

The Association of Vitamin D Receptor Polymorphisms of FokI and TaqI with Rheumatoid Arthritis in North-East of Iran

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Abstract

Background and objectives: Vitamin D receptor (VDR) has been identified as a susceptibility gene for several autoimmune diseases. This study was designed to investigate the association of VDR gene polymorphisms with the susceptibility to rheumatoid arthritis (RA).

Methods: A case-control study was performed on 130 RA patients and 128 healthy subjects in the north-east of Iran using restriction fragment length polymorphism-polymerase chain reaction (RFLP-PCR) technique.

Results: Our findings suggested a significant association of T allele ($p=0.01$) of TaqI (rs731236), and f allele ($p=0.01$) of FokI (rs10735810) genetic variants of the VDR gene with RA susceptibility. These significant associations were also found in the T/T genotype of TaqI ($p=0.009$), and F/f genotype of FokI ($P=0.014$). The f-T haplotype was more significantly detected in-patients than in healthy controls ($p=0.007$).

Conclusion: The RA group showed an increase in the f allele and heterozygous F/f genotype and also in the T allele and homozygous T/T and heterozygous T/t genotypes as compared to the control group. Our results demonstrated that polymorphisms of TaqI and FokI in the VDR gene might be involved in the development of RA in an Iranian population.

Keywords: FokI; TaqI; Vitamin D receptor; Rheumatoid arthritis; restriction fragment length polymorphism-polymerase chain reaction (RFLP-PCR)

Introduction

Rheumatoid arthritis (RA) is a heterogeneous and polygenic autoimmune disease characterized by chronic inflammation of multiple peripheral joints which results in progressive tissue damage to cartilage and systemic bone loss (1). Both environmental and genetic factors are involved in the pathogenesis of autoimmune diseases including RA (2). Vitamin D (VD) as an effective immune regulator hormone and genetic alterations of its receptor (VDR) is of the most important environmental and genetic factors in the pathogenesis of the RA (3-5). As T lymphocytes are of great importance for development of RA (6), previous studies found that VDR activity plays an important role in T cell function (7). Calcitriol, biologically active form of the steroid hormone of VD, as 1 α , 25-dihydroxy vitamin D3 (1, 25(OH)₂ D3) binds to two distinct forms of the VDR called: mVDR (membrane) and nVDR (nuclear). VD-nVDR complex with the retinoid X receptors (RXR) transcription factor alters the expression of various VD dependent genes. Calcitriol also exerts non-genomic actions by mVDR-caveolin-1 complex (8). The VD endocrine system plays a vital role in calcium and phosphate homeostasis and bone metabolism (9, 10). VDR is a member of the cytoplasmic/nuclear hormone receptor superfamily (11). The VDR gene (HGNC: 12679) is located on chromosome 12q13.11 and contains 9 exons encoding the protein of the receptor (12). These receptors are expressed in many cells of the immune system including dendritic cells, monocytes/macrophages, and activated lymphocytes. It is, therefore, accepted that vitamin D through its effect on the immune system, affects the RA (13). Several single

nucleotide polymorphisms (SNPs) have been reported in the VDR gene, including FokI (rs10735810) at the start codon in exon 2 and TaqI (rs731236) in exon 9 at the 3' untranslated regions (3'UTR) of the gene (14). FokI genetic variant results from a C>T nucleotide change, creating an extra start codon (ACG-ATG codon exchange) leading to add three amino acids to VDR phosphoprotein with less activity (15-17). Moreover, TaqI SNP is characterized by T>C transition at codon 352 (ATT-ATC codon exchange), resulting in a silent codon alteration, keeping the identical amino acid isoleucine (I352I), but with improved stability and translational activity of the VDR mRNA (18). The potential mechanism underlying the association of FokI and TaqI polymorphisms with RA is not completely elucidated. Previous investigations on the genetic association between various VDR polymorphisms and RA resulted in controversial outcomes. The current study aimed to assess an associate FokI and TaqI polymorphisms with RA susceptibility in Gorgan, north-east of Iran.

Materials and Methods

Patient selection

A total of 130 patients with established RA disease were recruited from the Joint, Bone, Connective tissue, Rheumatology Research Center (JBCRC), Sayyad Shirazi educational hospital of Golestan University of Medical Sciences (GOUMS). All patients with RA were confirmed by an expert rheumatologist according to the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria for RA (19). Patients with endocrinal disorders, other autoimmune diseases, hepatic and renal disorders, malignancy were excluded from the

study. One hundred twenty-eight sex- and age-matched (p -value > 0.05) healthy individuals who were free of chronic inflammatory disorders and had a negative family history of arthritis were also recruited as controls. Most patients with RA received modifying antirheumatic drugs (DMARDs) or steroids. This study was approved by the Ethics Committee of GOUMS and written informed consent was obtained from all participants after a full explanation of procedures and aim of the genetic study.

DNA extraction and Genotyping

A total of 2 ml of peripheral venous whole blood in EDTA was obtained and stored at -20°C . Genomic DNA was extracted by spin-columns blood DNA isolation kit according to the protocol provided by the manufacturer (Dena Zist, Mashhad, Iran). The presence of the VDR FokI (rs10735810) Exon 2 (C/T) and the TaqI (rs731236) exon 9 (T/C) SNPs were assessed using polymerase chain reaction/restriction fragment-length polymorphism (PCR/RFLP) analysis. PCR primers, conditions, allele size (bp), and restriction enzymes are summarized in Table 1. DNA amplification was performed by PCR on each sample in a total volume of 25 μl reaction solution including 1 μl of DNA template (50 ng), 12.5 μL of 2x master mix (2x PCR buffer, 0.4mM dNTPs, 3.2 mM MgCl_2), 0.5 μL of each primer, 0.25 μL of Taq DNA polymerase (5U/ μl), and diluted to the final volume with 10.25 μL deionized H_2O (Yekta Tajhiz Azma, Tehran, Iran). Amplified PCR products were digested with FokI and TaqI restriction enzymes (Fermentas, Stockholm, Sweden) according to the manufacturer's instructions. Digested PCR products were separated by agarose gel electrophoresis on 2.5% agarose containing SYBR Safe stain (Invitrogen, Groningen, The

Netherlands), and the existence or lack of fragments were visualized by UV light. VDR FokI and TaqI genotype and allele frequencies were counted directly. Regarding FokI polymorphism, the C nucleotide (ACG codon) was defined as an F allele and the T nucleotide (ATG codon) was defined as allele f (presence of the restriction site). The FokI polymorphism was then divided into three groups: non-excisable homozygote (F/F), excisable homozygote (f/f) and heterozygote (F/f). Regarding TaqI polymorphism, the T nucleotide was defined as allele T (absence of the restriction site) and the C nucleotide was defined as allele t. The TaqI polymorphism was then divided into three groups: an excisable homozygote (t/t), non-excisable homozygote (T/T) and heterozygote (T/t). The PCR/RFLP-based genotyping results were confirmed by Sanger sequencing.

Statistics

Allele and genotype frequencies of the VDR gene polymorphisms were calculated using Statistical Package for Social Sciences (SPSS) -IBM software version 22.0 (IBM Corporation, Armonk, NY, USA). Based on the logistic regression method, genetic associations between RA and SNPs, haplotype estimation, and Hardy-Weinberg equilibrium (HWE) were tested and Odds ratios (OR) and confidence intervals (95%CI) were calculated by the executive SNP Analyzer 2.0 (BMC Bioinformatics 2008, 9:290). The statistical significance level was considered to be two-tailed $p \leq 0.05$ in all performed tests.

Table 1: Conditions of PCR/RFLP of FokI and TaqI polymorphisms

PCR-RFLP details	VDR/FokI (rs10735810) Exon 2 (C/T)	VDR/TaqI (rs731236) Exon 9 (T/C)
Primers	F: 5'- AGCTGGCCCTGGCACTGACTCTGCTCT-3' R: 5'- ATGGAAACACCTTGCTTCTTCTCCCTC-3'	F: 5'- CAGAGCATGGACAGGGAGCAA-3' R: 5'- GCAACTCCTCATGGCTGAGGTCTC-3'
PCR program	95°C, 5 min, 35 cycles: [95°C, 30 sec; 61°C, 40 sec; 72°C, 1 min], 72°C, 7 min	95°C, 5 min, 35 cycles: [95°C, 30 sec; 63°C, 40 sec; 72°C, 1 min], 72°C, 7 min
PCR products	265 bp	745bp
Restriction enzymes	Fok I (5 units/ Overnight in 37 °C)	Taq I (5 units/ Overnight in 37 °C)
Genotypes	F/F : 265 bp and F/f: 265+196+69 bp and f/f: 196+69 bp	T/T : 745 bp and T/t: 745+595+150 bp and t/t: 595+150 bp

Results

VDR FokI and TaqI genotypes and alleles analysis

The distribution of F and f alleles for the FokI gene in the study population were 0.83 (426/514) and 0.17 (88/514), respectively. Regarding genotype frequencies, F/F was 0.68 (174/257), F/f was 0.3 (78/257), and f/f was 0.02 (5/257). Moreover, neither controls ($X^2 = 0.22$, $p = 0.63$) nor cases ($X^2 = 1.74$, $p = 0.19$) deviated from HWE.

Besides, the distribution of T and t alleles for the TaqI gene were 0.55 (275/498) and 0.45 (223/498), respectively. Regarding genotype frequencies, the frequency of t/t was 0.23 (57/249), T/t was 0.44 (109/249), and T/T was 0.33 (83/249) in all subjects. Neither controls ($X^2 = 0.98$, $p = 0.32$) nor cases ($X^2 = 1.76$, $p = 0.18$) deviated from HWE for the TaqI SNP.

Table 2 demonstrates the allele and genotype distributions of these two SNPs within patients and healthy controls. For the FokI SNP, f allele was more frequent in the RA patients than the healthy controls (0.21 versus 0.13). The F/f genotype was more frequent in the RA patients than the healthy controls ($p = 0.014$). For the TaqI SNP, T allele was more frequently observed in the patients than the healthy controls (0.5 versus 0.39). The T/T genotype was more frequent in RA patients than the healthy controls ($p = 0.009$). Total P values for Hardy-Weinberg proportions (HWEP) of the SNPs are shown in Table 2. Comparing two studied SNPs of the VDR gene, the allele distributions of the FokI (OR = 1.80; 95% CI = 1.12 - 2.90; $x^2 = 6.024$; $p = 0.0141$) and the TaqI (OR = 1.60; 95% CI = 1.12 - 2.29; $x^2 = 6.761$; $p = 0.0093$), no statistically significant difference between RA patients and healthy controls was observed. Logistic regression was used for association analysis by modeling the effect of the SNPs in the additive, co-dominant, dominant, and

recessive models. FokI SNP showed a significant difference between cases and controls in the co-dominant (OR = 1.68; 95% CI = 0.98 - 2.88; p =0.0049), dominant (OR = 1.86; 95% CI = 1.10 - 3.17; p =0.02) and log-additive (OR = 1.97; 95% CI = 1.20 - 3.23; p =0.0063) models (Table 3). Likewise, TaqI SNP showed a significant difference between patients and controls in dominant (OR = 1.79; 95% CI = 1.05 - 3.06; p =0.031) and log-additive (OR = 1.51; 95% CI = 1.07 - 2.12; p =0.018) models (Table 4).

FokI/TaqI haplotypes had a significant association with the RA

The association of VDR haplotypes derived from FokI/TaqI with RA was assessed using the combination of genotypes by logistic regression. The distribution of haplotype frequencies in patients and healthy subjects are shown in Table 5. Our data indicated that the FokI/TaqI haplotypes had a significant association with the RA (p = 0.003). The f-T haplotype (OR = 3.54, 95%CI = 1.41 - 8.92; p=0.007) was more significantly detected in patients than in healthy controls.

Table 2: the allele and genotype distributions of the FokI and TaqI polymorphism in patients and healthy controls

SNP-VDR		Proportion (Count)						Total HWEP
		Allele		Genotype			P	
FokI (rs10735810)		F	f	F/F	F/f	f/f		0.26
	Patients	0.79 (201)	0.21(55)	0.61(78)	0.35(45)	0.04(5)	0.014	
	Controls	0.87 (225)	0.13(33)	0.74(96)	0.26(33)	0.0(0)		
TaqI (rs731236)		t	T	T/T	T/t	t/t		0.07
	Patients	0.5 (122)	0.5(124)	0.28(34)	0.46(56)	0.27(33)	0.009	
	Controls	0.61 (153)	0.39(99)	0.18(23)	0.42(53)	0.4(50)		

Table 3: The VDR-Fok1 SNP association with RA by using logistic regression

Model	Genotype	Controls %	Patients %	OR (95% CI)	P-value
Codominant	F/F	74.4	60.9	1.00	0.0049
	F/f	25.6	35.2	1.68 (0.98-2.88)	
	f/f	0	3.9	NA (0.00-NA)	
Dominant	F/F	74.4	60.9	1.00	0.02
	F/f-f/f	25.6	39.1	1.86 (1.10-3.17)	
Recessive	F/F-F/f	100	96.1	1.00	0.0078
	f/f	0	3.9	NA (0.00-NA)	
Overdominant	F/F-f/f	74.4	64.8	1.00	0.095
	F/f	25.6	35.2	1.58 (0.92-2.70)	
Log-additive	---	---	---	1.97 (1.20-3.23)	0.0063

Table 4: The VDR-TaqI SNP association with RA by using logistic regression

Model	Genotype	Controls %	Patients %	OR (95% CI)	P-value	AIC	BIC
Codominant	t/t	39.7	26.8	1.00	0.058	345.5	356
	T/t	42.1	45.5	1.60 (0.90-2.85)			
	T/T	18.2	27.6	2.24 (1.13-4.46)			
Dominant	t/t	39.7	26.8	1.00	0.031	344.5	351.5
	T/t-T/T	60.3	73.2	1.79 (1.05-3.06)			
Recessive	t/t-T/t	81.8	72.4	1.00	0.077	346	353.1
	T/T	18.2	27.6	1.71 (0.94-3.12)			
Overdominant	t/t-T/T	57.9	54.5	1.00	0.58	348.8	355.9
	T/t	42.1	45.5	1.15 (0.70-1.90)			
Log-additive	---	---	---	1.51 (1.07-2.12)	0.018	343.5	350.6

Table 5: Estimated haplotype proportion and the association analysis with RA

Haplotype	Sequence	Controls	Patients	Total	OR (95% CI)	P-value
FokI/ TaqI	Ft	0.51	0.38	0.45	1.00	---
	FT	0.36	0.40	0.38	1.50 (0.98 - 2.30)	0.064
	ft	0.09	0.12	0.10	1.90 (0.92 - 3.93)	0.086
	fT	0.04	0.10	0.07	3.54 (1.41 - 8.92)	0.007

Global haplotype association p-value: 0.003

Discussion

The current study is the first case-control association study from north-east of Iran addressing the genetic association of FokI (rs10735810) and TaqI (rs731236) VDR gene polymorphisms with RA susceptibility. RA is a chronic inflammatory and multifactorial disorder in which genetic factors are important determinants. Vitamin D has anti-inflammatory and immunomodulatory roles, and its most biological activities are mediated by the VDR (5). Polymorphisms in the VDR gene could lead to significant receptor dysfunction and may change the immune

response and an individual's susceptibility to developing RA. Many studies investigated the polymorphisms of the VDR gene in different diseases worldwide. The most common genetic variations associated with RA include the FokI and TaqI genes (18, 20, 21). FokI located within the start codon of gene and leads to the expression of VDR protein in at least two different lengths. Most of the previous studies indicated that shorter encoded protein with 424 aa by the wild-type F allele is more efficient in transactivation of the vitamin D signaling than the longer ones with 427aa encoded by f allele (15, 16). Located at an end of the VDR gene, TaqI

polymorphism does not change the amino acid sequence or size of the protein, but t allele is involved in increased transcriptional activity and mRNA stability. The 3'-end of the VDR gene encodes a region that is a piece of the VD-binding domain (16, 18). Our results highlight that the FokI and TaqI polymorphisms are associated with susceptibility to RA. Our data are consistent with the meta-analysis results by Tizaoui *et al.* who demonstrated the association for both FokI and TaqI polymorphisms with RA (1). A recent study demonstrated the strong association of rs10735810 and rs731236 polymorphisms with the onset of RA in the Pakistani population (22). Within two separate meta-analysis studies by Lee *et al.* and Song *et al.*, results from their analysis showed that there is a significant association between VDR FokI polymorphism and RA, but they reported no evidence linking the TaqI polymorphism to disease (23, 24). In a separate study, no association was shown between TaqI and RA in Tunisians (25). In our study, for the FokI SNP, the RA group showed an increase in the f allele and heterozygous F/f genotype as compared to the control group. The f/f and F/F genotype were not found to be higher in the RA group as compared to the healthy control group. For the TaqI SNP, the RA group showed an increase in the T allele and homozygous T/T and heterozygous T/t genotypes as compared to the control group. The T/t and t/t genotypes had a nonsignificant distribution in the control group as compared to the case group. The t/t genotype was found to be lowered in the RA group compared to the healthy control group. These results supported the considerable role of polymorphisms of VDR in RA disease. Most previous studies showed that the f allele of the FokI and T allele of the TaqI VDR SNPs have not been effective in

transactivation of the VD signaling (15, 17, 21, and 26). As a result, by further expression of the VDRs with f and T alleles in RA patients, the immunosuppressive effects of vitamin D seem to be disrupted with increased susceptibility to developing RA. Besides, our statistical results indicated that the combination of the f-T haplotype is associated with the RA. However, other investigations on FokI VDR SNP have created controversial findings. Results of a meta-analysis showed a significant association between the F allele and RA in European populations (27). A study in Tunisia also indicated that the F allele is associated with RA (28). In a correlation with our findings, results of a meta-analysis study showed that patients with genotypes having at least one copy of the T allele of TaqI were at increased risk to developed, RA (1). Nonetheless, the results of a study in Turkey showed that VDR polymorphisms of TaqI and FokI do not play a role RA susceptibility (29). A previous study performed in a central India population also showed that the FokI VDR gene was not significantly different between the case and control groups (30). Also, in a previous genome-wide association study indicated that the VDR region of chromosome 12 was not associated with RA susceptibility (31). The reason behind the discrepancies may be due to the different genetic backgrounds between populations, small sample sizes, different environmental factors and complexity of RA with contributions from multiple genes. So, due to the complexity of the RA, to better diagnosis and treatment, the patients have to be classified based on the genetic background of individuals in different geographical areas, types of effective genes and environmental factors. In this way, further study to identify the factors in each region can be helped to advance this goal.

Conclusion

Our results demonstrated that polymorphisms of TaqI and FokI in the VDR gene might be involved in the development of RA in an Iranian population.

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Conflict of interest

The authors declare that they have no financial or non-financial conflicts of interest related to the subject matter or materials discussed in the article.

Authors' contributions

All authors have the same contribution to this work.

Ethical Approval Considerations

This study was approved by the Ethics Committee of GOUMS (Code of Ethics: IR.GOUMS.REC.1394.278).

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