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Original Article

Lipoprotein(a) levels and genetic polymorphisms in LPA genes may contribute to risk of coronary heart disease

Jun-Xu Gu*, Shan-Shan Li*, Ming Su, Ai-Min Zhang, Yue Yin, Na Zhang, Mei Jia

*Department of Clinical Laboratory, Peking University People's Hospital, Beijing, P.R. China. *Equal contributors.*

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Abstract: Objective: Elevated lipoprotein(a) [Lp(a)] levels may increase risks of coronary heart disease (CHD). Genetic variants in rs6415084 and rs12194138 single nucleotide polymorphisms (SNPs) in Lp(a) genes (*LPA*) are correlated with Lp(a) levels. However, whether these SNPs are associated with risk of CHD remains unknown. The current study investigated the correlation between Lp(a) levels and CHD. This study determined Lp(a) expression levels in SNPs variants of *LPA,* evaluating the correlation between these SNPs and incidence of CHD in Chinese Han people. Methods: Prevalence of rs6415084 and rs12194138 SNPs was examined by genotyping 1,129 Chinese Han participants (657 CHD patients and 472 control subjects). Next, this study assessed whether these SNPs were associated with incidence of CHD. Concentrations of serum lipids were determined by biochemical methods. Results: Lp(a) levels in the CHD group were significantly higher than those in control subjects [41.72 (46.45) nmol/L vs 28.93 (23.56) nmol/L]. This study adjusted for age and gender, blood glucose, total cholesterol, triglycerides, apolipoprotein A1 (ApoA1), apolipoprotein B (ApoB), hypersensitive C-reactive protein (hs-CRP), homocysteine (HCY), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), and small dense low density lipoprotein cholesterol (sdLDL-C). The current study also calculated the risk of the fourth Lp(a) quartile (OR = 4.139, 95%, CI = 2.104-7.860) via multiple logistic regression. There were significant differences in genotype (C/T, A/T) and major allele frequencies (MAF) of variants rs6415084 and rs12194138 between the CHD group and control subjects. Moreover, rs6415084 and rs12194138 variants were associated with increased Lp(a) levels [98.62 (59.15) nmol/L vs 32.67 (23.93) nmol/L (CC; TT), $P < 0.001$; 88.15 (59.26) nmol/L vs 34.81 (34.58) nmol/L (AA; TT), $P < 0.001$]. *LPA* variants rs6415084 and rs12194138 were correlated with CHD (OR: 1.682; 95% CI: 1.39-2.876; $P = 0.007$; OR: 1.656; 95% CI: 1.121-2.996; $P = 0.026$). Conclusion: Results found that variants rs6415084 and rs12194138 of LPA were associated with increased serum Lp(a) levels and increased incidence of CHD.

Keywords: Coronary heart disease, lipoprotein(a), single nucleotide polymorphism

Introduction

Coronary heart disease (CHD) is one of the most common diseases worldwide. It is associated with very high rates of morbidity and mortality. Many cardiovascular risk factors have been identified and have been used for risk stratification and prognosis assessment of cardiovascular diseases. Lipoprotein(a) [Lp(a)] is one of the well-established risk factors for CHD [1-6].

Lp(a) is a lipoprotein synthesized from the liver. It is composed of apolipoprotein B100 and apolipoprotein(a), which are covalently linked through disulfide bonds. The structure of Lp(a) is homologous to plasminogen. It has atherosclerotic and thrombotic properties [7]. The physiological function of Lp(a) and consequences of high concentrations of Lp(a) remain unclear, compared to those of most other lipoproteins. Elevated plasma Lp(a) concentrations have been found to be associated with increased CHD risks, although results have been inconsistent between different populations [8-10].

The inter-individual variation in Lp(a) levels is 90%. This is due to a high variation in the LPA locus on chromosome six across different races. In recent years, many single nucleotide polymorphisms (SNPs) of LPA have been confirmed to be associated with risk of CHD [11-13]. Of these, a common *LPA* polymorphism,

rs6415084, has been extensively studied. Moreover, rs6415084 is a short variation in the 5' haplotype block of *LPA*, which is located at the 6q27 chromosomal region. This variation is strongly associated with plasma Lp(a) concentrations in Caucasians populations. Several studies have shown that rs6415084 is significantly associated with CHD and coronary artery occlusion in Caucasians [14, 15]. The SNP rs12194138 is also a short variation in the 5' haplotype block of *LPA*. However, less research has been conducted on this variant in the Han population. The purpose of the current study was to investigate the relationship between rs6415084, rs12194138, and CHD in Chinese Han patients, determining the correlation between Lp(a) and classical risk factors, as well as coronary heart disease.

Materials and methods

Study population

Six hundred and fifty-seven Chinese Han patients (413 males, 244 females), from Peking University People's Hospital, were sequentially enrolled between April 2017 and October 2018. Inclusion criteria: All patients that underwent a coronary angiography and were found to have at least one major coronary occlusion or a stenosis ≥ 75%. Exclusion criteria: 1) Any known inflammatory and infectious diseases or confirmed or suspected cancer; 2) Acute coronary syndrome in the past 6 six months; 3) Percutaneous coronary intervention in the past 3 months; 4) History of coronary artery bypass operation; 5) Chronic heart failure, cardiomyopathy, valvular heart disease; 6) Pulmonary heart disease; or 7) Severe liver and kidney dysfunction. The control subjects were 472 healthy people (274 males, 198 females) recruited from the Physical Examination Center of Peking University People's Hospital, between April 2018 and September 2018. All healthy individuals were confirmed to be negative for hypertension, heart disease, diabetes, and kidney disease. The current study was approved by the Research Ethics Committee and written informed consent was obtained from all patients.

Genotyping

Genomic DNA was extracted, according to manufacturer instructions, with the PureGene DNA isolation kit (TianGen Biotech, Beijing, China). This method used 3.5 mL of peripheral blood obtained in EDTA anticoagulant blood tubes (Becton, Dickinson and Company, USA). Incidence of *LPA* variants rs6415084 or rs12194138 was determined for each participant using gene sequencing (TsingKe Biological Technology, Beijing, China).

Blood lipid determination

Serum lipid concentrations of glucose, total cholesterol, triglycerides, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), apolipoprotein A1 (apoA1), apolipoprotein B (apoB), homocysteine (HCY), hypersensitive C-reactive protein (HsCRP), small dense low-density lipoprotein cholesterol (sdLDL-C), and Lp(a) were determined on the second day after admission. Lp(a) in the serum samples was measured using a latex enhanced immunoturbidimetry Lp(a) kit (Roche Inc., Germany). An AU5832 analyzer was used for additional analyses (Beckman Coulter Inc., USA).

Statistical analysis

Data was analyzed with sample Kolmogorov-Smirnov tests, determining whether the distribution of quantitative variables was normal. Normally distributed data are reported as mean ± SD. Differences between various groups were compared with Student's *t*-tests. Abnormally distributed continuous variables are reported as medians (interquartile ranges). Differences between various groups were compared with Mann-Whitney U-tests. Moreover, χ^2 tests were used to examine the Hardy-Weinberg equilibrium for each variant, comparing the distribution of allele and genotype frequencies between CHD patients and control subjects. Association of SNPs with CHD was analyzed by multivariate logistic regression adjusted for age, gender, glucose, total cholesterol, triglycerides, HDL-C, LDL-C, ApoA1, ApoB, HCY, hs-CRP, and sdLDL. The significance level of all statistical tests is $P < 0.05$. SPSS 22.0 for Windows (SPSS Inc., USA) was employed for all statistical analyses.

Results

Baseline characteristics between CHD patients and control subjects

Table 1 shows comparisons between the CHD group and control groups. Levels of glucose,

Table 1. Baseline characteristics between the CHD group and healthy group

	Cases N = 657	Control Subjects N = 472	*P* Value
Age (yrs)	64.73±11.23	62.62±12.28	0.695
Male (%)	62.9	58.1	0.108
Glucose (mmol/L)	5.80±1.43	5.44±1.23	< 0.001
Total cholesterol (mmol/L)	4.73±1.04	4.25±1.09	< 0.001
Triglycerides (mmol/L)	1.62±0.55	1.57±0.45	0.705
HDL-C (mmol/L)	1.03±0.30	1.33±0.42	< 0.001
LDL-C (mmol/L)	3.01±0.78	2.64±0.75	< 0.001
ApoA1 (g/L)	116.83±29.67	175.83±30.04	< 0.001
ApoB (g/L)	93.56±24.71	73.56±21.28	< 0.001
HCY (umol/L)	11.99 (10.22)	9.58 (5.61)	< 0.001
hs-CRP (mg/L)	4.14 (7.65)	1.05 (1.45)	< 0.001
sdLDL-C (mmol/L)	0.824 (0.443)	0.609 (0.361)	< 0.001
LP(a) (nmol/L)	41.72 (46.45)	28.93 (23.56)	< 0.001

Data are reported as means ± SD or median (interquartile range). HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; apoA1: apolipoprotein A1; apoB: apolipoprotein B; HCY: homocysteine; HsCRP: hypersensitive C-reactive protein; sdLDL-C: small dense low-density lipoprotein cholesterol. Statistical analysis was performed with Student's t-tests or Mann-Whitney U-tests.

total cholesterol, LDL-C, apoB, HCY, hs-CRP, sdLDL-C, and LP(a) in the CHD group were higher than those in the control group. The CHD group had significantly lower HDL-C and apoA1 levels, compared with the control group.

Correlation between Lp(a) and CHD

Table 1 shows that Lp(a) levels in the CHD group were significantly higher than those in the healthy group [41.72 (46.45) nmol/L vs 28.93 (23.56) nmol/L]. All subjects were divided into four quartiles of Lp(a) levels. The risk of CHD in individuals with different Lp(a) levels was assessed. Association between different Lp(a) levels was assessed by multiple-factor and single-factor logistic regression. Multiple-factor logistic regression was applied to adjust for age, gender, glucose, total cholesterol, triglycerides, ApoA1, ApoB, hs-CRP, HCY, HDL, LDL, and sdLDL levels. Through univariate logistic regression, the risk of the fourth quartile of Lp(a) levels (OR = 5.469, 95%, CI = 2.776-9.523) was greater than the first quartile of Lp(a) levels. The risk of the fourth quartile of the Lp(a) was (OR = 4.139, 95%, CI = 2.104-7.860), according to multiple logistic regression (**Table 2**).

Effects of two SNPs on serum Lp(a) levels in Chinese Han people

Results showed that Lp(a) levels were significantly higher in CT/TT and AT/TT genotypes than in rs-6415084 (CC) and rs12194138 (AA) genotypes in all subjects [98.62 (59.15) nmol/L vs 32.67 (23.93) nmol/L, $P < 0.001$; 88.15 (59.26) nmol/L vs 34.81 (34.58) nmol/L, $P < 0.001$] (**Table 3**).

Both SNPs were associated with risk of CHD

Frequencies of the two tested variants did not deviate significantly from Hardy-Weinberg equilibrium: rs6415084, F = 2.666, $P = 0.102$; rs12194138, F = 0.067, $P = 0.794$. SNP genotypes and allele frequency distributions are shown in **Table 4**. There were significant differences in genotypes and allele frequencies between the CHD group and control subjects ($P < 0.05$ for both). Association levels remained after adjusting for age, gender, glucose, total cholesterol, triglycerides, ApoA1, ApoB, hs-CRP, HCY, HDL, LDL, and sdLDL levels, according to multivariate logistic regression analysis. Results suggest that the two SNPs are risk factors for CHD. SNP rs6415084 was significantly associated with CHD. Its *P*-value of 0.007 is considered significant. The *P*-value for SNP rs12194138 (0.022) was < 0.05.

Discussion

Recently, the roles of Lp(a) in cardiovascular disease have attracted more and more attention [16, 17]. Many studies have found high Lp(a) to be an independent risk factor for atherosclerosis due to its similarity with the plasminogen structure. It can competitively inhibit the conversion of plasminogen to plasmin [18, 19]. It was also found that elevated plasma Lp (a) levels can promote thrombosis [20]. Kamstrup et al. showed a correlation between Lp(a) and atherosclerotic stenosis, but not with venous thrombosis [21]. Early observations, like recent meta-analyses and prospective studies, have confirmed that Lp(a) is an independent

Table 2. Multivariate logistic regression for the presence of CHD according to Lp(a) levels

	n	Univariate		Multivariate	
		Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*
Lp(a) (nmol/L)					
6.00-24.40	283	1		1	
24.40-36.31	282	1.516 (1.062-2.164)	0.022	1.787 (0.933-3.421)	0.080
36.31-62.76	282	3.698 (1.866-7.328)	< 0.001	2.572 (1.779-3.676)	< 0.001
62.76-242.35	282	5.469 (2.776-9.523)	< 0.001	4.139 (2.104-7.860)	< 0.001

Multivariate logistic regression was adjusted for age, gender, glucose, total cholesterol, triglycerides, ApoA1, ApoB, hs-CRP, HCY, HDL, LDL, and sdLDL. Lp(a): lipoprotein(a); CI: confidence interval.

Table 3. Serum Lp(a) levels in all subjects carrying different LPA SNP genotypes

SNP	rs6415084		*P*	rs12194138		*P*
Genotype	CC	CT/TT		AA	AT/TT	
LP(a)	32.67	98.62	< 0.001	34.81	88.15	< 0.001
nmol/L	(23.93)	(59.15)		(34.58)	(59.26)	

LPA: Lp(a) gene, SNP: single nucleotide polymorphism.

risk factor for coronary heart disease, peripheral artery disease, and strokes [22-25].

Present results were in accord with previous reports. Lp(a) levels were found to be associated with coronary heart disease. The current study found that association in the CHD group was significantly higher than that in control subjects. Of all the participants, the risk of the fourth Lp(a) quartile was highest (OR = 4.139, 95%, CI = 2.104-7.860), according to multiple logistic regression. Using logistic equation analysis, this study determined that elevated Lp(a) can increase risks of CHD. Current data and other findings suggest that Lp(a) can be used for risk stratification and outcome evaluation.

In the current study, in addition to exploring correlation levels between Lp(a) levels and CHD, association levels of *LPA* SNPs rs6415084 and rs12194138 with CHD were also studied in Chinese Han people. There were significant differences in genotype frequencies between the CHD group and control subjects. Moreover, it was found that *LPA* variants rs6415084 and rs12194138 were associated with both increased Lp(a) levels and increased risks of CHD. Previous studies and present results suggest that rs6415084 and rs12194138 variants could be used as independent risk factors for CHD.

Several studies have also explored the impact of genetic variations in LPA genes on the risk of atherosclerosis, as well as its complications. Egaña-Gorroño et al. determined that there was a correlation between SNP rs6415084 and CHD [26]. Lanktree et al. identified 49 *LPA* SNPs and the *LPA* KIV-2 variant in Europeans, Indians, and Chinese populations [12]. SNP rs6415084 was associated with KIV-2 variant-mediated risks of CHD.

However, there are few studies concerning SNP rs12194138. The current study proves that rs12194138 is associated with CHD in Chinese Han people and that rs12194138 variant is a risk factor for CHD.

CHD is a multifactorial disease, caused by many genetic and complex environmental factors. Therefore, the current study had several limitations. First, this was a single-center study involving a small number of patients with CHD. This did not allow present researchers to make any generalizations. Second, only two SNPs of *LPA* were studied. The research population was also limited. Considering the complexity of the genetic background of polygenic diseases, more *LPA* SNPs and larger sample sizes are necessary to further confirm the roles of Lp(a) in CHD.

Conclusion

In the current study, elevated Lp(a) levels were identified as independent CHD predictors. Lp(a) may promote occurrence of atherosclerosis. LPA SNPs rs6415084 and rs12194138 variants were found to be correlated with CHD.

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Disclosure of conflict of interest

None.

Table 4. Association of the two SNPs with CHD

SNP	Groups	Genotype, n (%)			M ↔ m	Mm + mm ↔ MM	
		MM	Mm	mm	Crude OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
rs6415084	Control subjects	420 (90.0)	50 (9.6)	2 (0.4)	1.717 (1.233-2.392)	1.714 (1.419-2.676)	1.682 (1.319-2.876)
	Cases	542 (82.5)	106 (16.1)	9 (1.4)	*P* = 0.001	*P* = 0.002	*P* = 0.007
rs12194138	Control subjects	447 (94.7)	25 (5.3)	0 (0.0)	1.820 (1.135-2.911)	1.797 (1.109-2.913)	1.656 (1.121-2.996)
	Cases	597 (90.9)	58 (8.8)	2 (0.3)	*P* = 0.012	*P* = 0.016	*P* = 0.022

Crude OR was determined by χ^2 test, cases vs control subjects. Adjusted OR was obtained via multivariate logistic regression after controlling for age, sex, glucose, total cholesterol, triglycerides, HDL-C, LDL-C, ApoA1, ApoB, HCY, hs-CRP, and sdLDL. M = C and m = T for single nucleotide polymorphism (SNP) rs6415084; M = A and m = T for single nucleotide polymorphism (SNP) rs12194138. CHD = coronary heart disease; CI = confidence interval.

Address correspondence to: Mei Jia, Department of Clinical Laboratory, Peking University People's Hospital, No. 11 South Street, Xi Zhi Men, Beijing 100044, P.R. China. Tel: +86-15810631814; Fax: +86-1088326317; E-mail: jiamei00718@sina.com

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