

Original Article

The association of LOX-1 rs1050283 polymorphism with renal hypertension susceptibility in a Chinese population

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Received September 8, 2016; Accepted November 3, 2016; Epub February 1, 2017; Published February 15, 2017

Abstract: The lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) is a type II membrane surface glycoprotein, which belongs to C type lectin family with multiple biological functions in various types of mammalian cells. This study was designed to evaluate whether genetic polymorphisms of LOX-1 is associated with renal hypertension susceptibility. A case-control study was carried out with enrollment of 245 patients with renal hypertension (RH) and 257 normotensives (NTs) in a Chinese population. Genotyping was performed by sequencing method. The distribution of genotype and the frequency of T allele of rs1050283 in RH patients were significantly higher than those in controls ($P<0.05$). The frequency of T allele was also significantly higher in male and elder subjects ($P<0.05$) after stratification analysis. The peripheral blood mononuclear cells (PBMCs) from RH patients showed a significantly higher LOX-1 mRNA expression than controls ($P<0.01$) and the LOX-1 mRNA expression from TT genotype was higher than other genotypes ($P<0.05$). Individuals with TT genotype also showed a higher serum sLOX-1 concentration and systolic blood pressure (SBP) in RH patients ($P<0.01$). In conclusion, the LOX-1 polymorphism rs1050283 is associated with RH susceptibility in Chinese population. Furthermore, the polymorphism rs1050283 is also involved in the regulation of LOX-1 expression and serum sLOX-1 level.

Keywords: LOX-1, renal hypertension, sLOX-1, gene polymorphism

Introduction

Renal hypertension (RH) is a common disease caused by lesions of renal blood vessels or renal parenchyma. RH can not only aggravate the renal vascular lesions, but also lead to renal atherosclerosis, hypertensive encephalopathy and acute left cardiac insufficiency. RH is a complicated disease that is thought to result from an interaction between the inheritance of several susceptibility genes and multiple environmental determinants. However, the genetic regulation of the pathogenesis of RH is far from fully understood.

The lectin-like oxidized low-density lipoprotein receptor-1, LOX-1 (the type D scavenger receptor) is a type II membrane surface glycoprotein, which belongs to C type lectin family [1-4]. In 1997, the Japanese scholar Sawamura firstly cloned and confirmed the presence of LOX 1 receptors from bovine aortic endothelial cells

by using molecular cloning library, on the basis that LOX 1 can bind to oxidized low density lipoprotein (ox-LDL) in vitro through copper. In the following studies, they confirmed LOX 1 had capability of specific binding to, internalizing and degrading ox-LDL in endothelial cells, and was a main receptor for ox-LDL in endothelial cells from a variety of species [5]. The expression of LOX 1 can be induced by ox-LDL and inflammatory factors, such as interleukin 1 beta, interleukin 6 and tumor necrosis factor alpha, interferon gamma, endothelin 1 (ET-1), hyperlipidemia, hypercholesterolemia, mental stress, shear stress, pneumonia chlamydia [3, 6-11]. LOX 1 is a natural ligand of ox-LDL. Under physiological conditions, LOX-1 can clear cell debris and other related substances, such as aged red blood cells, apoptotic cells and pathogenic microorganisms [12], which plays a positive role in body's defenses. However, under pathological conditions, LOX 1 is capable of

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regulating the repair, activation and conversion function in endothelial cells, macrophages and other cells, and the process is associated with the formation of atherosclerosis (AS) and abnormalities which are caused by accumulation of degeneration material.

In addition, LOX 1 is closely related to hypertension and hypertensive renal damage. Asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of nitric oxide synthase (NOS), which can suppress the synthesis of NO, and plays an important role in the occurrence and development of hypertension. Studies have shown that increased ADMA level could significantly elevate the levels of LOX-1 and MCP-1 in the process of switch from monocytes to macrophages [13]. Renin-angiotensin-aldosterone system (RAAS) plays a crucial role in the regulation of blood pressure through controlling blood volume and peripheral resistance. It is reported that angiotensin II induced LOX 1 expression in a AT1R dependent pathway and losartan, an AT1R blocker and angiotensin converting enzyme inhibitor, can inhibit the expression of LOX 1 [14]; LOX 1 activation, in turn, increases the expression of AT1R [15]. There is a positive feedback loop among angiotensin II, AT1R and LOX 1, and the loop surrounds the generation of reactive oxygen species (ROS) and mitogen-activated protein kinase (MAPKs).

There are also some recent studies focusing on the association between genetic polymorphisms of LOX 1 and cardiovascular diseases. Kurnaz O and colleagues have identified a functional SNP in LOX 1 3'-UTR which was involved in the susceptibility to coronary artery disease. In their study, they found that the LOX-1 3'UTR 188 CT TT genotype was positively associated with the decreased level of HDL-cholesterol in controls and increased level of VLDL-C in patients [16]. Liu X and colleagues have also reported that the G501C polymorphism of LOX-1 gene was associated with cerebral infarction and the C allele of G501C in the patients with cerebral infarction was significantly higher than those in controls group [17]. Recently, a research in China demonstrated that the G501C polymorphism of LOX 1 gene and the serum LOX 1 level may be used to predict the development of LVH among EH patients [18].

As LOX 1 can influence the cardiovascular system through various ways, we hypothesized

that LOX 1 polymorphisms may affect the blood pressure and even renal hypertension susceptibility. Therefore, in this paper we aimed to explore the association of rs1050283 of LOX 1 gene with the susceptibility to RH and as well as the relation between LOX 1 genotypes and the serum concentration of sLOX 1.

Material and methods

Subjects

The study cohort consisted of 695 Chinese Han subjects, with 335 patients with renal hypertension and 360 normotensives (NT), and all were enrolled at the outpatient clinics in The Third Xiangya Hospital in Hunan provinces. All cases and controls were Han nationality and resided in Changsha or around counties. The blood pressure was measured in the right upper arm with a standard mercury column sphygmomanometer in a sitting position. Systolic and diastolic blood pressures were determined by the first and fifth Korotkoff sounds, respectively. Hypertension was diagnosed when three consecutive blood pressure measurements >140 mmHg (SBP) and/or >90 mmHg (DBP). Hypertensive subjects with BP of $>140/90$ mmHg with no secondary hypertension etiology were considered for the study. None of the RH patients took antihypertensive medications. All controls were healthy individuals with SBP <140 mmHg and DBP <90 mmHg. Five-milliliter venous blood samples were drawn into ethylenediaminetetraacetic acid-containing tubes. Plasma and peripheral leukocytes were isolated immediately and stored separately at -20°C until later analysis. Serum levels of alanine transaminase (ALT), aspartate transaminase (AST), total cholesterol (TC), triglyceride (TG), high density lipoprotein (HDL), low density lipoprotein (LDL) and creatinine (Cr) were detected in all participants. Data concerning the age (or age at diagnosis for RH cases), gender, body mass index (BMI), history of cigarette smoking and alcohol drinking, history of coronary heart diseases, and family history of RH in the first degree relatives for all cases and controls were collected by a structured questionnaire (**Table 1**). Written informed consents were obtained from all subjects. The study was performed with the approval of the Ethical Committee of the colleague of The Third Xiangya Hospital.

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Table 1. General characteristics of case and control populations

Parameters	Case (n=335)	Control (n=360)	P
Gender			NS
Male (%)	207 (61.8)	226 (62.8)	
Female (%)	128 (38.2)	134 (37.2)	
Age, year	54±10	46±12	<0.001
SBP, mmHg	155±14	124±10	<0.001
DBP, mmHg	94±9	75±6	<0.001
BMI, kg/m ²	24.2±3.2	22.8±3.5	<0.001
Total cholesterol (TC), mmol/L	4.32±1.28	4.34±0.98	NS
Triglyceride (TG), mmol/L	1.74±1.22	1.73±2.57	NS
High density lipoprotein-cholesterol (HDL-C), mmol/L	1.38±0.45	1.35±0.49	NS
Low density lipoprotein-cholesterol (HDL-C), mmol/L	2.55±1.13	2.62±1.34	NS
Fasting plasma glucose, mmol/L	5.48±2.36	5.38±2.05	NS
Creatinine (Cr), μmol/L	98.0±36.5	84.0±24.8	<0.001
Positive history of smoking, %	77 (23.0)	85 (23.6)	NS
Positive history of alcohol consumption, %	64 (19.1)	71 (19.7)	NS
EH family history, %	94 (28.1)	55 (15.3)	<0.001
Hyperlipidemia, %	140 (41.8)	152 (42.2)	NS
Coronary heart disease, %	51 (15.2)	5 (1.4)	<0.001

Genotyping

Genomic DNA samples from peripheral blood leukocytes were extracted according to a DNA Purification kit (Promega Inc., Madison, WI, USA) following the manufacturer's instructions. PCR was performed with a personal thermal cycler (Biometra®, Germany). For genotyping the rs1050283 polymorphism, a 471 bp fragment was amplified from genomic DNA by using the following primers: forward primer: 5-ATTTGAAGGCTCTGGAAG-3'; reverse primer 5-TTCTTGATTTCGG AATGG-3. The PCR reaction was performed in a total volume of 15 μl with 100 ng genomic DNA, 1.5 μl 10 × PCR buffer, 5 pmol of each primer, 200 μM of each dNTP, and 1 U Taq DNA polymerase. The PCR amplification condition was as follows: a denaturation step at 95°C for 5 min, followed by 38 cycles at 94°C for 30 s, 60°C for 30 s, 72°C for 30 s, and a final incubation at 72°C for 10 min. Genotype analysis was performed using DNA sequencing completed by Ying-Jun Biological Company (Representative sequencing results were shown in **Figure 1**).

Real-time PCR analysis

To assess the differentially expressed LOX-1 mRNA in peripheral blood mononuclear cells (PBMCs) from the RH patients and controls,

Real-time PCR was performed according to manufacturer's instructions by ABI 7900 real-time PCR system using SYBR Green method. Sequences of primers were as follows: LOX-1: 5'-CTGATGACTCCTCCCCAGAA-3' (sense) and 5'-CGAGCATCAAGATGGAG ACA-3' (antisense); GAPDH (endogenous control): 5'-CTGCACCACCAACTGC TTAG-3' (sense); 5'-AGGTCCACCAC-TGACACGTT-3' (antisense). Relative expression of LOX-1 mRNA was normalized to the expression level of GAPDH.

Determination of sLOX-1 concentration in the plasma

Plasma level of sLOX-1 was measured behind an immunoassay (Quantikine LOX-1, R&D Systems). The intra-assay and inter-assay coefficients of variation were 5% and 6%, respectively.

Statistical analysis

Test of fitness to Hardy-Weinberg equilibrium (HWE) of each polymorphism was assessed by the LDA program (<http://www.chgb.org.cn/lda/lda.htm>). Continuous variables were expressed as mean ± standard deviation (SD). SPSS11.5 software was used for statistical analysis. Differences in genotype and allele frequencies

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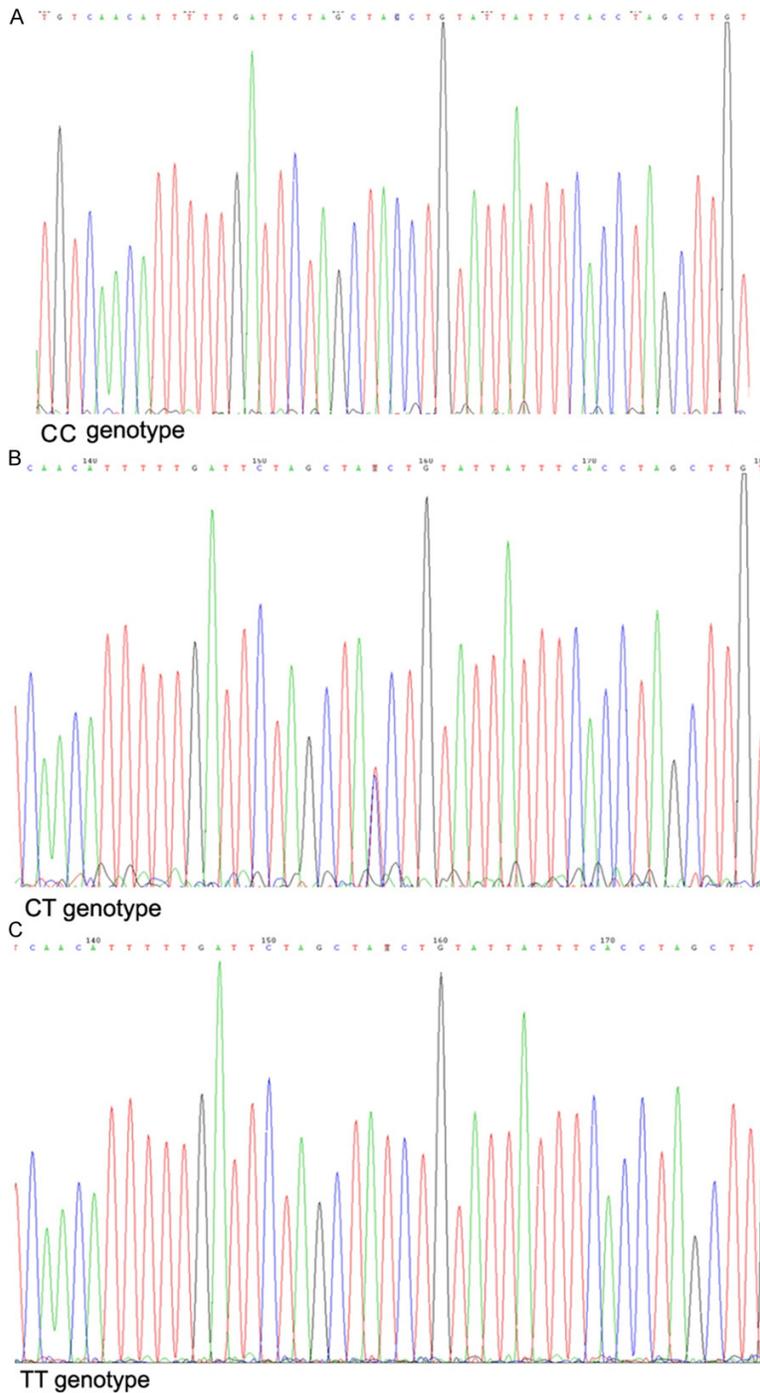


Figure 1. Representative genotype diagram. A: CC genotype; B: CT genotype; C: TT genotype. Genomic DNA was extracted from peripheral blood leukocytes followed by PCR amplification. Then the PCR product was sequenced to analyze the genotyping of the rs1050283 polymorphism.

between groups were evaluated by using χ^2 test. Comparisons of age of onset, systolic and diastolic blood pressure among genotypes were analyzed by one-way analysis of variance (ANOVA). A *p* value of less than 0.05 was considered to be statistically significant.

Results

Clinical and laboratory characteristics of patients and controls

The demographic characteristics and distribution of risk factors in cases and controls were shown in **Table 1**. The RH patients had higher mean systolic BP (SBP) (155 ± 14 mmHg vs. 124 ± 10 mmHg, $P < 0.001$) and higher mean diastolic BP (DBP) (94 ± 9 mmHg vs. 75 ± 6 mmHg, $P < 0.001$). The cases were older and showed significantly higher BMI than controls (24.2 ± 3.2 kg/m² vs. 22.8 ± 3.5 kg/m², cases vs. controls, $P < 0.001$), as well as significantly higher level of creatinine (98.0 ± 36.5 mmol/L vs. 84.0 ± 24.8 mmol/L, $P < 0.001$).

Distribution of allele and genotype frequencies

Genotype distribution and allele frequencies were shown in **Table 2**. The distribution of genotypes was consistent with Hardy-Weinberg equilibrium for polymorphisms in both patients and controls. The frequency of TT genotype was significantly higher in the RH group than that in the control group (11.6% vs. 6.9%, $\chi^2 = 9.55$, $P = 0.008$, **Table 2**), and the frequency of T allele was significantly higher in the RH group than that in the control group.

The effect of LOX-1 gene polymorphism on LOX-1 mRNA expression

To observe the LOX-1 expression pattern in the RH patients, we collected PBMCs for extracting mRNA, which was used for analysis of real-time PCR. As shown in **Figure 2A**, the expression of LOX-1 mRNA in PBMCs from the RH patients was significantly higher than that from the

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Table 2. Genetic polymorphism of LOX-1 rs1050283 in RH patients and controls

	n	Genotype (%)			Allele (%)	
		CC	TC	TT	T	C
RH patients	335	166 (49.6)	130 (38.8)	39 (11.6)	208 (31.0)	462 (69.0)
Controls	360	217 (60.3)	118 (32.8)	25 (6.9)	168 (23.3)	552 (76.7)
χ^2			9.55		10.46	
P-value			0.008		0.001	
OR (95% CI)					1.48 (1.17~1.88)	

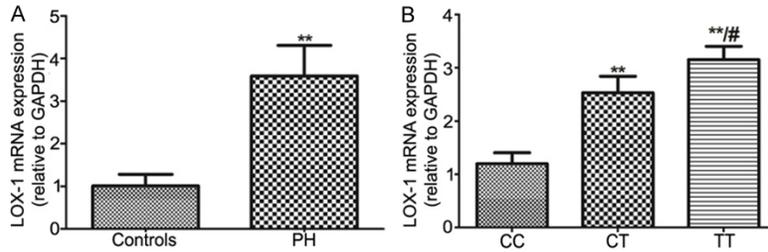


Figure 2. The difference of LOX-1 expression between RH patients and controls. A: LOX-1 mRNA expression in RH patients and controls. Data are expressed as mean \pm SD, n=200. LOX-1 mRNA expression in PBMCs was determined by real-time PCR and expressed as a ratio to control. ** P <0.01 vs. controls. B: LOX-1 mRNA expression in RH patients with different genotypes. Data are expressed as mean \pm SD, n=39. ** P <0.01 vs. CC genotype. # P <0.05 vs. CT genotype.

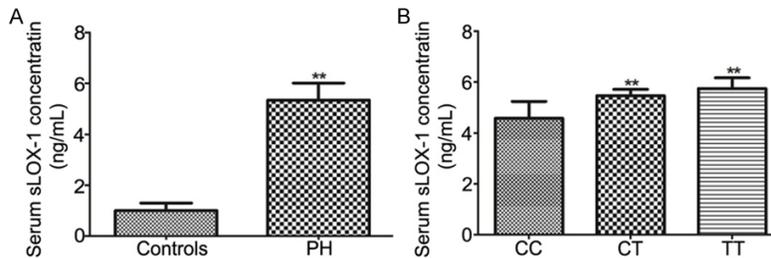


Figure 3. The difference of serum sLOX-1 levels between RH patients and controls. A: Serum sLOX-1 levels in RH patients and controls. Data are expressed as mean \pm SD, n=200. ** P <0.01 vs. controls. B: sLOX-1 levels in RH patients with different genotypes. Data are expressed as mean \pm SD, n=39. ** P <0.01 vs. CC genotype.

healthy controls (P <0.01), and the individuals with TT genotype displayed higher LOX-1 mRNA expression than individuals with CT and TT genotypes (**Figure 2B**).

Association of LOX-1 polymorphism rs1050283 with serum sLOX-1 concentration

To explore the relationship between LOX-1 polymorphism rs1050283 and sLOX-1 level, 200 blood samples from both RH patients and

healthy controls were collected and the serum sLOX-1 concentration was determined by an ELISA kit. As shown in **Figure 3A**, the sLOX-1 levels were significantly elevated in RHA patients compared with controls. Furthermore, in the male RH patients, as compared with LOX-1 rs1050283 C allele carriers, T allele carriers showed significantly higher sLOX-1 level (P <0.01) (**Figure 3B**). No differences in the serum sLOX-1 concentration were observed between different genotypes in the female subjects (data not shown).

The effect of rs1050283 polymorphism on blood pressure

As shown in **Figure 4**, there was a significant association of rs1050283 with SBP in RH patients with negative history of drinking (163.40 ± 22.82 mmHg for TT vs. 143.36 ± 5.75 mmHg for CC, P <0.05) (**Figure 4**). No significant associations between rs1050283 and blood pressure were noted in other divided groups (data not shown).

Discussion

To date, there is no report on association of LOX-1 polymorphisms with RH or

sLOX-1 although LOX-1 has significant effect on cardiovascular diseases. To investigate whether LOX-1 genetic polymorphisms are associated with RH susceptibility and sLOX-1, we genotyped the rs1050283 in a Han Chinese population by sequencing method. In this study, we found a significant association between rs1050283 T allele and RH susceptibility, and we also observed that the sLOX-1 levels in individuals with rs1050283 T allele were significantly higher than that in control groups.

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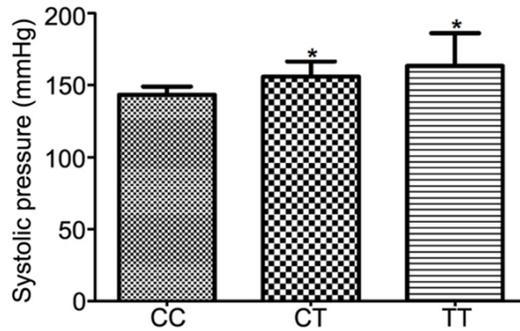


Figure 4. The difference of systolic pressure in RH patients with negative history of drinking. Data are expressed as mean \pm SD, n=30. * P <0.05 vs. CC genotype.

To our knowledge, this is the first study concerning the effect of LOX-1 genetic polymorphism on RH susceptibility and sLOX-1 levels. Previous association studies have indicated that carriers of rs1050283 T allele was associated with reduced volume of acetylcholine induced forearm blood flow in hypertensive patients but not in healthy subjects, indicating that the T allele of rs1050283 is strongly associated with an impaired endothelium-dependent vasodilatation, and may be a reliable predictor for cardiovascular events [19]. Another research in a Chinese population has showed that a functional single nucleotide polymorphism (SNP) rs1050283 was associated with increased susceptibility to coronary artery diseases (CAD). The researchers demonstrated that AA genotype and T allele of rs1050283 were significantly higher in patients with CAD than those in controls [20]. Xu X and colleagues have also reported that the 501G>C polymorphism located in intron 5 of LOX-1 might be used as a predictor for the development of left ventricular hypertrophy (LVH) in essential hypertension patients, and the 501G>C polymorphism was also associated with serum LOX-1 level, with CC genotype having the highest serum LOX-1 level [18]. As a soluble form of LOX-1, plasma level of sLOX-1 in peripheral blood was positively correlated with the expression level of LOX-1, and the detection of serum sLOX-1 is recently be used as a reliable index for diagnosis and prognosis in various cardiovascular diseases and metabolic diseases [21-23]. However, the relationship between rs1050283 of LOX-1 gene and RH susceptibility or serum sLOX-1 level is still unclear. In this study, we firstly found a significant associa-

tion between rs1050283 T allele and RH susceptibility, which may be used as an independent risk factor in the prediction of RH. Furthermore, we also explored the relationship among the serum sLOX-1 concentration, LOX-1 mRNA expression and rs1050283 in the present research. We observed T allele of rs1050283 is associated with higher serum sLOX-1 concentration in RH patients and higher LOX-1 mRNA expression, suggesting the rs1050283 might be involved in the regulation of LOX-1 level.

Another important finding of this study is that there was a significant association of rs1050283 T allele with SBP and DBP in either RH cases or healthy controls, with carriers of T allele having significantly higher BP than GG individuals. LOX-1 can influence blood pressure through regulating carotid elasticity [24]. Besides, LOX-1 can limit cardiac angiogenesis, which can further exert an effect on blood pressure [25]. Therefore, it is not hard to hypothesize that LOX-1 can increase the development of hypertension. All of the above mentioned mechanisms could account for the reason why carriers of T allele of rs1050283 showed higher BP.

In conclusion, our study demonstrated that the rs1050283 T allele was associated with RH susceptibility. However, the exact mechanism remains uncertain. Further studies regarding the role of LOX-1 gene polymorphism in the development and pathogenesis of RH are required.

Acknowledgements

This project supported by the National Natural Science Foundation of China (NO. 81470961).

Disclosure of conflict of interest

None.

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