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Original Article

Interactions of the several mutations and their haplotypes with alcohol consumption on lipid-associated phenotypes

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Abstract: The interactions of the dedicator of cytokinesis 7 (*DOCK7*), proprotein convertase subtilisin/kexin type 9 (*PCSK9*) and UDP-N-acetyl-alpha-D-galactosamine: polypeptide N-acetylgalactosaminyl-transferase 2 (*GALNT2*) mutations and their haplotypes and alcohol consumption on lipid-associated phenotypes have not been detected previously. This study was to determine the interactions of 9 mutations and their haplotypes with alcohol consumption on lipid-associated phenotypes. Genotyping was performed in 1235 nondrinkers and 1268 drinkers by polymerase chain reaction and restriction fragment length polymorphism combined with gel electrophoresis, and then confirmed by direct sequencing. The commonest haplotype was G-C-G-C-T-G-C-C-G. Significant associations between several mutations and triglyceride (TG; nondrinkers: rs10889332 and rs11122316; drinkers: rs11206517 and rs4846913) and low-density lipoprotein cholesterol (LDL-C; drinkers: rs11206517) were observed. Significant association between their haplotypes and total cholesterol (TC; nondrinkers: C-C-G-C-T-G-C-C-G, C-C-G-C-T-G-T-C-G, G-C-G-C-T-G-C-C-G and G-C-G-C-T-G-T-C-G; drinkers: C-C-G-C-T-G-C-C-G and G-C-G-C-T-G-C-C-G), TG (nondrinkers: C-C-G-C-T-G-C-C-G, C-C-G-C-T-G-T-C-G, C-T-G-C-T-G-C-C-G, G-C-G-C-T-G-C-C-A, G-C-G-C-T-G-C-C-G, G-C-G-C-T-G-T-C-A, and G-C-G-C-T-G-T-C-G; drinkers: C-C-G-C-T-G-C-C-G, and G-C-G-C-T-G-C-C-G), LDL-C (nondrinkers: C-C-G-C-T-G-C-C-G and C-C-G-C-T-G-T-C-G; drinkers: C-C-G-C-T-G-C-C-G, G-C-G-C-T-G-C-C-G and G-C-G-C-T-G-T-C-G), apolipoprotein (Apo) A1 (nondrinkers: G-C-G-C-T-G-T-C-G), ApoB (nondrinkers: G-C-G-C-T-G-T-C-G; drinkers: C-C-G-C-T-G-C-C-G and G-C-G-C-T-G-C-C-G) and ApoA1/ApoB ratio (nondrinkers: G-C-G-C-T-G-T-C-G; drinkers: C-C-G-C-T-G-C-C-G and G-C-G-C-T-G-C-C-G) were noted. Haplotypes could explain much more than any single mutation alone. The differences in lipid-associated phenotypes between the nondrinkers and drinkers might be partially attributed to the interactions of the detected mutations and their haplotypes and alcohol consumption.

Keywords: Several genes, lipid-associated phenotypes, alcohol consumption, interaction, cardiovascular disease

Introduction

The continued increase in the incidence of cardiovascular disease (CVD) has elicited the need to investigate in more depth and breadth the risk factors that contribute to this disease in order to have a more comprehensive vision of the process to illuminate the path towards more precise and effective preventive interventions [1-3]. In this regard, there is increasing evidence linking dyslipidemia with CVD [4].

Precision medicine [5-7], which is an emerging approach for disease prevention and treatment that takes into account people's individual variations in genes, environment, and lifestyle (www.nih.gov/precisionmedicine). As part of molecular biology, gene has thrown some new light on the mystery of life [8, 9]. Some genes [10], alcohol consumption [11], and their interactions [12] have been associated with lipid-associated phenotypes and hyperlipidemia. Recent years, for patients and physicians caught in this clinical bind, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors may represent a reasonable adjunctive therapy, particularly if the ongoing studies show evi-

dence of cardiovascular event reduction with a tolerable safety profile [13-15]. We hypothesize that there may be some interactions between these mutations and alcohol consumption on lipid-associated phenotypes. Therefore, the objective of this study was to detect 9 mutations in the dedicator of cytokinesis 7 (*DOCK7*) rs1168013 and rs10889332; *PCSK9* rs615-563, rs7552841 and rs11206517; and UDP-N-acetyl-alpha-D-galactosamine: polypeptide N-acetylgalactosaminyl-transferase 2 (*GALNT2*) rs1997947, rs2760537, rs4846913 and rs11122316, and evaluate their interactions with alcohol consumption on lipid-associated phenotypes in the nondrinkers and drinkers.

Materials and methods

Subjects

This study included 2,503 participants who were randomly selected from our previous stratified randomized samples [16-18]. All of the participants were rural agriculture workers residing in Wutou, Shanxin and Wanwei villages in Dongxing city, Guangxi, China. There were 1235 nondrinkers (male/female, 646/589) and 1268 drinkers (male/female, 692/576). The age ranged from 18 to 80 years, with an average age of 57.42 ± 13.48/56.55 ± 12.49 years in nondrinkers, and 57.94 ± 13.53/57.25 ± 10.91 in drinkers. The participants with any history of chronic disease including cardiac, cerebral, renal, digestive, thyroid disease and/or history of take lipid-lowering drugs (such as statin, fibrates, niacin and gene inhibitors) were excluded. The Ethics Committee of the First Affiliated Hospital, Guangxi Medical University approved the study protocol. After receiving a full explanation of the study, all participants provided written informed consents.

Demographic, clinical and anthropometric survey

The baseline examination included assessment of standard cardiovascular risk factors, medication use, socio-demographic factors and lifestyle variables especially alcohol consumption by validated questionnaires, using international standardized methods and following a common protocol [19]. The cross-sectional study was conducted between August 2012 and January 2013. Food consumption was determined by a validated semi-quantitative food frequency questionnaire (FFQ) [20]. Physical activity was estimated by the Minnesota Leisure-Time Physical Activity Questionnaire [21]. Alcohol consumption information included questions about the number of *liang* (about 50 mL) during the preceding 12 months. The total alcohol intake for each participant was computed by summing the contributions. The subjects who consumed alcohol less than once a month were classified as nondrinkers, whereas who consumed alcohol more than once a month were classified as drinkers [22-24], and categorized into groups of grams of alcohol per day: ≤ 25 and > 25. Self-reported information on cigarette smoking was recorded. Smoking status was categorized into groups of cigarettes per day: ≤ 20 and > 20. Blood pressure was measured in triplicate with a 5-minute interval between each measurement with the patients seated and at rest in a peaceful setting. The means of these measurements were calculated. Systolic blood pressure (SBP) was determined by the first Korotkoff sound, and diastolic blood pressure (DBP) by the fifth Korotkoff sound. Pulse pressure (PP) was calculated as the SBP minus the DBP. Height and weight were measured with calibrated scales and a wall-mounted stadiometer, respectively. Height was measured to the nearest 0.1 cm on a portable stadiometer. Weight was measured to the nearest 0.1 kg with the subjects standing motionless on the scale. Body mass index (BMI) was calculated as the ratio of subject weight (kg) to the square of subject height (m). Waist circumference was measured with a non-stretchable measuring tape, at the level of the smallest area of the waist, to the nearest 0.1 cm.

Biochemical determinations

At baseline, blood samples were obtained after an overnight fast. The levels of total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) in samples were determined enzymatically using commercially available kits: TC and TG (RANDOX Laboratories, Ardmore, Diamond Road, Crumlin Co. Antrim, United Kingdom, BT29 4QY), and HDL-C and LDL-C (Daiichi Pure Chemicals Co., Tokyo, Japan); respectively. Serum apolipoprotein (Apo) A1 and ApoB levels were measured by an immunoturbidimetric assay (RANDOX Laboratories) in the

Table 1. The anthropometri cand metabolic characteristics between the nondrinkers and drinkers

Characteristics	Nondrinker (n=1235)	Drinker (n=1268)	T (x^2)	*P*
Male/female	646/589	692/576	1.292	0.256
Age (years)	57.60±13.45	56.58±12.96	1.941	0.052
Education levels (years)	5.48±3.18	4.29±3.24	9.273	< 0.001
Physical activity (h/week)	55.35±8.44	53.21±8.13	6.458	> 0.001
Height (cm)	157.65±7.69	158.46±8.22	-2.556	0.011
Weight (kg)	57.43±9.70	58.24±9.88	-2.060	0.039
Body mass index (kg/m^2)	23.06±3.21	23.14±3.17	-0.618	0.536
> 24 kg/m^2 [n (%)]	436 (35.3)	466 (36.7)	0.568	0.451
Waist circumference (cm)	78.59±9.15	79.54±8.98	-2.606	0.009
Systolic blood pressure (mmHg)	131.01±20.07	135.49±19.73	-2.529	0.012
SBP ≥ 140 mmHg [n (%)]	390 (31.6)	452 (35.6)	4.637	0.031
Diastolic blood pressure (mmHg)	80.33±10.22	81.65±10.74	-3.145	0.002
DBP ≥ 90 mmHg [n (%)]	296 (24.0)	364 (28.7)	7.237	0.007
Pulse pressure (mmHg)	50.68±16.06	53.84±18.13	-1.866	0.062
Hypertensive prevalence [n (%)]	475 (38.5)	572 (45.1)	11.367	0.001
Cigarette smoking, n (%)				
Nonsmoker	1051 (85.1)	910 (71.8)		
≤ 20 cigarettes/d	58 (4.7)	64 (5.0)		
> 20 cigarettes/d	126 (10.2)	294 (23.2)	77.212	< 0.001
Alcohol consumption, n (%)				
Nondrinker	1235 (100)			
≤ 25 g/d		796 (62.8)		
> 25 g/d		472 (37.2)		
Total cholesterol (mmol/L)	4.96±0.90	5.05±0.88	-2.533	0.011
TC > 5.17 mmol/L [n (%)]	474 (38.4)	518 (40.9)	1.597	0.206
Triglyceride (mmol/L)	1.36 (1.07)	1.38 (1.11)	4.276	0.039
TG > 1.70 mmol/L [n (%)]	350 (28.3)	380 (30.0)	0.803	0.370
HDL-C (mmol/L)	1.74±0.48	1.84±0.51	-5.219	0.000
HDL-C < 0.91 mmol/L [n (%)]	23 (1.9)	24 (1.9)	0.003	0.955
LDL-C (mmol/L)	2.82±0.43	2.86±0.42	-2.586	0.010
LDL-C > 3.20 mmol/L [n (%)]	223 (18.1)	248 (19.6)	0.924	0.337
Apolipoprotein (Apo) A1 (g/L)	1.29±0.21	1.35±0.23	-7.528	0.000
ApoA1 < 1.00 g/L [n (%)]	72 (5.8)	44 (3.5)	7.884	0.005
ApoB (g/L)	1.04±0.24	1.06±0.24	-1.138	0.255
ApoB > 1.14g/L [n (%)]	384 (31.1)	394 (31.1)	0.000	0.991
ApoA1/ApoB	1.30±0.38	1.35±0.39	-3.287	0.001
ApoA1/ApoB < 1.00 [n (%)]	241 (19.5)	198 (15.6)	6.576	0.010

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Clinical Science Experiment Center of the First Affiliated Hospital of Guangxi Medical University [25-29].

DNA extraction and genotyping

Genomic DNA was extracted from the peripheral blood leukocytes by the phenol-chloroform method. Genotyping of the 9 selected mutations was performed using polymorphism chain reaction and restriction fragment length polymorphism (PCR-RFLP) [30]. Then 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 Hills, IL, USA) in Shanghai Sangon Biological Engineering Technology &

Table 2. The genotypic and allelic frequencies of *DOCK7*, *PCSK9* and *GALNT2* mutations between nondrinkers and drinkers [n (%)]

Mutation	Genotype/ allele	Nondrinker (n=1235)	Drinker (n=1268)	*P*-value
DOCK7 rs1168013	GG	544 (45.99)	550 (43.38)	
	CG	544 (44.05)	552 (43.53)	
	CC	123 (9.96)	166 (13.09)	0.043
	G	1680 (68.02)	1652 (65.14)	
	C	790 (31.98)	884 (34.86)	0.031
HWE (*P*)		0.663	0.140	
DOCK7 rs10889332	CC	692 (56.03)	684 (53.94)	
	CT	468 (37.90)	476 (37.54)	
	TT	75 (6.07)	108 (8.52)	0.060
	C	1852 (74.98)	1844 (72.71)	
	T	618 (25.02)	692 (27.29)	0.068
HWE (*P*)		0.726	0.055	
PCSK9 rs615563	GG	819 (66.32)	782 (61.67)	
	AG	363 (29.39)	419 (33.05)	
	AA	53 (4.29)	67 (5.28)	0.048
	G	2001 (81.01)	1983 (78.19)	
	A	469 (18.99)	553 (21.81)	0.013
HWE (*P*)		0.117	0.269	
PCSK9 rs7552841	CC	874 (70.77)	843 (66.48)	
	CT	324 (26.23)	370 (29.18)	
	TT	37 (3.00)	55 (4.34)	0.035
	C	2072 (83.89)	2056 (81.07)	
	T	398 (16.11)	480 (18.93)	0.009
HWE (*P*)		0.299	0.080	
PCSK9 rs11206517	TT	1085 (87.85)	1068 (84.23)	
	GT	141 (11.42)	188 (14.83)	
	GG	9 (0.73)	12 (0.94)	0.033
	T	2311 (93.56)	2324 (91.64)	
	G	159 (6.44)	212 (8.36)	0.009
HWE (*P*)		0.067	0.250	
GALNT2 rs1997947	GG	824 (66.72)	787 (62.07)	
	AG	359 (29.07)	414 (32.65)	
	AA	52 (4.21)	67 (5.28)	0.045
	G	2007 (81.26)	1988 (78.39)	
	A	463 (18.74)	548 (21.61)	0.012
HWE (*P*)		0.108	0.196	
GALNT2 rs2760537	CC	579 (46.88)	533 (42.03)	
	CT	518 (41.94)	573 (45.19)	
	TT	138 (11.17)	162 (12.78)	0.046
	C	1676 (67.85)	1639 (64.63)	
	T	794 (32.15)	897 (35.37)	0.016
HWE (*P*)		0.176	0.680	
GALNT2 rs4846913	CC	868 (70.28)	832 (65.61)	
	AC	324 (26.24)	382 (30.13)	
	AA	43 (3.48)	54 (4.26)	0.042

Services Co. Ltd., Shanghai China [31].

Diagnostic criteria

Hyperlipidemia was defined as TC > 5.17 mmol/L and/or TG >1.70 mmol/L. Hypertension was diagnosed as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg. The normal values of serum TC, TG, HDL-C, LDL-C, ApoA1 and ApoB levels, and the ratio of ApoA1 to ApoB in our Clinical Science Experiment Center were 3.10-5.17, 0.56-1.70, 0.91-1.81, 2.70-3.20 mmol/l, 1.00-1.78, 0.63-1.14 g/L, and 1.00-2.50; respectively. Normal weight, overweight and obesity were defined as a BMI < 24, 24-28, and > 28 kg/m^2; respectively [32, 33].

Statistical analysis

Data were organized and analyzed using SPSS version 21.0 (SPSS Inc., Chicago, IL). Continuous variables were presented as means ± SD, and categorical variables as frequencies or percentages. We used the Student's unpaired *t*-test and analysis of covariance (ANCOVA) tests to compare crude means of lipid-associated phenotypes indexes across genetic categories. Models were first adjusted for sex, age. Additional adjustments for education level, physical activity, BMI, cigarette smoking, and hyperlipidemia, adherence to the alcohol consumption was also carried out as indicated. All significant associations were corrected for multiple testing by applying a Bonferroni correction. A *P* value of ≤ 0.0056 was considered statistically significant after Bonferroni correction (0.05/9≈0.0056). Chi-square

	C	2060 (83.40)	2046 (80.68)	
	A	410 (16.60)	490 (19.32)	0.012
HWE (*P*)		0.065	0.230	
GALNT2 rs11122316	GG	548 (44.37)	505 (39.83)	
	AG	551 (44.62)	598 (47.16)	
	AA	136 (11.01)	165 (13.01)	0.049
	G	1647 (66.68)	1608 (63.41)	
	A	823 (33.32)	928 (36.59)	0.015
HWE (*P*)		0.887	0.562	

HWE, Hardy-Weinberg equilibrium.

testes were used to test differences between observed and expected genotype frequencies, assuming Hardy-Weinberg equilibrium, and to test differences in percentages. Genetic variables were tested using co-dominant models of polymorphisms individually. The interactions of 9 mutations and alcohol consumption on lipid-associated phenotypes were detected by using a factorial regression analysis after controlling for potential confounders. Multivariate adjustments for comparisons of continuous variables were carried out by generalized linear models; respectively. To the categorical analysis, the genotypes (common homozygote genotype = 1, heterozygote genotype = 2, rare homozygote genotype = 3) and/or alleles (the minor allele non-carrier = 1, the minor allele carrier = 2) were numerically coded.

Results

General characteristics between nondrinkers and drinkers

The general characteristics between the nondrinkers and drinkers are shown in **Table 1**. The levels of height, weight, waist circumference, SBP, DBP; the prevalence of hypertension; and the percentage of cigarette smoking were higher but the levels of education and physical activity were lower in drinkers than in nondrinkers ($P < 0.05$-0.01). There were no significant differences in BMI, PP and the sex and age structure between the nondrinkers and drinkers.

Lipid-associated phenotypes between nondrinkers and drinkers

As shown in **Table 1**, the levels of TC, TG, HDL-C, LDL-C, ApoA1 and the ratio of ApoA1 to ApoB were higher in drinkers than in nondrinkers ($P <$ 0.05-0.01). There were no significant differences in the levels of ApoB between the two groups ($P > 0.05$).

Genotypic and allelic frequencies between nondrinkers and drinkers

The genotypic distribution of 9 mutations among subjects did not deviate from Hardy-Weinberg equilibrium ($P >$ 0.05 for all). The genotypic and allelic frequencies of *DOCK7* rs1168013, *PCSK9* rs615563, *PCSK9* rs7552841, *PCSK9* rs11206517, *GALNT2* rs1997947, *GALNT2* rs2760537, *GALNT2* rs4846913, *GALNT2* rs11122316 were significantly different between the nondrinkers and drinkers ($P < 0.05$-0.01). The drinkers had higher genotype frequencies of rs1168013CC, rs615563AA, rs7552841TT, rs11206517GG, rs1997947AA, rs2760537TT, rs4846913AA and rs11122316AA than the nondrinkers. There were no significant differences in the genotypic and allelic frequencies of *DOCK7* rs10889332 between the two groups ($P > 0.05$ for each; **Table 2**).

Haplotypes among 9 mutations between nondrinkers and drinkers

The haplotype frequencies among 9 mutations are listed in **Table 3**. The commonest haplotype was G-C-G-C-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, *GALNT2* rs11122316; > 10% of the samples). The frequencies of the C-C-G-C-T-G-C-C-G, C-C-G-C-T-G-T-C-G, C-T-G-C-T-G-C-C-G, and G-C-G-C-T-G-C-C-G haplotypes were also different between the nondrinkers and drinkers ($P < 0.05$-0.01).

Genotypes and lipid-associated phenotypes between nondrinkers and drinkers

As shown in **Table 4**, the levels of TG (*DOCK7* rs10889332 and *GALNT2* rs11122316) in nondrinkers were different among the genotypes ($P < 0.005$-0.001), whereas the levels of TG (*PCSK9* rs11206517 and *GALNT2* rs4846913) and LDL-C (*PCSK9* rs11206517) in drinkers were different among the genotypes ($P <$ 0.005-0.001).

Table 3. Frequencies of haplotypes among 9 mutations of the DOCK7, PCSK9 and GALNT2 genes between nondrinkers and drinkers

Haplotype	Nondrinkers, N (frequency)	Drinkers, N (frequency)	X^2	*P*-value	OR (95% CI)
C-C-G-C-T-G-C-C-G	38 (0.015)	101 (0.041)	19.458	1.05×10^{-5}	0.428 (0.290, 0.630)
C-C-G-C-T-G-T-C-G	78 (0.031)	23 (0.009)	44.272	2.96×10^{-11}	4.449 (2.765, 7.159)
C-T-G-C-T-G-C-C-G	35 (0.014)	76 (0.031)	9.026	0.003	0.535 (0.354, 0.809)
G-C-G-C-T-G-C-C-A	121 (0.048)	157 (0.063)	0.289	0.591	0.932 (0.720, 1.205)
G-C-G-C-T-G-C-C-G	389 (0.153)	428 (0.173)	3.943	0.047	1.207 (1.002, 1.545)
G-C-G-C-T-G-T-C-A	56 (0.022)	81 (0.033)	1.015	0.314	0.834 (0.585, 1.188)
G-C-G-C-T-G-T-C-G	102 (0.040)	132 (0.053)	0.232	0.630	0.934 (0.708, 1.232)
Rare Hap (frequency < 3%) in both nondrinkers & drinkers has been dropped					

Loci chosen for hap-analysis: *DOCK7* rs1168013, *DOCK7* rs10889332, *PCSK9* rs615563, *PCSK9* rs7552841, *PCSK9* rs11206517, *GALNT2* rs1997947, *GALNT2* rs2760537, *GALNT2* rs4846913 and *GALNT2* rs1122316.

Haplotypes and lipid-associated phenotypes between nondrinkers and drinkers

The correlation of the haplotypes and lipid-associated phenotypes is shown in **Table 5**. Rare Hap (frequency < 3%) in both nondrinkers and drinkers has been dropped. There were statistically significant associations between the haplotypes and TC (C-C-G-C-T-G-C-C-G, C-C-G-C-T-G-T-C-G, G-C-G-C-T-G-C-C-G and G-C-G-C-T-G-T-C-G in nondrinkers; C-C-G-C-T-G-C-C-G and G-C-G-C-T-G-C-C-G in drinkers), TG (C-C-G-C-T-G-C-C-G, C-C-G-C-T-G-T-C-G, C-T-G-C-T-G-C-C-G, G-C-G-C-T-G-C-C-A, G-C-G-C-T-G-C-C-G, G-C-G-C-T-G-T-C-A, and G-C-G-C-T-G-T-C-G in nondrinkers; C-C-G-C-T-G-C-C-G, and G-C-G-C-T-G-C-C-G in drinkers), LDL-C (C-C-G-C-T-G-C-C-G and C-C-G-C-T-G-T-C-G in nondrinkers; C-C-G-C-T-G-C-C-G, G-C-G-C-T-G-C-C-G and G-C-G-C-T-G-T-C-G in drinkers), apolipoprotein (Apo) A1 (G-C-G-C-T-G-T-C-G in nondrinkers), ApoB (G-C-G-C-T-G-T-C-G in nondrinkers; C-C-G-C-T-G-C-C-G and G-C-G-C-T-G-C-C-G in drinkers) and ApoA1/ApoB ratio (G-C-G-C-T-G-T-C-G in nondrinkers; C-C-G-C-T-G-C-C-G and G-C-G-C-T-G-C-C-G in drinkers); $P < 0.05$, respectively. Haplotypes could explain much more serum lipid variation than any single mutation alone.

Correlation between genotypes and/or alleles and lipid-associated phenotypes

Table 6 depicts the direction and magnitude of associations between lipid parameters and alleles or genotypes of the 9 mutations in nondrinkers and drinkers. Adjusting for age, sex, BMI, smoking status, and exercise, logistic regression analysis showed several the examined mutations were significant correlated with lipid parameters.

Discussion

Although the magnitude of the effect in the whole sample was lower than that reported for the general population [34], the results of the present study showed that the levels of TC, TG, HDL-C, LDL-C, ApoA1 and the ratio of ApoA1 to ApoB were higher in drinkers than in nondrinkers. The subjects with *DOCK7* rs10889332TT and *GALNT2* rs11122316AA in the nondrinkers had higher serum TG levels than the subjects with other genotypes, whereas the subjects with *PCSK9* rs11206517GG and *GALNT2* rs4846913AA had higher serum TG levels and subjects with *PCSK9* rs11206517GG had higher serum LDL-C levels in drinkers than the subjects with other genotypes. The interactions between the examined mutations and alcohol consumption on serum lipid parameters were also detected by using a factorial design covariance analysis after controlling for potential confounders. These findings suggest that the effect of alcohol consumption on lipid-associated phenotypes may depend on the *DOCK7*, *PCSK9* and *GALNT2* genotypes. To the best of our knowledge, the interactions between *DOCK7*, *PCSK9* and *GALNT2* mutations and their haplotypes and alcohol consumption on lipid-associated phenotypes have not been previously explored.

In the current study, we found that the genotypic and allelic frequencies of *DOCK7* rs11-68013, *PCSK9* rs615563, *PCSK9* rs7552841, *PCSK9* rs11206517, *GALNT2* rs1997947, *GA-*

Table 4. Lipid-related phenotypes according to genotypes between nondrinkers and drinkers

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
DOCK7 rs1168013								
Nondrinkers								
GG	568	4.90±0.90	1.31 (1.04)	1.77±0.48	2.79±0.43	1.30±0.23	1.03±0.24	1.32±0.38
CG	544	5.00±0.90	1.40 (1.12)	1.74±0.43	2.84±0.44	1.29±0.21	1.05±0.25	1.29±0.38
CC	123	5.08±0.88	1.51 (1.19)	1.71±0.50	2.88±0.42	1.28±0.20	1.08±0.23	1.26±0.35
F		1.384	4.526	0.790	1.586	1.013	1.125	0.801
P		0.251	0.011	0.454	0.205	0.363	0.325	0.449
Drinlers								
GG	550	4.98±0.91	1.33 (1.01)	1.86±0.51	2.83±0.41	1.36±0.23	1.03±0.24	1.39±0.41
CG	552	5.08±0.85	1.40 (1.11)	1.84±0.51	2.88±0.43	1.36±0.23	1.07±0.24	1.33±0.37
CC	166	5.18±0.90	1.45 (1.20)	1.78±0.49	2.93±0.41	1.33±0.21	1.07±0.25	1.30±0.40
F		3.949	3.315	1.936	3.071	0.972	3.136	3.784
P		0.020	0.037	0.145	0.047	0.379	0.044	0.023
DOCK7 rs10889332								
Nondrinkers								
CC	692	4.91±0.91	1.31 (1.06)	1.77±0.50	2.79±0.43	1.30±0.22	1.03±0.24	1.31±0.38
CT	468	5.02±0.87	1.41 (1.13)	1.73±0.47	2.85±0.44	1.30±0.22	1.06±0.23	1.29±0.38
TT	75	5.04±0.88	1.56 (1.17)	1.72±0.47	2.86±0.44	1.28±0.20	1.06±0.25	1.28±0.33
F		0.562	6.860	0.543	1.251	1.032	0.812	0.097
P		0.570	0.001	0.581	0.286	0.357	0.444	0.908
Drinlers								
CC	684	5.02±0.90	1.29 (1.04)	1.85±0.51	2.84±0.41	1.37±0.21	1.05±0.24	1.36±0.39
CT	476	5.07±0.87	1.43 (1.14)	1.84±0.52	2.88±0.45	1.36±0.22	1.06±0.25	1.34±0.41
TT	108	5.13±0.85	1.50 (1.20)	1.81±0.46	2.93±0.38	1.35±0.24	1.08±0.24	1.33±0.36
F		0.299	3.037	0.299	0.415	0.916	0.571	0.190
P		0.741	0.048	0.741	0.660	0.400	0.565	0.827
PCSK9 rs615563								
Nondrinkers								
GG	819	4.94±0.89	1.34 (1.07)	1.76±0.42	1.75±0.44	1.30±0.23	1.02±0.22	1.32±0.34
AG	363	4.97±0.99	1.40 (1.12)	1.74±0.49	2.82±0.44	1.29±0.21	1.04±0.25	1.31±0.38
AA	53	5.00±0.89	1.51 (1.28)	1.74±0.48	2.83±0.43	1.28±0.19	1.05±0.24	1.28±0.38

F		0.323	4.708	0.179	1.621	1.074	1.241	1.378
P		0.724	0.009	0.836	0.198	0.342	0.289	0.252
Drinlers								
GG	782	5.01±0.89	1.35 (1.05)	1.86±0.52	2.85±0.43	1.37±0.24	1.05±0.25	1.38±0.41
AG	419	5.07±0.86	1.40 (1.11)	1.83±0.49	2.87±0.40	1.33±0.19	1.06±0.23	1.31±0.36
AA	67	5.33±0.90	1.68 (1.24)	1.72±0.45	2.99±0.41	1.31±0.22	1.12±0.24	1.22±0.34
F		3.593	4.665	0.831	4.210	4.469	1.681	5.069
P		0.028	0.010	0.436	0.015	0.012	0.187	0.006
PCSK9 rs7552841								
Nondrinkers								
CC	874	4.94±0.88	1.32 (1.07)	1.75±0.39	2.81±0.43	1.29±0.20	1.04±0.24	1.31±0.38
CT	324	4.98±0.70	1.46 (1.12)	1.74±0.49	2.84±0.45	1.28±0.24	1.06±0.26	1.28±0.38
TT	37	5.02±0.95	1.71 (1.26)	1.74±0.49	2.87±0.36	1.28±0.21	1.07±0.18	1.24±0.28
F		0.029	5.058	0.186	0.370	0.051	0.108	0.344
P		0.971	0.006	0.830	0.691	0.951	0.898	0.709
Drinlers								
CC	843	5.04±0.88	1.35 (1.05)	1.86±0.52	2.85±0.41	1.40±0.38	1.05±0.24	1.35±0.39
CT	370	5.04±0.90	1.39 (1.13)	1.85±0.49	2.89±0.45	1.35±0.22	1.06±0.25	1.35±0.41
TT	55	5.21±0.84	1.60 (1.19)	1.83±0.51	2.94±0.39	1.35±0.22	1.12±0.27	1.30±0.33
F		0.899	4.291	1.576	1.551	2.387	1.945	0.400
P		0.407	0.014	0.207	0.212	0.092	0.143	0.670
PCSK9 rs11206517								
Nondrinkers								
TT	1085	4.77±0.51	1.30 (1.08)	1.78±0.64	2.81±0.43	1.29±0.21	1.01±0.23	1.33±0.38
GT	141	4.96±0.89	1.37 (1.10)	1.73±0.46	2.82±0.44	1.28±0.21	1.05±0.25	1.30±0.38
GG	9	4.98±0.97	1.57 (1.26)	1.58±0.22	2.91±0.29	1.23±0.15	1.09±0.22	1.18±0.32
F		0.521	4.714	1.228	0.406	0.420	2.361	1.570
P		0.594	0.009	0.293	0.666	0.657	0.095	0.209
Drinlers								
TT	1068	5.00±0.86	1.35 (1.07)	1.86±0.50	2.50±1.02	1.36±0.23	0.99±0.13	1.36±0.42
GT	188	5.06±0.89	1.48 (1.17)	1.84±0.51	2.86±0.42	1.34±0.20	1.04±0.24	1.35±0.39
GG	12	5.26±0.56	1.58 (1.36)	1.72±0.28	2.88±0.39	1.26±0.15	1.06±0.24	1.29±0.20
F		0.759	5.980	0.502	6.970	1.810	1.668	0.156
P		0.468	0.003	0.605	0.001	0.164	0.189	0.856
GALNT2 rs1997947								

Nondrinkers								
GG	824	4.92±0.89	1.34 (1.08)	1.77±0.48	2.81±0.43	1.29±0.21	1.04±0.25	1.32±0.39
AG	359	5.03±0.90	1.36 (1.09)	1.74±0.54	2.84±0.43	1.29±0.21	1.06±0.23	1.27±0.34
AA	52	5.10±0.99	1.65 (1.32)	1.72±0.48	2.88±0.47	1.28±0.18	1.08±0.23	1.24±0.34
F		1.770	3.384	1.698	0.794	0.085	1.300	1.907
P		0.171	0.034	0.184	0.452	0.919	0.273	0.149
Drinlers								
GG	787	5.01±0.88	1.32 (1.05)	1.86±0.50	2.84±0.42	1.36±0.24	1.05±0.25	1.37±0.40
AG	414	5.07±0.86	1.44 (1.11)	1.84±0.60	2.89±0.40	1.35±0.20	1.06±0.24	1.34±0.38
AA	67	5.32±0.94	1.67 (1.22)	1.81±0.51	2.93±0.59	1.31±0.18	1.08±0.22	1.27±0.36
F		2.897	5.410	0.791	1.243	0.300	0.028	0.409
P		0.056	0.005	0.453	0.289	0.741	0.973	0.665
GALNT2 rs2760537								
Nondrinkers								
CC	579	4.90±0.89	1.30 (1.04)	1.75±0.47	2.79±0.44	1.29±0.20	1.04±0.24	1.31±0.36
CT	518	4.98±0.89	1.37 (1.10)	1.74±0.50	2.83±0.43	1.29±0.21	1.04±0.25	1.31±0.40
TT	138	5.13±0.94	1.56 (1.29)	1.67±0.49	2.89±0.42	1.28±0.22	1.09±0.24	1.23±0.36
F		2.233	4.431	1.074	2.281	0.013	1.751	1.316
P		0.108	0.012	0.342	0.103	0.987	0.174	0.269
Drinlers								
CC	533	5.03±0.87	1.35 (1.05)	1.86±0.51	1.94±0.41	1.36±0.25	1.05±0.23	1.38±0.41
CT	573	5.04±0.89	1.36 (1.07)	1.83±0.51	2.85±0.40	1.35±0.21	1.05±0.26	1.34±0.38
TT	162	5.15±0.92	1.52 (1.21)	1.81±0.49	2.85±0.44	1.34±0.19	1.09±0.23	1.28±0.34
F		0.804	4.315	1.552	1.802	2.056	0.780	2.037
P		0.448	0.014	0.212	0.165	0.128	0.459	0.131
GALNT2 rs4846913								
Nondrinkers								
CC	868	4.92±0.86	1.35 (1.07)	1.89±0.51	2.80±0.43	1.29±0.20	1.04±0.24	1.31±0.38
AC	324	5.00±0.95	1.37 (1.12)	1.73±0.53	2.84±0.44	1.28±0.22	1.05±0.24	1.28±0.37
AA	43	5.37±0.97	1.60 (1.21)	1.73±0.46	3.01±0.39	1.26±0.17	1.10±0.28	1.22±0.36
F		3.640	3.877	2.526	3.812	0.736	1.055	1.850
P		0.027	0.021	0.080	0.022	0.479	0.349	0.158
Drinlers								
CC	832	5.03±0.88	1.33 (1.05)	1.85±0.51	2.86±0.40	1.36±0.23	1.05±0.24	1.36±0.39
AC	382	5.08±0.90	1.44 (1.15)	1.84±0.50	2.87±0.46	1.35±0.23	1.06±0.25	1.34±0.41

AA	54	5.14±0.80	1.62 (1.27)	1.73±0.47	2.89±0.50	1.31±0.18	1.09±0.19	1.25±0.33
F		0.433	6.416	0.272	0.168	0.230	0.566	1.026
P		0.648	0.002	0.762	0.845	0.795	0.568	0.359
GALNT2 rs11122316								
Nondrinkers								
GG	548	4.90±0.91	1.30 (1.02)	1.75±0.48	2.80±0.37	1.29±0.21	1.03±0.22	1.32±0.43
AG	551	5.02±0.91	1.44 (1.12)	1.73±0.51	2.80±0.44	1.29±0.20	1.04±0.25	1.31±0.37
AA	136	4.94±0.77	1.48 (1.24)	1.71±0.41	2.85±0.44	1.28±0.21	1.05±0.24	1.28±0.37
F		2.169	6.713	0.585	1.783	0.179	1.326	1.752
P		0.115	0.001	0.557	0.169	0.836	0.266	0.174
Drinlers								
GG	505	4.98±0.90	1.31 (1.05)	1.85±0.51	2.82±0.46	1.36±0.28	1.05±0.23	1.37±0.43
AG	598	5.07±0.86	1.37 (1.08)	1.84±0.49	2.89±0.40	1.35±0.23	1.05±0.25	1.34±0.36
AA	165	5.18±0.86	1.54 (1.25)	1.81±0.57	2.92±0.40	1.35±0.20	1.08±0.25	1.33±0.41
F		3.601	3.106	0.051	5.036	0.743	0.629	0.177
P		0.028	0.045	0.950	0.007	0.476	0.533	0.837

Table 5. Lipid-associated phenotypes according to haplotypes between nondrinkers and drinkers

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-C-T-G-C-C-G	Nondrinkers	1235							
	Non-carrier	38	4.95±0.90	1.34 (1.06)	1.77±0.48	2.81±0.43	1.29±0.21	1.04±0.24	1.30±0.38
	Carrier	1197	4.98±0.89	1.38 (1.11)	1.72±0.49	2.84±0.45	1.28±0.19	1.04±0.25	1.30±0.38
	F		5.081	28.039	2.863	6.406	0.087	3.694	2.719
	P		0.024	0.000	0.091	0.011	0.768	0.055	0.099
	Drinkers	1268							
	Non-carrier	101	5.05±0.84	1.32 (1.09)	1.87±0.49	2.86±0.43	1.35±0.23	1.05±0.24	1.35±0.40
	Carrier	1167	5.05±0.90	1.41 (1.10)	1.83±0.52	2.87±0.41	1.35±0.21	1.06±0.24	1.35±0.39
	F		7.632	15.924	1.753	7.142	0.147	7.553	8.547
	P		0.006	0.000	0.186	0.008	0.702	0.006	0.004
C-C-G-C-T-G-T-C-G	Nondrinkers	1235							
	Non-carrier	78	4.93±0.89	1.34 (1.09)	1.75±0.48	2.80±0.43	1.29±0.21	1.04±0.24	1.31±0.37
	Carrier	1157	5.07±0.92	1.75 (1.05)	1.74±0.48	2.88±0.45	1.28±0.20	1.07±0.26	1.27±0.40
	F		4.793	13.438	0.452	6.530	0.508	3.337	1.938
	P		0.029	0.000	0.501	0.011	0.476	0.068	0.164

	Drinkers	1268							
	Non-carrier	23	5.01±0.92	1.37 (1.10)	1.85±0.51	2.85±0.44	1.36±0.23	1.05±0.25	1.36±0.41
	Carrier	1245	5.06±0.87	1.39 (1.09)	1.84±0.51	2.87±0.42	1.35±0.21	1.06±0.24	1.35±0.39
	F		0.304	1.406	0.898	0.194	0.004	0.391	0.668
	P		0.582	0.236	0.343	0.660	0.949	0.532	0.414
C-T-G-C-T-G-C-C-G	Nondrinkers	1235							
	Non-carrier	35	4.94±0.90	1.35 (1.09)	1.80±0.51	2.81±0.43	1.30±0.21	1.04±0.24	1.30±0.38
	Carrier	1200	5.05±0.88	1.39 (1.11)	1.72±0.48	2.86±0.45	1.28±0.21	1.06±0.25	1.29±0.36
	F		3.134	8.121	3.518	3.298	0.092	1.447	0.958
	P		0.077	0.004	0.061	0.070	0.762	0.229	0.328
	Drinkers	1268							
	Non-carrier	76	5.04±0.89	1.35 (1.11)	1.87±0.49	2.85±0.42	1.35±0.23	1.05±0.24	1.35±0.41
	Carrier	1192	5.10±0.87	1.39 (1.10)	1.83±0.51	2.90±0.43	1.35±0.22	1.06±0.25	1.35±0.39
	F		0.881	1.467	0.376	2.148	0.276	0.796	0.416
	P		0.348	0.226	0.540	0.143	0.599	0.372	0.519
G-C-G-C-T-G-C-C-A	Nondrinkers	1235							
	Non-carrier	121	4.95±0.91	1.34 (1.09)	1.78±0.45	2.81±0.44	1.29±0.20	1.03±0.24	1.32±0.40
	Carrier	1114	4.98±0.88	1.37 (1.10)	1.71±0.50	2.82±0.43	1.28±0.21	1.05±0.25	1.29±0.36
	F		0.718	0.075	3.572	0.714	0.041	0.256	0.758
	P		0.397	0.784	0.059	0.398	0.840	0.613	0.384
	Drinkers	1268							
	Non-carrier	157	5.01±0.87	1.29 (1.01)	1.85±0.50	2.85±0.40	1.36±0.24	1.04±0.24	1.37±0.38
	Carrier	1111	5.07±0.89	1.41 (1.12)	1.83±0.51	2.87±0.44	1.35±0.22	1.06±0.25	1.34±0.40
	F		1.507	4.956	0.171	0.446	0.011	1.656	0.825
	P		0.220	0.026	0.679	0.504	0.918	0.198	0.364
G-C-G-C-T-G-C-C-G	Nondrinkers	1235							
	Non-carrier	389	5.03±0.90	1.52 (1.24)	1.72±0.44	2.85±0.43	1.29±0.20	1.06±0.24	1.28±0.39
	Carrier	846	4.92±0.89	1.28 (1.01)	1.75±0.51	2.80±0.44	1.29±0.22	1.03±0.25	1.31±0.37
	F		4.025	31.987	0.112	2.610	1.997	2.120	0.166
	P		0.045	0.000	0.737	0.106	0.158	0.146	0.684
	Drinkers	1268							
	Non-carrier	428	5.18±0.89	1.49 (1.20)	1.78±0.47	2.93±0.41	1.34±0.21	1.09±0.24	1.30±0.38
	Carrier	840	5.01±0.88	1.33 (1.04)	1.86±0.52	2.84±0.43	1.36±0.23	1.04±0.24	1.37±0.40
	F		12.059	16.300	2.009	12.908	0.569	5.170	6.138
	P		0.001	0.000	0.157	0.000	0.451	0.023	0.013

G-C-G-C-T-G-T-C-A	Nondrinkers	1235							
	Non-carrier	56	4.94±0.90	1.33 (1.08)	1.75±0.47	2.81±0.44	1.29±0.22	1.04±0.24	1.30±0.36
	Carrier	1179	5.03±0.87	1.51 (1.17)	1.71±0.51	2.86±0.42	1.29±0.20	1.06±0.25	1.30±0.43
	F		1.848	15.060	1.296	2.944	0.061	0.973	0.024
	P		0.174	0.000	0.255	0.086	0.805	0.324	0.878
	Drinkers	1268							
	Non-carrier	81	5.00±0.83	1.34 (1.05)	1.86±0.48	2.85±0.40	1.37±0.25	1.04±0.23	1.38±0.37
	Carrier	1187	5.06±0.90	1.39 (1.10)	1.84±0.51	2.87±0.43	1.35±0.22	1.06±0.25	1.34±0.40
	F		1.522	0.027	0.305	0.553	2.638	1.301	2.291
	P		0.218	0.869	0.581	0.457	0.105	0.254	0.130
G-C-G-C-T-G-T-C-G	Nondrinkers	1235							
	Non-carrier	102	4.96±0.89	1.36 (1.08)	1.75±0.47	2.81±0.44	1.30±0.21	1.04±0.24	1.31±0.37
	Carrier	1133	4.96±0.90	1.37 (1.11)	1.71±0.51	2.82±0.43	1.27±0.21	1.05±0.25	1.29±0.39
	F		0.001	0.482	1.406	0.112	4.101	0.004	0.452
	P		0.977	0.488	0.236	0.738	0.043	0.947	0.502
	Drinkers	1268							
	Non-carrier	132	4.96±0.87	1.28 (1.03)	1.87±0.49	2.83±0.41	1.36±0.20	1.04±0.24	1.38±0.40
	Carrier	1136	5.09±0.89	1.42 (1.11)	1.83±0.52	2.88±0.43	1.35±0.24	1.06±0.24	1.33±0.39
	F		8.016	5.371	1.518	4.053	0.755	3.345	5.460
	P		0.005	0.021	0.218	0.044	0.385	0.068	0.020

Table 6. Association of the alleles and genotypes of the *DOCK7*, *PCSK9* and *GALNT2* mutations and lipid-correlated phenotypes in nondrinkers and drinkers

Lipid-correlated phenotypes	Mutation	Alleles	Genotypes	Beta	Std.error	t	*P*-value
Non-drinkers							
TC	rs1168013		GG/CG/CC	0.066	0.038	2.356	0.019
	rs1168013	G/C		0.062	0.025	2.242	0.025
	rs1997947	G/A		0.058	0.026	2.100	0.036
	rs2760537		CC/CT/TT	0.067	0.037	2.395	0.017
	rs2760537	C/T		0.060	0.025	2.157	0.031
	rs4846913		CC/AC/AA	0.068	0.046	2.431	0.015
TG	rs1168013		GG/CG/CC	0.075	0.033	2.803	0.005
	rs1168013	G/C		0.080	0.022	2.978	0.003
	rs10889332		CC/CT/TT	0.096	0.036	3.581	0.000
	rs10889332	C/T		0.098	0.022	3.660	0.000
	rs615563		GG/AG/AA	0.083	0.037	3.224	0.001
	rs615563	G/A		0.081	0.022	3.181	0.002
	rs7552841		CC/CT/TT	0.085	0.040	3.286	0.001
	rs7552841	C/T		0.078	0.023	3.024	0.003
	rs11206517		TT/GT/GG	0.078	0.059	3.046	0.002
	rs11206517	T/G		0.079	0.032	3.076	0.002
	rs1997947		GG/AG/AA	0.060	0.037	2.312	0.021
	rs1997947	G/A		0.059	0.022	2.299	0.022
	rs2760537		CC/CT/TT	0.067	0.031	2.622	0.009
	rs2760537	C/T		0.077	0.021	3.009	0.003
	rs4846913		CC/AC/AA	0.074	0.038	2.882	0.004
	rs4846913	C/A		0.070	0.023	2.771	0.006
	rs11122316		GG/AG/AA	0.068	0.031	2.658	0.008
	rs11122316	G/A		0.090	0.021	3.494	0.000
HDL-C	rs1997947	G/A		0.054	0.014	1.984	0.047
LDL-C	rs1168013		GG/CG/CC	0.071	0.019	2.530	0.012
	rs1168013	G/C		0.070	0.012	2.485	0.013
	rs2760537		CC/CT/TT	0.061	0.018	2.192	0.029
	rs2760537	C/T		0.060	0.012	2.152	0.032
	rs4846913		CC/AC/AA	0.070	0.023	2.501	0.013
ApoB	rs1168013		GG/CG/CC	0.061	0.010	2.228	0.026
Drinkers							
TC	rs1168013		GG/CG/CC	0.086	0.035	3.184	0.001
	rs1168013	G/C		0.073	0.024	2.700	0.007
	rs615563		GG/AG/AA	0.069	0.040	2.540	0.011
	rs1997947		GG/AG/AA	0.062	0.041	2.272	0.023
	rs1997947	G/A		0.055	0.025	2.008	0.045
	rs11122316		GG/AG/AA	0.068	0.036	2.485	0.013
	rs11122316	G/A		0.054	0.025	1.992	0.047
TG	rs1168013	G/C		0.064	0.029	2.368	0.018
	rs10889332		CC/CT/TT	0.092	0.041	3.656	0.000
	rs10889332	C/T		0.078	0.029	2.894	0.004
	rs615563		GG/AG/AA	0.062	0.045	2.462	0.014
	rs7552841		CC/CT/TT	0.081	0.047	3.193	0.001

	rs7552841	C/T		0.083	0.029	3.243	0.001
	rs11206517		TT/GT/GG	0.091	0.067	3.582	0.000
	rs11206517	T/G		0.090	0.037	3.530	0.000
	rs1997947		GG/AG/AA	0.096	0.045	3.767	0.000
	rs1997947	G/A		0.089	0.028	3.506	0.000
	rs2760537		CC/CT/TT	0.066	0.039	2.609	0.009
	rs2760537	C/T		0.067	0.027	2.657	0.008
	rs4846913		CC/AC/AA	0.083	0.047	3.313	0.001
	rs4846913	C/A		0.072	0.028	2.860	0.004
LDL-C	rs1168013		GG/CG/CC	0.083	0.017	3.006	0.003
	rs1168013	G/C		0.075	0.012	2.692	0.007
	rs615563		GG/AG/AA	0.068	0.020	2.474	0.013
	rs7552841		CC/CT/TT	0.057	0.021	2.067	0.039
	rs7552841	C/T		0.058	0.012	2.106	0.035
	rs11122316		GG/AG/AA	0.092	0.017	3.352	0.001
	rs11122316	G/A		0.085	0.012	3.077	0.002
ApoA1	rs615563		GG/AG/AA	-0.081	0.011	-2.967	0.003
	rs615563	G/A		-0.084	0.006	-3.074	0.002
ApoB	rs1168013		GG/CG/CC	0.071	0.010	2.595	0.010
	rs1168013	G/C		0.079	0.007	2.872	0.004
ApoA1/ApoB	rs1168013		GG/CG/CC	-0.078	0.015	-2.896	0.004
	rs1168013	G/C		-0.075	0.011	-2.795	0.005
	rs615563		GG/AG/AA	-0.091	0.018	-3.398	0.001
	rs615563	G/A		-0.083	0.011	-3.093	0.002

LNT2 rs2760537, *GALNT2* rs4846913, *GALNT2* rs11122316 were significantly different between the nondrinkers and drinkers. The drinkers had higher genotype frequencies of rs1168013CC, rs615563AA, rs7552841TT, rs11206517GG, rs1997947AA, rs2760537TT, rs4846913AA and rs11122316AA than the nondrinkers. These results indicate that homozygous carries of rs1168013CC, rs615563AA, rs7552841TT, rs11206517GG, rs1997947AA, rs2760537TT, rs4846913AA and rs11122316AA may prefer to drink. But further studies are needed to confirm these results. In the present study, the study population, Jing, is an isolated and conservative minority. Strict intra-ethnic marriages have been performed from time immemorial. Thus, the hereditary characteristics or mutations of some genes in this population may be different from those in the other nationalities.

Results here not only confirm the increasing magnitude of associations between these mutations and their haplotypes on lipid-associated phenotypes, but also suggest an interaction between the *DOCK7*, *PCSK9* and *GALNT2* mutations and their haplotypes with alcohol consumption on lipid-associated phenotypes. The present study showed that the commonest haplotype was G-C-G-C-T-G-C-C-G (> 10% of the samples). There were significant associations between several mutations TG (rs10889332 and rs11122316 in nondrinkers; rs11206517 and rs4846913 in drinkers) and LDL-C (rs-11206517 in drinkers). Moreover, we detected a statistically significant association between the haplotypes and TC (C-C-G-C-T-G-C-C-G, C-C-G-C-T-G-T-C-G, G-C-G-C-T-G-C-C-G and G-C-G-C-T-G-T-C-G in nondrinkers; C-C-G-C-T-G-C-C-G and G-C-G-C-T-G-C-C-G in drinkers), TG (C-C-G-C-T-G-C-C-G, C-C-G-C-T-G-T-C-G, C-T-G-C-T-G-C-C-G, G-C-G-C-T-G-C-C-A, G-C-G-C-T-G-C-C-G, G-C-G-C-T-G-T-C-A, and G-C-G-C-T-G-T-C-G in nondrinkers; C-C-G-C-T-G-C-C-G, and G-C-G-C-T-G-C-C-G in drinkers), LDL-C (C-C-G-C-T-G-C-C-G and C-C-G-C-T-G-T-C-G, in nondrinkers; C-C-G-C-T-G-C-C-G, G-C-G-C-T-G-C-C-G and G-C-G-C-T-G-T-C-G in drinkers), apolipoprotein (Apo) A1 (G-C-G-C-T-G-T-C-G in nondrinkers), ApoB (G-C-G-C-T-G-T-C-G in nondrinkers; C-C-G-C-T-G-C-C-G and G-C-G-C-T-G-C-C-G in drinkers) and ApoA1/ApoB ratio (G-C-G-C-T-G-T-C-G in

nondrinkers; C-C-G-C-T-G-C-C-G and G-C-G-C-T-G-C-C-G in drinkers). Haplotypes could explain much more serum lipid variation than any single mutations alone.

Interestingly, the magnitude of effects of the *DOCK7, PCSK9* and *GALNT2* polymorphisms on lipid-associated phenotypes was not homogeneous in the whole populations. Regarding interactions of *DOCK7* rs10889353 with some glycemic-related traits including BMI and glucose and insulin levels, previously study has analyzed the statistical association of the polymorphism and serum TG, TC and LDL-C levels [35]. However, a recent analysis including 3041 Japanese healthy volunteers obtained from the Japan Pharmacogenomics Data Science Consortium (JPDSC) database with serum lipids concluded that there was a consistent statistical significant association with lipids, especially TG, and may serve as a candidate for a new drug target to treat lipid abnormality syndromes [36]. In another study [37], authors concluded GALNT2 susceptibility loci for elevated plasma HDL-C levels and outline methods that help interpret and prioritize novel mutations associated with a phenotypic trait of interest from large next-generation sequencing datasets.

The interactions of these mutations and their haplotypes with alcohol consumption on lipid-associated phenotypes have not been investigated previously. In the present study, the interactions of several mutations and their haplotypes with alcohol consumption on lipid-associated phenotypes were detected in our study population. These results suggest that some lipid-associated phenotypes in our study population were partly influenced by interactions of several mutations and their haplotypes with alcohol consumption. Therefore, healthy lifestyle is important for maintaining of normal lipid-associated phenotypes. These results suggest that the beneficial effects of alcohol consumption on lipid-associated phenotypes depend on the individuals' hereditary characteristics. The effect of different types of beverages and different volume of alcohol intake on lipid-associated phenotypes is not yet known. In our study population, 90% wine drunk by them was rice wine. The alcohol content is rather high. Thus, whether there is any interaction between these mutations and their haplotypes with kinds of beverage or volume of alcohol intake on lipid-associated phenotypes or hyperlipidemia warrants further investigation.

The current study had several limitations. First, alcohol consumption was collected through self-reports by questionnaires, the associations between polymorphisms and alcohol consumption on lipid-associated phenotypes may be small and require large samples with more events longer follow-up to detect. In addition, interactions of total energy, fat, carbohydrates or protein intake factors on lipid-associated phenotypes remain to be determined [38]. The most important one is the limitation of sample size and larger numbers are required to confirm these findings.

Conclusions

We extended our findings by reporting novel interactions of several *DOCK7, PCSK9* and *GALNT2* mutations and their haplotypes with alcohol consumption on lipid-associated phenotypes and also suggesting alcohol consumption modulation. Moreover, we report for the first time the differences in lipid-associated phenotypes between the nondrinkers and drinkers might be partially attributed to the interactions of these mutations and their haplotypes and alcohol consumption, suggesting that gene-alcohol interactions may significantly contribute to the CVD morbidity and mortality.

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Disclosure of conflict of interest

None.

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