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## Molecular analysis of vitamin D receptor gene polymorphisms rs2228570 (FokI) and rs1544410 (BsmI) in patients with Behcet's Disease

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**Abstract:** Recent studies have shown vitamin D3 has immune-modulatory effect. The functional differences in the immune-modulatory action of vitamin D is mediated via the vitamin D receptor (VDR) gene polymorphisms. In this study, we assessed the association between the two common polymorphisms of VDR gene (FokI, BsmI) and Behcet's Disease (BD), A chronic inflammatory and multisystem disorder. Using polymerase chain reaction and restriction fragment length polymorphism, we analyzed the prevalence of the common polymorphisms of VDR gene in patients with BD (n=50) and controls (n=50) in an Iranian Azari population. A significant difference was found for the FokI polymorphism between the BD and the control group. The f allele frequency of 26% was present in BD patients compared to 13% of controls and was significantly associated with BD (P = 0.03); (OR=0.42, 95% CI=0.2-0.88). There was no significant difference in the polymorphisms BsmI between the case and control groups. Accordingly, the FokI variant remains a candidate functional polymorphism; the f allele isoform interacts with the basal transcription factor HB less efficiently than does the F allele isoform, providing a possible mechanism for the reduced transactivation associated (connected) with this allele. The association between VDR polymorphisms and autoimmune diseases varies across different ethnic population. Results of our studies could be followed by further studies with more patients to discover other relationships.

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**Keywords:** Vitamin D Receptor Gene; Behcet's Disease; FokI; BsmI

### 1. Introduction

Behcet's disease (BD) is chronic inflammatory and multisystem disorder characterized by recurrent mouth and genital ulcers, uveitis and skin lesions. The BD is prevalent in East Asian countries including Iran (1,2). The prevalence in Iranian population is 80 cases per 100,000 (3). The etiopathogenesis of the BD have not been clearly defined (4,5). However, both genetic and environment factors have been suggested as causative and developing factors for the disease (6).

In recent laboratory and Epidemiological studies, have convincingly shown that vitamin D play a significant role in the regulation and modulation of immune system (7-11). Vitamin D deficiency associated with autoimmune disease and has suggested that the active metabolite of vitamin D (1,25-Dihydroxyvitamin D3 (1,25(OH)2D3, calcitriol) decreases the development and incidence of autoimmune disease (12-14). Vitamin D has immunosuppressant properties and modulates lymphocyte activity. Conceivably, these effects of

vitamin D may be important in the pathogenesis of Behcet's Disease (15). The biological effect of vitamin D is thought to occur by binding to its receptor (VDR) which belongs to the steroid receptor superfamily. VDR gene polymorphisms cause functional differences in immuno-modulatory action of vitamin D. This receptor is widely expressed in many cell types including antigen-presenting and lymphocytes cells (16-18). Indeed, using the VDR, vitamin D transmits signals to target cells, that is composed of both conserved DNA binding and ligand binding domains. The DNA binding domains act as the regulator of gene transcription (19). Immune cells produce a hydroxylase enzyme which cause convert 25-OH-D to 1,25-OH<sub>2</sub>-D, that is the functional form and an important regulator of the expression of genes involved in the proliferation, differentiation, angiogenesis, and apoptosis of cells (20).

The VDR gene is located in the human 12q12-q22 region and contains more than 470 single nucleotide polymorphisms (SNPs), some of which modulate 1,25-Dihydroxyvitamin D<sub>3</sub> uptake (21,22). Therefore, alteration in these polymorphisms which lead to point mutation can be considered as candidate variants to the disease. The most common polymorphisms (SNPs) of the VDR include rs2228570 (FokI) in exon 2 and rs1544410 (BsmI) that located in the intron separating exons 8 and 9 (22-26). Even more recent attention has focused on the possible role of these variants in the development of auto inflammatory and other disease related to immune system. The aim of this study is to investigate the most common polymorphisms of the VDR gene in Iranian Azari patients with BD.

## 2. Material and Methods

This cross-sectional study was conducted in the Connective Tissue Disorder Research Center and Tabriz Genetic Analysis Center of University of Medical Sciences, from February 2012 to May 2013. All participants have given an informed written consent, and the study protocol was reviewed and approved by the ethics committee of Tabriz University of Medical Sciences, which was in compliance with the Helsinki declaration. We recruited 50 Iranian native Azary patients with BD. The diagnosis of BD was based on the criteria of the International study Group (35). BD patients included 29 men and 21 women who were between 11 and 65 years of age ( $34.02 \pm 7.39$  years). Controls included 26 men and 24 women who were between 21 and 74 years of age ( $34.42 \pm 8.27$  years). A control group of 50 unrelated, healthy Iranian individuals who had no known medical problems from a health screening questionnaire were enrolled. We applied salting out

procedures to extract genomic DNA from blood samples which were collected in EDTA tubes (15,28). The FokI, BsmI, and polymorphic sites were considered in this study. Polymerase chain reaction (PCR) was performed by using their sets of primers (15) using the Techgene thermo cycler (Techne). After initial denaturation for 5 min at 95°C, samples were subjected to 30 cycles of amplification, 25<sub>s</sub> at 94°C, 20<sub>s</sub> at their primer pair annealing temperature and 20<sub>s</sub> at 72°C. The final step was a 5 min hold at 72°C. PCR products were digested with suitable amounts of reference restriction enzymes (Fermentas, Lithuania) in the restriction protocol according to the manufacturer's instructions. Digestion products were electrophoresed on 3% agarose gel containing 3 µl safe stains. The polymorphism was documented by photographing under UV illumination. All data regarding to restriction enzymes and their restriction patterns are in Table 1. Aliquots of 0.1 U of FokI, BsmI of restriction enzymes (Fermentas, Lithuania) and 2µL buffer were added to 5µL of the VDR PCR products. The alleles were designated as b (825 bp fragment) and B (650 bp and 175 bp fragments) for BsmI, f (265bp) and F (196 bp and 69 bp fragments) for FokI. We compared allele and genotype frequencies between the patient and control groups using the Chi2 test (MedCalc 11 software). P levels less than 0.05 were considered significant. The strength of associations was assessed by computing the odds ratios (ORs).

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### 3. Results

FokI genotype frequencies for the BD and control groups were FF:Ff:ff=52%:44%:4% and 74%:26%:0%, respectively; ( $P=0.04$ ). The ff genotype was significantly associated with BD. In addition, the f allele frequency of 26% was present in BD patients compared to 13% of controls and was significantly associated with BD ( $P = 0.03$ ); ( $OR=0.42$ , 95%  $CI=0.2-0.88$ ). So, the FokI VDR polymorphism was associated with susceptibility to BD.

There was no contribution of the VDR polymorphisms BsmI to BD. BsmI genotype frequencies for the BD and control groups were BB:Bb:bb=34%:28%:38% and 34%:30%:36%, respectively; ( $P=0.97$ ). Also, the frequency of the B and b alleles in patients and controls was similar at 47%:53% and 49%:51%, respectively, ( $P=0.8$ ) ( $OR=0.92$ ; 95% $CI=0.53-1.6$ ). Hardy-Weinberg principle was met in all groups (Table 2) and it was significant for BsmI ( $P<0.001$ ) and no bias occurred for FokI polymorphism, ( $P>0.05$  for all the analyses).

**Table 1** Characteristic features of the 2 studied polymorphisms in the vitamin D receptor (VDR) gene

Polymorphism fragments (bp)	Location in VDR gene	Restriction site	Digested alleles	Primer sequence	Annealing temperature (°C)	Digestion protocol	Digestion length (bp)
BsmI 650,175	Intron-8	GAATGC (1/-1)↓	B <sub>1</sub> ,b <sub>2</sub>	F: 5'-CAACCAAGACTACAAGTACCGGTGTCAGTGA-3' R: 5'-AAC CAG CGG GAA GAG GTC AAG GG-3'	63	37 °C overnight	825
FokI 196, 69	Exon-2	GGATG (9/13)↓	F <sub>1</sub> , f <sub>2</sub>	F: 5'-AGCTGGCCCTGGCACTGACTCTGCTCT-3' R: 5'-ATGGAAACACCTTGCCTTCTCCCTC-3'	68	37 °C overnight	265

**Table 2**

Comparison of allele and genotype frequencies for the FokI and BsmI, VDR polymorphisms between patients with Behcet's disease, and healthy controls.

SNP	Genotype frequency			$\chi^2$ (Pvalue)	Allele frequency		OR(95%CI)
	F/F	F/f	f/f		F	f	
<b>FokI</b>							
BD	26(52%)	22(44%)	2(4%)	0.04	74 (74%)	26(26%)	0.42 (0.2-0.88)
Controls	37(74)	13(26%)	0		87(87%)	13(13%)	
<b>BsmI</b>							
BD	17 (34%)	14(28%)	19(38)	0.97	47(47%)	53(53%)	0.92 (0.53-1.60)
Controls	17(34%)	15(30%)	18(36%)		49(49%)	51(51%)	

P = 0.005 for comparisons of genotype frequencies and allele of FokI (FF,Ff,ff) and BsmI(BB,Bb,bb) VDR polymorphisms, in the Behcet's disease group and control group. SNP, single-nucleotide polymorphism; BD, Behcet's disease; OR, Odds ratio; 95%CI, 95% confidence interval; HWE, Hardy-Weinberg equilibrium.

#### 4. Discussions

In the study, we investigated the possible association between the VDR gene polymorphisms in Iranian Azari patients with BD. We did not find that BsmI polymorphisms are associated with an individual's susceptibility to BD. Similarly, a meta-analysis found no evidence linking the BsmI VDR polymorphisms to BD in Tunisia (15). These findings were similar to results to studies in other autoimmune diseases, for example, Founded association of BsmI VDR polymorphism in patients with autoimmune thyroid diseases in china (32) MS in northwest Greece (33), and BsmI polymorphism with lupus and MS in Iran (34,35), lupus in Thailand (36) type 1 diabetes mellitus in Portugal (37) However, In Taiwanese (24) and Chinese (38) populations, the B allele of the BsmI VDR polymorphism was significantly associated with lupus. This apparent discrepancy may be related to the etiopathogenic differences between BD, lupus and ethnic populations. The BsmI VDR polymorphism does not appear to change VDR gene expression or VDR function. Diseases associated with these polymorphisms are therefore most probable caused by linkage disequilibrium with other functional variation within the VDR gene or with another closely linked gene or genes (21).

In contrast to the BsmI VDR polymorphism the FokI polymorphism was associated with susceptibility to BD in our Iranian Azari population, similar to the study of association between type 1 diabetes mellitus and the FokI VDR polymorphism in Italy (39) and with Autoimmune Addison's disease in Germany (40). This finding in contrast to the similar studies in BD and RA patients in Tunisian (15). In our study, a significant relationship was observed between f allele and Behçet's disease, but the study in Tunisian, this relationship was determined between F allele and BD and RA. However, no associations were found between Multiple sclerosis and the FokI VDR polymorphism in Netherlands (41) type 1 diabetes mellitus and the FokI VDR polymorphism in Iran (42), Portugal (43) and Germany (44).

The FokI site polymorphism in exon 2 of the hVDR gene has two variants differing from each other by three amino acids: the f/ M1 variant has 427 amino acids and the F/M4 variant 424 amino acids. The shorter (F/M4) receptor seems to be originated from the divergence of hominids from apes and has been called a "neomorph" (45), yet it actually includes about 65 Percent of VDR gene alleles in human subjects (46-53). This predominance of the F/M4 allele indicates an evolutionary advantage in human (54).

Accordingly, the FokI variant remains a candidate functional polymorphism; the f allele

isoform interacts with the basal transcription factor HB less efficiently than does the F allele isoform, providing a possible mechanism for the reduced transactivation associated (connected) with this allele (18). Also, Colin et al, confirm the higher activity of the 424 aa short VDR variant, (55) found that phytohemagglutinin stimulated growth of peripheral blood monocytes differs by FokI polymorphism. They found that the one-half maximal concentration for 1,25(OH)<sub>2</sub> vitamin D inhibition of phytohemagglutinin-stimulated growth was noticeably higher for cells containing the full-length VDR isoform (i.e., Ff and ff genotypes) than for those with the shorter isoform (FF genotype). Noticing the fact that recent studies have shown the immunomodulatory effect of vitamin D3 through the down-regulation of Toll-like receptor (TLR) expression in human monocytes. Inflammation triggered through TLR2 and TLR4 is important in the pathogenesis of BD (56). Nevertheless, serum 25-hydroxyvitamin D levels are decreased in patients with BD (4). This may be linked to vitamin D receptors functional polymorphisms. These factors together may increase susceptibility and promote the development of clinical manifestations of BD. Also, it seems that environmental factors that influence levels of active vitamin D are complex and a significant difference exists between vitamin D functions and VDR polymorphisms. It confirms that the association between VDR polymorphisms and autoimmune diseases varies across different ethnic population. Results of our studies could be followed by further studies with more patients to discover other relationships.

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#### References

- 1- Davatchi F, Jamshidi AR, Tehrani Banihashemi A, Gholami J, Forouzanfar MH, Moradi M, et al. prevalence of Behcet's disease in Iran: a WHO-ILAR COPCORD stage I study. *APLAR J Rheum* 2007; 10: 239-243.
- 2- Davatchi F, Shahram F, Chams-DavatchiCh, Shams H, Nadji A, Akhlaghi M, et al. Behcet's disease: from east to west. *Clin Rheumatol* 2010; 29: 823-833.
- 3- Davatchi F, Jamshidi AR, Tehrani Banihashemi A, Gholami J, Forouzanfar MH, Akhlagi M, et al. WHO-ILAR COPCORD study (Stage 1, urban study) in Iran. *J Rheumatol* 2008; 35: 1384-1390.

- 4- Karatay S, Yildirim K, Karakuzu A, Kiziltunc A, Engin RI, Eren YB. Vitamin D status in patients with Behcet's Disease. *Clinics* 2011; 66(5): 721-3.
- 5- HirohataSh, Kikuchi H. Behcet disease. *Arthritis Res Ther* 2003; 5: 139-146.
- 6- Zierhut M, Mizuki N, Ohno S, Inoko H, Gul A, Onoe K, et al. Immunology and functional genomics of Behcet's disease. *Cell Mol Life Sci* 2003; 60: 1903-22.
- 7- McGonagle D, McDermott MF. A proposed classification of the immunological disease. *PLoS Med* 2006; 3(8):297.
- 8- Deluca HF, Cantorna MT. Vitamin D its role and use in immunology. *FASEB J* 2001; 15: 2579-2585.
- 9- Adorini L. Immunomodulatory effects of vitamin D receptor ligands in autoimmune disease. *International Immunopharmacology* 2002; 2:1017-1028.
- 10- Hamilton B. Vitamin D and human skeletal muscle. *Scand J Med Sci Sports* 2010; 20: 182-90.
- 11- Michos ED, Melamed ML. Vitamin D and cardiovascular disease risk. *Curr Opin Clin Natur Metab Care* 2008; 11: 7-12.
- 12- Ali MM, Vaidya V. Vitamin D and cancer. *J Cancer Res Ther* 2007; 3:225-30.
- 13- Ascherio A, Munger KL, Simon KC. Vitamin D and multiple sclerosis. *Lancet Neurol* 2010; 9: 599-612.
- 14- Matheiu C, Adorini L. The coming of age of 1,25-dihydroxy vitamin D3 analogs as immunomodulatory agents. *Trends in Molecular Medicine* 2002; 8:174-179.
- 15- Garabedian M. La 1,25dihydroxyvitamin D et son recepteur. *Rev Rheum [EdFr]* 2000; 67: 39-41 [In French].
- 16- Karray EF, Ben Dhifallah I, Ben Abdelghani K, Ben Ghorbel I, Khanfir M, Houman H, et al. Associations of vitamin D receptor gene polymorphisms FokI and BsmI with susceptibility to rheumatoid arthritis and Behçet's disease in Tunisians. *Joint Bone Spine*; 79(2):144-8.
- 17- Morgan JW, Kouttab N, Ford D, Maizel AL. Vitamin D mediated gene regulation in phenotypically defined B cell subpopulation. *Endocrinology* 2000; 141: 3225-3234.
- 18- Veldman CM, Cantorna MT, Deluca HF. Expression of 1,25 dihydroxy vitamin D3 receptor in the immune system. *Archives of Biochemistry and Biophysics* 2000; 374: 334-338.
- 19- Lei L, Wu B, Liu J, Yang B. Vitamin D receptor gene polymorphisms and type 2 diabetes: A meta-analysis. *Arch Med Res* 2013; 44(3): 235-41.
- 20- Miyamoto K, Kesterson RA, Yamamoto H, Taketani Y, Nishiwaki E, Tatsumi S, et al. Structural organization of the human vitamin D receptor chromosomal gene and its promoter. *Mol Endocrinol* 1997; 11: 1165-1179.
- 21- Malloy PJ, Pike JW, Feldman D. The vitamin D receptor and the syndrome of hereditary 1,25-dihydroxyvitamin D-resistant rickets. *Endocrine Rev* 1999; 20: 156-88.
- 22- Zmuda JM, Cauley JA, Ferrell RE. Molecular epidemiology of vitamin D receptor gene variants. *Epidemiologic Reviews* 2000; 22(2): 203-217.
- 23- Zhang J, Chalmers MJ, Stayrook KR, Burris LL, Wang Y, Busby SA, et al. DNA binding alters coactivator interaction surfaces of the intact VDR-RXR complex. *Nat Struct Mol Biol* 2011; 18: 556-563.
- 24- McCullough ML, Bostick RM, Mayo TL. Vitamin D gene pathway polymorphisms and risk of colorectal, breast and prostate cancer. *Ann Rev Nutr* 2009; 29: 111-132.
- 25- Mostowska A, Lianeri M, Wudarski M, Olesińska M, Jagodziński PP. Vitamin D receptor gene BsmI, FokI, ApaI and TaqI polymorphisms and the risk of systemic lupus erythematosus. *Mol Biol Rep* 2013; 40(2): 803-10.
- 26- Lee YH, Bae SC, Choi SJ, Song JiG. Association between vitamin D receptor polymorphisms and susceptibility to rheumatoid arthritis and systemic lupus erythematosus: a meta-analysis. *Mol Biol Rep* 2011; 38 (6): 3643-3651.
- 27- Hitchon CA, Sun Y, Robinson DB, Pescheken CA, Bernstein CN, Siminovitch KA, et al. Vitamin D receptor polymorphism rs 2228570 (FokI) is associated with rheumatoid arthritis in North American natives. *J Rheumatol* 2012; 39(9): 1792-1797.
- 28- Davatchi F, Assaad-Khalili S, Calamia KT, Crook JE, Sadeghi-Abdollahi B, Schirmer M, et al. The international criteria for Behcet's disease (ICBD): a collaborative study of 27 countries on the sensitivity and specificity of the new criteria. *J EADV* 2013; DOI: 10.1111/jdv.12107.
- 29- PaniMA, Knapp M, Donner H. Vitamin D receptor allele combinations influence genetic susceptibility to type 1 diabetes in Germans. *Diabetes* 2000 ; 49: 504-507.
- 30- McDermott MF, Ramachandran A, Ogunkolade BW, Aganna E, Curtis D. Allelic variation in the vitamin D receptor influence susceptibility to IDDM in Indian Asian. *Diabetologia*1997; 40: 971-975.

- 31- Xiao.XH ,Liu ZI, Wang H, Sun Q, Li WH, Yang GH, Li QY. Effects of vitamin D receptor gene polymorphisms on susceptibility to type 1 diabetes mellitus. *Chinese Medical Sciences Journal* 2006; 21: 95–98.
- 32- Chang TJ, Lei HH, Yeh JI, Chiu KC, Lee KC, Chen MC, Tai TY, Chuang LM. Vitamin D receptor gene polymorphisms influence susceptibility to type 1 diabetes mellitus in the Taiwanese population. *Clinical Endocrinology* 2000; 52: 575–580.
- 33- Feng M, Li H, Chen SF, Li WF, Zhang FB. Polymorphisms in the vitamin D receptor gene and risk of autoimmune thyroid diseases: a meta-analysis. *Endocrine* 2013; 43(2): 318-26.
- 34- Sioka C, Papakonstantinou S, Markoula S, Gkartzou F, Georgiou A, Georgiou I, et al. Vitamin D receptor gene polymorphisms in multiple sclerosis patients in northwest Greece. *J Negat Results Biomed* 2011;10:3.
- 35- Nikseresht A, Dadkha B, Kamali Sarvastani E. The Association of Vitamin D Receptor Gene BsmI Polymorphism with Multiple Sclerosis in Iranian Patients. *Journal of Kerman University of Medical Sciences* 2009; 16(2): 116-123.
- 36- Abbasi M, Rezaieyazdi Z, Afshari JT, Hatf M, Sahebari M, Saadati N. Lack of association of vitamin D receptor gene BsmI polymorphisms in patients with systemic lupus erythematosus. *Rheumatol Int* 2010; 30(11): 1537-9.
- 37- Sakulpipatsin W, Verasertniyom O, Nantiruj K, Totemchokchayakarn K, Lertsrisatit P, Janwityanujit S. Vitamin D receptor gene BsmI polymorphisms in Thai patients with systemic lupus erythematosus. *Arthritis Res Ther* 2006; 8:48.
- 38- Lemos MC, Fagulha A, Coutinho E, Gomes L, Bastos M, Barros L, et al. Lack of association of vitamin D receptor gene polymorphisms with susceptibility to type 1 diabetes mellitus in the Portuguese population. *Human Immunology* 2008; 69: 134–8.
- 39- Huang CM, Wu MC, Wu JY. Association of vitamin D receptor gene BsmI polymorphisms in Chinese patients with systemic lupus erythematosus. *Lupus* 2002; 11: 31–4.
- 40- Capoluongo E, Pitocco D, Concolino P, Santonocito C, Di Stasio E, d'Onofrio G, et al. Slight association between type 1 diabetes and “ff” VDR FokI genotype in patients from the Italian Lazio Region. Lack of association with diabetes complications. *Clin Biochem* 2006; 39: 888–92.
- 41- Pani MA, Seissler J, Usadel KH, Badenhoop K. Vitamin D receptor genotype is associated with Addison's disease. *Eur J Endocrinol* 2002; 147(5): 635-40.
- 42- Smolders J, Damoiseaux J, Menheere P, Tervaert JW, Hupperts R. Fok-I vitamin D receptor gene polymorphism (rs10735810) and vitamin D metabolism in multiple sclerosis. *J Neuroimmunol* 2009 15; 207(1-2): 117-21.
- 43- Mohammadnejad Z, Ghanbari M, Ganjali R, Afshari JT, Heydarpour M, Taghavi SM, et al. Association between vitamin D receptor gene polymorphisms and type 1 diabetes mellitus in Iranian population. *Mol Biol Rep.*2012; 39(2): 831-7.
- 44- Lemos MC, Fagulha A, Coutinho E, Gomes L, Bastos M, Barros L, et al. Lack of association of vitamin D receptor gene polymorphisms with susceptibility to type 1 diabetes mellitus in the Portuguese population. *Hum Immunol.* 2008; 69(2): 134-8.
- 45- Fassbender WJ, Goertz B, Weismüller K, Steinhauer B, Stracke H, Auch D, et al. VDR gene polymorphisms are overrepresented in German patients with type 1 diabetes compared to healthy controls without effect on biochemical parameters of bone metabolism. *HormMetab Res.*2002; 34(6): 330-7.
- 46- McDonnell DP, Mangelsdorf DJ, Pike JW, Haussler MR, O'Malley BW. Molecular cloning of complementary DNA encoding the avian receptor for vitamin D. *Science* 1987; 235(4793): 1214-7.
- 47- Harris SS, Eccleshall TR, Gross C, Dawson-Hughes B, Feldman D. The vitamin D receptor starts codon polymorphism (FokI) and bone mineral density in premenopausal American black and white women. *J Bone Miner Res* 1997; 12(7): 1043-8.
- 48- Arai H, Miyamoto K-I, Taketani Y, Yamamoto H, Iemori Y, Morita K, et al. A vitamin D receptor gene polymorphism in the translation initiation codon: effect on protein activity and relation to bone mineral density in Japanese women. *J Bone Miner Res* 1997; 12: 915–921.
- 49- Gross C, Eccleshall TR, Malloy PJ, Villa ML, Marcus R, Feldman D. The presence of a polymorphism at the translation initiation site of the vitamin D receptor gene is associated with low bone mineral density in postmenopausal Mexican-American women. *J Bone Miner Res* 1996; 11: 1850–1855.
- 50- Gennari L, Becherini L, Mansani R, Masi L, Falchetti A, Morelli A, et al. FokI polymorphism at translation initiation site of the vitamin D receptor gene predicts bone mineral density and vertebral fractures in postmenopausal Italian women. *J Bone Miner Res* 1999; 14: 1379–1386.



- 51- [Ames SK, Ellis KJ, Gunn SK, Copeland KC, Abrams SA. Vitamin D receptor gene FokI polymorphism predicts calcium absorption and bone mineral density in children. J Bone Miner Res 1999; 14:740-746.](#)
- 52- [Ferrari S, Rizzoli R, Manen D, Slosman D, Bonjour JP. Vitamin D receptor gene start codon polymorphisms \(FokI\) and bone mineral density: interaction with age, dietary calcium, and 3'-end region polymorphisms. J Bone Miner Res 1998; 13: 925-930.](#)
- 53- [Eccleshall TR, Garnero P, Gross C, Delmas PD, Feldman D. Lack of correlation between start codon polymorphism of the vitamin D receptor gene and bone mineral density in premenopausal French women: the OFELY study. J Bone Miner Res 1998; 13: 31-35.](#)
- 54- [Haussler MR, Jurutka PW, Haussler CA, Hsieh J-C, Thompson PD, Remus LS, et al. VDR-mediated transactivation: interplay between 1,25\(OH\)2D3, RXR heterodimerization, transcription \(co\)factors and polymorphic receptor variants. University of California, Printing and Reprographics, Riverside, CA, 1997, 210-217](#)
- 55- [Jurutka PW, Remus LS, Whitfield GK, Thompson PD, Hsieh JC, Zitzer H, et al. The polymorphic N terminus in human vitamin D receptor isoforms influences transcriptional activity by modulating interaction with transcription factor IIB. University of Arizona, Tuscon 85724, USA.2000 Mar;14\(3\):401-20.](#)
- 56- [Colin EM, Weel AEAM, Uitterlinden AG, Buurman CJ, Birkenhager JC, Pols HAP, et al. Consequences of vitamin D receptor gene polymorphisms for growth inhibition of cultured human peripheral blood mononuclear cells by 1,25-dihydroxyvitamin D3. Clin Endocrinol 2000; 52: 211-16.](#)
- 57- [Do JE, Kwon SY, Park S, Lee ES. Effects of vitamin D on expression of Toll-like receptors of monocytes from patients with Behcet's disease. Rheumatology \(Oxford\) 2008; 47\(6\): 840-8.](#)

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