REVIEW ARTICLE

# Vitamin D Receptor (VDR) Gene Polymorphism: Implications on Non-Bone Diseases

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## ABSTRACT

Vitamin D, which is also known as "sunshine vitamin", plays a pivotal role in both bones as well as non-bone organs. The ubiquitous expression of VDR in numerous tissues, including the kidney, heart, muscle, breast, colon, prostate, brain and immune cells, makes this as a natural target of modulation in disease pathogenesis including variety of cancers, metabolic syndrome, renal transplant and dermal disorders. Low vitamin D levels have become an epidemic across the continent irrespective of amount of sunshine during different seasons. The epidemiological studies estimate that currently at least 1 billion people suffer from low vitamin D levels. Vitamin D receptors regulate a number of signaling pathways. These pathways are often involved in inflammation and tumor growth and especially in the epithelial cells of the skin, breast, prostate and colon in case of cancer. Vitamin D plays important roles in calcium homeostasis, cell proliferation and cell differentiation to many target tissues, which is considered to be mediated through the nuclear VDR control of target genes. Vitamin D dysfunction may be in part inherited as suggested by previous research and VDR polymorphisms is perceived to be the primary reasons of this inherited dysfunction of VDR. This review discuses studies highlighting the role of vitamin D with more emphasis in metabolic syndrome, diabetes, breast, ovarian and prostate cancer, psoriasis, and allograft outcomes other than vitamin D's traditional role related to bone health.

**Key words:** Vitamin D; Vitamin D receptor; VDR gene; polymorphism; VDR gene polymorphism; allograft outcomes

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## INTRODUCTION

Vitamin D, which is also known as "sunshine vitamin", plays a pivotal role in both bones as well as non-bone organs.[1] The paracrine and autocrine biological activities of vitamin D are exerted by binding to its intracellular receptor known as vitamin D receptor (VDR). The ubiquitous expression of VDR in numerous tissues, including the kidney, heart, muscle, breast, colon, prostate, brain and immune cells, makes this as a natural target of modulation in disease pathogenesis including variety of cancers, metabolic syndrome, renal transplant and dermal disorders [Table 1].[2-5] The underlying mechanisms of VDR-mediated protective roles can be explained in two broad categories, namely cell proliferation and immunological pathways. Increased cell proliferation and differentiation through dysregulation of VDR functions lead to cancerous conditions.[6] Similarly, lack of control in VDR-mediated regulated immunological pathways is responsible for dermal disorders; immunodeficiency conditions and transplants related complications.[7]

Low vitamin D levels have become an epidemic across the continent irrespective of amount of sunshine during different seasons. The epidemiological studies estimate that currently at least 1 billion people suffer from low vitamin D levels.[8] In spite of our ability to synthesize vitamin D3, majority of the population requires additional amounts through our diet or health supplements to maintain the optimum levels that are relevant to chemopreventive or therapeutic in nature. Vitamin D3 is physiologically converted into its active form called 1α,25-dihydroxyvitamin D3 [1α,25$(OH)_2D_3$ or calcitriol] which is responsible for binding to VDR and exerting its critical functions. Because vitamin D is not active in its native form and a specific receptor is present for its functions, it is also referred as a prohormone rather than a vitamin.

### Vitamin D receptor (VDR) components and their functions

Three distinct regions which include an N-terminal dual zinc finger DNA binding domain, a C-terminal ligand-binding activity domain and an unstructured region that links the two functional domains of this protein together constitutes the VDR protein. The C-terminal region of the molecule is the most complex and is comprised of 12 α-helices. Amino acid contacts within a subset of these α-helices form a dynamic ligand-binding pocket. Two independent protein interaction surfaces on the VDR protein are formed as a result of active vitamin D's selective binding. These two independent protein interaction surfaces facilitates interaction with a heterodimer partner required for specific DNA binding and the recruitment of large co-regulatory complexes required for gene modulation.[9]

VDR can also be post-transnationally modified through phosphorylation thereby modulating and fine-tuning its transcriptional activity.[10,11] These domains within the VDR create a macromolecule receptive to physiologically relevant levels of circulating active vitamin D. This further directs cellular regulatory mechanism to specific subsets of genes whose protein products are key to vitamin D response [Figure 1]. Vitamin D receptors regulate a number of signaling pathways. These pathways are often involved in inflammation and tumor growth and especially in the epithelial cells of the skin, breast, prostate and colon in case of cancer.[12] Vitamin D plays important roles in calcium homeostasis, cell proliferation and cell differentiation to many target tissues, which is considered to be mediated through the nuclear VDR control of target genes. Intracellular VDR, which mediates changes in gene expression, is responsible for various biological actions of active vitamin D.[13] Binding of receptor's to regulatory regions of target genes



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**Table 1:** VDR gene polymorphism and its impact on disease conditions

| Polymorphism | SNP | Disease Conditions |
|---|---|---|
| *Fok*I | rs2228570 | Metabolic syndrome, Obesity, diabetes, Breast cancer |
| *Apa* I | rs7975232 | Diabetes, Psoriasis, Ovarian cancer |
| *Taq* I | rs731236 | Metabolic syndrome, Obesity, breast cancer, new onset diabetes at transplant, |
| *Bsm* I | rs1544410 | Metabolic syndrome, Obesity, Breast cancer, BPH, Prostate cancer, allograft survival in renal transplant |

SNP- Single nucleotide protein; BPH-Benign Prostatic Hyperplasia

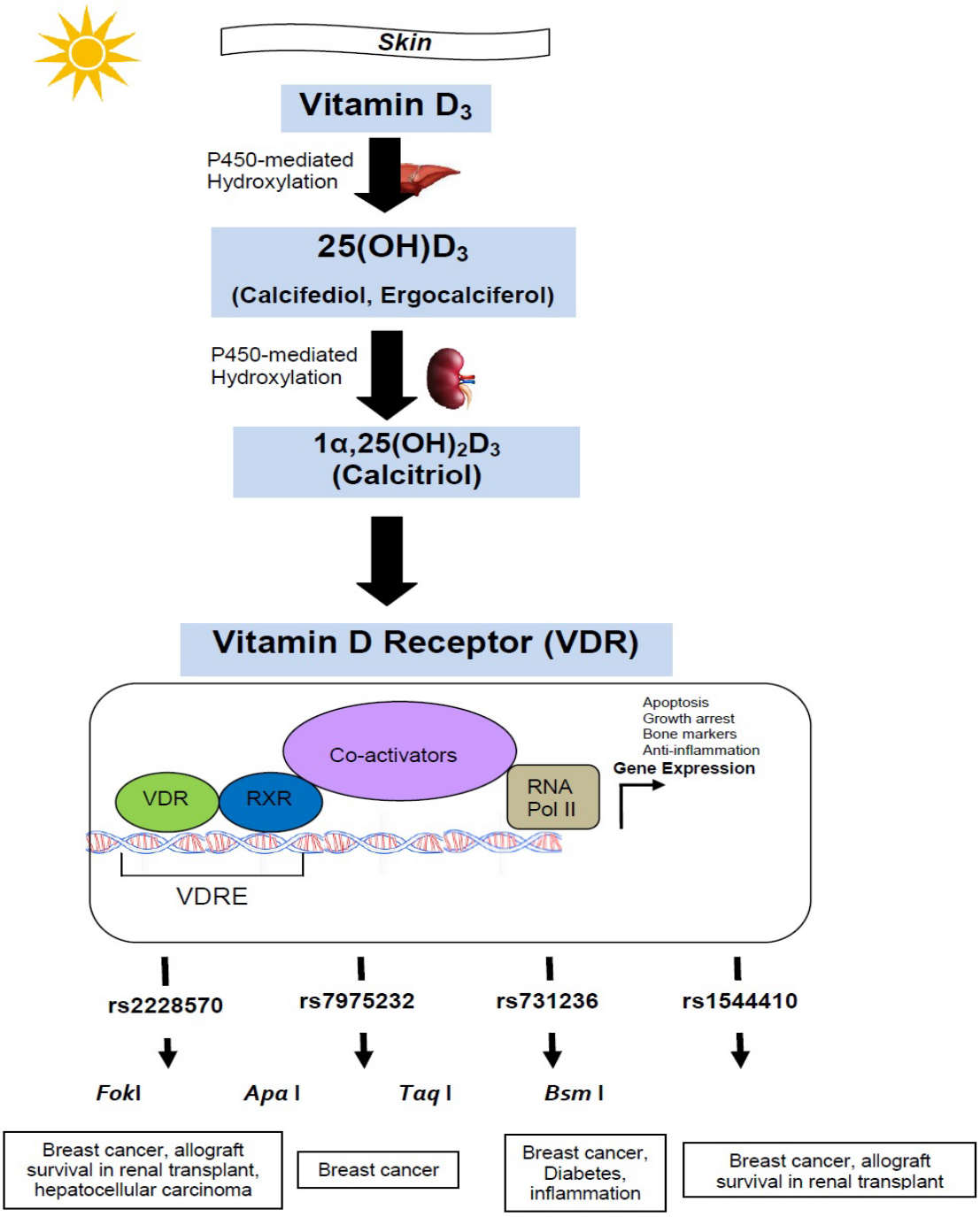


**Figure 1:** Vitamin D function cascade and implications of vitamin D receptor gene polymorphism on diseases pathogenesis. RXR- Retinoid X Receptor; VDRE- Vitamin D Responsive Elements

is prompted by the activation of the VDR through direct interaction with active vitamin D (this further leads to the formation of large protein complexes). Biological reactions in most target cells are triggered by the expression of networks of target genes. These reactions sometimes are tissue specific or highly complex performing homeostatic control of mineral metabolism to that of controlling the growth, differentiation and functional activity of numerous cell types including the immune system, skin, the pancreas and bone, where the genes targets are numerous.[14] Vitamin D and the cytokine gamma interferon (IFN-γ) are the activators of macrophage immune function. IFN-γ induces vitamin D synthesis by macrophages and inhibits vitamin D induction of 24-hydroxylase, a key enzyme in vitamin D inactivation, causing high levels of vitamin D in serum leading to hypercalcemia in conditions such as sarcoidosis, tuberculosis, and several granulomatoses.[15] Excessive vitamin D which results into hypercalcemia has also receiving much attention from the renal transplant community, since it has been associated with the negative impact on both the graft and patient outcomes in renal transplant recipients. On the other hand IFN-γ, which induces vitamin D synthesis, its polymorphisms have been associated with BK virus nephropathy and cytomegalovirus infection.[16,17]

## Role and impact of vitamin D receptor gene polymorphism

As stated earlier, at least half of adults in developed countries lacks adequate levels of vitamin D. Vitamin D dysfunction may be in part inherited as suggested by previous research and VDR polymorphisms is perceived to be the primary reasons of this inherited dysfunction of VDR. The involvement of vitamin D in the development of metabolic syndrome has been explored in one study.[18] Metabolic syndrome is a cluster of conditions such as high blood pressure, high blood sugar, excess body fat around the waist, and abnormal cholesterol or triglyceride levels that occur together thereby increasing the risk of developing cardiovascular disease and type 2 diabetes mellitus (T2DM). Although, the role of vitamin D in metabolic syndrome remains to be completely explained, it was suggested that the active vitamin D may be responsible for reduced insulin secretion and sensitivity, obesity, diabetes and hypertension.[19-21] Low conc. of active vitamin D also been suggested to play role in the development and progression of non-alcoholic fatty liver disease, which is an independent component of metabolic syndrome.[22] Several polymorphisms such as ApaI (VDR 7975232 C>T), BsmI (VDR 1544410 A>G), FokI (VDR 2228570 C>T), and TaqI (VDR 731236 T>C) have been reported for the VDR gene. Some of these polymorphisms are reported to be associated with type II diabetes mellitus, insulin secretion[23,24] as well as with metabolic changes related to obesity.[21] It has been suggested that a length of the VDR, affected by the presence of the polymorphisms, could lead a lower activation of target cells, since a longer VDR protein appears to have a decreased transcriptional activity.[25] In this study conducted in Brazil, the association of components of metabolic syndrome was investigated with the presence of polymorphisms in VDR gene [VDR 1544410 A>G (BsmI); VDR 2228570 C>T (FokI)] in Brazilian adults. Findings of this study have demonstrated the associations between VDR gene polymorphisms with insulin secretion, insulin resistance and HDL-cholesterol, suggesting that these polymorphisms can affect metabolic syndrome phenotype.[24] Genetic and immunologic analyses in obese and non-obese Saudi individuals without other concomitant chronic diseases were performed to explore the mechanisms underlying the suggested role of the VDR complex in the pathogenesis of obesity. Genomic DNA was genotyped for gene SNPs of VDR by allelic discrimination in 402 obese [body mass index (BMI) ≥ 30 kg/m$^2$) and 489 non-obese (BMI<30 kg/m$^2$) Saudis. The results of this study showed that the VDR SNPs rs731236 (G) (TaqI) and rs1544410 (T) (Bsm-I) minor allele polymorphisms were significantly more frequent in obese individuals. VDR haplotypes identified were positively (GTA) or negatively (ACC) associated with obesity and higher BMI scores. These results may help to define VDR fingerprints that can predict an increased risk of developing obesity, which might further contribute to the identification of novel therapeutic strategies for this metabolic condition.[25] VDR gene polymorphisms were also found associated with type I diabetes in a Taiwanese population. In this study, influence of VDR gene polymorphisms on susceptibility to type I diabetes, and rates of glutamic acid decarboxylase (GAD65) autoantibody and islet cell autoantibody (ICA512) were studied in 157 type I diabetic patients and 248 unrelated normal controls. The allele frequency of the BsmI and ApaI polymorphisms, but not TaqI polymorphism, differed between patients and controls. However, after correction for the three different polymorphisms tested, only the BsmI was found significantly associated with type I diabetes.[26]

The association of polymorphisms in the VDR gene including rs10735810 (FokI), rs11568820 (Cdx-2), rs1544410 (BsmI), rs7975232 (ApaI), rs731236 (TaqI), and BsmI-ApaI-TaqI combined genotypes with ovarian cancer risk was examined among 313 women with epithelial ovarian carcinoma and 574 controls in a study by Lurie and colleagues.[27] The associations of VDR polymorphisms with risk were found generally inconsistent across the ethnic groups. Heterozygous and homozygous ApaI A allele carriers were at increased ovarian carcinoma risk compared with homozygous carriers of the ApaI a allele among Caucasian women. Whereas, Caucasian heterozygous carriers of FokI f allele were also at increased risk of ovarian carcinoma compared with homozygous carriers of the common allele. Ovarian cancer risk was found significantly decreased among Cdx-2 A allele heterozygotes compared with homozygote G allele carriers among Japanese women. Compared with the bbaaTT BsmI-ApaI-TaqI genotype, bbaATT and BBAAtt genotypes were associated with increased ovarian cancer risk in Caucasian women compared to Japanese women. This investigation has provided some evidence that polymorphisms in the VDR gene might influence ovarian cancer susceptibility.[27] In a study by Habuchi and colleagues, association of inherited polymorphisms in the 3'-untranslated region (3'UTR) of the VDR gene with the risk and progression of prostate cancer in Japanese men was studied. Such association was explored among 222 prostate cancer and 209 benign prostatic hyperplasia (BPH) patients, and 128 male controls that were over 60 years old and without any evidence of prostate cancer or BPH, and 198 female controls. Heterozygosity or homozygosity in the BsmI polymorphism, the absence of the BsmI restriction site was associated with one-third the risk of prostate cancer and with one-half the risk of BPH compared with the male controls. This study results indicated that the BsmI polymorphism in the VDR gene plays a significant role in protection against prostate cancer and BPH.[28]

In a population based case control study conducted among Hispanic, African-American, and non-Hispanic White women aged 35-79 years from the San Francisco Bay Area of California in 1995 to 2003, possible associations of breast cancer with sun exposure, the principal source of vitamin D, and VDR gene polymorphisms (FokI, TaqI, BglI) were examined. A total of 1,788 newly diagnosed cases and 2,129 controls were interviewed in person and measurements on skin pigmentation were taken on the upper underarm (a sun-protected site that measures constitutive pigmentation) and on the forehead (a sun-exposed site) using reflectometry. A high sun exposure index based on reflectometry was associated with reduced risk of advanced breast cancer among women with light constitutive skin pigmentation. This study supported the hypothesis that sunlight exposure reduces the risk of advanced breast cancer among women with light skin pigmentation.[29]

In another study, polymorphisms in the 5' and 3' ends of the VDR gene were explored for their influence on breast cancer risk among 143

Latina women with breast cancer and 300 cohort controls. Both the BsmI and poly-A polymorphisms in the 3' end of the VDR gene were associated with breast cancer risk, with a trend for increasing risk with increasing number of BsmI B alleles or short (S) poly-A alleles. These results suggested that polymorphic variation in or near the 3' end of the VDR gene influences breast cancer risk in Latina women.[30]

Association of polymorphisms in the VDR gene with altered breast cancer risk was investigated in a UK Caucasian population of 241 women with a negative screening mammogram and 181 women with known breast cancer. Increased breast cancer risk was significantly associated with the VDR polymorphism BsmI, an intronic 3' gene variant. Investigations into the mechanisms of interactions of the VDR with genetic influences to alter breast cancer risk may lead to a new understanding of the role of vitamin D in the control of cellular and developmental pathways.[31]

In a study by Vu and colleagues, polymorphisms of VDR genes and Vitamin D binding protein (VDBP) were studied for their association with allograft survival or acute rejection in renal transplant recipients of Hispanic ethnicity.[5] A total of 502 Hispanic renal allograft recipients at the St. Vincent Medical Center between 2001 and 2010 were genotyped for four different single nucleotide polymorphisms of VDR: FokI C[T (rs2228570), BsmI G[A(rs1544410), ApaI T[G (rs7975232), and TaqI T[C(rs731236). Findings of this study indicated that VDBP (rs4588) and VDR gene polymorphisms (rs1544410) are associated with allograft survival or rejection. Survival was significantly improved for patients who were homozygous GG for the rs4588 G[T allele in the VDBP gene while GT genotype was associated with a higher risk of graft loss. The frequency of the haplotype GTCG (in the order of VDR FokI C>T, BsmI G>A, ApaI T>G, and TaqI T>C), was significantly differed in patients with graft rejection compared to the control, while ACCA haplotype was found to be associated with graft loss. These findings provided an important insight about Vitamin D polymorphism that affects transplant outcomes (allograft survival). Identifying this gene polymorphism in patients may prove useful in clinical practice as a predictive marker for triage patients who may have greater success with their allograft survival.[5]

In one study, a possible association of polymorphism in the gene encoding the vitamin D receptor and psoriasis was explored. Allelic frequencies of the VDR in psoriasis patients and in healthy controls were assessed. A significant increase in the frequency of the A allele absence of the restriction site at intron 8 by ApaI restriction fragment length polymorphism was observed in psoriasis patients compared to that of the control group, and the tendency was more accentuated in early onset psoriasis. A significant association between VDR genotypes and the mean age at onset was observed. Findings of this suggested that allelic variance in the VDR gene itself or other genes in linkage disequilibrium with this gene, could predispose patients to the development of psoriasis.[32]

## DISCUSSION

The low plasma vitamin D3 levels have been a global problem for last quarter century. However, one aspect that is often ignored is the inability of the VDR to execute the beneficial functions in the presence of genetic alterations in VDR. Even with the optimum level of vitamin D3 an individual may still get little or no vitamin D-related benefits due to polymorphic VDR expression. One other aspect of vitamin D conundrum is what level is considered optimum and is it same for all disease conditions? The U.S. National Academy of Medicine indicates that levels of <12 ng/mL are deficient, ≥20 ng/mL are sufficient and >50 ng/mL are potentially toxic.[33] In contrast, The Endocrine Society recognizes significantly higher levels for those categories: <20 ng/ml is deficient and 21-29 ng/ml is insufficient.[34] Based on the literature, it will be safe to opine that the required levels will vary based on the target organ; for bone a lower concentration will likely to be satisfactory, whereas for chemo preventive or therapeutic benefits in cancer, metabolic syndrome, or psoriasis a higher concentrations will be required. Irrespective of the target organ it is critical to recognize a functional VDR is essential to execute the molecular activities. Multiple clinical studies have identified VDR gene polymorphisms, such as FokI, Apa I, Taq I, Bsm I, which are associated with breast cancer, metabolic syndrome.[2,4] However, validation of the VDR polymorphisms is required and progress in this direction will enhance the integration of the polymorphic knowledge in the health outcomes. For example, FokI (SNP rs2228570) has been ascribed as a contributing factor in the development of breast cancer or allograft survival in renal transplant[5], however, the molecular biology and transgenic animal work is scarce to affirm this finding from the clinical or epidemiological population studies. A well-designed validation study for each of the major polymorphic VDR SNPs will establish the pathophysiological significance of each of these polymorphic forms. The abundance data across the ethnicity is another facet of VDR polymorphism area. It is a well-known fact in the pharmacogenomics domain that frequency of different genotypes is not consistent across the population; however, it is critical that we identify the potential target population for VDR polymorphism in a systematic way. Although there is strong likelihood regarding the involvement the VDR gene polymorphic forms in multiple disease conditions, there need to be validated data for any intervention related to that aberration.

Because of the abundance of VDR in the population, it is imperative that, aside from measuring vitamin D plasma levels, identification of VDR genotype at the point-of-care is implemented to understand the vitamin D function status in an individual. In general, vitamin D follows a U-shape dose-response curve, which means at higher concentrations (>100 ng/ml or more) the person may experience vitamin D toxicities such as kidney stone.[35] Knowledge of VDR functional status will ensure unnecessary supplementation of vitamin D3 at supraphysiological doses. Combining the VDR genotype and vitamin D level information will facilitate the understanding of the root cause of vitamin D deficiency effects in an individual. Other confounding factors such as concomitant intake of modulators of wild type and polymorphic VDR protein also need to be considered.

## CONCLUSIONS

Genetic studies combined with epidemiological data and can provide excellent opportunities to link molecular insights to reveal modest and subtle but true biological effects. To explain variation of risk in common diseases, abundance of polymorphisms in the human genome as well as their high frequencies in human populations made it possible to predict such risk. Polymorphisms in the VDR gene have been linked to several diseases, including osteoporosis, diabetes, cancer and cardiovascular disease etc. Polymorphisms are usually suspected of having only modest and subtle effects, however, recent studies have indicated otherwise. Even though, many VDR gene polymorphisms exist, their influences on VDR protein function are largely unknown. Eventually, results of such type of research will deepen our understanding of variability in the encoding genes of Vitamin D. This could further find applications in risk-assessment of disease and in predicting response to the treatment. Our review has summarized the vast amount of information regarding VDR polymorphisms and its links to various disease conditions and discussed its possible role as diagnostic tool or predictive marker in the future.

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