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Association of the LPA gene polymorphisms with coronary artery disease risk in the Xinjiang population of China

A case–control study

Yi-Wen Liu, MM[a], Chun-Lan Dong, MM[a], Xue Jiang, BS[b], Deng-Yao Liu, MM[c,*]

Abstract

Lipoprotein(a) is a well-known independent risk factor for coronary artery disease (CAD) and primarily determined by variation in the LPA gene coding for the apolipoprotein(a) moiety. Our study purpose was to evaluate the association between the human LPA gene polymorphisms and CAD in Han and Uyghur populations in Xinjiang, China. A case–control study was conducted with 831 Han people (392 CAD patients and 439 control subjects) and 829 Uygur people (513 CAD patients and 316 control subjects). All participants were genotyped for the same 3 single nucleotide polymorphisms (rs1801693, rs6923877, and rs9364559) of the LPA gene by a Real-time PCR instrument. In CAD patients, the levels of lipoprotein(a) were significantly higher in the Han population with the C/C genotype at the rs1801693 ($P = .018$) and the A/A genotype at the rs9364559 ($P = .029$) than in the Uyghur population. The polymorphisms rs1801693, rs6923877, and rs9364559 were found to be associated with CAD in the Han population. For men, the distribution of rs1801693 in genotypes, alleles and recessive model (CC vs CT + TT) showed a significant difference (all $P < .05$), and the difference in recessive model was retained after adjustment for covariates (odds ratio [OR]: 0.557, 95% confidence interval [CI]: 0.355–0.874, $P = .011$). But the distribution of rs6923877 in genotypes and dominant model (GG vs AG + AA) showed a significant difference (both $P < .05$) in both men and women, and the difference was kept in dominant model after adjustment (OR: 1.473, 95% CI:1.009–2.148, $P = .045$). For women, a significant difference was found in the distribution of rs9364559 in the alleles and dominant model (AA vs AG + GG) (for alleles: $P = .021$, for dominant model: $P = .025$, OR: 0.560, 95% CI:0.350–0.898, $P = .016$) after adjustment. Polymorphisms rs1801693, rs6923877, and rs9364559 of the LPA gene are associated with CAD in the Han population in Xinjiang Uygur Autonomous Region of China.

Abbreviations: apo(a) = apolipoprotein(a), CAD = coronary artery disease, CHP = Chinese Han population, CI = confidence interval, DBP = diastolic blood pressure, DM = diabetes mellitus, EH = essential hypertension, Lp(a) = lipoprotein(a), OR = odds ratio, SBP = systolic blood pressure, SD = standard deviation, SNPs= single nucleotide polymorphisms.

Keyword: case–control study, coronary artery disease, lipoprotein(a), LPA, single nucleotide polymorphisms.

1. Introduction

Coronary artery disease (CAD) is a contributor to global mortality,[1,2] which is felt to be largely preventable. CAD has been regarded as a complex, multifactorial, and polygenic disorder, especially resulting from several susceptibility genes and multiple environmental determinants.[2,3] Epidemiological studies have found that East Asians are significantly less likely to develop or die from CAD compared to Caucasians. Additionally, a range of cardiac CT features describe racial differences in CAD.[4] CAD is a complex inflammatory disease involving genetic influences on multiple cell types.[5] Studies have repeatedly documented that genetic predisposition is an important risk contributor to the etiology and pathogenesis of CAD, accounting for 40% to 60% of the risk.[6] In recent years, genome-wide association studies have paid close attention to CAD, and various gene variants have been found to be associated with CAD.[7]

Y-WL and C-LD contributed equally to this work.

Written informed consent was obtained from all the subjects.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

This study was approved by the Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University (20120220-55) and conducted according to the standards of the Declaration of Helsinki concurrently.

[a] *Oncology-Cardiology Department, Xinjiang Tumor Hospital Affiliated to Xinjiang Medical University, Urumqi, Xinjiang, China,* [b] *Pain Medicine Department, Xinjiang Tumor Hospital Affiliated to Xinjiang Medical University, Urumqi, Xinjiang, China,* [c] *Interventional Consulting Department, Xinjiang Tumor Hospital Affiliated to Xinjiang Medical University, Urumqi, Xinjiang, China.*

** Correspondence: Deng-Yao Liu, Interventional Consulting Department, Xinjiang Tumor Hospital Affiliated to Xinjiang Medical University, Urumqi, Xinjiang, China (e-mail: liudy9321@126.com).*

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Lipoprotein(a) [Lp(a)] was discovered in 1963 by Berg[8] and since then, numerous epidemiologic and genetic investigations have demonstrated elevated levels of Lp(a) as an independent risk factor for CAD.[9,10] Lp(a), like low-density lipoprotein (LDL), consists of cholesterol, cholesterol esters, phospholipids, triglycerides, and apolipoprotein B100 (ApoB), but also contains a unique apolipoprotein(a) [apo(a)].[11] Lp(a) is secreted exclusively from the liver and is involved in atherosclerosis and thrombosis; its site of catabolism in humans is yet unknown.[12] Plasma levels of Lp(a) are very highly heritable, ranging from 90 to 95%.[13] Over 90% of the variation in plasma Lp(a) concentrations is explained by the apo(a) gene polymorphisms.[14]

The LPA gene on the chromosome 6q26–27 in human, encoding apo(a) of the Lp(a) lipoprotein particle, has been demonstrated strongly associated with the risk for CAD.[15] The KIV-2 size polymorphism, a copy number variant of LPA gene, makes for a large number of differently sized isoforms of apo(a). In addition, it has been shown to exert a major influence on plasma Lp(a) levels and to explain 10–80% of the total concentration variation.[16,17] Strong research has been done to link a few LPA single nucleotide polymorphisms to CAD; these studies have mostly focused on haplotypes, genotypes, alleles, and the dominant/recessive model. The common LPA variants rs10455872 and rs3798220 have been shown to be strongly and independently associated with higher Lp(a) levels and increased CAD risk.[18] According to the study of Song et al,[19] rs9364559-G in the LPA gene has an association with increased risk of CAD in the Chinese Han population (CHP). However, the relationship between the various LPA gene polymorphisms and CAD remains unclear. The aim of our study is to investigate the association between the LPA gene polymorphisms and CAD in the Han and Uygur population in Xinjiang, China.

2. Methods

2.1. Ethical approval of the study protocol

This study was approved by the Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University (20120220-55) and conducted following the Declaration of Helsinki concurrently. Written informed consent was obtained from all the subjects, who explicitly provided permission for DNA analyses as well as for the collection of relevant clinical data without payment.

2.2. Subjects

The participants were from the Han and Uygur people living in the Xinjiang Uygur Autonomous Region in Northwest China. Both selected patients and controls were the inpatients with a differential diagnosis for chest pain at the Cardiac Catheterization Laboratory of the First Affiliated Hospital of Xinjiang Medical University from 2010 to 2014. In this study, we randomly sampled 392 Han CAD patients and 513 Uygur CAD patients. 439 Han Chinese and 316 Uygurs were matched as control groups in racial and geographical.

The inclusion criteria for the CAD group are as follows: the diagnosis of CAD conforms to the World Health Organization diagnostic criteria for coronary Atherosclerosis heart disease, that is, 2 or more experts perform coronary angiography at the same time to verify that at least one or more coronary arteries are narrowed by at least 50%. As for the exclusion criteria: patients with (1) incomplete clinical data; (2) congenital heart defect, heart valve disease, aortic dissection, cardiomyopathy; (3) liver or kidney dysfunction; (4) tumors or autoimmune disease, or individuals with mental system disorders who cannot cooperate.

The report of coronary angiography was interpreted by at least 2 experienced imaging specialists and undertaken by highly skilled physicians using the Judkins approach. The control subjects also underwent a coronary angiogram but did not show coronary artery stenosis as well as clinical or electrocardiogram evidence of myocardial infarction or CAD. Data and information about the known coronary risk factors (including hypertension, diabetes mellitus [DM], hyperlipidemia, Lp(a) level and smoking) and other biochemical indices were collected from all study participants. The diagnosis of hypertension was established if the mean of 3 measurements of systolic blood pressure (SBP) ≥ 140 mm Hg and/or diastolic blood pressure (DBP) ≥ 90 mm Hg or if patients were on antihypertensive medication. Diabetes mellitus and hyperlipidemia were defined on the basis of the World Health Organization criteria. Smoking was classified as smokers (including current and ex-smokers) or nonsmokers. Patients with congenital heart disease, valvular disease, multiple organ failure syndrome, malignancy or chronic inflammatory disease were eliminated from our study.

For the Control group, the inclusion criteria include: (1) hospitalized patients in the same period as the CAD group; (2) without a history of angina, coronary heart disease, or myocardial infarction; (3) with normal electrocardiogram, exercise treadmill stimulation test, and cardiac ultrasound results; (4) without abnormalities in laboratory serological myocardial markers; and (5) coronary angiography results indicating negative or <50% coronary stenosis. Exclusion criteria: patients (1) with incomplete clinical data, and/or receiving previous coronary stent implantation, surgical heart bypass grafting, and cervical vascular stent implantation; (2) with liver or kidney dysfunction; (3) with tumors or autoimmune diseases; or (4) individuals with mental system disorders who cannot cooperate.

2.3. Sample size calculation

The subjects in the control group were not completely healthy. They may have risk factors of coronary heart disease, such as hypertension, diabetes, hyperlipidemia, but they had no history of other heart related diseases such as myocardial infarction. The score of the modified Rankin scale is 0.

The sample size is calculated using the following formula:

$$n = 2\ \overline{pq}(\mu_\alpha + \mu_\beta)^2/(p_1 - p_0)^2$$

Estimation of minimum sample size, P0 = exposure rate of the control group; P1 = case group exposure rate; P Å = (p1 + p0)/2. In the preexperiment of this study, it was found that the exposure rate of the control group was p0 = 0.3, and the relative risk was 1.5. Therefore, the estimated sample size was n = 303. To explore the correlation between LPA gene polymorphisms and CAD, the confidence level was maintained at 95%, the test efficacy at 0.9, $\alpha = 0.05$ (bilateral), and $\beta = 0.10$; the sample size is 255 cases required for both the CAD group and the control group. Considering the current international requirements for the study of the association between gene polymorphisms and diseases as well as the possible factors (insufficient concentration of DNA extraction and failure of Genotyping) during the experiment, this study appropriately increased the sample size of the Han Chinese to 400 cases in the CAD group and 400 cases in the control group, and appropriately increased the sample size of the Uygurs to 400 cases in the CAD group and 400 cases in the control group. Therefore, 392 cases in the Han CAD group and 439 cases in the control group were the samples with the final successful typing and complete data, and there are 513 cases in the Uyghur CAD group and 316 cases in its control group.

2.4. Clinical measurements

Blood pressure was measured in a seated position using a standard mercury sphygmomanometer on the left arm, and no tea,

coffee, or smoking was allowed for 1 hour prior to the measurement. The first and fifth stages of Korotkoff sound were used for the measurement of SBP and DBP, respectively. SBP and DBP were calculated from 2 readings with a minimum interval of 10 minutes. Hypertension was defined as SBP ≥ 140 mm Hg and/or DBP ≥ 90 mm Hg and/or the need for antihypertensive drugs. Habitual smoking was defined as smoking more than 10 cigarettes per day. All instruments were corrected the day before the measurement.

2.5. Blood collection and DNA extraction

Before cardiac catheterization, 5 mL of the fasting blood samples were taken from each participant via venepuncture in the catheter room. The collected blood samples were put into a ethylene diamine tetraacetic acid tube and centrifuged at 4000 × g for 5 minutes to separate the plasma. Genomic DNA was extracted from the peripheral leukocytes using standard phenol–chloroform method, stored at −80 °C and diluted to a concentration of 50 ng/μL for use.

2.6. Genotyping

Using the National Center for Biotechnology Information SNP databases (http://www.ncbi.nlm.nih.gov/projects/SNP), we obtained 3 tag single nucleotide polymorphisms (SNPs) (SNP1: rs1801693, SNP2: rs6923877, and SNP3: rs9364559) based on the minor allele frequency ≥ 0.05 in the CHP. Genotyping was undertaken using the TaqMan® SNP Genotyping Assay (Applied Biosystems). The primers and probes used in the TaqMan® SNP Genotyping Assays (ABI) were chosen based on information at the ABI website (http://myscience.appliedbiosystems.com). Thermal cycling was conducted using the Applied Biosystems7900HT Standard Real-Time PCR System. Plates were read on Sequence Detection Systems automation controller software v2.3 (ABI). PCR amplification was performed using 2.5 μL of TaqMan Universal Master Mix, 0.5 μL of TE Buffer, 0.15 μL of probes and 1.85 μL of ddH_2O in a 6 μL of final reaction volume containing 1 μL of DNA samples. Thermal cycling conditions are as follows: 95 °C for 5 minutes; 40 cycles of 95 °C for 15 seconds; and 60 °C for 1 minute. All 96-well plates were also read on the Sequence Detection Systems automation controller software v2.3 (ABI).

2.7. Biochemical analysis

Blood samples were centrifuged at 1500 × g for 15 minutes at 4 °C and serum was collected. Serum concentrations of total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, apo(a), and apolipoprotein B100 [apoB], were measured using standard methods in the Central Laboratory of First Affiliated Hospital of Xinjiang Medical University as mentioned previously. Lp(a) levels was detected by latex-enhanced immunonephelometric method by a commercial kit (Beckman Coulter, lnc., Brea, CA). After the serum samples were processed in strict adherence to the instructions, the Beckman Coulter analyzer automatically calculated the concentration of Lp(a) for each sample.

2.8. Statistical analysis

All continuous variables were expressed as means ± standard deviation. The differences between the CAD group and the Control group were analyzed using an independent-samples *t*-Test. Differences in the frequencies of smoking, hypertension, DM, hyperlipidemias and LPA genotypes were analyzed using χ^2 test or Fisher exact test. The Bonferroni correction was applied to adjust the significance threshold for multiple hypotheses testing of both continuous and categorical variables. Hardy–Weinberg equilibrium was assessed by χ^2 analysis. Multiple logistic regression analyses with effect ratios (odds ratio [OR] and 95% confidence interval [CI]) were used to observe the contribution of the major risk factors in male, female, and overall CAD patients. All statistical analyses were performed using SPSS 22.0 for Windows (SPSS Institute, Chicago). Statistical test results with *P*-values <.05 were considered statistically significant.

3. Results

3.1. Characteristics of the study participants

Table 1 shows the demographic and clinical characteristics of the 831 Han and 829 Uygur participants, including both CAD patients and control subjects in male and female. It can be seen that there was no significant difference in age between CAD patients and control subjects. In the Han population, the plasma concentration of Lp(a) and apoB, and the prevalence of essential hypertension (EH) and DM were significantly higher in CAD patients than those in control participants in terms of total subjects, men, and women. Just for the total of the Han population, the frequency of smoking and the prevalence of hyperlipidemia were also much higher for CAD patients than for control participants. For total subjects and men, the plasma concentration of total cholesterol, LDL, apoB and the prevalence of EH were significantly higher in Uygur CAD patients than those in their control participants, whereas the HDL was lower than the controls. In regard to the Uygur women, the tendency was the same with the total subjects and men in terms of the levels of HDL and apoB as well as the prevalence of EH. Notably, the total subjects and women showed much higher frequency of smoking in Uygur CAD patients than their controls.

3.2. Distribution of LPA genotypes

Tables 2 and 3 show the distribution of genotypes and alleles of SNP1, SNP2 and SNP3 for the LPA gene (Table 2: Han population; Table 3: Uygur population). The genotype distribution for the 3 LPA gene SNPs was in consistent with the predicted Hardy–Weinberg equilibrium values ($P > .05$ for both CAD patients and control subjects; no data shown). In the Han population, for SNP1 (rs1801693), the distribution of genotypes, alleles and the recessive model (CC vs CT + TT) significantly differed between the CAD patients and control participants for men (for genotypes: $P = .025$, for alleles: $P = .016$, for the recessive model: $P = .008$, respectively). T allele of rs1801693 was notably higher in CAD patients than in control participants for men (55.2% vs 47.5%), whereas C allele of rs1801693 was observably lower in CAD patients than in control participants (44.8% vs 52.5%). The recessive model (CC vs CT + TT) of rs1801693 was significantly lower in CAD patients than in control participants (17.7% vs 27.8%). For SNP2 (rs6923877), the distribution of genotypes and the dominant model (GG vs AG + AA) significantly differed between Han CAD patients and their controls for men (for genotypes: $P = .021$, for dominant model: $P = .03$). The proportion of the dominant model (GG *vs*. AG + AA) of rs6923877 was much lower among CAD patients than control participants (for total subjects: 14.5% vs 20.3%; men: 14.8% vs 22.2%). As for SNP3 (rs9364559), the distribution of the dominant model (GG vs AG + AA) and allele frequency showed significant difference between CAD and control subjects in the Han women (for dominant model: $P = .025$, for alleles: $P = .021$). G allele of rs9364559 was significantly higher in CAD patients than in control participants (32.6% vs 24.4%), whereas A allele of rs2440472 was significantly lower in CAD patients than in control participants (67.4% vs 75.6%). CAD patients exhibited much lower proportion of the dominant model (AA *vs*. AG + GG) of rs9364559 than control participants

Table 1

Characteristics of study participants.

	Han (n = 831)						Uygur (n = 829)					
	Total			Men			Women			Total			Men			Women		
	CAD patients	Control subjects	*P* value	CAD patients	Control subjects	*P* value	CAD patients	Control subjects	*P* value	CAD patients	Control subjects	*P* value	CAD patients	Control subjects	*P* value	CAD patients	Control subjects	*P* value
Number (n)	392	439		271	216		121	223		513	316		375	153		138	163	
Age (years)	59.17 (9.21)	58.29 (8.47)	.152	59.25 (9.82)	58.47 (8.69)	.360	60.48 (9.73)	58.86 (8.25)	.104	58.67 (9.21)	57.79 (8.47)	.169	58.49 (9.45)	57.29 (8.68)	.176	59.36 (8.97)	57.42 (8.13)	.341
BMI (kg/m^2)	25.54 (3.22)	25.44 (1.26)	.673	25.73 (3.21)	25.78 (3.32)	.854	25.11 (3.20)	25.11 (3.49)	.996	27.07 (3.67)	27.00 (4.00)	.796	27.09 (3.60)	27.28 (3.72)	.587	27.02 (3.86)	26.73 (4.23)	.545
TC (mmol/L)	4.08 (1.36)	4.25 (1.19)	.061	4.01 (1.41)	4.19 (1.10)	.105	4.24 (1.23)	4.29 (1.28)	.691	4.07 (1.26)	3.14 (1.70)	<.001*	4.00 (1.26)	2.14 (1.74)	<.001*	4.26 (1.26)	4.08 (0.99)	.169
HDL (mmol/L)	1.11 (0.86)	1.20 (0.61)	.082	1.05 (0.57)	1.11 (0.56)	.239	1.24 (1.29)	1.29 (0.65)	.697	0.98 (0.69)	1.40 (0.88)	<.001*	0.99 (0.77)	1.74 (1.01)	<.001*	0.95 (0.43)	1.07 (0.60)	.039*
LDL (mmol/L)	2.55 (1.05)	2.56 (0.85)	.802	2.53 (1.14)	2.53 (0.84)	.997	2.59 (0.82)	2.60 (0.86)	.927	2.54 (1.01)	2.18 (0.97)	<.001*	2.52 (1.02)	1.80 (0.92)	<.001*	2.59 (0.99)	2.53 (0.89)	.632
ApoA (mmol/L)	1.21 (0.27)	1.24 (0.27)	.091	1.21 (0.27)	1.19 (0.26)	.385	1.20 (0.27)	1.29 (0.86)	.040	1.19 (0.38)	1.24 (0.50)	.123	1.18 (0.33)	1.26 (0.66)	.063	1.23 (0.50)	1.22 (0.27)	.904
ApoB (mmol/L)	1.05 (0.85	0.88 (0.36)	<.001*	0.97 (0.63)	0.87 (0.34)	.035	1.23 (1.18)	0.89 (0.39)	<.001*	1.12 (0.85)	1.08 (0.67)	.409	1.10 (0.83)	1.32 (0.85)	.008	1.17 (0.90)	0.85 (0.30)	<.001*
Lp(a) (mmol/L)	202.51	161.71	<.001*	204.64	150.80	<.001*	197.75	156.29	.026	177.93	180.68	.787	179.29	167.50	.361	174.22	192.98	.285
	(166.36)	(142.65)		(155.45)	(134.40)		(189.15)	(149.76)		(140.37)	(141.90)		(138.70)	(123.53)		(145.26)	(156.58)	
EH (%)	64.50	46.00	<.001*	63.50	43.10	<.001*	66.90	48.90	.001*	51.30	37.30	<.001*	46.70	26.80	<.001*	63.80	47.20	.005
DM (%)	51.30	37.40	<.001*	50.90	10.70	.028	52.10	34.10	.001*	51.30	44.00	.045	49.90	41.20	.084	55.10	46.60	.165
Hyperlipidemia (%)	8.20	4.10	.014	8.10	3.70	.057	8.30	4.50	.157	26.30	27.50	.747	26.70	26.80	.975	25.40	28.20	.604
Smoke (%)	42.60	28.90	<.001*	57.20	52.80	.359	9.90	5.80	.193	37.80	20.30	<.001*	47.70	40.50	.149	10.90	1.20	<.001*

According to the Bonferroni correction, $P < .004$ is considered to be statistically significant in these 12 variables. Continuous variable were expressed as mean (SD). *P* value of continuous variables was calculated by independent *t*-T test. The *P* value of categorical variable was calculated by Fisher exact test.

ApoA = apolipoprotein(a); ApoB = apolipoprotein B; BMI = body mass index; CAD = coronary artery disease; DM = diabetes mellitus; EH = essential hypertension; HDL = high density lipoprotein; LDL = low density lipoprotein; Lp(a) = lipoprotein(a); TC = total cholesterol.

*$P < .01$.

(43.0% vs 55.6%). In the Uygur population, the distribution of the 3 LPA gene SNPs genotypes, alleles, the dominant model and the recessive model showed no significant difference between the CAD patients and control subjects (for total participants, men or women).

In addition, Table 4 shows the relationship between polymorphisms of LPA gene and Lp(a) levels. In CAD patients, the levels of Lp(a) were significantly higher in the Han population with the C/C genotype at the rs1801693 locus ($P = .018$) and the A/A genotype at the rs9364559 locus ($P = .029$) than in the Uyghur population. In contrast, the levels of Lp(a) in other genotypes were not significantly different between the 2 races ($P > .05$). In the control group, there was no significant difference in the levels of Lp(a) between the Han and Uyghur populations with genotypes at the 3 SNP loci ($P > .05$).

3.3. Logistic regression analyses

As shown in Tables 5, 6, and 7, multiple logistic regression analyses were done with the plasma concentrations of apoB and Lp(a) as well as the incidence of EH and DM, because these variables showed significant difference between CAD patients and control subjects for total subjects, men and women (Table 1). For men, after adjustment for the plasma concentration of apoB and Lp(a), along with the incidence of EH and DM, rs1801693 remained significantly associated with CAD in dominant model (OR = 0.557, 95% CI: 0.355–0.874, $P = .011$) (Table 5). For total subjects, after adjustment for the plasma concentration of apoB and Lp(a), together with the incidence of EH and DM, rs6923877 was still significantly associated with CAD in recessive model (OR = 1.473, 95%CI: 1.009–2.148, $P = .045$) (Table 6). For women, after adjustment for the plasma concentration of apoB and Lp(a) as well as the incidence of EH and DM, rs9364559 kept significantly associated with CAD in recessive model (OR = 0.56, 95%CI: 0.350–0.898, $P = .016$) (Table 7).

4. Discussion

Plasma Lp(a) level, which is genetically determined by the LPA gene, has been found to be associated with the risk of CAD, peripheral artery disease, DM, ischemia stroke and cerebrovascular disease. The association between LPA gene polymorphisms and CAD has been demonstrated in a fraction of the worldwide ethnic lines. In the current study, we found that the variations in the LPA gene were associated with CAD in the northwestern CHP. After multivariate adjustment, the associations between LPA gene polymorphisms with CAD still existed. Our study is the first case-control study to investigate the association between common allelic variants in LPA gene and CAD in the Han and Uygur population of Xinjiang, China.

Multiple polymorphisms of LPA gene are associated with CAD risk, as revealed by prior studies. Rs3798220, encoding an isoleucine to methionine substitution in the protease-like domain of apo(a) at amino acid 4399 (I4399M), has repeatedly been reported to be associated with smaller apo(a) isoforms, elevated Lp(a) plasma levels and severe CAD and myocardial infarction.[20–22] Rs10455872, localized at intron 25 in the LPA gene, is associated with an increased Lp(a) level and a reduced copy number of K4 repeats in Caucasians.[18] It is also a strong genetic marker for CAD risk in Brazilian ethnically mixed populations,[23] in addition to strongly predicting prevalent CAD.[24] Consistently, the rs10455872 and rs3798220 polymorphisms were reported to be strongly associated with Lp(a) level and an increased risk of coronary disease.[18,25] Gu et al demonstrated that the elevated serum Lp(a) concentration and LPA SNPs rs6415084 and rs12194138 were responsible for the increased prevalence and severity of CHD, and that they also independently predicted cardiovascular events.[25] Recently,

Table 2

Genotypes and allele distributions in patients with CAD and control subjects (Han population).

				Total			Men			Women		
				CAD	Control		CAD	Control		CAD	Control	
				n (%)	n (%)	*P* value	n (%)	n (%)	*P* value	n (%)	n (%)	*P* value
rs1801693 (SNP1)	Genotype		T/T	103 (26.3)	120 (27.3)	.473	76 (28.0)	49 (22.7)	.025*	27 (22.3)	71 (31.8)	.136
			C/C	72 (18.4)	93 (21.2)		48 (17.7)	60 (27.8)		24 (19.8)	33 (14.8)	
			C/T	217 (55.4)	226 (51.5)		147 (54.2)	107 (49.5)		70 (57.9)	119 (53.4)	
		Dominant model	TT	103 (26.3)	120 (27.3)	.731	76 (28.0)	49 (22.7)	.179	27 (22.3)	71 (31.8)	.062
			CT + CC	289 (73.7)	319 (72.7)		195 (72.0)	167 (77.3)		94 (77.7)	152 (68.2)	
		Recessive model	CC	72 (18.4)	93 (21.2)	.310	48 (17.7)	60 (27.8)	.008*	24 (19.8)	33 (14.8)	.230
			CT + TT	320 (81.6)	346 (78.8)		223 (82.3)	156 (72.2)		97 (80.2)	190 (85.2)	
	Allele		T	423 (54.0)	466 (53.1)	.720	299 (55.2)	205 (47.5)	.016*	124 (51.2)	261 (58.5)	.662
			C	361 (46.0)	412 (46.9)		243 (44.8)	227 (52.5)		118 (48.8)	185 (41.5)	
rs6923877 (SNP2)	Genotype		G/G	57 (14.5)	89 (20.3)	.021*	40 (14.8)	48 (22.2)	.069	17 (14.0)	41 (18.4)	.300
			A/A	118 (30.1)	146 (33.3)		79 (29.2)	65 (30.1)		39 (32.2)	81 (36.3)	
			A/G	217 (55.4)	204 (46.5)		152 (56.0)	103 (47.7)		65 (53.7)	101 (45.3)	
		Dominant model	GG	57 (14.5)	89 (20.3)	.030*	40 (14.8)	48 (22.2)	.033*	17 (14.0)	41 (18.4)	.305
			AG + AA	335 (85.5)	350 (79.7)		231 (85.2)	168 (77.8)		104 (86.0)	182 (81.6)	
		Recessive model	AA	118 (30.1)	146 (33.3)	.329	79 (29.2)	65 (30.1)	.821	39 (32.2)	81 (36.3)	.447
			AG + GG	274 (69.9)	293 (66.7)		192 (70.8)	151 (69.9)		82 (67.8)	142 (63.7)	
	Allele		G	331 (42.2)	382 (43.5)	.596	232 (42.8)	199 (46.1)	.308	99 (40.9)	183 (41.0)	.975
			A	453 (57.8)	496 (56.5)		310 (57.2)	233 (53.9)		143 (59.1)	263 (59.0)	
rs9364559 (SNP3)	Genotype		A/A	182 (46.4)	221 (50.3)	.419	130 (48.0)	97 (44.9)	.790	52 (43.0)	124 (55.6)	.055
			G/G	41 (10.5)	37 (8.4)		110 (40.6)	92 (42.6)		10 (8.3)	10 (4.5)	
			A/G	169 (43.1)	181 (41.2)		31 (11.4)	27 (12.5)		59 (48.8)	89 (39.9)	
		Dominant model	AA	182 (46.4)	221 (50.3)	.260	130 (48.0)	97 (44.9)	.501	52 (43.0)	124 (55.6)	.025*
			AG + GG	210 (53.6)	218 (49.7)		141 (52.0)	119 (55.1)		69 (57.0)	99 (44.4)	
		Recessive model	GG	41 (10.5)	37 (8.4)	.316	31 (11.4)	27 (12.5)	.720	10 (8.3)	10 (4.5)	.153
			AG + AA	351 (89.5)	402 (91.6)		240 (88.6)	189 (87.5)		111 (91.7)	213 (95.5)	
	Allele		A	533 (68.0)	623 (71.0)	.189	370 (68.3)	286 (66.2)	.495	163 (67.4)	337 (75.6)	.021*
			G	251 (32.0)	255 (29.0)		172 (31.7)	146 (33.8)		79 (32.6)	109 (24.4)	

The *P* value of genotype was calculated by Fisher exact test.

CAD = coronary artery disease.

*$P < .05$.

Table 3

Genotypes and allele distributions in patients with CAD and control subjects (Uygur population).

				Total			Men			Women		
				CAD	Control		CAD	Control		CAD	Control	
				n (%)	n (%)	*P* value	n (%)	n (%)	*P* value	n (%)	n (%)	*P* value
rs1801693 (SNP1)	Genotype		T/T	105 (20.5)	55 (17.4)	.450	78 (20.8)	23 (15.0)	.304	27 (19.6)	32 (19.6)	.877
			C/C	154 (30.0)	105 (33.2)		111 (29.6)	50 (32.7)		43 (31.2)	76 (46.6)	
			C/T	254 (49.5)	156 (49.4)		186 (49.6)	80 (52.3)		68 (49.3)	55 (33.7)	
		Dominant model	TT	105 (20.5)	55 (17.4)	.278	78 (20.8)	23 (15.0)	.126	27 (19.6)	32 (19.6)	.988
			CT + CC	308 (9.5)	261 (82.6)		297 (79.2)	130 (85.0)		111 (80.4)	131 (80.4)	
		Recessive model	CC	154 (30.0)	105 (33.2)	.333	111 (29.6)	50 (32.7)	.486	43 (31.2)	76 (46.6)	.634
			CT + TT	259 (70.0)	261 (66.8)		264 (70.4)	103 (67.3)		95 (68.8)	87 (53.4)	
	Allele		T	464 (45.2)	266 (42.1)	.212	342 (45.6)	126 (41.2)	.189	122 (44.2)	140 (42.9)	.756
			C	562 (54.8)	366 (57.9)		408 (54.4)	180 (58.8)		154 (55.8)	186 (57.1)	
rs6923877 (SNP2)	Genotype		G/G	84 (16.4)	47 (14.9)	.410	61 (16.3)	20 (13.1)	.110	23 (16.7)	27 (16.6)	.829
			A/A	184 (35.9)	103 (32.6)		141 (37.6)	86 (56.2)		43 (31.2)	80 (49.1)	
			A/G	245 (47.8)	166 (52.5)		173 (46.1)	47 (30.7)		72 (52.2)	56 (34.4)	
		Dominant model	GG	84 (16.4)	47 (14.9)	.565	61 (16.3)	20 (13.1)	.355	23 (16.7)	27 (16.6)	.981
			AG + AA	429 (83.6)	269 (85.1)		314 (83.7)	133 (86.9)		115 (83.3)	136 (83.4)	
		Recessive model	AA	184 (35.9)	103 (32.6)	.336	141 (37.6)	86 (56.2)	.134	43 (31.2)	80 (49.1)	.556
			AG + GG	329 (64.1)	213 (67.4)		234 (63.4)	67 (43.8)		95 (68.8)	83 (50.9)	
	Allele		G	413 (40.3)	260 (41.1)	.721	295 (39.3)	126 (41.2)	.579	118 (42.8)	134 (41.1)	.683
			A	613 (59.7)	372 (58.9)		455 (60.7)	180 (58.8)		158 (57.2)	192 (58.9)	
rs9364559 (SNP3)	Genotype		A/A	266 (51.9)	161 (50.9)	.698	188 (50.1)	80 (52.3)	.676	78 (56.5)	81 (49.7)	.394
			G/G	46 (9.0)	24 (7.6)		33 (8.8)	10 (6.5)		13 (9.4)	14 (8.6)	
			A/G	201 (39.2)	131 (41.5)		154 (41.1)	63 (41.2)		47 (34.1)	68 (41.7)	
		Dominant model	AA	266 (51.9)	161 (50.9)	.801	188 (50.1)	80 (52.3)	.653	78 (56.5)	81 (49.7)	.237
			AG + GG	247 (48.1)	154 (49.1)		187 (49.9)	73 (47.7)		60 (43.5)	82 (50.3)	
		Recessive model	GG	46 (9.0)	24 (7.6)	.490	33 (8.8)	10 (6.5)	.388	13 (9.4)	14 (8.6)	.801
			AG + AA	467 (91.0)	192 (92.4)		342 (912.0)	143 (93.5)		125 (90.6)	149 (91.4)	
	Allele		A	733 (71.4)	453 (71.7)	.918	530 (70.7)	223 (72.9)	.471	203 (73.6)	230 (70.6)	.414
			G	293 (28.6)	179 (28.3)		220 (29.3)	83 (27.1)		73 (26.4)	96 (29.4)	

The *P* value of genotype was calculated by Fisher exact test.

CAD = coronary artery disease.

*$P < .05$.

Table 4

The relationship between polymorphisms of LPA gene and lipoprotein(a) levels in all study participants.

			Lipoprotein(a) levels (mmol/L)					
			CAD			Control		
			Han	Uygur	*P* value	Han	Uygur	*P* value
rs1801693	Genotype	T/T	197.54 (166.91)	178.49 (127.77)	.356	172.54 (170.95)	194.59 (145.97)	.409
(SNP1)		C/C	229.35 (169.35)	178.05 (141.45)	.018*	166.23 (136.88)	178.25 (150.16)	.559
		C/T	195.97 (164.99)	177.62 (145.13)	.200	154.11 (127.94)	177.35 (135.21)	.089
rs6923877	Genotype	G/G	195.34 (136.08)	204.514 (203.64)	.843	143.14 (110.10)	150.65 (100.76)	.789
(SNP2)		A/A	212.64 (208.24)	182.88 (149.87)	.351	159.32 (147.59)	194.54 (141.27)	.060
		A/G	190.66 (155.26)	170.02 (130.34)	.223	172.21 (147.70)	180.05 (150.37)	.615
rs9364559	Genotype	A/A	201.91 (183.49)	169.39 (131.19)	.029*	160.76 (154.08)	173.03 (130.26)	.421
(SNP3)		G/G	209.21 (172.91)	239.80 (200.63)	.451	143.14 (110.10)	150.65 (100.76)	.789
		A/G	201.54 (144.94)	175.07 (132.25)	.067	166.68 (134.09)	188.35 (156.87)	.191

Continuous variable were expressed as mean (SD). *P* value of continuous variables was calculated by independent T-T test.
CAD = coronary artery disease.
Symbol
* indicates statistical significance.

Table 5

Multiple logistic regression analysis for CAD patients and control subjects of Han population in recessive model (rs1801693).

	Total			Men			Women		
rs1801693	**OR**	**95%CI**	***P* value**	**OR**	**95%CI**	***P* value**	**OR**	**95%CI**	***P* value**
Recessive model (CC vs CT + TT)	0.827	0.579–1.181	.296	0.557	0.355–0.874	.011*	1.400	0.767–2.557	.273
ApoB (mmol/L)	1.591	1.164–2.175	.004*	1.667	0.972–2.858	.063	1.724	1.178–2.523	.005*
Lpo(a) (mmol/L)	1.002	1.001–1.003	.001*	1.003	1.001–1.004	.001*	1.001	0.999–1.002	.280
EH (%)	1.911	1.435–2.544	<.001*	2.074	1.420–3.028	<.001*	1.766	1.095–2.846	.020*
DM (%)	1.599	1.201–2.128	.001*	1.352	0.926–1.974	.119	1.837	1.149–2.939	.011*

ApoB = apoliprotein B; CAD = coronary artery disease; DM = diabetes mellitus; EH = essential hypertension; Lpo(a) = lipoprotein(a); OR = odds ratios; 95%CI = 95% confidence intervals.
*$P < .05$.

Table 6

Multiple logistic regression analysis for CAD patients and control subjects of Han population in dominant model (rs6923877).

	Total			Men			Women		
rs6923877	**OR**	**95%CI**	***P* value**	**OR**	**95%CI**	***P* value**	**OR**	**95%CI**	***P* value**
Dominant model (GG vs AG + AA)	1.473	1.009–2.148	.045*	1.572	0.970–2.548	.066	1.692	1.155–2.478	.007*
ApoB (mmol/L)	1.589	1.163–2.170	.004*	1.678	0.983–2.863	.058	1.001	0.999–1.002	.249
Lpo(a) (mmol/L)	1.002	1.001–1.003	.001*	1.002	1.001–1.004	.001*	1.781	1.104–2.871	.018*
EH (%)	1.915	1.438–2.551	<.001*	2.101	1.441–3.064	<.001*	1.925	1.200–3.086	.007*
DM (%)	1.603	1.203–2.135	.001*	1.337	0.917–1.950	.132	1.473	0.774–2.803	.238

ApoB = apoliprotein B; CAD = coronary artery disease; DM = diabetes mellitus; EH = essential hypertension; Lpo(a) = lipoprotein(a); OR = odds ratios; 95%CI = 95% confidence intervals.
*$P < .05$.

Table 7

Multiple logistic regression analysis for CAD patients and control subjects of Han population in dominant model (rs9364559).

	Total			Men			Women		
rs9364559	**OR**	**95%CI**	***P* value**	**OR**	**95%CI**	***P* value**	**OR**	**95%CI**	***P* value**
Dominant model (AA vs AG + GG)	0.861	0.649–1.144	.303	1.169	0.804–1.700	.414	0.560	0.350–0.898	.016*
ApoB (mmol/L)	1.602	1.173–2.188	.003*	1.693	0.993–2.886	.053	1.769	1.195–2.620	.004*
Lpo(a) (mmol/L)	1.002	1.001–1.003	.001*	1.002	1.001–1.004	.001*	1.001	0.999–1.002	0.248
EH (%)	1.904	1.430–2.535	<.001*	2.103	1.444–3.063	<.001*	1.725	1.067–2.790	.009*
DM (%)	1.600	1.202–2.130	.001*	1.353	0.929–1.972	.115	1.909	1.190–3.064	.007*

ApoB = apoliprotein B; CAD = coronary artery disease; DM = diabetes mellitus; EH = essential hypertension; Lpo(a) = lipoprotein(a); OR = odds ratios; 95%CI = 95% confidence intervals.
*$P < .05$.

Song et al have discovered the correlation between a new polymorphism, rs9364559 in the LPA gene, and the risk of CAD in the CHP. Moreover, the G allele and GG genotype were found at risk for CAD.[19] In the present study, we likewise found much higher levels of Lp(a) in the CHP CAD patients than in the Uyghur CAD patients with the rs1801693 C/C genotype and the rs9364559 A/A genotype. Accordingly, we hypothesized that rs1801693 and rs9364559 in the LPA gene in the CHP are implicated in the increase of CAD risk and Lp(a) levels in CAD patients.

In this study, polymorphisms of the LPA gene were associated with CAD in northwestern CHP. It has been reported that lipoprotein levels vary by race, and that gender may moderately regulate Lp(a) levels.[26,27] For SNP1 (rs1801693), there were significant differences in alleles, genotypes and the recessive model in men compared with women and even the general population. The frequency in the C allele and the recessive model (CC vs CT + TT) of rs1801693 is much lower in CAD patients than in control participants. After multivariate adjustment of confounding factors such as plasma concentration of ApoB and Lp(a), incidence of hypertension and diabetes, the above results remained significantly different. This indicated that the CC genotype and C allele of rs1801693 might be protected against CAD in men. However, Sun et al discovered that LPA rs1801693 had no significant effect on the risk of premature CAD in CHP.[28] For the distribution of SNP2 (rs6923877), there were significant differences in genotypes and dominant model in total subjects compared with men and women, and its frequency in GG genotype was higher in control subjects than in CAD patients. The significant differences were also retained after multivariate adjustment of confounding factors for CAD. It is logical to speculate that the GG genotype of rs6923877 might be a protective factor for CAD in total subjects. But there were no differences between men and women in terms of alleles, genotypes, dominant model and recessive model. As for the distribution of SNP3 (rs9364559), significant differences were observed in alleles and dominant model in women compared with men and total subjects; the frequency of the AA genotype in the dominant model (AA vs AG + GG) and A allele was also higher in control subjects than in CAD patients. Similarly, the significant difference still existed after multivariate adjustment of confounding factors for CAD. It follows that the AA genotype and A allele of rs9364559 might be protective factors for CAD in women, which is agreed with the conclusion of Song et al[19]

However, there was no difference in alleles, genotypes, the recessive model or the dominant model between Uygur CAD patients and their control subjects. In this case, we did not find an association between the 3 SNPs of the LPA gene and CAD. Uygur is one of the minority ethnic group mainly living in the Xinjiang Uygur Autonomous Region, northwestern China. They originates from the intermarriage between Caucasians and Mongolians, and have their own language, culture, religion and dietary structure. They mainly eat beef, mutton, nuts and dairy products, with no pork or lard in their daily lives. A clinical study has shown that high fat intake leads to significantly higher plasma levels of LP(a) in patients with CAD.[29] The different genomics and dietary habits of the Uygur population may generate different results compared with the Han Chinese.

The understanding and attention to Lp (a) has witnessed the increasing research on its pharmacological effects, low side effects and effective drug formulations. Reducing the concentration of Lp (a) through drugs will better reduce the risk of CAD, which is a powerful direction for future research. Nevertheless, there are several limitations to our study. First, the sample size is small, and the statistical inference is not very convincing. Second, the study was limited to Han Chinese in Northwest China only and may not be applicable to other regions of China. Third, no clear experimental research to date have demonstrated a certain correlation between LPA gene polymorphism and gender. The analysis of the experimental data alone could not completely explain the gender difference in the distribution of LPA genes, because it may be attributed to sample size and selection. Therefore, it is necessary to expand the sample size, balance the sample proportion and improve the multicenter comparative study as much as possible. Finally, further experimental studies are needed on the molecular mechanism of LPA gene polymorphisms associated with CAD.

5. Conclusions

In conclusion, this is the first study to investigate the association between the human LPA gene and CAD in the northwestern CHP, and to successfully demonstrate the correlation between the 3 polymorphisms of LPA gene and CAD in the Han population in Xinjiang Uygur Autonomous Region of China. The C allele of rs1801693 could be a protective genetic marker; the CC genotype of the recessive model (CC *vs.* CT + TT) could protect men from CAD; the GG genotype of rs6923877 might be a protective factor for CAD in total subjects; and the AA genotype and A allele of rs9364559 might be protective factors for CAD in women. More importantly, additional studies are needed to clarify the underlying molecular mechanism by which polymorphisms of the LPA gene are associated with CAD.

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Author contributions

Conceptualization: Yi-Wen Liu, Xue Jiang.
Data curation: Yi-Wen Liu.
Formal analysis: Yi-Wen Liu, Chun-lan Dong.
Supervision: Deng-Yao Liu.
Writing – original draft: Yi-Wen Liu, Xue Jiang.
Writing – review & editing: Chun-Lan Dong, Deng-Yao Liu.

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