









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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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 (*Apal*, *Bsml*, *FokI*, and *TaqI*) 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 *TaqI* 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 *Apal* 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 *FokI* 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 *Bsml* 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

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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 (*Apal*, *Bsm1*, *Fok1* e *Taq1*) 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 *Taq1*, 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 *Apal*, 3.406 pacientes e 4.415 controles (RP = 1,033; IC95% = 0,854–1,250; $p = 0,7356$). Para o polimorfismo *Fok1*, 2.998 pacientes e 4.146 controles (RP = 0,965; IC95% = 0,734–1,267; $p = 0,7958$). E, para o polimorfismo *Bsm1*, 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- κ B), 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 IBDs⁶ 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: *Apal*, *Bsm1* and *Taq1*, which are found at the 3' end of the VDR gene, exon 8, and *Fok1*, 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 2×2 contingency tables to compare the different odds ratios (ORs) and 95% confidence intervals (95%CI) 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: *TaqI* (rs731236), *Apal* (rs7975232), *FokI* (rs2228570), and *BsmI* (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 *TaqI* 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 significant for CD (OR=0.948; 95%CI=0.851–1.056; $p=0.3467$) (►Figure 1; ►Table 1).

The *Apal* 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 *FokI* polymorphism (rs2228570), with 7,144 subjects (2,998 patients and 4,146 controls); this polymorphism was not positively associated

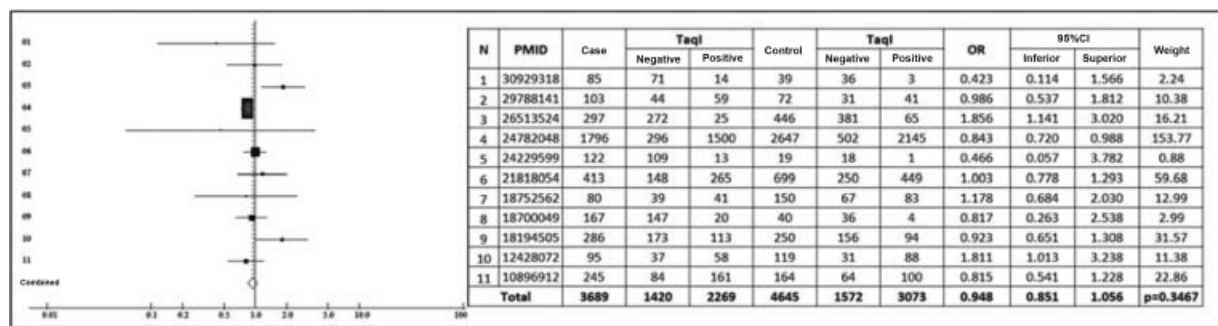


Fig. 1 Forest plot for the *TaqI* polymorphism among patients with Crohn's disease (cases) and healthy subjects (controls). Abbreviations: 95%CI, 95% confidence interval; OR, odds ratio.

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

N	Authors and year	Cases (n)	TaqI		Controls (n)	TaqI		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-Ferrández 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.

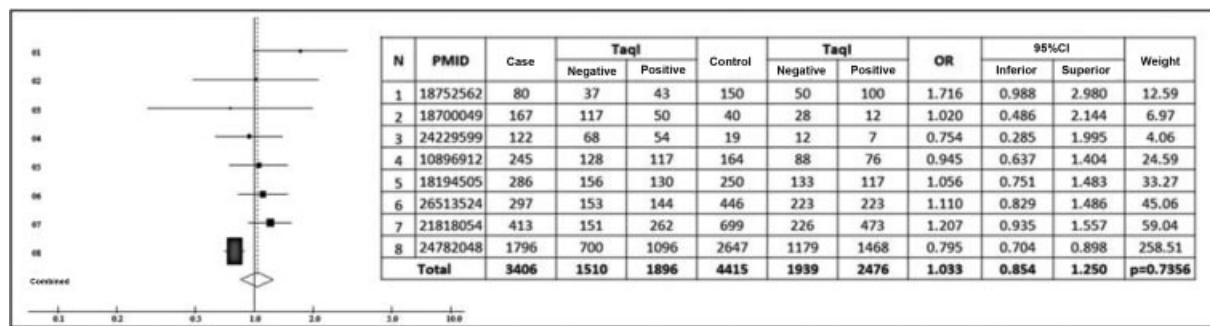


Fig. 2 Forest plot for the *Apal* polymorphism among patients with Crohn's disease (cases) and healthy subjects (controls). Abbreviations: 95%CI, 95% confidence interval; OR, odds ratio.

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

N	Authors and year	Cases (n)	<i>Apal</i>		Controls (n)	<i>Apal</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 *BsmI* 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 *FokI*, *BsmI*, *Apal*, and *TaqI* 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 *TaqI*, *FokI* and *BsmI* 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

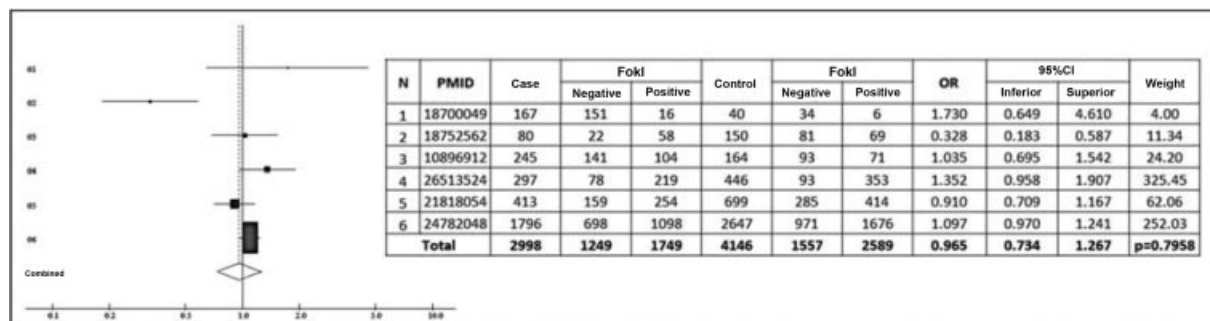
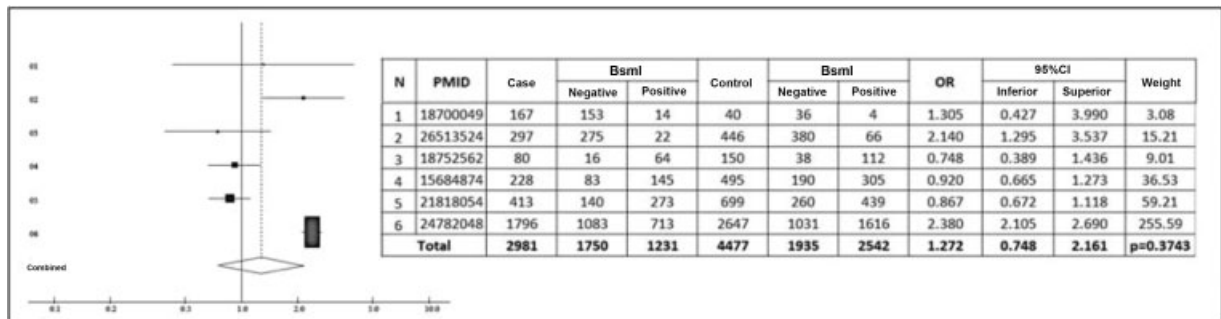


Fig. 3 Forest plot for the *FokI* polymorphism among patients with Crohn's disease (cases) and healthy subjects (controls). Abbreviations: 95%CI, 95% confidence interval; OR, odds ratio.

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

N	Authors and year	Cases (n)	<i>FokI</i>		Controls (n)	<i>FokI</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.

**Fig. 4** Forest plot for the *BsmI* 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 *BsmI* polymorphism among patients with Crohn's disease (cases) and healthy subjects (controls)

N	Authors and year	Cases (n)	<i>BsmI</i>		Controls (n)	<i>BsmI</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 *FokI* 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

TaqI polymorphism and CD. Xue et al.⁷ also reported that, in a subgroup analysis by ethnicity, the *TaqI* 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 *FokI* 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: *TaqI* (rs731236), *Apal* (rs7975232), *FokI* (rs2228570), and *BsmI* (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.

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