RESEARCH ARTICLE

Genetic Variants Influencing Lipid Levels and Risk of Dyslipidemia in Chinese Population

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Abstract

Recently, several human genetic and genome-wide association studies (GWAS)have discovered many genetic loci that are associated withthe concentration ofthe blood lipids. To confirm reported loci in Chinese population, weconducted a cross-section study to analyzethe association of25reported SNPs,genotyped by the ABI SNaPshot™ method, with the blood levels of total cholesterol (TC), low- density lipoprotein–cholesterol (LDL), high-density lipoprotein–cholesterol (HDL), and triglycerides (TG) in 1900individualsby Multivariate analysis. And logistic regression was applied to assess the association of the genetic loci with the risk of different types of dyslipidemia. Our study hasconvincingly identified that 12 out of 25 studied SNPs were stronglyassociated with one or moreblood lipid parameters (TC, LDL, HDL, and TG). Among of the 12 associated SNPs,10significantlyinfluence the risk of one or more types of dyslipidemia. We firstly found four SNPs (rs12654264 in *HMGCR*; rs2479409 in *PCSK9*; rs16996148 in *CILP2*,*PBX4*; rs4420638 in *APOE-C1-C4-C2*) robustly and independently associate with four types of dyslipidemia (mixed hyperlipidemia, MHL; isolated hypercholesterolemia, IHTC; isolated low HDL-C,ILH; isolated hypertriglyceridemia, IHTG, respectively).Our results suggest that genetic susceptibility is different on the same candidate locus for the different population. Meanwhile, most of reported genetic variants strongly influence one or more plasma lipid levels and the risk of dyslipidemiain Chinese population.

Key words: Dyslipidemia, Lipid Levels, single-nucleotide polymorphisms (SNPs), cardiovascular disease (CVD)，Genetics

Introduction

Cardiovascular disease (CVD) is the leading cause of death around theworld, and predicted to be the major causes of morbidity and mortality in most developing nationsby 2020 globally(Celermajer *et al.* 2012).One of major risk factors of CVD is dyslipidemia(Shanmugasundaram *et al.* 2010), a disorder of lipid and lipoprotein metabolism(Radovica *et al.* 2014). Dyslipidemia is characterized by increased the total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), or triglyceride (TG) concentration, or declined the high-density lipoprotein-cholesterol (HDL-C)concentration in the blood(Goldberg 2013.).The increasingcauses of dyslipidemia are obesity and high fat intake; however, many individuals vary in their responses to dietary cholesterol, indicating the importance of genetic factors(Radovica *et al.* 2014).

Recenthuman genetic and genome-wide association studies (GWAS)have discoveredmany genetic loci that are associated with the concentrations ofdifferent blood lipids (Abifadel *et al.* 2003; Chasman *et al.* 2009; Deo *et al.* 2009; Inouye *et al.* 2012; Kathiresan *et al.* 2008; Kim *et al.* 2011; Kooner *et al.* 2008; Sarzynski *et al.* 2011; Teslovich *et al.* 2010; Wallace *et al.* 2008; Willer *et al.* 2008).More than a hundred of them are at or near one of followinggenes, *ABCA1, APOB, APOE-C1-C4-C2, BCL7B,TBL2,MLXIPL, CELSR2,PSRC1,SORT1, GALNT2, GCKR, HMGCR, LIPG,ACAA2, PCSK9, MLXIPL, LPL, TRIR1, LIPC, CETP, CILP2,PBX4, APOA1-C3-A4-A5,ZNF259,BUD13*(Abifadel *et al.* 2003; Chasman *et al.* 2009; Deo *et al.* 2009; Inouye *et al.* 2012; Kathiresan *et al.* 2008; Kim *et al.* 2011; Kooner *et al.* 2008; Sarzynski *et al.* 2011; Teslovich *et al.* 2010; Wallace *et al.* 2008; Willer *et al.* 2008).These genetic variants have beenreported to significantlyinfluenceone or more lipids in the

blood.However, most of these associations haven't been confirmed in Chinese population, especially relationship between these genetic variants and the riskof dyslipidemia remains unclearly. Here,we report the associationsof the most-informative SNPs from previous studieswith four blood lipid parameters: TC, HDL-C,LDL-C, and TG in Chinesepopulation and to provide more information to characterize thegenetic factors that influence the blood lipid levels.Currently, predict dyslipidemia depends on analysis of environmental risk factors. If we built a database of lipid susceptibility loci of Chinese population, we can predict dyslipidemia with the combination of genetic and environmental risk factors. It will certainly improve the ability to predict dyslipidemia.

Materials and Methods

Subjectsand data collection

This study was a cross-sectional study regarding chronicdiseases and risk factors conducted in Chengdu in 2014. Two urban communities of health examination population in Chengdu were selected randomly.Citizenswere enrolled by a random sampling design.Approval was obtained from the Institutional Review Boards of the Sichuan Academyof Medical Sciences &Sichuan Provincial People's Hospital. Written informedconsent was obtained from all subjects prior to this study. This study was conducted inaccordance with the tenets of the Declarationof Helsinki. In the present study, a total number of 1900 participants, including 746men and 1154women, were recruited by the Hospital of theUniversity of Electronic Science and Technology of China, Sichuan ProvincialPeople's Hospital, Demographic features of the subjects are listed in **Table 1**. All participants were HanChinese from Southern

China.Dyslipidemia was diagnosed according to the criteria set by Joint Committee for Developing Chinese guidelines on Prevention Treatment of Dyslipidemia in Adults and classified into four phenotypes(Prevention *et al.* 2016).(a) isolated hypertriglyceridemia (IHTG) was defined as having TG ≥1.7mmol/L or on medication and TC <5.2 mmol/L; (b) isolated hypercholesterolemia (IHTC) was defined as having TC ≥5.2mmol/l or on medication and TG <1.7mmol/L; (c) mixed hyperlipidemia (MHL) was defined as having TG ≥1.7mmol/L and TC ≥5.2 mmol/L;and (d) isolated low HDL-C (ILH) was defined as having HDL-C ≤1.0 mmol/L. Normal control is defined as subjects without any of dyslipidemia.

Hypertension was defined as SBP ≥140 mmHg, DBP ≥90 mmHg, or current medication for hypertension(James *et al.* 2014).Height, weight, blood pressure,TC, TG, LDL-C and HDL-C were measured. Height and weight were measuredwiththesubject standing barefoot in light clothes. Body mass index (BMI) was calculated asweight (kg) divided by square of height (m). BMI were divided into three categaries: Low BMI, <24 kg/m^2; Middle BMI, 24□28 kg/m^2; High BMI >28 kg/m^2. High glucose was difined as > 6.1mmo/l. Bloodpressure was measured by standard mercury sphygmomanometer on the right arm in sitting position,afterthe participants have rested at least 5 minutes. Blood samples were collected from all the participantsafter an overnight fasting. All the biochemical assessments were conducted in the clinical laboratory of Sichuan Provincial People's Hospital. Concentrations offasting glucose (Glu), TC, HDL-C, TG, andLDL-C were measured using an auto analyzer (Hitachi 717, Hitachi Instruments Inc., Tokyo, Japan).

SNP Selection

Among the six recent GWAS and other five genetic studies on the plasma levels of different blood lipids, 18 genetic loci, including *ABCA1, APOB, APOE-C1-C4-C2, BCL7B-TBL2-MLXIPL, CELSR2,CELSR2-PSRC1-SORT1, GALNT2, GCKR, HMGCR, LIPG-ACAA2, PCSK9, MLXIPL, LPL, TRIR1, LIPC, CETP, CILP2-PBX4, APOA1-C3-A4-A5-ZNF259-BUD13*,were associatedwith one or more lipid traits(Abifadel *et al.* 2003; Chasman *et al.* 2009; Deo *et al.* 2009; Inouye *et al.* 2012; Kathiresan *et al.* 2008; Kim *et al.* 2011; Kooner *et al.* 2008; Sarzynski *et al.* 2011; Teslovich *et al.* 2010; Wallace *et al.* 2008; Willer *et al.* 2008)(**Supplementary table S1**).For HDL cholesterol, the minor alleles of six SNPs (rs3890182 in *ABCA1*, rs4846914 and rs10127775in *GALNT2*, rs2156552 in *LIPG-ACAA2*, rs1800775 in *CETP*,rs28927680 in *APOA1-C3-A4-A5-ZNF259-BUD13*)wereassociated with lower concentrations of HDL-C(Teslovich *et al.* 2010; Wallace *et al.* 2008). Inversely, the minor alleles of SNP rs17145738 in *BCL7B-TBL2-MLXIPL*, rs1077834 in *LIPC*, as well as SNP rs327 and rs331 in *LPL* were associated with higher concentrations of HDL-C(Deo *et al.* 2009; Teslovich *et al.* 2010).For LDL cholesterol, the minor alleles of four SNPs (rs693 and rs676210 in *APOB*, rs4420638 in *APOE-C1-C4-C2*,rs2479409 and rs11583680 in*PCSK9*) show robustly association with higher concentrations of LDL-C (Abifadel *et al.* 2003; Chasman *et al.* 2009; Kathiresan *et al.* 2008). Inversely, the minor alleles of five SNPs (rs599839 and rs646776 in the *CELSR2-PSRC1-SORT1*, rs12654264 and rs3846662 in the *HMGCR*,rs16996148 in *CILP2-PBX4*) were significantly associated with lower concentrations of LDL-C (Kathiresan *et al.* 2008; Wallace *et al.* 2008). For total cholesterol, three SNPs (rs4970834in CELSR2, rs2479409 and rs11583680 in *PCSK9*) were associated with the concentrations of TC(Abifadel *et al.* 2003; Teslovich *et al.* 2010;

Wallace *et al.* 2008). For triglycerides, the minor alleles of SNP rs693 in*APOB*, rs4846914 in *GALNT2*, rs780094 in *GCKR*, and rs28927680 in *APOA1-C3-A4-A5-ZNF259-BUD13*, show significant association with higher concentrations of TG(Kathiresan *et al.* 2008; Teslovich *et al.* 2010; Willer *et al.* 2008). Conversely, those of SNP rs17145738 in *BCL7B-TBL2-MLXIPL*, rs780092 in *GCKR*, rs327 and rs331 in LPL, rs17321515 in *TRIR1*, rs16996148 in *CILP2-PBX4* were associated with the lower concentrations of TG(Deo *et al.* 2009; Kathiresan *et al.* 2008; Kim *et al.* 2011; Teslovich *et al.* 2010; Willer *et al.* 2008). We selected 25 SNPs at 18 genetic lociand genotyped these SNPs in Chinese population.Thefinal SNP set with minor allele frequency higherthan 0.01 and the *P* value of Hardy-Weinberg equilibrium (*P*_HWE) higherthan 0.001.

Genotyping

Venous blood was collected from each subject and collected in anEDTA-containing tube. Genomic DNA was extracted from theblood byserial phenol/chloroform extractionand ethanol precipitation. SNP genotyping was performed by thedye terminator-based SNaPshot method, as previously described(Lu *et al.* 2010). All primers were listed in the **Supplementary table S2**. All 25 SNPs at 18 genetic lociweregenotyped.Genotyping success rate and accuracyweregreater than 98%, judging by random re-genotyping 10% ofthe samples in the subject group.

Statistical Analysis

All statistical were analyzedusing SPSS version 20.0 (IBM Corp).Continuous variables were presented as mean ± standarddeviation (SD) or median (interquartile range)

and categorical variables were presentedas frequencies and proportions. The independent sample t-test orMann–Whitney U test was used to investigate the relationship between continuousvariables.The normal distributions of all quantitative variables were measured with the mean value and its standard deviation (SD), and with the Shapiro–Wilk test. However, none of thelipid levels were normally distributed according to the Shapiro–Wilktest.Therefore, in order to assess the influence of the covariates, multivariate analysiswasemployed with less-stringent normalitycriteria: the 99.10–99.84–100 rule, according to which about 99.10% of values should fit withinan interval of one SD, 99.84% in two SDs, and 100% in three SDs. Among all variables measurements, the TG and glucoselevelswerenotless-stringent normally distributed, so they were Napierian logarithm (ln) transformed for further statistical analysis.A standard chi-square test was used to evaluate the Hardy-Weinberg equilibrium (HWE) and categoricalvariables. All results were considered to be statistically significant with$P < 0.05$.The Bonferroni correction was used to adjust P-values for multiple testing. Multivariate analysis wasused to evaluateassociation of genetic loci with lipid and cholesterol phenotypesadjustedforthe covariates (age, BMI, glucose levels).Logisticregressionwasapplied to assess the association of genetic loci with risk ofdyslipidemiabyusingpossible covariates (age, gender, BMI, glucose levels, blood pressure).Independent associationsamong significant SNPs for different types of dyslipidemia were detected with multiple logistic regression analyses.

Results

In this study, we recruiteda total of 1900individuals, including 746 males and 1154 femaleswith a mean age of 60.06±13.21and 59.61±10.85 years, respectively.Asthere were significant differences of four lipid parameters and BMIbetween men and women groups,gender stratification analysis was conducted for each genetic locus. Basic characteristic of the study subjects was list in **Table 1**.

All 25 SNPs were genotyped, and two SNPs (rs28927680 and rs676210) were excluded due to the MAF <0.01 and *P*_HWE <0.001, respectively.Thedistributions of the rest of 23 SNPs allele were within the Hardy-Weinberg equilibrium.Association analysis results of lipid parameters with Identified genetic loci in overall subjectsare shown in**Supplementary table S3.**12 SNPs located atnine genetic loci were significantly associated with one or more lipid traits (**Table 2**).For LDL cholesterol，the minor alleles of five SNPs (rs599839 and rs646776 in *CELSR2-PSRC1-SORT1*, rs12654264 and rs3846662 in*HMGCR*,rs4970834 in *CELSR*2) were significantly associated with lower concentrations of LDL-C. Moreover, three SNPs (rs12654264, rs599839 and rs646776) only showed associationin women group, while the other two SNPs (rs3846662 and rs4970834) showed significantly association within both men and women groups.For HDL cholesterol, five SNPs (rs3812316, rs327, rs331, rs1077834 and rs1800775) in *MLXIPL, LPL, LIPC* and*CETP*were associated with HDL-C.The minor alleles of two leading SNPs (rs327 and rs331) in the *LPL*gene were associated with lower concentrations of HDL-C.For total cholesterol, eight SNPs at six genetic lociwere associated with the TC concentration. For triglycerides, the minor alleles of two SNPs (rs327 and rs331) in the *LPL*gene, rs17145738 in *BCL7B-TBL2-MLXIPL*and rs3812316in*MLXIPL*were associated with lower concentrations of TG, which showed

association in women group (**Table 2**).After Bonferroni correction, several significant SNPs in *CELSR2*、*CELSR2-PSRC1-SORT1*、*HMGCR*、*LPL*still show significant association with corresponding phenotypes.

In order to investigate whether the 12 lipid-associatedSNPs were related to dyslipidemia, wedivided the 1900 participants into normal and four dyslipidemia phenotypes groups, andthen evaluated the allelefrequencies between normal group and each dyslipidemia group.After the association analysis, 10SNPs significantly associated with different kinds of dyslipidemiawere shown in **Table 3**. rs599839 and rs646776 in the *CELSR2, PSRC1, SORT1*,as well as rs12654264 in *HMGCR* show significant association with the MHL in overall subjects (*P*=0.001, OR=0.406; *P*=0.017, OR=0.501; *P*=0.033, OR=0.779, respectively). Moreover, rs599839 and rs646776 in the *CELSR2, PSRC1, SORT1* showmore rebust association with MLP in men group(*P*=0.007, OR=0.219; *P*=0.018, OR=0.26, respectively). However, rs17321515 in *TRIR1* just show weak association with the MHL and IHTC in women group (*P*=0.046, OR=1.376). Moreover, The minor allele of rs2479409 *PCSK9* and rs16996148 *CILP2,PBX4*is the risk factor for IHTC and ILH in men group (*P*=0.006, OR=1.63; *P*=0.013, OR=3.33, respectively).rs327 and rs331 in *LPL* are weakly associated with IHL and IHTG(*P*=0.042, OR=0.456; *P*=0.045, OR=0.694, respectively). rs4420638 in *APOE-C1-C4-C2* and rs28927680 in*APOA1-C3-A4-A5,ZNF259,BUD13* show association with IHTG in women group and overall group.

In order to detect the independent associationsamong the significant SNPs for dyslipidemia, multiple logistic regression analyses were conducted (**Table 4)**.For the phenotype of MHL, rs12654264 showedmost robust and independent association with

MHL in women group and overall group (*P*=0.001, OR=0.576; P=0.00,OR=0.584,respectively). For IHTC, rs2479409 is robustly and independently associated with IHTC in men group (*P*=0.003,OR=1.816). For IHL, rs16996148 show strongest and independent association with IHL in men group and overall group(*P*=0.005, OR=4.006; *P*=0.011, OR=2.78, respectively). For IHTG, rs4420638 is robustly and independently associated with IHTG in women group and overall group (*P*<0.001,OR=2.65; *P*=0.001,OR=1.91,respectively).

Discussion

This study aims to identify associations of 25Identified SNPs with the blood lipid levels anddifferent kinds of dyslipidemia in Chinese population. This is the first report, as far as we know,that the most genetic loctinvolvedin the lipid-related metabolic pathways, were simultaneously studied with a relatively large groupofChinese (746 males, 1154females). Our study hasconvincingly identified 12 out of the 25 SNPs were significantly associated withone or moreblood lipid parameters, and10outof the 12 associated SNPs were significantly associated with one or more types of dyslipidemia.Moreover, we further found four robust and indenpent association SNP for four kinds of dyslipidemia.

Inprevious studies, ten leading SNPs in *ABCA1*,*GALNT2*,*LIPG-ACAA2*, *CETP*,*APOA1-C3-A4-A5, ZNF259, BUD13* clusters,*BCL7B-TBL2-MLXIPL, LIPC, and LPL* were associated with the blood concentrations of HDL-C(Deo *et al.* 2009; Teslovich *et al.* 2010; Wallace *et al.* 2008).In this study, we confirmedfour SNPs in *LPL, LIPC,*and *CETP*, were associated withthe HDL–C levels and linked a novelSNPin*MLXIPL* to it. Moreover, the minor alleles of two leading SNPs (rs327 and rs331in *LPL*)

significantlyreduce the risk of ILH and IHTG, respectively. LPL is a triglyceride hydrolase hydrolyzing the triglycerides in triglyceride-rich lipoproteins (TRLs; chylomicrons and VLDL)(Korn 1955a; 1955b).LPLcould play a role in stimulating clearance of remnant lipoproteinsby the liver(Skottova *et al.* 1995). Recently,Smithet al identified rs327is the functional SNP in the20 Identified SNPsat *LPL*genetic locus (Smith *et al.* 2010).

For total cholesterol, three SNPs (rs4970834 in *CELSR2*, rs2479409 and rs11583680 in *PCSK9*) were associated with the concentrations of TC(Abifadel *et al.* 2003; Teslovich *et al.* 2010; Wallace *et al.* 2008). In our study, seven novel SNPs in five novel genetic loci (*CELSR2-PSRC1-SORT1*, *HMGCR*, *LPL, TRIR1* and *LIPC*) showed significantly association with TC. Rs4970834 in *CELSR2* was also associated with TC, inversely, rs2479409 and rs11583680 in *PCSK9* were not so.

For triglycerides, SNP rs693 in *APOB*, rs4846914 in *GALNT2*, rs780094 in *GCKR*, rs28927680 in *APOA1-C3-A4-A5-ZNF259-BUD13*, rs17145738 in *BCL7B-TBL2-MLXIPL*, rs780092 in *GCKR*, rs327 and rs331 in *LPL*, rs17321515 in *TRIR1* and rs16996148 in *CILP2-PBX4* were associated with the lower concentrations of TG(Deo *et al.* 2009; Kathiresan *et al.* 2008; Kim *et al.* 2011; Teslovich *et al.* 2010; Willer *et al.* 2008). We confirmed that rs17145738 in *BCL7B-TBL2-MLXIPL*, as well as rs327 and rs331 in LPL were associated with TG, while the other SNPs were not so in Chinese population.

For LDL cholesterol, previous studies found that 9SNPs (rs693 and rs676210 in *APOB*, rs4420638 in *APOE-C1-C4-C2*,rs2479409 and rs11583680 in*PCSK9*, rs599839 and rs646776 in *CELSR2-PSRC1-SORT1*, rs12654264 and rs3846662 in

HMGCR,rs16996148 in *CILP2-PBX4*) were significantly associated with LDL-C (Abifadel *et al.* 2003; Kathiresan *et al.* 2008; Wallace *et al.* 2008). We validated 4 SNPs in *CELSR2-PSRC1-SORT1* and *HMGCR*associated with LDL-C, and discovered two novel associated SNPs (rs4970834 and rs17321515) in *CELSR2* and *TRIR1*.Further investigation suggests that the minor alleles of 3 SNPs in*CELSR2*, *CELSR2-PSRC1-SORT1* and *HMGCR* significantly decreased the risk of MHL. And our results was consistent with the other replication study in a Japanese population(Nakayama *et al.* 2009).

For dyslipidemia, we found four SNPs show robustly and independently associate with four kinds of dyslipidemia. For the phenotype of MHL, rs12654264 in *HMGCR* (0.103mmol/l per A allele) showed strong evidence of association with MHL after multiple testing corrections. Many previous study have reported that rs12654264 is associated with trait of LDL-C in different population.(Hamrefors *et al.* 2010; Liu *et al.* 2011; Park *et al.* 2011; Taylor *et al.* 2013). For the phenotype of IHTC,the association between rs12654264 and IHTC in *PCSK9* proved to be gender-specific with signifcance observed only in males but not females. And rs16996148 is also gender-specific with signifcance observed only in males for ILH phenotype, which is consistent with previous study(Yan *et al.* 2011). For IHTG, rs4420638 show strong and independent association with rs4420638. rs4420638 showed strong evidence for association with LDL-C(Liu *et al.* 2011). Moreover, Huang et al report that rs4420638 genotype AA is significantly associated with the concentrations of circulating HDL-C and APOA-I in CHD in Han Chinese males(Huang *et al.* 2015). As far as we know, we firtly discover that rs4420638 sex-specific with signifcance observed only in women for IHTG phenotype.

However, our study have some limitations. Since the impact of the environmental factors on lipid levels is important, our study lack of the information on demographics, socioeconomic status, cigarette smoking, alcohol consumption, and physical activity. Further analysis concerning the correlation betweenSNPs in candidate genes is warranted.

In conclusion, Meanwhile, we firstly found four SNP (rs12654264 in *HMGCR*; rs2479409 in *PCSK9*; rs16996148 in *CILP2*,*PBX4*; rs4420638 in *APOE-C1-C4-C2*) robustly and independently associate with four types of dyslipidemia.Thus, our results suggest that the genetic variants strongly influence one or more plasma lipid levels and the risk of dyslipidemia in Chinese population.

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References

Abifadel M., Varret M., Rabes J. P., Allard D., Ouguerram K., Devillers M.*,et al*. 2003 Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. Nat Genet. **34**,154-156.

Celermajer D. S., Chow C. K., Marijon E., Anstey N. M., Woo K. S. 2012 Cardiovascular disease in the developing world: prevalences, patterns, and the potential of early disease detection. J Am Coll Cardiol. **60**,1207-1216.

Chasman D. I., Pare G., Mora S., Hopewell J. C., Peloso G., Clarke R.*,et al*. 2009 Forty-three loci associated with plasma lipoprotein size, concentration, and cholesterol content in genome-wide analysis. PLoS Genet. **5**,e1000730.

Deo R. C., Reich D., Tandon A., Akylbekova E., Patterson N., Waliszewska A.*,et al*. 2009 Genetic differences between the determinants of lipid profile phenotypes in African and European Americans: the Jackson Heart Study. PLoS Genet. **5**,e1000342.

Goldberg A. C. 2013. Dyslipidemia. http://www.merckmanuals.com/professional/endocrine_and_metabolic_disorders/lipid_disorders/dyslipidemia.html.

Hamrefors V., Orho-Melander M., Krauss R. M., Hedblad B., Almgren P., Berglund G.*,et al*. 2010 A gene score of nine LDL and HDL regulating genes is associated with fluvastatin-induced cholesterol changes in women. Journal of Lipid Research. **51**,625.

Huang Y., Ye H. D., Gao X., Nie S., Hong Q. X., Ji H. H.*,et al*. 2015 Significant interaction of APOE rs4420638 polymorphism with HDL-C and APOA-I levels in coronary heart disease in Han Chinese men. Genetics & Molecular Research Gmr. **14**,13414.

Inouye M., Ripatti S., Kettunen J., Lyytikainen L. P., Oksala N., Laurila P. P.*,et al*. 2012 Novel Loci for metabolic networks and multi-tissue expression studies reveal genes for atherosclerosis. PLoS Genet. **8**,e1002907.

James P. A., Oparil S., Carter B. L., Cushman W. C., Dennison-Himmelfarb C., Handler J.*,et al*. 2014 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). Jama. **311**,507-520.

Kathiresan S., Melander O., Guiducci C., Surti A., Burtt N. P., Rieder M. J.*,et al*. 2008 Six new loci associated with blood low-density lipoprotein cholesterol, high-density lipoprotein cholesterol or triglycerides in humans. Nat Genet. **40**,189-197.

Kim Y. J., Go M. J., Hu C., Hong C. B., Kim Y. K., Lee J. Y.*,et al*. 2011 Large-scale genome-wide association studies in East Asians identify new genetic loci influencing metabolic traits. Nat Genet. **43**,990-995.

Kooner J. S., Chambers J. C., Aguilar-Salinas C. A., Hinds D. A., Hyde C. L., Warnes G. R.*,et al*. 2008 Genome-wide scan identifies variation in MLXIPL associated with plasma triglycerides. Nat Genet. **40**,149-151.

Korn E. D. 1955a Clearing factor, a heparin-activated lipoprotein lipase. I. Isolation and characterization of the enzyme from normal rat heart. J Biol Chem. **215**,1-14.

Korn E. D. 1955b Clearing factor, a heparin-activated lipoprotein lipase. II. Substrate specificity and activation of coconut oil. J Biol Chem. **215**,15-26.

Liu Y., Zhou D., Zhang Z., Song Y., Zhang D., Zhao T.*,et al*. 2011 Effects of genetic variants on lipid parameters and dyslipidemia in a Chinese population. Journal of Lipid Research. **52**,354-360.

Lu F., Zhao P., Fan Y., Tang S., Hu J., Liu X.*,et al*. 2010 An association study of SERPING1 gene and age-related macular degeneration in a Han Chinese population. Mol Vis. **16**,1-6.

Nakayama K., Bayasgalan T., Yamanaka K., Kumada M., Gotoh T., Utsumi N.*,et al*. 2009 Large scale replication analysis of loci associated with lipid concentrations in a Japanese population. Journal of Medical Genetics. **46**,370-374.

Park M. H., Kim N. H., Lee J. Y., Park H. Y. 2011 Genetic loci associated with lipid concentrations and cardiovascular risk factors in the Korean population. Journal of Medical Genetics. **48**,10.

Joint Committee for Developing Chinese guidelines on Prevention and Treatment of Dyslipidemia in Adults. 2016 [Chinese guidelines on prevention and treatment of dyslipidemia in adults (2016 revised edition)]. Chinese Circulation Journal. **31**,937-953.

Radovica I., Fridmanis D., Silamikelis I., Nikitina-Zake L., Klovins J. 2014 Association between CETP, MLXIPL, and TOMM40 polymorphisms and serum lipid levels in a Latvian population. Meta Gene. **2**,565-578.

Sarzynski M. A., Jacobson P., Rankinen T., Carlsson B., Sjostrom L., Carlsson L. M.*,et al*. 2011 Association of GWAS-based candidate genes with HDL-cholesterol levels before and after bariatric surgery in the Swedish obese subjects study. J Clin Endocrinol Metab. **96**,E953-957.

Shanmugasundaram M., Rough S. J., Alpert J. S. 2010 Dyslipidemia in the elderly: should it be treated? Clin Cardiol. **33**,4-9.

Skottova N., Savonen R., Lookene A., Hultin M., Olivecrona G. 1995 Lipoprotein lipase enhances removal of chylomicrons and chylomicron remnants by the perfused rat liver. J Lipid Res. **36**,1334-1344.

Smith A. J., Palmen J., Putt W., Talmud P. J., Humphries S. E., Drenos F. 2010 Application of statistical and functional methodologies for the investigation of genetic determinants of

coronary heart disease biomarkers: lipoprotein lipase genotype and plasma triglycerides as an exemplar. Hum Mol Genet. **19**,3936-3947.

Taylor K. C., Carty C. L., Dumitrescu L., Bůžková P., Cole S. A., Hindorff L.*,et al*. 2013 Investigation of gene-by-sex interactions for lipid traits in diverse populations from the population architecture using genomics and epidemiology study. BMC Genetics. **14**,1-10.

Teslovich T. M., Musunuru K., Smith A. V., Edmondson A. C., Stylianou I. M., Koseki M.*,et al*. 2010 Biological, clinical and population relevance of 95 loci for blood lipids. Nature. **466**,707-713.

Wallace C., Newhouse S. J., Braund P., Zhang F., Tobin M., Falchi M.*,et al*. 2008 Genome-wide association study identifies genes for biomarkers of cardiovascular disease: serum urate and dyslipidemia. Am J Hum Genet. **82**,139-149.

Willer C. J., Sanna S., Jackson A. U., Scuteri A., Bonnycastle L. L., Clarke R.*,et al*. 2008 Newly identified loci that influence lipid concentrations and risk of coronary artery disease. Nat Genet. **40**,161-169.

Yan T. T., Yin R. X., Li Q., Huang P., Zeng X. N., Huang K. K.*,et al*. 2011 Sex-specific association of rs16996148 SNP in the NCAN/CILP2/PBX4 and serum lipid levels in the Mulao and Han populations. Lipids in Health & Disease. **10**,248.

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Tables

Table 1.Basic characteristic of the study subjects

	Men(n=746)	Women(n=1154)
Age(years),mean±SD *	60.06±13.21	59.61±10.85
BMI (kg/m^2),mean±SD *	24.25±3.08	23.84±3.18
Glu(mmol/L),median(Q1,Q3) *	4.97(4.6,5.4)	4.85(4.52,5.36)
IHTG, n (%)	120(16.1)	98(8.5)
TC(mmol/L) ,mean±SD	4.57±0.029	4.67±0.44
TG(mmol/L),median(Q1,Q3) *	2.28(1.91,2.96)	2.22(1.93,2.80)
HDL-C(mmol/L) ,mean±SD *	1.04±0.015	1.11±0.23
LDL-C(mmol/L) ,mean±SD *	2.77±0.031	2.80±0.44
IHTC, n (%)	174(23.3)	405(35.1)
TC(mmol/L) ,mean±SD	5.92±0.373	5.91±0.56
TG(mmol/L),median(Q1,Q3) *	1.11(0.86,1.39)	1.11(0.89,1.38)
HDL-C(mmol/L) ,mean±SD *	1.49±0.018	1.53±0.30
LDL-C(mmol/L) ,mean±SD *	3.70±0.046	3.61±0.72
MLP, n (%)	130(17.4)	200(17.3)
TC(mmol/L) ,mean±SD	5.98±0.042	6.19±0.78
TG(mmol/L),median(Q1,Q3) *	2.38(1.93,3.53)	2.25(1.92,2.97)
HDL-C(mmol/L) ,mean±SD *	1.18±0.013	1.26±0.24
LDL-C(mmol/L) ,mean±SD *	3.86±0.044	3.91±0.74
ILH, n (%)	42(5.6)	19(1.6)
TC(mmol/L) ,mean±SD	4.15±0.063	4.07±0.58
TG(mmol/L),median(Q1,Q3) *	1.16(0.91,1.41)	1.15(1.03,1.46)
HDL-C(mmol/L) ,mean±SD *	0.92±0.011	2.67±0.08
LDL-C(mmol/L) ,mean±SD *	2.69±0.068	0.89±0.66
Normal, n (%)	280(37.5)	432(37.4)
TC(mmol/L) ,mean±SD	4.50±0.019	4.54±0.47
TG(mmol/L),median(Q1,Q3) *	0.92(0.72,1.21)	0.94(0.73,1.21)
HDL-C(mmol/L) ,mean±SD *	1.33±0.009	1.42±0.25
LDL-C(mmol/L) ,mean±SD *	2.60±0.021	2.51±0.53

*Statistically significant difference (P<0.05) between men and women.SD, standard deviation; Q1, first quartile of the interquartile range; Q3, third quartile of the interquartile range; TC, total cholesterol; LDL-C, low-density lipoprotein-cholesterol; TG, triglyceride; HDL-C, the high-density lipoprotein-cholesterol. (a) isolated hypertriglyceridemia (IHTG) was defined as having TG ≥1.7mmol/L or on medication and TC <5.2 mmol/L; (b) isolated hypercholesterolemia (IHTC) was defined as having TC ≥5.2mmol/l or on medication and TG <1.7mmol/L; (c) mixed hyperlipidemia (MHL) was defined as having TG ≥1.7mmol/L and TC ≥5.2 mmol/L;and (d) isolated low HDL-C (ILH) was defined as having HDL-C ≤1.0 mmol/L. SNPs with P values<0.05 are marked in bold;

Table 2.SNPs significantly associated with lipid parameters

SNP (Minor allele)	Trait	Nearest genes	Position*	*P*_HWE	MAF	Men		Women		Overall	
						P	**B**	***P***	**B**	***P***	**B**
rs4970834(T)	LDL-C	*CELSR2*	chr1:109814880	0.92	0.039	**0.024**	-0.303	**0.006**	-0.282	**4.49x10^{-4}**	-0.286
	TC					0.238	-0.167	**0.01**	-0.284	**0.008**	-0.236
rs599839(G)	LDL-C	*CELSR2,PSRC1,SORT1*	chr1:109822166	0.505	0.065	0.116	-0.174	**1.83x10^{-4}**	-0.292	**1.5x10^{-5}**	-0.272
	TC					**0.03**	0.227	**0.001**	-0.283	**3.7x10^{-4}**	-0.242
rs646776(C)	LDL-C	*CELSR2,PSRC1,SORT1*	chr1:109818530	0.67	0.084	0.18	-0.156	**3.34x10^{-4}**	-0.297	**3.5x10^{-5}**	-0.275
	TC					**0.048**	0.218	**0.001**	-0.295	**0.001**	-0.248
rs12654264(A)	LDL-C	*HMGCR*	chr5:74648603	0.055	0.492	0.051	-0.105	**0.002**	-0.127	**0.001**	-0.103
	TC					0.277	-0.056	**8.6x10^{-5}**	-0.169	**1.4x10^{-5}**	-0.148
rs3846662(T)	LDL-C	*HMGCR*	chr5:74651084	0.181	0.49	**0.029**	-0.122	**0.003**	-0.122	**0.001**	-0.109
	TC					0.126	-0.079	**0.002**	-0.142	**9.9x10^{-5}**	-0.138
rs17145738(T)	Ln TG†	*BCL7B,TBL2,MLXIPL*	chr7:72982874			0.192	-0.076	0.063	-0.074	**0.008**	-0.088
rs3812316(G)	HDL-C	*MLXIPL*	chr7:73020337	0.283	0.089	0.215	0.042	0.119	0.038	**0.034**	0.042
	Ln TG†					0.764	-0.018	**0.009**	-0.11	**0.023**	-0.079
rs327(G)	HDL-C	*LPL*	chr8:19819536	0.323	0.189	**0.003**	0.071	0.053	0.036	**0.001**	0.049
	Ln TG†					0.102	-0.073	0.051	-0.062	**0.017**	-0.062
rs331(A)	HDL-C	*LPL*	chr8:19820405	0.31	0.184	**0.012**	0.062	**0.012**	0.045	**1.19x10^{-4}**	0.056
	TC					0.112	0.113	0.309	0.056	**0.048**	0.087
	Ln TG†					0.121	-0.069	**0.033**	-0.065	**0.01**	-0.065
rs17321515(A)	LDL-C	*TRIR1*	chr8:126486409	0.1	431	0.086	0.094	**0.017**	0.099	**0.005**	0.093
	TC					0.846	0.011	**0.002**	0.136	**0.017**	0.086
rs1077834(C)	HDL-C	*LIPC*	chr15:58723479	0.294	0.374	**0.032**	0.043	**0.032**	0.033	**0.004**	0.035
	TC					0.303	0.059	**0.007**	0.128	**0.016**	0.089
rs1800775(A)	HDL-C	*CETP*	chr16:56995236	0.284	0.458	0.129	-0.029	**0.013**	-0.037	**0.004**	0.034

*Genomic position and chromosome in build 37. †TG transformed by Napierian logarithm. SNPs with P values<0.05 are marked in bold; SNPs with P values <0.05 after Bonferroni correction (Corresponding P value×12 <0.05) are black highlighted with white letters. All calculations were made with a Univariate analysis with covariates (age, BMI, and glucose levels). TC, total cholesterol; LDL-C, low-density lipoprotein-cholesterol; TG, triglyceride; HDL-C, the high-density lipoprotein-cholesterol; *P*_HWE, *P* value of Hardy-Weinberg equilibrium; MAF, the minor allele frequency;

Table 3.SNPs significantly associated with different kinds of dyslipidemia

SNP (Minor allele)	Trait	Nearest genes	Position*	Men		Women		Overall	
				P	OR	*P*	OR	*P*	OR
rs599839(G)	MHL	*CELSR2,PSRC1,SORT1*	chr1:109822166	**0.007**	0.219	**0.046**	0.516	**0.001**	0.406
rs646776(C)	MHL	*CELSR2,PSRC1,SORT1*	chr1:109818530	**0.018**	0.26	0.23	0.67	**0.017**	0.501
rs12654264(A)	MHL	*HMGCR*	chr5:74648603	0.316	0.824	0.060	0.754	**0.033**	0.779
rs17321515(A)	MHL	*TRIR1*	chr8:126486409	0.797	0.949	**0.044**	1.376	0.238	1.156
	IHTC			0.760	0.948	**0.047**	1.274	0.164	1.147
rs2479409(A)	IHTC	*PCSK9*	chr1:55504650	**0.006**	1.631	0.965	0.995	0.108	0.175
rs16996148(T)	ILH	*CILP2,PBX4*	chr19:19658472	**0.013**	3.332	0.928	0.933	0.065	2.010
rs327(G)	ILH	*LPL*	chr8:19819536	0.093	0.460	0.200	0.378	**0.042**	0.456
rs331(A)	IHTG	*LPL*	chr8:19820405	0.222	0.719	0.050	0.60	**0.045**	0.694
rs4420638(G)	IHTG	*APOE-C1-C4-C2*	chr19:45422946	0.30	1.316	**0.004**	2.005	**0.002**	1.712
rs28927680(G)	IHTG	*APOA1-C3-A4-A5,ZNF259,BUD13*	chr11:116619073	0.626	0.907	**0.035**	0.661	0.066	0.778

*Genomic position and chromosome in build 37. † (a) isolated hypertriglyceridemia (IHTG) was defined as having TG ≥1.7mmol/L or on medication and TC <5.2 mmol/L; (b) isolated hypercholesterolemia (IHTC) was defined as having TC ≥5.2mmol/l or on medication and TG <1.7mmol/L; (c) mixed hyperlipidemia (MHL) was defined as having TG ≥1.7mmol/L and TC ≥5.2 mmol/L;and (d) isolated low HDL-C (ILH) was defined as having HDL-C <1.0 mmol/L. SNPs with P values<0.05 are marked in bold; SNPs with P values <0.05 after Bonferroni correction (Corresponding P value×10 <0.05) are black highlighted with white letters. The results of overall were made with a Logistic regression with covariates (age, gender, BMI, glucose levels, blood pressure), while the results of men or women were calculated by the Logistic regression with covariates (age, BMI, glucose levels, blood pressure).

Table 4.Multiple Logistic Regression Analysis of SNPs significantly associated with MLP of dyslipidemia in overall subjects

Trait	SNP (Minor allele)	Nearest genes	Men		Women		Overall	
			P	**OR**	***P***	**OR**	***P***	**OR**
MHL	rs599839(G)	*CELSR2,PSRC1,SORT1*	0.123	0.210	0.099	0.323	**0.026**	0.289
	rs646776(C)	*CELSR2,PSRC1,SORT1*	0.631	0.604	0.453	1.704	0.787	1.17
	rs12654264(A)	*HMGCR*	0.598	0.892	**0.001**	0.576	**0.004**	0.684
	rs17321515(A)	*TRIR1*	0.742	1.07	**0.006**	1.604	**0.027**	1.34
IHTC	rs17321515(A)	*TRIR1*	0.304	0.8278	**0.04**	1.295	0.256	1.124
	rs2479409(A)	*PCSK9*	**0.003**	1.816	0.70	0.95	0.186	1.15
ILH	rs16996148(T)	*CILP2,PBX4*	**0.005**	4.066	0.678	1.39	**0.011**	2.78
	rs327(G)	*LPL*	0.089	0.447	0.184	0.362	**0.023**	0.408
IHTG	rs331(A)	*LPL*	0.731	0.078	**0.038**	0.634	0.139	0.80
	rs4420638(G)	*APOE-C1-C4-C2*	0.467	1.232	**<0.001**	2.651	**0.001**	1.913
	rs28927680(G)	*APOA1-C3-A4-A5,ZNF259,BUD13*	0.423	0.842	0.154	0.73	0.071	0.762

SNPs with P values<0.05 are marked in bold; SNPs with P values <0.05 after Bonferroni correction (Corresponding P value×the number of SNPs in corespongding phenotype <0.05) are black highlighted with white letters. MHL, mixed hyperlipidemia ; Glu, glucose levels; BP, blood pressure; All calculations were calculated by a Logistic regression with covariates (age, gender, BMI, glucose levels, blood pressure)

Supplementary table S1.The general information of selected SNPs

NO.	SNP	Allele(minor/major)	Position*	Nearest genes	SNP type	Trait
1	rs3890182	A/G	chr9:107647655	*ABCA1*	intronic	HDL↓
2	rs693	T/C	chr2: 21232195	*APOB*	coding	LDL↑TG↑
3	rs676210	G/A	chr2:21231524	*APOB*	coding	oxLDL↑ LDL↑
4	rs4420638	G/A	chr19:45422946	*APOE-C1-C4-C2*	5'upstream	LDL↑
5	rs17145738	T/C	chr7:72982874	*BCL7B,TBL2,MLXIPL*	intergenic	TG↓HDL↑
6	rs4970834	T/C	chr1:109814880	*CELSR2*	intronic	TC↓
7	rs599839	G/A	chr1:109822166	*CELSR2,PSRC1,SORT1*	intergenic	LDL↓
8	rs646776	C/T	chr1:109818530	*CELSR2,PSRC1,SORT1*	intergenic	LDL↓
9	rs4846914	A/G	chr1:230295691	*GALNT2*	intronic	HDL↓TG↑
10	rs10127775	T/A	chr1:230295789	*GALNT2*	intronic	HDL↓
11	rs780092	G/A	chr2:27743154	*GCKR*	intronic	TG↓
12	rs780094	C/T	chr2:27741237	*GCKR*	intronic	TG↑

13	rs12654264	A/T	chr5:74648603	*HMGCR*	intronic	LDL↓
14	rs3846662	T/C	chr5:74651084	*HMGCR*	intronic	LDL↓
15	rs2156552	A/T	chr18:47181668	*LIPG,ACAA2*	intergenic	HDL↓
16	rs2479409	A/G	chr1:55504650	*PCSK9*	upstream variant 2KB	LDL↑TC↑
17	rs11583680	T/C	chr1:55505668	*PCSK9*	coding	LDL↑TC↑
18	rs3812316	G/C	chr7:73020337	*MLXIPL*	coding	TG↑
19	rs327	G/T	chr8:19819536	*LPL*	intronic	HDL↑TG↓
20	rs331	A/G	chr8:19820405	*LPL*	intron variant	HDL↑TG↓
21	rs17321515	A/G	chr8:126486409	*TRIR1*	3'downstream	TG↓
22	rs1077834	C/T	chr15:58723479	*LIPC*	intronic	HDL↑
23	rs1800775	C/A	chr16:56995236	*CETP*	5'upstream	HDL↓
24	rs16996148	T/G	chr19:19658472	*CILP2,PBX4*	intergenic	LDL↓TG↓
25	rs28927680	G/C	chr11:116619073	*APOA1-C3-A4-A5,ZNF259,BUD13*	5'upstream	HDL↓TG↑

*Genomic position and chromosome in build 37. ↑:the minor allele of corresponding SNPwas associated with higherconcentrations of corresponding trait.↓:the minor allele of corresponding SNPwas associated with lower concentrations of corresponding trait.

Supplementary table S2.The list of all primers

NO.	SNP	Forward(5'→3')	Reverse(5'→3')	Snapshot primer	Size
1	rs3890182	GGTTGCAGTGAGCCAAGATC	GTGTTTTTCAGGTGCCCTTG	ATCTCCATGGTCCCAATCCAAGCCTCTTCCTCACACCTGCGGTTAGATTG	313
2	rs693	GGAAAGCCTACAGGACACCA	TTAGCAGCAAGAGTCCACCA	AAGGCCAAATTCCGAGAGAC	234
3	rs676210	CTTCGTTTGCTGAGGTGGTT	GCCAGACTTCCGTTTACCAG	CAAAAGTAGGTACTTCAATTGTGTGTGAGATGTGGGGAAGCTGGAATTCT	236
4	rs4420638	CCCTGTGCTGAGGATGTTTT	GCTGAGATCGCACCACTGTA	CTAGCAATGTCACTATGCTACACTTTTCCT	310
5	rs17145738	CACTTCTGTCCCCACCTTCT	TGCTCTCGAACTCCTGACCT	ACTGACCCTTCACACATTTA	247
6	rs4970834	GACCTGAGCATGTGGAAGGT	CAGCAAGAAGGGGATGTAGC	TCCCAGCCTGGGGCCAGCCATCCCACTCCCCACTTACTGA	240
7	rs599839	CCTGGGTGACAGAGCAAGAT	TACTGGACTCTGGCCTGCTT	TTCTCTGTATATCTGGAAGT	231
8	rs646776	CCCTGCTTCTTGAATTCTGC	CTGTCCGCTTCTGTGTGGTA	CCAGCTATTTGGGAGCAGTGTCATGGACAT	371
9	rs4846914	TCATTGTGGACCTGTTGGAA	TCATGGAAGGGAGTGAGGAA	CCTACTCTGGAGGA GTCAGCTGCTGTGCCTTCTGGGACTGCCAA	304

10	rs10127775	TCATTGTGGACCTGTTGGAA	TCATGGAAGGGAGTGAGGAA	AGCCGCACCACCCAGGTGCTTCCCTCCTCCCCACTCCTAGGCCA	304
11	rs780092	CTGGGACTTGGTGAATGACC	GGCAACCCTATGTGAAAGGA	GCCTAGCTCAAAATACCACCCCTTCCATGAGGCCTTCTTT	239
12	rs780094	CGGGTATCAGACAGGAGGAG	CATCATGTTGGCTAGGCTTG	TGACTTATTCTGCTCCAGGGCCCCAGTTTTTTAGACCATGACTGACACAT	247
13	rs12654264	TGTTCACACCTTTAGGGCAA	CCATCTAAGAGCCCGATGTC	CTTTCTTTTCTGAAGCATCC	190
14	rs3846662	CACCTCCACCAAGCTACACA	GTTCCAATGGCAACAACAGA	GTATCACTAATTGTCCTTAAAACTCTTCTCATTGCCTTAC	229
15	rs2156552	CTGTGGCCTACTCCTCTTGG	GTGCTGCCTACAACCCATTT	CAATTAAAGAGCTGAAAGGAGAAGTCAG	255
16	rs2479409	TCCTCCTGCCTGGTACACAA	GCTTGCTTTTGATGTCCAGC	TCTGAATGTA CCTATATGAC	226
17	rs11583680	TCCTGAACTTCAGCTCCTGC	AGTCCTCAAGATCGTGCCAA	CTTGCG TTCCGAGGAG GACGGCCTGG	474
18	rs3812316	TTCTCAGACCCTCACCATCC	CTGTCCTGCTGACCACTTGA	TGGTGAAGAGAGTGTCTGAGATGTCGGACAAAAAGCAATTGAGGTCCAGGAG	312
19	rs327	CCCTCTGATTCTGATGTGGC	TTTAGCCCAGAATGCTCACC	ATCAAAACAATTACCCAGCATGATCATGTA	292
20	rs331	TGCCAAGCAAACAGAATGAG	GGATGTGTGGAGGTTGAAA	CCTTTAGG GCTAATCCAT GTGGCAGCTG TTAGCTGCAT CTTTCCAGAG CGTCAGTACT	219
21	rs17321515	GGCGTTGTGTTTCACTAGCA	AAAATTAGCCAGGCATGGTG	CCACACAGATGGTATTAGGCAGAACAAGGACTTTCGTCCTCTTCATACCT	396
22	rs1077834	GCCACTCAGCAAAATCAGGT	CGAACTCCTGACCTCGTGAT	GGGAAAAGGCGACCATAGATGGCTTTTGTGATATTTTTGG	317
23	rs1800775	ACAGCATCCTGCCCACAT	GCATCGACCTTTCCCTTG	TCCTCCCCACTCCTAGGCCA	451
24	rs16996148	CAATCTCCCACCCATTCACT	AAACTCCAGCAGAGCCCTTA	CTTGGCAAATCCGAACCTCCGCAGCTCTCACCCTTTCAGTCA	395
25	rs28927680	CAAGAAGGCAGTGGAGGAAC	ATGCTTCCTCTGAAAGCCAG	TGGAGCCCACACAGACCAGCAACTTGTTGAATGCCA	280

Supplementary table S3.Association of lipid parameters with GWAS-based genetic loci in overall subjects

ID	SNP ID (minor allele)	Nearest genes	TC			lnTG*			LDL-C			HDL-C		
			P	B	SE	P	B	SE	P	B	SE	P	B	SE

1	rs3890182(A)	ABCA1	0.55	-0.05	0.084	0.38	0.042	0.049	0.92	-0.008	0.077	0.880	-0.004	0.028
2	rs693(T)	APOB	0.77	-0.024	0.079	0.71	0.016	0.045	0.84	0.015	0.073	0.494	-0.018	0.026
4	rs4420638(G)	APOE-C1-C4-C2	0.47	-0.037	0.51	0.12	0.046	0.03	0.94	0.004	0.047	0.122	-0.026	0.017
5	rs17145738(T)	BCL7B,TBL2,MLXIPL	0.10	-0.096	0.058	**0.008**	-0.088	0.033	0.057	-0.102	0.054	0.065	0.035	0.019
6	rs4970834(T)	CELSR2	**0.008**	-0.236	0.088	0.39	-0.043	0.05	**$4.49x10^{-4}$**	-0.286	0.081	0.145	0.042	0.029
7	rs599839(G)	CELSR2,PSRC1,SORT1	**$3.7x10^{-4}$**	-0.242	0.068	0.41	-0.032	0.039	**$1.5x10^{-5}$**	-0.272	0.063	0.488	0.015	0.022
8	rs646776(C)	CELSR2,PSRC1,SORT1	**0.001**	-0.248	0.072	0.42	-0.033	0.041	**$3.5x10^{-5}$**	-0.275	0.066	0.455	0.017	0.023
9	rs4846914(A)	GALNT2	0.50	0.027	0.041	0.19	-0.03	0.024	0.33	0.037	0.037	0.283	0.014	0.013
10	rs10127775(T)	GALNT2	0.25	0.049	0.043	0.28	-0.026	0.024	0.32	0.04	0.04	0.093	0.024	0.014
11	rs780092(G)	GCKR	0.90	0.005	0.036	0.61	-0.01	0.021	0.88	-0.005	0.033	0.537	0.007	0.012
12	rs780094(C)	GCKR	0.57	0.02	0.034	0.19	0.026	0.02	0.504	0.021	0.032	0.155	-0.016	0.011
13	rs12654264(A)	HMGCR	**$1.4x10^{-5}$**	-0.148	0.034	0.20	-0.025	0.019	**0.001**	-0.103	0.031	0.24	-0.013	0.011
14	rs3846662(T)	HMGCR	**$9.9x10^{-5}$**	-0.138	0.036	0.25	-0.024	0.021	**0.001**	-0.109	0.032	0.693	0.005	0.012
15	rs2156552(A)	LIPG,ACAA2	0.60	-0.023	0.044	0.89	0.063	0.025	0.96	0.002	0.04	0.24	0.017	0.014
16	rs2479409(A)	PCSK9	0.17	0.05	0.036	0.96	-0.001	0.021	0.37	0.03	0.034	0.468	0.009	0.012
17	rs11583680(T)	PCSK9	0.96	0.003	0.056	0.31	-0.033	0.032	0.62	-0.025	0.051	0.871	0.003	0.018
18	rs3812316(G)	MLXIPL	0.54	0.037	0.061	**0.023**	-0.079	0.035	0.87	0.009	0.056	**0.034**	0.042	0.02
19	rs327(G)	LPL	0.091	0.07	0.045	**0.017**	-0.062	0.026	0.33	0.041	0.042	**0.001**	0.049	0.015
20	rs331(A)	LPL	**0.048**	0.087	0.044	**0.01**	-0.065	0.025	0.202	0.052	0.041	**$1.19x10^{-4}$**	0.056	0.014
21	rs17321515(A)	TRIR1	**0.017**	0.086	0.036	0.054	0.04	0.021	**0.005**	0.093	0.033	0.642	0.005	0.012
22	rs1077834(C)	LIPC	**0.016**	0.089	0.037	0.089	0.037	0.022	0.916	-0.004	0.034	**0.004**	0.035	0.012
23	rs1800775(A)	CETP	0.29	-0.038	0.036	0.293	0.022	0.021	0.921	0.003	0.033	**0.004**	0.034	0.012
24	rs16996148(T)	CILP2,PBX4	0.24	-0.085	0.073	0.814	-0.01	0.042	0.501	-0.045	0.067	0.815	-0.006	0.024

*****TG transformed by Napierian logarithm. SNPs with P values<0.05 are marked in bold; SNPs with P values <0.05 after Bonferroni correction are black highlighted with white letters. All calculations were made with aUnivariate analysis with covariates (age, BMI, and ln glucose levels). TC, total cholesterol; LDL-C, low-density lipoprotein-cholesterol; TG, triglyceride; HDL-C, the high-density lipoprotein-cholesterol.