

# Association Between Vitamin D Receptor Gene Polymorphism rs2228570 and Allergic Rhinitis

This article was published in the following Dove Press journal:  
*Pharmacogenomics and Personalized Medicine*

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**Background:** Vitamin D receptor (VDR) gene polymorphisms are involved in a variety of immune-related diseases, and VDR is associated with allergic rhinitis. The present study explored the associations between VDR gene polymorphisms and allergic rhinitis in the Chinese population.

**Methods:** The study population consisted of 400 patients with allergic rhinitis and 400 healthy controls. General characteristics were determined by interview. Blood DNA was extracted and genotyping was performed via matrix-assisted laser desorption/ionization time-of-flight mass spectrometry. The associations of each genetic variant with risk for AR were assessed by calculating the odds ratio (OR) with 95% confidence interval (95% CI).

**Results:** No significant differences were observed in general characteristics between cases and controls. The distributions of genotypes at the rs2228570 locus of the VDR gene conformed to Hardy–Weinberg equilibrium. There was a significant difference in the distribution of rs2228570 genotype ( $P < 0.001$ ) between cases and controls. Compared to GG and GA genotypes, the AA genotype increased the risk of AR (OR=3.27, 95% CI: 2.10–5.11,  $P = 0.000$ ; OR=2.58, 95% CI: 1.63–4.08,  $P < 0.001$ ). Similar results were also observed in the dominant model (OR=1.64, 95% CI: 1.24–2.17,  $P < 0.001$ ) and codominant model (OR=2.95, 95% CI: 1.93–4.51,  $P < 0.001$ ). The A allele was still associated with elevated risk gene for AR after adjusting for potential confounding factors. Subgroup analyses indicated an interaction between alcohol and rs2228570 in the risk of allergic rhinitis. The A allele also increased the risk for AR in the population without asthma (OR=1.85, 95% CI: 1.46–2.34,  $P < 0.001$ ).

**Conclusion:** VDR gene polymorphism is associated with AR, and the AA genotype of rs2228570 is associated with the increased risk of AR in the Chinese population.

**Keywords:** allergic rhinitis, gene polymorphism, case–control, vitamin D receptor

## Introduction

Allergic rhinitis (AR) is characterized by mucosal inflammation mediated by specific IgE after exposure of the nasal mucosa to allergens, leading to a series of clinical symptoms, including nasal itching, snoring, nasal discharge, and nasal congestion.<sup>1</sup> Its etiology of AR is not yet clear, but the complex interactions between individual genes and the environment are among risk factors for its pathogenesis.<sup>2</sup>

Various immune-related factors are involved in its development and progression, including chemokines and their receptors, EPO, interleukin and its receptors, and leukotrienes.<sup>3</sup> The vitamin D receptor (VDR) gene can regulate immune responses in the body, inhibit abnormal cell activation, and maintain the stability of cell function.<sup>4</sup> A number of clinical studies have confirmed that vitamin D can

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effectively prevent and treat bronchial asthma by regulating the immune system, and both AR and bronchial asthma have similar etiology and pathogenesis and belong to the same category of diseases.<sup>5,6</sup> Changes in vitamin D levels in the body can regulate the immune system, and thus affect the occurrence of AR.<sup>7,8</sup> Polymorphisms of the VDR gene (Apa I, TaqBI) may affect VDR expression level and are involved in many physiological and pathological processes.<sup>9</sup> Therefore, it is reasonable to assume that VDR gene polymorphisms may influence the occurrence of AR by regulating VDR expression level. In a previous study, VDR genes, BsmI (rs1544410), ApaI (rs7975232), and TaqI (rs731236) were associated with the risk for mite-sensitized persistent AR, whereas the genotype and allele frequencies of rs2228570 in VDR were not significantly associated with susceptibility to it. However, in stratification analyses, rs2228570 in VDR was significantly associated with AR.<sup>10</sup> Relatively few studies have investigated the associations between VDR gene polymorphisms and AR. In the present study, we selected the controversial SNP and perform a study in a different population and large sample to explore the association between VDR gene variant Fok I/rs2228570 and AR in the Chinese population.

## Materials and Methods

### Study Population

Using a case-control design, we enrolled 400 patients with AR treated at the Department of Otolaryngology Head and Neck Surgery, Renmin Hospital of Wuhan University. The diagnosis of AR was made based on the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines-2016 revision and:<sup>11</sup> (1) persistent runny nose, sneezing, nasal congestion and nasal itching; (2) pale and edema nasal mucosa; (3) at least one positive allergen, including in skin prick test (SPTs) 2 + + (Allergopharma, Merck, Germany) and/or serum specific IgE level >0.35 kU<sub>A</sub>/L. All patient diagnoses were confirmed by specialist physicians. Healthy control subjects (n=400) were from the physical examination center of Renmin Hospital of Wuhan University. The criteria for inclusion were as follows: (1) no symptoms or history of AR or other nasal diseases; (2) no symptoms or history of allergic dermatitis, asthma or other allergic diseases; (3) total serum IgE <200 kU<sub>A</sub>/L; (4) serum specific IgE screening test (Phadia) <0.35 kU<sub>A</sub>/L; (5) there is no history of AR or other allergic diseases in immediate family members. The exclusion criteria were as follows: (1) patients with

autoimmune diseases, severe mental diseases and other systemic diseases; acute upper respiratory tract infection, severe nasal septum deviation, suppurative sinusitis, nasal polyps and sinus tumors; use of glucocorticoids within 4 weeks or antihistamines, leukotriene receptor antagonists and other antiallergic drugs within 2 weeks.

The sample size was calculated using Quanto version 1.2.4, and followed by the conditions:  $\alpha=0.05$ ,  $\beta=0.10$ , expected OR=1.8, the calculated sample size was 248 in each of the case and control groups. The sample size was therefore sufficient. This study was approved by the Medical Ethics Committee of the Renmin Hospital of Wuhan University (201,905,130,036). The research was carried out in accordance with the World Medical Association Declaration of Helsinki, and all subjects provided written informed consent.

### Data Collection and Genotyping

General characteristics, including sex, age, body mass index (BMI), history of disease, and drinking and smoking habits were collected by interview.

In the morning, two samples of peripheral blood (5 mL) were collected from each subject using vacutainers and transferred to test tubes containing ethylenediamine tetra-acetic acid (EDTA). Levels of IgE, IL-6, IL-8, and IL-10 were determined using enzyme-linked immunosorbent assay (ELISAs).

Genomic DNA was isolated from whole blood using e QIAamp DNA Blood Mini Kits (Qiagen, Hilden, Germany). Genotyping was via using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) (MassARRAY; Agena Bioscience, San Diego, CA). Primer sequences of for Fok I/rs2228570 gene (c. G>A) SNPs were designed by Primer Premier 5.0 and synthesized using Sangon Biotech (Shanghai, China). Primer sequences for rs2228570 were: 5'-ACCGTGG CCTGCTTGCT-3' (forward) and 5'-AGGGTCAGGC AGGGAAGTG-3' (reverse). PCR was performed with an initial denaturation step at 96°C for 5 min followed by 30 cycles of denaturation at 96°C for 45 s, annealing at 55°C (or 62°C) for 40 s, and extension at 72°C for 60 s. PCR products were sequenced by Sangon Biotech.

### Reverse Transcription-Polymerase Chain Reaction

Total RNA was isolated from whole blood from the AR patients and healthy controls using Trizol reagent

(Invitrogen, Carlsbad, CA, USA) in accordance with the manufacturer's instructions. VDR gene (Fok I) expression was determined using RT-PCR with Hifair™ first-strand cDNA synthesis SuperMix and qPCR SYBR Green Master Mix (Yesen, Shanghai, China). The 2- $\Delta\Delta C_T$  method was used to calculate relative expression.

## Statistical Analysis

All statistical analyses were performed using SPSS 23.0 (SPSS, Chicago, IL). Continuous data are expressed as the mean  $\pm$  standard deviation, and the comparisons between case and control groups were performed using Student's *t*-test. Categorical data are expressed as numbers and percentages, and were analyzed using the Chi-square test. The Hardy–Weinberg equilibrium test was conducted in the case and control groups. The associations of each genetic variant with risk for AR were assessed by calculating the odds ratio (OR) with 95% confidence interval (95% CI). Stratification analysis was performed according to erythrocyte sedimentation rate age, sex, smoking habit, drinking habit, body mass index (BMI), IL-6, IL-8 and IL-10. The adjusted ORs and their 95% CIs were also calculated, including age, sex, smoking habit, drinking habit, BMI. In all analyses,  $P < 0.05$  was taken to indicate statistical significance.

## Results

### General Characteristics

The general characteristics of each group are presented in Table 1. There were no significant differences between the case and control groups in male ratio (79.5% vs 52.8%,  $P = 0.358$ ) age (57.1 vs 56.7 years,  $P = 0.366$ ), smoking ratio (32.8% vs 39.3%,  $P = 0.055$ ), drinking ratio (29.8% vs 31.5%,  $P = 0.591$ ). The levels of IgE (143.5 $\pm$ 23.1 vs 33.4 $\pm$ 6.1,  $P = 0.000$ ), IL-6 (158.3 $\pm$ 26.9 vs 125.3 $\pm$ 22.6,  $P < 0.001$ ), IL-8 (160.6 $\pm$ 22.8 vs 110.5 $\pm$ 16.3,  $P < 0.001$ ), and IL-10 (16.9 $\pm$ 3.4 vs 9.7 $\pm$ 2.3,  $P < 0.001$ ) levels were significantly higher in the case group than in the control group.

### Association Between Fok I/rs2228570 Gene Polymorphism and AR

The Hardy–Weinberg equilibrium test indicated no significant variance in the control group ( $P > 0.05$ ), indicating that the selected control group was a representative sample. There are three genotypes of rs2228570, ie, GG, GA, and AA. The frequency distribution of the case group was 41.8% for GG, 36.8% for GA, and 21.5% for AA, and that

**Table 1** Comparison of General Characteristic Between Case and Control Group

Factors	Case Group	Control Group	$\chi^2/t$	P
Sex			0.845	0.358
Male	198(49.5%)	211(52.8%)		
Female	202(50.5%)	189(47.3%)		
Age (year)	57.1 $\pm$ 7.0	56.7 $\pm$ 7.0	-0.905	0.366
BMI (kg/m <sup>2</sup> )	23.5 $\pm$ 3.0	23.7 $\pm$ 3.1	0.700	0.484
Smoking (n, %)			3.668	0.055
Yes	131(32.8%)	157(39.3%)		
No	269(67.3%)	243(60.8%)		
Drinking (n, %)			0.288	0.591
Yes	119(29.8%)	126(31.5%)		
No	281(70.3%)	274(68.5%)		
Asthma			106.634	<0.001
Yes	132(33.0%)	18(4.5%)		
No	268(67.0%)	382(95.5%)		
Severity of AR				
Mild	150(39.3%)	–		
Moderate	160(40.0%)	–		
Severe	83(20.8%)	–		
IgE, U/mL	143.5 $\pm$ 23.1	33.4 $\pm$ 6.1	92.165	<0.001
IL-6, ng/L	158.3 $\pm$ 26.9	125.3 $\pm$ 22.6	18.785	<0.001
IL-8, ng/L	160.6 $\pm$ 22.8	110.5 $\pm$ 16.3	35.751	<0.001
IL-10, ng/L	16.9 $\pm$ 3.4	9.7 $\pm$ 2.3	35.080	<0.001
rs2228570			28.833	<0.001
GG	167(41.8%)	216(54.0%)		
GA	147(36.8%)	150(37.5%)		
AA	86(21.5%)	34(8.5%)		

**Abbreviation:** IL, interleukin.

in the control group was 54.0% for GG, 37.5% for GA, and 8.5% for AA. The differences between the two groups were significant ( $P < 0.001$ ).

Table 2 presents the results of regression analyses of the associations between rs2228570 gene polymorphisms and AR. Compared to GG genotype, AA (OR=3.27, 95% CI: 2.10–5.11,  $P < 0.001$ ), and GA (OR=2.58, 95% CI: 1.63–4.08,  $P < 0.001$ ) increased the risk for AR. In the dominant model, the AA/GA genotype was associated with elevated risk for AR compared to GG genotype (OR=1.64, 95% CI: 1.24–2.17,  $P = 0.001$ ). In the codominant model, the AA genotype frequency was more common in the case group than the control group (OR=2.95, 95% CI: 1.93–4.51,  $P < 0.001$ ). The A allele frequency was 39.9% in the case group and the 27.3 in the control group, and this difference was significant (OR=1.77, 95% CI: 1.43–2.19,  $P < 0.001$ ). The A allele was still associated

**Table 2** Logistic Regression Analysis of Associations Between Fok I/rs2228570 Gene Polymorphism and Allergic Rhinitis

Genotype	Cases		Control		OR (95% CI)	P	aOR(95% CI)	aP
	n	%	n	%				
AA vs GG	86/167	21.5/41.8	34/216	8.5/54.0	3.27(2.10–5.11)	<0.001	2.76(2.08–4.56)	0.009
AA vs GA	86/147	21.5/36.8	34/150	8.5/37.5	2.58(1.63–4.08)	<0.001	1.96(1.14–3.32)	0.037
AA/GA vs GG	233/167	58.2/41.8	184/216	46.0/54.0	1.64(1.24–2.17)	0.001	1.14(1.08–1.78)	0.001
AA vs GA/GG	86/314	21.5/78.5	34/366	8.5/91.5	2.95(1.93–4.51)	<0.001	1.97(1.62–3.45)	0.033
A vs G	319/481	39.9/60.1	218/582	27.3/72.7	1.77(1.43–2.19)	<0.001	–	–

**Abbreviation:** aOR, adjusted OR; adjusting age, gender, smoking, drinking, asthma, BMI, IgE, IL6, IL-8, and IL-10.

with elevated risk for AR after adjusting for potential confounding factors, including age, sex, smoking habit, drinking habit, asthma, BMI, IgE, IL6, IL-8, and IL-10.

## Subgroup Analyses

We performed subgroup analyses to further explore the interactions between factors and gene variants (Table 3). Sex showed no effect on the associations between rs2228570 gene polymorphisms and risk for AR. Sex was significantly related to risk for AR in all models. Age seems not to influence risk for AR. The A allele frequency was high. There seemed to be no interaction between smoking habit and gene variant with regard to the risk AR. The AA genotype, AA/GA genotype, and A allele were associated with increased risk for AR. Similar results were also found for BMI. Drinking habit had some impact on the association between rs2228570 gene polymorphisms and AR; patients who drank alcohol had a strong association between rs2228570 gene polymorphisms and AR; significant interactions were found for the following model: AA vs GG (OR=3.51, 95% CI:1.81–6.81,  $P<0.001$ ), AA vs GA (OR=3.75, 95% CI: 2.07–6.77,  $P<0.001$ ), AA/GA vs GG (OR=1.65, 95% CI:1.18–2.30,  $P=0.031$ ) AA vs GA/GG: (OR=4.11, 95% CI:2.36–4.15,  $P<0.001$ ), and A vs G: (OR=1.91, 95% CI:1.48–2.46,  $P<0.001$ ). We performed further subgroup analyses with regard to asthma. In cases and controls with asthma, the rs2228570 gene polymorphism was not associated with AR. In cases and controls without asthma, the A allele increased the risk of AR (A vs G: OR=1.85, 95% CI: 1.46–2.34,  $P<0.001$ ). Significant associations were also found in the other gene models: AA vs GG (OR=3.84, 95% CI:2.33–6.31,  $P<0.001$ ), AA vs GA (OR=3.28, 95% CI: 1.96–5.48,  $P<0.001$ ), AA/GA vs GG (OR=1.61, 95% CI:1.18–2.20,  $P=0.003$ ), and AA vs GA/GG: (OR=3.59, 95% CI:2.23–5.76,  $P<0.001$ ). Next, we performed comparisons between Fok I/rs2228570 gene polymorphism and factors related to inflammation among the groups (Table 4). Compared to the IgE<143.5 group, the

IgE>143.5 group had higher A allele frequency (OR=2.47, 95% CI: 1.45–4.20,  $P=0.001$ ). The rs2228570 gene polymorphism was also related to the severity of AR (Sever vs mild: OR=1.73, 95% CI:1.19–2.52,  $P=0.004$ ).

The expression of VDR Fok I variant mRNA was regulated by the genotype of rs2228570 polymorphism (Figure 1). Our results indicate that FokI is upregulated in AR patients compared to healthy controls. There was a significant difference in the mRNA expression according to rs2228570 polymorphism ( $P<0.05$ ).

## Discussion

AR is an allergic disease characterized by the chemotaxis of eosinophils and their aggregation in the nasal mucosa.<sup>12</sup> It can aggravate damage of nasal mucosa by degranulation and release large numbers of inflammatory transmitters. Many inflammation factors are involved in the progression of AR, although the mechanisms remain unclear.<sup>13,14</sup> Our results indicated that polymorphisms of the VDR gene Fok I locus are associated with AR, and the A allele of FokI/rs2228570 increases the risk for AR; The Fok I/rs2228570 polymorphism also affects serum levels VDR mRNA. The IL-6, IL-8, and IL-10 levels were elevated in the AR group, indicating that inflammation plays an important role in the pathophysiology of AR.

VDR is an important gene transcription regulatory protein in the human body. The VDR gene is composed of nine exons and eight introns located on the chromosome 12q13 and its expression is widely distributed throughout the body.<sup>15</sup> VDR can regulate the immune response of the body, inhibit abnormal cell activation, and maintain the stability of cell function.<sup>16</sup> VDR gene contains recognition sites for several restriction enzyme sites, including Apa I and Taq I. They are closely related to a variety of immune imbalance disease.<sup>17</sup> The Fok I site is located in the second exon of the VDR gene. Studies have shown that gene polymorphisms of the VDR Fok I site are

Table 3 Subgroup Analyses Between Fok I/rs2228570 Gene Polymorphism and Allergic Rhinitis

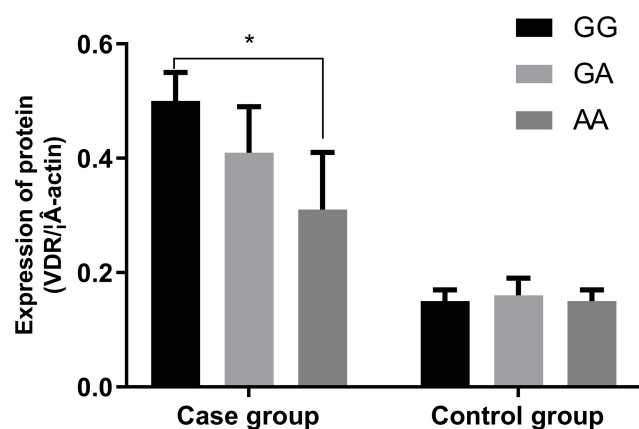
Variables	rs2228570 (Case/Control)				AA versus GG			AA/GA versus GG			AA versus GA/GG			A versus G		
	GG	GA	AA		OR (95% CI)	P		OR (95% CI)	P		OR (95% CI)	P		OR (95% CI)	P	
Gender	84/112	74/81	40/18		2.96(1.59–5.53)	<0.001		1.53(1.28–4.61)	0.006		2.71(1.50–4.92)	0.001		1.66(1.24–2.23)	0.001	
	83/104	73/69	46/16		3.60(1.90–6.82)	<0.001		2.72(1.41–5.24)	0.002		3.19(1.73–5.86)	<0.001		1.92(1.42–2.60)	<0.001	
Age (years)	91/128	93/96	59/23		3.61(2.08–6.26)	<0.001		2.65(1.51–4.64)	0.001		3.12(1.86–5.25)	<0.001		1.38(1.05–1.82)	0.019	
	76/88	54/54	27/11		2.84(1.32–6.11)	0.006		2.45(1.11–5.44)	0.025		2.68(1.28–5.62)	0.007		1.59(1.12–2.25)	0.009	
Smoking	51/92	45/47	35/18		3.51(1.81–6.81)	<0.001		1.90(0.95–3.82)	0.068		2.22(1.38–3.56)	0.001		2.08(1.47–2.96)	<0.001	
	116/124	102/103	51/16		3.41(1.84–6.31)	<0.001		3.22(1.72–6.01)	<0.001		3.32(1.84–6.00)	<0.001		1.59(1.22–2.07)	0.001	
Drinking	48/66	48/44	23/16		4.41(2.48–7.85)	<0.001		3.75(2.07–6.77)	<0.001		4.11(2.36–7.15)	<0.001		1.91(1.48–2.46)	<0.001	
	119/150	99/106	63/18		1.98(0.94–4.14)	0.068		1.32(0.62–2.81)	0.475		1.65(0.98–2.70)	0.059		1.51(1.04–2.20)	0.030	
BMI	70/78	63/61	31/14		2.47(1.21–5.01)	0.011		2.14(1.04–4.42)	0.037		2.31(1.18–4.54)	0.013		1.50(1.08–2.09)	0.016	
	97/138	84/89	55/20		1.94(2.20–6.95)	<0.001		1.66(1.61–5.27)	<0.001		3.45(1.99–5.96)	<0.001		1.97(1.50–2.59)	<0.001	
Asthma	53/8	54/5	25/5		0.75(0.22–2.54)	0.649		0.46(0.12–1.75)	0.247		0.61(0.20–1.86)	0.379		0.91(0.45–1.85)	0.793	
	114/208	93/145	61/29		3.84(2.33–6.31)	<0.001		3.28(1.96–5.48)	<0.001		3.59(2.23–5.76)	<0.001		1.85(1.46–2.34)	<0.001	



**Table 4** Comparison Between Fok I/rs2228570 Gene Polymorphism and Inflammation Factor

Cases	GG	GA	AA	G	A
IgE>143.5 IgE<143.5	62(37.8) 105(44.5)	51(31.1) 96(40.7)	51(31.1) 35(14.8)	175(53.4) 306(64.8)	153(46.6) 166(35.2)
<i>P</i> OR(95% CI) IL-6>158.3 IL-6≤158.3	1.00 88(23.6) 79(17.1)	0.654 0.90(0.57–1.43) 73(33.6) 74(41.9)	0.001 2.47(1.45–4.20) 39(42.8) 47(41.0)	1.00 249(62.3) 232(58.0)	1.61(1.21–2.15) 151(37.7) 168(42.0)
<i>P</i> OR(95% CI) IL-8>160.6 IL-8≤160.6	1.00 99(41.3) 68(42.5)	0.591 0.89(1.57–1.38) 90(37.58) 57(35.6)	0.268 0.74(0.44–1.26) 51(21.3) 35(21.9)	1.00 288(38.3) 193(43.1)	0.219 0.84(0.63–1.11) 192(61.7) 127(56.9)
<i>P</i> OR(95% CI) IL-10>16.9 IL-10≤16.9	1.00 89(41.8) 78(41.7)	0.726 1.08(0.69–1.71) 82(38.5) 65(37.8)	0.997 1.00(0.59–1.70) 42(19.7) 44(23.5)	1.00 260(61.0) 221(59.1)	0.929 1.01(0.76–1.35) 166(39.0) 153(40.9)
<i>P</i> OR(95% CI) Severity of AR Mild Moderate	1.00 69(43.9) 70(43.8)	0.659 1.11(0.71–1.73) 65(41.4) 59(36.9)	0.502 0.84(0.50–1.41) 23(14.6) 31(19.4)	1.00 203(61.1) 199(62.2)	0.576 0.92(0.69–1.22) 129(38.9) 121(37.8)
<i>P</i> OR(95% CI) Severe	1.00 28(33.7)	0.653 0.89(0.55–1.45) 23(27.7)	0.379 1.33(0.71–2.50) 32(38.6)	1.00 79(47.6)	0.784 0.96(0.70–1.31) 87(52.4)
<i>P</i> OR(95% CI)	1.00	0.678 0.87(0.46–1.67)	<0.001 3.43(1.17–6.85)	1.00	0.004 1.73(1.19–2.52)

related to the occurrence of idiopathic hypocarbia and may be a genetic marker of this condition.<sup>18</sup> Serum levels of vitamin D are significantly reduced in patients with pulmonary tuberculosis, and polymorphisms of the VDR gene Fok I locus are associated with susceptibility of pulmonary



**Figure 1** The mRNA expression by the genotypes of rs2228570 among cases and controls, \**P*<0.05.

tuberculosis to primary treatment.<sup>19</sup> Related studies have shown that the VDR gene Fok I polymorphism is not associated with susceptibility of children to milk allergy.<sup>20</sup> This may be related to differences in types of disease studied and differences between subjects. Mohamed et al reported that the VDR gene Fok I polymorphism was related to the occurrence of asthmatic diseases in children, and its distribution was different among children.<sup>21</sup> However, few studies have investigated the relationship between VDR gene rs2228570 mutation and AR susceptibility. Our results showed that the Fok I locus genotype distribution of the VDR gene conformed to Hardy–Weinberg equilibrium between the AR group and control group. A SNP mutation (G-A) was found in the AR group. Further analyses suggested that this mutation was associated with AR. Our results contradict a previous study. Chen et al examined the association between the VDR gene and AR in a southern Chinese population, and found that the VDR gene rs7975232 (C/A) locus was associated with risk for AR and there was no

positive relationship between the VDR gene rs2228570 and AR.<sup>22</sup> These discrepancies may have been due to differences in the study populations and sample sizes. That is, the study was performed in a northern Chinese population, and our sample size was larger than in this previous study that had only a small sample size consisting of 210 cases and 180 controls. More importantly, the previous study did not adjust for potential confounding factors. In addition, the relationship remained significant in our study after adjusting for a number of factors.

Mutations in multiple of the VDR gene were shown to affect the expression of VDR and 25-(OH)VitD<sub>3</sub>, and thus participate in the occurrence of AR and normal array.<sup>23</sup> Vitamin D is a fat-soluble steroid with hormone-like effects, which mainly regulates the balance of calcium and phosphorus metabolism in the human body.<sup>24</sup> However, recent studies have shown that it has a regulatory effect on human immune function and a variety of cytokines, and can participate in the occurrence and development of allergic diseases by inhibiting the production of IgE by B cells and blocking the humoral immune response of IgE.<sup>25</sup> In the present study, we did not determine the serum levels of 25-(OH) VitD<sub>3</sub>, but examined the relative expression of VDR. There was a significant difference in VDR protein level between the case group and control group. Shi et al examined genetic susceptibility to AR associated with the VDR gene rs7975232 polymorphism and investigate serum level of 25-(OH)VitD<sub>3</sub> in the AR patients. They found the rs7975232 polymorphism was associated with AR, and 25-(OH)VitD<sub>3</sub> levels were significantly lower in these patients than in a control group. The levels in a moderately severe AR group was significantly lower than those with mild AR. In addition, the levels were significantly lower in AR patients with AA genotype than in those with the AC and CC genotypes.<sup>26</sup> Thus, the rs2228570 may affect AR gene susceptibility in the same way. VDR is a nuclear hormone receptor for vitamin D and is expressed in many tissues and cells of the human body. There are three forms of vitamin D in the body: vitamin D<sub>3</sub>, 25(OH)D<sub>3</sub>, and 1,25(OH)<sub>2</sub>D<sub>3</sub>; 25(OH)D<sub>3</sub> is the active form of vitamin D<sub>3</sub>, while 1,25(OH)<sub>2</sub>D<sub>3</sub> is the most biologically active form of vitamin D and the form in which vitamin D<sub>3</sub> works.<sup>27</sup> Vitamin D receptors are expressed in a variety of immune cells, such as lymphocytes, monocytes, macrophages, and dendritic cells, 1,25(OH)<sub>2</sub>D<sub>3</sub> acts through the VDR, and therefore may play a regulatory role in the immune system through the immune cells mentioned above.<sup>28</sup> Vitamin D was associated with AR. Jerzynska et al suggested that

vitamin D supplementation combined with sublingual immunotherapy could significantly reduce the symptoms of AR and asthma.<sup>29</sup> A study of the correlation between vitamin D level and AR in an Iranian population showed that vitamin levels were lower in patients with AR than in controls, and deficiency was more severe in patients with severe AR. Vitamin D deficiency is more pronounced in women.<sup>31</sup> Quirk et al noted that in male mice, the prevalence of atopic contact dermatitis in normal mice is lower than in vitamin D-deficient mice, and further studies have indicated a positive correlation between adult serum levels of 25(OH)D<sub>3</sub> and total IgE levels.<sup>31</sup> AR is known to be a non-infectious chronic inflammatory disease of the nasal mucous membrane mainly mediated by IgE after exposure to allergens. 25 - hydroxyl can markedly inhibit the production by peripheral B cells of vitamin D IgE, type and its agonists can hinder allergy IgE humoral immune response.<sup>32</sup> It is an immunomodulatory hormone, which is closely related to the human immune system and is involved in the occurrence and development of allergic diseases. Studies have reported that 25-hydroxyvitamin D is involved in the immune response of T cells and regulates TH2 cells.<sup>33</sup> When T cells are exposed to vitamin D, the production of cytokines IL-2 and interferon are decreased, while levels of IL-4, IL-5 and IL-10 productions are increased, leading to a decrease in the proportion of Th2 and Th1/2 in the immune response.<sup>34</sup> In addition, 25-hydroxyvitamin D can also upregulate GATA binding protein 3, further promoting the immune response to Th2. However, variation in the vitamin D gene can affect the levels of VDR and vitamin D, thus affecting the occurrence of AR.

This study had several limitations. The first, we explored statistical associations only, and thus further research regarding the underlying mechanisms is required. In addition, we may not have included all potential confounding factors in the analyses, and the scores of rhinoconjunctivitis and quality of life questionnaire were not included in the study because we did not collect these data. Future studies should include these data for further analyses. The present findings must be verified in the other population setting.

In conclusion, VDR gene polymorphisms were associated with AR, and the AA genotype of rs2228570 was associated with the increased risk for AR in a Chinese population. We demonstrated a correlation between rs2228570 and AR. Future research should focus on the potential underlying molecular mechanisms and therapeutic targets for AR.

## Disclosure

The authors have no conflicts of interest to declare.

## References

- Meng Y, Wang C, Zhang L. Recent developments and highlights in allergic rhinitis. *Allergy*. 2019;74(12):2320–2328. doi:10.1111/all.14067
- Yang J, Zhong W, Xue K, Wang Z. Epigenetic changes: an emerging potential pharmacological target in allergic rhinitis. *Int Immunopharmacol*. 2019;71:76–83. doi:10.1016/j.intimp.2019.03.004
- Kouzegaran S, Zamani MA, Faridhosseini R, et al. Immunotherapy in allergic rhinitis: its effect on the immune system and clinical symptoms. *Open Access Maced J Med Sci*. 2018;6(7):1248–1252. doi:10.3889/oamjms.2018.264
- Yesil S, Tanyildiz HG, Tekgunduz SA, et al. Vitamin D receptor polymorphisms in immune thrombocytopenic purpura. *Pediatr Int*. 2017;59(6):682–685. doi:10.1111/ped.13273
- Jiao J, Castro M. Vitamin D and asthma: current perspectives. *Curr Opin Allergy Clin Immunol*. 2015;15(4):375–382. doi:10.1097/ACI.0000000000000187
- Jolliffe DA, Greenberg L, Hooper RL, et al. Vitamin D supplementation to prevent asthma exacerbations: a systematic review and meta-analysis of individual participant data. *Lancet Respir Med*. 2017;5(11):881–890. doi:10.1016/S2213-2600(17)30306-5
- Agarwal S, Singh SN, Kumar R, Sehra R. Vitamin D: a modulator of allergic rhinitis. *Indian J Otolaryngol Head Neck Surg*. 2019;71 (Suppl 3):2225–2230. doi:10.1007/s12070-019-01697-9
- Tian HQ, Cheng L. The role of vitamin D in allergic rhinitis. *Asia Pac Allergy*. 2017;7(2):65–73. doi:10.5415/apallergy.2017.7.2.65
- Mathieu C, Van Etten E, Gysemans C, et al. In vitro and in vivo analysis of the immune system of vitamin D receptor knockout mice. *J Bone Miner Res*. 2001;16(11):2057–2065. doi:10.1359/jbmr.2001.16.11.2057
- Tian HQ, Chen XY, Lu Y, et al. Association of VDR and CYP2R1 polymorphisms with mite-sensitized persistent allergic rhinitis in a Chinese population. *PLoS One*. 2015;10(7):e133162. doi:10.1371/journal.pone.0133162
- Brozek JL, Bousquet J, Agache I, et al. Allergic rhinitis and its impact on asthma (ARIA) guidelines-2016 revision. *J Allergy Clin Immunol*. 2017;140(4):950–958. doi:10.1016/j.jaci.2017.03.050
- Tomazic PV, Darnhofer B, Birner-Gruenberger R. Nasal mucus proteome and its involvement in allergic rhinitis. *Expert Rev Proteomics*. 2020;17:191–199. doi:10.1080/14789450.2020.1748502
- Wang G, Cheng N. Paeoniflorin inhibits mast cell-mediated allergic inflammation in allergic rhinitis. *J Cell Biochem*. 2018;119 (10):8636–8642. doi:10.1002/jcb.27135
- Liu RH, Zhang XM, Zhang SQ. [Study on mechanism of biminne in treating allergic rhinitis]. *Zhongguo Zhong Xi Yi Jie He Za Zhi*. 2007;27(7):623–625.
- Saccone D, Asani F, Bornman L. Regulation of the vitamin D receptor gene by environment, genetics and epigenetics. *Gene*. 2015;561(2):171–180. doi:10.1016/j.gene.2015.02.024
- Pesta M. [Vitamin D receptor gene polymorphism]. *Vnitr Lek*. 2012;58(5):381–385.
- Yang L, Wu L, Fan Y, Ma J. Associations among four polymorphisms (BsmI, FokI, TaqI and ApaI) of vitamin D receptor gene and end-stage renal disease: a meta-analysis. *Arch Med Res*. 2015;46 (1):1–7. doi:10.1016/j.arcmed.2014.11.017
- Zhu C, Ye Z, Chen Z, Xia D, Hu J. Association between vitamin D receptor gene polymorphisms and idiopathic hypocitraturia in the Chinese population. *Urol Int*. 2010;85(1):100–105. doi:10.1159/000304733
- Mohammadi A, Khanbabaie H, Nasiri-Kalmarzi R, Khademi F, Jafari M, Tajik N. Vitamin D receptor ApaI (rs7975232), BsmI (rs1544410), FokI (rs2228570), and TaqI (rs731236) gene polymorphisms and susceptibility to pulmonary tuberculosis in an Iranian population: a systematic review and meta-analysis. *J Microbiol Immunol Infect*. 2019. doi:10.1016/j.jmii.2019.08.011
- Zhang Y, Guo Y, Ma J, Lu XZ, Luo XQ. [Association of FokI rs2228570 and TMPRSS6 rs855791 polymorphisms with cow's milk protein allergy in children]. *Zhongguo Dang Dai Er Ke Za Zhi*. 2018;20(8):641–646.
- Mohamed NA, Abdel-Rehim AS. Influence of vitamin D receptor gene FokI and ApaI polymorphisms on glucocorticoid response in patients with asthma. *Int Forum Allergy Rhinol*. 2020;10(4):556–563. doi:10.1002/alr.22511
- Chen SM, Li ZQ, Zhou LM, Zhang YX. [Analysis on correlation between single nucleotide polymorphisms of vitamin D receptor gene with susceptibility to allergic rhinitis]. *Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi*. 2019;33(5):402–406. doi:10.13201/j.issn.1001-1781.2019.05.005
- Dong Y, Yang L, Luo W, et al. Mannose receptor C type 2 mediates 1,25 (OH)<sub>2</sub>D<sub>3</sub>/vitamin D receptor-regulated collagen metabolism through collagen type 5, alpha 2 chain and matrix metalloproteinase 13 in murine MC3T3-E1 cells. *Mol Cell Endocrinol*. 2019;483:74–86. doi:10.1016/j.mce.2019.01.007
- Demirbilek M, Lacin TN, Akturk S, Akca C. VitD<sub>3</sub>-loaded solid lipid nanoparticles: stability, cytotoxicity and cytokine levels. *J Microencapsul*. 2017;34(5):454–462. doi:10.1080/02652048.2017.1345995
- Wu L, Vendiola JA, Salazar GM, et al. Poor ovarian response is associated with serum vitamin D levels and pro-inflammatory immune responses in women undergoing in-vitro fertilization. *J Reprod Immunol*. 2019;136:102617. doi:10.1016/j.jri.2019.102617
- Shi J, Liu JG, Liu XG, Zou WY. Expression of vitamin D and polymorphism analysis of vitamin D receptor gene rs7975232 in serum of allergic rhinitis patients at Baoan District in Shenzhen. *BME & Clin Med*. 2020;24(5):328–332. doi:10.13339/j.cnki.sglc.20200414.010
- Sizar O, Khare S, Goyal A, Bansal P, Givler A. Vitamin D deficiency. 2020.
- Sun J. Dietary vitamin D, vitamin D receptor, and microbiome. *Curr Opin Clin Nutr Metab Care*. 2018;21(6):471–474. doi:10.1097/MCO.0000000000000516
- Jerzynska J, Stelmach W, Rychlik B, Lechanska J, Podlecka D, Stelmach I. The clinical effect of vitamin D supplementation combined with grass-specific sublingual immunotherapy in children with allergic rhinitis. *Allergy Asthma Proc*. 2016;37(2):105–114. doi:10.2500/aap.2016.37.3921
- Uysalol M, Mutlu LC, Saracoglu GV, et al. Childhood asthma and vitamin D deficiency in Turkey: is there cause and effect relationship between them? *Ital J Pediatr*. 2013;39:78. doi:10.1186/1824-7288-39-78
- Quirk SK, Rainwater E, Shure AK, Agrawal DK. Vitamin D in atopic dermatitis, chronic urticaria and allergic contact dermatitis. *Expert Rev Clin Immunol*. 2016;12(8):839–847. doi:10.1586/1744666X.2016.1171143
- Kang JW, Kim JH, Kim HJ, Lee JG, Yoon JH, Kim CH. Association of serum 25-hydroxyvitamin D with serum IgE levels in Korean adults. *Auris Nasus Larynx*. 2016;43(1):84–88. doi:10.1016/j.anl.2015.06.010
- Thorsen SU, Pipper CB, Skogstrand K, Pociot F, Svensson J. 25-Hydroxy vitamin D and peripheral immune mediators: results from two Nationwide Danish Pediatric Cohorts. *Nutrients*. 2017;9(4):365. doi:10.3390/nu9040365
- Overbergh L, Stoffels K, Waer M, Verstuyf A, Bouillon R, Mathieu C. Immune regulation of 25-hydroxyvitamin D-1α-hydroxylase in human monocytic THP1 cells: mechanisms of Interferon-γ-mediated induction. *J Clin Endocrinol Metab*. 2006;91 (9):3566–3574. doi:10.1210/jc.2006-0678



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