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Association between the MLX Interacting Protein-Like, BUD13 Homolog and Zinc Finger Protein 259 Gene Polymorphisms and Serum Lipid Levels

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This study aimed to detect the association between the MLX interacting protein-like (*MLXIPL*), BUD13 homolog (*BUD13*) and zinc finger protein 259 (*ZNF259*) single nucleotide polymorphisms (SNPs) and serum lipid levels in the Chinese Mulao and Han populations. Genotyping of 9 SNPs was performed in 825 Mulao and 781 Han participants. The genotype and allele frequencies of *ZNF259* rs2075290 and rs964184, and *BUD13* rs10790162 SNPs were different between the Mulao and Han populations ($P < 0.001$). The SNPs of *ZNF259* rs2075290 and *BUD13* rs10790162 were associated with serum total cholesterol levels; *ZNF259* rs2075290 and rs964184, *BUD13* rs10790162, and *MLXIPL* rs3812316 and rs13235543 were associated with triglyceride (TG); and *MLXIPL* rs35332062 was associated with apolipoprotein (Apo) A1 in the Mulaos ($P <$ 0.006–0.001). However, in the Hans, the SNPs of *ZNF259* rs2075290 and *BUD13* rs10790162 were associated with serum TG levels; *ZNF259* rs2075290 was associated with low-density lipoprotein cholesterol and the ApoA1/ApoB ratio ($P <$ 0.006–0.001). Significant linkage disequilibria were noted among *ZNF259* rs2075290 and rs964184 and *BUD13* rs10790162, and between *MLXIPL* rs3812316 and rs13235543 ($r^2 > 0.05$, $P < 0.001$). The haplotypes of A-C-G-A-C (rs2075290A-rs964184C-rs10790162G-rs17119975A-rs11556024C) and C-C-C-C (rs799161C-rs35332062C-rs3812316C-rs13235543C) accounted for over half of the % haplotype of each ethnic group.

Atherosclerotic cardiovascular disease (CVD) is a major disease burden worldwide[1,2] and lipid modification plays an important role in the reduction of CVD risk[2]. Although lipid modification was mainly focused on reducing the low-density lipoprotein cholesterol (LDL-C) level in the past, lowering both triglyceride (TG) and LDL-C levels was found to be more beneficial than lowering LDL-C alone in recent years[3]. Consequently, several research efforts have been made to control serum TG levels. Serum TG concentration is a complex polygenic trait that is determined by environmental and genetic factors including common and rare variants in multiple genes[4–7]. Therefore, the understanding of the variants modulating the serum TG level has become crucial in the development of novel markers for risk prediction, diagnosis, and prognosis of CVD.

Recent genome-wide association studies (GWASs) have identified a great number of TG-related loci[8–11]. The MLX interacting protein-like (*MLXIPL*; Gene ID: 51085; OMIM: 605678) gene, formerly known as carbohydrate response element binding protein (*ChREBP*), is located on chromosome 7q11.23 and encodes a basic helix-loop-helix leucine zipper transcription factor of the Myc/Max/Mad superfamily. *ChREBP* regulates the expression of pyruvate kinase, which channels glycolytic pyruvate into lipogenesis through the conversion of dietary carbohydrate to storage fat in the liver[12]. Suppression of *ChREBP* could diminish aerobic glycolysis and de novo lipogenesis by switching aerobic glycolysis to oxidative phosphorylation[13]. The BUD13 homolog (*BUD13*; Gene ID: 84811; HGNC: 28199) and zinc finger protein 259 (*ZNF259*; Gene ID: 8882; OMIM: 603901) genes are located on 11q23.3 and encode for BUD13 homolog protein and zinc finger protein (ZPR1), respectively. BUD13 is one of the subunits of the RES complex, which was previously identified in yeast as a splicing factor that affects nuclear pre-mRNA retention[14]. ZPR1 is an essential protein required for normal nucleolar function in proliferating cells[15].

Single nucleotide polymorphisms (SNPs) in the *BUD13* and *ZNF259* have been associated with serum lipid levels, especially with TG in western populations[8,9,16,17]; likewise, the *MLXIPL* SNPs were also associated with TG level in

European and Indian Asian populations[18]. However, little is known about the association of these SNPs and serum lipid levels in Southern Chinese populations. Therefore, this study was undertaken to determine the association of the *MLXIPL* (rs35332062 A358V, rs3812316 Q241H, rs13235543 P342P and rs799161 g.11092833T>C), *BUD13* (rs10790162 +1741T>C, rs17119975 -575A>G and rs11556024 *147C>T) and *ZNF259* (rs2075290 -336G>A and rs964184 +359C>G) SNPs with serum lipid levels in the Mulao and Han populations.

Results

General and biochemical characteristics of the subjects. As shown in Table 1, the value of BMI was lower and the levels of apolipoprotein (Apo) B and the percentage of subjects who consumed alcohol were higher in Mulao than in Han ($P < 0.01$–0.001). There were no significant differences in the levels of total cholesterol (TC), TG, high-density lipoprotein cholesterol (HDL-C), LDL-C and ApoA1 levels and the ratio of ApoA1 to ApoB between the two ethnic groups ($P > 0.05$ for all).

Results of electrophoresis. The polymerase chain reaction (PCR) products of rs2075290, rs964184, rs17119975, rs11556024, rs10790162, rs35332062, rs3812316, rs13235543 and rs799161 SNPs were 331-, 496-, 530-, 358-, 572-, 117-, 297-, 545- and 279-bp nucleotide sequences; respectively. After the restriction fragment length polymorphism (RFLP) reaction combined with electrophoresis, the genotypes were identified according to the number and length of the enzyme digestion fragments (Figure 1).

DNA sequencing. The genotypes detected by PCR-RFLP were also confirmed by direct sequencing (Figure 2). The sequencing results were directly submitted to GenBank's Gene Expression Omnibus (GEO) database. The GenBank accession numbers for the DNA sequences of the *ZNF259* rs2075290 AA/AG/GG genotypes were KF306313-306315, the *ZNF259* rs964184 CC/CG/GG genotypes were KF306310-306312, the *BUD13* rs10790162 GG/AG/AA genotypes were KF306302-306304, the *BUD13* rs17119975 AA/AG/GG genotypes were KF306316-306318, the *BUD13* rs11556024 CC/CT/TT genotypes were KF306305-306307, the *MLXIPL* rs799161 TT/CT/CC genotypes were KF306319-306321, the *MLXIPL* rs35332062 CC/CT/TT genotypes were KF306325-306327, the *MLXIPL* rs3812316 CC/CG/GG genotypes were KC853060-853062, and the *MLXIPL* rs13235543 CC/CT/TT genotypes were KF306322-306324, respectively.

Genotypic and allelic frequencies. As shown in Table 2, of the 9 SNPs, the genotype and allele frequencies of the *ZNF259* rs2075290 and rs964184, and *BUD13* rs10790162 SNPs were different between the Mulao and Han populations ($P < 0.001$ for each). The genotype frequencies but not the allele frequencies of *BUD13* rs17119975 SNP were different between the Mulao and Han populations ($P < 0.05$). All SNPs (except *MLXIPL* rs799161) were in the Hardy-Weinberg equilibrium ($P > 0.05$). Significant linkage disequilibria (LD) were found between *ZNF259* rs2075290 and rs964184 ($r^2 = 0.699$ in Mulao, $r^2 = 0.526$ in Han, $P < 0.001$); *ZNF259* rs2075290 and rs10790162 ($r^2 = 0.715$ in Mulao, $r^2 = 0.558$ in Han, $P < 0.001$); *ZNF259* rs964184 and *BUD13* rs10790162 ($r^2 = 0.866$ in Mulao, $r^2 = 0.718$ in Han, $P < 0.001$); and *MLXIPL* rs3812316 and rs13235543 ($r^2 = 0.482$ in Mulao, $r^2 = 0.588$ in Han, $P < 0.001$; Figure 3).

The frequencies of haplotypes are listed in Table 3. Six haplotypes (among 5 SNPs of *BUD13/ZNF259*) and 7 haplotypes (among 4 SNPs of *MLXIPL*) with a frequency >1% were identified in the Mulao and Han populations respectively. We combined 17 haplotypes (among 5 SNPs of *BUD13/ZNF259*) and 13 haplotypes (among 4 SNPs of *MLXIPL*) with frequencies less than 3% into one group, called "rare_hap". The haplotypes of A-C-G-A-C (among the *ZNF259* rs2075290 and rs964184, and *BUD13* rs10790162, rs17119975 and rs11556024 SNPs) and C-C-C-C (among the *MLXIPL* rs799161, rs35332062, rs3812316 and rs13235543 SNPs) accounted for over half of the % haplotype of each ethnic group. The frequencies of the

Table 1 | Comparison of demographic, lifestyle characteristics and serum lipid levels between the Mulao and Han populations

Characteristics	Mulao	Han	t (χ^2)	P-value
Number	825	781		
Male/female	354/471	307/474	−1.466	0.143
Age (years)	49.18 ± 16.13	49.25 ± 16.21	−0.082	0.934
Height (cm)	155.38 ± 8.05	154.6 ± 8.04	1.948	0.052
Weight (kg)	52.61 ± 9.41	53.43 ± 8.82	−1.808	0.071
Body mass index (kg/m^2)	21.72 ± 3.07	22.36 ± 3.48	−3.894	1×10^{-4}
Waist circumference (cm)	74.73 ± 8.59	75.03 ± 7.85	−0.720	0.472
Systolic blood pressure (mmHg)	127.81 ± 21.12	128.03 ± 18.91	−0.219	0.827
Diastolic blood pressure (mmHg)	80.35 ± 11.43	81.41 ± 11.19	−1.871	0.061
Pulse pressure (mmHg)	47.46 ± 15.77	46.62 ± 13.95	1.130	0.259
Cigarette smoking [n (%)]				
Nonsmoker	649 (78.7)	622 (79.7)		
≤20 Cigarette smoking/day	145 (17.6)	140 (17.9)	0.877	0.381
>20 Cigarette smoking/day	31 (3.7)	19 (2.4)		
Alcohol consumption [n (%)]				
Nondrinker	642 (77.8)	623(79.8)		
≤25 g/day	68(8.2)	79(10.1)	2.877	0.004
>25 g/day	115(13.9)	79(10.1)		
Blood glucose level (mmol/L)	5.91 ± 1.56	5.92 ± 1.48	−0.183	0.854
Total cholesterol (mmol/L)	4.94 ± 1.14	4.90 ± 1.00	0.702	0.483
Triglyceride (mmol/L)	1.04 (0.75)	1.03 (0.85)	−0.432	0.666
High-density lipoprotein cholesterol (mmol/L)	1.74 ± 0.47	1.73 ± 0.52	0.404	0.687
Low-density lipoprotein cholesterol (mmol/L)	2.91 ± 0.86	2.84 ± 0.83	1.614	0.107
Apolipoprotein (Apo) A1 (g/L)	1.30 ± 0.40	1.33 ± 0.26	−1.631	0.103
ApoB (g/L)	0.97 ± 0.58	0.84 ± 0.20	6.246	$<1 \times 10^{-7}$
ApoA1/ApoB	1.62 ± 0.99	1.67 ± 0.50	−1.296	0.195

The continuous variables were presented as the mean ± standard deviation and their differences between the two ethnic groups were tested by *t*-test. The categorical variables were presented as the frequencies or percentages and their differences between the groups were tested by Chi square tests. The values of triglyceride were presented as the median (interquartile range) and their differences between the ethnic groups were determined by the Wilcoxon-Mann-Whitney test.

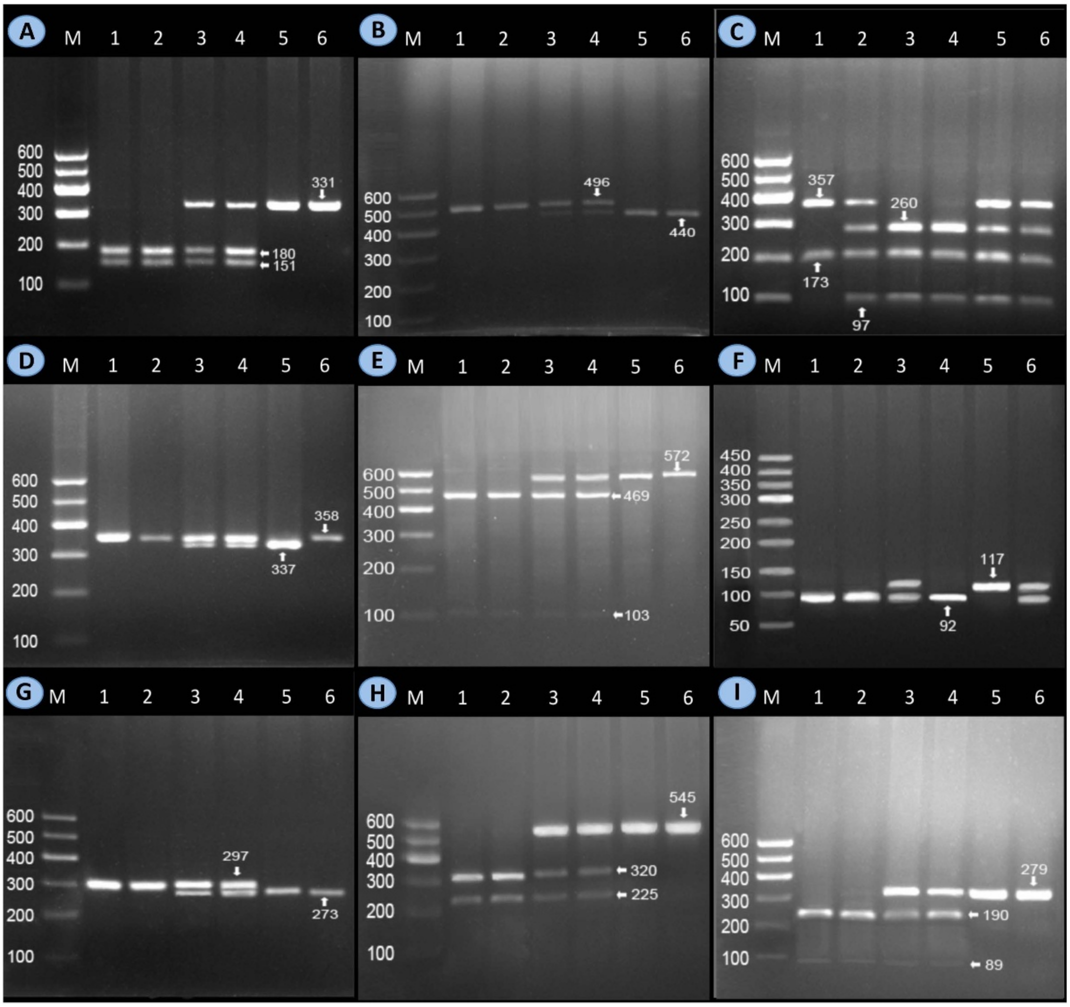

Figure 1 | Genotyping of the *MLXIPL*, *BUD13* and *ZNF259* SNPs. Lane M, 100 bp marker ladder; (A) *ZNF259* rs2075290: lanes 1 and 2, AA genotype (180- and 151-bp) lanes 3 and 4, GA genotype (331-, 180- and 151-bp); and lanes 5 and 6, GG genotype (331 bp). (B) *ZNF259* rs964184: lanes 1 and 2, CC genotype (496 bp); lanes 3 and 4, CG genotype (496-, 440- and 56-bp); and lanes 5 and 6, GG genotype (440- and 56-bp). (C) *BUD13* rs10790162: lane 1, AA genotype (357- and 173-bp); lanes 2, 5 and 6, AG genotype (357-, 260-, 173- and 97-bp); and lanes 3 and 4, GG genotype (260-, 173- and 97-bp). (D) *BUD13* rs17119975 SNP: lanes 1, 2 and 6, AA genotype (358 bp); lanes 3 and 4, AG genotype (358-, 337- and 21-bp); and lane 5, GG genotype (337- and 21-bp). (E) *BUD13* rs11556024: lanes 1 and 2, CC genotype (469- and 103-bp); lanes 3 and 4, CT genotype (572-, 469- and 103-bp); and lanes 5 and 6, TT genotype (572 bp). (F) *MLXIPL* rs799161: lanes 1, 2 and 4, CC genotype (92- and 25-bp); lanes 3 and 6, CT genotype (117-, 92- and 25-bp); and lane 5, TT genotype (117 bp). (G) *MLXIPL* rs35332062: lanes 1 and 2, CC genotype (297 bp); lanes 3 and 4, CT genotype (297-, 273- and 24-bp); and lanes 5 and 6, TT genotype (273- and 24-bp). (H) *MLXIPL* rs3812316: lanes 1 and 2, GG genotype (320- and 225-bp); lanes 3 and 4, CG genotype (545-, 320- and 225-bp); and lanes 5 and 6, CC genotype (545 bp). (I) *MLXIPL* rs13235543: lanes 1 and 2, CC genotype (190- and 89-bp); lanes 3 and 4, CT genotype (279-, 190- and 89-bp); and lanes 5 and 6, TT genotype (279 bp). The bands less than 90-bp fragments were not visible in the gel owing to their fast migration speed.

A-C-G-A-C and G-G-A-A-C haplotypes were significantly different between the two ethnic groups ($P < 0.01$ for each).

Genotypes and serum lipid levels. As shown in Table 4, the levels of TG (*ZNF259* rs2075290 and rs964184, *BUD13* rs10790162, and *MLXIPL* rs13235543), ApoA1 (*MLXIPL* rs35332062), ApoB (*MLXIPL* rs13235543) in the Mulao population were significantly different among the three genotypes ($P < 0.006$–0.001), whereas the levels of TG (*BUD13* rs10790162) and ApoA1 (*MLXIPL* rs11556024) in the Han population were different among the genotypes ($P <$ 0.006–0.001). When the minor homozygous genotype was combined with the heterozygous genotype to enhance power, the levels of TC (*ZNF259* rs2075290 and *BUD13* rs10790162), TG (*ZNF259* rs2075290 and rs964184, *BUD13* rs10790162, and *MLXIPL* rs3812316 and rs13235543) and ApoA1 (*MLXIPL* rs35332062) in the Mulao population were found to be significantly different between the two genotypes ($P < 0.006$–0.001); whereas, the levels of TG (*ZNF259* rs2075290 and *BUD13* rs10790162), LDL-C and the ratio of ApoA1/ApoB (*ZNF259* rs2075290) in the Han population were different between the genotypes ($P < 0.006$–0.001).

Table 5 shows the magnitude and direction of correlation between serum lipid levels and genotypes in the two populations. Many of the examining SNPs showed significant correlation with serum lipid levels in multiple linear regression analysis; although, these SNPs did not show significant association with serum lipid levels in the analysis of covariance (ANCOVA).

Discussion

The main findings of this study are as follows: we successfully replicated the association of *MLXIPL* rs3812316, *ZNF259* rs2075290 and rs964184 SNPs with serum TG in the Mulao population and of *ZNF259* rs2075290 and *BUD13* rs10790162 with serum TG in the

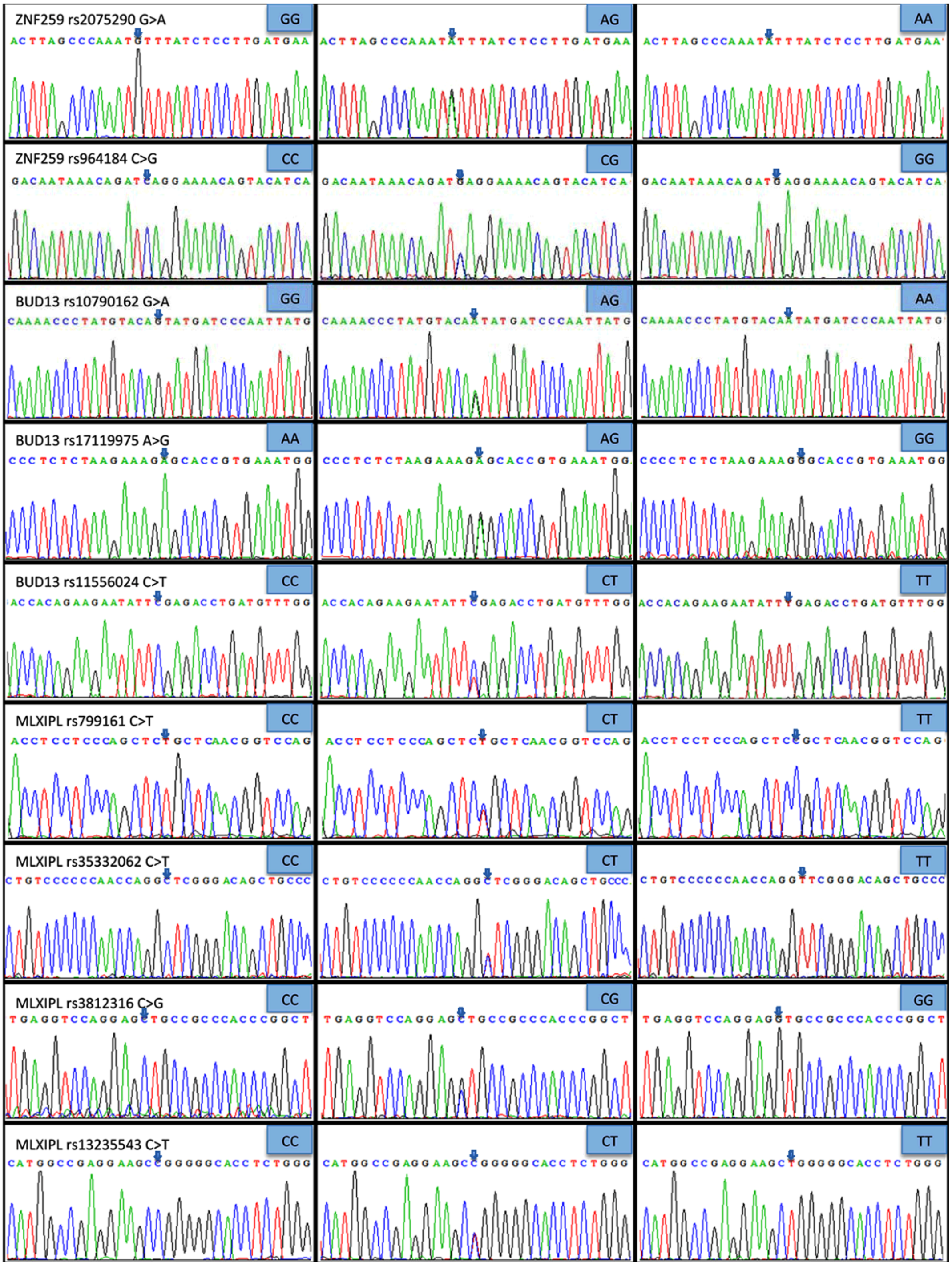

Figure 2 | A part of the nucleotide sequences of the *MLXIPL, BUD13* and *ZNF259* SNPs by direct sequencing. MLXIPL: MLX interacting protein-like, BUD13: BUD13 homolog and ZNF259: zinc finger protein 259.

Han population; and we explored a previously unreported association of *BUD13* rs11556024, and *MLXIPL* rs35332062 and rs13235543 SNPs with serum lipid levels. In addition, we reported the linkage disequilibrium status and the possible haplotype frequencies of these SNPs.

It has been noted that the genotype and allele frequencies of several SNPs are not consistent among different populations[8,9,19–22]. The G allele frequency of *MLXIPL* rs3812316 (Q241H) SNP was 0.05 in Mexicans[41], 0.10 in Europeans[18] and 0.09 in Indian Asians[18] and Japanese individuals[23]. Nakayama K, et al. found that in a worldwide survey, individuals from Africa (0.05), South Asia (0.06), East Asia (0.11) and South-East Asia (0.12) had lower frequencies of the minor G allele compared to those from Central Asian populations (0.21 to 0.26), including Mongolian, Tibetan and Uyghur[16]. The minor allele frequencies of our study populations (0.049 in Mulao, 0.051 in Han) were much closer to those of the African and South Asian populations. The genotype and allele frequencies of *ZNF259* rs2075290 and rs964184 and *BUD13* rs10790162 ($P < 0.05$ for each) were significantly different between Mulao and Han. The genotype frequencies but not the allele frequencies of *BUD13* rs17119975 were different between the Mulao and Han populations ($P > 0.05$). The minor allele frequencies of the *MLXIPL*, *BUD13* and *ZNF259* SNPs of our Han

Table 2 | Comparison of genotype and allele frequencies between the Mulao and Han populations [n (%)]

SNP	Genotype/Allele	Mulao (n = 825)	Han (n = 781)	χ^2	*P*-value
ZNF259 rs2075290	AA/GA/GG	413(50.1)/348(42.2)/64(7.7)	460(58.9)/279(35.7)/42(5.4)	13.494	0.001
	A/G	1174(71.2)/476(28.8)	1199(76.8)/363(23.2)	13.082	3×10^{-4}
ZNF259 rs964184	CC/CG/GG	467(56.6)/306(37.1)/52(6.3)	515(65.9)/234(30.0)/32(4.1)	15.514	4×10^{-4}
	C/G	1240(75.2)/410(24.8)	1264(80.9)/298(19.1)	15.548	8×10^{-5}
BUD13 rs10790162	GG/GA/AA	472(57.2)/295(35.8)/58(7.0)	519(66.5)/230(29.4)/32(4.1)	16.595	2×10^{-4}
	G/A	1239 (75.1)/411 (24.9)	1268 (81.2)/294 (18.8)	17.355	3×10^{-5}
BUD13 rs17119975	AA/AG/GG	537(65.1)/254(30.8)/34(4.1)	472(60.4)/284(36.4)/25(3.2)	6.032	0.049
	A/G	1328 (80.5)/322 (19.5)	1228 (78.6)/334 (21.4)	1.722	0.189
BUD13 rs11556024	CC/CT/TT	700(84.9)/120(14.5)/5(0.6)	671(85.9)/103(13.2)/7(0.9)	1.038	0.595
	C/T	1520 (92.1)/130 (7.9)	1445 (92.5)/117 (7.5)	0.171	0.680
MLXIPL rs799161	CC/CT/TT	361(43.8)/390(47.2)/74(9.0)	345(44.2)/378(48.4)/58(7.4)	1.285	0.526
	C/T	1112 (67.4)/538 (32.6)	1068 (68.4)/494 (31.6)	0.353	0.552
MLXIPL rs35332062	CC/CT/TT	717(86.9)/98(11.9)/10(1.2)	692(88.6)/83(10.6)/6(0.8)	1.482	0.477
	C/T	1532 (92.8)/118 (7.2)	1467 (93.9)/95 (6.1)	1.483	0.223
MLXIPL rs3812316	CC/CG/GG	751(91.0)/67(8.1)/7(0.9)	703(90.0)/76(9.7)/2(0.3)	3.726	0.155
	C/G	1569 (95.1)/81 (4.9)	1482 (94.9)/80 (5.1)	0.076	0.783
MLXIPL rs13235543	CC/CT/TT	704(85.3)/114(13.8)/7(0.9)	682(87.3)/94(12.0)/5(0.7)	1.401	0.496
	C/T	1522 (92.2)/128 (7.8)	1458 (93.3)/104 (6.7)	1.447	0.229

ZNF259, zinc finger protein 259; BUD13, BUD13 homolog; MLXIPL, MLX interacting protein-like.

population were in close proximity to those of CHB from the international haplotype map (HapMap; http://hapmap.ncbi.nlm.nih.gov/cgi-perl/gbrowse/hapmap24_B36/) data. Generally, the minor allele frequencies of the 9 observed SNPs were lower in European ancestries than in Asian ancestries[8,9,24,25]. These findings suggest that the genotype and allele frequencies of the *MLXIPL*, *BUD13* and *ZNF259* SNPs are different among diverse ethnic groups.

The association of variants in the *MLXIPL* gene and serum lipid levels among different ethnic populations is still controversial. The *MLXIPL* rs3812316-G allele was reported to be associated with decreased plasma TG levels in Asians[16,18,23] and in combined Northern Europeans and Indian Asians[26]. It was also reported to be related to the risk of CAD in the Han Chinese[27] and Japanese populations[23]. However, a notable absence of association was found between low- and high- triglyceridemia individuals in the central Europe white population[28] or between type 2 diabetes and normal controls of the North India Sikh population[26]. In contrast to previous studies, our results showed that the minor allele of *MLXIPL*

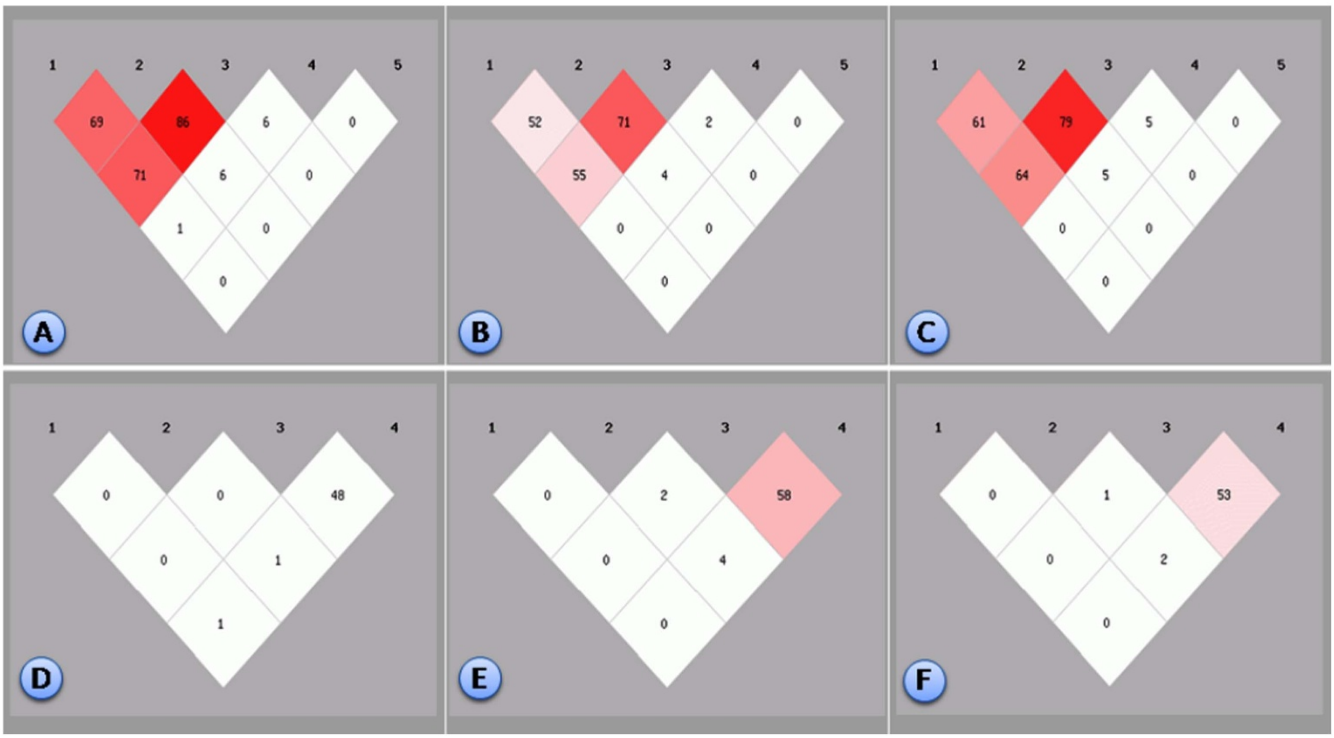

Figure 3 | Linkage disequilibrium statuses of the *MLXIPL, BUD13* and *ZNF259* SNPs. Linkage disequilibrium among the (1) *ZNF259* rs2075290, (2) *ZNF259* rs964184 and (3) *BUD13* rs10790162, (4) *BUD13* rs17119975 and (5) *BUD13* rs11556024 SNPs in the Mulao (A), Han (B) and combined Mulao and Han populations (C). Linkage disequilibrium among the (1) *MLXIPL* rs799161, (2) *MLXIPL* rs35332062, (3) *MLXIPL* rs3812316 and (4) *MLXIPL* rs13235543 SNPs in the Mulao (D), Han (E) and combined Mulao and Han populations (F). The linkage disequilibrium status is illustrated by the magnitude of the r^2 value.

Table 3 | Haplotype frequencies among 5 SNPs of the *BUD13/ZNF259* genes and 4 SNPs of the *MLXIPL* gene between the Mulao and Han populations [n(%)]

Haplotype					Mulao	Han	χ^2	*P*-value
ZNF259 rs2075290	*ZNF259* rs964184	*BUD13* rs10790162	*BUD13* rs17119975	*BUD13* rs11556024				
A	C	G	A	C	761 (54.0)	761 (54.7)	7.276	0.007
G	G	A	A	C	323 (22.9)	216 (15.5)	24.739	0.000
A	C	G	G	C	213 (15.1)	243 (17.5)	3.078	0.079
G	C	G	G	C	51 (3.6)	51 (3.7)	0.002	0.963
Rare Hap (<3%)					62 (4.4)	119 (8.6)	6.129	0.013
MLXIPL rs799161	MLXIPL rs35332062	MLXIPL rs3812316	MLXIPL rs13235543					
C	C	C	C		866 (60.6)	875 (61.9)	0.492	0.483
C	T	C	C		368 (25.7)	353 (25.0)	0.227	0.634
T	C	C	C		62 (4.3)	63 (4.4)	0.013	0.909
Rare Hap (<3%)					135 (9.4)	123 (8.7)	0.167	0.683

ZNF259, zinc finger protein 259; BUD13, BUD13 homolog; MLXIPL, MLX interacting protein-like.

rs3812316 SNP was associated with higher TG levels in the Mulao but not the Han population.

Many GWASs have reported that the G allele of rs964184 at the *ZNF259* region was strongly associated with increased serum TC, TG and LDL-C but was associated with decreased HDL-C in the European population[8,9,16,17] and resulted in a 1.13 fold increased in the risk of CAD and metabolic syndrome[28–30]. The G allele was also associated with decreased HDL-C in a combined population of white European and Asian Indian[11] and with a 1.8-times and 3.28-times increased risk of hypertriglyceridemia in Mexican[41] and European populations[31], respectively. Partially consistent with previous studies, we replicated the association of *ZNF259* rs964184 G allele with serum TC and TG levels in Mulao (but not in Han) population, but we did not find its association with the serum HDL-C level in our study population. The STAMPEED Consortium, which included 13 independent studies of European ancestry, reported that *ZNF259* rs2075290 and *BUD13* rs10790162 were correlated with TG, HDL-C, waist circumference levels and metabolic syndrome[32]; however, the mechanism of association is not well understood. In our study, we found that the minor allele carriers of *ZNF259* rs2075290 and *BUD13* rs10790162 were associated with higher TG (in Mulao and Han) and TC (in Han) compared to the minor allele non-carriers, yet no association with HDL-C was noted.

The reason for the discrepancy in association of the above-mentioned SNPs with serum lipid levels among different populations is not fully understood. It could be partly due to differences in their genetic background. Compared to the Han population, the Mulao population had higher ApoB levels and apparently similar remaining serum lipid parameters. Of 56 ethnic groups in China, Han is the largest one. Mulao, on the other hand, is one of the minorities, with a population of 207,352 according to the China's fifth national census in 2000. Approximately 90% of the Mulao population dwells in the Luocheng Mulao Autonomous County, Guangxi Zhuang Autonomous Region. The Mulams are the descendants of the ancient "Baiyue tribe" in southern China. Historical data trace the history of this ethnic minority back to the Jin Dynasty (AD 265–420). Interestingly, Mulams abide by their culture of consanguineous marriage to cousins on the maternal side. Hence, the Mulao population may have same genetic background and less heterogeneity within the population. Recent molecular anthropological data showed that Mulams are genetically much closer to the other neighboring ethnic groups in Guangxi than to the Han Chinese[33]. Therefore, some hereditary characteristics and genotypes of lipid metabolism-related genes in this population might be somewhat different from those in Han Chinese.

Another reason could be due to the ethnic difference in their LD pattern. Kooner, et al. reported that the LD status of *ZNF259* rs964184 with other SNPs were different between Europeans (high LD with 26 other SNPs) and Mexicans (not in high LD with any SNPs)[41]. In our study population, *ZNF259* rs2075290 and *BUD13* rs10790162 were in high LD with *ZNF259* rs964184. Therefore, ethnic differences in the LD pattern could partially explain the discrepancy in the association of these SNPs with plasma lipids among diverse populations. The third possible reason is that several environmental factors such as diet, alcohol consumption and obesity might further modify the effect of genetic variation on serum lipid levels[34–40]. The Mulao population had a higher percentage of subjects who consumed alcohol and had a lower BMI value than the Han population ($P < 0.05$–0.001). Therefore, it is possible that some uncontrollable or unmeasured environmental factors might further modify the effect of genetic variation on the serum lipid levels of our study populations. In addition, this study showed the association of *MLXIPL* rs35332062 SNP with ApoA1, *MLXIPL* rs13235543 with TG and ApoB in the Mulao population, and that of *MLXIPL* rs11556024 with ApoA1 in the Han population. Since this study is the first attempt to detect the association of these three SNPs with serum lipid levels, we are unable to make comparison with other studies. Thus, further studies with larger sample sizes are needed for the confirmation.

This study has some limitations. The sample size was relatively low compared to many GWAS and replication studies. Hence, further studies with larger sample sizes are needed to confirm our results. Secondly, we were not able to alleviate the effect of diet and several environmental factors during the statistical analysis. Thirdly, although we have detected the effects of the *MLXIPL* and *BUD13-ZNF259* SNPs on serum lipid levels in this study, several SNPs still remain to be studies. In addition, detecting the interactions of SNP-SNP and/or SNP-environmental is required for a clear understanding of the genetic background of plasma lipids in the Chinese population.

In summary, the SNPs of *ZNF259* rs2075290 and *BUD13* rs10790162 were associated with serum TC levels; *ZNF259* rs2075290 and rs964184, *BUD13* rs10790162, and *MLXIPL* rs3812316 and rs13235543 were associated with TG; and *MLXIPL* rs35332062 was associated with ApoA1 in the Mulao population. In Han, on the other hand, the SNPs of *ZNF259* rs2075290 and *BUD13* rs10790162 were associated with serum TG levels; *ZNF259* rs2075290 was associated with LDL-C and the ApoA1/ApoB ratio. Several *MLXIPL, BUD13* and *ZNF259* SNPs were associated with different serum lipid parameters in the two ethnic groups, suggesting that the associations of these variants on serum lipid levels might have ethnic specificity.

Methods

Study populations. The current study included 825 (354 males, 42.9% and 471 females, 57.1%) unrelated subjects of Mulao nationality from Luocheng Mulao Autonomous County, Guangxi Zhuang Autonomous Region, People's Republic of

Table 4 | Comparison of serum lipid levels among the genotypes in the Mulao and Han populations

Genotype	n	TC (mmol/L)	TG (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)	ApoA1 (g/L)	ApoB (g/L)	ApoA1/ApoB
***ZNF259* rs2075290 G>A**								
Mulao								
AA	413	4.83 ± 1.15	0.97(0.65)	1.72 ± 0.43	2.86 ± 0.84	1.32 ± 0.38	0.96 ± 0.56	1.70 ± 1.22
GA	348	4.96 ± 1.10	1.09(0.83)	1.76 ± 0.53	2.93 ± 0.88	1.28 ± 0.41	0.98 ± 0.60	1.54 ± 0.69
GG	64	5.26 ± 1.14	1.33(1.46)	1.69 ± 0.39	3.07 ± 0.85	1.31 ± 0.39	0.95 ± 0.47	1.62 ± 0.77
F		4.126	10.208	0.971	2.591	0.641	0.257	2.247
P		0.017	0.001	0.379	0.076	0.527	0.774	0.106
AA	413	4.83 ± 1.15	0.97(0.65)	1.72 ± 0.43	2.86 ± 0.84	1.32 ± 0.38	0.96 ± 0.56	1.70 ± 1.22
GA/GG	412	5.11 ± 1.11	1.12(0.83)	1.73 ± 0.51	3.00 ± 0.87	1.30 ± 0.41	0.97 ± 0.20	1.58 ± 0.71
F		8.127	−4.157	0.030	3.764	0.244	0.043	1.895
P		0.004	2×10^{-5}	0.862	0.053	0.622	0.836	0.169
Han								
AA	460	4.90 ± 0.98	0.970.82)	1.76 ± 0.59	2.87 ± 0.82	1.34 ± 0.26	0.84 ± 0.20	1.70 ± 0.52
GA	279	4.86 ± 1.09	1.15(0.85)	1.67 ± 0.39	2.77 ± 0.89	1.31 ± 0.26	0.83 ± 0.19	1.65 ± 0.45
GG	42	5.16 ± 0.73	1.10(1.51)	1.63 ± 0.43	3.05 ± 0.61	1.30 ± 0.21	0.89 ± 0.18	1.49 ± 0.41
F		1.899	6.073	3.310	3.569	1.174	2.844	4.233
P		0.150	0.014	0.037	0.029	0.310	0.059	0.015
AA	460	4.90 ± 0.98	0.97(0.82)	1.76 ± 0.59	2.87 ± 0.82	1.34 ± 0.26	0.84 ± 0.20	1.70 ± 0.52
GA/GG	321	5.01 ± 1.05	1.15(0.87)	1.65 ± 0.39	2.91 ± 0.86	1.30 ± 0.25	0.86 ± 0.19	1.57 ± 0.46
F		1.491	−3.017	5.101	7.266	1.993	2.273	8.307
P		0.222	0.003	0.024	0.007	0.158	0.132	0.004
***ZNF259* rs964184 C>G**								
Mulao								
CC	467	4.86 ± 1.14	0.97(0.66)	1.72 ± 0.41	2.89 ± 0.84	1.29 ± 0.39	0.95 ± 0.55	1.62 ± 0.83
CG	306	5.03 ± 1.10	1.00(0.83)	1.78 ± 0.55	2.97 ± 0.88	1.31 ± 0.41	0.99 ± 0.59	1.58 ± 0.73
GG	52	5.14 ± 1.20	1.11(1.29)	1.65 ± 0.41	3.01 ± 0.88	1.31 ± 0.36	0.94 ± 0.38	1.53 ± 0.61
F		2.724	10.903	2.376	1.164	0.146	0.501	0.372
P		0.066	0.001	0.094	0.313	0.864	0.606	0.689
CC	467	4.86 ± 1.14	0.97(0.66)	1.72 ± 0.41	2.89 ± 0.84	1.29 ± 0.39	0.95 ± 0.55	1.62 ± 0.83
CG/GG	358	5.08 ± 1.11	1.14(0.89)	1.71 ± 0.54	2.99 ± 0.88	1.31 ± 0.41	0.96 ± 0.57	1.56 ± 0.71
F		4.690	−4.025	0.002	1.910	0.180	0.111	0.681
P		0.031	6×10^{-5}	0.968	0.167	0.671	0.739	0.410
Han								
CC	515	4.85 ± 0.96	0.99(0.86)	1.75 ± 0.58	2.80 ± 0.82	1.33 ± 0.26	0.82 ± 0.19	1.71 ± 0.51
CG	234	4.96 ± 1.15	1.11(0.86)	1.66 ± 0.38	2.89 ± 0.92	1.31 ± 0.24	0.86 ± 0.20	1.59 ± 0.42
GG	32	5.20 ± 0.71	1.02(1.14)	1.74 ± 0.37	3.08 ± 0.65	1.35 ± 0.19	0.87 ± 0.19	1.67 ± 0.67
F		2.739	6.087	2.119	2.450	1.153	3.677	4.912
P		0.065	0.014	0.121	0.087	0.316	0.026	0.008
CC	515	4.85 ± 0.96	0.99(0.86)	1.75 ± 0.58	2.80 ± 0.82	1.33 ± 0.26	0.82 ± 0.19	1.71 ± 0.51
CG/GG	266	5.07 ± 1.11	1.07(0.86)	1.70 ± 0.38	2.99 ± 0.89	1.33 ± 0.23	0.86 ± 0.20	1.63 ± 0.46
F		5.416	−2.522	0.687	4.782	0.064	4.698	2.411
P		0.020	0.012	0.407	0.029	0.801	0.031	0.121
***BUD13* rs10790162 G>A**								
Mulao								
GG	472	4.83 ± 1.15	0.96(0.66)	1.73 ± 0.42	2.86 ± 0.82	1.30 ± 0.39	0.95 ± 0.57	1.64 ± 0.84
AG	295	4.98 ± 1.13	1.12(0.79)	1.77 ± 0.55	2.92 ± 0.90	1.29 ± 0.41	0.97 ± 0.57	1.58 ± 0.72
AA	58	5.25 ± 1.20	1.41(1.39)	1.63 ± 0.40	3.11 ± 0.91	1.31 ± 0.35	1.00 ± 0.48	1.50 ± 0.63
F		3.783	15.444	2.079	2.196	0.036	0.314	1.021
P		0.023	9×10^{-5}	0.126	0.112	0.964	0.730	0.361
GG	472	4.83 ± 1.15	0.96(0.66)	1.73 ± 0.42	2.86 ± 0.82	1.30 ± 0.39	0.95 ± 0.57	1.64 ± 0.84
AG/AA	353	5.11 ± 1.14	1.15(0.90)	1.70 ± 0.53	3.02 ± 0.90	1.30 ± 0.40	0.97 ± 0.56	1.54 ± 0.71
F		7.562	−5.000	0.361	4.320	0.013	0.608	2.008
P		0.006	1×10^{-6}	0.548	0.038	0.911	0.436	0.157
Han								
GG	519	4.86 ± 0.96	0.97(0.80)	1.77 ± 0.59	2.81 ± 0.82	1.34 ± 0.26	0.82 ± 0.19	1.71 ± 0.51
AG	230	4.96 ± 1.14	1.17(0.70)	1.66 ± 0.37	2.89 ± 0.92	1.31 ± 0.24	0.86 ± 0.20	1.60 ± 0.42
AA	32	5.07 ± 0.65	1.16(0.67)	1.67 ± 0.40	2.96 ± 0.62	1.29 ± 0.21	0.87 ± 0.20	1.62 ± 0.73
F		1.415	13.752	3.480	1.050	1.541	3.141	4.634
P		0.244	2×10^{-4}	0.031	0.350	0.215	0.044	0.010
GG	519	4.86 ± 0.96	0.97(0.80)	1.77 ± 0.59	2.81 ± 0.82	1.34 ± 0.26	0.82 ± 0.19	1.71 ± 0.51
AG/AA	262	5.02 ± 1.09	1.17(1.02)	1.66 ± 0.38	2.93 ± 0.89	1.30 ± 0.24	0.86 ± 0.20	1.61 ± 0.47
F		2.363	−3.989	3.367	1.675	2.354	4.250	4.176
P		0.125	7×10^{-5}	0.067	0.196	0.125	0.040	0.041
***BUD13* rs17119975 A>G**								
Mulao								
AA	537	4.96 ± 1.17	1.07(0.79)	1.74 ± 0.50	2.93 ± 0.88	1.32 ± 0.39	0.95 ± 0.53	1.62 ± 0.77
AG	254	4.90 ± 1.06	1.01(0.62)	1.73 ± 0.42	2.90 ± 0.83	1.25 ± 0.42	1.00 ± 0.64	1.62 ± 1.42
GG	36	4.57 ± 1.08	0.88(0.79)	1.68 ± 0.49	2.62 ± 0.66	1.37 ± 0.31	1.06 ± 0.81	1.65 ± 0.52

Table 4 | Continued

Genotype	n	TC (mmol/L)	TG (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)	ApoA1 (g/L)	ApoB (g/L)	ApoA1/ApoB
F		1.700	4.592	0.284	1.765	2.547	1.151	0.012
P		0.183	0.032	0.753	0.172	0.079	0.317	0.988
AA	537	4.96 ± 1.17	1.07(0.79)	1.74 ± 0.50	2.93 ± 0.88	1.32 ± 0.39	0.95 ± 0.53	1.62 ± 0.77
AG/GG	290	4.74 ± 1.07	1.00(0.63)	1.74 ± 0.43	2.76 ± 0.81	1.31 ± 0.41	1.03 ± 0.66	1.64 ± 1.36
F		3.345	−2.480	0.551	3.312	0.020	1.840	0.023
P		0.068	0.013	0.458	0.069	0.886	0.175	0.880
Han								
AA	472	4.95 ± 0.99	1.01(0.73)	1.74 ± 0.58	2.90 ± 0.82	1.33 ± 0.23	0.84 ± 0.20	1.66 ± 0.46
AG	284	4.85 ± 1.06	1.14(1.06)	1.69 ± 0.44	2.78 ± 0.89	1.33 ± 0.29	0.83 ± 0.18	1.66 ± 0.54
GG	25	4.99 ± 0.98	0.84(0.47)	1.77 ± 0.28	2.94 ± 0.97	1.31 ± 0.14	0.84 ± 0.23	1.71 ± 0.59
F		0.988	5.879	0.938	2.024	0.034	0.110	0.085
P		0.373	0.015	0.392	0.133	0.967	0.896	0.919
AA	472	4.95 ± 0.99	1.01(0.73)	1.74 ± 0.58	2.90 ± 0.82	1.33 ± 0.23	0.84 ± 0.20	1.66 ± 0.46
AG/GG	309	4.91 ± 1.06	1.10(1.04)	1.73 ± 0.43	2.86 ± 0.89	1.32 ± 0.29	0.84 ± 0.18	1.68 ± 0.55
F		0.074	−1.860	0.036	0.168	0.053	0.005	0.130
P		0.786	0.063	0.851	0.682	0.819	0.944	0.719
***BUD13* rs11556024 C>T**								
Mulao								
CC	700	4.92 ± 1.14	1.04(0.77)	1.72 ± 0.48	2.90 ± 0.86	1.29 ± 0.41	0.96 ± 0.57	1.61 ± 0.99
CT	120	4.91 ± 1.20	1.05(0.66)	1.78 ± 0.45	2.91 ± 0.95	1.34 ± 0.34	0.97 ± 0.58	1.74 ± 1.15
TT	5	5.64 ± 0.44	0.88(0.36)	1.83 ± 0.34	3.58 ± 0.48	1.58 ± 0.16	1.37 ± 0.74	1.39 ± 0.66
F		0.854	0.434	0.662	1.280	1.978	1.062	0.805
P		0.426	0.510	0.516	0.279	0.139	0.346	0.447
CC	700	4.92 ± 1.14	1.04(0.77)	1.72 ± 0.48	2.90 ± 0.86	1.29 ± 0.41	0.96 ± 0.57	1.61 ± 0.99
CT/TT	125	5.27 ± 1.19	1.04(0.64)	1.80 ± 0.44	3.24 ± 0.94	1.46 ± 0.34	1.17 ± 0.58	1.56 ± 1.14
F		1.534	−0.779	0.454	2.522	2.993	2.097	0.034
P		0.216	0.436	0.501	0.113	0.084	0.148	0.853
Han								
CC	671	4.87 ± 1.01	1.05(0.84)	1.70 ± 0.54	2.84 ± 0.86	1.31 ± 0.25	0.84 ± 0.19	1.65 ± 0.51
CT	103	4.98 ± 1.03	0.90(0.75)	1.86 ± 0.44	2.84 ± 0.74	1.42 ± 0.27[a]	0.81 ± 0.19	1.80 ± 0.39
TT	7	4.44 ± 0.46	0.83(0.88)	1.57 ± 0.18	2.55 ± 0.56	1.27 ± 0.05	0.82 ± 0.15	1.61 ± 0.34
F		1.218	1.573	3.855	0.373	7.668	0.877	4.450
P		0.297	0.210	0.022	0.689	0.001	0.416	0.012
CC	671	4.87 ± 1.01	1.05(0.84)	1.70 ± 0.54	2.84 ± 0.86	1.31 ± 0.25	0.84 ± 0.19	1.65 ± 0.51
CT/TT	110	4.71 ± 1.03	0.90(0.75)	1.71 ± 0.43	2.69 ± 0.74	1.34 ± 0.27	0.81 ± 0.19	1.71 ± 0.39
F		0.626	−1.342	0.004	0.693	0.338	0.351	0.314
P		0.429	0.179	0.951	0.405	0.561	0.554	0.575
***MLXIPL* rs799161 C>T**								
Mulao								
CC	361	4.96 ± 1.11	1.07(0.77)	1.74 ± 0.51	2.94 ± 0.84	1.30 ± 0.40	0.93 ± 0.50	1.61 ± 0.82
CT	390	4.90 ± 1.17	1.03(0.75)	1.72 ± 0.44	2.88 ± 0.89	1.30 ± 0.39	1.00 ± 0.63	1.64 ± 1.19
TT	74	4.89 ± 1.20	0.97(0.71)	1.72 ± 0.51	2.92 ± 0.85	1.30 ± 0.39	0.94 ± 0.50	1.62 ± 0.72
F		0.270	0.760	0.196	0.493	0.009	1.229	0.067
P		0.763	0.383	0.822	0.611	0.991	0.293	0.935
CC	361	4.96 ± 1.11	1.07(0.77)	1.74 ± 0.51	2.94 ± 0.84	1.30 ± 0.40	0.93 ± 0.50	1.61 ± 0.82
CT/TT	464	4.89 ± 1.18	1.03(0.71)	1.72 ± 0.44	2.90 ± 0.88	1.30 ± 0.39	0.97 ± 0.62	1.63 ± 1.13
F		0.448	−1.251	0.287	0.342	0.010	0.585	0.052
P		0.503	0.211	0.592	0.559	0.920	0.444	0.820
Han								
CC	345	4.84 ± 1.08	1.02(0.83)	1.75 ± 0.65	2.78 ± 0.89	1.34 ± 0.29	0.82 ± 0.21	1.72 ± 0.54
CT	378	4.93 ± 0.94	1.05(0.90)	1.71 ± 0.38	2.88 ± 0.77	1.32 ± 0.22	0.84 ± 0.18	1.64 ± 0.46[a]
TT	58	4.97 ± 1.12	1.00(0.71)	1.65 ± 0.46	2.99 ± 1.01	1.27 ± 0.17	0.84 ± 0.20	1.60 ± 0.40
F		0.868	0.150	1.043	2.480	2.060	0.839	3.380
P		0.420	0.698	0.353	0.084	0.128	0.433	0.035
CC	345	4.84 ± 1.08	1.02(0.83)	1.75 ± 0.65	2.78 ± 0.89	1.34 ± 0.29	0.82 ± 0.21	1.72 ± 0.54
CT/TT	436	4.95 ± 0.96	1.04(0.87)	1.68 ± 0.39	2.94 ± 0.80	1.29 ± 0.21	0.84 ± 0.18	1.62 ± 0.45
F		1.479	−0.181	2.082	4.771	3.882	0.881	5.762
P		0.224	0.856	0.149	0.029	0.049	0.348	0.017
***MLXIPL* rs35332062 C>T**								
Mulao								
CC	717	4.91 ± 1.15	1.03(0.76)	1.73 ± 0.48	2.89 ± 0.88	1.29 ± 0.41	0.95 ± 0.54	1.62 ± 1.04
CT	98	4.91 ± 0.98	1.19(0.70)	1.68 ± 0.39	2.91 ± 0.73	1.34 ± 0.30	1.05 ± 0.67	1.54 ± 0.59
TT	10	5.75 ± 0.58	1.53(0.54)	1.96 ± 0.51	3.48 ± 0.52	1.74 ± 0.51[ab]	1.37 ± 1.23	1.75 ± 0.88
F		2.333	4.991	1.549	1.970	5.780	3.393	0.393
P		0.098	0.025	0.213	0.140	0.003	0.034	0.675
CC	717	4.91 ± 1.15	1.03(0.76)	1.73 ± 0.48	2.89 ± 0.88	1.29 ± 0.41	0.95 ± 0.54	1.62 ± 1.04
CT/TT	108	5.33 ± 0.98	1.22(0.80)	1.82 ± 0.40	3.19 ± 0.73	1.54 ± 0.33	1.21 ± 0.73	1.64 ± 0.62

Table 4 | Continued

Genotype	n	TC (mmol/L)	TG (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)	ApoA1 (g/L)	ApoB (g/L)	ApoA1/ApoB
F		4.206	−2.681	1.012	3.664	11.554	6.049	0.009
P		0.041	0.007	0.315	0.056	0.001	6.049	0.923
Han								
CC	692	4.89 ± 1.04	1.04(0.84)	1.71 ± 0.42	2.83 ± 0.86	1.33 ± 0.26	0.84 ± 0.20	1.67 ± 0.51
CT	83	4.99 ± 0.84	0.98(0.85)	1.88 ± 1.03	3.02 ± 0.73	1.32 ± 0.17	0.84 ± 0.15	1.64 ± 0.38
TT	6	4.29 ± 0.15	2.28(1.52)	1.41 ± 0.26	2.18 ± 0.14	1.20 ± 0.09	0.74 ± 0.05	1.66 ± 0.27
F		1.461	0.196	4.883	3.824	0.718	0.738	0.218
P		0.233	0.658	0.008	0.022	0.488	0.478	0.804
CC	692	4.89 ± 1.04	1.04(0.84)	1.71 ± 0.42	2.83 ± 0.86	1.33 ± 0.26	0.84 ± 0.20	1.67 ± 0.51
CT/TT	89	4.64 ± 0.85	0.98(0.95)	1.64 ± 1.01	2.60 ± 0.75	1.26 ± 0.17	0.79 ± 0.15	1.65 ± 0.50
F		1.258	−0.207	0.284	1.563	1.411	1.271	0.061
P		0.262	0.836	0.594	0.212	0.235	0.260	0.806
***MLXIPL* rs3812316 C>G**								
Mulao								
CC	751	4.93 ± 1.16	1.03(0.74)	1.74 ± 0.48	2.91 ± 0.88	1.30 ± 0.42	0.95 ± 0.54	1.61 ± 0.80
CG	67	4.78 ± 1.04	1.24(0.78)	1.66 ± 0.40	2.80 ± 0.75	1.32 ± 0.31	1.06 ± 0.75	1.54 ± 0.66
GG	7	4.85 ± 1.16	1.19(0.84)	2.44 ± 0.42	2.86 ± 0.72	1.33 ± 0.32	1.09 ± 0.74	1.55 ± 0.65
F		2.733	7.293	2.029	2.054	2.756	1.168	0.128
P		0.066	0.007	0.132	0.129	0.064	0.312	0.880
CC	751	4.93 ± 1.16	1.03(0.74)	1.74 ± 0.48	2.91 ± 0.88	1.30 ± 0.42	0.95 ± 0.54	1.61 ± 0.80
CG/GG	74	6.02 ± 1.07	1.25(0.77)	2.05 ± 0.42	3.60 ± 0.72	1.77 ± 0.32	1.13 ± 0.74	1.75 ± 0.65
F		3.694	−2.751	1.708	2.593	5.486	0.403	0.120
P		0.055	0.006	0.192	0.108	0.019	0.526	0.730
Han								
CC	703	4.90 ± 1.03	1.03(0.81)	1.73 ± 0.54	2.83 ± 0.85	1.33 ± 0.25	0.84 ± 0.20	1.67 ± 0.51
CG	76	4.97 ± 0.91	1.16(0.89)	1.71 ± 0.38	2.95 ± 0.78	1.30 ± 0.22	0.83 ± 0.15	1.62 ± 0.39
GG	2	4.92 ± 1.02	1.10(0.68)	1.71 ± 0.38	2.90 ± 0.78	1.31 ± 0.22	0.82 ± 0.15	1.64 ± 0.39
F		0.448	0.008	0.145	1.301	0.722	0.042	1.054
P		0.503	0.929	0.704	0.254	0.396	0.838	0.305
CC	703	4.90 ± 1.03	1.03(0.81)	1.73 ± 0.54	2.83 ± 0.85	1.33 ± 0.25	0.84 ± 0.20	1.67 ± 0.51
CG/GG	78	4.97 ± 0.91	1.16(0.89)	1.70 ± 0.38	2.95 ± 0.78	1.30 ± 0.22	0.83 ± 0.82	1.62 ± 0.39
F		0.448	−0.207	0.145	1.301	0.722	0.042	1.054
P		0.503	0.836	0.704	0.254	0.396	0.838	0.305
***MLXIPL* rs13235543 C>T**								
Mulao								
CC	704	4.90 ± 1.16	1.01(0.71)	1.74 ± 0.49	2.89 ± 0.88	1.29 ± 0.41	0.94 ± 0.53	1.65 ± 1.05
CT	114	5.02 ± 1.00	1.22(0.73)	1.70 ± 0.37	2.96 ± 0.79	1.32 ± 0.33	1.10 ± 0.70[a]	1.48 ± 0.60
TT	7	5.41 ± 1.05	1.42(2.20)	1.76 ± 0.41	3.11 ± 0.77	1.53 ± 0.35	1.32 ± 0.85	1.46 ± 0.57
F		1.093	13.227	0.488	0.511	1.299	5.094	1.498
P		0.336	3×10^{-4}	0.614	0.600	0.274	0.006	0.224
CC	704	4.90 ± 1.16	1.01(0.71)	1.74 ± 0.49	2.89 ± 0.88	1.29 ± 0.41	0.94 ± 0.53	1.65 ± 1.05
CT/TT	121	5.22 ± 1.00	1.23(0.73)	1.73 ± 0.37	3.04 ± 0.78	1.43 ± 0.33	1.21 ± 0.71	1.47 ± 0.60
F		1.741	−3.862	0.017	0.628	2.538	5.190	0.750
P		0.187	1×10^{-4}	0.897	0.429	0.112	0.023	0.387
Han								
CC	682	4.89 ± 1.03	1.05(0.88)	1.72 ± 0.54	2.83 ± 0.86	1.33 ± 0.26	0.83 ± 0.20	1.67 ± 0.51
CT	94	4.99 ± 0.85	0.98(0.75)	1.74 ± 0.36	2.97 ± 0.72	1.32 ± 0.21	0.83 ± 0.14	1.63 ± 0.37
TT	5	4.29 ± 0.15	2.28(1.52)	1.41 ± 0.26	2.17 ± 0.14	1.20 ± 0.09	0.74 ± 0.05	1.65 ± 0.27
F		1.589	0.305	0.994	3.101	0.773	0.733	0.385
P		0.205	0.581	0.370	0.046	0.462	0.481	0.680
CC	682	4.89 ± 1.03	1.05(0.88)	1.72 ± 0.54	2.83 ± 0.86	1.33 ± 0.26	0.83 ± 0.20	1.67 ± 0.51
CT/TT	99	4.64 ± 0.85	0.98(0.73)	1.57 ± 0.37	2.57 ± 0.73	1.26 ± 0.25	0.79 ± 0.14	1.64 ± 0.37
F		1.223	−0.331	1.540	1.944	1.542	1.389	0.091
P		0.269	0.741	0.215	0.164	0.215	0.239	0.763

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 ApoA1 to ApoB. The association of genotypes and serum lipid parameters (TC, HDL-C, LDL-C, ApoA1, ApoB and ApoA1/ApoB) was tested by analysis of covariance (ANCOVA). Age, sex, body mass index (BMI), smoking and alcohol consumption were adjusted for the statistical analysis. The values of triglyceride were presented as the median (interquartile range), and the difference among the genotypes was determined by the Kruskal-Wallis test or the Wilcoxon-Mann-Whitney test.

F: F value determined by analysis of covariance (ANCOVA) or U value determined by the Kruskal-Wallis test or the Wilcoxon-Mann-Whitney test.

A *P*-value of less than 0.006, adjusted by Bonferroni correction, was considered statistically significant.

[a] $P < 0.006$ in comparison with the major homozygous genotype in the same ethnic group, analyzed by post-hoc test.

[b] $P < 0.006$ in comparison with the heterozygous genotype in the same ethnic group, analyzed by post-hoc test.

China. The subjects were randomly selected from our stratified, randomized cluster samples. During the same period, 782 (307 men, 39.3% and 474 women, 60.7%) unrelated individuals of Han nationality who resided in the same villages were also randomly selected from our stratified, randomized cluster samples. All of the participants were rural agricultural workers. The ages of the subjects ranged from 15 to 80 years, with an average age of 49.18 ± 16.13 years for Mulao and 49.25 ± 16.21 years for Han. The subjects had no evidence of diseases related to kidney, thyroid, atherosclerosis, CVD and/or diabetes. None of them used lipid-lowering medication such as statins or fibrates when the blood sample was taken. All experiments were performed in accordance with relevant guidelines and regulations. Verbal informed consents and their thumbprints (to express consent) of all subjects were obtained after they received a full explanation of the study. Verbal informed consents and

Table 5 | Correlation between the genotypes of the *MLXIPL, BUD13* and *ZNF259* SNPs and serum lipid levels in the Mulao and Han populations

Lipid	SNP	Affected allele/ Other allele	Affected genotype/ Other genotype	Beta	Std. error	*t*	*P-value*
Mulao plus Han							
TC	*BUD13* rs10790162		AA, GA/GG	0.167	0.049	3.407	0.001
TG	*BUD13* rs10790162	A/G		0.248	0.048	5.163	$<1 \times 10^{-7}$
LDL-C	*BUD13* rs17119975	G/A		0.513	0.183	2.800	0.005
	BUD13 rs10790162	A/G		0.099	0.039	2.546	0.011
	BUD13 rs13235543	T/C		0.149	0.069	2.164	0.031
ApoA1	*BUD13* rs13235543		TT, CT/CC	0.097	0.031	3.093	0.002
	BUD13 rs11556024	T/C		0.060	0.027	2.234	0.025
ApoB	*BUD13* rs13235543		TT, CT/CC	0.097	0.031	3.093	0.002
	BUD13 rs10790162	A/G		0.058	0.024	2.405	0.016
ApoA1/ApoB	*BUD13* rs10790162		AA, GA/GG	−0.083	0.030	−2.754	0.006
	BUD13 rs11556024	T/C		0.133	0.051	2.611	0.009
	BUD13 rs13235543	T/C		−0.113	0.053	−2.138	0.033
Mulao							
TC	*BUD13* rs10790162		AA, GA/GG	0.200	0.071	2.836	0.005
TG	*BUD13* rs10790162		AA, AG/GG	0.292	0.062	4.744	2×10^{-5}
	BUD13 rs13235543		TT, CT/CC	0.248	0.101	2.450	0.015
	ZNF259 rs964184		GG, CG/CC	−0.401	0.192	−2.083	0.037
LDL-C	*BUD13* rs10790162	A/G		0.167	0.067	2.485	0.013
ApoA1	*MLXIPL* rs35332062		TT, CT/CC	0.510	0.155	3.284	0.001
	MLXIPL rs35332062	T/C		−0.427	0.179	−2.392	0.017
ApoB	*BUD13* rs13235543		TT, CT/CC	0.214	0.059	3.608	4×10^{-4}
ApoA1/ApoB	*BUD13* rs13235543	T/C		−0.180	0.090	−1.999	0.046
	BUD13 rs10790162	A/G		−0.124	0.063	−1.978	0.048
Han							
TC	*MLXIPL* rs799161	T/C		0.127	0.062	2.042	0.042
TG	*BUD13* rs17119975	G/A		0.308	0.081	3.826	1×10^{-4}
	BUD13 rs10790162	A/G		0.268	0.083	3.211	0.001
	BUD13 rs17119975		GG, AG/AA	−0.561	0.240	−2.340	0.020
HDL-C	*MLXIPL* rs35332062	T/C		0.788	0.127	6.218	$<1 \times 10^{-7}$
	BUD13 rs13235543	T/C		−0.407	0.116	−3.501	5×10^{-4}
	BUD13 rs11556024		TT, CT/CC	0.175	0.061	2.852	0.004
	MLXIPL rs3812316		GG, CG/CC	−0.329	0.126	−2.614	0.009
LDL-C	*MLXIPL* rs799161	T/C		0.196	0.066	2.990	0.003
ApoA1	*BUD13* rs11556024	T/C		0.095	0.028	3.465	0.001
ApoB	*BUD13* rs10790162	A/G		0.055	0.017	3.198	0.001
	ZNF259 rs2075290		GG, AG/AA	−0.048	0.020	−2.396	0.017
	BUD13 rs11556024		TT, CT/CC	−0.039	0.019	−2.018	0.044
ApoA1/ApoB	*BUD13* rs11556024		TT, CT/CC	0.182	0.050	3.642	2×10^{-4}
	BUD13 rs10790162		AA, GA/GG	−0.091	0.031	−2.974	0.003
	MLXIPL rs799161	T/C		−0.107	0.036	−2.999	0.003

Multivariable linear regression analyses with stepwise modeling were performed to assess the correlation between serum lipid levels and genotypes in Mulao, Han, and combined the Mulao and Han populations.

thumbprints were also obtained from the parents of minor participants (<18 years old) who were involved in this study. Written informed consents were not obtained because of the poor educational level of the participants. The consent procedure was also approved by the Ethics Committee of the First Affiliated Hospital, Guangxi Medical University. An incentive of approximately ten dollars was provided to each participant in the study[19–22].

Epidemiological survey and biochemical measurements. The epidemiological survey was carried out using internationally standardized methods and following a common protocol[19]. Information on demographics, socioeconomic status, and lifestyle factors was collected using standardized questionnaires. The methods of measuring blood pressure, height, weight and waist circumference parameters were based on previous studies[19]. Fasting venous blood samples were taken and the levels of serum TC, TG, HDL-C, and LDL-C in the samples were directly determined by enzymatic methods with commercially available kits, Tcho-1, TG-LH (RANDOX Laboratories Ltd., Ardmore, Diamond Road, Crumlin Co. Antrim, United Kingdom, BT29 4QY), Cholestest N HDL, and Cholestest LDL (Daiichi Pure Chemicals Co., Ltd., Tokyo, Japan); respectively. Serum ApoA1 and ApoB levels were assessed by the immunoturbidimetric assay using a commercial kit (RANDOX Laboratories Ltd.)[19,20]. 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. 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, 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[21,22].

SNP selection. We selected SNPs in the *MLXIPL*, *BUD13* and *ZNF259* genes by three criteria: (1) Tag SNPs, which were established by Haploview (Broad Institute of MIT and Harvard, USA, version 4.2) or functional or missense SNPs (http://www.ncbi.nlm.nih.gov/SNP/snp), (2) a known minor allele frequency higher than 1% in the Human Genome Project Database, and (3) the target SNP region should be adequately replicated by PCR, and the polymorphic site should have a commercially available restriction endonuclease enzyme cleavage site to be genotyped with RFLP. The detailed procedure to establish tag SNPs is as follows. We chose the Chinese Han Bejing (CHB) population as the reference population, 11 as chromosome number and 0.8 as the r^2 value in the Haploview. The software captured 122 of 122 alleles at $r^2 \geq 0.8$ and 100 percent of alleles with a mean r^2 of 0.967 in the *BUD13-ZNF259* region, using 56 Tag SNPs in 56 tests. Among the 56 tag SNPs, we finally selected those that could proxy for at least two SNPs and could be genotyped with PCR-RFLP. *BUD13* rs17119975 was the proxy for *BUD13* rs17119975, rs11216126 and rs11216129. *BUD13* rs11556024 was the proxy for *BUD13* rs11556024, rs10466588 and rs17119920. *ZNF259* rs964184 was the proxy for *BUD13-ZNF259* rs964184, rs180349, rs2266788, rs180326, rs6589566, rs651821 and rs3825041. *ZNF259* rs2075290 and *BUD13* rs10790162 were previously reported in GWASs as lipid-related loci. For the *MLXIPL* gene, we selected 3 missense SNPs (*MLXIPL* rs35332062 p.Ala358Val, rs3812316 p.Gln241His and rs13235543 p.Pro342=) that were located in the coding region of *MLXIPL* (http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?locusId=51085) and one tag SNP, *MLXIPL* rs799161 which was the proxy for *MLXIPL* rs799160 and rs799161.

Genotyping and DNA sequencing. Genomic DNA was isolated from peripheral blood leukocytes using the phenol-chloroform method[21,22]. The genotyping of 9 SNPs was performed by PCR and RFLP. The characteristics of each SNP and the details of PCR-RFLP procedure including annealing temperature, length of the PCR products and corresponding restriction enzyme used for genotyping are summarized in Supplemental Tables 1 and 2, respectively. Genotypes were scored by an experienced reader who was blinded to the epidemiological data and serum lipid results. Then, for confirmation to the RFLP results, the PCR products of the 54 samples (each 2 samples of three different genotypes for 9 SNPs from the two ethnic groups) were sequenced with an ABI Prism 3100 (Applied Biosystems) at Shanghai Sangon Biological Engineering Technology & Services Co., Ltd., People's Republic of China.

Statistical analysis. Epidemiological data were recorded on a pre-designed form and managed with Excel software. The power and sample size of the study was evaluated by Quanto 1.2 software (http://biostats.usc.edu/software). This study sample size produced a power of 0.377 for recessive model and that of 0.821 for dominant model respectively. Therefore, we mainly used the results of dominant model for the discussion. The statistical analyses were performed using the statistical software package SPSS 17.0 (SPSS Inc., Chicago, Illinois). The quantitative variables were presented as the mean ± standard deviation for continuous variables (serum TG levels were presented as medians and interquartile ranges) and as frequencies or percentages for categorical variables. Chi square tests were used to compare the differences in percentages and to assess Hardy-Weinberg expectations. General characteristics between two ethnic groups were compared by Student's unpaired *t*-test. Pair-wise linkage disequilibria and haplotype frequencies among the SNPs were analyzed using Haploview (Broad Institute of MIT and Harvard, USA, version 4.2).

The association of genotypes and serum lipid parameters (except TG) was tested by ANCOVA and the association between subgroups was tested by a post-hoc test with the adjustment of potential confounders including sex, age, education level, physical activity, blood pressure, alcohol consumption, and cigarette smoking. As the distribution of TG levels in the general population does not follow normal distribution, non-parametric tests (Kruskal-Wallis 1 way analysis of variance ANOVA for k samples and Mann-Whitney U for 2 samples) were used to determine the association between genotypes and serum TG levels. Any variants associated with the serum lipid parameter at a value of $P < 0.006$ (corresponding to $P < 0.05$ after adjusting for nine independent tests by the Bonferroni correction) were considered statistically significant. Multivariable linear regression analyses with stepwise modeling were performed (by adjusting confounders incluidng age, gender, BMI, smoking and alcohol consumption) to assess the magnitude and direction of correlation between serum lipid levels and genotypes (common homozygote genotype = 1, heterozygote genotype = 2, rare homozygote genotype = 3) or alleles (the minor allele non-carrier = 1, the minor allele carrier = 2) in Mulao, Han and combined Mulao and Han populations.

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Author contributions

L.H.H.A. participated in the design, carried out the epidemiological survey, collected the samples, undertook genotyping, performed statistical analyses, drafted the manuscript and edited the final manuscript. R.X.Y. conceived the study, participated in the design, carried out the epidemiological survey, collected the samples, helped to draft the manuscript and edited the final manuscript. D.F.W., J.Z.W., H.L. and W.W. carried out the epidemiological survey, and collected the samples. All authors read and approved the final manuscript.

Additional information

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