Research Article

# Exploring Genetic Variability in VDR FokI and BsmI Polymorphisms and Their Association with Rheumatoid Arthritis

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**Article Info**

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**Keywords**

Rheumatoid Arthritis, Vitamin D Receptor, Polymorphism, RFLP, Gene Association

**Abstract**

**Background**: Rheumatoid Arthritis (RA) is a chronic, inflammatory autoimmune disease that mainly affects small joints and progresses to larger joints. It impacts approximately 1% of the global population, with women being three times more likely to develop it than men, typically between ages 40 and 50. Genetic and environmental factors, including vitamin D deficiency, contribute to RA development. The vitamin D receptor (VDR) gene plays a crucial role in regulating metabolism and inflammation, making it a key candidate in RA.

**Aims**: This study determines the relationship between VDR FokI (rs10735810) and VDR BsmI (rs1544410) gene polymorphisms in RA patients and healthy controls.

**Methods**: A total of 400 participants were included in the study, consisting of 200 RA patients and 200 healthy controls. Genetic varations of VDR genes was performed using the PCR-RFLP technique.

**Result**: Among 200 RA patients, 42 (21%) were male and 158 (79%) were female, while in the control group, 40 (20%) were male and 160 (80%) were female. The average age of RA patients was 43±17 years and a mean disease onset at age 30.3±19.3 years. The Ff and ff genotypes of the FokI polymorphism were significantly more frequent in RA patients (OR=1.8, p=0.011 and OR=2.8, p=0.004, respectively). For the BsmI polymorphism, the Bb genotype showed a significant association with RA (OR=1.5, p=0.049), while the bb genotype did not (OR=1.4, p=0.241). Gender-based analysis revealed higher frequencies of the Ff, ff, and bb genotypes in females, with significant associations for Ff (OR=3.0, p=0.009), ff (OR=4.5, p=0.002) for Bsml genotype only bb (OR=3.9, p=0.006) was significantly increase the risk of RA.

**Conclusions**: This study concluded that the VDR FokI (rs10735810) gene polymorphism was associated with RA, while the VDR BsmI (rs1544410) polymorphism did not appear to have a significant association with the disease.

## Introduction

Rheumatoid Arthritis (RA) is a chronic, systemic autoimmune disorder that primarily targets the synovial joints, particularly affecting the small joints of the hands and feet [1]. The hallmark features of RA include persistent inflammation, progressive joint destruction, and deformities, which can lead to significant functional disability and impaired quality of life [2,3]. The global prevalence of RA is estimated to be approximately 1%, with a notable disparity between the sexes, women are disproportionately affected at a ratio of 3:1 compared to men [4,5]. Although the disease most commonly presents between the ages of 40 and 50, it can occur at any age, including in children and the elderly, indicating that both genetic and environmental factors contribute to its onset.

The pathogenesis of RA is multifactorial, involving a complex interplay of genetic predisposition, environmental triggers, and immune system dysregulation [2,4]. In genetically predisposed individuals, environmental factors such as infections, smoking, and vitamin D deficiency may contribute to the initiation and progression of the disease [6]. Autoimmunity plays a central role in RA, with the immune system mistakenly targeting the body's own tissues, particularly the synovial membrane, leading to the chronic inflammation that characterizes the disease [7,8]. As the disease progresses, inflammation leads to cartilage and bone destruction, resulting in deformities and loss of joint function.

Among the genetic factors influencing the development of RA, the Vitamin D Receptor (VDR) gene has attracted significant attention due to its critical role in regulating immune function and inflammation [9]. Vitamin D, through its receptor VDR, plays a pivotal role in modulating immune responses by influencing the differentiation and activation of T cells, B cells, and macrophages, which are central players in autoimmune diseases such as RA [10]. Vitamin D deficiency has been associated with an increased susceptibility to autoimmune diseases, including RA, suggesting that alterations in VDR signaling may contribute to the disease's pathogenesis [11].

The VDR gene is located on chromosome 12q13 and encodes the vitamin D receptor, which mediates the biological actions of vitamin D [12,13]. Several polymorphisms in the VDR gene have been identified, and these genetic variations are thought to influence the receptor's ability to bind to vitamin D and regulate gene expression. Two of the most studied VDR polymorphisms in relation to autoimmune diseases are the FokI (rs10735810) and BsmI (rs1544410) polymorphisms [13-15].

The FokI polymorphism is located in the translation initiation site of the VDR gene and leads to the production of a variant receptor with a different length compared to the wild-type receptor [16]. The shorter form of the receptor, resulting from the presence of the F allele, is believed to be more transcriptionally active, potentially leading to altered immune responses. This polymorphism has been shown to affect the receptor's ability to regulate inflammatory cytokines, which are key mediators in RA [17-18]. The BsmI polymorphism, located in the 3' untranslated region of the VDR gene, has been associated with variations in VDR expression levels, though its functional significance remains less well understood [19,20]. Both of these polymorphisms have been implicated in various autoimmune conditions, including rheumatoid arthritis, suggesting that they may play a role in modulating susceptibility to the disease.

In this study, we aimed to examine the relationship between the VDR FokI and VDR BsmI gene polymorphisms and the susceptibility to RA. We hypothesized that certain genotypes of these polymorphisms could be associated with an increased risk of developing RA.

## Material and Methods

### Study Population

This cross-sectional study was conducted from November 2019 to October 2021 in the Department of Biochemistry and the Department of Medicine at Uttar Pradesh University of Medical Sciences (UPUMS), Saifai, Etawah. The sample collection and rhematoid markers (RA Factor, hs-CRP, Anti-CCP, and vitamin D) were done in the UPUMS, Saifai and the genotype study was done in VMMC & Safdarjung Hospital, New Delhi, India. The study encompassed 400 subjects, comprising 200 Rheumatoid Arthritis (RA) patients and 200 healthy controls who were matched for age and sex, all from the same ethnic group.

The diagnosis of RA was established based on the Revised American College of Rheumatology's 2010 clinical criteria. Patients were accommodated in the rheumatology clinic's inpatient wards and outpatient departments within the Department of Medicine. A comprehensive oral questionnaire was administered to each participant after obtaining their consent. This questionnaire included a detailed history and a clinical examination based on the Clinical Disease Activity Index (CDAI). This rigorous approach ensured a thorough evaluation of each participant's condition.

### Subject selection criteria

The study included patients who met the 2010 Revised American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria for Rheumatoid Arthritis [21]. However, individuals taking Vitamin D supplements or the hypolipidemic drug HAART (Highly Active Antiretroviral Therapy) were excluded. Additionally, subjects with chronic conditions such as Diabetes, Hypertension, Familial Hypercholesterolemia, Chronic Kidney Disease, and Tuberculosis were not considered for the study.

### Sample Collection

Blood samples were collected by venipuncture into labelled plain & EDTA vials. An EDTA sample was used to estimate for molecular study. The plain sample was centrifuged at 4500

rpm for 20 minutes for serum separation and then the serum was used for the analyses of rheumatoid markers (RA factor, hs-CRP, Anti-CCP, and vitamin D estimation.

**Molecular Analysis**

Reagent purchased

DNA Isolation Kit (CatLog No.: 51104, Qiagen, USA), PCR master mix (CatLog No. RR310A, Takara BioInc, Japan, FokI and BsmI enzymes (CatLog No.: R01095 and R01345, New England Biolabs Inc. New England).

**DNA Extraction**

Genomic DNA was extracted from peripheral blood samples using a commercially available DNA isolation kit. The DNA extraction kit is designed to efficiently isolate high-quality genomic DNA from human blood samples. This method ensures the removal of contaminants that could interfere with downstream applications, such as polymerase chain reaction (PCR). Briefly, whole blood was collected in EDTA tubes, and the extraction process followed the manufacturer's protocol. The purified DNA was quantified using a spectrophotometer and stored at -20°C until further use. The extracted DNA served as the template for subsequent genotyping of VDR gene polymorphisms.

**Genotyping**

Genotyping of the VDR FokI (rs10735810) and VDR BsmI (rs1544410) polymorphisms was performed using the polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) technique. PCR amplification of specific gene regions was followed by restriction enzyme digestion to detect the presence of specific alleles at each polymorphic site.

**Genotyping of VDR (FokI) (rs10735810)**

For the genotyping of VDR FokI polymorphism (rs10735810), PCR amplification was performed using specific primers: forward primer 5‟AGCTGGCCCTGGCACTGACTCTGCTCT3‟ and reverseprimer5‟ATGGAAACACCTTGCTTCTTCTCCCTC3‟. This amplification targeted a fragment of 265 base pairs. The amplified product was then digested using the FokI Fast Digest enzyme. The PCR conditions were as follows: an initial denaturation at 94°C for 5 minutes, followed by 35 cycles consisting of denaturation at 94°C for 1 minute, annealing at 61°C for 1 minute, and extension at 72°C for 1 minute, with a final extension step at 72°C for 7 minutes. The PCR products were separated on a 2% agarose gel under UV light for visualization.

The genotypes were identified based on the banding pattern: the FF (homozygous wild-type) genotype yielded a single 265 bp band, the Ff (heterozygous) genotype produced three bands at 265, 200, and 65 bp, and the ff (homozygous mutant) genotype produced two bands at 200 and 65 bp (Figure 1A).

**Genotyping of VDR (BsmI) (rs1544410)**

For the VDR BsmI polymorphism (rs1544410), PCR amplification was performed using the following primers: forward primer 5‟CAACCAAGACTCAAGTACCGCGTCAGTG3‟ and reverse primer 5‟AACCAGCGGAAGAGGTCAAGGG3‟. This reaction amplified a fragment of 825 base pairs, which was subsequently digested with the MvaI restriction enzyme. The PCR amplification profile consisted of an initial denaturation at 94°C for 5 minutes, followed by 40 cycles of denaturation at 94°C for 1 minute, annealing at 58°C for 1 minute, and extension at 72°C for 1 minute, with a final extension at 72°C for 7 minutes. The amplified products were analyzed on a 2% agarose gel under UV light.

Genotypes were determined based on the digestion pattern: the BB (homozygous wild-type) genotype produced a single band at 825 bp, the Bb (heterozygous) genotype resulted in three bands at 825, 650, and 175 bp, and the bb (homozygous mutant) genotype produced two bands at 650 and 175 bp (Figure 1B).

**Figure 1:** Electrophoresis gel image of genes

**Figure 1A**

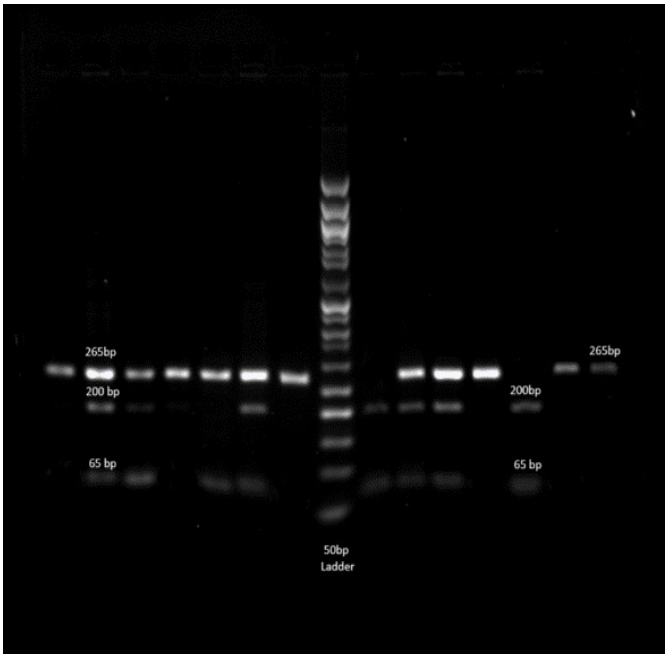
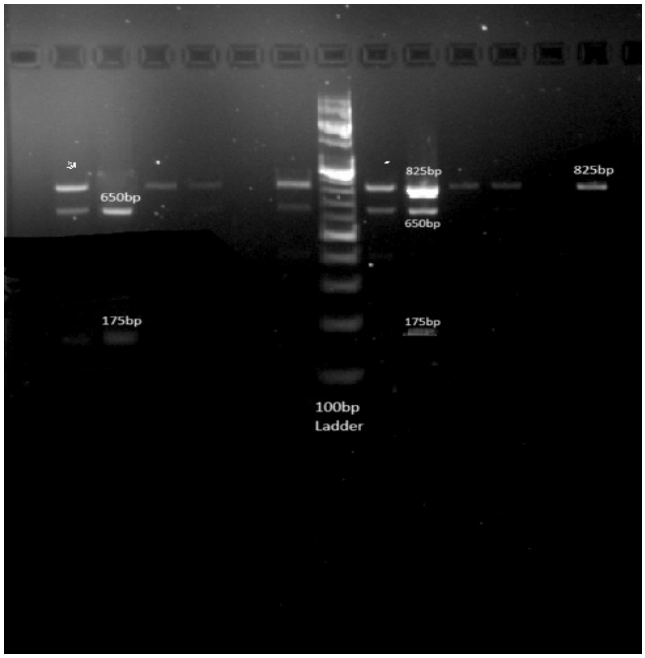



**Figure 1B**




1A FokI: Wild: 265bp, Heterozygous: 265bp, 200bp, 65bp, and Mutant: 200bp, 65bp.

1B BsmI: Wild: 825 bp, Heterozygous: 825bp, 650bp, 175bp, and Mutant: 650bp, 175bp.

### Statistical analysis

Data analysis was done using the Statistical Package for the Social Sciences (SPSS) version 21 software. Genotype and allele frequencies were calculated, and Chi-square analysis was applied to compare allele frequencies between the patient and healthy control groups. Odds ratios were computed to evaluate genotype distributions. A p-value of less than 0.05 was considered statistically significant.

## Result

### Demographic Characteristics

The demographic data of the study participants are summarized in Table 1. The average age of RA patients and healthy controls was comparable, with no significant difference between the two groups. There were also no significant differences in the gender distribution between the RA patients and the control group.

**Table 1:** Demographical characteristics of study population.

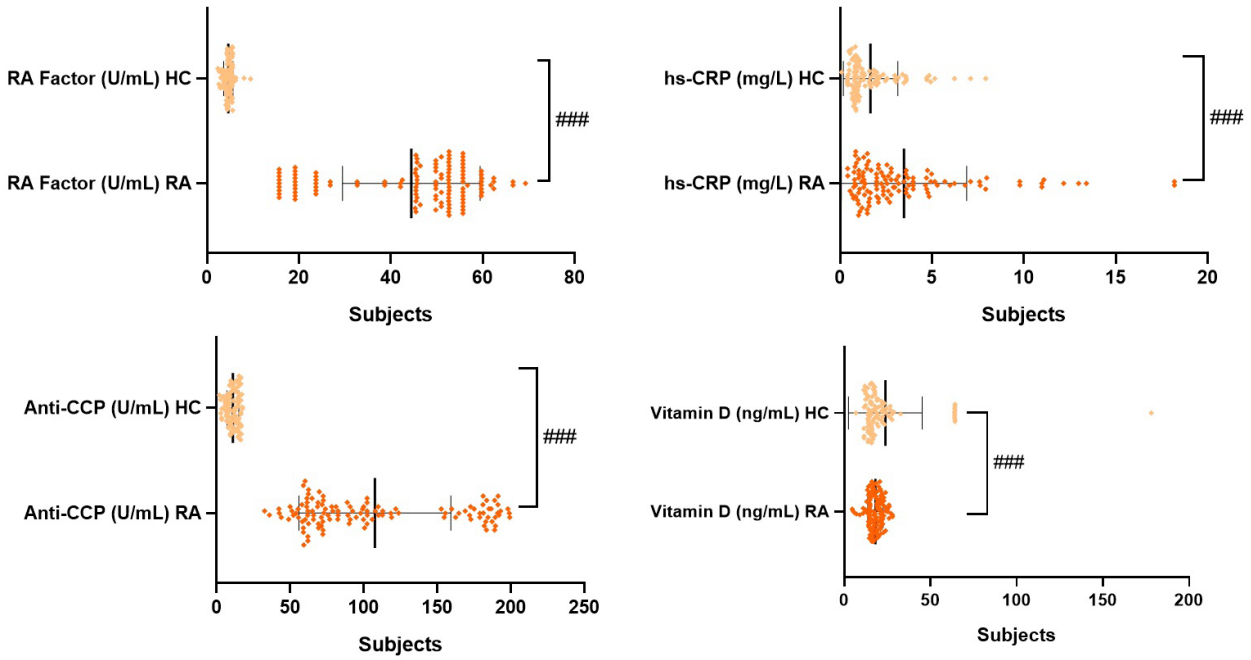
| Parameters | RA Patients (n=200) | Healthy Controls (n=200) | p-value |
|---|---|---|---|
| Male n (%) | 42 (21%) | 40 (20%) | 0.804* |
| Female n (%) | 158 (79%) | 160 (80%) | |
| Age (mean ± SD) | 43 ± 17 | 44 ± 16 | 0.545* |
| Age at Disease Onset (mean ± SD) | 30.3 ± 19.3 | - | |

The chi-square test was used calculate the p-value. *p<0.05 statistically significant.

**Comparison of rheumatoid markers among study groups**

Figure 2 represents the levels of hsCRP, vitamin D, Rh Factor, and anti-CCP among study groups. All the markers were significantly elevated in rheumatoid patients than the control except vitamin D. Vitamin D was significantly reduced in cases than the healthy controls.

**Figure 2:** Levels of RA Factor, Hs-CRP, Anti-CCP, and Vitamin D in Rheumatoid patients and healthy control.




Abbreviations: RA: Rheumatoid arthritis, HC: Healthy control, hs-CRP: high-sensitive C reactive protein, Anti-CCP: Anti-cyclic citrullinated peptide, ###: p<0.0001

**Genotypic and Allelic Frequencies of VDR FokI Polymorphism**

The genotypic distribution of the VDR FokI polymorphism in RA patients and healthy controls is presented in Table 2A. The Ff and ff genotypes were significantly more frequent in RA patients compared to controls. Specifically, the Ff genotype had an odds ratio (OR) of 0.3 (95% CI: 0.1–0.8, p=0.004), and the ff genotype had an OR of 4.9 (95% CI: 2.1–11.55, p=0.0001), suggesting a strong association with RA. The F allele was more frequent in RA patients (OR=15.5, p=0.000), further supporting the role of the FokI polymorphism in RA susceptibility.

**Table 2A:** VDR FoKI genotype polymorphism in the study population.

| Genotype | RA Patients (n=200) | Healthy Controls (n=200) | OR (95% CI) | p-value |
|---|---|---|---|---|
| FF | 40 (20%) | 66 (33%) | 1 | |
| Ff | 102 (51%) | 90 (45%) | 1.8 (1.1–3.0) | 0.011* |
| ff | 58 (29%) | 34 (17%) | 2.8 (1.6–5.0) | 0.004* |

Abbreviations: 1: Reference group, OR: Odd Ratio, CI: Class Interval, RA: Rheumatoid arthritis,

*p<0.05 considered as statistically significant.

**Genotypic and Allelic Frequencies of VDR BsmI Polymorphism**

The genotype distribution analysis between RA patients (n=200) and healthy controls (n=200) revealed that the Bb genotype was significantly associated with RA, with an odds ratio (OR) of 1.5 (95% CI: 1.0–2.4) and a p-value of 0.049. However, no significant association was observed for the bb genotype, with an OR of 1.4 (95% CI: 0.8–2.5) and a p-value of 0.241. The BB genotype showed similar frequencies between RA patients (27%) and healthy controls (26%), indicating no significant difference. Thus, the Bb genotype may have a potential role in RA susceptibility, while the bb genotype does not appear to be significantly associated (Table 2B).

**Table 2B:** VDR BsmI genotype polymorphism in the study population.

| Genotype | RA Patients (n=200) | Healthy Controls (n=200) | OR (95% CI) | p-value |
|---|---|---|---|---|
| BB | 54 (27%) | 72 (36%) | 1 | |
| Bb | 106 (53%) | 90 (45%) | 1.5 (1.0–2.4) | 0.049* |
| bb | 40 (20%) | 38 (19%) | 1.4 (0.8–2.5) | 0.241 |

1: Reference group, OR: Odd Ratio, CI: Class Interval, RA: Rheumatoid arthritis.

*p<0.05 considered as statistically significant.

**Genotypic and Allelic Frequencies of VDR FokI Polymorphism**

The analysis of VDR gene polymorphisms (FokI and BsmI) revealed significant gender-based differences in genotype distributions. For the FokI polymorphism, males were more likely to carry the Ff and ff genotypes, with odds ratios of 3.0 (1.3-6.9, p = 0.009) and 4.5 (1.7-11.7, p = 0.002), respectively, compared to females. For the BsmI polymorphism, the bb genotype was significantly more common in males (33%) than females (7%), with an odds ratio of 3.9 (1.5-10.5, p = 0.006). These findings suggest a notable gender-related difference in the distribution of these VDR polymorphisms, with females showing higher frequencies of the Ff, ff, and bb genotypes (Table 3).

**Table 3**: Genetic variations of VDR genes based on gender among RA Patients.

| Genes | Genotypes | Male (n=42) n (%) | Female (n=158) n (%) | OR | p-value |
|---|---|---|---|---|---|
| VDR (FokI) | FF | 10 (24%) | 82 (52%) | 1 | |
| VDR (FokI) | Ff | 20 (48%) | 54 (34%) | 3.0 (1.3–6.9) | 0.009* |
| VDR (FokI) | ff | 12 (28%) | 22 (14%) | 4.5 (1.7–11.7) | 0.002* |
| VDR (BsmI) | BB | 18 (43%) | 71 (45%) | 1 | |
| VDR (BsmI) | Bb | 13 (31%) | 76 (48%) | 0.7 (0.3–1.5) | 0.324 |
| VDR (BsmI) | bb | 11 (26%) | 11 (7%) | 3.9 (1.5–10.5) | 0.006* |

1: Reference group, OR: Odd Ratio, CI: Class Interval, RA: Rheumatoid arthritis.

*p<0.05 considered as statistically significant.

**Discussion**

In this study, we aimed to explore the relationship between two specific Vitamin D Receptor (VDR) gene polymorphisms: FokI (rs10735810) and BsmI (rs1544410)—and the risk of developing Rheumatoid Arthritis (RA). Our findings revealed a significant association between the VDR FokI polymorphism and RA, while the VDR BsmI polymorphism showed no such association. These results support the growing body of evidence suggesting that VDR gene variants may influence susceptibility to autoimmune diseases like RA.

The VDR gene encodes the receptor for Vitamin D, a hormone that plays a central role in regulating immune system function [5]. Vitamin D deficiency has been linked to increased susceptibility to autoimmune diseases, including RA [5,11]. The VDR is expressed on a wide range of immune cells, including T-cells, B-cells, dendritic cells, and macrophages, where it modulates immune responses. The activation of the VDR by Vitamin D leads to the suppression of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-17, which are central to the pathogenesis of RA [2-4]. Moreover, Vitamin D regulates the differentiation and activation of T-helper cells, balancing the immune response between Th1/Th17 and regulatory T-cells (Tregs), both of which are implicated in RA pathogenesis.

Rheumatoid arthritis (RA) is characterized by an overactive immune response that targets the synovial joints, leading to chronic inflammation, pain, and irreversible joint damage. The VDR's ability to regulate immune responses and inflammatory pathways makes its genetic variants an important area of investigation in RA research. Among the two polymorphisms studied, the FokI polymorphism, located in the translation initiation site of the VDR gene, results in a variant protein with a different functional profile. Individuals with the ff genotype express a shorter VDR protein, which may affect the receptor's ability to regulate immune responses effectively. This shorter VDR may result in a reduced capacity to control inflammatory processes, potentially contributing to autoimmune diseases like RA [16,17].

Our study found that the Ff and ff genotypes were significantly associated with RA, with the ff genotype showing a particularly strong association with increased risk. This observation aligns with previous studies that have suggested that the FokI polymorphism could alter the receptor's function and contribute to the development of autoimmune conditions. For example, similar associations between the FokI polymorphism

and systemic lupus erythematosus (SLE) have been reported by Zhang et al. (2025), and studies by Shirai et al. (2022) have highlighted its role in multiple sclerosis (MS), suggesting that VDR gene variants may serve as common genetic risk factors for autoimmune diseases [22,23]. The FokI polymorphism may therefore influence the receptor's efficiency in modulating inflammatory cytokine levels, skewing the immune response in a way that favors the development of RA. Moreover, Vitamin D deficiency, often prevalent in RA patients, may exacerbate the effects of these polymorphisms, further promoting disease onset and progression. A study by Raftery et al. (2012) emphasized that VDR gene polymorphisms could modulate disease activity in RA, underlining the importance of Vitamin D in managing autoimmune diseases [24].

While the FokI polymorphism showed a clear association with RA in this study, the BsmI polymorphism did not. The BsmI polymorphism, located in the 3' untranslated region of the VDR gene, has functional consequences that are less well-understood compared to FokI. The lack of an association in our study is consistent with findings from other studies, such as those by Tang et al. (2020), which have failed to establish a significant link between BsmI and RA [19,20,25-27]. One possible explanation for the absence of an association is the specific role of the BsmI polymorphism, which may influence VDR expression or its stability rather than directly altering the receptor's structure or function. This could result in a more subtle or context-dependent effect. Additionally, environmental factors, such as Vitamin D levels and geographic location (e.g., sunlight exposure), may modify the impact of the BsmI polymorphism, potentially explaining the variability in findings across studies.

Interestingly, while the BsmI polymorphism did not show an association with RA in this study, it has been implicated in other autoimmune diseases, such as Crohn's disease and psoriasis, suggesting that its effect might vary depending on the disease context [21]. Furthermore, the presence of other VDR polymorphisms or interactions with other genetic factors may modify the effect of BsmI on RA susceptibility. These complex interactions emphasize the need for further research to understand the broader genetic and environmental landscape that influences autoimmune disease susceptibility.

This study provides valuable insights into the role of VDR polymorphisms in RA. However, there are some limitations to be considered. The sample size, particularly for the BsmI polymorphism, may limit the generalizability of our findings. Further studies with larger sample sizes are needed to confirm these results and explore potential interactions with other genetic and environmental factors. Moreover, this study focused only on two polymorphisms within the VDR gene. Given that the VDR gene contains several other variants that could contribute to RA susceptibility, a comprehensive analysis of additional VDR polymorphisms—especially those that affect receptor binding affinity or downstream signaling pathways—could provide a more complete understanding of how Vitamin D signaling contributes to RA pathogenesis.

Finally, the role of Vitamin D deficiency and other environmental factors, such as smoking or diet, should be explored in more detail. These factors may modulate the effects of VDR polymorphisms, making it crucial to account for them in future studies. As the interplay between genetic predisposition and environmental influences becomes increasingly apparent, future research must aim to identify how these factors collectively contribute to the onset and progression of RA.

## Conclusions

In conclusion, this study provides strong evidence that the VDR FokI gene polymorphism is significantly associated with an increased risk of developing Rheumatoid Arthritis. The association of the Ff and ff genotypes with RA, along with the higher frequency of the f allele in RA patients, suggests that this polymorphism may influence disease susceptibility through altered immune regulation. In contrast, the VDR BsmI polymorphism did not show a significant association with RA. These findings highlight the importance of genetic factors in the pathogenesis of RA and suggest that VDR polymorphisms could serve as potential biomarkers for disease risk and therapeutic response. However, further research is needed to clarify the precise mechanisms by which these genetic variants contribute to RA and to explore the potential for personalized treatments based on VDR genotypes.

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## Declaration

This original article has not been published before and is not currently under consideration for publication elsewhere. All authors have read and approved the study. The authors declare no conflict of interest.

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