Associations between Squalene epoxidase gene polymorphisms and obesity (#112372)

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Associations between Squalene epoxidase gene polymorphisms and obesity

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Background: Among the known control points of cholesterol synthesis, squalene epoxidase (SQLE) is considered an important factor affecting cholesterol metabolism. Methods: A total of 1045 consecutive participants were divided into obese and control groups . Blood biochemical markers and extracted DNA from the included participants were tested. Statistical analysis was used to assess the associations of SQLE gene SNPs with obesity. Results: The C/C genotype of the SQLE gene SNP 1 (rs10104486) was significantly more strongly associated with obesity than the A/A genotype was . rs10104486 was significantly related to the genotype distribution frequency in the obesity group and control group. The difference in the distribution frequency of the genotype of the recessive model (CC vs. AC + AA) was statistically significant. SQLE gene SNP 2 (rs2288312) showed differences in genotype distribution frequency, allele frequency, and the frequency of the genotypes in the recessive model (GG vs. AA + AG) between the obese and control groups. Conclusions: The results of this study indicate a correlation between the rs10104486 and rs2288312 SQLE gene polymorphisms and obesity in a young population. Y oung participants carrying the C allele of the SQLE gene rs10104486 polymorphism were more likely to develop obesity than those carrying the A allele, and the CC genotype was a predisposing factor for obesity.

Associations between Squalene epoxidase gene polymorphisms and obesity

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Abstract

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Methods: A total of 1045 consecutive participants were divided into obese and control groups. Blood biochemical markers and extracted DNA from the included participants were tested. Statistical analysis was used to assess the associations of SQLE gene SNPs with obesity.
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Conclusions: The results of this study indicate a correlation between the rs10104486 and rs2288312 SQLE gene polymorphisms and obesity in a young population. Young participants carrying the C allele of the SQLE gene rs10104486 polymorphism were more likely to develop obesity than those carrying the A allele, and the CC genotype was a predisposing factor for obesity.

Keywords: Blood lipid metabolism, Body Mass Index, Gene, Gene polymorphisms, Obesity, Youth, Squalene epoxidase, Health Prevention

Introduction

Studies have revealed a causal relationship between low-density lipoprotein cholesterol (LDL-C) levels and obesity. An increased risk of coronary atherosclerotic heart disease (CAD) is considered associated with abnormally high LDL-C levels in obese people (Varbo, A.,et al, 2015).Dyslipidaemia is the result of the interaction of both environmental and genetic factors (Wijers, M.,et al, 2015). Abnormal cholesterol metabolism is also associated with a variety of human diseases (NCD Risk Factor Collaboration., 2017; Bouchard, C., 2021; Zhao, X., *et al,* 2022). Various studies have shown that alterations in squalene epoxgenase (SQLE), a key enzyme involved in cholesterol biosynthesis, in the cholesterol synthesis pathway are associated with various diseases associated with in cholesterol metabolism **(**Locke, A. E., *et al*, 2015; Haeusler, R. A.,*et al*, 2018; Speliotes, E. K., *et al*, 2010**).** However, genetic studies on the relationships between SQLE gene polymorphisms and obesity and blood lipid and metabolite levels are relatively rare.This study aimed to investigate the associations between lipid and metabolite levels and body mass index (BMI) and SQLE gene polymorphisms in a healthy young population.

Data and Methods

Selection and grouping of the study participants

This study was a cross-sectional survey. We measured height and weight via the standard method (Seca, Seca213) and an electronic weight scale (Seca, Seca877), which are accurate to 0.1 cm and 0.1 kg, respectively, and we calculated BMI as weight (kg)/height^2 (m^2). We double-numbered the data according to the physical examination date, from earlier to later dates, to establish a database. We used an extreme phenotype research strategy in this study to determine the LDL-C levels of people of different sexes from lower to higher levels and ultimately included 1045 participants after screening according to the inclusion and exclusion criteria. A total of 7095 healthy individuals who underwent physical examination at the Health Examination Center of Xinjiang Medical University from October to November 2018 were included in this study. In accordance with the Asia–Pacific population criteria, individuals with a physical fitness index >25 kg/m2 were included in the obese group (n=507), whereas those with a BMI 18.5~22.99 kg/m2 were included in the control group (n=538) if they met the strict inclusion and exclusion criteria. This study was approved by the Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University (approval number: 20211015-18), and all the participants provided written informed consent.

Inclusion and exclusion criteria

The inclusion criteria were as follows: 1) no respiratory system, digestive system or endocrine system disease; 2) no history of liver disease, kidney disease, or cardiovascular or cerebrovascular system disease; and 3) no history of infectious disease or other related history of surgery.The participant exclusion criteria were as follows: 1) no destruction of blood samples (such as through transportation, cold storage, extraction failure, or coagulation); 2) samples sent for DNA extraction were lost or no DNA was detected during the sequencing process; and 3) basic information and physical examination data were

missing from the general database.

Blood biochemical marker measurement and DNA extraction

All study participants were required to fast and drink only water for 8–10 h before the morning of blood collection. A 5 mL blood sample was drawn from the cubital vein. Four millilitres of this sample was used to measure total bilirubin (TBIL), blood urea nitrogen (BUN), creatinine (Cr), alanine aminotransferase (ALT), aminotransferase (AST), total cholesterol (TC), fasting blood glucose (FBG), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C) and LDL-C levels. The remaining 1 mL blood sample was used for DNA extraction, and the eligible DNA samples were genotyped via the SNPscan technique. Single-nucleotide polymorphism (SNP) site alleles were identified on the basis of the high specificity of the ligase chain reaction. We introduced different lengths of nonspecific sequences at the end of the ligation probe. Similarly, a ligase chain reaction was used to obtain ligation products of different lengths corresponding to the sites, and then, PCR was used to amplify the ligation products that were fluorescently labelled with universal primers. We then separated the amplified products via fluorescent capillary electrophoresis and used GeneMapper software to obtain the genotypes at the SNP sites.

Selection of SNP loci and detection of genetic variants

We downloaded the relevant gene sequences from the HapMap database and detected gene polymorphism loci via Haploview 4.2 software (the parameter conditions were set as r2>0.8 and minimum allele frequency [MAF] ≥0.05). We reviewed the relevant reports on the NCBI website and selected the rs10104486 (SNP 1) and rs2288312 (SNP 2) gene loci. We used SNPscan typing technology to genotype the above SNP sites, and we conducted quality control inspections through the analysis of double-blind samples and negative controls for Hardy–Weinberg equilibrium (HWE) and MAF.

Statistical analysis

PSS 26.0 statistical software was used for the statistical processing of the data. The measurement data are expressed as the means ± standard deviations ($\bar{x}\pm s$). Means were compared between two groups via the t test. One-way ANOVA was used for multigroup comparisons, and counting data were compared via the chi-square test. We performed the HWE test on the number and frequency of genotypes in two SNPs in the SQLE gene (rs10104486 and rs2288312) to confirm the population representativeness of the samples, and we compared the distribution frequencies between different genotypes via the chi-square test. Unconditional logistic regression was used to evaluate the correlation between the SQLE gene SNP and obesity (test level α=0.05). P <0.05 was considered to indicate a statistically significant difference.

Results

Comparison of the general data between the obesity group and the control group

This study included 507 obese participants (318 males and 189 females) and 538 control participants (259 males and 279 females). Compared with those in the control group, HDL-C, FBG, TG, and LDL-C levels were significantly greater in the obese group than in the control group, as were the incidence of hypertension and history of alcohol use ($P < 0.05$). There were no significant differences in diabetes incidence, smoking history or cholesterol levels between the two groups ($P > 0.05$), as shown in Table 1.

Distribution of HWE test results and genotype and allele frequencies

The genotype frequencies of two tag SNP sites (rs10104486 and rs2288312) in the SQLE gene were consistent with HWE ($P > 0.05$) in both groups and were population representative, as shown in Table 2. The frequency of SNP 1 (rs10104486) was different between the obese patients and controls, as was the frequency of the genotypes in the recessive model (CC vs. AC + AA). The differences in the distributions of genotype frequency and allele frequency and in the frequency of the genotypes in the recessive model (GG vs. AA + AG) were statistically significant ($P < 0.05$) for SNP 2 (rs2288312), as shown in Table 3.

Association between the rs10104486 genotype polymorphism and obesity

After controlling for age, sex and other factors, we found that the likelihood of obesity was significantly greater in participants with the C/C genotype of rs10104486 than in those with the A/A genotype (OR = 1.545, 95% CI=1.042--2.291, $P < 0.05$). The above results revealed that the C/C genotype can act as an independent risk factor for obesity, as shown in Table 4.

Logistic regression analysis of SQLE gene SNP 1 (rs10104486) and SNP 2 (rs2288312) in the obesity and control groups

Unconditional logistic regression was used to correct for age, HDL-C levels, sex, ethnicity, LDL-C levels, and TG levels, and the recessive model of rs10104486 (CC vs. AA + AC) and the stealth model of rs2288312 (GG vs. AA + AG) did not constitute obvious risk factors for obesity, as shown in Table 5.

Discussion

The number of people with cardiovascular diseases is increasing every year. Recently, several studies have shown that obesity and an excessive increase in LDL-C are the two main risk factors for CVD and that there is a causal relationship between CVD and these factors (Varbo, A, et al, 2015). Obesity is a metabolic syndrome that disrupts the metabolic balance of the human body. Fat accumulation occurs when the body consumes too much energy. Obesity is now considered a global epidemic that can increase the risk of a variety of diseases. In 2016, according to the World Health Organization (WHO), more than 1.9 billion adults were overweight (39% of the population), whereas more than 650 million people (13% of the population) were obese (Mandel, A. L., et al, 2010). Obesity can significantly induce various cardiovascular diseases. Previous studies have shown that environmental and genetic factors simultaneously influence the development of obesity and that BMI in the overall population is influenced by environmental factors, whereas the BMI distribution of individuals is mainly determined by genetic factors (Natarajan, P., et al, 2018).

According to the report in the Guidelines for the Prevention and Treatment of Dyslipidaemia in China (2016 Revision), the prevalence of hyperlipidaemia has gradually increased in recent years (Yuan, S., et al, 2023). Dyslipidaemia increasingly affects the development of atherosclerotic CVD. Dyslipidaemia is characterized by increased TC or LDL-C levels. Both elevated LDL-C and elevated TC are causally associated with the emergence of obesity, and one of the most important reasons for the increased risk of CAD in obese individuals is the increase (Varbo, A, et al, 2015) in LDL-C. Low TC and LDL-C levels are associated with a low incidence of atherosclerotic cardiovascular disease (Dos Santos, et al, 2022). When dyslipidaemia occurs, doctors usually recommend that individuals change their habits (such as quitting smoking, limiting alcohol use, exercising more and eating a low-fat diet) to reduce cholesterol or TGs. Approximately 70% of LDL-C in human blood enters all tissue cells through the LDLR-mediated classic endocytosis pathway, and the remainder is ingested via cell-mediated pathways, such as scavenger receptor and nonreceptor pathways (Xu, S. F., et al, 2022).

In recent years, additional research has focused on obesity, dyslipidaemia and genetic factors. Genetic polymorphisms are considered important factors of cardiovascular disease (such as early-onset coronary heart disease) (Li, Z., et al, 2023). Previous studies have shown that leptin is an anorexigenic hormone produced during adipose tissue formation. Leptin can cross the blood–brain barrier through a specific transport pathway and thereby convey information on the lipid content in adipose tissue to the hypothalamus, thus regulating lipid metabolism. The MC4R gene is involved in regulating the leptin signalling pathway. Patients with MC4R frameshift mutations develop significant SIM1 deletions that cause reduced MC4R synthesis, and these mutations also cause obesity (Guo, M., et al, 2023). The insulin signalling pathway has also been shown to be important for the regulation of energy metabolism balance. When blood glucose increases in the body, insulin secretion is activated. Several studies have shown that alterations in genes related to insulin signalling, such as HHEX-IDE, KCNQ1, MNTR1B, and GIPR, cause changes in BMI. Furthermore, AMY 1 gene mutation can affect the concentration of salivary amylase, subsequently affecting the sweetness of food and human appetite (Rask-Andersen, M., et al, 2019).

Recent studies have shown that sophisticated approaches have been developed to regulate the transcriptional and posttranslational levels of cholesterol (Howe, V., et al, 2017). The SQLE protein is found mainly in the endoplasmic reticulum. This protein is encoded by the human SQLE gene and is an important downstream cholesterol synthesis rate-limiting enzyme (Gudmundsson, J., et al, 2007; Gill, S.,

et al, 2011) located on the long arm 24.1 of human chromosome 8. Metabolic gene expression analysis clearly indicated that the reduction in and loss of SQLE expression are the causes of cellular cholesterol auxotrophy. The biological function of SQLE is to convert squalene to 2-3-oxidized squalene, which is further involved in the synthesis of sterol and cholesterol in vivo, as well as the regulation of cellular metabolism and organ specificity. Loss of this enzyme in the cholesterol synthesis pathway leads to the accumulation of the upstream metabolite squalene, which then changes the cytoplasmic profile to provide a growth advantage under oxidative stress conditions (Ma, Y. Q., et al, 2021). Several studies have shown that the protein expression of GLUT1 and LDH decreases significantly after SQLE expression is knocked down. Cell glucose consumption levels, lactate levels and ATP levels were significantly reduced after the expression of SQLE was inhibited. Some scholars have speculated that SQLE may regulate the AKT/mTOR signalling pathway and affect glucose metabolism, while lipid metabolism is also closely associated with glucose metabolism and causes changes in BMI (Speliotes, E. K., et al, 2010). At present, studies on the role of SQLE gene polymorphisms in cholesterol metabolism and the effects of these polymorphisms on obesity are in the primary stage, and identifying the specific mechanism of action of SQLE gene polymorphisms is important.

The liver is an important organ for glucose metabolism and cholesterol synthesis and metabolism and is closely related to the regulation of blood sugar and blood lipids. Both ALT and AST originate from the cytoplasm of hepatocytes. Studies have shown that elevated AST levels are associated with elevated blood glucose levels, insulin resistance and metabolic syndrome (MS), including cardiovascular disease and atherosclerosis, and that the rate of ALT abnormalities decreases with age. ALT can perform its normal physiological function in a healthy state. When hepatocytes are damaged for various reasons, ALT is released into the blood, causing abnormal ALT levels in the blood. Studies have shown that obesity, age, and HDL-C levels are factors that influence ALT (Wang, X. B., et al, 2019), whereas obesity is associated with abnormal lipid metabolism (Zhang, J., et al, 2020). Approximately 50% of LDL-C is cholesterol, and after further research, some scholars previously reported that LDL-C was positively related to ALT. These authors speculated that increased lipids (represented by TGs and TC), decreased lipid clearance ability (represented by HDL-C), and fatty liver impairment (represented by ALT) were causally related to increased serum LDL-C in patients with fatty liver.

In summary, this study reported the association between SQLE gene polymorphisms and obesity in a young population. This study found statistically significant differences in the levels of ALT, AST, TC, TG, LDL-C, HDL-C, and CREA between the obese group and the control group. The results of this study indicate a correlation between the rs10104486 and rs2288312 SQLE gene polymorphisms and obesity in a young population. Young participants carrying the C allele of the SQLE gene rs10104486 polymorphism were more likely to develop obesity than those carrying the A allele, and the CC genotype was a predisposing factor for obesity. These findings could lead to new insights at the biomolecular and genetic levels for key interventions for the prevention and treatment of fatty liver disease and cardiovascular disease in young obese people and for improving blood lipid metabolism to avoid early liver and coronary artery damage. Whether the dominant or recessive model can constitute protective or risk factors has not been determined, and the relevant mechanism has not been fully defined. Future research will clarify the relevant mechanism involved. Moreover, the sample size was relatively small, so further expanding the sample size is necessary, and the research methods should be further improved. We can study this topic in greater depth in the later stage.

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Table 1(on next page)

Comparison of general data between the obese and control groups

Table 1. Comparison of general data between the obese and control groups

Index	Control group (n=538)	Obesity group (n=507)	$t//X^2$	*P*
Sex (n (%))				
Male	259 (48.1)	318 (62.7)	22.4	< 0.001
Female	279 (51.9)	189 (37.3)		
Age (years)	20.77±1.49	20.86±1.51	-0.973	0.331
Systolic blood pressure (mmHg)	108.64±10.96	117.05±10.85	-12.449	< 0.001
Diastolic blood pressure (mmHg)	67.71±7.17	73.74±9.42	-11.687	< 0.001
HDL-C (mmol/L)	1.42±0.28	1.24±0.24	11.350	< 0.001
LDL-C (mmol/L)	2.18±0.51	2.45±0.6	-7.991	< 0.001
TGs (mmol/L)	0.84±0.35	1.16±0.71	-9.075	< 0.001
Cr (μmol/L)	76.45±11.26	80.39±15.12	-4.799	< 0.001
TC (mmol/L)	3.9±0.62	4.08±0.74	-4.158	< 0.001
FPG (mmol/L)	5±0.38	5.06±0.59	-1.753	0.084
BUN (mmol/L)	4.43±1.15	4.46±1.1	-.315	0.753
AST (U/L)	19.41±7.73	21.04±16.8	-2.026	< 0.001
ALT (U/L)	18.84±14.85	24.72±18.14	-5.745	0.047
TBIL (μmol/L)	13.92±6.21	13.54±5.64	1.054	0.292

Table 2(on next page)

Table 2. Hard–Weinberg equilibrium test results

1 **Table 2.** Hard–Weinberg equilibrium test results

Genotype	X^2	*P*
rs10104486	0.32	0.85
rs2288312	0.21	0.9

2

Table 3(on next page)

Table 3. Comparison of the distribution of the genotype and allele frequencies in each model in the obese and control groups (n(%))

Table 3. Comparison of the distribution of the genotype and allele frequencies in each model in the obese and control groups (n(%))

SNPs	Genotype	Control group	Obesity group	X^2	*P*
SNP1 (rs10104486)	AA	238 (44.24)	203 (40.04)	8.3	0.016
	AC	244 (45.35)	221 (43.59)		
	CC	56 (10.41)	83 (16.37)		
Explicit model	AA	238 (44.24)	203 (40.04)	1.9	0.17
	AC+CC	300 (55.76)	304 (59.96)		
Additive model	AC	244 (45.35)	221 (43.59)	0.329	0.57
	AA+CC	294 (54.65)	286 (56.41)		
Recessive model	CC	56 (10.41)	83 (16.37)	8.045	0.005
	AA+AC	482 (89.59)	424 (83.63)		
Allelic genes	A	720 (66.91)	627 (61.83)	5.9	0.15
	C	356 (33.09)	387 (38.17)		
SNP2 (rs2288312)	AA	236 (43.87)	204 (40.24)	6.32	0.042
	AG	237 (44.05)	214 (42.21)		
	GG	65 (12.08)	89 (17.55)		
Explicit model	AA	236 (43.87)	204 (40.24)	1.411	0.2
	AG+GG	302 (56.13)	303 (59.76)		
Additive model	AG	237 (44.05)	214 (42.21)	0.36	0.5
	AA+GG	301 (55.95)	293 (57.79)		
Recessive model	GG	65 (12.08)	89 (17.55)	6.2	0.01
	AA+AG	473 (87.92)	418 (82.45)		
Allelic genes	A	709 (65.89)	622 (61.34)	4.7	0.03
	G	367 (34.11)	392 (38.66)		

Table 4(on next page)

Table 4. Effects of the rs10104486 and rs2288312 genotype polymorphisms on the incidence of obesity

Table 4. Effects of the rs10104486 and rs2288312 genotype polymorphisms on the incidence of obesity

SNP	Group	Genotype		
		A/A	A/C	C/C
rs10104486				
	Control group	238	44	56
	Obesity group	203	221	83
	OR (95% CI)	1	1.127 (0.864~1.471)	1.545 (1.042~2.291)
	P		0.377	0.031

Table 5(on next page)

Table 5. Logistic regression analysis of SQLE gene SNP 1 (rs10104486) and SNP 2 (rs2288312) in the obesity and control groups

Table 5. Logistic regression analysis of SQLE gene SNP 1 (rs10104486) and SNP 2 (rs2288312) in the obesity and control groups

Index	*B*	*SE*	*Wald*	*OR (95% CI)*	*P*
SNP1					
Recessive model (CC vs. AA+AC)	-0.217	0.218	0.995	0.81(0.53~1.23)	0.319
Age/year	-0.037	0.049	0.561	0.96 (0.88~1.06)	0.454
Sex	-0.094	0.201	0.22	0.91 (0.61~1.35)	0.639
Nationality	0.423	0.151	7.815	1.53 (1.14~2.05)	0.005
Blood pressure	-24.381	4248.842	0	-	0.995
HDL-C (mmol/L)	4.078	0.924	19.454	59 (9.64~361.22)	< 0.001
LDL-C (mmol/L)	1.503	0.92	2.668	4.5 (0.74~27.29)	0.102
TGs (mmol/L)	-0.195	0.23	0.719	0.82 (0.52~1.29)	0.397
Cr (μmol/L)	-0.019	0.007	6.996	0.98 (0.97~1)	0.008
TC (mmol/L)	-1.885	0.833	5.121	0.15 (0.03~0.78)	0.024
FPG (mmol/L)	0.044	0.156	0.079	1.05 (0.77~1.42)	0.778
BUN (mmol/L)	0.126	0.067	3.597	1.14 (1~1.29)	0.058
AST (U/L)	-0.025	0.009	8.007	0.98 (0.96~0.99)	0.005
ALT (U/L)	0.029	0.015	3.931	1.03 (1~1.06)	0.047
TBIL (μmol/L)	0.019	0.013	2.238	1.02 (0.99~1.05)	0.135
SNP2					
Recessive model (GG vs. AA+AG)	-0.206	0.208	0.979	0.81 (0.54~1.22)	0.322
Age/year	-0.036	0.049	0.548	0.96 (0.88~1.06)	0.459
Sex	-0.093	0.201	0.213	0.91 (0.61~1.35)	0.644
Nationality	0.427	0.151	8.014	1.53 (1.14~2.06)	0.005
Blood pressure	-24.55	4224.004	0	-	0.995
HDL-C (mmol/L)	4.051	0.924	19.207	57.43 (9.39~351.46)	< 0.001
LDL-C (mmol/L)	1.473	0.92	2.56	4.36 (0.72~26.49)	0.11
TG (mmol/L)	-0.2	0.23	0.757	0.82 (0.52~1.29)	0.384
Cr (μmol/L)	-0.019	0.007	7.067	0.98 (0.97~1)	0.008
TC (mmol/L)	-1.856	0.833	4.964	0.16 (0.03~0.8)	0.026
FPG (mmol/L)	0.052	0.156	0.112	1.05 (0.78~1.43)	0.738
BUN (mmol/L)	0.128	0.067	3.663	1.14 (1~1.3)	0.056
AST (U/L)	-0.025	0.009	8.151	0.98 (0.96~0.99)	0.004
ALT (U/L)	0.03	0.015	4.117	1.03 (1~1.06)	0.042
TBIL (μmol/L)	0.019	0.013	2.29	1.02 (0.99~1.05)	0.13