Association between the DOCK7, PCSK9 and GALNT2 Gene Polymorphisms and Serum Lipid levels

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This study was to determine the association between several single nucleotide polymorphisms (SNPs) in the dedicator of cytokinesis 7 (DOCK7), proprotein convertase subtilisin/kexin type 9 (PCSK9) and polypeptide N-acetylgalactosaminyltransferase 2 (GALNT2) and serum lipid levels. Genotyping of 9 SNPs was performed in 881 Jing subjects and 988 Han participants. Allele and genotype frequencies of the detected SNPs were different between the two populations. Several SNPs were associated with triglyceride (TG, rs10889332, rs615563, rs7552841, rs1997947, rs2760537, rs4846913 and rs11122316), high-density lipoprotein (HDL) cholesterol (rs1997947), low-density lipoprotein (LDL) cholesterol (rs1168013 and rs7552841), apolipoprotein (Apo) A1 (rs1997947), ApoB (rs10889332 and rs7552841), and ApoA1/ApoB ratio (rs7552841) in Jing minority; and with TG (rs10889332, rs615563, rs7552841, rs11206517, rs1997947, rs4846913 and rs11122316), HDL cholesterol (rs11206517 and rs4846913), LDL cholesterol (rs1168013), ApoA1 (rs11206517 and rs4846913), ApoB (rs7552841), and ApoA1/ApoB ratio (rs4846913) in Han nationality. Strong linkage disequilibria were noted among the SNPs. The commonest haplotype was G-C-G-C-T-G-C-C-G (>10%). The frequencies of C-C-G-C-T-G-T-C-G, G-C-A-C-T-G-C-C-G, G-C-G-C-T-A-C-C-A, G-C-G-C-T-G-C-C-A, G-C-G-C-T-G-T-C-A haplotypes were different between the two populations. Haplotypes could explain much more serum lipid variation than any single SNP alone especially for TG. Differences in lipid profiles between the two populations might partially attribute to these SNPs and their haplotypes.

Cardiovascular disease (CVD) remains as the leading cause of morbidity and mortality worldwide, and its prevalence is expected to increase further, which exerts a significant economic burden1,2. Most of the current prevention strategies are focused on identifying and managing the established risk factors including hyperlipidemia3 that can be effectively addressed for individuals and populations suffering from atherosclerosis. It is generally agreed that dyslipidemia is complex and the result of the interactions4,5 of multiple genes6–8 and multiple environmental factors9,10. Statins are highly effective for lowering low-density lipoprotein (LDL) cholesterol levels and, consequently, cardiovascular event rates. However, statins do not eliminate cardiovascular risk. High triglyceride (TG) level is a significant risk factor for independent cardiovascular disease and is a marker for atherogenic remnant lipoproteins, such as very low-density lipoprotein (VLDL) cholesterol. Additionally, with elevated TG levels, a combination of LDL cholesterol with VLDL cholesterol in the measure of non-high-density lipoprotein (HDL) cholesterol may be a better predictor of cardiovascular risk than LDL cholesterol alone. Therefore, improved understanding of TG-related loci may optimize patient management strategies, provide potential new targets for future individual therapy, and thereby improve patients’ chances for survival.

Candidate gene and genome-wide association studies (GWASs)11–13 have identified a number of sequence variants that explain some of the individual variation in the susceptibility for high TG levels. The dedicator of cytokinesis 7 (DOCK7; Gene ID: 85440; MIM: 615730) formerly known as ZIR2 and EIEE23, is located on chromosome 1p31.3 and the protein encoded by this gene is a guanine nucleotide exchange factor (GEF) that plays

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a role in axon formation and neuronal polarization. The encoded protein displays GEF activity toward RAC1 and RAC3 Rho small GTPases but not toward CDC42. Several transcript variants encoding different isoforms have been found for this gene. The proprotein convertase subtilisin/kexin type 9 (PCSK9; Gene ID: 255738; MIM: 607786) gene, also known as FH3, PC9, NARC1, LDLQ1, NARC-1 and HCHOLA3, is located on 1p32.3 and this gene encodes a member of the subtilisin-like proprotein convertase family, which includes proteases that process protein and peptide precursors trafficking through regulated or constitutive branches of the secretory pathway. The encoded protein undergoes an autocatalytic processing event with its proteoglycan domain in the ER and is constitutively secreted as an inactive propeptide into the extracellular matrix and trans-Golgi network. It is expressed in liver, intestine and kidney tissues and escorts specific receptors for lysosomal degradation. It plays a role in cholesterol and fatty acid metabolism. Mutations in this gene have been associated with autosomal dominant familial hypercholesterolemia. Alternative splicing can result in multiple transcript variants. The poly peptide N-acetylgalactosaminyltransferase 2 (GALNT2; Gene ID: 255738; MIM: 607786) gene, formerly known as GalNAc-T2, is located on chromosome 1q41-q42 and encodes a member of the glycosyltransferase 2 protein family. Members of this family initiate mucin-type O-glycosylation of peptides in the Golgi apparatus. The encoded protein may be involved in O-linked glycosylation of the immunoglobulin A1 hinge region. This gene may influence TG levels, and may be involved type 2 diabetes, as well as several types of cancer. Alternative splicing can also result in multiple transcript variants (http://www.ncbi.nlm.nih.gov/gene/).

Human genetic studies of lipid levels can identify targets for new therapies for cholesterol management and prevention of heart disease especially monoclonal anti-PCSK9 antibodies are already on the market to significantly reduced levels of LDL cholesterol when added to statin therapy administered at the maximum tolerated dose. For comparison with the nonsynonymous single nucleotide polymorphisms (SNPs) in known drug therapies genes, we scored point mutations at synonymous point mutations in housekeeping genes or genes of unknown function on the approximate locations of the chromosome 1. The exact positions of the PCSK9 SNPs were located in the similar position area of the DOCK7 and GLANT2 SNPs (http://hapmap.ncbi.nlm.nih.gov/).

Several genetic variants in the DOCK7, PCSK9 and GLANT2 have been associated with serum lipid parameters, especially with TG in Western populations, e.g. the SNPs of DOCK7 rs1167998, rs10889354, PCSK9 rs11591417 and GALNT2 rs4846914 were associated with TG levels in European and PCSK9 rs5051518 and GALNT2 rs2144330 and rs4846914 in the Asian populations. However, the association of the DOCK7 (rs1168013 and rs10889332), PCSK9 (rs615563, rs7552841 and rs1126517) and GALNT2 (rs1997947, rs2760537, rs4846913 and rs11122316) SNPs and serum lipid levels has not been previously reported. Since ancient times China is a multi-ethnic country. Among 56 nationalities in China, the Han nationality is the biggest one. Jing is one of the smallest population of ethnic minorities in southern China with a population of 22,517 (in 2000 the fifth national census statistics of China), China's only a coastal fishery ethnic minority, and China's only national ocean at the same time. Jing populations live in Dongxing city, Guangxi Zhuang Autonomous Region. Diet to rice is give priority to, fresh fish and shrimp more, like to use fish sauce to taste. The history of Jing ethnic minority shows Jing nationality is a relatively conservative and isolated minority, and preserves their custom of intra-ethnic marriage. Thus, their genetic background may be less heterogeneous within the population. Little is known about the association of SNPs and lipid phenotypes in the Jing population. Therefore, this research was undertaken to detect the association of the DOCK7 rs1168013, DOCK7 rs10889332, PCSK9 rs615563, PCSK9 rs7552841, PCSK9 rs11206517, GALNT2 rs1997947, GALNT2 rs2760537, GALNT2 rs4846913, and GALNT2 rs11122316 SNPs and lipid profiles in the two ethnic groups.

**Results**

**Demographic and clinical characteristics.** Table 1 summarized the value of weight, waist circumference, body mass index (BMI), and total cholesterol (TC) and TG levels which were higher and the % of participants who consumed alcohol and the ratio of apolipoprotein (Apo) A1 to ApoB were lower in Jing ethnic minority than in Han nationality (P < 0.01–0.001). However, no such difference in the levels of HDL cholesterol, LDL cholesterol, ApoA1 and ApoB between the two populations (P > 0.05 for all).

**Genotyping.** Polymerase chain reaction (PCR) products of DOCK7 rs1168013, DOCK7 rs10889332, PCSK9 rs615563, PCSK9 rs7552841, PCSK9 rs11206517, GALNT2 rs1997947, GALNT2 rs2760537, GALNT2 rs4846913 and GALNT2 rs11122316 SNPs were 365-, 368-, 365-, 496-, 367-, 480-, 284-, 436- and 456-bp nucleotide sequences after electrophoresis; respectively (Fig. 1). After restriction fragment length polymorphism (RFLP) reaction and then imaged by 2% agarose gel electrophoresis, the genotypes of the SNPs identified were labeled according to the presence and absence of the enzyme restriction sites (Fig. 2).

**Results of sequencing.** The genotypes shown in Fig 2 by PCR-RFLP, the genotypes were also confirmed by the nucleotide direct sequencing (Fig. 3); respectively.

**Allelic and genotypic frequencies.** Tables 2 and 3 describe the allelic and genotypic frequencies of the detected SNPs which were different between the two ethnic groups (P < 0.05 for all). All of the detected SNPs were in the Hardy–Weinberg equilibrium (P > 0.05) except DOCK7 rs10889332 (P < 0.05). Linkage disequilibria (LD) were found between PCSK9 rs615563 and PCSK9 rs11206517, PCSK9 rs7552841 and PCSK9 rs11206517, DOCK7 rs1168013 and DOCK7 rs10889332 and GALNT2 rs11122316 and GALNT2 rs1997947 in Jing, and PCSK9 rs7552841 and PCSK9 rs615563, DOCK7 rs1168013 and DOCK7 rs10889332 and GALNT2 rs11122316 and GALNT2 rs1997947 in Han (P < 0.01 for all; Fig. 4).

**Haplotype frequencies.** The haplotype frequencies are listed in Table 4. The commonest haplotype was G-C-G-T-G-C-C-G (in the order of DOCK7 rs1168013, DOCK7 rs10889332, PCSK9 rs615563, PCSK9 rs7552841, PCSK9 rs11206517, GALNT2 rs1997947, GALNT2 rs2760537, GALNT2 rs4846913 and GALNT2
rs11122316; >10% of the samples). The frequencies of the C-C-G-T-G-T-C-G, G-C-A-C-T-G-C-C-A, G-C-G-C-T-G-C-G-C-A, and G-C-G-C-T-G-T-C-A haplotypes were also different between the Jing and Han populations (P < 0.05 – 0.001).

| Characteristics | Jing | Han | test-statistic | P-value |
|-----------------|------|-----|----------------|---------|
| Number (n)      | 881  | 988 |                |         |
| Gender (Male/Female) | 456/425 | 536/452 | 1.161 | 0.281 |
| Age (years)     | 56.69 ± 13.39 | 56.18 ± 12.85 | −0.726 | 0.468 |
| Height (cm)     | 156.51 ± 7.67 | 156.03 ± 7.79 | 1.133 | 0.257 |
| Weight (kg)     | 57.62 ± 9.86 | 55.66 ± 9.37 | 3.768 | 0.000 |
| Body mass index (kg/m²) | 23.46 ± 3.25 | 22.82 ± 3.23 | 3.642 | 0.000 |
| SBP (mmHg)      | 131.65 ± 22.03 | 132.66 ± 41.95 | −0.550 | 0.582 |
| DBP (mmHg)      | 80.37 ± 10.54 | 80.84 ± 10.17 | −0.848 | 0.397 |
| Pulse pressure (mmHg) | 51.28 ± 17.54 | 51.82 ± 10.15 | −0.315 | 0.753 |
| Cigarette smoking (n [%]) | 775 (87.9) | 846 (85.6) |            |         |
| Alcohol consumption [n (%)] | 50 (5.7) | 35 (3.5) | 25.016 | 0.000 |
| Blood glucose level (mmol/L) | 6.71 ± 1.71 | 6.63 ± 1.08 | 0.983 | 0.326 |
| Total cholesterol (mmol/L) | 5.13 ± 0.93 | 4.89 ± 0.87 | 4.834 | 0.000 |
| Triglyceride (mmol/L) | 1.41 (1.12) | 1.32 (1.09) | −2.890 | 0.004 |
| HDL cholesterol (mmol/L) | 1.79 ± 0.52 | 1.80 ± 0.45 | −0.231 | 0.817 |
| LDL cholesterol (mmol/L) | 2.85 ± 0.44 | 2.82 ± 0.44 | 0.131 | 0.189 |
| Apolipoprotein (Apo) A1 (g/L) | 1.30 ± 0.23 | 1.32 ± 0.20 | −1.592 | 0.112 |
| ApoB (g/L) | 1.06 ± 0.25 | 1.03 ± 0.24 | 0.187 | 0.066 |
| ApoA1/ApoB | 1.30 ± 0.38 | 1.35 ± 0.37 | −2.465 | 0.014 |

Table 1. Lipid profiles and clinical characteristics in the two ethnic groups. SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high density lipoprotein; LDL, low density lipoprotein; 1Mean ± SD determined by t-test. 2Median (interquartile range) tested by the Wilcoxon-Mann-Whitney test.

The correlation of the haplotypes and lipid profiles is shown in Table 6. Rare Hap (frequency < 3%) in both Jing and Han populations has been dropped. The carriers of C-C-G-T-G-T-C-G haplotype had lower TG and higher HDL cholesterol levels in Jing plus Han populations and lower TG levels in Jing population than the non-carriers of C-C-G-T-G-T-C-G haplotype (P < 0.05). There were no differences in lipid parameters between the carriers and non-carriers of C-C-G-T-G-T-C-G haplotype in the Han population. Haplotype G-C-A-C-T-G-C-C-G carriers had lower serum TG in the Han populations than the haplotype.
non-carriers ($P < 0.05$). Haplotype G-C-G-C-T-A-C-C-A carriers had higher serum TG and lower ApoA1 levels in Jing plus Han population, and higher serum TG and lower HDL cholesterol and ApoA1 in Jing population than the haplotype G-C-G-C-T-A-C-C-A non-carriers ($P < 0.05$ for each). Haplotype G-C-G-C-T-G-C-C-A carriers had lower TC, TG, LDL cholesterol and ApoB levels in Jing plus Han population, lower TC, TG and ApoB in Jing ethnic minority and lower TG levels than the haplotype G-C-G-C-T-A-C-C-A non-carriers ($P < 0.05$ for all).

**Correlation between lipid parameters and alleles or genotypes.** Table 7 depicts the direction and magnitude of associations between lipid parameters and alleles or genotypes of the 9 SNPs in the Jing and Han populations. Adjusting for age, sex, BMI, smoking status, alcohol use, and exercise, logistic regression analysis showed that several examined SNPs were significantly correlated with lipid parameters.

**Discussion**

In the present study, we showed for the first time the association of the **DOCK7** (rs1168013 and rs10889332), **PCSK9** (rs615563, rs7552841, rs11206517), **GALNT2** (rs1997947, rs2760537, rs4846913 and rs11122316) SNPs and other serum lipid parameters; the LD status and the haplotype frequencies of the detected SNPs.

In addition, we also successfully replicated the association of **DOCK7** rs10889332, **PCSK9** rs615563, **PCSK9** rs7552841, **GALNT2** rs1997947, **GALNT2** rs2760537 and **GALNT2** rs4846913 with the levels of serum TG in the Jing ethnic minority; and **DOCK7** rs10889332, **PCSK9** rs615563, **PCSK9** rs7552841, **PCSK9** rs11206517, **GALNT2** rs1997947, **GALNT2** rs4846913 and **GALNT2** rs11122316 with serum TG levels in the Han nationality.

The SNPs of rs636523 and rs12130333 are near the **DOCK7**/**ANGPTL3**, **PCSK9** and **GALNT2** SNPs and other serum lipid parameters have not been reported previously. The genotype and allele frequencies of several SNPs in this study were also not reported previously in different racial/ethnic groups. In the present study, we revealed that the genotypic and allelic frequencies of the **DOCK7** rs1168013, **DOCK7** rs10889332, **PCSK9** rs615563, **PCSK9** rs7552841, **PCSK9** rs11206517, **GALNT2** rs1997947, **GALNT2** rs2760537, **GALNT2** rs4846913 and **GALNT2** rs11122316 SNPs were different between the two ethnic groups. All of the detected SNPs were in the Hardy-Weinberg equilibrium except **DOCK7** rs10889332. The minor allele or rare homozygote genotype frequencies of the 9 SNPs in the Han nationality were in close proximity to those of CHB from the international haplotype map (HapMap; http://hapmap.ncbi.nlm.nih.gov/cgi-perl/gbrowse/hapmap24_B36/) data. The minor allele or rare homozygote genotype frequencies of the 9 detected SNPs were also lower in European ancestries.
than in Asian nationalities from the data. These results suggest that the prevalence of the minor allele or rare homozygote genotype frequencies of the 9 SNPs may have a racial/ethnic-specificity.

In the present research, our findings also showed that there may be a racial/ethnic specific association of the 9 SNPs and lipid parameters. The association of other SNPs near DOCK7, PCSK9 and GALNT2 and lipid profiles has been reported previously. Through fine-mapping, previous study discovered the SNP with significant associations, with consistent effect on TG levels across ancestral groups: rs636523 near DOCK7/ANGPTL3. African LD patterns did not assist in narrowing association signals. PCsK9 (TG, HDL cholesterol, ApoB and ApoA1/ApoB) was shown interactions with overweight/obesity to influence serum lipid levels. Our team reported that the correlations of both GALNT2 rs2144300 and GALNT2 rs4846914 SNPs and lipid parameters were different between the two ethnic groups. However, Several GWASs and candidate gene researches failed to find the association between the GALNT2 polymorphisms and lipid parameters. There was no any effect of the GALNT2 rs4846914 on the levels of serum TC or TG reported by Polgár et al. previously. In Whitehall II, there was a significant correlation of the GALNT2 variants and serum lipoprotein (a) levels. Whereas any of these findings did not confirmed in the previously meta-analysis of six studies. It could be due to the effects of these SNPs were modest on serum lipid concentrations and/or lower statistical power to determine the correlation was present. In addition, gene-environmental and environmental- environmental factors on lipid parameters remain to be interpreted.

Many GWASs have reported that the association of other variants near DOCK7, PCSK9 and GALNT2 and serum lipid levels is still controversial. Pleiotropic effects on the lipid profile, the potential correspondence was detected for ANGPTL3 and DOCK7 being highly associated with cholesterol and LDL cholesterol levels. Loss-of-function mutations in the ANGPTL3 were associated with decreased levels of LDL cholesterol, HDL...
Figure 3. The parts of the nucleotide direct sequencing results of the DOCK7, PCSK9 and GALNT2 SNPs. DOCK7: dedicator of cytokinesis 7, PCSK9: proprotein convertase subtilisin/kexin type 9 and GALNT2: polypeptide N-acetylgalactosaminyltransferase 2.
cholesterol and TG. The associations observed for the DOCK7 locus, which is involved in neurogenesis, myelination and axon formation but not in lipid metabolism probably reflect the co-localization of this gene with ANGPTL3. As expected, rare variants that contribute to population differences tend to be population specific, exemplified by multiple African-specific variants in PCSK9 associated with LDL cholesterol. The SNPs in intron 1 of a GalNac transferase (GALNT2) were identified as a novel lipid-associated region from GWAS and subsequent knock-down and overexpression of this gene in mouse liver clearly demonstrated that GALNT2 can influence HDL cholesterol levels.

The cause of the contradictions in correlation of the detected SNPs with lipid parameters among the different population is not completely understood. This could be because of the differences in genetic background in some degree. Compared to the Han nationality, the Jing ethnic minority had higher the value of weight, BMI, waist circumference, the serum TC and TG levels and the lower percentage of participants who consumed alcohol and the ratio of ApoA1 to ApoB. Among 56 nationalities in China, Han nationality is the largest one. Jing ethnic minority was less population nationality with the population of 22517 according to the China’s fifth national census in 2000. Approximately 90% of the Jing people live in the three islands of Wanwei, Wutou and Shanxin in the Dongxing city, Guangxi, China. About 1511, their ancestors emigrated from Vietnam to China and first settled on the aforementioned three islands. Therefore, some hereditary background and alleles/genotypes of lipid metabolism-related genes in Jing ethnic minority might be somewhat different from those in Han nationality.

| SNP                  | Genotype | Jing (n = 881) | Han (n = 988) | X² | P-value |
|----------------------|----------|---------------|---------------|----|---------|
| DOCK7 rs1168013 G>C  | GG       | 367 (41.65)   | 482 (48.75)   | 7.457 | 0.024   |
|                      | CG       | 409 (46.40)   | 413 (41.81)   |     |         |
|                      | CC       | 105 (11.95)   | 93 (9.44)     |     |         |
|                      | HWE (P)  | 0.581         | 0.739         |     |         |
| DOCK7 rs10889332 C>T | CC       | 447 (50.69)   | 575 (58.19)   | 10.851 | 0.004   |
|                      | CT       | 341 (38.74)   | 347 (35.14)   |     |         |
|                      | TT       | 93 (10.57)    | 66 (6.67)     |     |         |
|                      | HWE (P)  | 0.023         | 0.168         |     |         |
| PCSK9 rs615563 G>A   | GG       | 536 (60.80)   | 664 (67.22)   | 6.223 | 0.045   |
|                      | AG       | 294 (33.38)   | 279 (28.20)   |     |         |
|                      | AA       | 51 (5.82)     | 45 (4.58)     |     |         |
|                      | HWE (P)  | 0.208         | 0.271         |     |         |
| PCSK9 rs7552841 C>T  | CC       | 571 (64.78)   | 689 (69.72)   | 6.063 | 0.048   |
|                      | CT       | 264 (30.01)   | 269 (27.22)   |     |         |
|                      | TT       | 46 (5.21)     | 30 (3.06)     |     |         |
|                      | HWE (P)  | 0.359         | 0.549         |     |         |
| PCSK9 rs11206517 T>G | TT       | 723 (82.08)   | 859 (86.95)   | 6.357 | 0.042   |
|                      | GT       | 146 (16.54)   | 121 (12.22)   |     |         |
|                      | GG       | 12 (1.38)     | 8 (0.83)      |     |         |
|                      | HWE (P)  | 0.142         | 0.108         |     |         |
| GALNT2 rs1997947 G>A | GG       | 529 (60.03)   | 661 (66.94)   | 7.586 | 0.023   |
|                      | AG       | 297 (33.69)   | 283 (28.61)   |     |         |
|                      | AA       | 55 (6.28)     | 44 (4.45)     |     |         |
|                      | HWE (P)  | 0.129         | 0.056         |     |         |
| GALNT2 rs2760537 C>T | CC       | 344 (39.05)   | 446 (45.14)   | 6.291 | 0.043   |
|                      | CT       | 406 (46.10)   | 427 (43.19)   |     |         |
|                      | TT       | 131 (14.85)   | 115 (11.67)   |     |         |
|                      | HWE (P)  | 0.531         | 0.408         |     |         |
| GALNT2 rs4846913 C>A | CC       | 554 (62.94)   | 685 (69.30)   | 6.292 | 0.043   |
|                      | AC       | 281 (31.85)   | 263 (26.67)   |     |         |
|                      | AA       | 46 (5.21)     | 40 (4.03)     |     |         |
|                      | HWE (P)  | 0.188         | 0.232         |     |         |
| GALNT2 rs11122316 G>A| GG       | 320 (36.29)   | 410 (41.53)   | 6.541 | 0.038   |
|                      | AG       | 429 (48.70)   | 468 (47.36)   |     |         |
|                      | AA       | 132 (15.01)   | 110 (11.11)   |     |         |
|                      | HWE (P)  | 0.546         | 0.171         |     |         |

Table 2. Prevalence of genotype frequencies in the different populations [n (%)]. SNP: single nucleotide polymorphism; HDL, high density lipoprotein; LDL, low density lipoprotein; HWE, Hardy-Weinberg equilibrium; DOCK7: Dedicator of cytokinesis 7; PCSK9: Proprotein convertase subtilisin/kexin type 9; GALNT2: N-acetylgalactosaminyltransferase 2.
Another reason could be because of the ethnic difference in their LD pattern. In this research, we detected that the frequencies of the C-C-G-C-T-G-T-C-G, G-C-A-C-T-G-C-C-G, G-C-G-C-T-A-C-C-A, G-C-G-C-T-G-C-C-A, G-C-G-C-T-G-T-C-A haplotypes were significantly different between the Jing and Han populations. The haplotypes with nine SNPs could explain much more serum lipid variation than any single SNP alone, especially for TG. Therefore, ethnic differences in the LD pattern could partially explain the discrepancy in the correlation of the detected SNPs with lipid parameters among diverse nationalities.

Several environmental factors independently such as hypertension, obesity, physical activity, dietary patterns and lifestyle are related with lipid parameters strongly. There was association of gender, age, BMI, cigarette smoking, alcohol consumption, blood pressure and lipid levels in both Jing and Han populations. These detected data determined some environmental factors play an important role in determining lipid parameters. For approximately half a century it has been acknowledged that diets of high-fat particularly contain the large quantities of saturated fatty acids raise predispose individuals to hyperlipidemia and

Table 3. Prevalence of allele frequencies in the different populations [n (%)]. SNP: single nucleotide polymorphism; DOCK7: Dedicator of cytokinesis 7; PCSK9: Proprotein convertase subtilisin/kexin type 9; GALNT2: N-acetylgalactosaminyltransferase 2.

| SNP     | Allele | Jing (n = 881) | Han (n = 988) | X²  | P-value |
|---------|--------|---------------|---------------|-----|---------|
| DOCK7 rs1168013 | G/C   | 1143 (64.85)/619 (35.15) | 1376 (69.65)/600 (30.35) | 7.173 | 0.007   |
| DOCK7 rs10889332 | C/T   | 1234 (70.06)/528 (29.94) | 1497 (75.76)/479 (24.24) | 11.313 | 0.001   |
| PCSK9 rs615563 | G/A   | 1365 (77.49)/397 (22.51) | 1607 (81.32)/369 (18.68) | 6.167  | 0.015   |
| PCSK9 rs7552841 | C/T   | 1406 (79.78)/356 (20.21) | 1647 (83.33)/329 (16.67) | 5.752  | 0.016   |
| PCSK9 rs11206517 | T/G | 1592 (90.35)/170 (9.65) | 1839 (93.06)/137 (6.94) | 6.626  | 0.013   |
| GALNT2 rs1997947 | G/A   | 1355 (76.88)/407 (23.12) | 1606 (81.25)/370 (18.75) | 7.646  | 0.005   |
| GALNT2 rs7552841 | C/T   | 1094 (62.10)/668 (37.90) | 1319 (66.74)/657 (33.26) | 6.437  | 0.011   |
| GALNT2 rs1997947 | G/A   | 1390 (78.87)/372 (21.13) | 1633 (82.64)/343 (17.36) | 6.293  | 0.012   |

Table 4. Frequencies of haplotypes among 9 SNPs of the DOCK7, PCSK9 and GALNT2 genes in the two ethnic groups [n (%)]. A, DOCK7 rs1168013; B, DOCK7 rs10889332; C, PCSK9 rs615563; D, PCSK9 rs7552841; E, PCSK9 rs11206517; F, GALNT2 rs1997947; G, GLANT2 rs2760537; H, GLANT2 rs4846913; I, GLANT2 rs11122316; DOCK7, Dedicator of cytokinesis 7; PCSK9, Proprotein convertase subtilisin/kexin type 9; GALNT2, N-acetylgalactosaminyltransferase 2.

| Haplotype | Jing | Han | X²  | P-value |
|-----------|------|-----|-----|---------|
| A B C D E F G H I | 61 (3.1) | 47 (2.7) | 0.011 | 0.916   |
| C G C T G C C G  | 5 (0.2) | 59 (3.3) | 63.522 | 1.66 × 10^{-15} |
| G C A C T G C C G  | 92 (4.7) | 47 (2.7) | 6.786  | 0.009   |
| G C G C T A C C A  | 4 (0.2) | 55 (3.1) | 60.831  | 6.52 × 10^{-15} |
| G C G C T G C C A  | 133 (6.8) | 66 (3.7) | 11.968  | 0.001   |
| G C G C T G C C G  | 262 (13.3) | 187 (10.6) | 1.908  | 0.167   |
| G C G C T G T C A  | 80 (4.1) | 42 (2.4) | 5.642  | 0.018   |
| G C G C T G T C G  | 105 (5.3) | 86 (4.9) | 0.088  | 0.767   |

Figure 4. The linkage disequilibrium (LD) of the DOCK7, PCSK9 and GALNT2 SNPs. LD among the (1) PCSK9 rs7552841, (2) PCSK9 rs615563, (3) PCSK9 rs11206517, (4) DOCK7 rs10889332, (5) DOCK7 rs1168013, (6) GALNT2 rs11122316, (7) GALNT2 rs1997947, (8) GALNT2 rs4846913 and (9) GALNT2 rs2760537 SNPs in the Jing (A), Han (B) and combined Jing and Han populations (C). The LD status is expounded by the r² value.

Another reason could be because of the ethnic difference in their LD pattern. In this research, we detected that the frequencies of the C-C-G-C-T-G-T-C-G, G-C-A-C-T-G-C-C-G, G-C-G-C-T-A-C-C-A, G-C-G-C-T-G-C-C-A, G-C-G-C-T-G-T-C-A haplotypes were significantly different between the Jing and Han populations. The haplotypes with nine SNPs could explain much more serum lipid variation than any single SNP alone, especially for TG. Therefore, ethnic differences in the LD pattern could partially explain the discrepancy in the correlation of the detected SNPs with lipid parameters among diverse nationalities.

Several environmental factors independently such as hypertension, obesity, physical activity, dietary patterns and lifestyle are related with lipid parameters strongly. There was association of gender, age, BMI, cigarette smoking, alcohol consumption, blood pressure and lipid levels in both Jing and Han populations. These detected data determined some environmental factors play an important role in determining lipid parameters. For approximately half a century it has been acknowledged that diets of high-fat particularly contain the large quantities of saturated fatty acids raise predispose individuals to hyperlipidemia and
| Genotype | Total cholesterol (mmol/L) | Triglyceride (mmol/L) | HDL cholesterol (mmol/L) | LDL cholesterol (mmol/L) | Apolipoprotein (Apo A1) (g/L) | Apolipoprotein (Apo B) (g/L) | ApoA1/ApoB |
|---------|--------------------------|----------------------|--------------------------|--------------------------|-------------------------------|-------------------------------|------------------|
| **DOCK7 rs1168013 G > C** | | | | | | | |
| Han     | | | | | | | |
| GG      | 367                       | 4.97 ± 0.92          | 1.40 (1.10)              | 1.81 ± 0.47              | 2.67 ± 0.55                   | 1.31 ± 0.21                   | 1.04 ± 0.24    | 1.31 ± 0.37  |
| CG      | 409                       | 5.13 ± 0.94          | 1.41 (1.14)              | 1.80 ± 0.42              | 2.83 ± 0.42                   | 1.30 ± 0.25                   | 1.06 ± 0.28    | 1.29 ± 0.39  |
| CC      | 105                       | 5.17 ± 0.91          | 1.51 (1.18)              | 1.71 ± 0.45              | 2.84 ± 0.42                   | 1.29 ± 0.19                   | 1.07 ± 0.25    | 1.29 ± 0.37  |
| F       | 4.430                     | 3.504                | 1.840                    | 6.747                    | 0.225                         | 3.360                         | 1.390           |
| P       | 0.012                     | 0.031                | 0.160                    | 0.001                    | 0.775                         | 0.035                         | 0.250           |
| **DOCK7 rs10889332 C > T** | | | | | | | |
| Han     | | | | | | | |
| GG      | 482                       | 4.80 ± 0.87          | 1.27 (1.04)              | 1.86 ± 0.54              | 2.80 ± 0.44                   | 1.35 ± 0.21                   | 1.00 ± 0.24    | 1.37 ± 0.39  |
| CG      | 413                       | 4.95 ± 0.87          | 1.31 (1.06)              | 1.75 ± 0.51              | 2.87 ± 0.44                   | 1.30 ± 0.21                   | 1.04 ± 0.25    | 1.36 ± 0.36  |
| CC      | 93                        | 5.09 ± 0.72          | 1.60 (1.26)              | 1.65 ± 0.45              | 2.97 ± 0.41                   | 1.30 ± 0.19                   | 1.14 ± 0.23    | 1.18 ± 0.29  |
| F       | 2.894                     | 3.458                | 2.436                    | 5.794                    | 1.491                         | 3.561                         | 1.960           |
| P       | 0.056                     | 0.032                | 0.088                    | 0.003                    | 0.226                         | 0.029                         | 0.142           |
| **PCSK9 rs615563 G > A** | | | | | | | |
| Han     | | | | | | | |
| GG      | 536                       | 5.07 ± 0.88          | 1.34 (1.10)              | 1.87 ± 0.64              | 2.80 ± 0.43                   | 1.33 ± 0.24                   | 1.03 ± 0.23    | 1.33 ± 0.38  |
| AG      | 294                       | 5.18 ± 0.94          | 1.51 (1.21)              | 1.81 ± 0.42              | 2.83 ± 0.45                   | 1.31 ± 0.24                   | 1.09 ± 0.26    | 1.24 ± 0.37  |
| AA      | 51                        | 5.41 ± 1.18          | 1.58 (1.26)              | 1.76 ± 0.45              | 2.98 ± 0.46                   | 1.29 ± 0.22                   | 1.12 ± 0.33    | 1.27 ± 0.38  |
| F       | 1.544                     | 5.479                | 1.668                    | 2.125                    | 1.065                         | 1.906                         | 1.598           |
| P       | 0.214                     | 0.004                | 0.190                    | 0.120                    | 0.345                         | 0.150                         | 0.203           |
| **PCSK9 rs7552841 C > T** | | | | | | | |
| Han     | | | | | | | |
| GG      | 664                       | 4.84 ± 0.85          | 1.26 (1.04)              | 1.90 ± 0.40              | 2.82 ± 0.43                   | 1.37 ± 0.19                   | 1.02 ± 0.24    | 1.37 ± 0.38  |
| AG      | 279                       | 4.98 ± 0.90          | 1.27 (1.15)              | 1.78 ± 0.53              | 2.89 ± 0.45                   | 1.32 ± 0.20                   | 1.06 ± 0.26    | 1.32 ± 0.27  |
| AA      | 45                        | 5.05 ± 0.77          | 1.47 (1.15)              | 1.78 ± 0.52              | 2.95 ± 0.41                   | 1.31 ± 0.20                   | 1.07 ± 0.23    | 1.30 ± 0.37  |
| F       | 0.825                     | 5.674                | 0.533                    | 1.105                    | 1.101                         | 2.041                         | 1.674           |
| P       | 0.439                     | 0.001                | 0.587                    | 0.332                    | 0.333                         | 0.131                         | 0.188           |
| **PCSK9 rs11206517 T > G** | | | | | | | |
| Han     | | | | | | | |
| TT      | 723                       | 5.07 ± 0.90          | 1.40 (1.12)              | 1.83 ± 0.45              | 2.80 ± 0.44                   | 1.35 ± 0.25                   | 1.04 ± 0.23    | 1.31 ± 0.37  |

Continued
| Genotype | n   | Total cholesterol (mmol/L) | Triglyceride (mmol/L) | HDL cholesterol (mmol/L) | LDL cholesterol (mmol/L) | Apolipoprotein (Apo) A1 (g/L) | Apolipoprotein (Apo) B (g/L) | ApoA1/ApoB |
|----------|-----|---------------------------|-----------------------|--------------------------|--------------------------|-------------------------------|-----------------------------|-------------|
| GT       | 146 | 5.36 ± 0.98               | 1.47 (1.10)           | 1.79 ± 0.44              | 2.89 ± 0.43               | 1.29 ± 0.23                   | 1.14 ± 0.30                 | 1.27 ± 0.41  |
| GG       | 12  | 5.61 ± 1.16               | 1.75 (1.35)           | 1.41 ± 0.57              | 3.03 ± 0.57               | 1.27 ± 0.26                   | 1.30 ± 0.44                 | 1.02 ± 0.20  |
| F        | 0.356 | 4.366                    | 4.202                 | 0.164                    | 3.059                    | 2.062                        | 1.692                       |
| P        | 0.694 | 0.013                    | 0.015                 | 0.849                    | 0.048                    | 0.128                        | 0.185                       |

Continued
**Materials and methods**

**Subjects and research design.** For the current study, 881 unrelated subjects (456 males, 51.76% and 425 females, 48.24%) of Jing and 988 (536 men, 54.25% and 452 women, 45.75%) unrelated individuals of Han from Dongxing city, Guangxi Zhuang Autonomous Region, China were selected randomly from our randomized, stratified samples. The subjects’ age ranged from 15 to 80 years and with the average age of 56.69 ± 13.39 years in Jing and 56.18 ± 12.85 years in Han. All participants were healthy with no disease history of atherosclerosis, CVD, diabetes, thyroid and/or kidney. When blood samples were taken, none of them used lipid-modulating therapy such as fibrates or statins. The study design was approved by the Ethics Committee of the First Affiliated Hospital, Guangxi Medical University. Written informed consent was obtained from all participants. All experiments were performed in accordance with relevant guidelines and regulations.

**Data collection**

**Epidemiological investigation and measurements of biochemical markers.** Participants participated in baseline examination conducted in the study center by trained staff following standardized protocols, which included anthropometric, blood pressure measurements, height, weight (without shoes) and waist circumference parameters (in cm was measured at the midpoint between the lower ribs and the iliac crest), a blood sample collection as well as a personal interview on medical history, a sociodemographic, socioeconomic status and lifestyle questionnaire and a self-administered food frequency questionnaire; BMI was calculated.
| Haplotype      | Group          | n  | Total cholesterol (mmol/L) | Triglyceride (mmol/L) | HDL cholesterol (mmol/L) | LDL cholesterol (mmol/L) | Apolipoprotein (Apo) A1 (g/L) | Apolipoprotein (Apo) B (g/L) | ApoA1/ApoB |
|---------------|----------------|----|---------------------------|----------------------|-------------------------|--------------------------|-------------------------------|-------------------------------|-------------|
| C-C-G-T-G-T-C-G | Jing plus Han  | 1869 | 4.98 ± 0.86  | 1.30 (1.08) | 1.84 ± 0.50  | 2.82 ± 0.43  | 1.31 ± 0.23  | 1.03 ± 0.24  | 1.34 ± 0.38 |
|                | Carrier       | 64  | 4.98 ± 0.86  | 1.30 (1.08) | 1.84 ± 0.50  | 2.82 ± 0.43  | 1.31 ± 0.23  | 1.03 ± 0.24  | 1.34 ± 0.38 |
|                | Non-carrier   | 1805| 4.99 ± 0.90  | 1.39 (1.10) | 1.75 ± 0.49  | 2.84 ± 0.43  | 1.31 ± 0.21  | 1.05 ± 0.25  | 1.31 ± 0.38 |
|                |               |     | F             | 0.035     | −2.397       | 5.661        | 0.269          | 0.011          | 0.736        | 0.355       |
|                |               |     | P             | 0.852     | 0.017        | 0.017        | 0.604          | 0.916          | 0.391        | 0.552       |
| C-G-A-C-T-G-C-C-G | Jing plus Han | 1869 | 4.98 ± 0.88  | 1.36 (1.06) | 1.79 ± 0.46  | 2.83 ± 0.43  | 1.32 ± 0.21  | 1.04 ± 0.24  | 1.33 ± 0.38 |
|                | Carrier       | 139 | 4.98 ± 0.88  | 1.36 (1.06) | 1.79 ± 0.46  | 2.83 ± 0.43  | 1.32 ± 0.21  | 1.04 ± 0.24  | 1.33 ± 0.38 |
|                | Non-carrier   | 1730| 5.01 ± 0.94  | 1.37 (1.10) | 1.77 ± 0.50  | 2.84 ± 0.44  | 1.30 ± 0.22  | 1.05 ± 0.24  | 1.31 ± 0.38 |
|                |               |     | F             | 0.015     | −0.926       | 0.112        | 0.009          | 0.925          | 0.011        | 0.387       |
|                |               |     | P             | 0.901     | 0.354        | 0.738        | 0.924          | 0.336          | 0.915        | 0.534       |
| G-C-G-T-A-C-C-A | Jing plus Han | 1869 | 4.99 ± 0.91  | 1.48 (1.19) | 1.77 ± 0.40  | 2.83 ± 0.44  | 1.28 ± 0.20  | 1.05 ± 0.25  | 1.29 ± 0.38 |
|                | Carrier       | 59  | 4.99 ± 0.91  | 1.48 (1.19) | 1.77 ± 0.40  | 2.83 ± 0.44  | 1.28 ± 0.20  | 1.05 ± 0.25  | 1.29 ± 0.38 |
|                | Non-carrier   | 1810| 4.97 ± 0.77  | 1.35 (1.07) | 1.77 ± 0.51  | 2.83 ± 0.38  | 1.31 ± 0.22  | 1.04 ± 0.22  | 1.32 ± 0.38 |
|                |               |     | F             | 0.775     | −3.088       | 0.009        | 0.005          | 5.947          | 0.296        | 1.381       |
|                |               |     | P             | 0.379     | 0.002        | 0.765        | 0.944          | 0.015          | 0.587        | 0.240       |
|                | Han           | 988 | 4.87 ± 0.90  | 1.25 (0.98) | 1.79 ± 0.46  | 2.85 ± 0.45  | 1.35 ± 0.20  | 1.03 ± 0.24  | 1.39 ± 0.37 |
|                | Carrier       | 47  | 4.88 ± 0.86  | 1.34 (1.09) | 1.76 ± 0.54  | 2.85 ± 0.43  | 1.31 ± 0.20  | 1.04 ± 0.24  | 1.33 ± 0.38 |
|                | Non-carrier   | 941 | 5.17 ± 0.96  | 1.51 (1.16) | 1.78 ± 0.45  | 2.82 ± 0.42  | 1.29 ± 0.21  | 1.06 ± 0.25  | 1.28 ± 0.38 |
|                |               |     | F             | 1.009     | −0.756       | 0.183        | 0.105          | 0.157          | 0.152        | 0.309       |
|                |               |     | P             | 0.315     | 0.450        | 0.669        | 0.746          | 0.692          | 0.697        | 0.578       |
|                | Han           | 988 | 4.89 ± 0.79  | 1.34 (1.16) | 1.75 ± 0.54  | 2.89 ± 0.41  | 1.32 ± 0.19  | 1.04 ± 0.23  | 1.33 ± 0.38 |
|                | Carrier       | 55  | 4.89 ± 0.79  | 1.34 (1.16) | 1.75 ± 0.54  | 2.89 ± 0.41  | 1.32 ± 0.19  | 1.04 ± 0.23  | 1.33 ± 0.38 |
|                | Non-carrier   | 933 | 4.87 ± 0.88  | 1.31 (1.06) | 1.86 ± 0.41  | 2.84 ± 0.44  | 1.32 ± 0.20  | 1.04 ± 0.25  | 1.34 ± 0.38 |
|                |               |     | F             | 0.021     | −1.490       | 1.910        | 0.876          | 0.231          | 0.198        | 0.616       |
|                |               |     | P             | 0.885     | 0.136        | 0.167        | 0.350          | 0.631          | 0.657        | 0.433       |

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as the ratio of weight (kg) to squared height (m²). During the blood sample collection, 5 ml of venous blood were drawn, rapidly processed and serum lipids, lipoproteins, and apolipoproteins were measured by enzymatic methods with commercially available kits: RANDOX Laboratories Ltd., Ardmore, Diamond Road, Crumlin Co. Antrim, United Kingdom, BT29 4YQ and Daiichi Pure Chemicals Co., Ltd., Tokyo, Japan, and the immunoturbidimetric assay using a commercial kit: RANDOX Laboratories Ltd. in the Clinical Science Experiment Center of the First Affiliated Hospital, Guangxi Medical University with an autoanalyzer: Type 7170A; Hitachi Ltd., Tokyo, Japan. The normal values of serum lipid phenotypes in our Clinical Science Experiment Center were as follows: TC, 3.10–5.17 mmol/L; TG, 0.56–1.70 mmol/L; HDL cholesterol, 1.16–1.42 mmol/L; LDL cholesterol, 2.70–3.10 mmol/L; ApoA1, 1.20–1.60 g/L; ApoB, 0.80–1.05 g/L; and the ratio of ApoA1 to ApoB, 1.00–2.50; respectively. The SNPs selection. Nine TG-related loci in the DOCK7, PCSK9 and GALNT2 were selected by three criteria encompass (i) Tag SNPs, which were established by Haplovie (Broad Institute of MIT and Harvard, USA, version 4.2) and functional/missense SNPs in functional area of the gene fragments (http://www.ncbi.nlm.nih.gov/SNP/snp); (ii) a known minor allele frequency higher than 1% in European ancestry from the Human Genome Project Database; and (iii) the target SNP region should be adequately replicated by PCR, and the polymorphic site should have a commercially available restriction endonuclease enzyme cleavage site to be genotyped with RFLP.

Genotyping. DNA was isolated from blood samples using DNA Blood Midi kits (Qiagen, Hilden, Germany) following the protocol recommended by the vendor. We identified 9 SNPs genotyping by PCR-RFLP. The characteristics of each SNP and the details of each primer pair, annealing temperature, length of the PCR products and corresponding restriction enzyme used for genotyping are summarized in supplemental Tables 1 and 2. The PCR products of the samples (two samples of each genotype) were sequenced with an ABI Prism 3100 (Applied Biosystems, international Equipment Trading Ltd., Vernon Hill, IL, USA) in Shanghai Sangon Biological Engineering Technology & Services Co., Ltd., China.

Statistical methods. The statistical analyses were done with the statistical software package SPSS 17.0 (SPSS Inc., Chicago, Illinois). Data were presented as the mean ± SD for those, that are normally distributed, and the medians and interquartile ranges for TG, which is not normally distributed. Clinical characteristics between the Jing and Han populations were compared by Student's unpaired t-test. The allele, genotype and haplotype distribution between the Jing and Han populations were analyzed by the chi-squared test; and the standard goodness-of-fit verified the test Hardy-Weinberg equilibrium. Haplovie (Broad Institute of MIT and Harvard, USA, version 4.2) analyzed the haplotype frequencies and pair-wise LD among the detected SNPs. The correlation of genotypes and lipid profiles was calculated by ANCOVA. Any SNPs associated with the lipid profiles at the value of P < 0.005 (corresponding to P < 0.05 after adjusting for 9 independent tests by the Bonferroni correction) were considered statistically significant. Unconditional logistic regression was used to assess the association between lipid parameters and genotypes (common homozygote genotype = 1, heterozygote genotype = 2, rare homozygote genotype = 3) or alleles (the minor allele non-carrier = 1, the minor allele carrier = 2). Gender, age, BMI, alcohol consumption, cigarette smoking and hypertension were adjusted for statistical analysis. Two-sided P value of less than 0.05 was considered statistically significant.

| Haplotype     | Group         | n  | Total cholesterol (mmol/L) | Triglyceride (mmol/L) | HDL cholesterol (mmol/L) | LDL cholesterol (mmol/L) | Apolipoprotein (Apo) A1 (g/L) | Apolipoprotein (Apo) B (g/L) | ApoA1/ApoB |
|---------------|---------------|----|---------------------------|-----------------------|--------------------------|---------------------------|-------------------------------|-------------------------------|-------------|
|               | Jing plus Han | 1869 |                          |                       |                          |                           |                               |                               |             |
|               | Carrier       | 122 | 4.94 ± 0.86               | 1.36 (1.16)           | 1.81 ± 0.53              | 2.81 ± 0.40               | 1.31 ± 0.23                   | 1.03 ± 0.23                   | 1.35 ± 0.42  |
|               | Non-carrier   | 1747| 5.00 ± 0.90               | 1.37 (1.07)           | 1.76 ± 0.48              | 2.84 ± 0.44               | 1.31 ± 0.21                   | 1.05 ± 0.25                   | 1.31 ± 0.37  |
| F             |               |     | 1.882 ± 0.43              | 1.209 ± 0.19          | 1.204 ± 0.24             | 0.015 ± 0.001             | 3.363 ± 0.35                  | 3.350 ± 0.46                  |             |
| P             |               |     | 0.170 ± 0.666             | 0.272 ± 0.273         | 0.903 ± 0.067            | 0.067 ± 0.067             |                               |                               |             |
| Jing          | 881           |     | 5.06 ± 0.86               | 1.42 (1.11)           | 1.78 ± 0.46              | 2.79 ± 0.41               | 1.30 ± 0.26                   | 1.04 ± 0.24                   | 1.32 ± 0.44  |
| Carrier       | 80            |     | 5.13 ± 0.91               | 1.44 (1.16)           | 1.78 ± 0.43              | 2.82 ± 0.43               | 1.30 ± 0.22                   | 1.06 ± 0.25                   | 1.28 ± 0.37  |
| Non-carrier   | 801           |     | 5.06 ± 0.86               | 1.42 (1.11)           | 1.78 ± 0.46              | 2.79 ± 0.41               | 1.30 ± 0.26                   | 1.04 ± 0.24                   | 1.32 ± 0.44  |
| F             |               |     | 1.922 ± 0.637             | 0.179 ± 0.085         | 0.144 ± 0.078            | 0.798 ± 0.054             | 0.372 ± 0.45                  |                               |             |
| P             |               |     | 0.337 ± 0.524             | 0.673 ± 0.354         | 0.704 ± 0.372            | 0.457 ± 0.45              |                               |                               |             |
| Han           | 988           |     | 4.83 ± 0.84               | 1.31 (1.04)           | 1.83 ± 0.60              | 2.83 ± 0.40               | 1.33 ± 0.20                   | 1.01 ± 0.23                   | 1.38 ± 0.41  |
| Carrier       | 42            |     | 4.89 ± 0.88               | 1.33 (1.17)           | 1.75 ± 0.51              | 2.85 ± 0.45               | 1.32 ± 0.20                   | 1.04 ± 0.25                   | 1.33 ± 0.37  |
| Non-carrier   | 946           |     | 4.89 ± 0.88               | 1.33 (1.17)           | 1.75 ± 0.51              | 2.85 ± 0.45               | 1.32 ± 0.20                   | 1.04 ± 0.25                   | 1.33 ± 0.37  |
| F             |               |     | 1.143 ± 0.1183            | 2.233 ± 0.372         | 0.496 ± 0.237            | 2.237 ± 2.717             |                               |                               |             |
| P             |               |     | 0.285 ± 0.237             | 0.135 ± 0.054         | 0.482 ± 0.135            | 0.135 ± 0.100             |                               |                               |             |

Table 6. Lipid profiles according to haplotypes for the two ethnic groups. HDL, high density lipoprotein; LDL, low density lipoprotein.
| Lipid | SNP | Affected allele/ Other allele | Affected genotype/ Other genotype | Beta | Std.error | t | P-value |
|-------|-----|-------------------------------|---------------------------------|------|-----------|---|---------|
| **TC** | DOCK7 rs10889332 | CC,CT/TT | 0.081 | 0.036 | 3.161 | 0.002 |
| | DOCK7 rs10889332 | G/T | 0.057 | 0.047 | 2.231 | 0.026 |
| | PCSK9 rs615563 | GG,AG/AA | 0.068 | 0.039 | 2.634 | 0.009 |
| | PCSK9 rs615563 | G/A | 0.059 | 0.048 | 2.292 | 0.022 |
| | PCSK9 rs7552841 | CC,CT/TT | 0.108 | 0.041 | 4.234 | 0.000 |
| | GALNT2 rs2760537 | CC,CT/TT | 0.055 | 0.034 | 2.154 | 0.031 |
| | GALNT2 rs11122316 | | −0.055 | 0.047 | −2.145 | 0.032 |
| | DOCK7 rs1168013 | GG,CG/CC | 0.087 | 0.033 | 3.426 | 0.001 |
| | DOCK7 rs10889332 | CC,CT/TT | 0.099 | 0.034 | 3.903 | 0.000 |
| | PCSK9 rs615563 | GG,AG/AA | 0.094 | 0.035 | 3.995 | 0.000 |
| | PCSK9 rs7552841 | CC,CT/TT | 0.126 | 0.037 | 5.325 | 0.000 |
| | PCSK9 rs11206517 | T/G | −0.056 | 0.035 | −2.155 | 0.031 |
| | GALNT2 rs1997947 | GG,AG/AA | 0.083 | 0.035 | 3.440 | 0.001 |
| | GALNT2 rs2760537 | CC,CT/TT | 0.114 | 0.030 | 4.811 | 0.000 |
| | GALNT2 rs4846913 | CC,AC/AA | 0.104 | 0.036 | 4.384 | 0.000 |
| | GALNT2 rs4846913 | C/A | −0.109 | 0.027 | −4.235 | 0.000 |
| | GALNT2 rs11122316 | GG,AG/AA | 0.119 | 0.031 | 4.978 | 0.000 |
| **HDL cholesterol** | PCSK9 rs615563 | G/A | 0.052 | 0.024 | 1.988 | 0.047 |
| | PCSK9 rs7552841 | C/T | 0.100 | 0.025 | 3.816 | 0.000 |
| | PCSK9 rs11206517 | TLTG/GG | −0.067 | 0.032 | −2.573 | 0.010 |
| | GALNT2 rs1997947 | GG,AG/AA | −0.081 | 0.021 | −3.111 | 0.002 |
| | GALNT2 rs4846913 | GG,AG/AA | −0.078 | 0.022 | −3.014 | 0.003 |
| **LDL cholesterol** | DOCK7 rs10889332 | CC,CT/TT | 0.069 | 0.018 | 2.617 | 0.009 |
| | PCSK9 rs615563 | GG,AG/AA | 0.068 | 0.020 | 2.595 | 0.010 |
| | PCSK9 rs7552841 | C/T | 0.114 | 0.021 | 4.337 | 0.000 |
| | PCSK9 rs1168013 | GG,AG/AA | 0.100 | 0.025 | 3.816 | 0.000 |
| **ApoA1** | DOCK7 rs1168013 | G/C | 0.053 | 0.011 | 2.050 | 0.041 |
| | DOCK7 rs10889332 | CC,CT/TT | 0.065 | 0.009 | 2.485 | 0.013 |
| | GALNT2 rs1997947 | GG,AG/AA | −0.128 | 0.010 | −4.905 | 0.000 |
| | GALNT2 rs1997947 | G/A | −0.089 | 0.012 | −3.434 | 0.001 |
| | GALNT2 rs4846913 | CC,AC/AA | −0.117 | 0.010 | −4.488 | 0.000 |
| | GALNT2 rs4846913 | G/A | −0.128 | 0.012 | −4.901 | 0.000 |
| **ApoB** | DOCK7 rs10889332 | CC,CT/TT | 0.103 | 0.010 | 4.023 | 0.000 |
| | DOCK7 rs10889332 | C/T | 0.060 | 0.013 | 2.341 | 0.019 |
| | PCSK9 rs615563 | GG,AG/AA | 0.091 | 0.011 | 3.572 | 0.000 |
| | PCSK9 rs615563 | G/A | 0.093 | 0.013 | 3.598 | 0.000 |
| | PCSK9 rs7552841 | CC,CT/TT | 0.175 | 0.011 | 6.843 | 0.000 |
| | PCSK9 rs7552841 | C/T | 0.164 | 0.014 | 6.386 | 0.000 |
| | PCSK9 rs7552841 | G/A | −0.073 | 0.016 | −2.860 | 0.004 |
| | PCSK9 rs615563 | G/A | −0.087 | 0.020 | −3.420 | 0.001 |
| | PCSK9 rs7552841 | CC,CT/TT | −0.115 | 0.017 | −4.543 | 0.000 |
| | PCSK9 rs7552841 | C/T | −0.112 | 0.020 | −4.390 | 0.000 |
| | GALNT2 rs1997947 | GG,AG/AA | −0.089 | 0.016 | −3.443 | 0.001 |
| | GALNT2 rs1997947 | G/A | −0.060 | 0.020 | −2.321 | 0.020 |
| | GALNT2 rs4846913 | CC,AC/AA | −0.088 | 0.017 | −3.483 | 0.001 |
| | GALNT2 rs4846913 | C/A | −0.095 | 0.020 | −3.747 | 0.000 |
| **Ing** | DOCK7 rs1168013 | GG,CG/CC | −0.109 | 0.054 | −2.819 | 0.005 |
| | DOCK7 rs10889332 | CC,CT/TT | 0.111 | 0.054 | 2.823 | 0.005 |
| | PCSK9 rs615563 | CC,CT/TT | 0.116 | 0.058 | 3.159 | 0.002 |
| | PCSK9 rs7552841 | C/T | 0.133 | 0.072 | 3.561 | 0.000 |
| | GALNT2 rs2760537 | CC,CT/TT | 0.079 | 0.049 | 2.138 | 0.033 |
| | GALNT2 rs11122316 | G/A | −0.076 | 0.071 | −2.048 | 0.041 |
| **Continued** | | | | | | | |
| Lipid         | SNP         | Affected allele/Other allele | Affected genotype/Other genotype | Beta    | Std. error | t       | P-value |
|--------------|-------------|-----------------------------|----------------------------------|---------|-----------|---------|---------|
| TG           | DOCK7 rs1168013 | G/C                         | GG,CG/CC                         | 0.094   | 0.045     | 2.512   | 0.012   |
| TG           | DOCK7 rs1168013 | G/C                         | CC,CT/TT                         | 0.089   | 0.046     | 2.460   | 0.014   |
| TG           | PCSK9 rs165563  | C/T                         | GG,AG/AA                         | 0.072   | 0.048     | 2.131   | 0.034   |
| TG           | PCSK9 rs7552841 | C/T                         | CC,CT/TT                         | 0.141   | 0.049     | 4.169   | 0.000   |
| HDL cholesterol | GALNT2 rs1979747 | G/A                         | GG,AG/AA                         | 0.104   | 0.048     | 3.015   | 0.003   |
| HDL cholesterol | GALNT2 rs1979747 | G/A                         | CC,CT/TT                         | 0.107   | 0.061     | 3.048   | 0.002   |
| LDL cholesterol | DOCK7 rs1168013 | G/C                         | GG,CG/CC                         | 0.139   | 0.062     | 4.022   | 0.000   |
| LDL cholesterol | PCSK9 rs615563  | C/T                         | CC,CT/TT                         | 0.116   | 0.061     | 3.337   | 0.001   |
| LDL cholesterol | PCSK9 rs7552841 | C/T                         | CC,AC/AA                         | 0.095   | 0.049     | 2.806   | 0.005   |
| LDL cholesterol | PCSK9 rs7552841 | C/T                         | CC,CT/TT                         | 0.103   | 0.061     | 3.004   | 0.003   |
| LDL cholesterol | PCSK9 rs11122316 | G/A                         | GG,AG/AA                         | 0.124   | 0.043     | 3.605   | 0.000   |
| LDL cholesterol | PCSK9 rs11122316 | G/A                         | CC,CT/TT                         | 0.117   | 0.062     | 3.342   | 0.001   |
| ApoA1        | PCSK9 rs11206517 | T/G                         | GG,AG/AA                         | −0.010  | 0.027     | −2.766  | 0.006   |
| ApoA1        | GALNT2 rs1979747 | G/A                         | GG,AG/AA                         | −0.106  | 0.034     | −2.916  | 0.004   |
| ApoB         | DOCK7 rs1168013 | G/C                         | GG,CG/CC                         | −0.139  | 0.026     | −3.487  | 0.001   |
| ApoB         | PCSK9 rs7552841 | C/T                         | CC,CT/TT                         | 0.145   | 0.028     | 3.836   | 0.000   |
| ApoB         | PCSK9 rs7552841 | C/T                         | CC,CT/TT                         | 0.155   | 0.035     | 4.052   | 0.000   |
| ApoB         | PCSK9 rs7552841 | C/T                         | GG,CG/CC                         | −0.112  | 0.014     | −2.923  | 0.004   |
| ApoB         | PCSK9 rs7552841 | C/T                         | CC,AC/AA                         | −0.076  | 0.015     | −2.010  | 0.045   |
| ApoB         | PCSK9 rs7552841 | C/T                         | CC,CT/TT                         | −0.090  | 0.018     | −2.369  | 0.018   |
| ApoB         | PCSK9 rs7552841 | C/T                         | GG,AG/AA                         | −0.157  | 0.014     | −4.121  | 0.000   |
| ApoB         | PCSK9 rs7552841 | C/T                         | CC,CT/TT                         | 0.125   | 0.019     | 3.200   | 0.001   |
| ApoB         | PCSK9 rs7552841 | C/T                         | CC,CT/TT                         | 0.236   | 0.019     | 6.435   | 0.000   |
| ApoB         | PCSK9 rs7552841 | C/T                         | TT,GT/GG                         | 0.093   | 0.022     | 2.444   | 0.015   |
| ApoB         | PCSK9 rs7552841 | C/T                         | GG,AG/AA                         | −0.098  | 0.023     | −2.597  | 0.000   |
| ApoB         | PCSK9 rs7552841 | C/T                         | CC,CT/TT                         | 0.085   | 0.025     | 2.222   | 0.027   |
| Han          | DOCK7 rs1168013 | G/C                         | GG,CG/CC                         | 0.101   | 0.047     | 2.381   | 0.005   |
| Han          | DOCK7 rs1168013 | G/C                         | CC,CT/TT                         | 0.103   | 0.061     | 2.902   | 0.004   |
| Han          | PCSK9 rs165563  | G/A                         | GG,CG/CC                         | 0.075   | 0.029     | −2.017  | 0.044   |
| Han          | DOCK7 rs1168013 | G/C                         | CC,CT/TT                         | 0.084   | 0.049     | 2.316   | 0.021   |
| Han          | DOCK7 rs1168013 | G/C                         | CC,CT/TT                         | 0.111   | 0.052     | 3.083   | 0.002   |
| Han          | DOCK7 rs1168013 | G/C                         | GG,AG/AA                         | 0.116   | 0.060     | 3.435   | 0.001   |
| Han          | PCSK9 rs155563  | G/A                         | GG,AG/AA                         | 0.123   | 0.052     | 3.661   | 0.000   |
| Han          | PCSK9 rs155563  | G/A                         | CC,CT/TT                         | 0.153   | 0.064     | 4.476   | 0.000   |
| Han          | PCSK9 rs155563  | G/A                         | CC,CT/TT                         | 0.119   | 0.056     | 3.509   | 0.000   |
| TG           | DOCK7 rs1168013 | G/C                         | GG,CG/CC                         | 0.100   | 0.065     | 2.933   | 0.003   |
| TG           | PCSK9 rs7552841 | C/T                         | TT,GT/GG                         | 0.105   | 0.079     | 3.121   | 0.002   |
| TG           | PCSK9 rs11206517 | T/G                         | CC,CT/TT                         | 0.076   | 0.088     | 2.248   | 0.025   |
| TG           | GALNT2 rs2760537 | C/T                         | GG,AG/AA                         | 0.126   | 0.052     | 3.640   | 0.000   |
| TG           | GALNT2 rs2760537 | C/T                         | CC,CT/TT                         | 0.078   | 0.059     | 2.312   | 0.021   |
| TG           | GALNT2 rs4846913 | C/T                         | CC,AC/AA                         | 0.121   | 0.044     | 3.666   | 0.000   |
| TG           | GALNT2 rs11122316 | G/A                         | GG,AG/AA                         | 0.090   | 0.060     | 2.690   | 0.007   |
Table 7. Association of the alleles and genotypes of the DOCK7, PCSK9 and GALLNT2 SNPs and serum lipid traits in the Jing and Han populations. HDL, high density lipoprotein; LDL, low density lipoprotein; Association of serum lipid traits and allele and genotypes in Jing, Han and combined the Jing and Han populations were assessed by multivariable linear regression analyses with stepwise modeling.

| Lipid       | SNP     | Affected allele/ Other allele | Affected genotype/ Other genotype | Beta     | Std.error | t      | P-value |
|-------------|---------|-------------------------------|----------------------------------|----------|-----------|-------|---------|
| HDL cholesterol | DOCK7 rs1168013 | G/C | TT,GT/GG | 0.084 | 0.037 | 2.351 | 0.019 |
|             | PCSK9 rs1206517 | T/G | CC,AC/AA | 0.116 | 0.033 | 3.444 | 0.000 |
|             | DOCK7 rs1168013 | G/C | GG,C/C  | 0.107 | 0.024 | 2.965 | 0.003 |
| LDL cholesterol | DOCK7 rs1168013 | G/C | TT,GT/GG | 0.082 | 0.012 | 2.315 | 0.021 |
|             | PCSK9 rs1206517 | T/G | GG,AG/AA | 0.079 | 0.020 | 3.444 | 0.000 |
|             | DOCK7 rs1168013 | G/C | GG,C/C  | 0.119 | 0.013 | 3.314 | 0.000 |
| ApoA1       | DOCK7 rs1168013 | G/C | TT,GT/GG | 0.114 | 0.020 | 1.027 | 0.043 |
|             | PCSK9 rs1206517 | T/G | GG,AG/AA | 0.072 | 0.020 | 3.444 | 0.000 |
|             | DOCK7 rs1168013 | G/C | GG,C/C  | 0.101 | 0.018 | 2.979 | 0.005 |
| ApoB        | DOCK7 rs1168013 | G/C | TT,GT/GG | 0.108 | 0.018 | 2.979 | 0.005 |
|             | PCSK9 rs615563 | G/A | GG,AG/AA | 0.087 | 0.015 | 3.467 | 0.000 |
|             | DOCK7 rs1168013 | G/C | GG,C/C  | 0.080 | 0.019 | 2.200 | 0.028 |
| ApoA1/ApoB  | DOCK7 rs1168013 | G/C | TT,GT/GG | 0.073 | 0.020 | 2.074 | 0.038 |
|             | PCSK9 rs615563 | G/A | GG,AG/AA | 0.118 | 0.023 | 3.363 | 0.001 |
|             | DOCK7 rs1168013 | G/C | GG,C/C  | 0.104 | 0.017 | 3.314 | 0.000 |

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Author Contributions

T.G. participated in the research design, carried out the epidemiological investigation, collected the samples, undertook genotyping, performed statistical analyses, and drafted the manuscript. R.-X.Y. conceived the study, participated in the research design, carried out the epidemiological investigation, collected samples, helped to draft the manuscript and edited the final manuscript. F.H., L.-M.Y., W.-X.L. and S.-L.P. carried out the epidemiological investigation, and collected samples. All authors had read and approved the final manuscript.

Additional Information

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