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Original Article

Association of vitamin d receptor-a gene polymorphisms with coronary heart disease in Han Chinese

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Abstract: Objective: To assess the association between coronary heart disease (CHD) and vitamin D receptor (VDR) gene polymorphisms in Han Chinese adults. Methods: A total of 215 CHD patients and 67 controls were recruited. In both groups, the VDR gene single nucleotide polymorphisms (SNP) of Tru9I (rs757343), ApaI (rs7975232), TaqI (rs731236) and FokI (rs2228570) were detected, and the frequencies of VDR genotypes were compared between patients and controls. The relationship between VDR FokI genotype and risk for CHD was assessed by logistic regression analysis after adjusting for age and sex. In addition, the clinical parameters and biochemical characteristics of CHD subgroups were compared according to the VDR FokI polymorphism. Results: The frequencies of FokI genotypes in CHD patients were 23.7% for AA, 47.9% for AG, and 28.4% for GG. The frequency of FokI-GG genotype significantly decreased in CHD patients as compared to control group ($P = 0.039$). No significant differences were observed in other VDR SNPs (rs7975232, rs731236 and rs757343) ($P > 0.05$) between groups. FokI-A allele carriers had a 2.61-fold increase in the odds (95% CI: 1.116-6.102, $P = 0.027$) as compare to CHD subjects with FokI mutation. In CHD subgroup, patients with GG genotype had a significantly higher concentration of high-density lipoprotein cholesterol than those with AG genotype or A* genotype ($P = 0.001$, respectively). Conclusion: VDR FokI polymorphisms appear to be associated with CHD. GG genotype predicts a higher HDL-cholesterol in CHD adults.

Keywords: Vitamin D receptor, coronary heart disease, gene polymorphism

Introduction

Coronary heart disease (CHD) is the most common cause of death in developed countries and the second most common cause of death in developing countries [1]. The mortality of CHD patients and the risk factors of CHD have substantially increased and continue to rise rapidly in China [2]. Although environmental factors play important roles in the pathogenesis of CHD [3, 4], genetic factors (such as single nucleotide polymorphism; SNP) also affect the occurrence of CHD [5, 6]. However, the exact mechanism underlying the influence of SNP on the pathogenesis of CHD is poorly understood. Some common variants of coronary diseases show allelic heterogeneity or copy number variation.

The vitamin D endocrine system is involved in a wide variety of biological processes including bone metabolism, regulation of cell proliferation and differentiation and modulation of immune responses [7]. The role of vitamin D and vitamin D receptor (VDR) in the skeletal metabolism is well known. VDR gene plays an important role in the vitamin D pathway, and belongs to the steroid hormone family of nuclear receptors which are responsible for the transcriptional regulation of a number of hormone responsive genes. Polymorphisms within the VDR gene may potentially influence the vitamin D expression and the stability of VDR mRNA. Recent studies have well-characterized four VDR polymorphisms Fok1, Bsm1, Apa1 and Taq1 [7]. More recent attention has been focused on the possible role of VDR gene polymorphisms in the development of a range of diseases, including osteoarthritis, psoriasis, diabetes, as well as CHD [8]. However, some results are conflicting. Van Schooten et al. [9] reported an association between VDR BsmI polymorphism and coronary artery disease (CAD) of European white in the Netherlands,

Table 1. Baseline characteristics of CHD patients and controls

	Control	CHD	P
Age	59.64 ± 13.31	62.14 ± 9.40	0.088
Gender (M/F)	44/23	161/54	0.158
Smoking (yes/no)	20/47	113/102	0.001
TG	1.56 ± 1.09	1.44 ± 0.97	0.391
TC	4.53 ± 0.86	4.26 ± 0.99	0.048
HDL-C	1.28 ± 0.35	1.20 ± 0.38	0.112
LDL-C	2.73 ± 0.80	2.66 ± 0.84	0.548
CR	71.67 ± 17.49	78.21 ± 25.29	0.049
FPG	4.95 ± 1.15	5.85 ± 2.41	0.004

Note: TG: triglyceride; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; CR: creatinine; FPG: fasting plasma glucose.

Table 2. Frequencies of VDR FokI, Tru9I, Apa1 and Taq1 genotypes

Genotypes		Controls	Patients	x^2	P
FokI	A	51	205	3.810	0.051
	G	83	225		
	AA	12 (17.9%)	51 (23.7%)	0.994	0.319
	AG	27 (40.3%)	103 (47.9%)	1.190	0.275
	GG	28 (41.8%)	61 (28.4%)	4.258	0.039
Tru9I	A	35	96	0.825	0.364
	G	99	334		
	AA	6	10	1.768	0.184
	AG	23	76	0.023	0.879
	GG	38	129	0.228	0.633
TaqI	T	130	410	0.696	0.404
	C	4	20		
	TT	63	195	1.499	0.221
	TC	4	20	1.499	0.221
	CC	0	0		
ApaI	A	43	129	0.210	0.646
	C	91	301		
	AA	7	18	0.272	0.602
	AC	29	93	0.000	0.997
	CC	31	104	0.091	0.763

while Ortlepp et al. [10] reported no association on the CAD of Aachen in Germany. To date, only a few study has assessed the association between vitamin D related FokI (rs2228570) and BsmI (rs1544410) SNPs and risk for CAD [10, 11], while no comparable study on other SNPs of VDR gene has been carried out. Therefore, this study was undertaken to investigate the association of 4 SNPs of VDR (Tru9I [rs757343], ApaI [rs7975232], TaqI [rs731236] and FokI [rs2228570]) with risk for CHD in Han Chinese.

Materials and methods

Patient selection

A total of 282 subjects who received a clinical assessment and initial treatments between March 2013 and March 2014 were consecutively recruited from the cardiology clinic of the First Affiliated Hospital of Nanchang University. Exclusion criteria included endocrine disorders, inflammatory diseases, history of heart diseases, prior cardiac surgery, malignancies, and known chronic diseases associated with VDR gene polymorphisms. The Ethics Committee of Endocrinology and Metabolism Research Institute approved the whole study protocol. On recruitment, all participants provided written informed consent and were voluntary to participate in this study and receive DNA genotyping.

Coronary angiography

An experienced cardiologist performed angiography on each subject if angiography was indicated. Following angiography, subjects were divided to two groups. In CHD group, more than 50% stenosis was observed. In control group, coronary artery was normal.

Genetic analyses

Fasting blood samples were collected from all the subjects into EDTA-coated tubes for genotyping and DNA was extracted using a Flexi-Gen DNA kit (QIAGEN kit) according to the manufacturer's instructions. The Tru9I, ApaI, TaqI and FokI polymorphisms of VDR gene were detected by polymerase chain reaction. Genotyping was done by sequencing total PCR products. Genotyping of VDR Tru9-I (rs757343), Fok-I (rs2228570), Apa-I (rs7975232) and Taq-I (rs731236) were done with predesigned SNP Genotyping Assay (Applied Biosystems, Carlsbad, CA, USA).

Statistical analysis

Hardy-Weinberg equilibrium was tested by a x^2 goodness-of-fit test. The chi-square test was employed to compare categorical variables. Descriptive data are presented as mean ± standard deviation (SD). Paired t test was per-

Table 3. Clinical and biochemical characteristics of CHD subgroups

	Genotypes		
	A*	GG	P
Age	62.11 ± 9.36	62.23 ± 9.57	0.933
TG	1.46 ± 0.98	1.38 ± 0.94	0.566
TC	4.23 ± 0.90	4.34 ± 1.18	0.425
HDL	1.16 ± 0.33	1.34 ± 0.41	0.001
LDL	2.63 ± 0.79	2.73 ± 0.95	0.397
FPG	5.91 ± 2.62	5.71 ± 1.78	0.597
CR	77.53 ± 24.81	79.28 ± 28.00	0.654
Coronary artery integral	51.85 ± 32.03	53.53 ± 35.79	0.737

Note: TG: triglyceride; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; CR: creatinine; FPG: fasting plasma glucose.

Table 4. Logistic regression of traits associated with VDR FokI polymorphism in the study population

		B	Sig.	95.0% CI for EXP (B)		Exp (B)
				Lower	Upper	
Step 1	CA	-5.414	0.000	0.000	0.059	0.004
Step 2	FPG	0.405	0.002	1.155	1.946	1.499
	CA	-6.102	0.000	0.000	0.036	0.002
Step 3	Smoking	-.726	0.022	0.260	0.902	0.484
	FPG	0.388	0.004	1.136	1.915	1.475
	CA	-5.931	0.000	0.000	0.045	0.003
Step 4	Smoking	-.818	0.012	0.233	0.834	0.441
	FPG	0.394	0.004	1.132	1.940	1.482
	CA	-6.081	0.000	0.000	0.041	0.002
	FokI		0.044	1.116	6.102	
	FokI-AA	0.959	0.027	1.010	3.923	2.609
	FokI-AG	0.688	0.047	0.000	0.059	1.990

Note: CA: serum calcium; FPG: Fasting plasma glucose.

formed for different parameters in each group. The association of VDR FokI genotype with risk for CHD was assessed by logistic regression analysis after adjusting for age and sex. A value of $P < 0.05$ was considered statistically significant. Statistical analysis was done with SPSS software version 11.5.

Results

A total of 215 CHD patients and 67 controls were recruited into present study and the association of VDR gene polymorphisms of FokI, BsmI, ApaI, Tru9I, and TaqI with CHD was evaluated. Demographic characteristics of patients and controls are shown in **Table 1**. There were no significant differences in the age and sex. The genotype and allele frequencies of ApaI, TaqI, Tru9I and FokI polymorphisms of patients and controls are shown in **Table 2**. The genotype distributions were in Hardy-Weinberg equilibrium in both groups. The genotype frequencies of FokI in CHD patients were 23.7% for AA, 47.9% for AG, and 28.4% for GG. Statistical analysis showed the proportion of CHD patients with GG genotype reduced significantly when compared with controls ($P = 0.039$, OR = 0.552, 95% CI 0.312-0.974). No significant differences were observed in the genotype and allele frequencies of ApaI, TaqI and Tru9I polymorphisms between patients and controls (ApaI: = 0.646, OR = 1.103, 95% CI 0.726-1.673; TaqI: $P = 0.404$, OR = 1.585, 95% CI 0.532-4.722, Tru9I: $P = 0.364$, OR = 1.23, 95% CI 0.786-1.924). The association of FokI-A allele genotype and CHD was then assessed within all individuals with a binary logistic regression model after adjusting for age and sex. In CHD subgroups, GG genotype predicted a higher HDL-cholesterol as compared to AG genotype and A* genotype (**Table 3**; $P = 0.001$, respectively). Interestingly, FokI-A allele carriers had a 2.61-fold increase in the odds (95% CI: 1.116-6.102, $P = 0.027$) as compared to CHD subjects with FokI mutation (**Table 4**).

Discussion

Vitamin D is initially metabolized to the intermediate compound 25-hydroxyvitamin D in the liver which subsequently binds to the intracellular receptors to regulate gene expression. Results from cross-sectional studies examining the relation between vitamin D and CAD in the general population are conflicting [12]. In type 1 diabetic patients, vitamin D deficiency has

been shown to independently predict both prevalence and development of CAD [13]. However, a study in type 2 diabetic patients with a history of cardiovascular disease (CVD) found a strong inverse association between low vitamin D level and prevalence of coronary, cerebrovascular, and peripheral CVD [14]. Furthermore, a low vitamin D level is associated with increased cardiovascular morbidity and mortality in the general population [15].

VDR is an important regulator of vitamin D pathway, which involves the conversion of serum 25-hydroxyvitamin D into the active hormone, 1,25-dihydroxyvitamin D. VDR is required for the functions of vitamin D [16]. VDR is an intracellular hormone receptor that specifically binds the biologically active form of calcitriol or vitamin D, 1,25-dihydroxyvitamin D and interacts with specific nucleotide sequences of target genes to produce a variety of biologic effects [17].

VDR gene plays an important role in the vitamin D pathway. VDR protein is known to display polymorphic variation and belongs to the steroid hormone family of nuclear receptors which are responsible for the transcriptional regulation of a number of hormone responsive genes. As VDR is expressed in a large number of tissues, it is not surprising that ligand-activated VDR modulates the expression of multiple targeted genes [18], which is consistent with the fact that vitamin D deficiency has been associated with risk factors for cardiovascular disease, metabolic syndrome and even with overall mortality [19]. VDR harbors several known functional polymorphisms and several of these polymorphisms have been commonly investigated [7]. The human VDR gene is mapped tp chromosome 12q12-q14, and five common polymorphisms have been typically associated with VDR activity [20-22], namely VDR Tru9I (rs757343), FokI (rs2228570), TaqI (rs731236), BsmI (rs1544410) and ApaI (rs7975232). CAD is the leading cause of death worldwide. Although environmental factors play important roles in the pathogenesis of CAD [4], genetic factors also affect the occurrence of CAD [5-7].

Fang, et al [23] found that BsmI, ApaI and TaqI existed strong linkage disequilibrium, and they were in the same haploid domain with 3'UTR, and the haploid domain included 4-9 exons and 3'UTR. 3'UTR is related to the regulation of gene expression, especially the regulation of mRNA stability. Studies showed that ApaI polymorphism was related to the insulin secretion, fasting glucose, abnormal glucose tolerance and diabetes [24, 25]. Ye et al. [26] for the first time identified the VDR Tru9I polymorphism in 2000. However, few studies have reported the genetic polymorphism of this site and its impact on the VDR expression in tissues and cells [27, 28]. Although, Tru9I polymorphism fails to change the amino acid sequence of VDR protein, the 3' terminal of mRNA transcribed from VDR gene can affect not only the expression and stability of the mRNA, but also the affinity of enhancer and target area.

VDR FokI polymorphism was described in the exon 2 in early 1990s, and consists of a T to C change, which locates in a start codon (ATG). Thus, when the C variant is present, an alternative start site is used producing a protein with different sizes. Most of experiments conducted so far point to the fact that the protein (424 AA) of short form is more active than that of long form (427 AA) in terms of its transactivation activity as a transcription factor. However, it seems to be gene-specific and cell type-specific. Thus, a certain genes and cell types will be more sensitive to the polymorphism than others [7].

We focused on four SNPs of VDR: Tru9I (rs757343), FokI (rs2228570), Apa1 (rs7975232) and Taq1 (rs731236). Fok1 restriction enzyme gene has a polymorphic site in the exon 2 at the 5' end of VDR gene. Three other polymorphisms are identified by their restriction endonuclease cleavage sites (Tru9I, Apa1 and Taq1) [23]. According to our results, FokI-GG genotype, a mutant SNP, showed significant difference between patients (36.1%) and controls (47.5%). GG genotype frequency of CHD patients was significantly lower. This was inconsistent with the findings of Pan et al. [29], which may be ascribed to the different regions and different types of CHD. AS we known that the genetic characteristics of different types of CHD are likely to present obvious difference. In addition, sample size may be another contributing factor causing this discrepancy [30]. A binary logistic regression model revealed that FokI-A allele carriers had a 2.61-fold increase in the odds (95% CI: 1.116-6.102, P = 0.027) as compared to CHD patients with FokI mutation. VDR FokI polymorphisms were independent factors

affecting CHD. In addition, the clinical parameters and biochemical characteristics of CHD subgroups were compared on the basis of VDR FokI polymorphism. Results showed that patients with FokI-GG genotype had a higher HDL ($P = 0.001 < 0.05$) as compared to those with FokI-A* genotype, which was consistent with the findings of Natielen et al [31]. However, Tru9I, ApaI and TaqI polymorphisms were not related to the increased risk for CHD. Tru9I, ApaI and TaqI polymorphisms are promising SNPs causing CHD. In Chinese, the frequencies of Tru9I-AA and TaqI-CC genotypes are low. Thus, it is necessary to increase the sample size for further investigation. A few studies conducted in CAD patients have investigated the distribution of VDR polymorphisms. Arash et al [32] investigated the relationship between VDR FokI polymorphism and collateralization in CAD patients. They found there was no relationship between VDR genotype and severity of CAD. Consistent with this result, Pan et al. [29] found no association between FokI polymorphism and CAD, but they did not investigate other VDR gene polymorphisms.

In conclusion, our findings support the hypothesis that VDR FokI-GG genotype may predict a low risk for CHD. VDR FokI polymorphism appears to be associated to CHD. However, due to a small sample size, further studies with elegant study design are needed to confirm our findings and investigate the potential mechanisms underlying this association.

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Disclosure of conflict of interest

None.

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