# Polymorphisms of the Vitamin D Receptor Gene in Crohn's Disease

## *Polimorfismos do gene do receptor de vitamina D na doença de Crohn*

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J Coloproctol 2021;41(2):182–187.

**Abstract**

**Introduction** Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory conditions of the gastrointestinal tract. Studies have shown that polymorphisms of the vitamin D receptor (VDR) gene may help elucidate the pathogenesis of CD.

**Objectives** To analyze the role of VDR gene polymorphisms (*Apa*I, *Bsm*I, *Fok*I, and *Taq*I) in the development of CD.

**Methods** The present study is a systematic review with meta-analysis. a total of 50 articles in English and Portuguese published from 2000 to 2020 were selected from 3 databases. The relationship between CD and the VDR gene was addressed in 16 articles.

**Results** The *Taq*I polymorphism was analyzed in 3,689 patients and 4,645 control subjects (odds ratio [OR] = 0.948; 95% confidence interval [95%CI] = 0.851–1.056; $p = 0.3467$). The *Apa*I polymorphism was studied in 3,406 patients and 4,415 control subjects (OR = 1,033; 95%CI = 0.854–1.250; $p = 0.7356$). For *Fok*I polymorphism, there were 2,998 patients and 4,146 control subjects (OR = 0.965; 95%CI = 0.734–1.267; $p = 0.7958$). Lastly, the *Bsm*I polymorphism was analyzed in 2,981 patients and 4,477 control subjects (OR = 1,272; 95%CI = 0.748–2.161; $p = 0.3743$).

**Conclusion** These four VDR gene polymorphisms were not associated with CD. Therefore, further studies with larger samples are required to corroborate or rectify the conclusions from the present meta-analysis.

**Keywords**
- genetic polymorphism
- vitamin D
- Crohn's disease

**received**
August 10, 2020
**accepted**
September 7, 2020
**published online**
May 24, 2021

**DOI** https://doi.org/10.1055/s-0041-1726052.
**ISSN** 2237-9363.



Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

## Resumo

**Introdução** A doença de Crohn (DC) e a retocolite ulcerativa (RU) são condições inflamatórias crônicas do trato gastrointestinal. Estudos indicam que os polimorfismos do gene do receptor de vitamina D (RVD) são promissores para a patogênese da DC.
**Objetivos** Avaliar papel dos os polimorfismos do gene do RVD (*Apa*I, *Bsm*I, *Fok*I e *Taq*I) no desenvolvimento da DC.
**Métodos** Trata-se de uma revisão sistemática com metanálise. Foram identificados 50 artigos em inglês e português publicados entre 2000 a 2020 em 3 bases de dados. Destes, foram selecionados 16 artigos que contemplavam a relação entre a DC e o gene do RVD.
**Resultados** Para o polimorfismo *Taq*I, a amostra foi composta por 3.689 pacientes e 4.645 controles (razão de probabilidade [RP] = 0,948; intervalo de confiança de 95% [IC95%] = 0,851–1,056; $p = 0,3467$). Para o polimorfismo *Apa*I, 3.406 pacientes e 4.415 controles (RP = 1,033; IC95% = 0,854–1,250; $p = 0,7356$). Para o polimorfismo *FokI*, 2.998 pacientes e 4.146 controles (RP = 0,965; IC95% = 0,734–1,267; $p = 0,7958$). E, para o polimorfismo *Bsm*I, 2.981 pacientes e 4.477 controles (RP = 1,272; IC95% = 0,748–2,161; $p = 0,3743$).
**Conclusão** Esses quatro polimorfismos do gene do RVD não apresentaram associação com a DC. Logo, sugere-se a realização de mais estudos com amostras maiores a fim de corroborar ou retificar a conclusão desta metanálise.



**Palavras-chave**
- polimorfismo genético
- vitamina D
- doença de Crohn


## Introduction

Inflammatory bowel diseases (IBDs) are chronic, recurrent inflammatory conditions of the gastrointestinal tract that affect genetically susceptible patients.[1] There are two IBD subtypes: Crohn's disease (CD) and ulcerative colitis (UC),[2] with overlapping albeit distinct clinical and pathological features.[3] The etiology of CD remains unknown; this condition affects the entire gastrointestinal tract, from the mouth to the anus. It may be unifocal or multifocal, with varying intensity, and it is not curable by clinical or surgical treatments. In addition to its transmural nature, CD can result in complications such as fistulas in other organs or the abdominal cavity. The most frequently-involved sites are the small and large intestines, and perianal manifestations can affect more than 50% of the patients.[4] Crohn's disease may cause manifestations outside the gastrointestinal tract, affecting the skin, joints, eyes, liver, and the genitourinary tract. Although CD can affect subjects from any age group, most diagnoses occur at the second and third decades of life.

Vitamin D is a hormone that regulates serum calcium, and it is responsible for the balance of calcium between mineralized bone and the blood. It also has immunoregulatory effects and antiproliferative properties, mainly mediated by T cells, suppressing lymphocyte proliferation and immunoglobulin production. Vitamin D inhibits pro-inflammatory factors, including nuclear factor kappa B (NF-kB), and the production of cytokines such as interleukin (IL)-2, IL-12, and interferon.[5] At the intestine, vitamin D has additional functions such as promoting junctional integrity, increasing the absorption of epithelial folate, and activating intestinal cytochrome P450 3a4.[1]

Several lines of evidence support that vitamin D plays a role in the development of IBDs[6] because its effects are mediated by steroid receptors regulating the transcription of multiple cellular genes.[5] The vitamin D receptor (VDR) gene is expressed by macrophages, monocytes, B and T cells, and dendritic cells. Vitamin D binding to VDR triggers a cascade of intracellular molecular signaling that regulates the transcription of multiple genes.[7] The VDR gene has several polymorphic sites, and 4 polymorphisms recognized by restriction enzymes are reported: *Apa*I, *Bsm*I and *Taq*I, which are found at the 3' end of the VDR gene, exon 8, and *Fok*I, which is found at the 5' end of the VDR gene, exon 2.[5]

Thus, IBDs are more prevalent among populations living in geographic areas with reduced vitamin D synthesis by the skin due to lower exposure to sunlight. In addition, vitamin D deficiency often occurs in IBD patients though the disease may be in remission.[1] Previous studies have revealed an association between the VDR gene polymorphisms and prostate cancer, infectious diseases, type-1 diabetes mellitus, bone mineral disorders in postmenopausal women, skin melanoma, renal cell carcinoma, autoimmune hepatitis, Graves' disease, celiac disease, and CD.[5]

## Methods

The present is a cross-sectional, analytical, descriptive study. Three databases, namely the Virtual Health Library, PubMed and Microsoft Academic, were queried to identify studies published in journals specialized on the proposed theme, using the following descriptors: *genetic polymorphism*; *vitamin D*; and *Crohn's disease*. The search resulted in 50 articles. The inclusion criteria were articles published in English or Portuguese between 2000 and 2020. Articles regarding VDR polymorphisms in diseases other than CD that did not fit the proposed time

frame were excluded, along with those discussing polymorphisms in other receptors and with a different approach. Thus, 16 articles on CD and VDR receptors were retrieved.

The heterogeneity of studies grouped in a meta-analysis is defined by their diversity, which can strongly influence results. Such diversity can be assessed by the Chi-squared test for heterogeneity. The frequencies of polymorphisms from all articles were grouped in a single table. Diversity was assessed using the Chi-squared test in $2 \times 2$ contingency tables to compare the different odds ratios (ORs) and 95% confidence intervals (95%CIs) of each study.

A Chi-squared test for heterogeneity revealing a *p*-value $> 0.05$ confirms the null hypothesis, indicating that the studies are homogeneous. In this case, fixed-effect tests, which assume that all studies point in the same direction, are recommended, such as the Mantel-Haenszel test, which is the most used test in this category. On the other hand, a Chi-squared test resulting in $p < 0.05$ indicates heterogeneity among studies; therefore, a random-effects test, such as the DerSimonian-Laird test, is recommended.

Next, global association tests were used to assess the significance of the correlation between polymorphisms and CD; to do so, values from each study were combined and submitted to both fixed- and random-effects tests using the BioEstat (Manuel Ayres, Belém, Pará, Brazil) software, version 5.3.

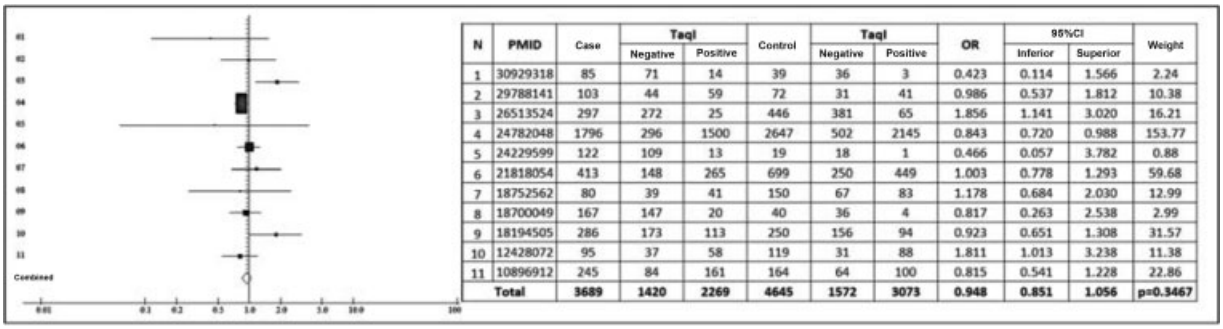
## Results and Discussion

The present meta-analysis evaluated the following VDR gene polymorphisms: *Taq*I (rs731236), *Apa*I (rs7975232), *Fok*I (rs2228570), and *Bsm*I (rs1544410). In total, 13 scientific articles on these polymorphisms were included, with 9,301 subjects; 4,161 (44.7%) had CD (case group) and 5,140 (55.3%) were healthy subjects (control group).

The *Taq*I polymorphism (rs731236) was analyzed in 11 articles, with a total sample of 8,334 subjects (3,689 patients and 4,645 controls); this polymorphism was not statistically signficant for CD (OR = 0.948; 95%CI = 0.851–1.056; $p = 0.3467$) (►**Figure 1**; ►**Table 1**).

The *Apa*I polymorphism (rs7975232) was analyzed in 8 articles, with 7,821 subjects (3,406 patients and 4,415 controls); this polymorphism was not associated with CD (OR = 1.033; 95%CI = 0.854–1.250; $p = 0.7356$) (►**Figure 2**; ►**Table 2**).

In total, 6 articles analyzed the *Fok*I polymorphism (rs2228570), with 7,144 subjects (2,998 patients and 4,146 controls); this polymorphism was not positively associated




| N | PMID | Case | TaqI | | Control | TaqI | | OR | 95%CI | | Weight |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Negative | Positive | | Negative | Positive | | Inferior | Superior | |
| 1 | 30929318 | 85 | 71 | 14 | 39 | 36 | 3 | 0.423 | 0.114 | 1.566 | 2.24 |
| 2 | 29788141 | 103 | 44 | 59 | 72 | 31 | 41 | 0.986 | 0.537 | 1.812 | 10.38 |
| 3 | 26513524 | 297 | 272 | 25 | 446 | 381 | 65 | 1.856 | 1.141 | 3.020 | 16.21 |
| 4 | 24782048 | 1796 | 296 | 1500 | 2647 | 502 | 2145 | 0.843 | 0.720 | 0.988 | 153.77 |
| 5 | 24229599 | 122 | 109 | 13 | 19 | 18 | 1 | 0.466 | 0.057 | 3.782 | 0.88 |
| 6 | 21818054 | 413 | 148 | 265 | 699 | 250 | 449 | 1.003 | 0.778 | 1.293 | 59.68 |
| 7 | 18752562 | 80 | 39 | 41 | 150 | 67 | 83 | 1.178 | 0.684 | 2.030 | 12.99 |
| 8 | 18700049 | 167 | 147 | 20 | 40 | 36 | 4 | 0.817 | 0.263 | 2.538 | 2.99 |
| 9 | 18194505 | 286 | 173 | 113 | 250 | 156 | 94 | 0.923 | 0.651 | 1.308 | 31.57 |
| 10 | 12428072 | 95 | 37 | 58 | 119 | 31 | 88 | 1.811 | 1.013 | 3.238 | 11.38 |
| 11 | 10896912 | 245 | 84 | 161 | 164 | 64 | 100 | 0.815 | 0.541 | 1.228 | 22.86 |
| | Total | 3689 | 1420 | 2269 | 4645 | 1572 | 3073 | 0.948 | 0.851 | 1.056 | p=0.3467 |

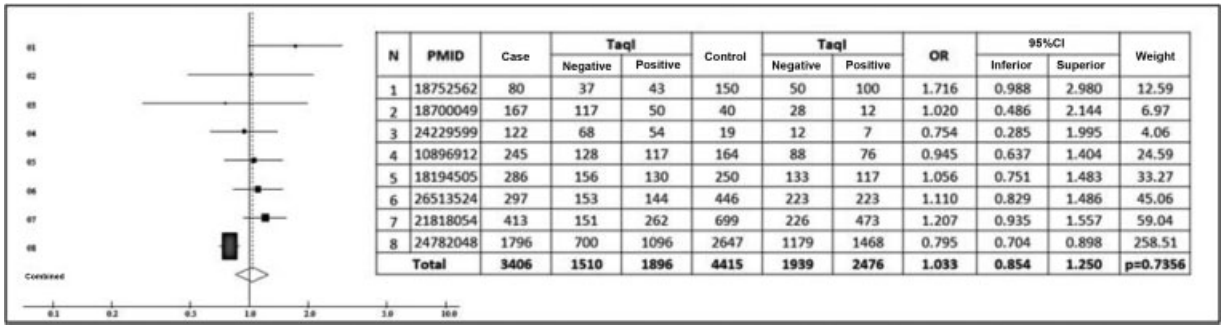
**Fig. 1** Forest plot for the *Taq*I polymorphism among patients with Crohn's disease (cases) and healthy subjects (controls). Abbreviations: 95%CI, 95% confidence interval; OR, odds ratio.

**Table 1** Metanalysis data for the *Taq*I polymorphism among patients with Crohn's disease (cases) and healthy subjects (controls).

| N | Authors and year | Cases (*n*) | *Taq*I | | Controls (*n*) | *Taq*I | | OR | 95%CI | | Weight |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Negative | Positive | | Negative | Positive | | Inferior | Superior | |
| 1 | Chen et al.,[8] 2008 | 167 | 147 | 20 | 40 | 36 | 4 | 0.817 | 0.263 | 2.538 | 2.99 |
| 2 | Gisbert-Ferrándiz et al.,[3] 2018 | 103 | 44 | 59 | 72 | 31 | 41 | 0.986 | 0.537 | 1.812 | 10.38 |
| 3 | Hughes et al.,[4] 2011 | 413 | 148 | 265 | 699 | 250 | 449 | 1.003 | 0.778 | 1.293 | 59.68 |
| 4 | Luo et al.,[5] 2013 | 122 | 109 | 13 | 19 | 18 | 1 | 0.466 | 0.057 | 3.782 | 0.88 |
| 5 | Martin et al.,[9] 2002 | 95 | 37 | 58 | 119 | 31 | 88 | 1.811 | 1.013 | 3.238 | 11.38 |
| 6 | Naderi et al.,[10] 2008 | 80 | 39 | 41 | 150 | 67 | 83 | 1.178 | 0.684 | 2.030 | 12.99 |
| 7 | Noble et al.,[11] 2008 | 286 | 173 | 113 | 250 | 156 | 94 | 0.923 | 0.651 | 1.308 | 31.57 |
| 9 | Szymczak-Tomczak et al.,[12] 2019 | 85 | 71 | 14 | 39 | 36 | 3 | 0.423 | 0.114 | 1.566 | 2.24 |
| 10 | Wang et al.,[13] 2014 | 1,796 | 296 | 1,500 | 2,647 | 502 | 2,145 | 0.843 | 0.720 | 0.988 | 153.77 |
| 11 | Xia et al.,[14] 2016 | 297 | 272 | 25 | 446 | 381 | 65 | 1.856 | 1.141 | 3.020 | 16.21 |
| **Total** | | **3,689** | **1,420** | **2,269** | **4,645** | **1,572** | **3,073** | **0.948** | **0.851** | **1.056** | $p = 0.3467$ |

**Abbreviations:** 95%CI, 95% confidence interval; OR, odds ratio.




| N | PMID | Case | TaqI | | Control | TaqI | | OR | 95%CI | | Weight |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Negative | Positive | | Negative | Positive | | Inferior | Superior | |
| 1 | 18752562 | 80 | 37 | 43 | 150 | 50 | 100 | 1.716 | 0.988 | 2.980 | 12.59 |
| 2 | 18700049 | 167 | 117 | 50 | 40 | 28 | 12 | 1.020 | 0.486 | 2.144 | 6.97 |
| 3 | 24229599 | 122 | 68 | 54 | 19 | 12 | 7 | 0.754 | 0.285 | 1.995 | 4.06 |
| 4 | 10896912 | 245 | 128 | 117 | 164 | 88 | 76 | 0.945 | 0.637 | 1.404 | 24.59 |
| 5 | 18194505 | 286 | 156 | 130 | 250 | 133 | 117 | 1.056 | 0.751 | 1.483 | 33.27 |
| 6 | 26513524 | 297 | 153 | 144 | 446 | 223 | 223 | 1.110 | 0.829 | 1.486 | 45.06 |
| 7 | 21818054 | 413 | 151 | 262 | 699 | 226 | 473 | 1.207 | 0.935 | 1.557 | 59.04 |
| 8 | 24782048 | 1796 | 700 | 1096 | 2647 | 1179 | 1468 | 0.795 | 0.704 | 0.898 | 258.51 |
| | Total | 3406 | 1510 | 1896 | 4415 | 1939 | 2476 | 1.033 | 0.854 | 1.250 | p=0.7356 |

**Fig. 2** Forest plot for the *Apa*I polymorphism among patients with Crohn's disease (cases) and healthy subjects (controls). Abbreviations: 95%CI, 95% confidence interval; OR, odds ratio.

**Table 2** Metanalysis data for the *Apa*I polymorphism among patients with Crohn's disease (cases) and healthy subjects (controls)

| N | Authors and year | Cases (*n*) | *Apa*I | | Controls (*n*) | *Apa*I | | OR | 95%CI | | Weight |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Negative | Positive | | Negative | Positive | | Inferior | Superior | |
| 1 | Chen et al.,[8] 2008 | 167 | 117 | 50 | 40 | 28 | 12 | 1.020 | 0.486 | 2.144 | 6.97 |
| 2 | Hughes et al.,[4] 2011 | 413 | 151 | 262 | 699 | 226 | 473 | 1.207 | 0.935 | 1.557 | 59.04 |
| 3 | Luo et al.,[5] 2013 | 122 | 68 | 54 | 19 | 12 | 7 | 0.754 | 0.285 | 1.995 | 4.06 |
| 4 | Naderi et al.,[10] 2008 | 80 | 37 | 43 | 150 | 50 | 100 | 1.716 | 0.988 | 2.980 | 12.59 |
| 5 | Noble et al.,[11] 2008 | 286 | 156 | 130 | 250 | 133 | 117 | 1.056 | 0.751 | 1.483 | 33.27 |
| 6 | Simmons et al.,[15] 2000 | 245 | 128 | 117 | 164 | 88 | 76 | 0.945 | 0.637 | 1.404 | 24.59 |
| 7 | Wang et al.,[13] 2014 | 1796 | 700 | 1096 | 2647 | 1179 | 1468 | 0.795 | 0.704 | 0.898 | 258.51 |
| 8 | Xia et al.,[14] 2016 | 297 | 153 | 144 | 446 | 223 | 223 | 1.110 | 0.829 | 1.486 | 45.06 |
| **Total** | | **3,406** | **1,510** | **1,896** | **4,415** | **1,939** | **2,476** | **1.033** | **0.854** | **1.250** | ***p* = 0.7356** |

**Abbreviations:** 95%CI, 95% confidence interval; OR, odds ratio.

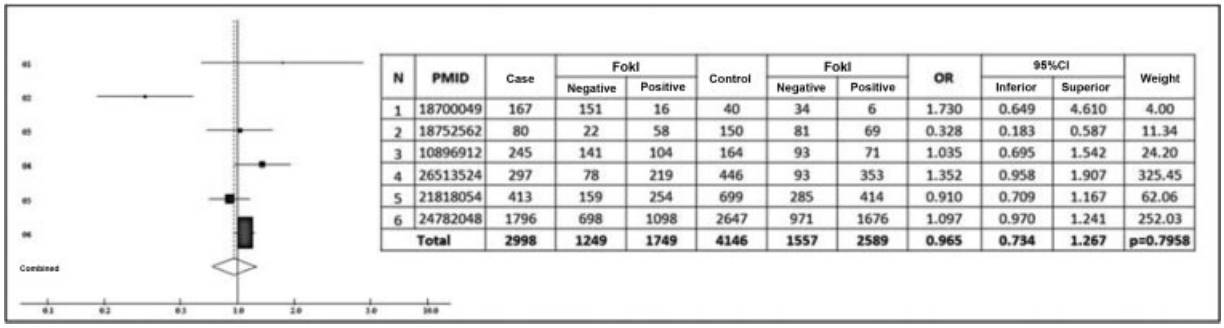
with the susceptibility to develop CD (OR = 0.965; 95% CI = 0.734–1.267; $p = 0.7958$) (►**Figure 3**; ►**Table 3**).

Lastly, 6 articles analyzed the *Bsm*I polymorphism (rs1544410), with 7,458 subjects (2,981 patients and 4,477 controls); this polymorphism was not associated with CD (OR = 1.272; 95%CI = 0.748–2.161; $p = 0.3743$) (►**Figure 4**; ►**Table 4**).

The present study aimed to determine the relationship between the *Fok*I, *Bsm*I, *Apa*I, and *Taq*I VDR gene polymorphisms and the increased risk of developing CD in both a homogeneous and heterogeneous manner in populations from different countries. However, we found no significant associations regarding the heterozygous or homozygous alleles of the VDR gene and the risk of developing CD.[16]

Consistent with our study, Hughes et al.[4] in 2011, in a cohort of 1,359 Irish subjects, observed no significant association for any variant when analyzing data from 413 patients with CD separately.[16] Moreover, in a meta-analysis regarding VDR polymorphisms associated CD development, Xue et al.[7] found no significant association between the *Taq*I, *Fok*I and *Bsm*I polymorphisms and the general risk of developing CD.

Bentley et al.[17] investigating the association of 3 single nucleotide polymorphisms (SNPs) of the VDR gene in a




| N | PMID | Case | FokI | | Control | FokI | | OR | 95%CI | | Weight |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Negative | Positive | | Negative | Positive | | Inferior | Superior | |
| 1 | 18700049 | 167 | 151 | 16 | 40 | 34 | 6 | 1.730 | 0.649 | 4.610 | 4.00 |
| 2 | 18752562 | 80 | 22 | 58 | 150 | 81 | 69 | 0.328 | 0.183 | 0.587 | 11.34 |
| 3 | 10896912 | 245 | 141 | 104 | 164 | 93 | 71 | 1.035 | 0.695 | 1.542 | 24.20 |
| 4 | 26513524 | 297 | 78 | 219 | 446 | 93 | 353 | 1.352 | 0.958 | 1.907 | 325.45 |
| 5 | 21818054 | 413 | 159 | 254 | 699 | 285 | 414 | 0.910 | 0.709 | 1.167 | 62.06 |
| 6 | 24782048 | 1796 | 698 | 1098 | 2647 | 971 | 1676 | 1.097 | 0.970 | 1.241 | 252.03 |
| | Total | 2998 | 1249 | 1749 | 4146 | 1557 | 2589 | 0.965 | 0.734 | 1.267 | p=0.7958 |

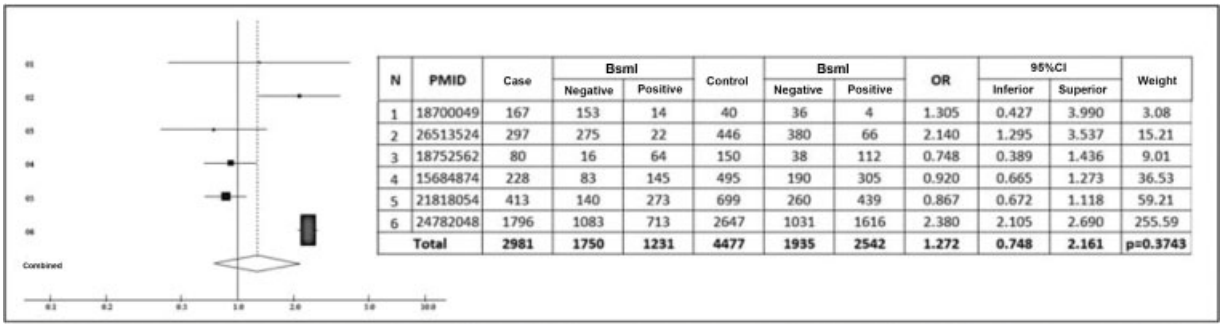
**Fig. 3** Forest plot for the *Fok*I polymorphism among patients with Crohn's disease (cases) and healthy subjects (controls). Abbreviations: 95%CI, 95% confidence interval; OR, odds ratio.

**Table 3** Metanalysis data for the *Fok*I polymorphism among patients with Crohn's disease (cases) and healthy subjects (controls)

| N | Authors and year | Cases (*n*) | *Fok*I | | Controls (*n*) | *Fok*I | | OR | 95%CI | | Weight |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Negative | Positive | | Negative | Positive | | Inferior | Superior | |
| 1 | Chen et al.,[8] 2008 | 167 | 151 | 16 | 40 | 34 | 6 | 1.730 | 0.649 | 4.610 | 4.00 |
| 2 | Hughes et al.,[4] 2011 | 413 | 159 | 254 | 699 | 285 | 414 | 0.910 | 0.709 | 1.167 | 62.06 |
| 3 | Naderi et al.,[10] 2008 | 80 | 22 | 58 | 150 | 81 | 69 | 0.328 | 0.183 | 0.587 | 11.34 |
| 4 | Simmons et al.,[15] 2000 | 245 | 141 | 104 | 164 | 93 | 71 | 1.035 | 0.695 | 1.542 | 24.20 |
| 5 | Wang et al.,[13] 2014 | 1796 | 698 | 1098 | 2647 | 971 | 1676 | 1.097 | 0.970 | 1.241 | 252.03 |
| 6 | Xia et al.,[14] 2016 | 297 | 78 | 219 | 446 | 93 | 353 | 1.352 | 0.958 | 1.907 | 325.45 |
| **Total** | | **2,998** | **1,249** | **1,749** | **4,146** | **1,557** | **2,589** | **0.965** | **0.734** | **1.267** | ***p* = 0.7958** |

**Abbreviations:** 95%CI, 95% confidence interval; OR, odds ratio.




| N | PMID | Case | BsmI | | Control | BsmI | | OR | 95%CI | | Weight |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Negative | Positive | | Negative | Positive | | Inferior | Superior | |
| 1 | 18700049 | 167 | 153 | 14 | 40 | 36 | 4 | 1.305 | 0.427 | 3.990 | 3.08 |
| 2 | 26513524 | 297 | 275 | 22 | 446 | 380 | 66 | 2.140 | 1.295 | 3.537 | 15.21 |
| 3 | 18752562 | 80 | 16 | 64 | 150 | 38 | 112 | 0.748 | 0.389 | 1.436 | 9.01 |
| 4 | 15684874 | 228 | 83 | 145 | 495 | 190 | 305 | 0.920 | 0.665 | 1.273 | 36.53 |
| 5 | 21818054 | 413 | 140 | 273 | 699 | 260 | 439 | 0.867 | 0.672 | 1.118 | 59.21 |
| 6 | 24782048 | 1796 | 1083 | 713 | 2647 | 1031 | 1616 | 2.380 | 2.105 | 2.690 | 255.59 |
| | **Total** | **2981** | **1750** | **1231** | **4477** | **1935** | **2542** | **1.272** | **0.748** | **2.161** | **p=0.3743** |

**Fig. 4** Forest plot for the *Bsm*I polymorphism among patients with Crohn's disease (cases) and healthy subjects (controls). Abbreviations: 95% CI, 95% confidence interval; OR, odds ratio.

**Table 4** Metanalysis data for the *Bsm*I polymorphism among patients with Crohn's disease (cases) and healthy subjects (controls)

| N | Authors and year | Cases (*n*) | *Bsm*I | | Controls (*n*) | *Bsm*I | | OR | 95%CI | | Weight |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Negative | Positive | | Negative | Positive | | Inferior | Superior | |
| 1 | Chen et al.,[8] 2008 | 167 | 153 | 14 | 40 | 36 | 4 | 1.305 | 0.427 | 3.990 | 3.08 |
| 2 | Dresner-Pollak et al.,[2] 2004 | 228 | 83 | 145 | 495 | 190 | 305 | 0.920 | 0.665 | 1.273 | 36.53 |
| 3 | Hughes et al.,[4] 2011 | 413 | 140 | 273 | 699 | 260 | 439 | 0.867 | 0.672 | 1.118 | 59.21 |
| 4 | Naderi et al.,[10] 2008 | 80 | 16 | 64 | 150 | 38 | 112 | 0.748 | 0.389 | 1.436 | 9.01 |
| 5 | Wang et al.,[13] 2014 | 1796 | 1083 | 713 | 2647 | 1031 | 1616 | 2.380 | 2.105 | 2.690 | 255.59 |
| 6 | Xia et al.,[14] 2016 | 297 | 275 | 22 | 446 | 380 | 66 | 2.140 | 1.295 | 3.537 | 15.21 |
| **Total** | | **2,981** | **1,750** | **1,231** | **4,477** | **1,935** | **2,542** | **1.272** | **0.748** | **2.161** | ***p* = 0.3743** |

**Abbreviations:** 95%CI, 95% confidence interval; OR, odds ratio.

cohort of 897 Caucasian patients with IBD, found 449 subjects with CD. Therefore, they concluded that these three SNPs were not associated with CD or its subphenotypes. However, among studies regarding the relationship with CD in cases and controls with reduced receptors with FokI polymorphism in Iranian homozygotes, Naderi et al.[10] reported that 80 CD patients were more likely to present polymorphic FokI allele compared to controls ($n = 150$) ($p < 0.001$, OR = 2.68, 95% CI = 1.79–4.01).

Similarly, in a meta-analysis including 27 case-control studies, Cho et al.[16] showed that the *Fok*I polymorphism at the f allele was positively associated with the risk of developing IBDs, including CD. In a genetic analysis of 240 subjects with CD, Limketkai et al.[18] found an association between the *Taq*I polymorphism and CD. Xue et al.[7] also reported that, in a subgroup analysis by ethnicity, the *Taq*I polymorphism was associated with CD among Europeans (OR = 1.23; 95% CI = 1.02–1.49); in the gender stratification, men were considered genotype carriers, with a moderately high risk of developing CD (OR = 1.84; 95%CI = 1.19–2.83) compared to the TT genotype.[7]

A limitation of the present study is the low statistical power to detect small effects of the VDR polymorphisms on the risk of developing CD.[15,16] However, Naderi et al.[10] in a study conducted in Iran, reported that their 80 CD patients were more likely to present the polymorphic *Fok*I allele compared to controls (n = 150) ($p < 0.001$; OR = 2.68; 95% CI = 1.79–4.01).

## Conclusion

We could not find an association between the risk of developing CD (or any protection against it) and the 4 VDR gene polymorphisms analyzed: *Taq*I (rs731236), *Apa*I (rs7975232), *Fok*I (rs2228570), and *Bsm*I (rs1544410). Further studies using larger samples with the same CD-related polymorphisms are required to corroborate or rectify the conclusion of the present meta-analysis. The assessment of nutritional interactions with SNPs of the VDR gene, 25-hydroxy-vitamin D levels, analyses of ethnic groups with a high incidence of CD, and investigations on the relationships with these polymorphisms are also suggested to elucidate this association.

### References


1 Eloranta JJ, Wenger C, Mwinyi J, et al; Swiss IBD Cohort Study Group. Association of a common vitamin D-binding protein polymorphismwith inflammatory bowel disease. Pharmacogenet Genomics 2011;21(09):559–564

2 Dresner-Pollak R, Ackerman Z, Eliakim R, Karban A, Chowers Y, Fidder HH. The BsmI vitamin D receptor gene polymorphism is associated with ulcerative colitis in Jewish Ashkenazi patients. Genet Test 2004;8(04):417–420

3 Gisbert-Ferrándiz L, Salvador P, Ortiz-Masiá D, et al. A single nucleotide polymorphism in the Vitamin D receptor gene is associated with decreased levels of the protein and a penetrating pattern in Crohn's disease. Inflamm Bowel Dis 2018;24(07):1462–1470

4 Hughes DJ, McManus R, Neary P, O'morain C, O'sullivan M. Common variation in the vitamin D receptor gene and risk of inflammatory bowel disease in an Irish case-control study. Eur J Gastroenterol Hepatol 2011;23(09):807–812

5 Luo YY, Shu XL, Zhao H, et al. Association between vitamin D receptor gene polymorphisms and pediatric Crohn's disease in China: A study based on gene sequencing. Chin J Contemporary Pediatr 2013;15(11):1006–1008

6 DeSilva P, Ananthakrishnan AN. Vitamin D and IBD: more pieces to the puzzle, still no complete picture. Inflamm Bowel Dis 2012; 18(07):1391–1393

7 Xue LN, Xu KQ, Zhang W, Wang Q, Wu J, Wang XY. Associations between vitamin D receptor polymorphisms and susceptibility to ulcerative colitis and Crohn's disease: a meta-analysis. Inflamm Bowel Dis 2013;19(01):54–60

8 Chen M, Peyrin-Biroulet L, Xia B, Guéant-Rodriguez RM, Bronowicki JP, Bigard MA, Guéant JL. Methionine synthase A2756G polymorphism may predict ulcerative colitis and methylenetetrahydrofolate reductase C677T pancolitis, in Central China. BMC Med Genet 2008;9(78)

9 Martin K, Radlmayr M, Borchers R, Heinzlmann M, Folwaczny C. Candidate genes colocalized to linkage regions in inflammatory bowel disease. Digestion 2002;66(02):121–126

10 Naderi N, Farnood A, Habibi M, et al. Association of vitamin D receptor gene polymorphisms in Iranian patients with inflammatory bowel disease. J Gastroenterol Hepatol 2008;23(12): 1816–1822

11 Noble CL, McCullough J HoW, et al. Lowbody mass not vitamin D receptor polymorphisms predict osteoporosis in patients with inflammatory bowel disease. Aliment Pharmacol Ther 2008;27 (07):588–596

12 Szymczak-Tomczak A, Krela-Kaźmierczak I, Kaczmarek-Ryś M, et al. Vitamin Dreceptor (VDR) TaqI polymorphism, vitamin Dand bone mineral density in patients with inflammatory bowel diseases. Adv Clin Exp Med 2019;28(07):955–960

13 Wang L, Wang ZT, Hu JJ, Fan R, Zhou J, Zhong J. Polymorphisms of the vitamin D receptor gene and the risk of inflammatory bowel disease: a meta-analysis. Genet Mol Res 2014;13(02): 2598–2610

14 Xia SL, Lin XX, Guo MD, et al. Association of vitamin D receptor gene polymorphisms and serum 25-hydroxyvitamin D levels with Crohn's disease in Chinese patients. J Gastroenterol Hepatol 2016; 31(04):795–801

15 Simmons JD, Mullighan C, Welsh KI, Jewell DP. Vitamin D receptor gene polymorphism: association with Crohn's disease susceptibility. Gut 2000;47(02):211–214

16 Cho YA, Lee J, Oh JH, et al. Vitamin D receptor FokI polymorphism and the risks of colorectal cancer, inflammatory bowel disease, and colorectal adenoma. Sci Rep 2018;8(01):12899

17 Bentley RW, Keown D, Merriman TR, et al. Vitamin D receptor gene polymorphismassociated with inflammatory bowel disease in New Zealand males. Aliment Pharmacol Ther 2011;33(07): 855–856

18 Limketkai BN, Singla MB, Rodriguez B, et al. Levels of Vitamin D Are Low After Crohn's Disease Is Established But Not Before. Clin Gastroenterol Hepatol 2020;18(08):1769–1776.e1