Vitamin D Receptor Genetic Polymorphism Is Significantly Associated With Decreased Risk of Hypertension in a Chinese Han Population

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The aim of this study was to investigate the association of vitamin D receptor (VDR) gene polymorphism and hypertension in a Chinese Han population. The authors genotyped 3 tagSNPs (rs11574129, rs2228570, and rs739837) of the VDR gene using TaqMan assays in a case-control study including 2409 patients with hypertension and 3063 controls. The results showed that rs2228570 presented statistical correlations with decreased risk of male hypertension after adjustment for confounding factors, odds ratios (ORs) and 95% confidence intervals (CIs) of additive, dominant, and recessive models were 0.828 (0.74–0.927), 0.75 (0.631–0.89), and 0.816 (0.67–0.995), and *P* values were .001, .001, and .044, respectively. Significant associations were found in the smoking population and ORs (95% CIs) of additive and dominant models were 0.81 (0.69–0.952) and 0.71 (0.552–0.913) (*P* values .011 and .008), respectively, after adjustment for covariates. Quantitative trait analysis indicated that the untreated cases with TT genotype of rs2228570 showed higher systolic blood pressure compared with the TC/CC genotype (*P*=.015). Our findings suggest that VDR genetic polymorphism rs2228570 is significantly associated with the decreased risk of hypertension in Chinese men and smokers. *J Clin Hypertens (Greenwich).* 2014; 16:634–639. © 2014 Wiley Periodicals, Inc.

Vitamin D deficiency is very common in Chinese individuals and previous studies have shown that low vitamin D levels represent a risk for hypertension.[1,2] Vitamin D undergoes hydroxylation in the maternal liver to form 25-hydroxy vitamin D(25[OH]D), which is an inactive form of this hormone.[3] The active form of vitamin D (1,25-dihydroxy vitamin D_3) results from the activity of 1-a-hydroxylase, mainly in the kidneys.[4] The effect of vitamin D is mediated by the vitamin D receptor (VDR), a member of the nuclear receptor superfamily of ligand-inducible transcription factors involved in various pathological processes.[5–7] The vitamin D–VDR complex was reported as a potential regulator of renin activity in humans[8] and vitamin D may also regulate blood pressure (BP) through effects on calcium homeostasis,[9] vascular smooth muscle cell,[10] and endothelial cell[11] function. In addition, vitamin D may participate in the regulation of inflammation[12] and insulin sensitivity.[13]

Since the discovery of the VDR gene, common single nucleotide polymorphisms (SNPs) have been described in the gene encoding VDR. A previous genome-wide association study (GWAS) reported that the SNP FokI (rs2228570) in the VDR gene is associated with hypertension in the French population.[14] In a study of healthy Spanish patients, systolic BP (SBP) with BsmI (rs1544410) CC genotype was higher than TC or TT genotypes in men but not in women.[15] On the contrary, in a Korean study, BsmI T allele carriers had higher SBP, higher diastolic blood pressure (DBP), and higher prevalence of hypertension than CC carriers.[16] Recently, a prospective cohort of American men found suggestive evidence for associations of VDR BsmI and FokI polymorphisms with hypertension risk.[17] Data from an Indian study also suggest that VDR gene FokI polymorphism is associated with the risk of developing essential hypertension.[18] To evaluate whether VDR gene variants are associated with risk of hypertension in Chinese individuals, we conducted a case-control study in a Han Chinese population.

METHOD

Patients

A total of 2409 patients with hypertension and 3063 age-matched (5 years group) controls were recruited from a community-based epidemiological survey in Jiangsu Province, China. Both the case and control populations were of Han ethnicity. All patients taking antihypertensive drugs and/or individuals with SBP ≥140 mm Hg and/or DBP ≥90 mm Hg for consecutive measurements were selected. The individuals free of hypertension and with SBP <140 mm Hg and DBP <90 mm Hg were assigned to the control group. The individuals with self-reported history of chronic diseases of the kidney or liver or cancer were excluded from the study. Diabetes in this study was defined as serum fasting blood glucose >7 mmol/L (126 mg/dL) or history of a previous diagnosis of diabetes. The experimental protocol was approved by the institutional ethic board of our institution. All patients accepted written informed consent.

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Each participant was interviewed using a standardized questionnaire that included information on sex, age, history of hypertension, diabetes, and smoking. Height and weight were measured and used for calculation of body mass index (BMI) in kg/m^2. BP was measured using a mercury sphygmomanometer. The measurement was taken on the right arm in a sitting position with the elbow at the level of the right atrium using an appropriately sized cuff after the participant rested for 15 minutes in a seated position. SBP was determined by the onset of the "tapping" Korotkoff sounds (K1) and DBP was determined by the fourth Korotkoff sound (K4). Three readings were taken 5 minutes apart and the average of the 3 measurements was recorded. Participants were not permitted to smoke or drink alcohol or coffee in the hour before the BP measurement. The serum levels of low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), triglycerides (TGs), and fasting blood glucose (GLU) were measured enzymatically on a Hitachi automatic biochemistry analyzer 7100 (Hitachi High-Technologies Corporation, Tokyo, Japan). Moreover, smokers were defined as patients who smoked ≥20 cigarettes per week for more than 3 consecutive months each year.

SNPs Selection

The VDR gene (gene ID: 7421) is located on chromosome 12 at q11–q13. We searched the SNPs with minor allele frequency ≥0.05 from HapMap of Han Chinese in Beijing, China (dbSNP, build125; available at http://www.ncbi.nlm.nih.gov/SNP/; HapMap Data Rel 21/phaseII Jul 06) and applied the linkage disequilibrium method to select tagging SNPs (tagSNPs) with $r^2 \geq 0.80$ as candidate SNPs. We also selected tagSNPs as well as priory selecting potential function with bioinformatics effect prediction (Table S1). Three SNPs (rs11574129, rs2228570, and rs739837) were selected. The rs11574129 and rs739837 were located in the 3′ untranslated region, which is predicted to regulate the micoRNA banding. The SNP rs2228570 lay in the exon coding region as predicted as a splicing enhancer, which was reported to be associated with hypertension in GWAS.[14]

Genotyping

Genomic DNA was extracted from leukocytes using the Tiangen RelaxGene Blood DNA System (No. DP319, Tiangen Biotech, Beijing, China). All samples were processed by technicians blinded to the identity of case and control samples. Genotyping was performed using the TaqMan allelic discrimination assay on the platform of 7900HT Real-Time Polymerase Chain Reaction System (Applied Biosystems, Foster City, CA) without knowing the patients' status (case or control). The genotyping results were determined by using SDS 2.3 Allelic Discrimination Software (Applied Biosystems). The success rates of all 3 SNPs were 99.7%. From randomly selected samples, 5% were genotyped again for quality control with complete concordance.

Statistical Analysis

Measurement data are presented as means ± standard deviations. Mean comparison between two groups was performed with *t* test and multiple group means were compared with one-way analysis of variance. Chi-square or Fisher exact tests were used for categorical variables. Multiple logistic regression was applied to adjust for covariates including age, sex, TG, TC, LDL-C, HDL-C, GLU, and smoking. The general linear model (GLM) was applied to compare blood pressure levels between genotypes and adjusted for confounding factors. The probability for entry was 0.05 and that for removal was 0.1. The data were statistically analyzed with SPSS version 13.0 (SPSS, Inc, Chicago, IL).

Hardy-Weinberg equilibrium (HWE) was assessed by Fisher exact chi-square test using the program HWE in controls. All tests were two-sided and the statistical significance level was set at $P<.05$.

RESULTS

Clinical Characteristics

The clinical characteristics of the case and control groups are shown in Table I. There were 1137 men and 1272 women in the case group and 1499 men and 1564 women in the control group. There was no significant difference in terms of sex proportions between patients and controls. However, the case group had a higher mean age (60.72±11.16 years) and BMI (24.73±3.43) compared with the control group (58.13±11.02 years and 23.67±3.05; $P<.05$), although the age-matched (5 years group) method was used. The mean TC, LDL-C, HDL-C, and smoking prevalence did not differ between patients and controls. As expected, patients had significantly higher SBP (141±14 mm Hg) and DBP (88±8 mm Hg) than controls (121±12 mm Hg, 77±7 mm Hg), respectively ($P<.05$). The mean TG and GLU levels of patients were significantly higher than those in controls ($P<.05$), and there was a higher prevalence of diabetes compared with the control group ($P<.05$).

Association Analyses for Hypertension

In Table II, we summarized the genotype and allele distributions of the 3 SNPs between hypertension cases and controls. All 3 SNPs in controls were consistent with the HWE ($P>.1$). The results indicated that there were no significant differences in genotype and allele frequencies of the 3 SNPs observed between case and control groups, even after adjusting for covariates of sex, age, BMI, TC, TG, HDL-C, LDL-C, GLU, and smoking ($P>.05$).

We further evaluated the associations of 3 candidate SNPs and hypertension in subgroups stratified by sex, age, and smoking. In the male group, rs2228570 presented statistical correlations with decreased risk of hypertension after adjusting for confounding factors. Odds ratios (ORs) and 95% confidence intervals (CIs) of additive, dominant, and recessive models were 0.828

TABLE I. Clinical Characteristics of Hypertension Cases and Controls

	Case Patients (n=2409)	Controls (n=3063)	χ^2/t	*P* Value
Men/women, No.	1137/1272	1499/1564	1.637	.201
Age, y	60.72±11.16	58.13±11.02	8.579	<.001
BMI, kg m^{-2}	24.73±3.43	23.67±3.05	11.953	<.001
SBP, mm Hg	141±14	121±12	57.131	<.001
DBP, mm Hg	88±8	77±7	52.695	<.001
GLU, mmol/L	5.78±1.88	5.44±1.5	7.046	<.001
TC, mmol/L	4.98±1.05	4.93±1.01	1.791	.073
TGs, mmol/L	1.87±1.57	1.57±2.07	5.876	<.001
LDL-C, mmol/L	2.87±0.88	2.84±0.79	1.396	.168
HDL-C, mmol/L	1.35±0.33	1.36±0.33	0.921	.375
Smoking, %	24.11	22.2	2.7	.1
Diabetes, %	15.6	10.3	34.6	<.001

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; GLU, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

TABLE II. Association Analysis of the Three SNPs of VDR Gene and Hypertension

		Genotype OR (95% CI)[a]					Allele		
SNP	Group	WT	Ht + MT	Additive	Dominant	Recessive	Major/Minor	OR (95% CI)	*P* Value
rs11574129		TT	TC + CC				T/C		
	Case	1636	691 + 82	1.041 (0.941–1.152)	1.046 (0.93–1.177)	1.073 (0.791–1.456)	3963/855	0.97 (0.88–1.07)	.603[b]
	Control	2098	864 + 99	*P*=.432	*P*=.454	*P*=.648	5060/1062		.385[c]
rs2228570		TT	TC + CC				T/C		
	Case	756	1180 + 472	0.951 (0.88–1.028)	0.939 (0.834–1.058)	0.929 (0.81–1.065)	2692/2124	1.07 (0.99–1.15)	.096[b]
	Control	910	1500 + 648	*P*=.203	*P*=.302	*P*=.292	3320/2796		.161[c]
rs739837		TT	TC + CC				T/C		
	Case	1249	970 + 185	1.053 (0.966–1.148)	1.077 (0.965–1.203)	1.032 (0.84–1.269)	3468/1340	0.96 (0.88–1.05)	.361[b]
	Control	1638	1186 + 235	*P*=.242	*P*=.186	*P*=.761	4462/1656		.319[c]

Abbreviations: CI, confidence interval; Ht, heterozygote; MT, mutant type; OR, odds ratio; SNP, single nucleotide polymorphism; VDR, vitamin D receptor; WT, wild type. [a]Adjusted for sex, age, body mass index, total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, glucose, and smoking. [b]*P* value of χ^2 test for comparison of allele between the case and control groups. [c]*P* value of Fisher exact χ^2 test for Hardy-Weinberg equilibrium.

(0.74–0.927; *P*=.001), 0.75 (0.631–0.89; *P*=.001), and 0.816 (0.67–0.995; *P*=.044), respectively. The additive and dominant models still presented statistical significance after Bonferroni correction (*P*×6). Significant associations were also found in smokers, and ORs (95% CI) of additive and dominant models were 0.81 (0.69–0.952; *P*=.011) and 0.71 (0.552–0.913; *P*=.008), respectively, after adjusting for covariates (Table III). However, there were no significant associations between the other two SNPs (rs11574129 and rs739837) and hypertension in subgroups stratified by sex, age, and smoking, even after adjusting for covariates (*P*>.05) (Table S2 and Table S3).

Quantitative Trait Analysis for BP

Since antihypertensive drugs affect the BP of treated patients, we divided the patients into two subgroups by treatment to compare BP levels between genotypes (Table IV). Quantitative trait analysis with GLM showed that the TC/CC group of rs2228570 had lower SBP than the TT genotype group in treated hypertension case patients (*P*=.002). After adjustment for confounding factors of sex, age, BMI, TC, TG, HDL-C, LDL-C, GLU, and smoking, the differences among treated groups remained statistical significant (*P*=.002) and the untreated hypertension cases with the TT genotype of rs2228570 showed higher SBP compared with patients with the TC/CC genotype (*P*=.015). Neither significant SBP differences among genotypes of rs11574129 and rs739837 nor significant DBP differences among different genotypes of the 3 SNPs were found in treated and untreated hypertension cases.

DISCUSSION

Vitamin D regulates BP through the renin-angiotensin system (RAS).[19] Previous studies have shown that vitamin D can down-regulate the RAS, a key regulatory cascade controlling BP. Treatment of cells with active vitamin D directly reduced the promoter activity on the renin gene.[19] In VDR knockout mouse, renin expression

TABLE III. Stratified Analysis for Association of rs2228570 and Hypertension

Stratum	Group	WT/Ht/MT	Genotype OR (95% CI)[a]		
			Additive	Dominant	Recessive
Sex					
Male	Case	388/533/215	0.828 (0.74–0.927)	0.75 (0.631–0.89)	0.816 (0.67–0.995)
	Control	416/748/330	*P*=.001	*P*=.001	*P*=.044
Female	Case	368/647/257	1.067 (0.957–1.19)	1.129 (0.955–1.334)	1.042 (0.861–1.261)
	Control	494/752/318	*P*=.242	*P*=.155	*P*=.673
Age					
<55 y	Case	234/391/154	0.983 (0.864–1.119)	1.069 (0.875–1.307)	0.873 (0.697–1.095)
	Control	390/608/291	*P*=.799	*P*=.513	*P*=.24
≥55 y	Case	522/789/318	0.928 (0.841–1.023)	0.873 (0.752–1.013)	0.95 (0.8–1.129)
	Control	520/892/357	*P*=.132	*P*=.074	*P*=.56
Smoking					
Smoking	Case	191/271/119	0.810 (0.69–0.952)	0.710 (0.552–0.913)	0.811 (0.614–1.071)
	Control	183/336/160	*P*=.011	*P*=.008	*P*=.14
Nonsmoking	Case	565/909/353	0.991 (0.906–1.083)	1.003 (0.876–1.149)	0.967 (0.826–1.132)
	Control	727/1164/488	*P*=.836	*P*=.965	*P*=.676

Abbreviations: Ht, heterozygote; MT, mutant type; WT, wild type. [a]Adjusted for sex, age, body mass index, total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein, glucose, and smoking.

TABLE IV. Quantitative Trait Analysis for Blood Pressure (mm Hg) Between Genotypes of VDR Gene

SNPs	Genotype	SBP			DBP		
		Case			Case		
		Treated	Untreated	Control	Treated	Untreated	Control
rs11574129	WT	140.74±16.901 (836)	142.77±10.346 (800)	120.87±12.458 (2098)	87.18±9.226 (836)	89.57±6.377 (800)	77.3±6.67 (2098)
	Ht	138.99±16.221 (383)	142.44±10.91 (308)	120.37±12.62 (864)	85.9±9.122 (383)	89.09±6.432 (308)	77.29±6.78 (864)
	MT	140.95±16.491 (44)	139.59±8.267 (38)	121.4±12.05 (99)	87.52±9.202 (44)	89.47±4.191 (38)	77.24±6.08 (99)
	F	1.29	1.59	0.418	1.862	0.907	0.022
	P[a]	.276	.204	.658	.156	.404	.978
rs2228570	WT	139±15.591 (404)	143.72±10.652 (352)	121.16±12.23 (910)	86.54±9.051 (404)	90.04±6.181 (352)	77.36±6.76 (910)
	Ht	141.85±16.982 (628)	142.28±10.458 (552)	120.57±12.68 (1500)	87.22±9.341 (628)	89.17±6.348 (552)	77.11±6.56 (1500)
	MT	137.98±17.347 (230)	141.61±10.01 (242)	120.76±12.45 (648)	86.15±9.095 (230)	89.19±6.472 (242)	77.66±6.87 (648)
	F	6.249	4.225	1.244	2.168	2.304	2.256
	P[a]	**.002**	**.015**	.289	.115	.1	.105
rs739837	WT	140.48±16.731 (649)	142.56±9.949 (600)	120.89±12.32 (1638)	86.97±8.971 (649)	89.41±6.428 (600)	77.4±6.59 (1638)
	Ht	140.17±16.85 (508)	142.83±11.096 (462)	120.55±12.74 (1186)	86.71±9.411 (508)	89.45±6.472 (462)	77.12±6.85 (1186)
	MT	138.57±15.226 (104)	141.52±10.385 (81)	120.9±12.4 (235)	86.05±9.417 (104)	89.54±4.764 (81)	77.5±6.69 (235)
	F	0.664	0.771	0.592	0.525	0.151	0.88
	P[a]	.515	.463	.553	.592	.859	.415

Abbreviations: DBP, diastolic blood pressure; Ht, heterozygote; MT, mutant type; SBP, systolic blood pressure; SNP, single nucleotide polymorphism; VDR, vitamin D receptor; WT, wild type. [a]Adjusted for sex, age, body mass index, total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein, glucose, and smoking.

and plasma angiotensin II concentrations dramatically increased and BP elevated.[19] In individuals with insufficient vitamin D, plasma concentrations of renin[20] and angiotensin II were higher, and renal plasma flow response to infused angiotensin II was blunted.[21] Genetic variation at the FokI (rs2228570) polymorphism of the VDR gene, in combination with 25(OH)D levels, was associated with plasma renin activity (PRA) in hypertension.[8] In fact, the pandemic of vitamin D deficiency could be the other face of increased RAS activity, which could potentially cause lower activity or lower levels of vitamin D.[22]

The T and C allele frequencies of FokI (rs2228570) were 55.9%, 44.1%, and 54.3% and 44.7%, respectively, in hypertension cases and controls in this study. These values are similar to data in the Chinese population in HapMap, whereas they are inconsistent with previous reports in Indian[17] and American[17] populations. Thus, it is necessary to replicate the association of VDR polymorphisms and hypertension

in the Chinese population. The results of this study indicated that SNP rs2228570 was significantly associated with hypertension in men. In addition, further correlation of genetic variation and the trait of SBP were replicated in untreated hypertension cases in accordance with American reports.[17]

The SNP FokI (rs2228570) consisted of a T to C variation at translation initiation codon (AGT) in the exon 2.[13,23] The change appears to result in the synthesis of a smaller (49.5 kD) protein with increased biological activity[24] and might be associated with a decreased risk of hypertension. The reason for the difference in activity of the two proteins, for example, whether it is caused by a difference in the ability to bind 1,25-dihydroxy vitamin D_3 or to activate transcription, remains to be determined.

The FokI (rs2228570) polymorphism and 25(OH)D were reported to regulate PRA of hypertension patients[8] and that might be helpful to explain the genetic effect of VDR on the decreased risk of hypertension as well as BP. In the Spanish study, a positive correlation between serum 25(OH)D and SBP was found only in men with VDR BsmI (rs1544410) TT genotype.[15] The authors postulated that the carriers of the BsmI (rs1544410) T allele might be more sensitive to the effect of vitamin D, but no significant interactions of circulating vitamin D metabolites and FokI (rs2228570) polymorphism was found for hypertension.[17]

Smoking is reported as a strong and independent risk factor of hypertension. The findings of this study suggest that smoking modified the genetic effect of SNP rs2228570, which was similar to the findings reported in an Indian population.[18] Meanwhile, cigarette smoke extracts were proven to inhibit the translocation of VDR from the nucleus to microsomes in a dose-dependent manner.[25] As men have a relatively high prevalence of smoking, further study to distinguish the independent modification of sex or smoking for VDR genetic effect on hypertension is warranted.

STUDY LIMITATIONS

Although there are some limitations in our study, including the lack of plasma vitamin D levels and potential bias from case-control study, the current investigation is the largest study in terms of sample size in a Chinese population to investigate the relationship between VDR genetic polymorphism and hypertension. We adjusted for confounding factors and carried out subgroup analysis by sex, smoking, and age. The findings of this study provide new insights into the genetic variants at VDR gene and the susceptibility of hypertension.

CONCLUSIONS

This study provides further evidence that rs2228570 in the VDR gene is associated with decreased risk of hypertension and SBP in a Chinese Han population. Further population and functional studies of VDR gene as well as other risk factor and hypertension will provide important validation for these results.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Biological Information Analysis for Candidate SNPs of VDR.

Table S2. Stratified Analysis for Association of rs11574129 and Hypertension.

Table S3. Stratified Analysis for Association of rs739837 and Hypertension.