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Association Between Polymorphisms of ADRBK1 Gene and Plasma Renin Activity in Hypertensive Patients: A Case-Control Study

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Manuscript Preparation E
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Background: Renin is the first step of the RAS cascade, which is a major regulator of salt-volume homeostasis. Adrenergic beta receptor kinase 1 (ADRBK1) plays important roles in regulating blood pressure via the epithelial Na^+ channel (ENaC), which plays an important role in Na^+ reabsorption in the renal collecting duct. The present case-control study was designed to investigate the potential relationship between polymorphisms of ADRBK1 and plasma renin activity (PRA) in hypertension.

Material/Methods: We recruited 1831 hypertensive and 422 normotensive Han Chinese subjects. Sitting PRA (ng/mL/h) was measured using radioimmunoassay method. Hypertensive patients were classified into 4 renin categories via PRA quartile. Single-nucleotide polymorphisms (SNPs) of the ADRBK1 gene (rs1894111, rs4930416, rs7127431, rs12286664, and rs3730147) were identified via TaqMan polymerase chain reaction.

Results: Comparison of the hypertensive group and the control group showed significant differences in distribution of genotypes and alleles of rs1894111 ($P<0.05$). Moreover, distribution of the dominant model (CC *vs.* CT+TT) in rs1894111 was lower in the hypertensive group than in the control group ($P<0.05$). Subjects were classified into 4 subgroups based on PRA quartile; the dominant model (CC *vs.* CT+TT) of rs1894111 was significantly lower in the quartile 1 group (the group with the lowest PRA) than in the control group ($P<0.05$). Logistic regression analysis demonstrated that the dominant model (CC *vs.* CT+TT) of rs1894111 was significantly different in the hypertensive group (OR=1.590, 95%CI=1.022–2.474, $P<0.05$), particularly in the quartile 1 group (OR=1.845, 95%CI=1.119–3.042, $P<0.05$), but not in the quartile 4 group.

Conclusions: The dominant model (CC *vs.* CT+TT) of rs1894111 polymorphism in the ADRBK1 gene might be associated with low-renin hypertension in Han Chinese.

MeSH Keywords: Hypertension • Polymorphism, Single Nucleotide • Receptors, CCR10 • Renin

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Background

Hypertension is a common disease caused by interactions between genetic and environmental factors. Genetic factors are estimated to account for 30–60% of hypertension pathogenesis [1]. The renin-angiotensin system (RAS) is thought to exert an important role in the pathogenesis of hypertension and is a hormonal cascade initiated by renin [2,3]. Renin is a major regulator of blood pressure through its modulation of salt and water homeostasis [2,3]. Researchers proposed that, based on plasma rennin activity (PRA) level, essential hypertension can be divided into high-renin hypertension, medium-renin hypertension, and low-renin hypertension [4]. Tested plasma renin activity is an important guidance value for prognosis and guided therapeutics in essential hypertension [2,5,6]. Researchers showed that high-renin hypertension is strongly associated with blood vessel contraction, indicating that the renin-angiotensin system is over-activated and salt volume is depleted. Low-renin hypertension is characterized by a physiological response to over-loaded salt volume with decreased levels of renin [5]. Its incidence increases with aging.

The epithelial Na^+ channel (ENaC) is a common and requisite component of salt-volume-dependent forms of hypertension [7]. ENaC has a primary role in water and salt metabolism balance by regulating Na^+ reabsorption in the renal collecting duct [8]. The activity and degradation of ENaC is regulated by many upstream substances [9–11]. Recent research showed that the products encoded by the ADRBK1 gene are involved in blood pressure regulation, mediating the activity and degradation of ENaC [12–14]. The ADRBK1 gene could be a candidate gene for hypertension. Expression of the kinase encoded by the ADRBK1 gene decrease ENaC degradation by phosphorylation and increase the number of ENaC at the cell surface, leading to increased Na^+ reabsorption in the collection duct, and thus finally causes hypertension. In this study, we aimed to assess the potential association between genetic polymorphism of ADRBK1 and plasma renin activity (PRA) in hypertensive Han Chinese patients.

Material and Methods

Ethics approval of study protocol

The current study was approved by the Ethics Committee of the People's Hospital of Xinjiang Uygur Autonomous Region (Urumqi, China) and was conducted in accordance with the standards of the Declaration of Helsinki. Informed consent was obtained from each participant prior to providing permission for DNA analyses, as well as for collection of relevant clinical data.

Study subjects

A total of 1831 hypertensive inpatients aged 30–60 years and 422 normotensive subjects aged 30 years or older, of Han Chinese ethnicity, were recruited from the People's Hospital of Xinjiang Uygur Autonomous Region from January 2007 to July 2014. Hypertension was defined as: (1) a systolic blood pressure (SBP) ≥140 mmHg and/or a diastolic blood pressure (DBP) ≥90 mmHg, (2) use of antihypertensive medication, or (3) physician diagnosis of hypertension as per clinical history [15]. Normotensive subjects were defined as those with a SBP ≤130 mmHg and a DBP ≤80 mmHg and no physician diagnosis of hypertension. Hypertensive patients were excluded if they presented: (1) adrenal mass (e.g., aldosterone-producing adenoma, aldosterone carcinoma, or pheochromocytoma); (2) renal parenchyma hypertension and renovascular hypertension; (3) Cushing syndrome; (4) excessive alcohol consumption; (5) pregnancy; or (6) hypertension combined with congestive heart failure, acute or chronic liver dysfunction, or renal insufficiency. Normotensive subjects were also excluded if they exhibited congestive heart failure, acute or chronic liver dysfunction, and/or renal insufficiency. In addition, hypertensive patients were advised to discontinue diuretics (including spironolactone) for 6 weeks, and to discontinue β-blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers for 4 weeks, and to not take any antihypertensive medications at least 2 weeks before the PRA measurement [16]. When necessary, patients were allowed to take α-blockers (doxazosin mesylate controlled release or terazosin hydrochloride) and/or non-dihydropyridine calcium channel blockers (verapamil slow release) for at least 4–6 weeks [16]. After being recruited, sitting PRA was tested in hypertensive patients, and hypertensive patients were stratified into 4 renin categories by quartile [17]: quartile 1 group, <0.44 ng/mL/h, n=457; quartile 2 group, 0.44 to 1.07 ng/mL/h, n=458; quartile 3 group, 1.08 to 2.36 ng/mL/h, n=456; and quartile 4 group, >2.36 ng/mL/h, n=460, based on sitting PRA. All data, including weight, height, body mass index (BMI), office SBP and DBP, mean artery pressure (MAP), and pulse pressure (PP), were acquired from all subjects.

PRA assays

Following an overnight fast, blood samples were obtained from an antecubital vein in a sitting position after at least 15 min of rest at 9 AM. Blood tubes were then centrifuged in a refrigerated centrifuge, and plasma was separated from the cells immediately after centrifugation. Blood cells were stored at –80°C until subsequent genotyping. Followed by reacting the sample with direct antibodies, the plasma samples were divided into 2 parts: one part was used for the determination of plasma Ang I concentration as AIa, and the other part for the determination of plasma Ang I concentration as AIb following 1-h

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Table 1. baseline characteristics of control and hypertensive groups with various PRA.

	Control group (n=422)	Hypertensive group (n=1831)				*P*
		Quartile 1 (n=457)	Quartile 2 (n=458)	Quartile 3 (n=456)	Quartile 4 (n=460)	
Age (y)	54.45±9.76	47.70±6.85[a]	46.09±7.03[a,b]	43.76±6.52[a,b,c]	42.04±7.24[a,b,c,d]	<0.001
Male (%)	192 (45.4)	258 (56.5)[a]	315 (68.8)[a,b]	311 (68.2)[a,b]	357 (77.6)[a,b,c,d]	<0.001
BMI (kg/m^2)	24.21±2.73	26.65±3.41[a]	26.84±3.43[a]	26.84±3.20[a]	26.63±3.52[a]	<0.001
Office SBP (mmHg)	116.66±11.59	138.65±17.66[a]	140.85±18.14[a]	141.01±16.96[a,b]	143.73±21.41[a,b,c,d]	<0.001
Office DBP (mmHg)	74.89±7.55	91.80±11.29[a]	93.6±11.62[a,b]	95.13±12.61[a,b]	98.43±14.35[a,b,c,d]	<0.001
MAP	88.81±7.90	107.42±12.16[a]	109.35±12.67[a,b]	110.42±12.95[a,b]	113.53±15.82[a,b,c,d]	<0.001
PP	41.77±9.58	46.86±13.61[a]	47.25±13.29[a]	45.88±12.41[a]	45.31±13.36[a,c]	<0.001

BMI – body mass index; Office SBP – office systolic pressure; Office DBP – office diastolic pressure; MAP – mean arterial pressure; PP – pulse pressure; Compared with the control group, [a] $P<0.05$. Compared with the quartile 1 group [b] $P<0.05$. Compared with the quartile 2 group [c] $P<0.05$. Compared with the quartile 3 group [d] $P<0.05$.

incubation at 37°C. The sitting PRA was calculated using the following formula: (AIb-AIa)/hours [16]. Ang I was measured by radioimmunoassay (Beifang Biology Technique Center, Beijing, China). The reference range for PRA was 0.20–1.90 ng/mL/h. For the kit, the intra- and inter-assay coefficients of variation were ≤10–15%.

SNPs selection and genotyping

There are 2194 SNPs for the ADRBK1 gene listed in the National Center for Biotechnology Information SNP database (*http://www.ncbi.nlm.nih.gov/SNP*). Using Haploview 4.2 software and the HapMap phrase II database, we obtained 1 tag SNP (rs7127431) via minor allele frequency (MAF) ≤0.05 and linkage disequilibrium patterns with r2 ≥0.8 as the cutoff. Because about 50%–60% of Chinese hypertensive patients have low-renin hypertension, we selected the other 4 SNPs (rs1894111, rs4930416, rs12286664, and rs3730147) described in hypertension in blacks [18], in whom low-renin hypertension is highly prevalent. We found that rs1894111, rs7127431, rs4930416, and rs3730147 were located in the intron region and rs12286664 in the 5' untranslated regions. Genomic DNA was extracted from the peripheral leukocytes using the DNeasy blood and tissue kit of Qiagen (cat. no. 69504), according to the manufacturer's instructions and used as a template for PCR-based genotyping using a previously described Taq amplification method in the 7900 HT Fast Real-Time PCR System (Applied Biosystems Inc, USA) [19]. The TaqMan SNP genotyping assay primers and probes were chosen based on information in the ABI website (*http://myscience.appliedbiosystems.com*). All 384 well plates were read using Sequence Detection Systems automation controller software v2.3.

Statistical analysis

Data are presented as the mean ± standard deviation (SD) for continuous variables and frequency and percentage for categorical variables. The distribution of Han Chinese patient characteristics among patients with various levels of PRA hypertension and control groups was analyzed using one-way ANOVA or chi square test, and pairwise comparison used the SNK test. The differences in distributions of genotypes and alleles were analyzed by chi square test. Logistic regression analyses with effect ratios (odds ratio [*OR*] and 95% confidence interval [*95%CI*]) were used to assess the contribution of gender, age, and BMI. This was a case-control study, so linkage disequilibrium and the Hardy-Weinberg equilibrium were analyzed using SNPAlyze, version 7.0 Pro (DYNACOM Co. Ltd., Mobara, Japan) [19]. Statistical analyses were performed with SPSS for Windows, version 16.0. A value of $P<0.05$ was considered to indicate statistical significance.

Results

Baseline characteristics of control group and groups with various levels of PRA hypertension

A total of 1831 hypertensive patients and 422 controls were finally included in this study. As shown in Table 1, there were statistical differences in baseline data, such as age, gender ratio, BMI, office SBP, office DBP, MAP, and PP, among the 5 groups ($P<0.05$). Hypertensive patients showed higher male proportion, BMI, office SBP, office DBP, MAP, and PP than did the control group ($P<0.05$), as well as younger age ($P<0.05$). Statistically significant differences also existed in all

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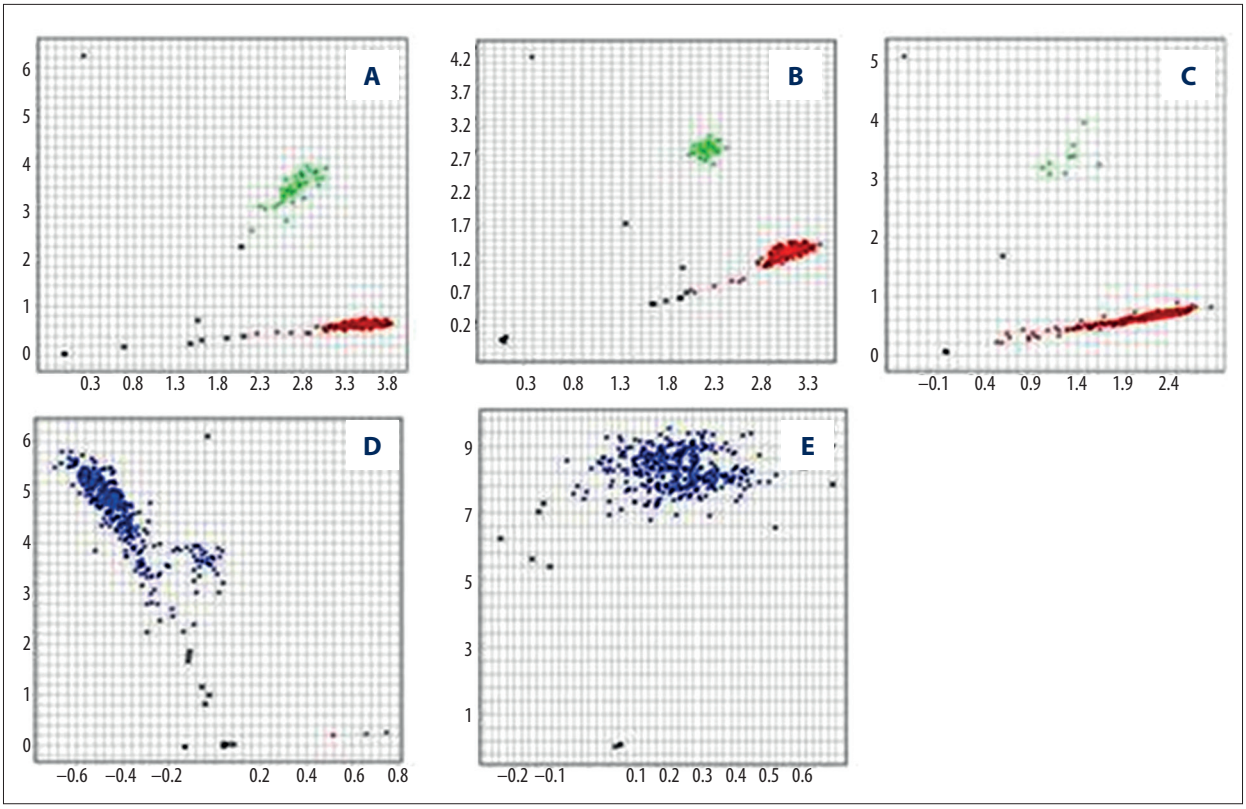

Figure 1. ADRBK1 gene rs7127431, rs1894111, rs4930416, rs3730147, rs12286664, identification with TaqMan-PCR. (**A**) 7127431, (**B**) 1894111, (**C**) 4930416, (**D**) 3730147, (**E**) 12286664. (**A**) Red fluorescent spots for CC type, green fluorescent spots for CT type, blue fluorescent spots for TT type, × for amplification failure, ■ for the blank control; (**B**) Red fluorescent spots for CC type, green fluorescent spots for CT type, blue fluorescent spots for TT type, × for amplification failure, ■ for the blank control; (**C**) Red fluorescent spots for AA type, green fluorescent spots for AC type, blue fluorescent spots for CC type, × for amplification failure, ■ for the blank control; (**D**) Red fluorescent spots for AA type, green fluorescent spots forAG type, blue fluorescent spots for GG type, × for amplification failure, ■ for the blank control; (**E**) Blue fluorescent spots for GG type, × for amplification failure, ■ for the blank control.

characteristics between the quartile 1 group and the control group. Male proportion, BMI, office SBP and DBP, MAP, and PP in the quartile 1 group were significantly higher than in the control group, but the age was younger ($P<0.05$).

Distribution of genotypes and alleles in control and hypertensive groups

Five SNPs (rs1894111, rs7127431, rs4930416, rs3730147, and rs12286664) were successfully genotyped in the ADRBK1 gene (Figure 1). The rs3730147 was genotyped in 2238 subjects with only 8 homozygous mutations and without heterozygous type. The rs12286664 was genotyped for 2243 subjects, but no mutation was found. Therefore, the other 3 SNPs (rs1894111, rs7127431, and rs4930416) associated with hypertension were analyzed in the current study. The genotype distribution of each SNP was in Hardy-Weinberg equilibrium. The rs1894111 (MAF=10.9%) and rs7127431 (MAF=10.0%) were common SNPs, and rs4930416 was a rare SNP (MAF=3.1%).

Table 2 shows the distribution of genotypes and alleles of rs1894111, rs7127431, and rs4930416 for the ADRBK1 gene in the control and hypertensive groups. In the control group, the percentage of C/T genotype in rs1894111 was 7.6% and there was no T/T genotype, but in the hypertensive group, not only did the percentage of C/T genotype increase to 11.4%, but also T/T genotype was observed in 3 cases ($P=0.047$). The allele frequency of T was significantly higher in the hypertensive group than in the control group (5.9% *vs.* 3.8%, $P=0.016$). Further analysis showed that the percentage of CC genotype was significantly lower in the hypertensive group than in the control group (88.4% *vs.* 92.4%, $P=0.016$), whereas the CT+TT genotype was reversed (11.6% *vs.* 7.6%, $P=0.016$). No significant differences between the control and hypertensive groups were observed in genotypes or alleles distribution of rs7127431 and rs4930416.

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Table 2. distribution of genotypes and alleles in control and hypertensive group.

			Control group (%)		Hypertensive group (%)		*P*
rs1894111	Genotype	C/C	390	(92.4)	1604	(88.4)	0.047
		C/T	32	(7.6)	208	(11.4)	
		T/T	0	(0.0)	3	(0.2)	
	Dominant model	CC	390	(92.4)	1604	(88.4)	0.016
		CT+TT	32	(7.6)	211	(11.6)	
	Allele	C	812	(96.2)	3416	(94.1)	0.016
		T	32	(3.8)	214	(5.9)	
rs7127431	Genotype	C/C	370	(88.1)	1649	(90.4)	0.142
		C/T	50	(11.9)	169	(9.3)	
		T/T	0	(0.0)	5	(0.3)	
	Dominant model	CC	370	(88.1)	1649	(90.4)	0.146
		CT+TT	50	(11.9)	174	(9.5)	
	Allele	C	790	(94.0)	3467	(95.1)	0.216
		T	50	(6.0)	179	(4.9)	
rs4930416	Genotype	A/A	410	(97.6)	1761	(96.7)	0.583
		A/C	10	(2.4)	59	(3.2)	
		C/C	0	(0.0)	1	(0.1)	
	Dominant model	AA	410	(97.6)	1761	(96.7)	0.328
		AC+CC	10	(2.4)	60	(3.3)	
	Allele	A	830	(98.8)	3581	(98.3)	0.311
		C	10	(1.2)	61	(1.7)	

P<0.05 was considered significant.

Distribution of genotypes and alleles in control group and hypertensive groups with various levels of PRA

Tables 3 showed the distribution of genotypes and alleles of rs1894111, rs7127431, and rs4930416 for the ADRBK1 gene in the control group and hypertensive groups with various levels of PRA. Hypertensive patients were divided into 4 groups based on quartile of PRA. For rs1894111, the genotype and allele distribution showed significant differences among the 5 groups. We found that the 208 heterozygous mutations distributed in each group were 60 (13.2%), 42 (9.3%), 51 (11.2%), and 55 (12.1%), respectively. All the 3 (0.7%) homozygous types were found only in the quartile 1 group, but the difference was not significant (P>0.05). There was a significant difference in the dominant model among the 5 groups (P<0.05). Distribution of dominant model (CC *vs.* CT+TT) in the quartile 1 group was the lowest among the 5 groups (*P*<0.05), followed by the quartile 4 group. For rs7127431 and rs4930416, there were no significant differences in distribution of genotypes and alleles between the control group and hypertensive groups with various levels of PRA.

Logistic regression analysis in control group and hypertensive groups with various levels of PRA

As shown in Table 4, logistic regression analysis was performed by adjusting for potential confounding covariates, including age, gender, and BMI. In hypertensive groups, the dominant model (CC *vs.* CT+TT) of rs1894111 increased by 1.590 fold the risk for hypertension (OR=1.590, 95% CI=1.022–2.474, P=0.040). In addition, the OR of the dominant model (CC *vs.* CT+TT) of rs1894111 in the quartile 1 group showed a statistically significant difference (OR=1.845, 95%CI=1.119–3.042, P=0.016). In the quartile 4 group, the dominant model (CC *vs.* CT+TT) of rs1894111 was not significantly different (OR=1.657, 95% CI=0.905–3.036, P=0.102). Therefore, these results suggest that the dominant models (CC *vs.* CT+TT) of rs1894111 could be a risk factor in hypertensive groups, especially in the quartile 1 group.

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Table 3. Genotypes and alleles distribution in control and hypertensive groups with various PRA.

		Genotype	Control group (%)	Hypertension group (%)				P
				Quartile 1	Quartile 2	Quartile 3	Quartile 4	
rs1894111	Additive model	C/C	390 (92.4)	390 (86.1)	412 (90.7)	403 (88.8)	399 (87.9)	0.257
		C/T	32 (7.6)	60 (13.2)	42 (9.3)	51 (11.2)	55 (12.1)	
		T/T	0 (0.0)	3 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	
	Dominant model	CC	390 (92.4)	390 (86.1)	412 (90.7)	403 (88.8)	399 (87.9)	0.026
		CT+TT	32 (7.6)	63 (13.9)[a]	42 (9.3)[b]	51 (11.2)	55 (12.1)[a]	
	Allele	C	812 (96.2)	840 (92.7)	866 (95.4)	857 (94.4)	853 (93.9)	0.016
		T	32 (3.8)	66 (7.3)[a]	42 (4.6)[b]	51 (5.6)	55 (6.1)[a]	
rs7127431	Additive model	C/C	370 (88.1)	422 (92.3)	410 (90.1)	410 (90.7)	407 (88.7)	0.788
		C/T	50 (11.9)	33 (7.2)	45 (9.9)	40 (8.8)	51 (11.1)	
		T/T	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.5)	1 (0.2)	
	Dominant model	CC	370 (88.1)	422 (92.3)	410 (90.1)	410 (90.7)	407 (88.7)	0.228
		CT+TT	50 (11.9)	35 (7.7)	45 (9.9)	42 (9.3)	52 (11.3)	
	Allele	C	790 (94.0)	877 (96.0)	865 (95.1)	860 (95.1)	865 (94.2)	0.360
		T	50 (6.0)	37 (4.0)	45 (4.9)	44 (4.9)	53 (5.8)	
rs4930416	Additive model	A/A	410 (97.6)	449 (98.2)	432 (95.8)	438 (96.5)	442 (96.3)	0.067
		A/C	10 (2.4)	8 (1.8)	19 (4.2)	16 (3.5)	16 (3.6)	
		C/C	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	
	Dominant model	AA	410 (97.6)	449 (98.2)	432 (95.8)	438 (96.5)	442 (96.3)	0.189
		AC+CC	10 (2.4)	8 (1.8)	19 (4.2)	16 (3.5)	17 (3.7)	
	Allele	A	830 (98.8)	906 (99.1)	883 (97.9)	892 (98.2)	900 (98.0)	0.173
		C	10 (1.2)	8 (0.9)	19 (2.1)	16 (1.8)	18 (2.0)	

P<0.05 was considered significant. Compared with the control group, [a] *P*<0.05. Compared with the quartile 1 group [b] *P*<0.05.

Discussion

The protein encoded by the ADRBK1 gene, originally termed G protein-coupled receptor kinase 2 (GRK2), is a member the G protein-coupled receptor kinase family of serine/threonine protein kinases, which are key proteins of G protein-coupled receptor phosphorylation and desensitization [20]. It phosphorylates β-adrenergic receptor to induce activation of adenylate cyclase and decrease blood vessel contraction [21]. It also mediates C-terminus in β-ENaC subunits or WW domains in these ubiquitin protein ligases through the action of G protein-coupled receptor phosphorylation and desensitization, induced to decrease activation of ENaC degradation response to increase the body salt volume with lower renin levels [12,13], involved in regulating blood pressure. Gros et al. [20] declared that expression of ADRBK1 protein in lymphocytes and tissues of salt-sensitive hypertensive rats was increased compared to salt-insensitive ones, while salt-sensitive hypertension was associated with low renin levels. Cohn et al. [21] suggested that the expression and activity of ADRBK1 were related with hypertension in black Americans [22], in whom low-renin hypertension is highly prevalent. However, the association between expression of ADRBK1 protein and low-renin hypertension is still unclear. Low-renin hypertensive patients are estimated to account for 50–60% of all Chinese hypertensive patients. The present study is the first to examine the relationship between genetic variations in the ADRBK1 gene and PRA in Chinese hypertensive patients.

In our study, 3 SNPs (rs1894111, rs7127431, and rs4930416) of the ADRBK1 gene associated with hypertension were analyzed. We found that the dominant model (CC *vs.* CT+TT) and allele of T of ADRBK1 rs1894111 were significantly different between hypertensive and control subjects, possibly indicating that those who carry CT or TT genotype of ADRBK1 rs1894111 might be at higher risk for hypertension. When hypertensive

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Table 4. logistic regression analysis in hypertensive group and various PRA hypertensive groups.

	Hypertension group			Quartile 1			Quartile 4		
	OR	95%CI	*P*	OR	95%CI	*P*	OR	95%CI	*P*
rs1894111									
CC	1			1			1		
CT+TT	1.590	1.022–2.474	0.040	1.845	1.119–3.042	0.016	1.657	0.905–3.036	0.102
Age	1.150	1.135–1.175	<0.001	1.102	1.081–1.124	<0.001	1.191	1.161–1.221	<0.001
Gender									
Female	1			1			1		
Male	1.991	1.537–2.579	<0.001	1.446	1.059–1.975	0.020	5.174	3.446–7.770	<0.001
BMI									
≤24	1			1			1		
>24	2.764	2.119–3.604	<0.001	2.817	2.027–3.915	<0.001	1.830	1.223–2.739	0.003

BMI – body mass index; OR – odds ratio; 95%CI – 95% confidence interval. P<0.05 was considered significant. Logistic regression model enter with indicator variables for age, gender, BMI, dominant model (CC *vs.* CT+TT) of rs1894111 as independent variables.

patients were divided into subgroups according to PRA, the distribution of the dominant model (CC *vs.* CT+TT) of ADRBK1 rs1894111 in the quartile 1 group with the lowest PRA was found to be the lowest. Furthermore, logistic regression analysis indicated that the dominant model (CC *vs.* CT+TT) of ADRBK1 rs1894111 was significantly associated with an increased OR of hypertension in the quartile 1 group with the lowest PRA, even after adjustment for age, gender, and BMI, but was not significantly different from quartile 4 with the highest PRA. We did not find relationships between rs7127431/rs4930416 and hypertension. Thus, the study suggests that variation of ADRBK1 rs1894111 might more easily happen in low-renin hypertension, potentially indicating that the risk of hypertension is higher in low-renin hypertensive patients with CT or TT genotype of rs1894111. Johnson [18] showed that the variation of ADRBK1 rs1894111 and rs4930416 in hypertensive patients varied significantly in response to diuretics during decreased blood pressure. Diuretics might be a better choice for low-renin hypertension patients. We reached the same conclusion in the present study, which study indicates that rs1894111 of the ADRBK1 gene might be a susceptible locus for low-renin hypertension and might offer a therapeutic strategy for low-renin hypertension. However, further studies on associations between genetic variations of ADRBK1 and low-renin hypertension are needed.

Our study has several limitations. First, study subjects included middle-aged individuals and males accounted for most of the subjects, which may to some extent limit the validity of our findings. Second, because it was a case-control study, we cannot conclude there is a causal relationship between genetic variation of ADRBK1 and low-renin hypertension, suggesting that further studies are needed to verify our speculations. Finally, further studies should expand the sample size to investigate or verify our study conclusion regarding the interaction between ADRBK1 variation and various PRA hypertension groups.

Conclusions

We found that polymorphisms of the ADRBK1 gene may be associated with low-renin hypertension in Han Chinese. Genetic variation of ADRBK1 rs1894111 might more easily occur in low-renin hypertension. The CC genotype of ADRBK1 rs1894111 might be a protective genetic marker for low-renin hypertension, but T allele may be a genetic risk marker for this subtype of hypertension in Han Chinese.

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Conflict of interest

The authors declare that they have no conflict of interest.

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