0.47	0.98±0.56		
<i>VPS33B</i>	rs199921354	C/T	CC	CT		<0.0001
			1.53±0.47	1.69±0.44		
<i>ADGRL3</i>	rs192210727	G/T	GG	GT	TT	<0.0001
			1.53±0.47	1.67±0.44	1.91±0.49	
<i>TMOD4</i>	rs115287176	G/A	GG	GA		<0.0001
			1.53±0.47	1.68±0.44		
<i>COL6A3</i>	rs146092501	C/T	CC	CT		<0.0001
			1.53±0.47	1.68±0.44		
<i>MARCH1</i>	rs61734696	G/T	GG	GT		<0.0001
			1.53±0.47	1.69±0.44		
<i>PLCB2</i>	rs200787930	C/T	CC	CT		<0.0001
			1.53±0.47	1.69±0.44		
<i>MOB3C</i>	rs139537100	C/T	CC	CT		<0.0001
			1.53±0.47	1.68±0.44		
<i>CXCL8</i>	rs188378669	G/T	GG	GT		<0.0001
			1.53±0.47	1.69±0.44		
<i>EHD3</i>	rs116417209	G/A	GG	GA		<0.0001
			1.54±0.47	1.09±0.48		
<i>ZNF77</i>	rs146879198	G/A	GG	GA		<0.0001
			1.53±0.47	1.69±0.44		
<i>OR4F6</i>	rs141569282	G/A	GG	GA		<0.0001
			1.48±0.46	1.72±0.43		
<i>ACAD10</i>	rs11066015	G/A	GG	GA	AA	<0.0001
			1.57±0.48	1.51±0.47	1.43±0.43	
<i>CACNA1D</i>	rs35874056	G/A	GG	GA		<0.0001
			1.51±0.47	0.94±0.64		
<i>ALDH2</i>	rs671	G/A	GG	GA	AA	<0.0001
			1.57±0.48	1.51±0.47	1.43±0.43	
	rs3764261	G/T	GG	GT	TT	<0.0001
			1.50±0.46	1.59±0.48	1.72±0.49	
	rs247616	C/T	CC	CT	TT	<0.0001
			1.50±0.46	1.59±0.48	1.71±0.50	
<i>BRAP</i>	rs3782886	A/G	AA	AG	GG	<0.0001
			1.57±0.48	1.52±0.47	1.44±0.43	
<i>CETP</i>	rs1532624	G/T	GG	GT	TT	<0.0001
			1.50±0.46	1.56±0.47	1.64±0.48	
<i>HECTD4</i>	rs11066280	T/A	TT	TA	AA	<0.0001
			1.57±0.47	1.52±0.47	1.44±0.42	
<i>HECTD4</i>	rs2074356	C/T	CC	CT	TT	<0.0001
			1.57±0.48	1.51±0.47	1.44±0.43	
<i>LILRB2</i>	rs73055442	C/T	CC	CT		<0.0001
			1.54±0.47	0.88±0.31		

Table XI. Continued.

Gene	SNP		Serum HDL-cholesterol (mmol/l)		P-value
<i>DCLRE1C</i>	rs150854849	C/T	CC 1.54±0.47	CT 0.92±0.68	<0.0001
<i>SPOPL</i>	rs114501427	G/A	GG 1.54±0.47	GA 1.41±0.58	0.0041

Data are presented as mean ± standard deviation and were compared among genotypes by one-way analysis of variance. Based on Bonferroni's correction, $P < 0.0018$ ($0.05/28$) was considered statistically significant. SNP, single nucleotide polymorphism; HDL, high density lipoprotein.

Table XII. Association of SNPs identified in the present study to serum LDL-cholesterol concentration.

Gene	SNP		Serum LDL-cholesterol (mmol/l)			P-value
<i>APOE</i>	rs7412	C/T	CC 3.20±0.85	CT 2.74±0.80	TT 2.39±1.48	<0.0001
<i>COL6A3</i>	rs146092501	C/T	CC 3.16±0.86	CT 3.24±0.82		0.1168
<i>TMOD4</i>	rs115287176	G/A	GG 3.16±0.86	GA 3.23±0.82		0.1624
<i>CXCL8</i>	rs188378669	G/T	GG 3.16±0.86	GT 3.24±0.82		0.1158
<i>VPS33B</i>	rs199921354	C/T	CC 3.16±0.86	CT 3.24±0.81		0.1121
<i>ZNF77</i>	rs146879198	G/A	GG 3.16±0.86	GA 3.22±0.81		0.2277
<i>MOB3C</i>	rs139537100	C/T	CC 3.16±0.86	CT 3.21±0.82		0.2422
<i>PLCB2</i>	rs200787930	C/T	CC 3.16±0.86	CT 3.22±0.81		0.1860
<i>MUC17</i>	rs78010183	A/T	AA 3.15±0.87	AT 3.26±0.78		0.0096
<i>MARCH1</i>	rs61734696	G/T	GG 3.16±0.86	GT 3.21±0.80		0.3029
<i>APOB</i>	rs13306206	G/A	GG 3.14±0.85	GA 3.42±0.98	AA 4.20±0.86	<0.0001
<i>COL6A5</i>	rs200982668	G/A	GG 3.16±0.86	GA 3.20±0.80		0.3549
<i>PTCH2</i>	rs147284320	C/T	CC 3.17±0.82	CT 3.20±0.82		0.5075
<i>ADGRL3</i>	rs192210727	G/T	GG 3.16±0.86	GT 3.20±0.81	TT 2.99±0.82	0.6309
<i>APOC1</i>	rs445925	C/T	CC 3.19±0.86	CT 2.96±0.86	TT 2.99±1.21	<0.0001
<i>HSPA1B</i>	rs6457452	C/T	CC 3.14±0.85	CT 3.24±0.89	TT 3.38±0.88	<0.0001
<i>C6orf48</i>	rs11968400	C/T	CC 3.14±0.85	CT 3.24±0.89	TT 3.37±0.88	<0.0001
	rs12210887	G/T	GG 3.14±0.85	GT 3.24±0.89	TT 3.37±0.89	<0.0001
<i>UBD</i>	rs64036	C/A	CC 3.13±0.85	CA 3.19±0.87	AA 3.27±0.85	0.0004

Table XII. Continued.

Gene	SNP		Serum LDL-cholesterol (mmol/l)			P-value
			CC	CG	GG	
<i>CCHCR1</i>	rs147733073	C/G	3.14±0.85	3.23±0.89	3.37±0.88	<0.0001
<i>VARS</i>	rs11751198	G/A	GG	GA	AA	<0.0001
			3.14±0.85	3.24±0.89	3.37±0.89	
<i>LY6G6F</i>	rs2596574	G/A	GG	GA	AA	<0.0001
			3.14±0.85	3.24±0.89	3.35±0.86	
<i>LY6G6F</i>	rs9267547	G/A	GG	GA	AA	<0.0001
			3.14±0.85	3.23±0.89	3.37±0.89	
<i>NEU1</i>	rs13118	T/A	TT	TA	AA	<0.0001
			3.14±0.85	3.24±0.89	3.37±0.89	
<i>SLC17A3</i>	rs34902660	C/A	CC	CA	AA	<0.0001
			3.14±0.85	3.26±0.90	3.35±0.91	
<i>FAM65B</i>	rs150142878	C/T	CC	CT	TT	<0.0001
			3.14±0.85	3.30±0.94	3.18±0.88	
<i>TUBB</i>	rs9500864	G/A	GG	GA	AA	0.0002
			3.13±0.85	3.19±0.87	3.28±0.90	
<i>TUBB</i>	rs204999	A/G	AA	AG	GG	<0.0001
			3.14±0.85	3.24±0.89	3.36±0.91	
<i>TUBB</i>	rs3130663	A/G	AA	AG	GG	0.0010
			3.14±0.85	3.22±0.88	3.22±0.90	
<i>VARS</i>	rs5030798	G/A	GG	GA	AA	<0.0001
			3.14±0.85	3.24±0.89	3.37±0.89	
<i>LY6G6F</i>	rs9267546	G/A	GG	GA	AA	<0.0001
			3.14±0.85	3.24±0.89	3.36±0.87	
<i>PRRC2A</i>	rs11538264	G/A	GG	GA	AA	<0.0001
			3.14±0.85	3.24±0.90	3.36±0.88	
<i>DPCR1</i>	rs11970154	G/C	GG	GC	CC	<0.0001
			3.13±0.85	3.23±0.89	3.32±0.86	
<i>MSH5</i>	rs11754464	C/T	CC	CT	TT	<0.0001
			3.14±0.85	3.24±0.89	3.37±0.89	
<i>PCSK9</i>	rs151193009	C/T	CC	CT	TT	<0.0001
			3.17±0.86	2.77±0.73	2.05	
<i>GABBR1</i>	rs29243	C/T	CC	CT	TT	0.0001
			3.14±0.85	3.23±0.89	3.34±0.86	
<i>KIAA0319</i>	rs4576240	G/T	GG	GT	TT	<0.0001
			3.14±0.85	3.30±0.93	3.17±0.89	
<i>LY6G6F</i>	rs17200983	C/A	CC	CA	AA	<0.0001
			3.14±0.85	3.24±0.89	3.36±0.88	
<i>TNXB</i>	rs140770834	C/G	CC	CG	GG	<0.0001
			3.14±0.85	3.24±0.89	3.37±0.92	
<i>TNXB</i>	rs11751545	A/C	AA	AC	CC	<0.0001
			3.14±0.85	3.24±0.89	3.37±0.92	
<i>DPCR1</i>	rs6933400	C/T	CC	CT	TT	<0.0001
			3.13±0.85	3.23±0.89	3.32±0.87	
<i>LY6G6C</i>	rs117894946	G/C	GG	GC	CC	<0.0001
			3.14±0.85	3.24±0.89	3.36±0.88	
<i>SLC44A4</i>	rs117127493	G/C	GG	GC	CC	<0.0001
			3.14±0.85	3.24±0.89	3.36±0.91	
<i>ZSCAN26</i>	rs76463649	A/G	AA	AG	GG	<0.0001
			3.14±0.85	3.24±0.89	3.37±0.85	
<i>DHX16</i>	rs7749235	T/C	TT	TC	CC	0.0010
			3.14±0.85	3.20±0.87	3.28±0.90	

Table XII. Continued.

Gene	SNP		Serum LDL-cholesterol (mmol/l)			P-value
			TT	TC	CC	
<i>LOC105375015</i>	rs9264942	T/C	3.13±0.84	3.15±0.87	3.25±0.88	0.0001
<i>ZSCAN31</i>	rs6922302	C/G	3.14±0.85	3.24±0.90	3.37±0.85	<0.0001
<i>MDC1</i>	rs2269702	A/G	3.14±0.85	3.20±0.87	3.28±0.91	0.0013
<i>MDC1</i>	rs28986465	C/T	3.14±0.85	3.20±0.87	3.28±0.91	0.0013
<i>MDC1</i>	rs2075015	G/A	3.14±0.85	3.20±0.87	3.28±0.91	0.0013
<i>DHX16</i>	rs2285321	T/C	3.14±0.85	3.20±0.87	3.28±0.91	0.0011
<i>SKIV2L</i>	rs492899	A/G	3.14±0.85	3.23±0.89	3.36±0.91	0.0001
<i>MDC1</i>	rs6924270	A/G	3.14±0.85	3.20±0.87	3.28±0.91	0.0012
	rs2508015	C/T	3.14±0.85	3.22±0.88	3.31±0.86	0.0005
<i>TUBB</i>	rs25527	C/T	3.14±0.86	3.19±0.86	3.27±0.89	0.0008
<i>PPP1R18</i>	rs9468805	G/A	3.14±0.85	3.20±0.87	3.28±0.91	0.0016
<i>DHX16</i>	rs6937357	T/C	3.14±0.85	3.20±0.87	3.28±0.91	0.0016
<i>HECTD4</i>	rs11066280	T/A	3.12±0.88	3.19±0.85	3.24±0.81	0.0005
<i>TRIM40</i>	rs2523995	G/A	3.14±0.85	3.22±0.89	3.32±0.87	0.0008
<i>PPP1R18</i>	rs6457254	C/T	3.14±0.85	3.20±0.87	3.28±0.91	0.0010
<i>TUBB</i>	rs3132584	C/A	3.13±0.86	3.19±0.86	3.27±0.90	0.0008
	rs3130685	T/C	3.20±0.89	3.14±0.84	3.14±0.85	0.0234
<i>GIT2</i>	rs2292354	C/T	3.18±0.86	3.15±0.87	3.05±0.82	0.0077
<i>PPP1R18</i>	rs2394392	T/G	3.14±0.85	3.20±0.87	3.28±0.91	0.0013
	rs2524272	T/C	3.13±0.86	3.18±0.87	3.27±0.87	0.0005

Data are presented as mean ± standard deviation and were compared among genotypes by one-way analysis of variance. Based on Bonferroni's correction, $P < 0.0008$ (0.05/65) was considered statistically significant (indicated in bold). SNP, single nucleotide polymorphism; LDL, low density lipoprotein.

were associated with diabetes mellitus-associated phenotypes. The remaining 16 genes (*PTCH2*, *MOB3C*, *TMOD4*, *COL6A3*, *COL6A5*, *ADGRL3*, *KIAA0319*, *FAM65B*, *ZSCAN26*, *UBD*, *DHX16*, *LOC105375015*, *NEU1*, *MUC17*, *GIT2*, *ZNF77*) had not been related to circulating LDL-cholesterol or other dyslipidemia-related phenotypes.

Network analysis of genes identified in the present study. Network analysis of the 10 genes (*MOB3C*, *TMOD4*, *LPGAT1*, *EHD3*, *COL6A3*, *ZNF860*, *CACNA1D*, *COL6A5*, *DCLRE1C*, *ZNF77*) or three genes (*KIAA0319*, *FAM65B*, *UBD*) associated in the present study with hypo-HDL-cholesterolemia or hyper-LDL-cholesterolemia, respectively, was performed

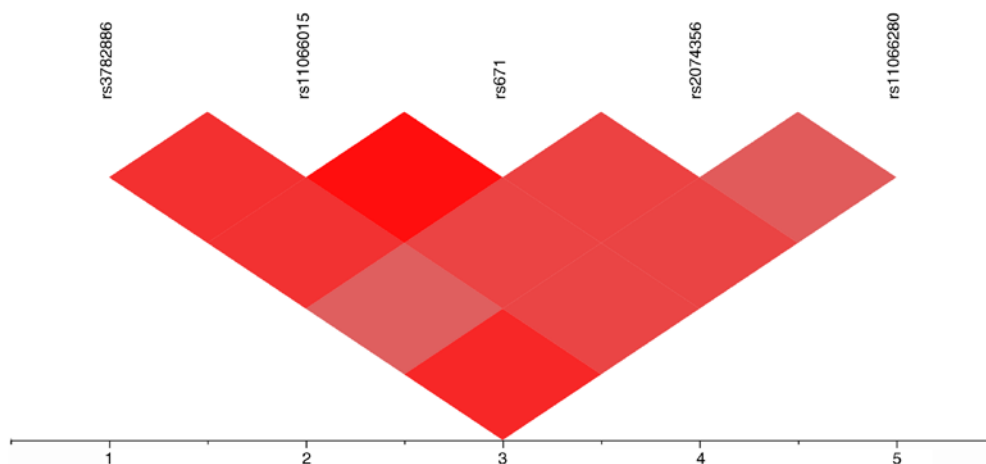


Figure 3. LD map for five SNPs at chromosomal region 12q24.12 to 12q24.13 associated with hypo-HDL-cholesterolemia. LD was calculated as the square of the correlation coefficient (r^2), with the extent of LD increasing according to the color order of gray to red. LD, linkage disequilibrium; SNP, single nucleotide polymorphism.

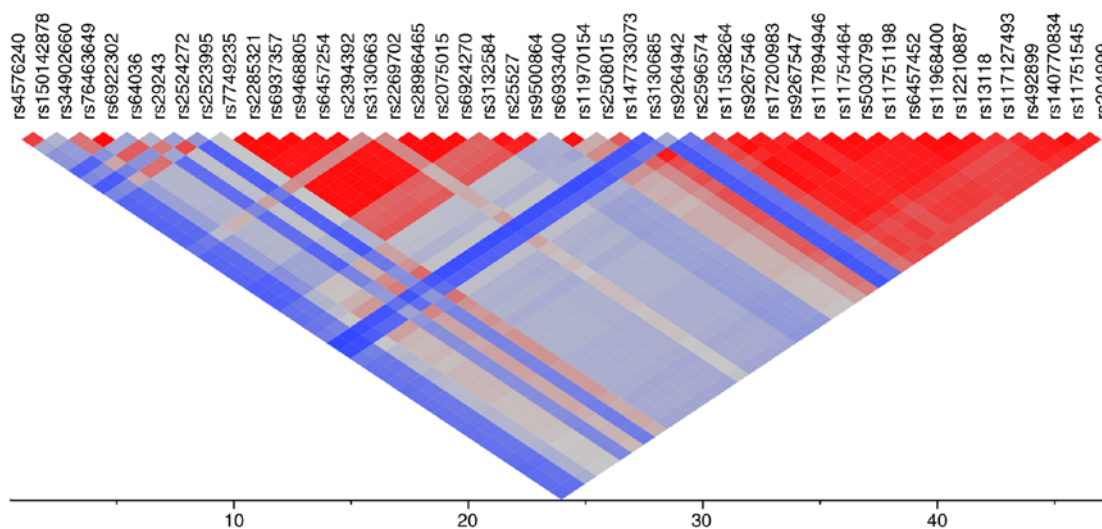


Figure 4. LD map for 47 SNPs at 6p22.3 to 6p21.3 associated with hyper-LDL-cholesterolemia. LD was calculated as the square of the correlation coefficient (r^2), with the extent of LD increasing according to the color order of blue to gray to red. LD, linkage disequilibrium; SNP, single nucleotide polymorphism.

to predict functional gene-gene interactions, with the use of the GeneMANIA Cytoscape plugin (<http://apps.cytoscape.org/apps/genemania>; Donnelly Centre for Cellular and Biomolecular Research, University of Toronto, Toronto, Canada) (35-37) and Cytoscape v3.4.0 software (<http://www.cytoscape.org>; The Cytoscape Consortium, San Diego, CA, USA) (38). Given that *LOC105375015* protein has not been characterized, it was not examined. A set of 50 dyslipidemia-related genes were selected from the DisGeNET database (<http://www.disgenet.org/web/DisGeNET>; Integrative Biomedical Informatics Group, Research Programme on Biomedical Informatics, Barcelona Biomedical Research Park, Barcelona, Spain) (39,40) according to the rank order (high to low) of scores for association with dyslipidemia. The network analysis revealed that the 10 or three genes associated in the present study with hypo-HDL-cholesterolemia or hyper-LDL-cholesterolemia, respectively, have potential direct or indirect interactions with the 50 genes previously demonstrated to be associated with dyslipidemia (Fig. 5).

Discussion

Dyslipidemia is an important public health problem because of its high prevalence and role as a risk factor for more serious conditions, including coronary artery disease, ischemic stroke, and colorectal cancer (9-12). The identification of genetic variants that confer susceptibility to dyslipidemia is thus clinically important for prevention of these conditions. The present study has performed novel EWASs for hypertriglyceridemia, hypo-HDL-cholesterolemia, and hyper-LDL-cholesterolemia in subjects with early-onset forms of these disorders, which may have a greater genetic component compared with late-onset forms.

Among 25 SNPs in six genes and five chromosomal loci significantly associated with early-onset hypertriglyceridemia, the present study newly identified rs11085421 at 19p12 as a susceptibility locus for this condition. This SNP was significantly associated with serum triglyceride concentration, with the minor C allele being protective against hypertriglyceridemia.

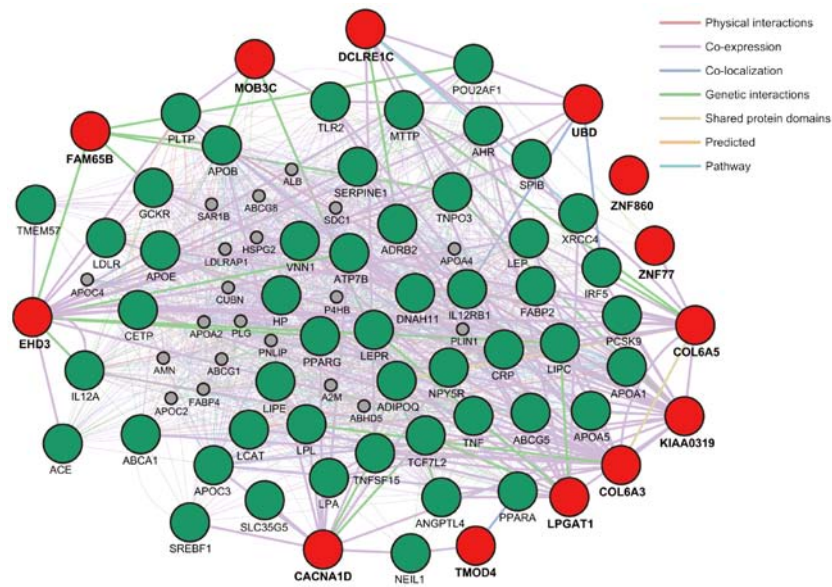


Figure 5. Network analysis of the genes identified in the present study with known dyslipidemia-related genes. The 10 genes (*MOB3C*, *TMOD4*, *LPGAT1*, *EHD3*, *COL6A3*, *ZNF860*, *CACNA1D*, *COL6A5*, *DCLRE1C*, *ZNF77*) and three genes (*KIAA0319*, *FAM65B*, *UBD*) associated in the present study with hypo-HDL-cholesterolemia and hyper-LDL-cholesterolemia, respectively, are indicated in red circles. The 50 dyslipidemia-related genes selected from the DisGeNET database (<http://www.disgenet.org/> web/ DisGeNET) are indicated in green circles. Interactions between red circles or between red and green circles are indicated by bold lines. Molecules represented by gray circles are putative mediators of interactions between the genes.

Among 28 SNPs in 24 genes and two chromosomal loci significantly associated with hypo-HDL-cholesterolemia, the current study newly identified 13 genes (*MOB3C*, *TMOD4*, *LPGAT1*, *EHD3*, *SPOPL*, *COL6A3*, *ZNF860*, *CACNA1D*, *COL6A5*, *ADGRL3*, *DCLRE1C*, *OR4F6*, *ZNF77*) as potential susceptibility loci for this condition. SNPs of 12 of these genes were significantly associated with serum HDL-cholesterol levels, with minor alleles of *LPGAT1*, *EHD3*, *ZNF860*, *CACNA1D*, and *DCLRE1C* representing risk factors for hypo-HDL-cholesterolemia and minor alleles of *MOB3C*, *TMOD4*, *COL6A3*, *COL6A5*, *ADGRL3*, *OR4F6*, and *ZNF77* being protective against this condition. Given that rs114501427 of *SPOPL* was not significantly related to serum HDL-cholesterol concentration, this gene was excluded as a novel susceptibility locus. Furthermore, given that significant LD was apparent among SNPs of *ADGRL3*, *CXCL8*, and *MARCH1*, as well as between SNPs of *OR4F6* and *VPS33B*, *ADGRL3* and *OR4F6* were also removed from the final list of novel significant loci. In addition, significant LD was detected between SNPs of *MOB3C* and *TMOD4* as well as between those of *ZNF860* and *CACNA1D*. We thus identified eight novel loci (*MOB3C-TMOD4*, *LPGAT1*, *EHD3*, *COL6A3*, *ZNF860-CACNA1D*, *COL6A5*, *DCLRE1C*, *ZNF77*) that confer susceptibility to early-onset hypo-HDL-cholesterolemia.

Among 65 SNPs in 44 genes and two chromosomal loci significantly associated with hyper-LDL-cholesterolemia, the present study newly identified 16 genes (*PTCH2*, *MOB3C*, *TMOD4*, *COL6A3*, *COL6A5*, *ADGRL3*, *KIAA0319*, *FAM65B*, *ZSCAN26*, *UBD*, *DHX16*, *LOC105375015*, *NEU1*, *MUC17*, *GIT2*, *ZNF77*) as potential susceptibility loci for this condition. SNPs of six of these genes (*KIAA0319*, *FAM65B*, *ZSCAN26*, *UBD*, *LOC105375015*, *NEU1*) were significantly associated with serum LDL-cholesterol levels, with minor alleles of these genes representing risk factors for

hyper-LDL-cholesterolemia. Given that SNPs of 10 genes (*PTCH2*, *MOB3C*, *TMOD4*, *COL6A3*, *COL6A5*, *ADGRL3*, *DHX16*, *MUC17*, *GIT2*, *ZNF77*) were not significantly related to the serum LDL-cholesterol concentration, these genes were removed from the list of novel susceptibility loci, even though this discrepancy may be attributable to the effects of lipid-lowering medication. Given that rs13118 of *NEU1* was in significant LD with rs492899 of *SKIV2L* in a large LD block and that rs76463649 of *ZSCAN26* was in LD with SNPs of *SLC17A3*, *ZSCAN31*, *GABBR1*, and *TRIM40*, both *NEU1* and *ZSCAN26* were also excluded from the final results. In addition, significant LD was detected between SNPs of *KIAA0319* and *FAM65B*. We thus identified three novel loci (*KIAA0319-FAM65B*, *UBD*, *LOC105375015*) that confer susceptibility to early-onset hyper-LDL-cholesterolemia.

A recent study has reported that network analysis of functional gene-gene interactions may be informative with regard both to clarification of biological processes underlying coronary artery disease and to the identification of therapeutic targets for this condition (41). A network analysis was therefore performed in the present study in order to predict biological processes related to the identified genes and the interactions of these genes with those previously known to be associated with dyslipidemia. The results from the network analysis revealed that the 10 or three genes associated in the present study with hypo-HDL-cholesterolemia or hyper-LDL-cholesterolemia respectively, had direct or indirect interactions with the 50 dyslipidemia-related genes selected from the DisGeNET database (39,40). The underlying molecular mechanisms of these interactions, however, remain to be elucidated.

Our group has previously reported that two, three and nine SNPs were associated with hypertriglyceridemia ($P < 1.71 \times 10^{-4}$), hypo-HDL-cholesterolemia ($P < 1.44 \times 10^{-4}$),

Table XIII. Relation of genes, chromosomal loci, and SNPs associated with hypertriglyceridemia in the present study to previously examined dyslipidemia-related phenotypes.

Gene/chr locus	SNP	Chr	Position	Previously examined phenotypes
<i>GCKR</i>	rs1260326	2	27508073	Triglycerides (20686565, 21423719, 23063622, 22629316, 19060906, 18193043)
	rs780093	2	27519736	
2p23	rs1260333	2	27525757	Triglycerides (20686565, 19060906, 20864672, 19802338)
<i>LPL</i>	rs301	8	19959423	Triglycerides (20686565)
	rs326		19961928	
	rs328		19962213	
	rs13702		19966981	
	rs15285		19967156	
8p21.3	rs10096633	8	19973410	Triglycerides (20686565, 19060906, 19060911, 21943158, 20139978, 23063622, 23505323, 19060910, 19802338)
8p21.3	rs17482753	8	19975135	Triglycerides (20686565, 23063622, 19060906, 18193043, 21943158, 18179892, 19913121, 17463246)
8p21.3	rs12678919	8	19986711	Triglycerides (20686565, 19060906, 21909109, 21943158, 20139978, 23063622, 23505323)
8p21.3	rs10503669	8	19990179	Triglycerides (20686565, 23063622, 21909109, 19060906, 18193043, 21943158, 19913121)
8p21.3	rs2083637	8	20007664	Triglycerides (20686565, 19060906, 19060911, 21943158, 19802338, 23063622)
8p21.3	rs1441756	8	20010875	Triglycerides (20686565, 19060906)
8p21.3	rs7016880	8	20019235	Triglycerides (20686565, 19060906)
8q24.2	rs2954033	8	125481504	Triglycerides (22479202, 20686565, 23063622, 19060906, 21386085)
<i>BUDI3</i>	rs10790162	11	116639104	Triglycerides (20686565, 23202125, 23063622, 20139978, 19060906, 20864672, 18193046)
	rs7350481	11	116715567	Triglycerides (20686565, 20139978, 19060906)
11q23.3	rs9326246	11	116741017	Triglycerides (23202125, 20686565, 19060906)
<i>ZPR1</i>	rs964184	11	116778201	Triglycerides (20686565, 23063622, 21909109, 19060906, 20864672, 22629316, 20139978, 21943158, 23505323, 23726366, 19913121)
	rs2075290	11	116782580	
<i>APOA5</i>	rs2266788	11	116789970	Triglycerides (20686565, 23063622, 22629316, 19060906, 21943158, 19913121, 18193043, 19802338, 23505323, 23236364)
	rs2075291	11	116790676	
<i>APOA4</i>	rs5104	11	116821618	Triglycerides (20686565, 23063622, 19060906, 23505323, 19197348, 19913121)
	rs11085421	19	20985948	None

Data were obtained from the Genome-Wide Repository of Associations Between SNPs and Phenotypes (GRASP) Search database (<https://grasp.nhlbi.nih.gov/Search.aspx>) with a P-value of $<1.0 \times 10^{-6}$. Numbers in parentheses are PubMed IDs. SNP, single nucleotide polymorphism; Chr, chromosome.

Table XIV. Relation of genes, chromosomal loci and SNPs associated with hypo-HDL-cholesterolemia in the present study to previously examined dyslipidemia-related phenotypes.

Gene/chr locus	SNP	Chr	Position	Previously examined phenotypes
<i>MOB3C</i>	rs139537100	1	46615006	None
<i>TMOD4</i>	rs115287176	1	151170961	None
<i>LPGAT1</i>	rs150552771	1	211783358	None
<i>EHD3</i>	rs116417209	2	31249417	None
<i>SPOPL</i>	rs114501427	2	138568946	None
<i>COL6A3</i>	rs146092501	2	237371861	None
<i>ZNF860</i>	rs140232911	3	31989561	None
<i>CACNA1D</i>	rs35874056	3	53702798	None
<i>COL6A5</i>	rs200982668	3	130470894	None
<i>ADGRL3</i>	rs192210727	4	61909615	None
<i>CXCL8</i>	rs188378669	4	73741568	Total cholesterol (23063622)
<i>MARCH1</i>	rs61734696	4	164197303	Adiponectin concentrations (20887962)
6p22.1	rs9261800	6	30408822	Type 1 diabetes (17554300)
<i>DCLRE1C</i>	rs150854849	10	14934704	None
<i>APOA5</i>	rs2075291	11	116790676	HDL-cholesterol (23063622, 20686565, 22629316, 21386085)
<i>BRAP</i>	rs3782886	12	111672685	HDL-cholesterol (21572416)
<i>ACAD10</i>	rs11066015	12	111730205	LDL-cholesterol (20686565)
<i>ALDH2</i>	rs671	12	111803962	HDL-cholesterol (21572416)
<i>HECTD4</i>	rs2074356	12	112207597	HDL-cholesterol (21572416, 21909109, 22751097)
	rs11066280	12	112379979	
<i>PLCB2</i>	rs200787930	15	40289298	Triglycerides (23063622)
<i>VPS33B</i>	rs199921354	15	91013841	Type 2 diabetes (22885922)
<i>OR4F6</i>	rs141569282	15	101806068	None
16q13	rs247616	16	56955678	HDL-cholesterol (20686565, 19060906, 20339536, 20838585, 19060911, 20031538)
16q13	rs3764261	16	56959412	HDL-cholesterol (20686565, 23063622, 19060911, 21943158, 21347282, 18193043, 20694148, 21589926, 19802338, 19913121)
<i>CETP</i>	rs1532624	16	56971567	HDL-cholesterol (20686565, 23063622, 22629316, 21347282, 21589926, 19060911, 20031564, 19060906, 18193044, 21943158)
<i>ZNF77</i>	rs146879198	19	2934109	None
<i>LILRB2</i>	rs73055442	19	54279838	HDL-cholesterol (20686565)

Data were obtained from the Genome-Wide Repository of Associations Between SNPs and Phenotypes (GRASP) Search database (<https://grasp.nhlbi.nih.gov/Search.aspx>) with a P-value of $<1.0 \times 10^{-6}$. Numbers in parentheses are PubMed IDs. SNP, single nucleotide polymorphism; Chr, chromosome.

and hyper-LDL-cholesterolemia ($P < 1.10 \times 10^{-4}$), respectively, as determined by multivariable logistic regression analysis with adjustment for age and sex, following an initial EWAS screening of allele frequencies among subjects with early- or late-onset forms of these conditions (28). The associations of the two SNPs [rs10790162 ($P = 3.58 \times 10^{-24}$) and rs7350481 ($P = 7.94 \times 10^{-23}$)] with hypertriglyceridemia were replicated ($P < 0.05$) in the present study. The associations of two of the three SNPs [rs147317864 ($P = 0.0139$) and rs12229654 ($P = 0.0001$)] with hypo-HDL-cholesterolemia were replicated in the present study. The associations of eight of the nine

SNPs [rs7771335 ($P = 1.00 \times 10^{-7}$), rs2071653 ($P = 1.61 \times 10^{-5}$), rs2853969 ($P = 6.16 \times 10^{-8}$), rs2269704 ($P = 2.92 \times 10^{-7}$), rs2269703 ($P = 3.67 \times 10^{-7}$), rs495089 ($P = 0.0001$), rs2269702 ($P = 5.13 \times 10^{-7}$) and rs1233399 ($P = 0.0009$)] with hyper-LDL-cholesterolemia were replicated in the present study. Although the association of most SNPs with dyslipidemia identified in our previous study (28) was replicated, genetic variants associated with hypertriglyceridemia, hypo-HDL-cholesterolemia, or hyper-LDL-cholesterolemia appear to differ, at least in part, between early- and late-onset forms of the diseases.

Table XV. Relation of genes, chromosomal loci and SNPs associated with hyper-LDL-cholesterolemia in the present study to previously examined dyslipidemia-related phenotypes.

Gene/chr locus	SNP	Chr	Position	Previously examined phenotypes
<i>PTCH2</i>	rs147284320	1	44828589	None
<i>MOB3C</i>	rs139537100	1	46615006	None
<i>PCSK9</i>	rs151193009	1	55043912	LDL-cholesterol (23063622, 21347282, 18193044, 20686565, 22629316)
<i>TMOD4</i>	rs115287176	1	151170961	None
<i>APOB</i>	rs13306206	2	21019859	LDL-cholesterol (20686565, 23202125, 23063622)
<i>COL6A3</i>	rs146092501	2	237371861	None
<i>COL6A5</i>	rs200982668	3	130470894	None
<i>ADGRL3</i>	rs192210727	4	61909615	None
<i>CXCL8</i>	rs188378669	4	73741568	Total cholesterol (23063622)
<i>MARCH1</i>	rs61734696	4	164197303	Adiponectin concentrations (20887962)
<i>KIAA0319</i>	rs4576240	6	24596250	None
<i>FAM65B</i>	rs150142878	6	24847657	None
<i>SLC17A3</i>	rs34902660	6	25850874	Serum urate (23263486), type 1 diabetes (17554300)
<i>ZSCAN26</i>	rs76463649	6	28271963	None
<i>ZSCAN31</i>	rs6922302	6	28327533	Type 1 diabetes (17554300)
<i>UBD</i>	rs64036	6	29559490	None
<i>GABBR1</i>	rs29243	6	29631325	Type 1 diabetes (17554300)
6p22.1	rs2524272	6	29714623	Type 1 diabetes (17554300)
<i>TRIM40</i>	rs2523995	6	30134407	Type 1 diabetes (17554300, 17632545)
<i>DHX16</i>	rs7749235	6	30667816	None
	rs2285321	6	30670221	
	rs6937357	6	30672547	
<i>PPP1R18</i>	rs9468805	6	30675932	Type 1 diabetes (17632545)
	rs6457254	6	30681357	
	rs2394392	6	30682541	
6p21.3	rs3130663	6	30698817	Type 1 diabetes (17632545, 17554300)
<i>MDC1</i>	rs2269702	6	30707358	Fat mass (19584900), type 1 diabetes (17554300), body mass index (19584900)
	rs28986465	6	30712785	
	rs2075015	6	30712831	
	rs6924270	6	30714203	
<i>TUBB</i>	rs3132584	6	30720650	Type 1 diabetes (17554300)
	rs25527	6	30723161	
	rs9500864	6	30725455	
<i>DPCR1</i>	rs6933400	6	30939399	Type 1 diabetes (17554300, 17632545)
	rs11970154	6	30952101	
6p21.3	rs2508015	6	31042423	Type 1 diabetes (17632545), triglycerides (20686565)
<i>CCHCR1</i>	rs147733073	6	31145462	Triglycerides (20686565)
6p21.3	rs3130685	6	31238429	Triglycerides (20686565), type 1 diabetes (17554300)
<i>LOC105375015</i>	rs9264942	6	31306603	None
6p21.3	rs2596574	6	31366397	LDL-cholesterol (23063622), total cholesterol (23063622), type 1 diabetes (17554300, 17632545)
<i>PRRC2A</i>	rs11538264	6	31635412	Type 1 diabetes (17554300, 17632545), triglycerides (20686565), total cholesterol (20686565)
<i>LY6G6F</i>	rs9267546	6	31705659	Triglycerides (20686565)
	rs17200983	6	31707506	
	rs9267547	6	31707724	
<i>LY6G6C</i>	rs117894946	6	31719250	Type 1 diabetes (17554300, 17632545)
<i>MSH5</i>	rs11754464	6	31755958	Type 1 diabetes (17554300, 17632545), triglycerides (20686565), total cholesterol (20686565)

Table XV. Continued.

Gene/chr locus	SNP	Chr	Position	Previously examined phenotypes
<i>VAR5</i>	rs5030798	6	31779733	Type 1 diabetes (17632545)
	rs11751198	6	31785749	
<i>HSPA1B</i>	rs6457452	6	31827773	Type 1 diabetes (17554300, 17632545)
<i>C6orf48</i>	rs11968400	6	31836952	Triglycerides (20686565), total cholesterol (20686565), type 1 diabetes (17632545)
6p21.3	rs12210887	6	31847946	Type 1 diabetes (17554300, 17632545), triglycerides (20686565), total cholesterol (20686565)
<i>NEU1</i>	rs13118	6	31859509	None
<i>SLC44A4</i>	rs117127493	6	31869232	Type 1 diabetes (17632545), triglycerides (20686565), total cholesterol (20686565)
<i>SKIV2L</i>	rs492899	6	31965741	LDL-cholesterol (20686565), type 1 diabetes (17554300, 17632545), triglycerides (20686565), total cholesterol (20686565)
<i>TNXB</i>	rs140770834	6	32064851	Type 1 diabetes (17554300, 17632545), triglycerides (20686565), total cholesterol (20686565)
6p21.3	rs11751545	6	32073266	
	rs204999	6	32142202	Type 1 diabetes (17632545)
<i>MUC17</i>	rs78010183	7	101035329	None
<i>GIT2</i>	rs2292354	12	109930396	None
<i>HECTD4</i>	rs11066280	12	112379979	LDL-cholesterol (21572416, 20686565), HDL-cholesterol (21572416, 21909109, 22751097)
<i>PLCB2</i>	rs200787930	15	40289298	Triglycerides (23063622)
<i>VPS33B</i>	rs199921354	15	91013841	Type 2 diabetes (22885922)
<i>ZNF77</i>	rs146879198	19	2934109	None
<i>APOE</i>	rs7412	19	44908822	LDL-cholesterol (23100282, 23063622, 20686565, 22629316, 19060911)
<i>APOC1</i>	rs445925	19	44912383	LDL-cholesterol (20686565, 21347282, 18193044, 23063622, 18193043, 20864672, 23100282)

Data were obtained from the Genome-Wide Repository of Associations Between SNPs and Phenotypes (GRASP) Search database (<https://grasp.nhlbi.nih.gov/Search.aspx>) with a P-value of $<1.0 \times 10^{-6}$. Numbers in parentheses are PubMed IDs. SNP, single nucleotide polymorphism; Chr, chromosome.

There are several limitations to the present study. Firstly, given that the results were not replicated, their validation will be necessary in independent study populations or in other ethnic groups. The identified SNPs were not tested in a clinical setting to validate the assessment of genetic risk for dyslipidemia in patients. In addition, it is possible that SNPs identified in the present study may be in LD with other genetic variants in the same gene or in nearby genes that are actually responsible for the development of hypertriglyceridemia, hypo-HDL-cholesterolemia, or hyper-LDL-cholesterolemia. Finally, the functional relevance of identified SNPs to the pathogenesis of hypertriglyceridemia, hypo-HDL-cholesterolemia, or hyper-LDL-cholesterolemia remains to be elucidated.

In conclusion, the present study has identified chromosome 19p12, eight loci (*MOB3C-TMOD4*, *LPGATI*, *EHD3*, *COL6A3*, *ZNF860-CACNAID*, *COL6A5*, *DCLREIC*, *ZNF77*) and three loci (*KIAA0319-FAM65B*, *UBD*, *LOC105375015*) that confer susceptibility to early-onset hypertriglyceridemia, hypo-HDL-cholesterolemia and hyper-LDL-cholesterolemia, respectively. Determination of genotypes for the SNPs at these loci may prove informative for assessment of genetic

risk for hypertriglyceridemia, hypo-HDL-cholesterolemia and hyper-LDL-cholesterolemia in the Japanese population.

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Availability of data and materials

All data underlying the findings described in the article are available on request from the corresponding author.

Authors' contributions

YYam contributed to conception and design of the study; to acquisition, analysis, and interpretation of the data; and to drafting of the manuscript. KK, MO, HH, and TF each

contributed to acquisition of the data and to revision of the manuscript. YYas, IT, and JS contributed to analysis and interpretation of the data as well as to revision of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study protocol complied with the Declaration of Helsinki and was approved by the Committees on the Ethics of Human Research of Mie University Graduate School of Medicine, Hirosaki University Graduate School of Medicine, and participating hospitals (Gifu Prefectural Tajimi Hospital, Gifu Prefectural General Medical Center, Japanese Red Cross Nagoya First Hospital, Northern Mie Medical Center Inabe General Hospital, and Hirosaki Stroke and Rehabilitation Center). Written informed consent for participation in the study was obtained from all subjects.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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