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Original Article

Association between vitamin D receptor genetic polymorphisms and haplotypes and risk of lumbar degenerative disc disease in a Chinese population

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Abstract: Degenerative disc disease is a continuous degeneration process of intervertebral discs. We performed a case-control study to investigate the association between 16 common SNPs of VDR and degenerative disc disease risk in a Chinese population. A total of 482 pairs of patients with degenerative disc disease and controls were collected between May 2014 and May 2016. The genotyping of VDR rs1544410, rs2239181, rs2107301, rs2239179, rs2189480, rs3819545, rs2239186, rs2254210, rs2238136, rs4760648, rs11168287, rS4328262, rS4334089, rs3890733, rs10783219 and rS7299460 was done in a 384-well plate format on the sequenom MassARRAY platform (Sequenom, San Diego, USA). We observed that the TC (OR=2.13, 95% CI=1.34-3.40) and CC (OR=2.73, 95% CI=1.75-4.28) genotypes of rs2239179 were associated with an increased risk of degenerative disc disease when compared with the TT genotype. However, there was no significant correlation between other fifth SNPs of VDR and degenerative disc disease risk. The haplotype analysis revealed that the rs2239179 had linkage disequilibrium with rs2107301 (D'=0.97, r^2=0.25) and rs2238136 (D'=0.81, r^2=0.15). The rs2239179 polymorphism was associated with drinking habit (Spearman correlation coefficient =0.09, P=0.006) in the risk of intervertebral disc disease. In conclusion, our study indicated that the VDR genetic polymorphism may contribute to the development of degenerative disc disease in the Chinese population.

Keywords: VDR, polymorphism, haplotype, degenerative disc disease

Introduction

Degenerative disc disease is a continuous degeneration process of intervertebral discs [1, 2]. The development of degenerative disc disease seems to be determined by the many environmental and genetic factors. It is reported that long-term high pressure and low pressure load contribute to the risk of degenerative disc disease [3, 4]. A study with 172 monozygotic twins and 154 binovular twins have reported that the 74% at the lumbar spine and 73% at the cervical spine intervertebral disc disease can be attributed to hereditary [5]. Another heritability study has followed up 436 monozygotic twins, and it indicates that heritability contributes to 30% of the intervertebral disc degeneration prevalence [6]. Therefore, heritability plays an important role in the pathogenesis of degenerative disc disease. Identification of molecular factors involves in this disease is essential.

Previous studies have investigated the association between genetic factors and risk of degenerative disc disease in many populations [7, 8]. The vitamin D receptor (VDR) is a derivative of steroids and belongs to superfamily members of steroid/thyroid hormone receptor, and it has a function of rachitic properties. Many biological functions of vitamin D are achieved by VDR mediated regulation of target gene transcription [9]. The VDR mediates the biological function of 1,25-dihydroxyvitamin D3 through signal transduction pathways, and plays an important role in the intestinal Ca^{2+} transport, bone remodeling, electrolyte homeostasis and cell proliferation [10]. The VDR is located on chro-

Table 1. Demographic and clinical characteristics of enrolled patients and controls

Variables	Patients N=482	%	Controls N=482	%	t or χ^2 value	*P* value
Sex						
Male	289	59.96	289	59.96		
Female	193	40.04	193	40.04	-	1
Age, years		45.30±9.55		43.45±10.12	2.53	0.01
BMI						
<24	267	55.39	238	49.38		
≥24	215	44.61	244	50.62	3.5	0.06
Smoking habit						
No	274	56.85	263	54.56		
Yes	208	43.15	219	45.44	0.51	0.48
Drinking habit						
No	317	65.77	329	68.26		
Yes	165	34.23	153	31.74	0.68	0.41
Physical labor						
No	184	38.17	205	42.53		
Yes	298	61.83	277	57.47	1.9	0.17
Family history of intervertebral disc disease						
No	315	65.35	357	74.07		
Yes	167	34.65	125	25.93	8.67	0.003
Lumbar injury						
No	453	93.98	469	97.3		
Yes	29	6.02	13	2.7	6.37	0.12
Schneiderman stage						
II	214	44.4				
III	268	55.6				

mosome 12 (12q12-14), and about 25 SNPs are reported in the VDR gene. Previous studies have reported an association between VDR genetic polymorphisms and degenerative disc disease risk [11-14], but the results are inconsistent. Therefore, we performed a case-control study to investigate the role of 16 common SNPs of VDR in the development of degenerative disc disease in a Chinese population. We also examined the effect of gene-environmental interactions on degenerative disc disease risk.

Materials and methods

Subjects

We recruited 482 patients with degenerative disc disease from the Department of Orthopedics of the Affiliated Hospital of Inner Mongolia Medical University between May 2014 and May 2016. The disease was diagnosed in all individuals by both X ray and magnetic resonance imaging (MRI). The image classification was based on Schneiderman MRI [15]. Those who had prior history of spinal trauma, spinal deformity, spinal infections and metabolic diseases were excluded.

A total of 482 controls were recruited from the outpatient clinics in physical examination center of the Affiliated Hospital of Inner Mongolia Medical University between May 2014 and May 2016. Controls were matched with patients by sex and age (±5 years). All controls were confirmed to be free of discogenic low back pain and history of intervertebral disc disease.

The demographic and clinical information of all the participants were obtained from medical records. These information included sex, age, body mass index (BMI), physical labor, lumbar injury and Schneiderman stage. The physical labor was defined as never, occasionally and

Table 2. Association between 16 SNPs of VDR and risk of degenerative disc disease

SNPs	Patients N=482	%	Controls N=482	%	χ^2	*P* value	HWE in controls	OR (95% CI)[1]	*P* value
rs1544410									
CC	424	87.97	416	86.31				1.0 (Ref.)	
CT	58	12.03	66	13.69				0.81 (0.54-1.20)	0.29
TT	0	0	0	0	0.59	0.44	0.11	-	
rs2239181									
AA	297	61.62	292	60.58				1.0 (Ref.)	
AC	158	32.78	164	34.02				1.14 (0.63-2.07)	0.66
CC	27	5.6	26	5.39	0.17	0.92	0.64	1.11 (0.62-2.00)	0.72
rs2107301									
GG	236	48.96	239	49.59				1.0 (Ref.)	
GA	202	41.91	201	41.7				0.99 (0.61-1.60)	0.95
AA	44	9.13	42	8.71	0.07	0.97	0.98	1.05 (0.65-1.69)	0.85
rs2239179									
TT	242	50.21	293	60.79				1.0 (Ref.)	
TC	167	34.65	159	32.99				2.13 (1.34-3.40)	0.002
CC	73	15.15	33	6.85	20.33	<0.001	0.08	2.73 (1.75-4.28)	<0.001
rs2189480									
GG	236	48.96	244	50.62				1.0 (Ref.)	
GT	195	40.46	190	39.42				1.03 (0.66-1.63)	0.89
TT	51	10.58	48	9.96	0.29	0.87	0.22	1.11 (0.71-1.73)	0.65
rs3819545									
AA	270	56.02	274	56.85				1.0 (Ref.)	
AG	182	37.76	183	37.97				1.20 (0.66-2.16)	0.55
GG	30	6.22	25	5.19	0.49	0.78	0.43	1.24 (0.70-2.21)	0.46
rs2239186									
AA	139	28.84	156	32.37				1.0 (Ref.)	
AG	232	48.13	220	45.64				0.97 (0.70-1.36)	0.87
GG	111	23.03	106	21.99	1.41	0.49	0.09	1.17 (0.81-1.68)	0.4
rs2254210									
GG	215	44.61	228	47.3				1.0 (Ref.)	
GA	235	48.76	220	45.64				0.95 (0.56-1.62)	0.85
AA	32	6.64	34	7.05	0.94	0.63	0.05	1.09 (0.64-1.85)	0.76
rs2238136									
CC	283	58.71	289	59.96				1.0 (Ref.)	
CT	186	38.59	184	38.17				1.50 (0.61-3.70)	0.37
TT	13	2.7	9	1.87	0.8	0.67	<0.001	1.54 (0.63-3.76)	0.34
rs4760648									
TT	182	37.76	185	38.38				1.0 (Ref.)	
TC	238	49.38	241	50				1.13 (0.74-1.72)	0.57
CC	62	12.86	56	11.62	0.35	0.84	0.09	1.11 (0.72-1.70)	0.65
rs11168287									
AA	208	43.15	215	44.61				1.0 (Ref.)	
GA	215	44.61	213	44.19				1.12 (0.73-1.72)	0.59

GG	59	12.24	54	11.2	0.35	0.84	0.91	1.18 (0.77-1.81)	0.45
rs4328262									
TT	198	41.08	185	38.38				1.0 (Ref.)	
GT	210	43.57	220	45.64				0.89 (0.61-1.31)	0.56
GG	74	15.35	77	15.98	0.73	0.69	0.39	1.03 (0.70-1.51)	0.89
rs4334089									
GG	191	39.63	205	42.53				1.0 (Ref.)	
GA	251	52.07	241	50				1.16 (0.71-1.91)	0.55
AA	40	8.3	36	7.47	0.91	0.64	0.002	1.27 (0.77-2.10)	0.35
rs3890733									
CC	456	94.61	461	95.64				1.0 (Ref.)	
CT	26	5.39	21	4.36				1.16 (0.63-2.14)	0.63
TT	0	0	0	0	0.56	0.46	0.62	-	
rs10783219									
AA	162	33.61	177	36.72				1.0 (Ref.)	
TA	246	51.04	238	49.38				1.03 (0.70-1.53)	0.86
TT	74	15.35	67	13.9	1.14	0.57	0.36	1.21 (0.80-1.81)	0.36
rs7299460									
TT	158	32.78	147	30.5				1.0 (Ref.)	
CT	254	52.7	253	52.49				0.90 (0.62-1.31)	0.57
CC	70	14.52	82	17.01	1.35	0.51	0.13	0.85 (0.57-1.27)	0.43

1. Adjusted for age, family history of intervertebral disc disease and lumbar injury.

frequently. BMI is defined as the body mass divided by the square of the body height (kg/m^2). The performance of our study was approved by the ethics committee of the Affiliated Hospital of Inner Mongolia Medical University. Written informed consents were obtained from all participants prior to enrollment.

DNA extraction and genotyping

Peripheral venous blood samples were kept in tube with 0.5 M ethylene diamine tetraacetic acid, and was stored in a refrigerator at 4°C until utilization. The DNA was extracted by the Blood DNA kit produced by Tiangen Biotech Co., Ltd (Tiangen, Beijing, China) according to the manufacturer's instructions. The blood samples were kept in -20°C until use. Genotyping of VDR rs1544410, rs2239181, rs2107301, rs2239179, rs2189480, rs3819545, rs2239186, rs2254210, rs2238136, rs4760648, rs11168287, rS4328262, rS4334089, rs3890733, rs10783219 and rS7299460 was done in a 384-well plate format on the sequenom MassARRAY platform (Sequenom, San Diego, USA). Primers of the 16 SNPs for polymerase chain reaction amplification and single base extension assays were designed by Sequenom Assay Design 3.1 software. The PCR reaction was carried out in 5 μL, following by the SAP and iPLEX reaction. Then the PCR products were desalted and dispensed to a SpectroCHIP, and analyzed with MALDI-TOF MS.

Statistical analysis

Categorical variables were displayed as percentages and frequencies (%), and continued variables were expressed by mean ± standard deviation (SD). The differences between patients with degenerative disc disease and controls in terms of demographic and clinical variables were analyzed by Chi-square test or student t test. Departure from the Hardy-Weinberg equilibrium was analyzed by Chi-square (χ^2) test with one degree of freedom. Multivariate conditional logistic regression analysis was taken to estimate the relationship between VDR SNPs and degenerative disc disease risk, and the results were displayed by odds ratios (ORs) and 95% confidence intervals (CIs). Linkage disequilibrium and hap-

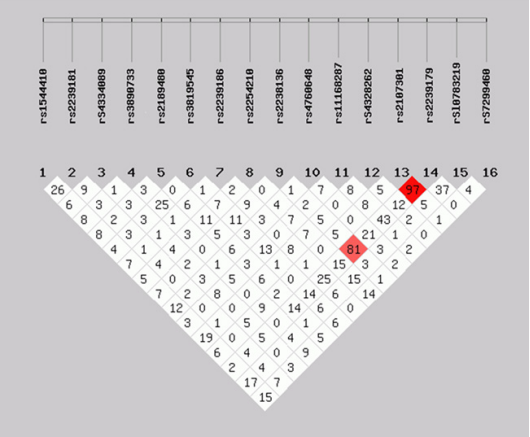

Figure 1. The linkage disequilibrium of 16 SNPs of VDR.

lotype analyses were evaluated by SHEsis software (http://analysis.bio-x.cn/myAnalysis.php) [16]. All statistical analysis was carried out using IBM SPSS Statistics for Windows, Version 21.0 (Armonk, NY: IBM Corp).

Results

The demographic and clinical characteristics of the subjects are shown in **Table 1**. When compared with controls, patients with degenerative disc disease were more likely to have high age (t=2.53, P=0.01) and a family history of intervertebral disc disease (χ^2=8.67, P=0.003). 214 patients with degenerative disc disease were at II schneiderman stage, and 268 were at III stage.

We observed that the TC (OR=2.13, 95% CI=1.34-3.40) and CC (OR=2.73, 95% CI=1.75-4.28) genotypes of rs2239179 were associated with an increased risk of degenerative disc disease when compared with the TT genotype (**Table 2**). However, there was no significant association between other fifth SNPs of VDR and risk of degenerative disc disease.

The haplotype analysis revealed linkage disequilibrium between rs2107301 and rs2239179 (D'=0.97, r^2=0.25; **Figure 1**), and rs2238136 and rs2239179 also showed significant linkage disequilibrium (D'=0.81, r^2=0.15; **Figure 1**).

We observed a significant interaction between rs2239179 polymorphism and drinking habit (Spearman correlation coefficient=0.09, P=0.006) in the risk of intervertebral disc disease (**Table 3**).

Discussion

The development of degenerative disc disease is involved in multifactorial disease, such as environmental and genetic factors. Pathogenesis of various diseases can be affected by a single base mutation that can lead to alteration of protein expression. This study evaluated the role of VDR SNPs in the pathogenesis of degenerative disc disease, and showed that the TC and CC genotypes of rs2239179 were related to the risk of degenerative disc disease when compared with the TT genotype.

VDR gene is located at 12qchromosome, and its biological effect is mediated through $1,25(OH)_2D3$. $1,25(OH)_2D3$ is reported to be involved in the regulators of cell proliferation and production of specific cytokines in the lumbar anulus [17]. Balmain et al. observed the immunoreactive VDR receptors in nucleoli of chondrocytes, especially in the fibrillar component, and VDR may be directly involved in differentiation, proliferation and maturation of cartilage cells [18]. In addition, in vitro study has indicated that vitamin D could influence the synthesis of proteoglycan in articular cartilage cells, and the disc contains rich proteoglycans [19]. VDR participates into metabolism of VDR, and influences the pathogenesis of degenerative disc disease.

Currently, many previous studies have reported the association between VDR genetic polymorphism and degenerative disc disease risk, but the results are inconsistent [13, 14, 20-25]. Yuan et al. carried out a study with 178 patients and 284 controls, and they reported that individuals carrying the A allele of VDR rs35068180 are more vulnerable to developing lumbar disc degeneration [25]. Eser et al. revealed that VDR genetic polymorphism was associated with risk of disc degeneration [24]. Zawilla et al. performed a case-control study with 84 lumbar disc degeneration and 60 controls, and indicated that VDR Apal polymorphism was correlated with risk of lumbar disc degeneration [23]. Vieira et al. indicated that VDR FokI/T2C polymorphism was related to the development of intervertebral disc degeneration [22]. Zhao et al. found that VDR rs2228570

Table 3. Interaction between rs2239179 polymorphisms and environmental factors in the risk of intervertebral disc disease

Variables	rs2239179			χ^2 value	*P* value	Spearman correlation coefficient	*P* value
	TT	TC	CC				
Sex							
Male	313	212	53				
Female	222	111	53	9.18	0.01	0.009	0.79
Age							
<45	250	152	51				
≥45	285	171	55	0.07	0.97	-0.008	0.81
BMI							
<24	271	175	59				
≥24	264	148	47	1.52	0.47	-0.04	0.23
Smoking habit							
No	300	179	58				
Yes	235	144	48	0.08	0.96	0.01	0.77
Drinking habit							
No	382	197	67				
Yes	153	126	39	10.66	0.01	0.09	0.006
Family history of intervertebral disc disease							
No	366	230	76				
Yes	169	93	30	0.97	0.62	-0.03	0.35

polymorphism showed an increased risk for intervertebral disc degeneration in a Chinese population [20]. However, Colombini et al. [23] and Serrano et al. [21] did not report significant association between VDR genetic variants and development or progression of osteoarthritis and intervertebral disc degeneration. In our study, we found the VDR rs2239179 played an important role in the risk of degenerative disc disease. Discrepancies between the previous results may be caused by differences in study design, ethnicities and sample size.

Previous studies reported significant interaction between alcohol intake and vitamin D related gene polymorphisms in risk of diseases [26, 27]. Deschasaux M et al. performed a case-control study with 233 women with breast cancer and 466 controls, and reported a correlation between vitamin D-related gene polymorphisms and alcohol intake in breast cancer risk [26]. Gu H et al. indicated that VDR gene polymorphism was associated with a heavy risk of esophageal cancer in patients having drinking habit [27]. Moreover, we observed that the VDR rs2107301 and rs2238136 showed linkage disequilibrium with rs2239179. A previous Chinese study also reported a linkage disequilibrium block between rs2107301 and rs2239179 [28], which is similar with our results. Further studies are greatly required to confirm this finding.

Two limitations should be mentioned in this study. First, enrolled subjects were collected from one hospital, and they may not be sufficiently representative of other population. Second, only VDR gene was considered in this study, and the possibility of gene-gene interaction between other genes and VDR may contribute to the pathogenesis of degenerative disc disease.

In conclusion, our study revealed that the VDR genetic polymorphism may contribute to the development of degenerative disc disease in the Chinese population, suggesting that VDR polymorphisms could be used as biomarkers in early detection of this disease. Further large-scale studies should be conducted to gain better insight into the effect of VDR genetic polymorphism on degenerative disc disease risk.

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Disclosure of conflict of interest

None.

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