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Original Article

Sexually dimorphic association of the pleiotropic *GALNT2* SNPs and haplotypes and serum lipid traits in Jing and Han populations

Tao Guo[1], Rui-Xing Yin[1], Shang-Ling Pan[2], Jin-Zhen Wu[1], Wei-Xiong Lin[3], De-Zhai Yang[3]

[1]Department of Cardiology, Institute of Cardiovascular Diseases, The First Affiliated Hospital, Guangxi Medical University, Nanning, Guangxi, China; [2]Department of Pathophysiology, School of Premedical Sciences, Guangxi Medical University, Nanning, Guangxi, China; [3]Department of Molecular Genetics, Medical Scientific Research Center, Guangxi Medical University, Nanning, Guangxi, China

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Abstract: The current study was undertaken to detect the association of the *GALNT2* rs1997947, rs2760537, rs4846913 and rs11122316 single nucleotide polymorphisms (SNPs) and their haplotypes with serum lipid traits between males and females in the Chinese population. Genotyping of the SNPs was performed in 1869 unrelated subjects (992 males and 877 females) by polymerase chain reaction and restriction fragment length polymorphism combined with gel electrophoresis, and then confirmed by direct sequencing. The allelic and genotypic frequencies of rs1997947 and rs4846913 SNPs were different between males and females. There were 16 haplotypes identified in our population, and haplotype of G-C-C-G was the commonest one. The haplotypes of A-C-A-G, A-T-C-A and A-T-C-G were associated with reduced risk of dyslipidaemia, and G-C-C-A and G-T-C-A were associated with increased risk of hyperlipidaemia. Haplotypes of A-C-A-G, A-T-C-A, A-T-C-G, G-C-C-A and G-T-C-A showed consistent association with serum triglyceride (TG) levels. In addition, haplotype of A-C-A-G had decreased serum HDL-C, apolipoprotein (Apo) A1 levels and the ApoA1/ApoB ratio, while G-C-C-A carriers had lower plasma TC levels. These results indicate that the *GALNT2* SNPs and their haplotypes are associated with serum lipid levels. The haplotypes with four SNPs can explain much more serum lipid variation than any single SNP alone, especially for serum TC, TG, HDL-C and ApoA1 levels.

Keywords: Lipids, single-nucleotide polymorphism (SNP), haplotype, the polypeptide N-acetylgalactosaminyltransferase 2 (*GALNT2*), environmental factors

Introduction

Lipid metabolism plays a significant role in the process of age-related diseases including atherosclerotic cardiovascular disease [1], which is a leading cause of morbidity and mortality from infancy to old age [2]. Prospective epidemiological researches have demonstrated that negative serum lipid levels such as ascending levels of total cholesterol (TC) [3], triglyceride (TG) [4], low-density lipoprotein cholesterol (LDL-C) [5], and apolipoprotein (Apo) B [6], together with descending levels of high-density lipoprotein cholesterol (HDL-C) [7] and ApoA1 [8] are the essential risk factors for coronary heart disease (CHD) and recommended as a treatment target. It is well-known that dyslipidaemia is a miscellaneous outcome resulting from multiple environmental [9-11] and genetic factors [12, 13] and their interactions [14-16]. The heritability estimation of the individual difference in serum lipid phenotypes from both twins and families researches are in the range of 40%-60% [17-19], suggesting a considerable genetic contribution, and discovery of the genes that contribute to these changes may give rise to a better understanding of these processes.

Genome-wide association studies (GWAs) have promulgated new genetic determinants of several complex quantitative traits including dyslipidaemia [20-23]. These researches evaluated sizable sample of normolipidaemic individuals and demonstrated that several new single nucleotide polymorphisms (SNPs) had replica-

ble modest associations with serum concentrations of TC, TG, LDL-C, and HDL-C [20-23]. One of these newly identified SNPs is the UDP-N-acetyl-alpha-D-galactosamine: polypeptide N-acetylgalactosaminyltransferase 2 gene (*GALNT2*; Gene ID: 2590; MIM: 602274) [21, 23, 24]. *GALNT2* is a member of a family of GalNAc-transferases, which transfer an N-acetyl galactosamine to the hydroxyl group of a serine/threonine residue in the first step of O-linked oligosaccharide biosynthesis [25]. It is generally known that ApoC3, lecithin-cholesterol acyltransferase (LCAT), low-density lipoprotein receptors, and very low-density lipoprotein are all O-glycosylated [26]. *GALNT2* is a gene in the mapped locus on chromosome 1q42-q42 within 150 kb of the lead SNP, which is located in an intron of the gene [27]. The *GALNT2* polymorphisms have been associated with alterations of plasma or serum TG [21, 23, 32-36] and HDL-C [23, 27-33] concentrations in some GWA studies but not in others [37-39]. Thus, further studies will be required to characterize the full impact of these SNPs on lipid metabolism. Members of this family initiate mucin-type O-glycoslation of peptides in the Golgi apparatus. The association between *GALNT2* rs4846914 [40] and rs2144300 [41] SNPs and serum or plasma lipid traits in humans has been evaluated in several previous studies. However, little is known about the association of the *GALNT2* rs1997947, rs2760537, rs4846913 and rs11122316 SNPs and their haplotypes with serum lipid levels in the Chinese population especially between males and females. Many of previous studies for this gene cluster come from studies of hyperlipidaemia subjects [32, 34, 35] and CHD patients [27]. Studies of differences in the association between *GALNT2* polymorphisms and serum lipid levels in normolipidaemic men and women are extremely limited. Therefore, the aim of the present study was to detect the association of *GALNT2* rs1997947, rs2760537, rs4846913 and rs11122316 SNPs and their haplotypes with serum lipid levels between males and females in the Chinese population.

Materials and methods

Study populations

A total of 1869 unrelated subjects who reside in Dongxing city, Guangxi Zhuang Autonomous Region, People's Republic of China were randomly selected from our previous stratified randomized samples [42]. The ages of the subjects ranged from 15 to 89 years, with an average age of 57.84±13.16 years. There were 992 males (53.08%) and 877 females (46.92%). All subjects were rural agricultural workers. The subjects had no evidence of diseases related to atherosclerosis, CHD and diabetes. None of them were using lipid-lowering medication such as statins or fibrates when the blood sample was taken. The present study was approved by the Ethics Committee of the First Affiliated Hospital, Guangxi Medical University. Written informed consents were obtained from all subjects after they received a full explanation of the study.

Epidemiological survey

The survey was carried out using internationally standardized methods. Information on demographics, socioeconomic status, and lifestyle factors was collected with standardized questionnaires. The alcohol information included questions about the number of liangs (about 50 g) of rice wine, corn wine, rum, beer, or liquor consumed during the preceding 12 months. Alcohol consumption was categorized into groups of grams of alcohol per day: 0 (nondrinker), ≤ 25 and > 25. Smoking status was categorized into groups of cigarettes per day: 0 (nonsmoker), ≤ 20 and > 20. At the physical examination, several parameters including body height, weight, and waist circumference were measured. Sitting blood pressure was measured three times with the use of a mercury sphygmomanometer while participants were seated and had rested for at least 5 min, and the average of the three measurements was used for the level of blood pressure. Body weight was measured with a portable balance scale and height with a portable steel measuring device. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Waist circumference was measured with a nonstretchable measuring tape, at the level of the smallest area of the waist.

Biochemical analysis

A venous blood sample of 5 ml was obtained from all subjects after at least 12 hours of fasting. A part of the sample (2 ml) was collected into glass tubes and used to determine serum

lipid levels. Another part of the sample (3 ml) was transferred to tubes with anticoagulate solution (4.80 g/l citric acid, 14.70 g/l glucose, and 13.20 g/l tri-sodium citrate) and used to extract deoxyribonucleic acid (DNA). Measurements of serum TC, TG, HDL-C, and LDL-C levels in the samples were performed by enzymatic methods with commercially available kits (RANDOX Laboratories Ltd., Ardmore, Diamond Road, Crumlin Co. Antrim, United Kingdom, BT29 4QY; Daiichi Pure Chemicals Co., Ltd., Tokyo, Japan). Serum ApoA1 and ApoB levels were detected by the immunoturbidimetric immunoassay using a commercial kit (RANDOX Laboratories Ltd.). All determinations were performed with an autoanalyzer (Type 7170A; Hitachi Ltd., Tokyo, Japan) in the Clinical Science Experiment Center of the First Affiliated Hospital, Guangxi Medical University.

DNA preparation and genotyping

Total genomic DNA of the samples was isolated from peripheral blood leukocytes according to a standard phenol-chloroform method. The extracted DNA was placed at -80°C. Genotypes of the four SNPs were determined using modified polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP) [43]. The SNPs were selected using two criteria: bioinformatics functional assessment and linkage disequilibrium (LD) structure. Computational analysis of *GALNT2* SNPs (http://www.ncbi.nlm.nih.gov/SNP/buildhistory.cgi) ascribed potential functional characteristics to each variant allele. In addition, the four SNPs selected for genotyping also based on the frequency of Beijing Han population from the Human Genome Project Database. The heterozygosity values were higher than 10% for the minor allele frequency. Transform bases were used for the genotyping. The sequences of the forward and backward primers used for *GALNT2* rs1997947, rs2760537, rs4846913 and rs11122316 were 5'-TTGCTTGTTGGAGGTTGG-3' and 5'-AGGAAGGGACTGTGCTGA-3', 5'-CTGGCTGGAACCCCTCTTTA-3' and 5'-ACACGCCCATCTCTCTTTCA-3', 5'-CGCCACCTCCCATCACAGA-3' and 5'-AAGCCTCACATCAACAGCAAAG-3', 5'-CACAGTGGTCCCGTAAGA-3' and 5'-GGCATAAGCTCCAGAGGC-3' (Sangon, Shanghai, People's Republic of China); respectively. Each reaction system of a total volume of 25 μl, comprised 100 ng (2 μl) of genomic DNA; 1.0 μl of each primer (10 μmo1/l); 12.5 μl 2 × *Taq* PCR MasterMix (constituent: 0.1 U *Taq* polymerase/μl, 500 μM dNTP each and PCR buffer) and nuclease-free water 8.5 μl. For the amplification, initial denaturation at 95°C for 5 min was followed by 33 cycles of denaturation at 95°C for 45 s, annealing at 56-62°C for 45 s, and extension at 72°C for 1 min, with final extension at 72°C for 10 min. After electrophoresis on a 2.0% agarose gel with 0.5 μg/ml ethidium bromide, the amplifican products were visualized under ultraviolet light. Then each restriction enzyme reaction was performed with 6 μl of amplified DNA; nuclease-free water 7.5 μl and 1 μl of 10 × buffer solution; and 5 U restriction ezyme (*Taq*I for rs199797, *Hae*III for rs2760537, *Pst*I for rs4846913 and *Taq*I for rs11122316) in a total volume of 15 μl digested at 37°C overnight. After restriction enzyme digestion of the amplified DNA, the digestive products were separated by electrophoresis on sepharose gel. The length of each digested DNA fragment was determined by comparing migration of a sample with that of standard DNA marker. Stained with ethidium bromide, the gel was visualized under ultraviolet light and photographed. Genotypes were scored by an experienced reader blinded to epidemiological data and serum lipid levels.

DNA sequencing

Twenty-four samples (each genotype in two) detected by the PCR-RFLP were also confirmed by direct sequencing. The PCR products were purified by low melting point gel electrophoresis and phenol extraction, and then the DNA sequences were analyzed by using an ABI Prism 3100 (Applied Biosyatems) in Shanghai Sangon Biological Engineering Technology & Services Co., Ltd., People's Republic of China.

Diagnostic criteria

The normal values of serum TC, TG, HDL-C, LDL-C, ApoA1, ApoB levels and the ratio of ApoA1 to ApoB in our Clinical Science Experiment Center were 3.10-5.17, 0.56-1.70, 1.16-1.42, 2.70-3.10 mmol/l, 1.20-1.60, 0.80-1.05 g/l, and 1.00-2.50; respectively. The individuals with TC > 5.17 mmol/l and/or TG > 1.70 mmol/l were defined as hyperlipidaemic. Hypertension was diagnosed according to the criteria of 1999 World Health Organization-International Society of Hypertension Guidelines for the manage-

Table 1. Comparison of general characteristics and serum lipid levels of the participants according to sex categories (male and female)

Parameter	Male (n = 992)	Female (n = 877)	*t* (x^2)	*P-value*
Age (years)	56.90±13.09	56.48±12.01	0.723	0.470*
Height (cm)	162.54±6.28	152.70±6.03	34.476	0.000*
Weight (kg)	60.78±9.41	54.22±8.96	15.389	0.000*
Body mass index (kg/m^2)	22.97±3.03	23.22±3.37	-1.685	0.092*
> 24 kg/m^2 [n (%)]	346 (34.88)	323 (36.83)	0.771	0.380†
Waist circumference (cm)	79.58±9.17	78.16±8.97	3.378	0.001*
Systolic blood pressure (mmHg)	133.50±8.84	131.43±11.34	1.158	0.247*
Diastolic blood pressure (mmHg)	81.21±10.61	80.29±10.18	1.921	0.055*
Pulse pressure (mmHg)	52.29±17.18	51.15±17.10	0.677	0.498*
Cigarette smoking [n (%)]				
Nonsmoker	632 (63.71)	874 (99.66)		
≤ 20 Cigarette smoking/day	88 (8.87)	2 (0.23)	384.459	0.000†
> 20 Cigarette smoking/day	272 (27.42)	1 (0.11)		
Alcohol consumption [n (%)]				
Nondrinker	646 (65.12)	869 (99.09)		
≤ 25 g/day	112 (11.29)	6 (0.68)	350.363	0.000†
> 25 g/day	234 (23.59)	2 (0.23)		
Blood glucose level (mmol/L)	6.73±1.52	6.63±1.35	1.443	0.149*
Total cholesterol (mmol/L)	4.97±0.84	4.94±0.88	0.839	0.402*
Triglyceride (mmol/L)	1.37 (1.08)	1.36 (1.11)	-0.873	0.383‡
High-density lipoprotein cholesterol (mmol/L)	1.72±0.51	1.83±0.47	-4.960	0.000*
Low-density lipoprotein cholesterol (mmol/L)	2.86±0.39	2.84±0.45	0.903	0.367*
Apolipoprotein (Apo) A1 (g/L)	1.30±0.21	1.32±0.22	-1.567	0.117*
ApoB (g/L)	1.06±0.24	1.04±0.25	1.562	0.118*
ApoA1/ApoB	1.30±0.40	1.34±0.36	-1.874	0.061*

*Comparison between the two sex categories by *t*-test. †Comparison between the two sex categories by chi-squared test. ‡Comparison between the two sex categories by non-parametric test. The values of triglyceride were presented as median (interquartile range).

ment of hypertension. The diagnostic criteria of overweight and obesity were according to the Cooperative Meta-analysis Group of China Obesity Task Force. Normal weight, overweight and obesity were defined as a BMI < 24, 24-28, and > 28 kg/m^2; respectively [42, 43].

Statistical analysis

Epidemiological data were recorded on a predesigned form and managed with Excel software. The statistical analyses were done with the statistical software package SPSS 19.0 (SPSS Inc., Chicago, Illinois). Data are presented as mean ± standard deviation for continuous variables (serum TG levels are presented as medians and interquartile ranges) and as frequencies or percentages for categorical variables. Allele frequency was determined via direct counting, and the standard goodness-of-fit test was used to test the Hardy-Weinberg equilibrium. Difference in genotype distribution between the groups was estimated by using the chi-square test. The difference in general characteristics between two ethnic groups was tested by the Student's unpaired *t*-test. The associations of genotypes and serum lipid parameters were determined using analysis of covariance (ANCOVA). Any variants associated with the serum lipid parameter at value of $P < 0.01$ (corresponding to $P < 0.05$ after adjusting for four independent tests by the Bonferroni correction). The confounding factors such as age, sex, BMI, blood pressure, alcohol consumption, and cigarette smoking were adjusted for the statistical analysis. Pair-wise linkage dis-

Table 2. The genotypic and allelic frequencies of *GALNT2* polymorphisms between males and females

SNP	Group	n	HWE (*P*)	Genotype [n (%)]			Allele [n (%)]	
				AA	AB	BB	A	B
rs1997947	Male	992	0.309	588 (59.27)	344 (34.68)	60 (6.05)	1520 (76.61)	464 (23.39)
G > A	Female	877	0.064	588 (67.05)	250 (28.50)	39 (4.45)	1426 (81.30)	328 (18.70)
	X^2	-	-		12.301		12.247	
	P	-	-		0.002		0.000	
rs2760537	Male	992	0.0819	428 (43.15)	428 (43.15)	136 (13.70)	1284 (64.72)	700 (35.28)
C > T	Female	877	0.842	362 (41.28)	405 (46.18)	110 (12.54)	1129 (64.37)	625 (35.63)
	X^2	-	-		1.828		0.050	
	P	-	-		0.401		0.823	
rs4846913	Male	992	0.367	652 (65.73)	299 (30.14)	41 (4.13)	1603 (80.80)	381 (19.20)
C > A	Female	877	0.052	623 (71.04)	223 (25.43)	31 (3.53)	1469 (83.75)	285 (16.25)
	X^2	-	-		6.061		5.552	
	P	-	-		0.048		0.018	
rs11122316	Male	992	0.367	398 (40.12)	471 (47.48)	123 (12.40)	1267 (63.86)	717 (36.14)
G > A	Female	877	0.337	332 (37.86)	426 (48.57)	119 (13.57)	1090 (62.14)	664 (37.86)
	X^2	-	-		1.219		1.178	
	P	-	-		0.544		0.278	

Genotype AA: rs1997947GG, rs2760537CC, rs4846913CC or rs11122316GG; Genotype AB: rs1997947AG, rs2760537CT, rs4846913AC or rs11122316AG; Genotype BB: rs1997947AA, rs2760537TT, rs4846913AA or rs11122316AA; Allele A: rs1997947G, rs2760537C, rs4846913C or rs11122316G; Allele B: rs1997947A, rs2760537T, rs4846913A or rs11122316A; HWE, Hardy-Weinberg equilibrium.

equilibria (LD) among the four SNPs were estimated as correlation coefficients (r^2) using the HelixTree program (GOLDEN Helix, Bozeman, MN, USA). In order to assess the association of serum lipid levels with genotypes (rs1997947: GG = 1, AG = 2, AA = 3; rs2760537: CC = 1, CT = 2, TT = 3; rs4846913: CC = 1, AC = 2, AA = 3; rs11122316: GG = 1, AG = 2, AA = 3) and several environment factors, multivariable linear regression analyses were also performed in the total population, males and females; respectively. Two-sided *P* values < 0.05 were considered statistically significant.

Results

Demographic and biochemical characteristics

The demographic and biochemical characteristics of the participants according to sex categories are presented in **Table 1**. The levels of body height, weight, waist circumference and the percentages of subjects who smoked cigarettes or consumed alcohol were higher in males than in females ($P < 0.05$-0.001), whereas the levels of HDL-C were lower in males than in females ($P < 0.05$). There was no significant difference in the levels of age, BMI, Systolic blood pressure, Diastolic blood pressure, Pulse pressure, Blood glucose level, TC, TG, LDL-C, ApoA1, ApoB, and the ratio of ApoA1 to ApoB ($P > 0.05$ for all).

Results of electrophoresis and genotyping

After the genomic DNA of the samples was amplified by PCR and imaged by agarose gel electrophoresis for the *GALNT2* rs1997947, the PCR product of 480-bp nucleotide sequences could be seen in the samples. The GG (480-bp), AG (480-, 352- and 128-bp) and AA (352- and 128-bp) genotypes are shown, respectively. The PCR product of the *GALNT2* rs2760537 was 284-bp nucleotide sequences. The CC (249- and 55-bp), CT (249-, 217-, 55- and 32-bp) and TT (217-, 55- and 32-bp) genotypes are shown, respectively. The PCR product of the *GALNT2* rs4846913 was 436-bp nucleotide sequences. The CC (436-bp), AC (436-, 243- and 193-bp) and AA (243- and 193-bp) genotypes are shown, respectively. The PCR product of the *GALNT2* rs11122316 was 456-bp nucleotide sequences. The GG (456-bp), AG (456-, 428- and 28-bp) and AA (428- and 28-bp) genotypes are shown, respectively.

Results of sequencing

The results were shown as GG, AG and AA genotypes of the *GALNT2* rs1997947; CC, CT and TT

Table 3. The *GALNT2* genotypes and serum lipid levels between males and females

SNP	Genotype	n	TC (mmol/L)	TG (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)	ApoA1 (g/L)	ApoB (g/L)	ApoA1/ ApoB
GALNT2	Male	992							
rs1997947G > A	GG	588	4.93±0.81	1.29 (1.03)	1.76±0.46	2.87±0.41	1.32±0.21	1.04±023	1.34±0.38
	AG	344	4.97±0.57	1.52 (1.16)	1.72±0.53	2.85±0.39	1.30±0.23	1.07±0.25	1.29±0.44
	AA	60	5.05±0.92	2.03 (1.43)	1.43±0.39	2.85±0.29	1.15±0.14	1.14±0.19	1.03±0.21
	F	-	2.075	9.645	5.577	0.309	13.404	4.449	11.963
	P	-	0.126	0.000	0.004	0.735	0.000	0.012	0.000
	Female	877							
	GG	588	4.90±0.89	1.29 (1.07)	1.87±0.47	2.76±0.56	1.33±0.23	1.02±0.25	1.37±0.37
	AG	250	5.00±0.86	1.50 (1.18)	1.79±0.47	2.83±0.46	1.30±0.20	1.06±0.25	1.29±0.35
	AA	39	5.11±0.87	1.96 (1.62)	1.47±0.27	2.87±0.43	1.18±0.13	1.07±0.19	1.14±0.29
	F	-	0.428	15.982	11.341	0.931	7.692	0.204	4.559
	P	-	0.652	0.000	0.000	0.395	0.000	0.816	0.011
GALNT2	Male	992							
rs2760537C > T	CC	428	5.04±0.87	1.48 (1.19)	1.67±0.51	2.88±0.37	1.29±0.22	1.06±0.27	1.28±0.35
	CT	428	4.94±0.80	1.44 (1.10)	1.71±0.55	2.84±0.40	1.30±0.22	1.06±0.22	1.31±0.41
	TT	136	4.88±0.89	1.31 (1.01)	1.77±0.48	2.81±0.42	1.33±0.19	1.05±0.24	1.34±0.48
	F	-	2.403	9.538	4.302	2.325	1.128	0.168	1.316
	P	-	0.091	0.000	0.014	0.098	0.324	0.846	0.269
	Female	877							
	CC	362	5.19±0.94	1.50 (1.24)	1.82±0.41	2.90±0.55	1.29±0.21	1.08±0.29	1.26±0.35
	CT	405	4.93±0.87	1.33 (1.07)	1.82±0.51	2.84±0.43	1.31±0.20	1.04±0.25	1.34±0.35
	TT	110	4.88±0.87	1.35 (1.11)	1.85±0.52	2.81±0.44	1.33±0.24	1.02±0.24	1.35±0.38
	F	-	6.183	7.383	0.173	2.060	1.683	1.937	2.453
	P	-	0.002	0.001	0.841	0.128	0.186	0.145	0.087
GALNT2	Male	992							
rs4846913C > A	CC	652	4.93±0.84	1.26 (1.00)	1.76±0.51	2.83±0.39	1.33±0.22	1.04±0.24	1.35±0.42
	AC	299	5.02±0.83	1.68 (1.19)	1.76±0.43	2.90±0.39	1.25±0.18	1.08±0.22	1.21±0.34
	AA	41	5.34±0.83	1.70 (1.48)	1.63±0.49	2.94±0.41	1.24±0.19	1.12±0.26	1.16±0.33
	F	-	3.993	16.873	5.043	3.940	8.409	2.591	8.976
	P	-	0.019	0.000	0.007	0.020	0.000	0.075	0.000
	Female	877							
	CC	623	4.80±0.95	1.31 (1.09)	1.90±0.47	2.75±0.64	1.34±0.22	1.03±0.26	1.36±0.36
	AC	223	4.90±0.85	1.53 (1.18)	1.70±0.44	2.82±0.43	1.27±0.19	1.04±0.25	1.29±0.37
	AA	31	4.96±0.89	1.96 (1.66)	1.46±0.44	2.85±0.45	1.20±0.23	1.08±0.20	1.14±0.29
	F	-	1.190	26.851	22.090	0.934	11.345	0.388	5.910
	P	-	0.305	0.000	0.000	0.393	0.000	0.679	0.003
GALNT2	Male	992							
rs11122316G > A	GG	398	5.05±0.82	1.46 (1.18)	1.69±0.47	2.90±0.34	1.29±0.21	1.07±0.25	1.29±0.39
	AG	471	5.00±0.85	1.39 (1.08)	1.74±0.53	2.87±0.40	1.30±0.21	1.05±0.24	1.30±0.39
	AA	123	4.93±0.84	1.31 (0.99)	1.79±0.56	2.84±0.40	1.32±0.22	1.05±0.23	1.31±0.42
	F	-	1.195	3.772	2.343	1.878	1.978	0.388	0.261
	P	-	0.303	0.023	0.097	0.154	0.139	0.679	0.771
	Female	877							
	GG	332	4.95±0.86	1.46 (1.21)	1.80±0.43	2.88±0.44	1.31±0.24	1.05±0.24	1.32±0.37
	AG	426	4.94±0.92	1.40 (1.13)	1.82±0.52	2.83±0.47	1.32±0.20	1.04±0.25	1.33±0.34
	AA	119	4.89±0.88	1.28 (1.04)	1.86±0.43	2.82±0.45	1.34±0.20	1.03±0.26	1.36±0.36
	F	-	0.300	4.100	0.780	1.530	0.862	0.537	0.293
	P	-	0.741	0.017	0.459	0.217	0.423	0.585	0.746

SNP, single nucleotide polymorphism; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; ApoA1/A poB, the rati o of a polipoprote in A1 to apolipoprote in B. The values of TG were presented as median (interquartile range). The difference among the genotypes was determined by the Kruskal-Wallis test or the Wilcoxon-Mann-Whitney test.

Table 4. The haplotype frequencies of *GALNT2* polymorphism between the males and females

Haplotype (rs1997947-rs2760537-rs4846913-rs11122316)	Males n (freq)	Females n (freq)	Chi2	*P*	OR (95% CI)
A-C-A-A (Rare Hap (< 0.03))	39 (0.022)	51 (0.026)	0.379	0.538	0.88 (0.58, 1.34)
A-C-A-G (Rare Hap (< 0.03))*	20 (0.011)	46 (0.023)	7.358	0.007	0.49 (0.29, 0.83)
A-C-C-A	87 (0.050)	90 (0.045)	0.411	0.521	1.10 (0.82, 1.49)
A-C-C-G	88 (0.050)	101 (0.051)	0.024	0.878	0.98 (0.73, 1.31)
A-T-A-A (Rare Hap (< 0.03))	8 (0.005)	6 (0.003)	0.832	0.362	1.64 (0.56, 4.77)
A-T-A-G (Rare Hap (< 0.03))	18 (0.010)	24 (0.012)	0.348	0.556	0.83 (0.45, 1.54)
A-T-C-A*	34 (0.019)	67 (0.034)	7.479	0.006	0.56 (0.37, 0.85)
A-T-C-G*	35 (0.020)	80 (0.040)	13.444	0.000	0.48 (0.32, 0.71)
G-C-A-A	45 (0.026)	69 (0.035)	2.746	0.098	0.73 (0.50, 1.06)
G-C-A-G	85 (0.049)	96 (0.048)	0.001	0.970	1.01 (0.75, 1.36)
G-C-C-A*	261 (0.149)	255 (0.128)	3.283	0.007	1.19 (1.00, 1.43)
G-C-C-G	504 (0.287)	577 (0.291)	0.054	0.816	0.98 (0.85, 1.13)
G-T-A-A (Rare Hap (< 0.03))	20 (0.011)	32 (0.016))	1.507	0.220	0.70 (0.40, 1.24)
G-T-A-G (Rare Hap (< 0.03))	50 (0.028)	58 (0.029)	0.020	0.889	0.97 (0.66, 1.43)
G-T-C-A*	170 (0.097)	148 (0.075)	5.849	0.016	1.33 (1.06, 1.67)
G-T-C-G	292 (0.166)	285 (0.144)	3.554	0.059	1.19 (0.99, 1.42)

*The haplotypes of A-C-A-G, A-T-C-A, A-T-C-G, G-C-C-A and G-T-C-A were associated with dyslipidaemia.

genotypes of the *GALNT2* rs2760537; CC, AC and AA genotypes of the *GALNT2* rs4846913; and GG, AG and AA genotypes of the *GALNT2* rs11122316 by PCR-R FLP, the genotypes were also confirmed by sequencing; respectively. We have deposited the raw data at Genbank's Gene Expression Omnibus (GEO) database.

Genotypic and allelic frequencies

All genotypic frequencies of four loci were in Hardy-Weinberg equilibrium ($P > 0.05$ for all). A significant linkage disequilibrium (LD) was noted between the rs1997947 and rs11122316 SNPs ($r^2 > 0.5$, $P < 0.001$). The frequency of rs1997947CC, AG and AA genotypes was 59.27%, 34.68% and 6.05% in males, and 67.05%, 28.50% and 4.45% in females ($P < 0.005$); respectively. The frequency of rs1997947G and A alleles was 76.61% and 23.39% in males, and 81.30% and 18.70% in females ($P < 0.001$); respectively. The frequency of rs4846913CC, AC and AA genotypes was 65.73%, 30.14% and 4.13% in males, and 71.04%, 25.43% and 3.53% in females ($P < 0.05$); respectively. The frequency of rs4846913C and A alleles was 80.80% and 19.20% in males, and 83.75% and 16.25% in females ($P < 0.05$); respectively. There was no difference in the genotypic and allelic frequencies of the rs2760537 and rs11122316 SNPs between the males and females ($P > 0.05$ for all; **Table 2**).

Genotypes and serum lipid levels

As shown in **Table 3**, the levels of TG, HDL-C, ApoA1 and the ratio ApoA1 to ApoB in males were different among the rs1997947 genotypes, whereas the levels of TC, HDL-C and ApoA1 in females were different among the genotypes ($P < 0.01$-0.001).

The levels of TG in males were different among the three rs2760537 genotypes ($P < 0.001$), whereas the levels of TC and TG in females were different among the genotypes ($P < 0.01$ for each).

The levels of TG, HDL-C, ApoA1 and the ratio ApoA1 to ApoB in males or females were different among the three rs4846913 genotypes ($P < 0.01$ for all).

Serum lipid levels in males or females were not different among the three rs11122316 genotypes ($P > 0.01$ for all).

Haplotypes and serum lipid levels

To examine the combined effect of four variants (in the order of rs1997947, rs2760537, rs4846913 and rs11122316) in the cluster, we conducted haplotype analysis with these SNPs on the serum lipid traits (**Table 4**). There were 16 haplotypes identified in the cluster in our population. The haplotype of G-C-C-G was the commonest one (30%). The haplotypes of

Table 5. Association between *GALNT2* haplotypes and serum lipid levels in the males and females

Haplotype	Group	TC (mmol/L)	TG (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)	ApoA1 (g/L)	ApoB (g/L)	ApoA1/ ApoB
A-C-A-G	Males plus Females							
	Carrier	4.98±0.78	1.72 (1.24)	1.61±0.46	2.85±0.43	1.21±0.15	1.08±0.22	1.17±0.33
	Non-carrier	4.96±0.87	1.34 (1.08)	1.79±0.50	2.83±0.38	1.32±0.12	1.04±0.24	1.33±0.38
	F	0.053	-7.129	12.05	0.758	12.99	1.557	18.084
	P	0.818	0.000	0.001	0.384	0.000	0.212	0.000
	Males							
	Carrier	5.03±0.78	1.77 (1.20)	1.63±0.47	2.86±0.40	1.20±0.15	1.08±0.22	1.17±0.36
	Non-carrier	4.97±0.85	1.34 (1.05)	1.73±0.51	2.84±0.34	1.32±0.22	1.05±0.24	1.32±0.40
	F	0.306	-5.005	0.944	0.619	20.924	0.562	8.476
	P	0.580	0.000	0.332	0.432	0.000	0.454	0.004
	Females							
	Carrier	4.94±0.89	1.69 (1.31)	1.58±0.43	2.84±0.46	1.23±0.16	1.08±0.23	1.18±0.29
	Non-carrier	4.91±0.77	1.34 (1.10)	1.85±0.47	2.83±0.43	1.33±0.22	1.03±0.25	1.35±0.37
	F	0.929	-5.172	18.361	0.259	11.293	0.636	8.306
	P	0.335	0.000	0.000	0.611	0.001	0.425	0.004
A-T-C-A	Males plus Females							
	Carrier	5.01±0.92	1.60 (1.24)	1.75±0.49	2.88±0.42	1.29±0.20	1.08±0.27	1.28±0.46
	Non-carrier	4.95±0.85	1.34 (1.07)	1.78±0.50	2.84±0.42	1.31±0.22	1.04±0.24	1.32±0.37
	F	0.979	-6.919	0.042	1.079	3.186	3.484	1.991
	P	0.322	0.000	0.837	0.299	0.074	0.062	0.158
	Males							
	Carrier	4.98±0.82	1.62 (1.22)	1.71±0.45	2.86±0.38	1.27±0.20	1.06±0.27	1.30±0.37
	Non-carrier	4.92±0.94	1.34 (1.04)	1.72±0.52	2.83±0.42	1.31±0.22	1.06±0.23	1.31±0.52
	F	0.243	-5.124	0.007	0.390	4.530	0.137	0.004
	P	0.622	0.000	0.934	0.532	0.034	0.711	0.951
	Females							
	Carrier	5.16±0.86	1.59 (1.27)	1.82±0.54	2.96±0.41	1.31±0.21	1.12±0.26	1.24±0.35
	Non-carrier	4.91±0.88	1.34 (1.10)	1.83±0.47	2.82±0.46	1.32±0.22	1.03±0.25	1.35±0.36
	F	4.345	-4.649	0.157	4.020	0.133	6.602	6.103
	P	0.037	0.000	0.692	0.045	0.716	0.010	0.014
A-T-C-G	Males plus Females							
	Carrier	5.02±0.92	1.57 (1.21)	1.74±0.49	2.86±0.41	1.29±0.23	1.08±0.26	1.26±0.43
	Non-carrier	4.95±0.85	1.34 (1.07)	1.78±0.50	2.84±0.42	1.31±0.21	1.04±0.24	1.33±0.37
	F	0.782	-5.573	0.262	0.078	3.521	5.139	5.183
	P	0.377	0.000	0.609	0.781	0.061	0.024	0.023
	Males							
	Carrier	5.00±0.94	1.59 (1.20)	1.72±0.49	2.85±0.41	1.28±0.23	1.08±0.26	1.26±0.48
	Non-carrier	4.97±0.81	1.33 (1.05)	1.72±0.51	2.85±0.39	1.31±0.21	1.05±0.23	1.31±0.38
	F	0.097	-4.389	0.194	0.149	2.938	4.085	2.573
	P	0.756	0.000	0.660	0.699	0.087	0.044	0.109
	Females							
	Carrier	5.05±0.90	1.53 (1.24)	1.77±0.49	2.89±0.43	1.30±0.21	1.08±0.26	1.26±0.33
	Non-carrier	4.92±0.88	1.34 (1.10)	1.84±0.47	2.83±0.46	1.32±0.22	1.03±0.25	1.35±0.37
	F	0.986	-3.320	2.149	0.329	1.321	1.213	3.389
	P	0.321	0.001	0.143	0.566	0.251	0.271	0.066
G-C-C-A	Males plus Females							
	Carrier	4.82±0.83	1.22 (0.97)	1.75±0.45	2.78±0.39	1.33±0.21	1.01±0.21	1.37±0.35
	Non-carrier	4.97±0.86	1.40 (1.11)	1.78±0.50	2.85±0.42	1.31±0.22	1.05±0.25	1.31±0.39
	F	4.803	-5.772	0.243	3.720	2.356	2.538	2.750
	P	0.029	0.000	0.622	0.054	0.125	0.111	0.097

	Males							
	Carrier	4.87±0.82	1.12 (0.94)	1.64±0.50	2.78±0.37	1.33±0.23	1.02±0.20	1.36±0.36
	Non-carrier	4.99±0.84	1.44 (1.10)	1.73±0.51	2.86±0.39	1.30±0.21	1.06±0.24	1.30±0.40
	F	1.120	-5.740	2.246	3.216	2.224	1.950	1.592
	P	0.290	0.000	0.134	0.073	0.136	0.163	0.207
	Females							
	Carrier	4.77±0.85	1.30 (1.10)	1.88±0.35	2.79±0.43	1.33±0.19	1.01±0.23	1.38±0.35
	Non-carrier	4.96±0.89	1.36 (1.11)	1.83±0.49	2.84±0.46	1.32±0.22	1.04±0.25	1.33±0.36
	F	4.192	-2.100	0.953	0.941	0.565	0.636	1.114
	P	0.041	0.036	0.329	0.332	0.452	0.425	0.292
G-T-C-A	Males plus Females							
	Carrier	4.97±0.87	1.42 (1.17)	1.76±0.47	2.87±0.41	1.30±0.21	1.05±0.25	1.31±0.37
	Non-carrier	4.95±0.85	1.35 (1.06)	1.81±0.54	2.84±0.42	1.32±0.22	1.05±0.24	1.33±0.40
	F	0.269	-3.049	2.815	2.305	0.437	0.058	0.399
	P	0.604	0.002	0.094	0.129	0.509	0.809	0.528
	Males							
	Carrier	4.99±0.83	1.44 (1.18)	1.70±0.51	2.86±0.39	1.30±0.19	1.06±0.23	1.29±0.39
	Non-carrier	4.94±0.87	1.36 (1.03)	1.76±0.49	2.85±0.38	1.30±0.22	1.04±0.24	1.33±0.43
	F	0.466	-2.947	1.692	0.012	0.803	1.682	1.385
	P	0.495	0.003	0.194	0.914	0.370	0.195	0.240
	Females							
	Carrier	4.99±0.88	1.41 (1.15)	1.82±0.42	2.88±0.44	1.31±0.20	1.06±0.26	1.33±0.38
	Non-carrier	4.91±0.89	1.35 (1.10)	1.86±0.57	2.81±0.46	1.34±0.25	1.03±0.25	1.34±0.36
	F	2.287	-1.438	1.415	4.481	3.267	2.334	0.089
	P	0.131	0.151	0.235	0.035	0.071	0.127	0.766

SNP, single nucleotide polymorphism; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; ApoA1/A poB, the rati o of a polipoprote in A1 to apolipoprote in B. The values of TG were presented as median (interquartile range). The difference among the genotypes was determined by the Kruskal-Wallis test or the Wilcoxon-Mann-Whitney test.

A-C-A-G, A-T-C-A and A-T-C-G were associated with reduced risk of dyslipidaemia (OR: 0.49, 95% CI: 0.29-0.83, $P = 0.007$; OR: 0.56, 95% CI: 0.37-0.85, $P = 0.006$ and OR: 0.48, 95% CI: 0.32-0.71, $P < 0.001$; respectively). The haplotypes of G-C-C-A and G-T-C-A were associated with increased risk of hyperlipidaemia (OR: 1.19, 95% CI: 1.00-1.43, $P = 0.007$ and OR: 1.33, 95% CI: 1.06-1.67, $P = 0.016$; respectively). Haplotypes of A-C-A-G, A-T-C-A, A-T-C-G, G-C-C-A and G-T-C-A showed consistent association with serum TG levels. In addition, carriers of the A-C-A-G haplotype had decreased serum concentration of HDL-C, ApoA1 and the ratio ApoA1 to ApoB, while G-C-C-A carriers had lower plasma TC levels. We also found that the haplotypes with four SNPs can explain much more serum lipid variation than any single SNP alone, especially for serum TC, TG, HDL-C and ApoA1 levels (**Table 5**).

Correlated factors for serum lipid parameters

For males, multivariable linear regression analyses showed that the levels of TC were correlated with the rs4846913 genotypes and alleles; TG with the rs1997947, rs2760537 and rs4846913 genotypes and alleles, and the rs11122316 alleles; HDL-C with the rs4846913 genotypes, and the rs2760537 and rs4846913 alleles; LDL-C with the rs4846913 genotypes and alleles; ApoA1 with the rs1997947 and rs4846913 genotypes and alleles; ApoB with the rs1997947 and rs4846913 genotypes and alleles; and the ratio of ApoA1 to ApoB with the rs1997947 and rs4846913 genotypes and alleles (**Table 6**).

For females, the levels of TC were correlated with the rs1997947 genotypes and rs2760537 alleles; TG with the rs1997947, rs4846913 and rs11122316 genotypes and alleles, and the rs2760537 genotypes; HDL-C with the rs-1997947 and rs4846913 genotypes and alleles; ApoA1 with the rs1997947 and rs-4846913 genotypes and alleles; ApoB with the rs1997947 genotypes and alleles; and the ratio of ApoA1 to ApoB with the rs1997947 and rs4846913 genotypes and alleles (**Table 6**).

Table 6. Correlation between serum lipid parameters and the alleles/genotypes in the males and females

Lipid parameter	SNP	Allele	Genotype	Beta	Std. error	*t*	*P*-value
Males plus Females							
TC	rs1997947		GG/AG/AA	0.060	0.034	2.599	0.009
	rs1997947	G/A		0.065	0.041	2.812	0.005
	rs2760537		CC/CT/TT	0.049	0.029	2.117	0.034
	rs2760537	C/T		0.048	0.040	2.099	0.036
TG	rs1997947		GG/AG/AA	0.136	0.034	6.012	0.000
	rs1997947	G/A		0.195	0.044	8.679	0.000
	rs2760537		CC/CT/TT	0.107	0.029	4.820	0.000
	rs2760537	C/T		0.112	0.042	4.949	0.000
	rs4846913		CC/AC/AA	0.204	0.037	9.103	0.000
	rs4846913	C/A		0.079	0.042	3.483	0.001
	rs11122316		GG/AG/AA	0.055	0.030	2.461	0.014
	rs11122316	G/A		0.075	0.041	3.363	0.001
HDL-C	rs1997947		GG/AG/AA	-0.095	0.019	-4.152	0.000
	rs1997947	G/A		-0.054	0.023	-2.366	0.018
	rs2760537	C/T		0.055	0.023	2.403	0.016
	rs4846913		CC/AC/AA	-0.136	0.021	-5.897	0.000
	rs4846913	C/A		-0.147	0.024	-6.441	0.000
ApoA1	rs1997947		GG/AG/AA	-0.127	0.008	-5.568	0.000
	rs1997947	G/A		-0.155	0.011	-6.778	0.000
	rs4846913		CC/AC/AA	-0.147	0.009	-6.453	0.000
	rs4846913	C/A		-0.094	0.010	-4.118	0.000
ApoB	rs1997947		GG/AG/AA	0.084	0.010	3.628	0.000
	rs1997947	G/A		0.078	0.012	3.390	0.001
	rs4846913		CC/AC/AA	0.058	0.010	2.510	0.012
	rs4846913	C/A		0.058	0.012	2.527	0.012
ApoA1/ApoB	rs1997947		GG/AG/AA	-0.134	0.015	-5.843	0.000
	rs1997947	G/A		-0.106	0.018	-4.649	0.000
	rs4846913		CC/AC/AA	-0.136	0.016	-5.954	0.000
	rs4846913	C/A		-0.139	0.019	-6.108	0.000
Males							
TC	rs4846913		CC/AC/AA	0.093	0.047	2.930	0.000
	rs4846913	C/A		0.072	0.056	2.271	0.023
TG	rs1997947		GG/AG/AA	0.117	0.051	3.772	0.000
	rs1997947	G/A		0.097	0.063	3.110	0.002
	rs2760537		CC/CT/TT	0.109	0.044	3.535	0.000
	rs2760537	C/T		0.087	0.062	2.828	0.005
	rs4846913		CC/AC/AA	0.203	0.055	6.563	0.000
	rs4846913	C/A		0.205	0.065	6.633	0.000
	rs11122316	G/A		0.063	0.063	2.044	0.041
HDL-C	rs2760537	C/T		0.086	0.032	2.731	0.006
	rs4846913		CC/AC/AA	-0.078	0.028	-2.456	0.014
	rs4846913	C/A		-0.099	0.034	-3.156	0.002
LDL-C	rs4846913		CC/AC/AA	0.094	0.022	2.960	0.003
	rs4846913	C/A		0.093	0.026	2.941	0.003
ApoA1	rs1997947		GG/AG/AA	-0.132	0.011	-4.213	0.000
	rs1997947	G/A		-0.089	0.014	-2.837	0.005

	rs4846913		CC/AC/AA	-0.148	0.012	-4.727	0.000
	rs4846913	C/A		-0.165	0.014	-5.292	0.000
ApoB	rs1997947		GG/AG/AA	0.097	0.012	3.051	0.002
	rs1997947	G/A		0.084	0.015	2.661	0.008
	rs4846913		CC/AC/AA	0.089	0.013	2.804	0.005
	rs4846913	C/A		0.092	0.016	2.910	0.004
ApoA1/ApoB	rs1997947		GG/AG/AA	-0.129	0.021	-4.112	0.000
	rs1997947	G/A		-0.090	0.025	-2.885	0.004
	rs4846913		CC/AC/AA	-0.155	0.022	-4.958	0.000
	rs4846913	C/A		-0.168	0.026	-5.377	0.000
Females							
TC	rs1997947		GG/AG/AA	0.077	0.052	2.272	0.023
	rs2760537		CC/CT/TT	0.103	0.044	3.044	0.002
TG	rs1997947		GG/AG/AA	0.165	0.045	5.012	0.000
	rs1997947	G/A		0.120	0.055	3.633	0.000
	rs2760537		CC/CT/TT	0.109	0.037	3.387	0.001
	rs4846913		CC/AC/AA	0.208	0.047	6.405	0.000
	rs4846913	C/A		0.175	0.057	5.316	0.000
	rs11122316		GG/AG/AA	0.075	0.038	2.318	0.021
	rs11122316	G/A		0.103	0.053	3.127	0.002
HDL-C	rs1997947		GG/AG/AA	-0.133	0.027	-4.046	0.000
	rs1997947	G/A		-0.106	0.033	-3.214	0.001
	rs4846913		CC/AC/AA	-0.208	0.029	-6.320	0.000
	rs4846913	C/A		-0.199	0.034	-6.022	0.000
ApoA1	rs1997947		GG/AG/AA	-0.118	0.013	-3.530	0.000
	rs1997947	G/A		-0.097	0.016	-2.889	0.004
	rs4846913		CC/AC/AA	-0.145	0.014	-4.332	0.000
	rs4846913	C/A		-0.139	0.016	-4.172	0.000
ApoB	rs1997947		GG/AG/AA	0.069	0.015	2.048	0.041
	rs1997947	G/A		0.070	0.018	2.080	0.038
ApoA1/ApoB	rs1997947		GG/AG/AA	-0.136	0.021	-4.038	0.000
	rs1997947	G/A		-0.123	0.026	-3.674	0.000
	rs4846913		CC/AC/AA	-0.109	0.023	-3.237	0.001
	rs4846913	C/A		-0.098	0.027	-2.938	0.003

SNP, single nucleotide polymorphism; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; ApoA1/ApoB, the ratio of apolipoprote in A1 to apolipoprote in B.

Table 7. Correlation between serum lipid parameters and several environmental factors in the males and females

Lipid parameter	Risk factor	B	Std. error	Beta	*t*	*P*-value
Males plus Females						
TC	Age	0.009	0.002	0.126	5.557	0.000
	BMI	0.014	0.006	0.052	2.311	0.021
	Glucose	0.118	0.014	0.199	8.753	0.000
TG	Age	-0.007	0.002	-0.096	-4.207	0.000
	Height	-0.021	0.003	-0.183	-6.938	0.000
	BMI	-0.034	0.012	-0.120	-2.820	0.005
	Waist circumference	0.040	0.004	0.404	9.164	0.000
	Diastolic BP	0.007	0.002	0.085	3.898	0.000

	Cigarette smoking	0.282	0.029	0.224	9.753	0.000
	Glucose	0.099	0.014	0.159	7.359	0.000
HDL-C	Gender	0.163	0.030	0.164	5.399	0.000
	Height	0.005	0.002	0.076	2.619	0.009
	Waist circumference	-0.016	0.001	-0.290	-12.365	0.000
	Diastolic BP	0.003	0.001	0.058	2.555	0.011
	Cigarette smoking	-0.067	0.018	-0.098	-3.804	0.000
	Alcohol consumption	0.115	0.018	0.159	6.286	0.000
LDL-C	Age	0.003	0.001	0.085	3.677	0.000
	Diastolic BP	0.003	0.001	0.082	3.582	0.000
	Glucose	0.036	0.007	0.124	5.348	0.000
ApoA1	Weight	-0.005	0.001	-0.221	-9.572	0.000
	Diastolic BP	0.001	0.000	0.053	2.341	0.019
	Alcohol consumption	0.057	0.007	0.182	8.010	0.000
	Glucose	-0.014	0.003	-0.093	-4.145	0.000
ApoB	Age	0.002	0.000	0.120	5.329	0.000
	Waist circumference	0.005	0.001	0.200	8.678	0.000
	Diastolic BP	0.001	0.001	0.056	2.422	0.016
ApoA1/ApoB	Gender	0.065	0.019	0.085	3.464	0.001
	Age	-0.002	0.001	-0.081	-3.622	0.000
	BMI	-0.012	0.005	-0.098	-2.399	0.017
	Waist circumference	-0.008	0.002	-0.189	-4.579	0.000
	Alcohol consumption	0.074	0.014	0.132	5.423	0.000
	Glucose	-0.019	0.006	-0.070	-3.137	0.002
Males						
TC	Age	0.008	0.002	0.117	3.738	0.000
	BMI	0.021	0.009	0.075	2.433	0.015
	Glucose	0.106	0.017	0.193	6.163	0.000
TG	Age	-0.015	0.002	-0.199	-6.122	0.000
	Height	-0.017	0.006	-0.107	-2.871	0.004
	Weight	-0.018	0.007	-0.168	-2.404	0.016
	Waist circumference	0.047	0.007	0.429	6.873	0.000
	Diastolic BP	0.009	0.003	0.101	3.455	0.001
	Cigarette smoking	0.239	0.034	0.212	7.028	0.000
	Glucose	0.119	0.019	0.182	6.249	0.000
HDL-C	Age	0.003	0.001	0.066	1.989	0.047
	Weight	0.009	0.003	0.167	2.676	0.008
	Waist circumference	-0.023	0.003	-0.416	-6.747	0.000
	Cigarette smoking	-0.063	0.019	0.208	6.578	0.000
	Alcohol consumption	0.124	0.019	0.208	6.578	0.000
LDL-C	Diastolic BP	0.003	0.001	0.087	2.749	0.006
	Glucose	0.032	0.008	0.127	4.030	0.000
ApoA1	Height	-0.003	0.001	-0.084	-2.726	0.007
	Waist circumference	-0.005	0.001	-0.228	-7.374	0.000
	Alcohol consumption	0.069	0.008	0.273	9.125	0.000
	Glucose	-0.008	0.004	-0.059	-1.963	0.050
ApoB	Age	0.001	0.001	0.071	2.285	0.023
	Waist circumference	0.006	0.001	0.213	6.713	0.000
	Diastolic BP	0.002	0.001	0.092	2.911	0.004

ApoA1/ApoB	Waist circumference	-0.013	0.001	-0.297	-9.844	0.000
	Alcohol consumption	0.082	0.014	0.175	5.805	0.000
	Glucose	-0.018	0.008	-0.069	-2.300	0.022
Females						
TC	Age	0.010	0.002	0.139	4.202	0.000
	Glucose	0.138	0.022	0.211	6.411	0.000
TG	Height	-0.017	0.004	-0.134	-4.115	0.000
	Waist circumference	0.026	0.003	0.297	9.096	0.000
	Cigarette smoking	0.870	0.301	0.092	2.885	0.004
	Glucose	0.075	0.018	0.130	4.061	0.000
HDL-C	Waist circumference	-0.013	0.002	-0.246	-7.508	0.000
LDL-C	Age	0.006	0.001	0.170	5.116	0.000
	Glucose	0.045	0.011	0.135	4.047	0.000
ApoA1	BMI	-0.009	0.002	-0.143	-4.266	0.000
	Glucose	-0.015	0.005	-0.092	-2.741	0.006
ApoB	Age	0.003	0.001	0.145	4.101	0.000
	Height	-0.005	0.002	-0.121	-3.350	0.001
	Waist circumference	0.006	0.001	0.204	6.119	0.000
ApoA1/ApoB	Age	-0.003	0.001	-0.105	-2.956	0.003
	Height	0.046	0.013	0.764	3.553	0.000
	Weight	-0.055	0.018	-1.362	-3.035	0.002
	BMI	0.118	0.043	1.094	2.763	0.006
	Waist circumference	-0.007	0.003	-0.168	-2.617	0.009
	Glucose	-0.019	0.009	-0.072	-2.209	0.027

SNP, single nucleotide polymorphism; TC, total cholesterol; TG, triglyceride; HDL-C, high -density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; ApoA1/ApoB, the ratio of apolipoprote in A1 to apolipoprote in B.

Serum lipid parameters were also correlated with several environmental factors such as age, alcohol consumption, cigarette smoking, blood pressure, blood glucose, waist circumference, and BMI (**Table 7**).

Discussion

The results of the present study clearly showed that the levels of HDL-C were lower in males than in females. There was no significant difference in the levels of TC, TG, LDL-C, ApoA1, ApoB, and the ratio of ApoA1 to ApoB between the two sex categories. These findings are in good agreement with those of previous epidemiological studies [44, 45]. Although the effects of gonadal hormones on blood lipids are considered contributing factors, the reasons for gender differences in serum lipid levels are still not fully understood. It is commonly accepted that androgens induce changes in lipid concentrations that would predispose towards CHD, whereas estrogens are held to have opposite effects [46, 47]. However, much of the evidence for this comes from studies of changes associated with administration of synthetic gonadal steroids or with changes in gonadal function. Studies of differences in lipid metabolism in normal men and women are extremely limited.

The present study shows that the allelic and genotypic frequencies of rs1997947 and rs4846913 SNPs were different between males and females. There was no difference in the genotypic and allelic frequencies of the rs2760537 and rs11122316 SNPs between the males and females. In some previous studies, there were no significant differences in the genotypic and allelic frequencies of *GALNT2* rs2144300 and rs4846914 SNPs in different races [24, 32]. Also, the allelic frequency of *GALNT2* rs4846914 in patients with stroke did not significantly differ from that in control group [37]. In the present study, we showed that the genotypic frequencies of our population were similar to those obtained in other populations and to data available in the International

HapMap Project's data-base (http://www.hapmap.org) for the Caucasian CEPH population of European origin. Thus, our results suggest that there may be significant sex-specificity variation of genotypic and allelic frequencies in the *GALNT2* rs1997947 and rs4846913 SNPs.

The potential relationship between the *GALNT2* polymorphisms and plasma or serum lipid levels in humans has been evaluated in several previous GWA studies. However, previous findings on the association of these SNPs with the changes in plasma lipid levels are inconsistent. Several studies reported that the minor allele of *GALNT2* polymorphisms was associated with high TG [21, 23, 32-36] and low HDL-C levels [23, 27-33]. Several GWA and candidate gene studies, however, failed to find a significant association between the *GALNT2* polymorphisms and plasma lipid levels [37-39]. In a previous study, Polgár et al. [37] could not detect any effect of the *GALNT2* rs4846914 variant on serum TC and TG levels. The mean blood lipid concentrations did not significantly differ in heterozygous and homozygous carriers from those of the non-carriers in either the stratified stroke subgroups or the overall stroke disease group. In Whitehall II, there was a significant association of the *GALNT2* polymorphisms and plasma levels of the lipoprotein (a). However, a meta-analysis of the six studies did not confirm any of these findings [39]. This may be because of that the effects of these variants were modest on lipid concentrations or lower statistical power for detecting the association was present [37, 48]. Also, different genetic and environmental factors might lead to variable levels of associations in different populations. The findings of the present study encompass (*i*) the levels of TG, HDL-C and ApoA1 in males or females were different among the rs1997947 genotypes; (*ii*) the levels of TG in males were different among the three rs2760537 genotypes, whereas the levels of TC and TG in females were different among the genotypes; (*iii*) the levels of TG, HDL-C, ApoA1 and the ratio ApoA1 to ApoB in males or females were different among the three rs4846913 genotypes; and (iv) there was no difference in serum lipid levels among the rs11122316 genotypes in males or females.

Important intra- and inter-genic LD associations have been found in this study, which replicate previous findings [36, 38]. These LD patterns in *GALNT2* are rather complex and highly specific to the population under study and indicate the functional dependencies of the encoded proteins. In the present study, haplotype analysis with all four SNPs further supports the strong association between *GALNT2* polymorphisms and serum lipid levels in our study population. The haplotype of G-C-C-G was the commonest one and represented ~30% of the samples. The haplotypes of A-C-A-G, A-T-C-A and A-T-C-G were associated with reduced risk of dislipidaemia, and G-C-C-A and G-T-C-A with increased risk of hyperlipidaemia. Haplotypes of A-C-A-G, A-T-C-A, A-T-C-G, G-C-C-A and G-T-C-A showed consistent association with TG. In addition, carriers of A-C-A-G haplotype had decreased serum concentration of HDL-C, ApoA1 and the ratio ApoA1 to ApoB, while G-C-C-A carriers had lower plasma TC levels. We also found that haplotypes with four SNPs could explain much more serum lipid variation than any single SNP alone, especially for TC, TG, HDL-C and ApoA1.

It is well known that environmental factors such as dietary patterns, lifestyle, obesity, physical activity, and hypertension are all strongly related with serum lipid levels. In the present study, we also showed that serum lipid parameters were also correlated with several environmental factors such as age, alcohol consumption, cigarette smoking, blood pressure, blood glucose, waist circumference, and BMI. It is commonly accepted that the high-fat diet especially containing large quantities of saturated fatty acids, raise serum cholesterol concentrations and predispose subjects to CHD [49]. We also found that the percentages of individuals who consumed alcohol were higher in males than females. Although the effects of alcohol intake on LDL-C appear to vary by specific patient types or patterns of alcohol intake, and perhaps by population and sex hormone, this topic has been the focus of much recent research [50]. A recent study in older Italian individuals (65-84 years old) has found that alcohol intake reaches higher serum LDL-C levels [51]. Another recent study of Turks also found promotes in LDL-C, as well as in ApoB and TG, with alcohol in men, while women had fall off TG and no change in LDL-C or ApoB with alcohol [52].

The present study has some shortcomings. Firstly, the size of our study population is a bit small, which might not have had the power to detect the LD across the *GALNT2* locus. It has

been postulated that an adequate analysis of the polymorphic variants of the *GALNT2* gene complex requires a sample of at least 600 subjects to allow the detection of a twofold increased risk of disease [53]. Secondly, the levels of body height, weight, waist circumference and the percentages of subjects who smoked cigarettes or consumed alcohol were higher in males than in females. Although age, BMI, blood pressure, cigarette smoking, and alcohol consumption have been adjusted for the statistical analysis, we can not completely exclude the influence of these factors on serum lipid levels among different genotypes in both sex categories. Thirdly, because we selected the SNPs from literature and did not cover the extensive *GALNT2* locus, we might miss some information from other SNPs.

Conclusions

The genotypic and allelic frequencies of the *GALNT2* rs1997947 and rs4846913 but not rs2760537 and rs11122316 SNPs in the Chinese population were different between males and females. There were 16 haplotypes identified in our study population. The *GALNT2* SNPs and their haplotypes are closely sexually dimorphic associated with serum lipid traits. The haplotypes with four SNPs can explain much more serum lipid variation than any single SNP alone, especially for serum TC, TG, HDL-C and ApoA1 levels.

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Disclosure of conflict of interest

None.

Address correspondence to: Rui-Xing Yin, Department of Cardiology, Institute of Cardiovascular Diseases, The First Affiliated Hospital, Guangxi Medical University, 22 Shuangyong Road, Nanning 530021, Guangxi, China. Tel: +86-771-5358832; Fax: +86-771-5353342; E-mail: yinruixing@163.com

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