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Original Article

Association of lipid metabolism relevant gene FBXW7 polymorphism with coronary artery disease in Uygur Chinese population in Xinjiang, China: a case-control

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Abstract: Background: Hyperlipidemia is a major risk factor for coronary artery disease (CAD). As F-box and WD repeat domain-containing 7 (FBXW7) gene is an important regulating factor for lipid metabolism, the aim of the present study is to assess the association between human FBXW7 gene polymorphisms and CAD among Han Chinese and Uygur Chinese populations in Xinjiang, China. Methods: A total of 1,312 Han Chinese (650 CAD patients and 662 controls) and 834 Uygur Chinese (414 CAD patients and 420 controls) were enrolled in this case-control study. Three single nucleotide polymorphisms (SNPs) rs2255137 T>C, rs2292743 A>T, rs35311955 G>C of FBXW7 were selected and genotyped using the improved multiplex ligase detection reaction (iMLDR) method. Results: We found that the rs2255137 CC genotype was very common in the CAD patients compared with the control subjects in the Uygur Chinese populations. After adjustments for several confounders: age, gender, smoking, drinking, hypertension, diabetes, TG, TC, HDL-C and LDL-C, this association remained significant. Furthermore, we investigated the relationships between rs2255137 genotypes and the circulating serum lipid levels and found that people carrying the C allele of rs2255137 may have higher serum lipid levels in the Uygur Chinese populations. Conclusion: Our results indicate that rs2255137 in FBXW7 gene is associated with CAD in the Uygur Chinese population in China.

Keywords: FBXW7, single-nucleotide polymorphisms, coronary artery disease, case-control study

Introduction

Lipid is an important energy source, components of cellular membranes and a precursor for bile acids, vitamin D, and steroid hormone [1]. A large number of epidemiological studies have confirmed a strongly positive relationship between high plasma lipid levels and coronary artery disease (CAD) [2-4]. Furthermore, accumulated evidence suggests that genetic factors such as single nucleotide polymorphisms (SNPs) give rise to 40%~60% of the variation in plasma lipid concentrations and components [5, 6].

Lipid homeostasis is mainly maintained by endogenous synthesis, intestinal absorption, biliary and fecal excretion in the human body [7]. And the endogenous synthesis is regulated by a family of transcription factors designated as sterol regulatory element-binding proteins (SREBPs) [8]. The SREBP family controls cholesterol and fatty acids (FA) synthesis by activating the expression of SREBP target genes, such as fatty acid synthase, 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, HMG-CoA synthase, and the low-density lipoprotein (LDL) receptor [9, 10].

A previous study reported that mature SREBP family members are highly unstable due to their susceptibility to ubiquitin-dependent degradation [11]. The F-box and WD repeat domain-containing 7 (FBXW7) mediates the recognition of phosphorylated substrates such as SREBPs for proteolysis as a ubiquitin-E3 ligase-targeting factor [12-14]. FBXW7 interacts with nuclear SREBP family genes and enhances their ubiquitination, which leads to their degradation [11-15]. In contrast, inactivation of endogenous

FBXW7 results in the stabilization of SREBP family genes, then induces the expression of endogenous SREBP target genes and enhances the synthesis of cholesterol and fatty acids as well as the uptake of LDL [16]. In addition, a study by Onoyama I et al. showed that FBXW7 could be an important regulator of lipogenesis and cell proliferation and differentiation in the mouse liver [14]. And another study showed that FBXW7 controls adipocyte differentiation by targeting C/EBP α for degradation, thereby, FBXW7 regulates energy and lipid metabolism [17]. Therefore, we hypothesized that the FBXW7 gene might be associated with CAD.

To date, no case-control studies have been conducted to assess the association between FBXW7 gene and CAD. Therefore, the current study was designed to clarify the relationship between polymorphism of FBXW7 (rs2255137 T>C, rs2292743 A>T, rs35311955 G>C) with CAD among Han Chinese and Uygur Chinese populations in Xinjiang, China.

Materials and methods

Subjects

This study was approved by the Ethics Committee of the First Affiliated Hospital in the Xinjiang Medical University, Xinjiang, China, and conducted according to the standards of the Declaration of Helsinki. All participants provided written informed consent of this study protocol.

Han and Uygur Chinese populations were studied independently. We enrolled a total of 1,312 Han Chinese populations (CAD=650; control =662), and 834 Uygur Chinese populations (CAD=414; control=420). All participants were recruited from the First Affiliated Hospital of Xinjiang Medical University from 2013 to 2016 and were unaffected by renal dysfunction, valvular disease and chronic inflammatory disease. The patients with CAD were diagnosed via coronary angiography, which was indicated by the presence of at least one significantly stenotic coronary artery affecting more than 50% of the luminal diameter. Participants of the control group were confirmed to be free of coronary artery stenosis also by undergoing coronary angiography. In addition, the control group participants did not show clinical or electrocardiographic evidence of myocardial infarction (MI) or CAD [18, 19]. However, some of them had cardiovascular risk factors, such as essential hypertension (EH), diabetes mellitus (DM) or hyperlipidaemia, but did not have a history of MI or CAD. Information and data regarding EH, DM, hyperlipidaemia and smoking status were collected from all study participants, and these parameters were used to match between CAD patients and controls individually.

Biological measurements and the definition of cardiovascular risk factors

Standard biochemical analyses using an AR/AVL Clinical Chemistry System (Dimension, Newark, NJ, USA) and a Sysmex XN 2000 hematology analyzer (Tokyo, Japan) were conducted at the Clinical Laboratory Department of the First Affiliated Hospital of Xinjiang Medical University. Biological parameters include serum concentrations of total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), Uric acid, blood urea nitrogen (BUN) and creatinine (Cr). Major CAD risk factors were defined based on current national guidelines. Hypertension was defined as mean SBP≥140 mmHg and/or mean DBP≥90 mmHg among 3 measurements or the use of antihypertensive drugs [20]. DM was diagnosed as fasting plasma glucose (FPG)≥6.99 mmol/L or a prior DM diagnosis and/or the use of a diabetes drug [21]. Height and body weight were measured as described previously [22], and the formula for the body mass index (BMI) is the weight in kilograms divided by height in meters squared. Smoking status was defined as currently smoking cigarettes.

DNA extraction

Blood samples were taken from all participants using the standard venipuncture technique and ethylene diamine tetraacetic acid (EDTA)-containing tubes. As previously described, DNA were extracted from peripheral blood leukocytes by using a whole blood genome extraction kit (Beijing Bioteke Corporation, Beijing, China) [23].

SNP selection

The human FBXW7 gene consists of 707 amino acids and is located on chromosome 4q31.3. It contains 17 exons, which are further separated

Table 1. General characteristics of the study participants (Han Chinese)

Variables	CAD (n=650)	Control (n=662)	*P* value
Age, (years)	57.73±7.80	58.36±7.49	0.136
BMI (kg/m^2)	25.58±3.14	25.31±3.04	0.110
Gender			0.875
Female	230 (35.4%)	237 (35.8%)	
Male	420 (64.6%)	425 (64.2%)	
Smoking status			0.004
Never	306 (47.1%)	365 (55.1%)	
Ever	344 (52.9%)	297 (44.9%)	
Drinking status			0.001
Never	403 (62.0%)	467 (70.5%)	
Ever	247 (38.0%)	195 (29.5%)	
Hypertension			<0.001
No	254 (39.1%)	356 (53.8%)	
Yes	396 (60.9%)	306 (46.2%)	
Diabetes			<0.001
No	419 (64.5%)	498 (75.2%)	
Yes	231 (35.5%)	164 (24.8%)	
TG (mmol/L)	1.83±1.15	1.78±1.16	0.404
TC (mmol/L)	4.01±1.03	3.79±1.13	<0.001
HDL-C (mmol/L)	1.06±0.30	1.11±0.33	0.011
LDL-C (mmol/L)	2.76±0.71	2.58±0.87	<0.001
Uric acid (umol/L)	314.98±85.59	319.11±80.35	0.369
BUN (mmol/L)	5.40±1.41	5.29±1.55	0.168
Cr (mmol/L)	73.40±16.18	72.37±18.29	0.281

BMI body mass index, TG triglyceride, TC total cholesterol, HDL-C high density lipoprotein cholesterol, LDL-C low density lipoprotein cholesterol, BUN blood urea nitrogen, Cr creatinine. The *P* value of the continuous variables was calculated by the independent-sample t-test. The *P* value of the categorical variables was calculated by X^2 test.

by 16 introns. In the present study, we screened the 1000 Genomes (http://www. 1000genomes. org/) and Haploview 4.2 software and selected three SNPs (rs 2255137 T>C, rs2292743 A>T, rs35311955 G>C). As a cutoff, each of them conforms to the standards of minor allele frequency (MAF) ≥0.05 and linkage disequilibrium patterns with r^2≥0.8.

Genotyping

Genotyping the SNPs by using an improved multiplex ligase detection reaction method (iMLDR, Genesky Bio-Tech Cod., Ltd., Shanghai, China) as previously described [24]. We genotyped the selected SNP loci in one ligation reaction. Two multiplex PCR reactions were designed to amplify fragments covering all SNP loci. The PCR reaction mixture (20 μl) contained 1 × GC-I buffer (Takara), 3.0 mM Mg^{2+}, 0.3 mM dNTP, 1 U HotStarTaq polymerase (Qiagen Inc), 1 μl of sample DNA and 1 μM of each primer. The PCR programme for both reactions was 95°C, 2 min; 11 cycles × (94°C, 20 s; 65°C/cycle, 40 s; 72°C, 1 min 30 s); 24 cycles × (94°C, 20 s; 59°C, 30 s; 72°C, 1 min 30 s); 72°C, 2 min; hold at 4°C. The ligation cycling programme was carried out in 1 μl of 10 × binding buffer, 0.25 μl of thermostable Taq DNA ligase, 0.4 μl of 5' ligation primers mixture (1 μM), 0.4 uL of 3' ligation primers mixture (2 μM), 2 μl of purified multiplex PCR product, 6 μl of double distilled H_2O. The reaction mixtures were subjected to 38 cycles × (94°C, 1 min; 56°C, 4 min); hold at 4°C. Half a microliter of the reaction mixtures were denatured at 95°C for 5 minutes in 9 μl Hi-Di formamide along with 0.5 μl of the LIZ-500 SIZE STANDARD, and run on the ABI 3730XL and the raw data were analyzed by GeneMapper 4.1 (Applied Biosystems, USA). All primers, probes and labelling oligos were designed by and ordered from Genesky Biotechnologies Inc. DNA sequencing was used to validate the genotyping by ligation detection reaction method. Results of ligation detection reaction corresponded with the results of sequencing for the randomly selected DNA samples from each genotype.

Statistical analysis

All continuous variables were expressed by mean ± standard deviation (SD), and the participants in the CAD and control groups were compared using an independent-sample t-test. Numbers and percentages (%) were used to show the categoric variables and the distribution of genotypes and models, and the two groups were compared by the χ^2 test or Fisher's exact test. In addition, to compensate for multiple comparisons of genotypes, we applied Bonferroni's correction in the statistical analysis. The Hardy-Weinberg equilibrium (HWE) was evaluated using SNP Stats (available online at http://bioinfo. iconcologia. net/SNPstats). Moreover, logistic regression analysis was performed to assess the contribution of a certain model of variants rs2255137 T>C, rs2292743 A>T and rs35311955 G>C of FBXW7 to CAD. To determine the strength of the association between SNPs and CAD, we calculated the

Table 2. General characteristics of the study participants (Uygur Chinese)

Variables	CAD (n=414)	Control (n=420)	*P* value
Age, (years)	58.00±7.56	57.63±7.48	0.476
BMI (kg/m^2)	26.91±3.34	26.85±3.89	0.794
Gender			0.545
Female	98 (23.7%)	107 (25.5%)	
Male	316 (76.3%)	313 (74.5%)	
Smoking status			0.029
Never	278 (67.1%)	311 (74.0%)	
Ever	136 (32.9%)	109 (26.0%)	
Drinking status			0.004
Never	300 (72.5%)	340 (81.0%)	
Ever	114 (27.5%)	80 (19.0%)	
Hypertension			<0.001
No	164 (39.6%)	225 (53.6%)	
Yes	250 (60.4%)	195 (46.4%)	
Diabetes			<0.001
No	238 (57.5%)	321 (76.4%)	
Yes	176 (42.5%)	99 (23.6%)	
TG (mmol/L)	2.03±1.19	1.79±1.40	0.007
TC (mmol/L)	4.15±1.13	3.99±0.91	0.029
HDL-C (mmol/L)	0.90±0.33	1.00±0.33	<0.001
LDL-C (mmol/L)	2.88±0.60	2.62±0.43	<0.001
Uric acid (umol/L)	315.12±85.71	302.28±73.95	0.021
BUN (mmol/L)	5.52±1.85	5.48±1.76	0.716
Cr (mmol/L)	75.92±21.31	72.13±15.95	0.004

BMI body mass index, TG triglyceride, TC total cholesterol, HDL-C high density lipoprotein cholesterol, LDL-C low density lipoprotein cholesterol, BUN blood urea nitrogen, Cr creatinine. The *P* value of the continuous variables was calculated by the independent-sample t-test. The *P* value of the categorical variables was calculated by X^2 test.

odds ratios and 95% CI. After adjustments for age; gender; plasma concentrations of TG, TC, HDL-C, LDL-C; diabetes; hypertension; drinking and smoking habits, a multivariate analysis was performed. All statistical analyses were performed using SPSS version 22.0 for Windows (SPSS Inc., USA), and statistical significance was established at two-tailed *P*-values of 0.05.

Results

General characteristics of the study participants

The present study consisted of two ethnic groups (Han and Uygur Chinese population). The general characteristics of the Han Chinese population are listed in **Table 1**. There were 650 patients with CAD and 662 healthy controls. Among the CAD patients, 230 (35.4%) were women and 420 (64.6%) were men, and the mean age of all CAD patients was 57.73±7.80 years old. Among the controls, 237 (35.8%) were women and 425 (64.2%) were men, and the mean age of all controls was 58.36±7.49 years old. There were significant differences in the following parameters between the CAD and control groups, such as smoking (P=0.004), drinking (P=0.001), hypertension (P<0.001), diabetes (P<0.001), TC (P<0.001), HDL-C (P=0.011) and LDL-C (P<0.001). However, no significant differences were found in age (P=0.136), gender (P=0.875), BMI (P=0.110), TG (P=0.404), uric acid (P=0.369), BUN (P=0.168) and Cr (P=0.281) levels.

The general characteristics of the Uygur Chinese population are listed in **Table 2**. There were 414 patients with CAD and 420 healthy controls. Among the CAD patients, 98 (23.7%) were women and 316 (76.3%) were men, and the mean age of all CAD patients was 58.00±7.56 years old. Among the controls, 107 (25.5%) were women and 313 (74.5%) were men, and the mean age of all controls was 57.63±7.48 years old. There were significant differences in the following parameters between the CAD and control groups, such as smoking (P=0.029), drinking (P=0.004), hypertension (P<0.001), diabetes (P<0.001), TG (P=0.007), TC (P=0.029), HDL-C (P<0.001), LDL-C (P<0.001), uric acid (P=0.021) and creatinine (Cr, P=0.004) levels. However, we did not observe significant differences between patients and controls regarding age (P=0.476), gender (P=0.545), BMI (P=0.794) and BUN (P=0.716).

The genotype distribution of selected SNPs in CAD patients and controls

Tables 3 and **4** show the genotype distributions of selected SNPs in patients with CAD and control participants. In the Han Chinese and Uygur Chinese populations, the genotype distributions of the three SNPs for both CAD patients and controls were in accordance with the Hardy-Weinberg equilibrium (data not shown).

Table 3. The distribution of genotypes and alleles in patients with CAD and control participants (Han Chinese)

Genotype	CAD (n, %)	Control (n, %)	P[a]	Crude OR (95% CI)	P	Adjusted OR (95% CI)[b]	P[b]
rs2255137 T>C			0.386				
TT	214 (32.9%)	207 (31.3%)		1.00		1.00	
CT	296 (45.5%)	326 (49.2%)		1.050 (0.773-1.426)	0.756	1.058 (0.770-1.454)	0.726
CC	140 (21.5%)	129 (19.5%)		0.878 (0.686-1.125)	0.304	0.907 (0.702-1.172)	0.456
Dominant model	434 (66.8%)	457 (69.0%)	0.380	1.109 (0.880-1.399)	0.380	1.079 (0.848-1.371)	0.536
Recessive model	503 (77.4%)	533 (80.5%)	0.164	1.207 (0.925-1.575)	0.165	1.189 (0.902-1.568)	0.219
Additive model	363 (55.8%)	334 (50.5%)	0.050	0.805 (0.648-1.000)	0.050	0.834 (0.666-1.044)	0.114
rs2292743 A>T			0.653				
AA	180 (27.7%)	185 (27.9%)		1.00		1.00	
TA	300 (46.2%)	318 (48.0%)		0.910 (0.675-1.226)	0.535	0.920 (0.675-1.252)	0.595
TT	170 (26.2%)	159 (24.0%)		0.882 (0.675-1.153)	0.359	0.941 (0.713-1.241)	0.665
Dominant model	465 (71.5%)	477 (72.1%)	0.836	1.026 (0.807-1.305)	0.836	0.996 (0.777-1.278)	0.976
Recessive model	475 (73.1%)	503 (76.0%)	0.227	1.166 (0.909-1.495)	0.227	1.109 (0.857-1.435)	0.430
Additive model	360 (55.4%)	344 (52.0%)	0.214	0.871 (0.701-1.083)	0.214	0.927 (0.740-1.161)	0.507
rs35311955 G>C			0.138				
GG	338 (52.0%)	362 (54.7%)		1.00		1.00	
GC	252 (38.8%)	258 (39.0%)		1.530 (1.004-2.332)	0.048	1.391 (0.900-2.151)	0.138
CC	60 (9.2%)	42 (6.3%)		1.046 (0.833-1.314)	0.699	1.037 (0.819-1.314)	0.761
Dominant model	312 (48.0%)	300 (45.3%)	0.330	0.898 (0.723-1.115)	0.330	0.918 (0.733-1.150)	0.457
Recessive model	590 (90.8%)	620 (93.7%)	0.051	1.501 (0.996-2.262)	0.052	1.370 (0.896-2.094)	0.146
Additive model	398 (61.2%)	404 (61.0%)	0.940	0.991 (0.794-1.238)	0.940	0.995 (0.791-1.253)	0.969

a, X^2 test for genotype distributions between myocardial infarction patients and controls; b, Adjusted for age, gender, smoking, drinking, hypertension, diabetes, triglyceride, total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol.

In the Han Chinese population, there were no significant differences in the distribution of genotypes and genetic models (dominant, recessive and additive) for variants in rs 22-55137 T>C, rs2292743 A>T and rs35311955 G>C of FBXW7 between the CAD patients and control groups.

In the Uygur Chinese population, we found that the distribution of 2255137 T>C genotypes and dominant model (TT vs. CC+CT) showed significant difference between CAD patients and control subjects (P=0.047, P=0.013 respectively). Nevertheless, the difference of the distribution of genotypes (P=0.047) was no longer significant after Bonferroni's correction (P>0.05/3= 0.0167). But the recessive model (CC vs. TT+CT) and additive model (CT vs. TT+CC) showed no significant difference between CAD patients and control subjects (P=0.454, P=0.146 respectively). In addition, multiple logistic regression analysis showed that compared to non-carriers, carriers of rs 2255137 C allele had a significantly elevated CAD risk [CC vs. TT: adjusted odds ratio (AOR)=1.585, 95% CI=1.040-2.417; TT vs. CC/CT: AOR=1.517, 95% CI=1.073-2.146] after adjustment for age, gender, smoking, drinking, hypertension, diabetes, TG, TC, HDL-C and LDL-C. However, the distribution of rs2292743 A>T genotypes, dominant model (AA vs. TT+TA), recessive model (TT vs. AA+TA) and additive model (TA vs. AA+TT) showed no significant difference between CAD patients and control subjects (all P>0.05, respectively). Similarly, the distribution of rs35311955 G>C genotypes, dominant model (GG vs. CC+GC), recessive model (CC vs. GG+GC) and additive model (GC vs. GG+CC) showed no significant difference between CAD patients and control subjects (all P>0.05, respectively).

Relationship between FBXW7 genetic polymorphism and serum lipid level

To further investigate the functional role of the FBXW7 polymorphism, we adjusted age and gender, then compared the concentrations of

Table 4. The distribution of genotypes and alleles in patients with CAD and control participants (Uygur Chinese)

Genotype	CAD (n, %)	Control (n, %)	P[a]	Crude OR (95% CI)	P	Adjusted OR (95% CI)[b]	P[b]
rs 2255137 T>C			0.047				
TT	114 (27.5%)	85 (20.2%)		1.00		1.00	
CT	198 (47.8%)	222 (52.9%)		0.988 (0.711-1.373)	0.943	1.068 (0.746-1.528)	0.721
CC	102 (24.6%)	113 (26.9%)		1.486 (1.008-2.190)	0.045	1.585 (1.040-2.417)	0.032
Dominant model	300 (72.5%)	335 (79.8%)	0.013	1.498 (1.086-2.065)	0.014	1.517 (1.073-2.146)	0.018
Recessive model	312 (75.4%)	307 (73.1%)	0.454	0.888 (0.651-1.212)	0.454	0.826 (0.588-1.159)	0.268
Additive model	216 (52.2%)	198 (47.1%)	0.146	0.818 (0.623-1.073)	0.146	0.854 (0.636-1.146)	0.292
rs2292743 A>T			0.173				
AA	145 (35.0%)	154 (36.7%)		1.00		1.00	
TA	191 (46.1%)	207 (49.3%)		0.712 (0.474-1.070)	0.102	0.677 (0.435-1.056)	0.086
TT	78 (18.8%)	59 (14.0%)		0.698 (0.472-1.032)	0.072	0.733 (0.480-1.121)	0.152
Dominant model	269 (65.0%)	266 (63.3%)	0.621	0.931 (0.701-1.236)	0.621	0.855 (0.627-1.164)	0.319
Recessive model	336 (81.2%)	361 (86.0%)	0.062	1.420 (0.982-2.055)	0.063	1.410 (0.944-2.105)	0.093
Additive model	223 (53.9%)	213 (50.7%)	0.362	0.881 (0.672-1.157)	0.363	0.957 (0.713-1.286)	0.772
rs35311955 G>C			0.335				
GG	281 (67.9%)	296 (70.5%)		1.00		1.00	
GC	120 (29.0%)	117 (27.9%)		1.956 (0.769-4.974)	0.159	2.535 (0.929-6.914)	0.069
CC	13 (3.1%)	7 (1.7%)		1.080 (0.798-1.462)	0.616	1.004 (0.724-1.393)	0.980
Dominant model	133 (32.1%)	124 (29.5%)	0.416	0.885 (0.660-1.188)	0.416	0.926 (0.674-1.272)	0.636
Recessive model	401 (96.9%)	413 (98.3%)	0.164	1.913 (0.755-4.843)	0.171	2.532 (0.932-6.882)	0.069
Additive model	294 (71.0%)	303 (72.1%)	0.718	1.057 (0.782-1.428)	0.718	0.977 (0.705-1.353)	0.889

a, X^2 test for genotype distributions between myocardial infarction patients and controls; b, Adjusted for age, gender, smoking, drinking, hypertension, diabetes, triglyceride, total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol.

serum lipid levels between each rs2255137 genotype of control and CAD patients in the Uygur Chinese population. The TG concentrations were significantly higher in CAD patients than control subjects in those with the rs2255137 CC genotype (2.231 mmol/L vs. 1.657 mmol/L). The TC concentrations were significantly higher in CAD patients than control subjects in those with the rs2255137 CC genotype (4.248 mmol/L vs. 3.878 mmol/L). The HDL-C concentrations were significantly lower in CAD patients than control subjects in those with the rs2255137 CT genotype (0.884 mmol/L vs. 1.005 mmol/L). The LDL-C concentrations were significantly higher in CAD patients than control subjects in those with the rs2255137 CT and CC genotypes (2.836 mmol/L vs. 2.620 mmol/L and 2.936 mmol/L vs. 2.570 mmol/L) (**Figure 1**).

Discussion

In the current study, we found that variation in FBXW7 gene is associated with CAD in the Uygur Chinese population but were not associated with CAD in the Han Chinese population. To the best of our knowledge, this is the first endeavor to study the common allelic variant in FBXW7 gene and it's association with CAD.

FBXW7 is a tumour suppressor. Previous studies have indicated that mutations in this gene are related to several cancers, including breast, endometrial, ovarian, colon and lung cancer [25-27]. FBXW7 had been shown as playing a role of regulating lipid metabolism by Onoyama I et al. It is not only from the point of view of basic biology but also from the medical standpoint referring that FBXW7 plays key roles in regulating lipogenesis and cell proliferation and differentiation in the liver [14]. And another study indicated that FBXW7 is a negative regulator of adipogenesis by targeting phosphorylated C/EBP α for proteasome-mediated degradation. FBXW7 inhibits C/EBP α -dependent transcription and inactivation of FBXW7 results in the accumulation of C/EBP α. Importantly, inactivation of FBXW7 in mouse

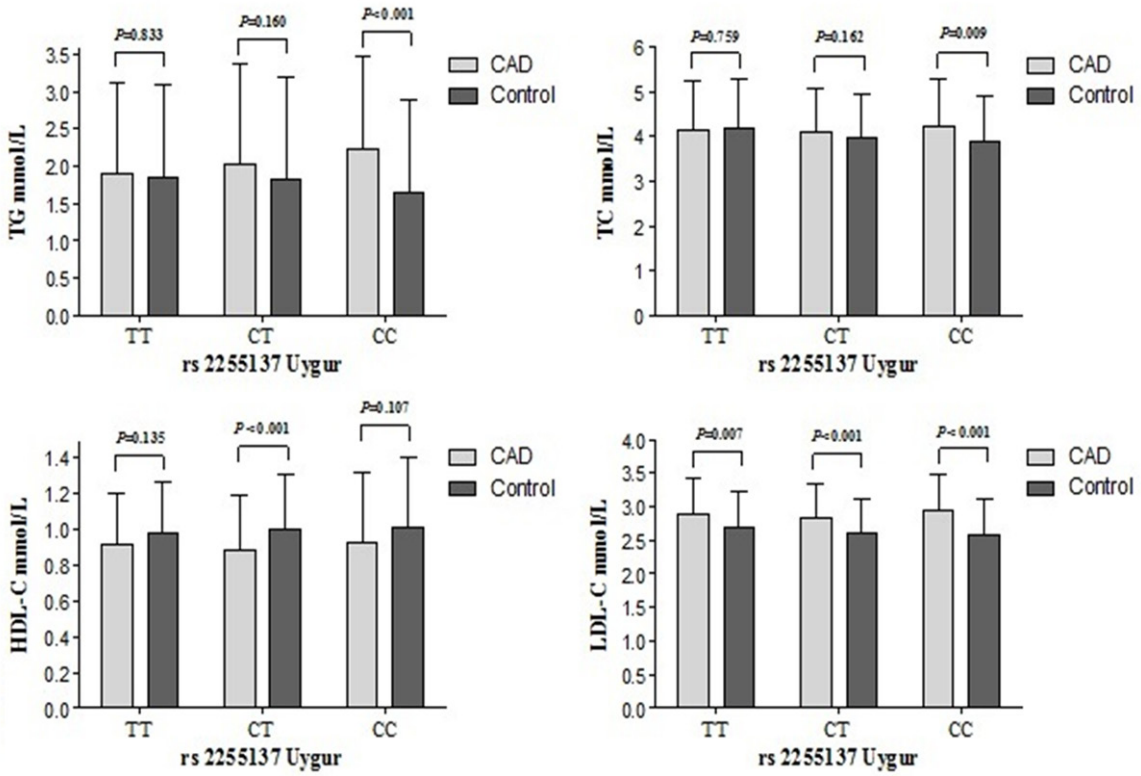

Figure 1. Circulating serum lipid levels between CAD patients and control subjects in the Uygur Chinese population. Circulating serum lipid levels after adjustment for gender and age (mean ± SD) between each rs2255137 genotype of CAD patients and control subjects in the Uygur Chinese population (CAD: TT:114; CT:198; and CC:102; controls: TT:85; CT:222; and CC:113). TG triglyceride, TC total cholesterol, HDL-C high density lipoprotein cholesterol, LDL-C low density lipoprotein cholesterol.

preadipocytes and adult human stem cells enhances their differentiation into mature adipocytes. Taken all together, their results suggest that FBXW7 is an important regulator of adipocyte differentiation [17]. In addition, as previously mentioned, inactivation of FBXW7 results in the accumulation of transcriptionally active SREBP family and enhanced expression of SREBP family target genes, most of which are involved in lipid metabolism. Suggesting that FBXW7 could regulate blood lipids [13]. Accumulative studies have established that disorders of lipid metabolism are involved in the pathogenesis of CAD [28, 29]. Therefore, we hypothesized that the FBXW7 gene might be associated with CAD. However, the relationship between the FBXW7 gene and cardiovascular diseases has not yet been studied.

In the present study, we performed two independent case-control studies to observe the relationship between rs2255137 and CAD. We found that the rs2255137 CC genotype was very common in the CAD patients compared with the control subjects in the Uygur Chinese populations. After adjustments for several confounders: age, gender, smoking, drinking, hypertension, diabetes, TG, TC, HDL-C and LDL-C, this association remained significant, indicating that the rs2255137 CC genotype is an independent risk factor for CAD. Furthermore, we investigated the relationships between rs2255137 and the circulating serum lipid levels and found that people carrying the C allele of rs2255137 may have higher serum lipid levels in the Uygur Chinese populations.

Our results identified a significant association of FBXW7 variant with CAD in the Uygur Chinese population, but not in the Han Chinese population. The possible reasons for this difference may be due to the following aspects: Firstly, it may be due to the interaction between ethnic differences and environmental factors; the Uygur population is a relatively isolated group, accounting for approximately 47% of the total population in Xinjiang, China. Their eating habits and lifestyles are more consistent and dif-

ferent from that of the Han Chinese population [30]. For example, the Uygur Chinese population primarily ingest high calorie foods, such as pasta, nuts, beef, mutton, and milk products, and exhibit a low intake of vegetables, fruit and rice compared to the Han Chinese population. Secondly, ethnic differences may also contribute to the different results between Han Chinese and Uygur Chinese populations. Thirdly, if we consider the genetic diversity across different populations, the extent of linkage disequilibrium among the genetic variants are likely to vary, and this could also explain our study results in a certain degree.

Despite the promising findings in this study, several limitations should be mentioned. First of all, when participants were recruited from our hospital, we did not collect dietary information despite understanding that dietary information may be insightful. In addition, the Uygur Chinese population is an admixed population that mainly lives in the Xinjiang Uygur Autonomous Region of China, and there is a lack of individual genetic background information. Eventually, because of the time limitation, we conducted a retrospective study. Therefore, a prospective cohort study should be conducted over a reasonably long time period.

In conclusion, the rs2255137 polymorphism of the FBXW7 gene is associated with CAD in the Uygur Chinese population in China. This relationship is independent of serum levels of lipid and other determinants of CAD risk. However, our results need to be verified by a larger sample sized, multicentre, case-control study.

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Disclosure of conflict of interest

None.

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