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The association between vitamin D receptor gene polymorphism and susceptibility to hypertension: a meta-analysis

Y.-B. ZHU, Z.-Q. LI, N. DING, H.-L. YI

Department of Cardiovascular Surgery II, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China

Abstract. – OBJECTIVE: Current studies reporting the association between VDR polymorphisms and susceptibility to hypertension are controversial. This meta-analysis aims to obtain a precise correlation estimate between VDR polymorphisms and susceptibility to hypertension.

MATERIALS AND METHODS: Relevant studies were searched in PubMed, Web of Science, CNRI, Wanfang, and VIP using the keywords as "Vitamin D receptor, hypertension", "Vitamin D receptor polymorphism, hypertension", and "VDR, hypertension". ORs and corresponding 95%CI of eligible studies were calculated using RevMan5.3 and STATA12.0.

RESULTS: Seven independent studies reporting the association between VDR gene polymorphisms and hypertension were enrolled. VDR rs1544410 (BsmI) was associated with susceptibility to hypertension. The frequency of VDR BsmI AA genotype decreased in hypertension patients compared with healthy controls. The population carrying VDR BsmI AA genotype had lower susceptibility to hypertension relative to those carrying GA or GG genotype (OR = 0.69, 95% CI = 0.54-0.89, *p* = 0.005). Meanwhile, the frequency of A allele was higher in the case group than that of control group (OR = 0.83, 95% CI = 0.69-0.99, *p* = 0.04). No significant correlation was found between VDR FokI or VDR ApaI with susceptibility to hypertension.

CONCLUSIONS: VDR BsmI gene polymorphism is closely related to the susceptibility to hypertension.

Key Words:
Hypertension, Polymorphisms, VDR.

Introduction

Hypertension, defined as blood pressure equal to or greater than 140/90 mmHg, affects 25-43% of the population over 18 years globally. It is a major risk factor for death from cardiovascular diseases[1-3]. As a common chronic disease, long-term, and severe hypertension can lead to stroke, a disease with high disability and mortality[4]. Essential hypertension (EH) is a polygenic disease resulting from the interaction of genetic and environmental factors. Gene researches on hypertension have been widely conducted[5].

Recent studies have shown that vitamin D deficiency is associated with many non-skeletal chronic diseases, including cardiovascular diseases and hypertension. Vitamin D can downregulate the renin-angiotensin system (RAS), which is the key to control blood pressure (BP)[6]. Vitamin D deficiency is very common in the Chinese population. Low level of vitamin D is considered to be a risk factor for hypertension[7]. Vitamin D receptor (VDR) is a typical nuclear protein receptor. VDR mediates the physiological role of vitamins by regulating related target genes in the nucleus, thus participating in many pathophysiological processes. A great number of reports[7-9] considered that the susceptibility to hypertension is negatively correlated to vitamin D level. However, reports on exploring VDR and hypertension are rare. Wang et al[10] found that the VDR BsmI and FokI polymorphisms are associated with hypertension in the US population. Swapna et al[11] conducted in the Indian population suggested that the VDR FokI polymorphism is a risk factor for EH. Nevertheless, conclusions on the association between VDR and hypertension are inconsistent due to differences in individual samples and design schemes. The meta-analysis is an effective tool for improving statistical effectiveness by summarizing data from different studies. This research focused on the association between VDR polymorphism and susceptibility to hypertension.

Corresponding Author: Zhiqiang Li, MD; e-mail: cardiacsurgoen@yeah.net

Materials and Methods

Literature Searching

Relevant studies in PubMed, Web of Science, CNRI, Wanfang, and VIP published before April 2019 were searched using the keywords as "Vitamin D receptor, hypertension", "Vitamin D receptor polymorphism, hypertension", and "VDR, hypertension". References in each report were manually checked.

Inclusive criteria: (1) Subjects in case group were those with SBP ≥ 140 mmHg and/or DBP≥90 mmHg, and took anti-hypertension drugs; subjects in control group were non-hypertension (SBP < 140 mmHg and DBP<90 mmHg). (2) Subjects in case group did not have other medical history or limited factors except for hypertension. (3) Data were adequate that provided the frequency of each genotype or raw data for calculating the genotype frequency. (4) Studies reporting the association between VDR polymorphisms and susceptibility to hypertension. (5) Genotype frequency was in accordance with HWE (Hardy-Weinberg equilibrium).

Exclusive criteria: (1) Reviews, comments, animal experiments, mechanism researches and case reports. (2) Repeatedly published articles. (3) Non-polymorphism researches. (4) Studies with inadequate data.

The flow diagram of the publication selection process was depicted in Figure 1.

Data Extraction

Data were independently extracted and analyzed by two researchers. Any disagreement was solved by the third researcher. Extracted data included: first author, year of publication, country of publication, genotype number, and distribution, case number, etc.

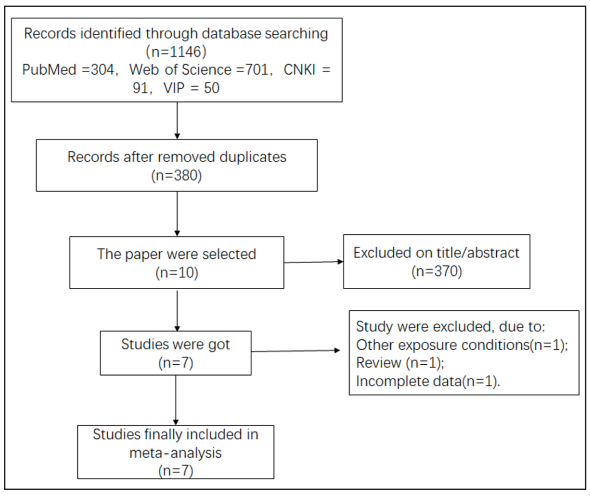

Figure 1. Flow diagram of the publication selection process.

Statistical Analysis

Heterogeneity test was conducted by calculating ORs and the corresponding 95% CI with the I^2 test and the Q test. The pooled OR in studies lacking the heterogeneity was calculated by the fix-effect model; otherwise, a random-effect model was used. Sensitivity analysis was performed by removing one study each time and analyzing the ORs of the remaining in a combined way. The HWE of control genotype distribution was evaluated using the χ^2-test and $p<0.05$ considered as inequivalent. Publication bias was evaluated by depicting funnel plots and quantified by Egger's test. Data analyses were conducted using RevMan 5.3 and STATA12.0 (London, UK).

Results

Baseline Characteristics of Eligible Studies

Initially, a total of 1146 relevant studies were searched from the databases. 380 replicates and 370 irrelevant studies were excluded after the first-round screening. For the 10 remaining, one study with inadequate data, one review, and one study included other exposure factors were excluded. At last, 7 eligible studies were enrolled in this study (Figure 1)[10-16].

Baseline characteristics of these 7 studies were listed in Table I. They were published from 2011 to 2019. Totally, 4011 subjects were in case group and 4847 were in control group. The number in case group and control group of each study was 71-2409 and 72-3063, respectively. Blood samples of subjects were analyzed by PCR/PCR-RFLP/TaqMan. Meanwhile, genotype frequency in control group was in accordance with HWE.

Meta-Analysis Results

Correlation analysis of VDR rs2228570 (FokI) and susceptibility to hypertension.

Seven studies[10-16] including 4011 hypertension patients and 4847 healthy controls carrying VDR rs2228570 (FokI) were analyzed. Different genetic models were utilized for assessing their correlation. According to the heterogeneity test results, a fixed-effect model ($I^2 > 50\%$, $p < 0.05$)

Table I. Main characteristics of studies included in the meta-analysis.

Author	Year	Country	Journal name/ publication origin	Genotyping methods	SNP loci (p_{HWE})	Sample size	Control	Sample
Swapna et al[11]	2011	Indian	Indian J Hum Genet	PCR-RFLP	rs2228570 (p_{HWE} = 0.67)	280 (male = 149, females = 131)	200 (males = 138, females = 62)	Blood
Wang et al[10]	2013	USA	Eur J Nutr	PCR	rs2228570 (p_{HWE} = 0.34); rs1544410 (p_{HWE} = 0.12)	537	376	Blood
Jia et al[12]	2014	China	J Clin Hypertens	TaqMan	rs2228570 (p_{HWE} = 0.52)	2409 (males = 1137, females = 1272)	3063 (males = 1499, females = 1564)	Blood
Cottone et al[13]	2015	Italy	J Hum Hypertens	PCR-RFLP	rs2228570 (p_{HWE} = 0.38); rs1544410 (p_{HWE} = 0.62)	71	72	Blood
Lai et al[14]	2018	China	Strait J Prev Med	PCR-RFLP	rs2228570 (p_{HWE} = 0.13)	212 (males = 110, female = 102)	315 (males = 157, females = 158)	Blood
Zhang et al[16]	2018	China	J Clin Med Pract	TaqMan-MGB	rs2228570 (p_{HWE} = 0.36); rs7975232 (p_{HWE} = 0.25)	289 (males = 132, females = 157)	650 (males = 315, females = 335)	Blood
Xia et al[15]	2019	China	Chin J Geriatr Heart Brain Vessel Dis	PCR-RFLP	rs1544410 (p_{HWE} > 0.05); rs2228570 (p_{HWE} = 0.80); rs7975232 (p_{HWE} = 0.18)	228	184	Blood

SNP = Single nucleotide polymorphism; HWE = Hardy-Weinberg equilibrium; pHWE = *p*-value of Hardy-Weinberg Equilibrium test in controls for each locus; PCR = polymerase chain reaction.

was conducted except for the recessive genetic model (CC *vs.* TT & TC), which was analyzed in the random-effects model (I^2 = 32%, p = 0.18). We did not identify a significant correlation between VDR rs2228570 (FokI) and susceptibility to hypertension (Table II).

Subgroup Analyses

Four studies[12,14-16] reported the relation between VDR rs2228570 (FokI) and susceptibility to hypertension in Chinese population. According to the heterogeneity test, a fixed-effect model was used (Figure 2). We did not identify a significant correlation between VDR rs2228570 (FokI) and susceptibility to hypertension in the dominant genetic model (CC *vs.* CT&TT), recessive model (TT *vs.* CC&CT), super-dominant genetic model (CT *vs.* CC&TT), and allelic model (C Allele *vs.* T Allele) ($p > 0.05$).

Correlation Analysis of VDR rs1544410 (BsmI) and Susceptibility to Hypertension

Three studies involving 826 hypertension patients and 627 healthy controls carrying VDR rs1544410 (BsmI) were analyzed. I^2 for the dominant genetic model, recessive model, super-dominant genetic model, and allelic model was 39%, 23%, 41%, and 49%, respectively ($p > 0.05$). Higher risk of hypertension was observed in the population carrying GA&AA genotype relative to those carrying GG genotype (OR = 1.32, 95% CI = 1.05-1.68, p = 0.02). In addition, hypertension risk was lower in the population carrying AA genotype relative to those with GA or GG genotype (OR = 0.69, 95% CI = 0.54-0.89, p = 0.005). Consistently, in the super-dominant genetic model, people carrying GA genotype had a higher risk of hypertension than those carrying AA or GG genotype (OR = 1.27, 95% CI = 1.01-1.60, p = 0.04). The frequency of A allele was higher in the case group than that of control group (OR = .83, 95% CI = 0.69-0.99, p = 0.04) (Table III).

Correlation Analysis of VDR rs7975232 (ApaI) and Susceptibility to Hypertension

Two studies including 517 hypertension patients and 355 healthy controls carrying VDR rs7975232 (ApaI) were analyzed[15,16]. I^2 for the four genetic models was 36%, 70%, 81%, and 0%, respectively. Hence, a fixed-effect model was utilized in the dominant genetic model and allelic model, and the others were analyzed in the random-effect model. The data showed no remarkable correlation between VDR rs7975232 (ApaI) and susceptibility to hypertension (Table IV).

Sensitivity Analysis

Heterogeneity was observed in the 7 enrolled studies, which were still present after the removal of any single study (data not shown).

In subgroup analyses on reporting the relation between VDR rs1544410 (FokI) and susceptibility to hypertension in the Chinese population, a remarkable heterogeneity was identified. Heterogeneity existed after removing one study each time (data not shown).

Publication Bias

Egger's test showed no publication biases in studies reporting the association between VDR rs2228570 (FokI), rs1544410 (BsmI), and susceptibility to hypertension (Tables II, III). Besides, sample size of people carrying rs7975232 (ApaI) was too small for conducting the Egger's test.

Discussion

EH is a major risk factor for stroke, coronary heart disease, and death in the Chinese population[17]. The pathogenesis of hypertension is complex. Genetic factors are one of the important reasons for the pathogenesis of hypertension. At present, only a few studies[10-16] have found that VDR gene polymorphisms may be associated with the onset of hypertension.

Vitamin D is known for its important role in regulating calcium and phosphorus levels, and bone mineralization[18]. In addition, it also participates in anti-oxidation, free radical scavenging, and neuroprotection[19]. Therefore, vitamin D is of significance in the occurrence and development of hypertension. It is reported that vitamin D regulates blood pressure through the RAS[20].

The VDR gene locates on the chromosome 12q13.11 and consists of 9 exons and 8 introns[21,22]. As a ligand-activated transcription factor, VDR is widely expressed in various tissues. VDR is mainly responsible for the degradation and synthesis of vitamin D by forming a complex, thus affecting its metabolic concentration[21]. Mean-

Table II. Correlation analysis of VDR rs2228570 (FokI) and susceptibility to hypertension.

Comparison	Included studies, no.	Case no.	Control no.	Heterogeneity test			Meta-analysis		Egger (p)
				I^2, %	p (I^2)	Model	OR (95% CI)	p	
TC&CC *vs.*TT	7	4011	4847	86%	< 0.00001	R	1.02 (0.75-1.38)	0.90	0.892
CC *vs.* TT&TC	7	4011	4847	32%	0.18	F	0.98 (0.88-1.09)	0.68	0.629
TC *vs.* TT&CC	7	4011	4847	78%	0.0001	R	0.97 (0.77-1.23)	0.82	0.534
T *vs.* C	7	8022	9694	82%	< 0.00001	R	1.02 (0.84-1.23)	0.86	0.883

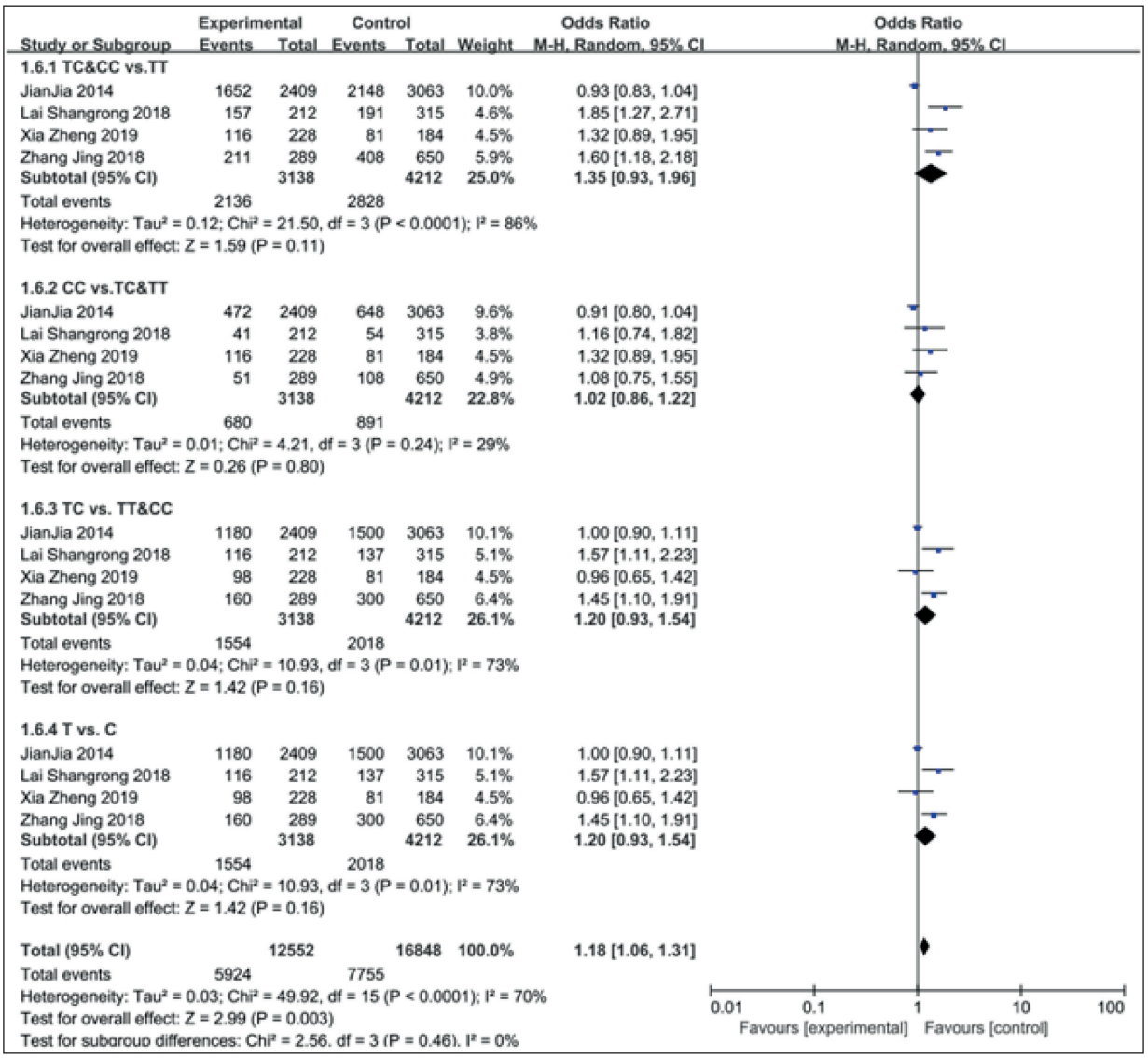

Figure 2. Forest map of subgroup analysis on the correlation between VDR rs2228570 (FokI) and susceptibility to hypertension.

while, the complex is also a potential factor in the regulation of renin activity. Many studies have investigated the relationship between VDR gene polymorphism and susceptibility to hypertension, while they obtain controversial results.

In our work, we examined the association between VDR gene polymorphisms and susceptibility to hypertension using different genetic models. The reliability of our conclusion was confirmed by heterogeneity analysis and sensitivity analysis.

Among the three VDR gene polymorphisms FokI, BsmI and ApaI, VDR BsmI was associated with susceptibility to hypertension. The frequency of VDR BsmI AA genotype was lower in hypertension patients compared with healthy controls. It is suggested that the population carrying VDR BsmI AA genotype has a lower hypertension risk relative to those carrying GA or GG genotype. Meanwhile, the frequency of A allele was higher in case group than that of control group. As a result, VDR BsmI AA genotype is a protective factor for hypertension. In a study conducted in the Spanish population, serum level of VDR in male population carrying VDR BsmI BB genotype is strongly positively correlated with SBP and DBP[23]. Hence, the presence of the A allele in the BsmI locus is protective for some diseases.

Heterogeneity was observed in the 7 enrolled studies focusing on the association between VDR

Table III. Correlation analysis of VDR rs1544410 (BsmI) and susceptibility to hypertension.

Comparison	Included studies, no.	Case no.	Control no.	Heterogeneity test			Meta-analysis		Egger (p)
				I^2, %	p (I^2)	Model	OR (95% CI)	p	
GA&AA *vs*. GG	3	826	627	39%	0.19	F	1.32 (1.05-1.68)	0.02	0.498
AA *vs*. GG&GA	3	826	627	23%	0.27	F	0.69 (0.54-0.89)	0.005	0.471
GA *vs*. GG&AA	3	826	627	41%	0.18	F	1.27 (1.01-1.60)	0.04	0.146
G *vs*. A	3	1652	1254	49%	0.14	F	0.83 (0.69-0.99)	0.04	0.365

Table IV. Correlation analysis of VDR rs7975232 (ApaI) and susceptibility to hypertension.

Comparison	Included studies, no.	Case no.	Control no.	Heterogeneity test			Meta-analysis	
				I^2, %	p (I^2)	Model	OR (95% CI)	p
GT&TT *vs*. GG	2	517	355	36%	0.21	F	1.05 (0.84-1.32)	0.66
TT *vs*. GG&GT	2	517	355	70%	0.07	R	1.21 (0.54-2.71)	0.64
GT *vs*. GG&TT	2	517	355	81%	0.02	R	0.95 (0.54-1.67)	0.87
G *vs*. T	2	1034	1664	0%	0.83	F	1.04 (0.87-1.23)	0.68

FokI polymorphisms and susceptibility to hypertension. However, the heterogeneity still existed after the removal of any single study. In the four genetic models, no relation was found between FokI polymorphisms and susceptibility to hypertension. Consistently, Cottone et al[13] demonstrated that VDR FokI and BsmI polymorphisms were not correlated to the risk of hypertension. Nevertheless, Swapna et al[11] showed a higher risk for hypertension in populations carrying FF and F allele genotypes of VDR FokI. Ff genotype presents a protective effect on hypertension. In this paper, the subgroup analysis was conducted in the Chinese population. The enrolled 4 studies identified no relation between VDR FokI polymorphisms and susceptibility to hypertension in the Chinese population, which was consistent with the conclusion obtained by Xia et al[15]. Zhang et al[16] reported that VDR FokI Ff genotype may be a risk factor for the onset of hypertension. Such a difference could be explained by differences in the sample sizes, populations or ethnicities of the subjects.

We also found no significant association between the VDR rs7975232 (ApaI) and the risk of hypertension, which was consistent with the results of the included studies. The ApaI polymorphism locates on the 3'UTR of the VDR gene. It is involved in the regulation of gene expressions, mRNA stability, and protein translation efficacy[22]. The association between SNPs and metabolic diseases has been extensively studied. Motohashi et al[24] clarified that VDR rs7975232 (ApaI) polymorphism is related to insulin secretion. Wehr et al[25] showed lower fasting insulin, weaker insulin resistance, and higher insulin sensitivity in polycystic ovary patients carrying AA genotype of VDR.

Some shortcomings of this study should be pointed out. The unadjusted pooled ORs were calculated due to inadequate data that may affect the associated estimates (such as age, gender, etc.). A remarkable heterogeneity was identified in the subgroup analysis. The pooled data in a random-effect model may lead to inaccurate results. Therefore, the findings obtained from this meta-analysis should be carefully accepted.

Conclusions

These results demonstrated that VDR BsmI gene polymorphism is closely related to the susceptibility to hypertension.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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