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Vitamin D Receptor in Human Health and Disease: An Overview

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Abstract

Vitamin D Receptor (VDR) is a key regulator of bone metabolism and calcium homeostasis. Various investigations suggest its association with many life-threatening diseases including bone-related disorders, cancers, diabetes, cardiovascular diseases, infectious diseases and metabolic disorders. VDR forms a heterodimeric complex with Retinoid X Receptor (RXR) when activated with 1α,25-dihydroxyvitamin D3 and binds to vitamin D response elements (VDREs) in the DNA sequences located upstream of target genes. Ligand binding and heterodimerization play critical roles in receptor activation and gene regulation. Many studies have shown that any change in VDR function influences target gene functions. Numerous VDR polymorphisms have been reported in various populations around the world. Additionally, a number of case-control studies have established a link between the VDR polymorphism(s) and human diseases. However, some contradictory studies have also been reported. Recent investigations have identified several critical VDR polymorphism(s) that may influence or alter the receptor's function and contribute to the genesis/etiology of disease states. In this review, we have highlighted and analyzed the relevance of VDR and its polymorphism(s) *vis-a-vis* risk to some disease conditions. The current review highlights the importance of VDR-SNPs in decoding the importance of a receptor as a transcription factor as well as a molecular marker for diagnosis of diverse health conditions.

Keywords: Nuclear Receptors, Polymorphism, Retinoid X Receptor, Transcription Factors, Vitamin D Receptor

1. Introduction

Members of the Nuclear Receptor superfamily (NRs) are defined as intracellular ligand-modulated transcription factors, with 48 members identified in humans. This superfamily presides over the expression of thousands of genes which are involved in several physiological processes including reproduction, cell proliferation and differentiation, development and metabolism[1]. Depending upon the broad mode of transcriptional function members of this superfamily are divided into three broad categories: (i) Type I NRs include classic homodimeric receptors, mainly steroid hormone receptors, such as Androgen Receptor (AR), Estrogen Receptor (ER), Progesterone Receptor (PR), etc. (ii) Type II NRs primarily function as heterodimers with RXR; in presence of well-characterized physiological ligands, which include Thyroid Receptor (THR), Farnesoid X Receptor (FXR), pregnane and Xenobiotic Receptor (PXR), Vitamin D Receptor (VDR), etc. (iii) Type III family members include orphan receptors whose target genes, ligands, and functions are still unclear or unknown, and include Small Heterodimeric Partner (SHP), Liver X Receptor (LXR), etc[1].

VDR is a type II heterodimeric receptor that is one of the most important members of the nuclear receptor superfamily. It acts as a receptor for 1α,25-dihydroxyvitamin D3 or calcitriol which is an active metabolite of vitamin D and mediates its biological functions by binding to response elements of its target genes. It serves as a 'master regulator', governing various biological processes in the human body such as cell proliferation, bone metabolism, immune responses, fat and lipid metabolism, and apoptosis. VDR is an important

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modulator of calcium mobilization in bone, calcium and phosphate absorption in intestine and calcium reabsorption in kidney[2]. Any dysregulation in functioning of VDR may lead to disease states such as osteoarthritis, cancer, diabetes, tuberculosis, cardiovascular diseases, and PCOS[3].

1.1 Structural and Functional Features of VDR

The human VDR cDNA was first cloned in 1988 from the human intestine[4]. The gene for VDR has remained conserved during evolution. Human VDR gene contains 1281 nucleotides long ORF that codes for a 4.6 kb long transcript and 427 amino acids long VDR protein with a molecular mass of ~49kDa[5]. The gene is located on chromosome number 12 and comprises of 11 exons and intervening introns spanning approximately 75 kb total length. The 5' non-coding end of the VDR gene contains three exons: 1A, 1B, and 1C. In addition to this, eight exons (exons 2–9) encode the structural portion of the VDR gene product[5]. VDR has three key functional domains, like all other members of the NR superfamily: The central DNA binding domain (C domain or DBD), which is a highly conserved region of the NR superfamily. DBD contains two zinc fingers (the zinc atom is tetrahedrally arranged with four cysteine residues) that recognize and bind to target sequences of vitamin D response element (VDRE). At the N-terminus, a highly variable A/B domain, containing activation function-1 (AF-1), is present, which may contribute to the receptor's basal activity independent of the LBD interaction with the ligand. A ligand-binding domain (E domain, LBD) is located at the C-terminal and consists of activation function-2 (AF-2) which gets activated upon ligand binding. A hinge domain (D domain) bridges DBD and LBD domains together. The DBD contains a NLS (Nuclear Localization Signal) sequence that, upon ligand binding, mediates the translocation of the receptor-ligand complex into the nucleus. VDR also contains putative Nuclear Export Signals (NES) in LBD and DBD that help in nuclear export through CRM-1 receptor- (exportin1) dependent and CRM-1 receptor-independent pathways, respectively[6,7]. Structural and functional domain organization of VDR is represented in Figure 1[8].

VDR is highly expressed in several tissues such as kidney, intestine, parathyroid gland, and bone. Relatively low expression is reported in the intestinal epithelium, skin (keratinocytes), pituitary gland, renal tubules, skeleton (osteoblasts and chondrocytes), pancreas (beta islet cells), immune system (monocytes, macrophages, and T-lymphocytes), mammary epithelium and germ tissues[2]. Thus, its differential expression profile implies its defined functional roles in diverse tissues and organs.

VDR is activated when it binds to its natural ligand 1α, 25-dihydroxyvitamin D3 (calcitriol), a secosteroid. There are two forms of vitamin D viz., D2 (ergocalciferol) and D3 (cholecalciferol). Vitamin D2 is derived from the plant sterol i.e., ergosterol, and vitamin D3 is synthesized in the skin. When exposed to UV-B (290-315 nm) photochemical light, pro-vitamin D3 (7-dehydrocholesterol) is bio-transformed to pre-vitamin D3 (pre-calciferol), which is then converted to vitamin D3 (cholecalciferol) in the skin through thermal isomerization. Vitamin D3 then binds

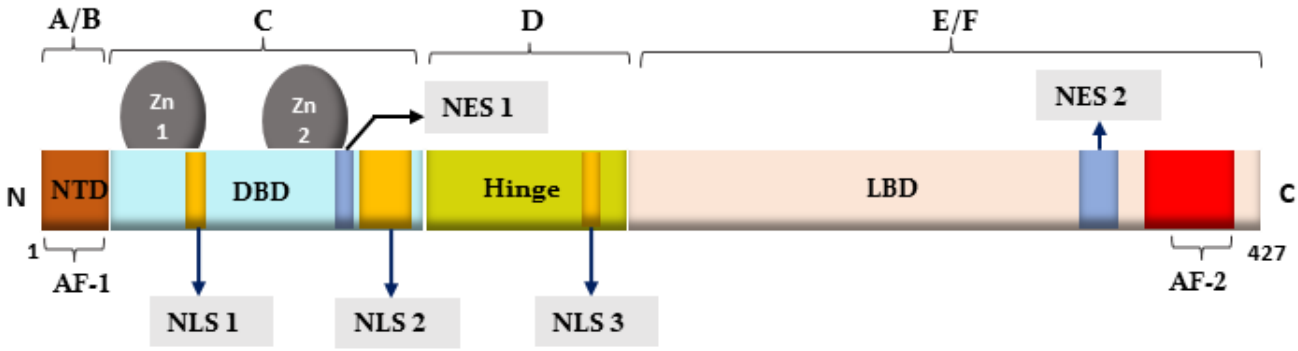

Figure 1. Protein domain structure of VDR: Exons 2-9 encode the full-length VDR protein (427 amino acid residues). VDR contains six domains (A-F). The ligand binds to the hormone-binding domain and undergoes heterodimerization with RXR via the dimerization domain. Activation of VDR leads to VDR-RXR heterodimer formation that subsequently associates with the target gene promoters employing DNA binding domain.

to vitamin D-Binding Protein (DBP) and transported to the liver where it is first hydroxylated in the presence of 25-hydroxylase (mainly CYP 2R1) and converted to 25-hydroxyvitamin D3. The second hydroxylation occurs in the kidney where it is modified into the active form of vitamin D i.e., 1α,25-Dihydroxyvitamin D3 (calcitriol) in presence of 1-α hydroxylase as shown in Figure 2[9]. This activated 1α,25-dihydroxyvitamin D3 regulates many biological and physiological processes such as cell proliferation, metabolism, growth and immunity.

The ligand binding to VDR leads to conformational changes in the receptor and forms a structure explained by 'mouse-trap model'. In the unliganded state, 12th helix of LBD of VDR is projected away from the core of LBD but upon ligand binding VDR undergoes conformational switch and leads to the repositioning of helix 12 such that it seals the ligand binding pocket and provides an interface for possible transcriptional machinery interaction as represented in Figure 3[5].

1α,25-Dihydroxyvitamin D3 maintains calcium and phosphate homeostasis in the body. Therefore, it is prescribed during vitamin D deficiency or rickets. It offers immense therapeutic potential for a variety of disorders including diabetes, cardiovascular diseases, infections, and cancers. Some vitamin D analogues are commercially available for the treatment of various diseases which include alfacalcidiol, maxacalcitol, calcipotriol, EB1089 (seocalcitol), tacacalitol, etc. In addition to these, some 20-epimer analogs CB1039 and KH1060 are also present that have more contact points with ligand-binding pocket of VDR than the natural hormone itself.

Recently, some synthetic analogues of 1α,25-dihydroxyvitamin D3 that enhance the therapeutic value of the natural hormone have been discovered. These modifications were made in A ring, CD ring and triene system of 1α,25-Dihydroxyvitamin D3 as indicated in Table 1.

1.2 Antagonists of VDR

Like an agonist, the antagonist plays a prominent role in modulating the receptor functions since it has the same binding site as an agonist, but it destabilizes the receptor instead of stabilizing it. In the case of VDR, antagonists

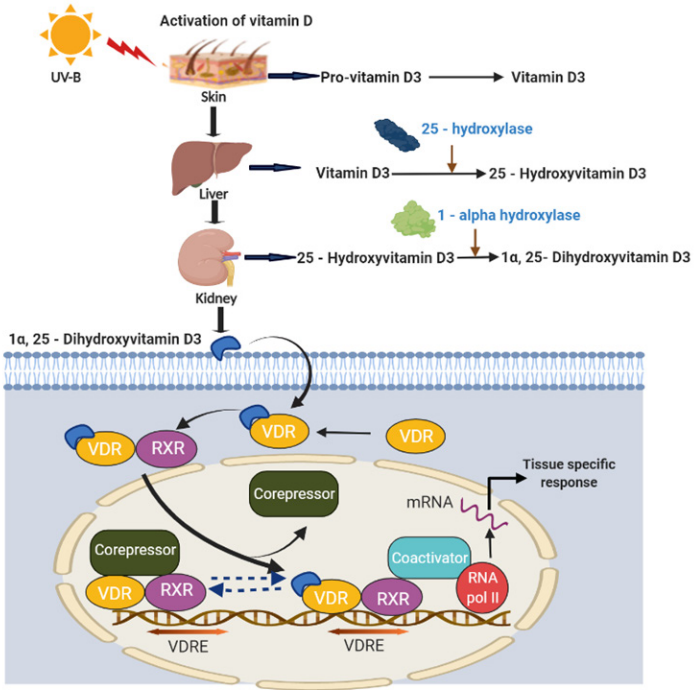

Figure 2. Schematic of biotransformation of pro-vitamin D3 into its active metabolite *1α,25 dihydroxyvitamin D3* (calcitriol) and its mechanism of action: UV-B light converts pro-vitamin D3 into pre-vitamin D3 in skin followed by thermal isomerization that converts it into vitamin D3 which enters the liver and undergoes first hydroxylation process to form 25-hydroxyvitamin D3. Second hydroxylation occurs in kidney resulting in formation of 1α,25-dihydroxyvitamin D3. For its activation, VDR interacts with 1α,25-dihydroxyvitamin D3 and its heterodimeric partner RXR to modulate expression of its target genes. (Model created with BioRender.com).

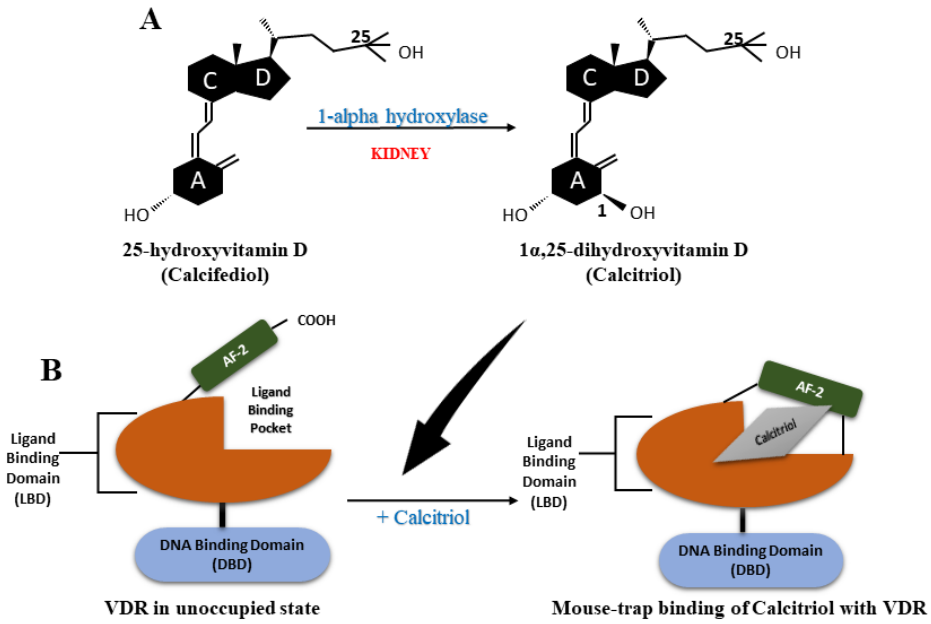

Figure 3. Structure and mechanism of calcitriol binding to VDR **(A)** Structural biotransformation of 25-hydroxyvitamin D3 to 1α,25dihydroxyvitamin D3 (calcitriol) in kidney, **(B)** VDR conformation in the unoccupied condition. Conformational switch in VDR's ligand binding domain in presence of calcitriol referred to as 'mouse-trap' model is shown.

bind to the same H12 helix where the agonist binds and thus prevents stabilization of the receptor. VDR antagonists have therapeutic potential to treat certain diseases and hypercalcemia. There are two types of commercially known VDR antagonists (i) 25-carboxylic esters, such as ZK168281 and ZK159222, and (ii) 26,23-lactone TEI-9647. Compared with the natural hormone and VDR agonists, these compounds have longer side chains and bulkier ring structure which assists them in stronger binding with VDR. TEI-9647 is comparatively short and shows a 10-fold lower affinity for VDR than the carboxylic ester analogues. However, ZK159222 and TEI-9647 act as partial antagonists in comparison to ZK168281 which is a pure antagonist[23]. MeTC7, a novel VDR antagonist that is extremely selective and non-hypercalcemic, has recently gained a foothold as a treatment for melanoma and for targeting VDR-mediated carcinogenic activities.

1.3 VDR and Heterodimeric Partner RXR

Type II NRs, like VDR, form heterodimeric complex with RXR that bind to response elements of target genes[24]. Although the ligand-binding domain of the receptor is identified to be responsible for heterodimerization, another study supported that the T-box of VDR is capable of forming VDR-RXR complex and binds to DNA. The role of T-box, which is an amino acid stretch between the α helix and zinc finger, was investigated by mutating Lys-91 and Glu-92 residues to Asn-Gln that abolished about 60% VDRE binding in the presence of RXR and 90% transcriptional activity of the receptor. The Lys-91 and Glu-92 appeared to mediate this interaction by forming salt bridges with D-box of RXR[25].

A study identified the importance of some key amino acid residues in VDR LBD present at positions 244-263 that are involved in mediating heterodimerization with RXR. To examine the role of five conserved residues i.e., Phe-244, Lys-246, Leu-254, Gln-259, and Leu-262 these were individually mutated to glycine by site-directed mutagenesis[26]. It was observed that four of the mutants were normal in ligand binding but significantly defective in heterodimerization with RXR and could also not activate transcription of target genes. On the contrary, when compared, Lys-246 mutant exhibited ligand binding and heterodimerization with RXR that was similar to wild type VDR. However, it failed to activate transcription of its target gene. This study was further extended by co-expressing excess RXR with all these five mutants. Interestingly, Gln-259 mutant restored its transcriptional activity similar to the wild type. Nonetheless, Lys-

Table 1. Overview of various synthetic analogues of VDR and their mechanism of action with favorable outcome

Analogues	Cellular Response	Clinical Application	References
Side chain analogues			
AMCR277A	Higher transactivation than natural ligand	Anti-proliferative and pro-differentiating properties	10,11
CD578	Co-activators interact with VDR with higher efficiency, make additional contact with H-12 helix of LBD region and higher transactivation	Resistant to degradation by 24-hydroxylase	12,13
Triciferol	Acts as deacetylase inhibitor, and induces tubulin hyperacetylation	More antiproliferative and cytotoxic activity in-vitro	14
Analogues with A-ring modifications			
1α-methyl-2α-(3-hydroxypropyl)-25-hydroxyvitaminD3	Able to bind with R274 VDR mutant with 7.3- fold higher activity than 1α,25 $(OH)_2$D3	Can be used to treat monogenetic diseases caused by mutant VDR where natural ligand (1α, 25-dihydroxyvitamin D3) cannot bind	15,16
QW-1624F2-2	Two fluorine atoms of the analogues prevent 24-hydroxylation process and catabolism by 24 hydroxylases	Low calcemic, highly anti-proliferative	17
KSP-BCS-1αCHF2-16,24F2-2	Transcriptionally active as 1α,25$(OH)_2$D3	Low calcemic, highly anti-proliferative	18
Analogues with CD-ring modifications			
CD578, WU515, WY1113	Exhibit strong VDR-coactivator interaction	Show increased differentiation activity on ADH human colon cancer cells, inhibitors of β-catenin/TCF4 signalling are also repressed	19, 20
Analogues with triene system modifications			
6-methyl-1α,25$(OH)_2$D3	Similar binding affinity as 1α, 25-dihydroxyvitamin D3	Have lower potency for biological activities	21
1α,25$(OH)_2$-14-epi-19-nor-tachysterol	Higher affinity for VDR binding	Acts as a potential drug target for many diseases	22

246 mutant failed to do so, probably due to loss of its interaction with transcriptional machinery itself[26].

1.4 Sub-cellular Localization of VDR

Several reports state that unliganded VDR is predominantly a nuclear protein with partial cytoplasmic distribution. The cytoplasmic receptor fraction shifts to the nuclear compartment in the presence of its natural ligand, 1α,25-dihydroxyvitamin D3[27–29]. It is reported that members of the steroid/nuclear receptor superfamily contain a Nuclear Localization Signal (NLS), which is a short amino acid stretch rich in positively charged residues such as arginine and lysine[28]. For example, amino acid residues 638-642 of the progesterone receptor, 171-301of estrogen receptor, 497-524 (NLS1) and 540-795 (NLS2) of glucocorticoid receptor have all been validated as NLS for their respective receptors[30].

Similarly, Luo *et al.*, identified a short stretch of amino acid residues from 76 to102 in VDR that exhibited similarity with the NLS of other steroid receptors[30]. Hsieh and Haussler also found a NLS between Arg-49 and Lys-

55 in the DNA binding domain of VDR. It was observed that when this unique array of five basic amino acid residues were deleted or mutated to non-basic amino acid residues, there was a significant shift towards cytoplasmic compartment over nuclear subcellular distribution. This deletion mutant of VDR failed to bind to its target VDRE resulting in loss of transcriptional activity[31].

Michigami *et al.,* in a deletion mutant study, identified a NLS in the hinge domain of VDR. These authors demonstrated that the hinge domain from amino acid residues 154-173 acts as a bipartite NLS for VDR[32]. All of these findings emphasize the central role of NLS in the receptor's transcriptional regulation.

RXR acts as an obligatory partner for VDR function, and its heterodimerization helps in nuclear translocation of VDR. However, there are some conflicting observations associated with VDR nuclear localization in the presence of RXR. Prufer *et al.,*[7] investigated the role of RXR in nuclear import as well as export of VDR. Mutational analysis and Leptomycin B (LMB) treatment studies revealed that RXR affects both the transport processes in case of unliganded VDR. It was shown that NLS mutant of RXR retained unliganded VDR in the cytoplasmic compartment and decreased its transcriptional activity, confirming that import of unliganded VDR is mediated *via* interaction with RXR. In addition to this, these authors analysed the effect of CRM-1 receptor-mediated export of VDR using specific CRM-1 receptor inhibitor i.e., LMB. It was discovered that LMB treatment inhibits the nuclear export of unliganded VDR and retain it inside the nucleus. However, co-expression of RXR slowed the rate of VDR export in unliganded state upon LMB treatment. To determine the region of VDR responsible for the CRM-1 mediated export, a mutational study was performed that identified a region located between 320 and 325 amino acid residues which helps in nuclear export of unliganded VDR and functions as an NES. On the contrary, export of liganded VDR was found to be CRM-1 independent[7]. The above findings imply that RXR assists in nuclear import and export of only unliganded VDR. In contrast to this report, Yasmin *et al.,* identified that VDR and RXR translocate to the nucleus by distinct pathways. RXR translocates to the nucleus after binding to importin β whereas VDR binds and translocates through importin α. Their binding and translocation increased in the presence of their corresponding ligands 9-cis-retinoic acid and 1α,25(OH)$_2$D3. Surprisingly, they also found that in the presence of 1α,25(OH)$_2$D3, VDR-RXR heterodimeric complex translocates to the nucleus through importin α instead of importin β[33]. These authors confirmed the dominance of VDR over RXR in nuclear translocation of heterodimers in the presence of ligand.

The study presented above supports that VDR nuclear translocation occurs in the presence of its ligand1α,25(OH)$_2$D3. But the mechanism of translocation of VDR-RXR heterodimer to the nucleus is ambiguous and remains to be clarified[34]. We have also studied sub-cellular localization of VDR using live cell microscopy with GFP- and RFP-tagged constructs of the receptor both in presence and absence of ligand calcitriol[35]. Our study confirmed that when expressed alone unliganded GFP-VDR was uniformly distributed between the nucleus and cytoplasm while RFP-VDR was primarily localized in the nuclear compartment. However, both GFP and RFP-VDR translocate to the nucleus in the presence of calcitriol (unpublished data; Figure 4).

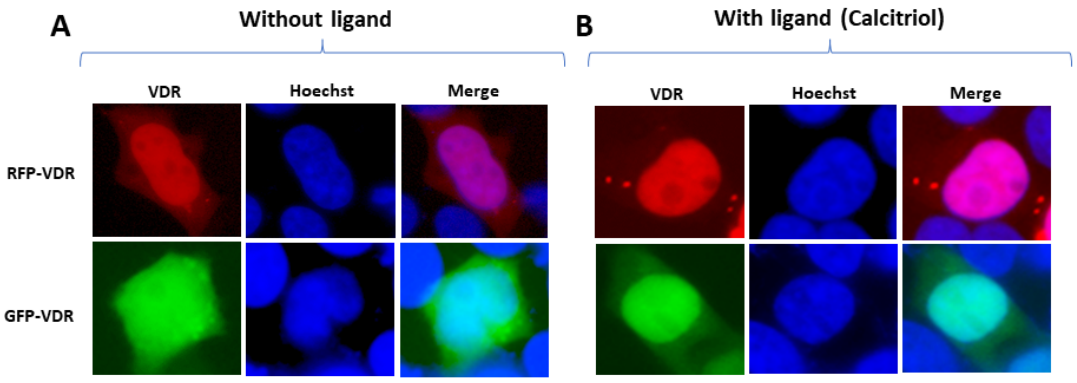

Figure 4. Subcellular localization of VDR determined by live cell imaging: Fluorescent protein tagged VDR was expressed in HEK293T cells and analysed for its subcellular localization. **(A)** In the absence of ligand RFP-VDR showed predominantly nuclear distribution whereas GFP-VDR exhibited uniform distribution between nucleus and cytoplasm. **(B)** In the presence of ligand calcitriol, VDR translocate to the nucleus with little or no cytoplasmic distribution.

1.5 Transcriptional Regulation of Target Genes by VDR

VDR regulates the expression of hundreds of genes that play a crucial role in the maintenance of cellular homeostasis. VDR plays important roles in calcium and phosphate absorption in intestine and supports bone formation[36]. The active form of vitamin D, 1α,25$(OH)_2$D3, up regulates the expression of FGF23 (fibroblast growth factor 23) increasing PTH (parathyroid hormone) levels that in turn reduces serum phosphate levels[37]. It also regulates the expression of TRPV6 (transient receptor potential vanilloid type 6), an intestinal epithelial cell membrane channel that contains VDRE binding sites at -1.2, -2.1, -3.5, -4.3 and -5.5 kb and plays a crucial role in intestinal calcium entry[38]. It is also revealed that 1α,25$(OH)_2$D3 regulates the expression of RANKL (receptor activator of nuclear factor kappa-B ligand), a TNF (tumor necrosis factor)-like factor that is important for osteoclastogenesis. The ChIP analysis also revealed that RANKL contains five VDRE binding sites located 16, 22, 60, 69 and 76kb upstream from the transcription start site[39].

VDR plays an immense role in the regulation of genes that mediate cell cycle arrest in G1 phase. Treatment of moderate to high concentrations of 1α,25$(OH)_2$D3 has been reported to increase the expression of cyclin-dependent kinase inhibitors CDKN1A (p21) and CDKN1B (p27) that block passage of the cell into the S phase[40]. In addition, cyclin D was found to be down regulated in the presence of 1α,25$(OH)_2$D3[41]. It is also involved in the induction of IGFBP-3 (insulin-like growth factor binding protein-3) promoter that modulates the activity of IGF (insulin-like growth factor) I and II. IGFBP-3 is shown to contain a VDRE sequence at -3296/3282, a direct repeat motif that is 92% identical to that of rat 24-hydroxylase[42].

Overall, VDR appears to regulate a diverse array of genes that are involved in the maintenance of various biological processes in the body (Table 2).

2. VDR Polymorphisms and Disease Associations

In addition to its classical function of regulation of bone and mineral homeostasis, VDR is also reported to play a

Table 2. Target genes regulated by VDR and their implications in maintaining numerous processes of human body

Target Gene	Function	References
Bone sialoprotein (BSP)	Integrin binding protein present in extracellular matrix of bone	5
Parathyroid hormone-related protein (PTHrP)	Paracrine factor involved in bone development	5
Cytochrome P450 family 24 subfamily (CYP24)	Enzyme catalyzing hydroxylation reaction in the mitochondria, degrades vitamin D_3	5
Activator protein (AP-1)	Transcription factor	5
NaPi-IIb	Sodium-dependent intestinal phosphate transporter involved in phosphate metabolism	37
Klotho	Transmembrane protein with β-glucuronidase activity, regulates calcium metabolism	37
Fibroblast growth factor (FGF 23)	Responsible for phosphate and vitamin D metabolism	38
Transient receptor potential cation channel subfamily V member 6 (TRPV6)	Membrane calcium channel protein involved in intestinal calcium entry	38
Receptor activator of nuclear factor kappa-B ligand (RANKL)	Member of TNF superfamily, membrane protein having a role in osteoclastogenesis	39
Cyclin dependent kinase inhibitor 1A (p21) and cyclin dependent kinase inhibitor 1B (p27)	Inhibits cyclin/cyclin-dependent kinase complexes	40
Cyclin D1	Role in cell cycle progression	41
Insulin-like growth factor-binding protein (IGFBP-3)	Transport protein for insulin-like growth factor I (IGF-I) and II (IGF-II) and modulates their biological action	42

significant role in several other non-classical physiological processes of the body such as cell cycle regulation, cellular differentiation, gut microbiome regulation, immunity, and glucose tolerance[43–49].

Some harmful mutations in the VDR gene have been investigated, which have gained much attention in recent years. Some of the VDR polymorphisms such as *Fok*1, *Apa*1, *Cdx*2, *Taq*1 and *Bsm*1 have been reported in diseases including cancer, osteoporosis, diabetes, tuberculosis, PCOS and leprosy[50–54]. These polymorphisms can occur in both coding and non-coding regions of the gene and affect the functionality of the receptor.

2.1 VDR Polymorphisms

Numerous polymorphisms in the VDR promoter region, exons, and intron have been documented in the literature. The following section provides a detailed account.

2.1.1 Fok1 in Start Codon

In 1996, Gross *et al.,* extrapolated an association between *Fok*1 polymorphism and Bone Mineral Density (BMD)[50]. *Fok*1 polymorphism occurs in the first start codon (ATG) of VDR. The cDNA of VDR was found to contain two potential translation start codons having the second ATG sequence present at the 4th position. Prior investigations revealed that T/C transition (ATG to ACG) in the first start codon results in the synthesis of VDR protein shorter by three amino acids (424 aa). An individual with T polymorphism (ATG) synthesizes protein from the first amino acid start codon whereas an individual with C polymorphism (ACG) starts protein synthesis from the second amino acid start codon[55]. Another group in 1997 investigated an association between BMD and start codon polymorphism in Japanese women[56]. They found that BMD in mm homozygote (m allele is ACG) is significantly higher in premenopausal Japanese women than MM homozygotes (M allele is ATG). This study corroborates with previous studies and further surmises the association between *Fok*1 polymorphism and BMD. This investigation also showed that vitamin D-dependent transcriptional activity is 1.7-fold higher in 'm' type protein than 'M' type protein in transfected HeLa cells[56].

Gross *et al.,* further highlighted the functional importance of *Fok*1 polymorphism by transfecting COS-1 cells with two different forms (F and f) of VDR and compared their ligand binding and DNA binding affinities. Here, f indicates presence of first ATG and F indicates its absence[57]. These authors also analyzed the transactivation of their target genes by these two forms. This study provided evidence that there is no significant difference in ligand binding and DNA binding affinities in both forms. These forms even failed to show any significant variation in activation of their target gene in luciferase assays. Both these reports analysed the importance of start codon polymorphism. However, the inconclusive difference in the outcome highlights the need for further research.

2.1.2 Cdx2 in Promoter

Takeda and co-workers in 1999 were the first to identify the regulation of VDR gene expression in the small intestine[58]. In this investigation, it was found that *Cdx*2 (a homeodomain related protein, caudal) binds to VDR promoter at -3731 to -3720 bp from the transcription start site and activates transcription of VDR genes in the small intestine. This study deduced the importance of *Cdx*2 in the regulation of intestinal VDR transcription and maintenance of intestinal calcium absorption. Another group further explored *Cdx*2 polymorphism in Japanese women[59]. In this study, genotyping of VDR gene was performed in 261 Japanese women and *Cdx*-A/G polymorphism was identified. When assessed, 48 were *Cdx*-A genotype, 82 were *Cdx*-G and 131 were *Cdx*-A/G. BMD of these postmenopausal Japanese women was 12% lower in the *Cdx*-G genotype as compared to *Cdx*-A homozygote. In functional studies, it was also observed that DNA binding affinity decreased significantly in *Cdx*-G allele, as compared to the *Cdx*-A allele. *Cdx*-G allele also exhibited 70% less transcriptional activity as compared to the wild type *Cdx*-A allele.

2.1.3 Bsm1, Apa1, and Taq1 near 3'Promoter

In addition to the polymorphisms in the start codon and promoter regions, VDR carries mutation near 3'promoter region. *Bsm*1 and *Apa*1 are VDR polymorphisms that are present in intron at 3' end of the VDR gene[60,61]. These VDR polymorphisms do not affect the functionality of the protein as these are not present in the coding region of VDR except *Taq*1 which is a synonymous polymorphism, present at 352 amino acid position in exon9[62]. Fang *et al.,* investigated the effect of 3'UTR polymorphism of VDR gene and demonstrated that it may influence mRNA stability and, therefore, regulation of gene expression. This study identified that VDR regulates the expression

of its downstream genes calbindin, TRPV5, and TRPV6 which are involved in calcium absorption. Therefore, any dysregulation in VDR transcriptional function affects the BMD and may increase fracture risk[63]. This study further substantiates the relevance of *Bsm*1-*Apa*1-*Taq*1 polymorphism in mRNA stability and regulation of the downstream genes.

2.1.4 Other Lesser-Known Polymorphisms

A group in 2004 surveyed a novel SNP A-1012G located 1012 bp upstream, relative to the transcription start site of exon 1A that resulted in adenine to guanine substitution[64]. Another lesser known and novel *Tru*91 polymorphism located in intron 8 at +443 bp relative to the end of exon 8 that leads to substitution of adenine for guanine was reported by another group[65]. *Bgl*1, another polymorphism situated 303 bp downstream of the stop codon in exon9 was also investigated[66]. The relevance of these substitutions in context to VDR function awaits further work. The intron-exon structure and polymorphisms of VDR are presented in Figure 5.

2.2 VDR Polymorphisms and their Association with Human Diseases

The VDR polymorphisms listed above are associated with a multitude of diseases including bone disorders, cancer, diabetes, cardiovascular diseases, and infectious diseases. The following section provides a detailed analysis.

2.2.1 VDR Polymorphisms and Bone-related Disorders

Morrison *et al.,* in 1992 first illustrated the connecting link between VDR gene polymorphism and osteocalcin protein, a marker of bone turnover that VDR regulates[60]. They investigated the 3' UTR polymorphisms, *Bsm1* and *Apa1,* in Caucasians and observed considerably higher osteocalcin levels in the absence of restriction sites (BB and AA) than in the presence of restriction sites (bb and aa) for *Bsm1* and *Apa1*, respectively. This group further studied 3'UTR polymorphism *Bsm*1-*Apa*1-*Taq*1 through minigene analysis to explore the effects of 3'UTR polymorphism on mRNA stability and transcriptional activity. In this study, 3.2 kb of 3'UTR of two most common haplotypes baT and BAt was inserted into the firefly luciferase expression vector and transfected in COS-7 and ROS-17/2.8 cells. In both cell lines, BAt haplotype displayed significantly higher transcriptional activity. This observation suggests that VDR polymorphism located in UTR may affect their target gene (osteocalcin) activity and influence the bone density and calcium homeostasis[67]. A group further performed a large population-based study and found that the BB genotype was associated with increased BMD but no differences were observed in *ApaI* and *TaqI* genotypes[68]. Several other studies have also revealed the relation between VDR polymorphism and BMD. Tokitan *et al.,* in 1996 conducted a population-based study in premenopausal Japanese women and observed

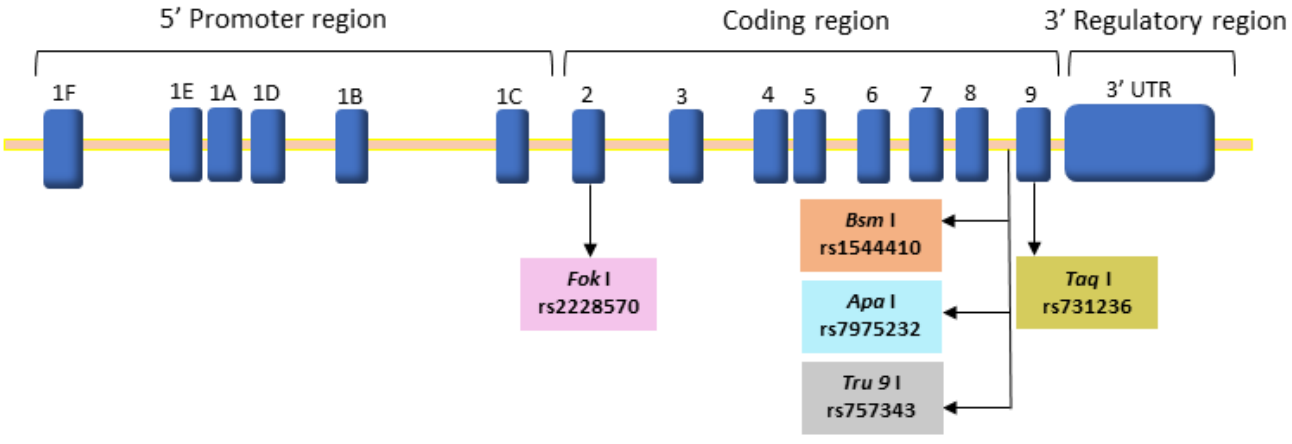

Figure 5. Intron-exon structure of VDR gene and polymorphisms. The human VDR gene located on chromosome 12q contains non-translated exons (1A-1F) and translated exon 2-9 which encode the VDR protein. VDR polymorphism *Fok*1 and *Taq*1 are present in exon 2 and 9, respectively, and *Bsm*1, *Apa*1 and *Tru*91 in intron 8 as shown in structure.

that in BbAATt genotype, lumbar spine BMD was 9.3% lower than bbaaTT genotype[69]. Other related studies were reported from Mclure group in postmenopausal Mexican American women and Tsai *et al.,* in Chinese men and women[70,71].

2.2.2 VDR Polymorphisms and Cancers

Numerous studies corroborate the link between VDR polymorphism and some types of cancers. A study on prostate cancer discovered an increase in vitamin D3 levels in the presence of the *Taq1* site (tt), and established a relationship between mRNA stability and increased prostate cancer risk[51]. In 1999, a study examined the *Taq1* VDR polymorphism in young women with breast cancer. While no association was detected between the two, patients lacking the *Taq*1 site (TT) had a significantly increased risk of lymph node metastasis[72]. Similarly, *Fok*1 polymorphism (FF genotype) was found associated with decreased cancer risk, while a weak and inverse relationship was identified in *Apa*1 AA and aa genotypes[73]. There are some contradictory reports that suggest no association between *Fok*1 polymorphism and prostate cancer[7,75]. The above studies have also been substantiated by Cicek's group who identified the role of six VDR polymorphism *Cdx*2, *Taq*1, *Fok*1, *Apa*1, *Bsm*1, and PolyA site and observed an association between *Fok*1 and *Apa*1 polymorphism and prostate cancer. VDR polymorphism has also been reported in skin cancers. In an 11-year case-control study, participants with *Fok*1 recessive genotype showed decreased risk for SCC, while meta-analysis identified that *Bsm*1 recessive genotype is associated with lower risk for SCC, and *Apa*1 and *Bgl*1 recessive genotype exhibited decreased risk for BCCs[76]. Another study, that included *Fok*1, *Apa*1, *Bsm*1 and *Taq*1 polymorphism, failed to show any relationship with melanoma except *Bsm*1 polymorphism with Bb+bb genotypes[77]. Some other studies also explored the relationship between VDR polymorphism and skin cancer[78,79].

2.2.3 VDR Polymorphisms and Cardiovascular Diseases

Hajj *et al.,* explored the association between cardiovascular diseases and VDR polymorphism. These authors investigated 69 men and women to examine an association between *Bsm*1, *Cdx*-2, *Apa*1, *Taq*1 and *Fok*1 polymorphisms with Waist Circumference (WC), body mass index (BMI), blood pressure, adiponectin and lipid/glycemic levels. This study suggested that *Apa*1, *Taq*1, and *Bsm*1 exhibit significantly higher WC and BMI, and *Fok*1 were found to be associated with High-Density Lipoprotein (HDL) and triglycerides in men, whereas *Cdx*-2 and *Bsm*1 were correlated with adiponectin levels. In the case of women, *Apa*1 showed an association with systolic blood pressure which highlights the significance of gender-specific association of VDR polymorphism with cardiovascular diseases[80]. Another study illustrated a relationship between VDR polymorphism and Coronary Heart Diseases (CHD). This study involved the *Fok*1, *Tru*9I, *Apa*1 and *Taq*1 polymorphism in patients and controls where only *Fok*1 (GG genotype) was associated with CHD as this genotype was decreased in the patient samples as compared to the controls. This genotype exhibited a significantly high HDL levels in CHD patients[81]. These studies were further validated by other investigations that deduced the importance of VDR polymorphisms in cardiovascular diseases[82].

2.2.4 VDR Polymorphisms and Diabetes

VDR has been associated with both type 1 and type 2 diabetes. Glimcher *et al.,* in 1984 identified the role of VDR in type 1 diabetes which is known to be an autoimmune disease[83,84]. This study revealed that vitamin D3 inhibits antigen-induced activation of T-cells possibly by masking the antigen's T-cell recognition to the stimulator cell surface. This was further proven by another group who confirmed the immunosuppressive activity of vitamin D3 as it inhibits the synthesis of lymphokines (IL-2 and IFN-γ) and monocyte-derived chemokines (IL-12) that consequently inhibit the T-cell (Th1) activation[85]. Another group identified that β-cells express VDR and it becomes defective in insulin secretion in the absence of vitamin D3[86].

Several studies advocate an association between type 2 diabetes and VDR polymorphism, as *BsmI* has been reported in Indian Asians and Japanese but no association was found in Caucasian and Chilean populations[87–90]. Similarly, *Apa*1 was found to be associated in Taiwanese population but not in the Finnish population[91,92]. In another study of type 2 diabetes *Bsm*1 (Bb genotype) showed association in Egyptian population, Asian Indians and Germans but not in Bangladeshi and French populations[93–96]. Likewise, *Taq*1 polymorphism has also been found to be associated in Asian Indians and Iranian

patients whereas *Fok*1 polymorphism in Santiago de Chile patients[97–99].

2.2.5 VDR Polymorphisms and Infectious Diseases

VDR influences numerous physiological processes, and any functional deficiency or dysregulation may lead to various infections in the body. Huang *et al.,* analysed the importance of *Fok*1 polymorphism in Tuberculosis (TB) in meta-analysis and established an association with tuberculosis susceptibility[53]. Similar results were obtained in Peruvian population where *Fok*1 and *Taq*1 were discovered to be associated with tuberculosis[100].

VDR is also reported to have a role in leprosy which is a chronic infection caused by *Mycobacterium leprae*. The significance of VDR polymorphism in leprosy infection was expounded in another study where occurrence of tt genotype was significantly higher in tuberculoid leprosy and TT genotype in patients with lepromatous leprosy compared to controls[101]. Similar investigation underlines the interaction of *Taq*1 polymorphism and leprosy in a case-control study in a Brazilian population[102].

Mahyar *et al.,* identified the VDR polymorphism in UTI (urinary tract infection), where implications of *Taq*1, *Bsm*1, *Apa*1 and *Fok*1 polymorphism were studied in children. According to the findings of this study *Apa*1 and *Bsm*1 were found to be related with UTI, but not with *Fok*1 and *Taq*1[103].

VDR polymorphism has also been discovered to play a crucial role in Crohn's disease susceptibility. Crohn's disease is an inflammatory bowel disease that leads to inflammation in the digestive tract. A link between VDR polymorphism and Crohn's disease was deduced in a patient study which investigated *Taq*1, *Apa*1 and *Fok*1 polymorphisms and confirmed the association of *Taq*1 polymorphism with Crohn's disease[104].

In addition to these infectious diseases, VDR polymorphism has been associated with numerous other diseases including *Fok*1 in *Trypanosoma cruzi* and/or chronic chagas cardiomyopathy infection, BsmI in *Helicobacter pylori* infection in Brazilian population, *Taq*1 in hepatitis B virus infection in African population, *Bsm*1 polymorphism (AA genotype) with progression to AIDS and *Fok*1 for susceptibility to symptomatic pertussis[105–109].

All of these findings evidenced that VDR is crucial in regulating several processes of human body and even a single amino acid substitution may lead to life-threatening diseases as represented in Table 3.

2.2.6 Role of Vitamin D in Coronavirus Disease (COVID-19)

COVID-19 emerged as a recent medical emergency and affected around 220 countries across the world, according to the World Health Organisation (WHO). This disease caused by the virus SARS-CoV-2 shows a common symptom of respiratory illness in affected individuals. Vitamin D deficiency and malnutrition are reported risk factors of this disease involving impaired immune response[147].

It has been observed that deficiency of vitamin D in the body influences the risk of COVID-19 because ligand-bound vitamin D receptor, present abundantly in respiratory epithelial cells and immune cells, restricts the adaptive immune response by reducing the maturation of antigen presenting cells (dendritic cells) and helps in changing the T-cell profile from proinflammatory group of cells (Th1 and Th17 cells) to anti-inflammatory T group of cells (Th2 and Treg). This results in inhibition of pro-inflammatory response and, therefore, plays a crucial role in curtailing cytokine storm involved in causing severe respiratory syndrome in COVID-19. Vitamin D is known to have immunomodulatory effects on cytokines TNF, IL6, CXCL8, and CXCL 10, which have vital role in the progression of a viral infection[148]. It is accredited to the VDR expression in most immune cells that they become responsive to regulation by vitamin D. Enhanced expression of C-reactive protein, β-defensins, and cathelicidins by ligand-activated VDR accounts for a part of the innate immune response to pathogens[149]. A study on acute respiratory tract infections showed that vitamin D supplementation could prevent the disease in individuals receiving regular doses of it daily or weekly[150]. VDR polymorphism and vitamin D insufficiency may impact the risk of COVID-19 and patient's outcome affecting both the innate and adaptive immune systems[151].

Association of vitamin D with ACE 2 (Angiotensin Converting Enzyme 2) receptor is recently shown[152]. ACE2 receptor is reported to help cell entry of SARS-CoV-2 and enhancing its own expression which demonstrates its key role in COVID-19 infection[152]. However, another study has conditionally disapproved this potential relationship between the concentration of vitamin D and susceptibility to COVID 19 in different ethnic populations[153].

FokI polymorphism is found to be associated with the risk of viral infection in individuals with recessive T allele genotype only, instead of individuals with

Table 3. Studies indicating association of VDR polymorphism with various diseases in diverse populations

Disease(s)	Polymorphism	Population studied	Type of study	The outcome of the study	References
Bone disorders	*TaqI, ApaI*	Iranian women	Case-control study	No significant differences between *TaqI* and *ApaI* genotype in menopausal cases and controls were observed	110
	BsmI	African-American and White women and their children	Case-control study	A significant ethnic difference among African Americans and white. No African American had BB genotype whereas in whites 25% adults and 24% of children had BB genotype. The bb genotype was associated with higher bone mass than BB genotype	111
	FokI	Mexican-American Caucasian	Case-control study	Patients with ff genotype had a low bone mineral density in lumbar spine than FF genotype, whereas Ff genotype had an intermediate bone density	50
	BsmI, TaqI, ApaI, and FokI	Caucasian and East Asians	Meta-analysis	Allele contrast indicated heterogeneity among the population and were not significant	112
	ApaI, BsmI, TaqI and cdx-2	Belarusian and Lithuanian women	Case-control study	Genotyping showed a statistically significant relationship between cases and control post-menopausal. *ApaI* (C/C genotype) and *BsmI* (G/G genotype) were significantly higher in patients and linkage disequilibrium analysis showed that C-G-C haplotype of *ApaI-BsmI-TaqI* were associated with higher postmenopausal osteoporosis	113
	BsmI, TaqI, ApaI, and FokI	Chinese	Case-control study	No significant association when considered independently but cross-genotyping of *FokI* and *TaqI* and *FokI* and *ApaI* were observed to be associated with BMD	114

	BsmI	Caucasian, Africans, Asians, Turkish, Jewish, Mexican	Meta-analysis	bb genotype was discovered to be significantly associated with decreased risk for osteoporosis. In Africans (bb/Bb *vs* BB) were observed to exhibit decreased risk for osteoporosis but not in Caucasians, Asians, and Turkish population	115
	BsmI	Caucasian and Asians	Meta-analysis	*BsmI* was found to be associated with osteoporosis risk in Caucasians but not in Asians	116
	BsmI	Spanish	Case-control study	No significant association was detected	117
Cancer (a) Breast Cancer	*BsmI, FokI*	UK Caucasian	Case-control study	*BsmI* was found significantly associated with probability of breast cancer whereas *FokI* failed to show any association with cancer	118
	FokI, BsmI	Caucasian	Nested case control Study	*FokI* (ff genotype) was significantly associated with breast cancer but *BsmI* failed to show any relation	119
	BsmI, poly A	African American and Caucasian	Case-control study	*BsmI* (bb genotype) established an association with risk of breast cancer in Caucasians but not in African Americans. Poly A polymorphism failed to show any association in either population group	120
	FokI, BsmI, ApaI, TaqI, polyA	Caucasian and Chinese	Meta-analysis	*FokI* was observed to be associated with risk of breast cancer	121
(b) Prostate cancer	*TaqI, poly A, FokI, BsmI*	European, African and Asian descent	Meta-analysis	No significant association was found for these polymorphisms with risk of cancer	122
	TaqI, polyA, ApaI, FokI, BsmI	Black, White, Japanese, Taiwanese, Chinese descent	Meta-analysis	No polymorphism found to be significantly associated with cancer	123
	BsmI, TaqI, ApaI	Japanese	Case-control study	A significant association detected between *BsmI* and risk of prostate cancer. *TaqI* and *ApaI* failed to show any significant association with cancer	
	TaqI	Caucasian, African, Asian	Meta-analysis	*TaqI* found to be significantly associated with risk of prostate cancer	124

(c) Ovarian cancer	*ApaI, BsmI, FokI, Cdx-2, TaqI*	African American, Caucasians, Japanese	Meta-analysis	Only *FokI* was detected to be associated with risk of cancer	125
	FokI	Japanese	Case-control study	Association observed between *FokI* (CC genotype) and risk of cancer	126
	FokI, Cdx-2, ApaI, BsmI, TaqI	Caucasian, Japanese	Case-control study	In the Caucasian population, patients with *ApaI,* and *FokI* polymorphism have higher chance of developing cancer whereas in Japanese *Cdx-2* polymorphism showed decreased susceptibility for cancer	127
(d) Colorectal carcinoma	*ApaI, TaqI, Cdx-2, BsmI, FokI*	Chinese	Meta-analysis	*BsmI* is significantly associated with cancer. *FokI* might serve as a risk factor for cancer	128
	Cdx-2, FokI, BsmI, ApaI, TaqI	American, Asian, European	Meta-analysis	Only *BsmI* showed association with colorectal cancer	129
	BsmI, TaqI	Caucasian	Case-control study	*BsmI* and *TaqI* polymorphism resulted in significant association with cancer	130
(e) Skin cancer	*FokI, BsmI, TaqI, ApaI*	Caucasian	Meta-analysis	*FokI, TaqI,* and *ApaI* were found to be significantly associated with the risk of skin cancer whereas *BsmI* was not significantly associated	131
	BsmI, TaqI, ApaI	US population	Case-control study	Only *BsmI* polymorphism was found associated with the risk of developing cancer	132
	BsmI, FokI, A1012G	Italian	Case-control study	A significant association was found between *BsmI* and malignant melanoma	133
Diabetes	*FokI, BsmI, ApaI, TaqI*	Asian, Caucasian	Meta-analysis	*FokI* was associated with increased risk of type2 diabetes mainly in Asian population	52
	ApaI, BsmI, TaqI, FokI	Turkish	Case-control study	Only *FokI* was found to be associated with gestational diabetes mellitus	134
	BsmI, TaqI, FokI	Northeast India	Case-control study	*BsmI* found significantly associated with the risk of diabetes	135
	TaqI, BsmI, FokI	Asian Indian	Case-control study	*TaqI* was shown to provide protection against diabetes	97
	BsmI	Egyptian	Case-control study	*BsmI* was observed to be associated with risk of diabetes	93
Infectious diseases (a)Leprosy	*TaqI*	Brazilian	Case-control study	tt genotype suggested higher risk for leprosy development	136

	TaqI, FokI, ApaI	North Indian	Case-control study	An association was observed in risk of leprosy and *FokI* and *TaqI*	137
	TaqI, FokI, ApaI	Andhra Pradesh, India	Case-control study	*FokI* and *ApaI* were detected to be associated with risk of leprosy but not *TaqI*	138
(b) Tuberculosis	*TaqI, BsmI, FokI*	Korean	Case-control study	No significant association was detected between the polymorphism and risk for tuberculosis	139
	FokI	East and Southeast Asian	Meta-analysis	Subgroup analysis discovered an association between *FokI* and increased risk for TB	140
	FokI	North India	Case-control study	*FokI*, f allele was detected to be associated with increased risk to TB	141
(c) Chronic chagas cardiomyopathy	*TaqI, ApaI, BsmI, FokI*	Colombian	Case-control study	Only *FokI* was found to be associated with risk of disease	142
	FokI, BsmI, ApaI, TaqI	Brazilian	Case-control study	No significant association found	143
(d) Leishmaniasis	*BsmI, FokI, TaqI*	Iranian	Case-control study	No significant association observed	144
(e) Urinary tract infections	*FokI, TaqI, BsmI, ApaI*	Iranian	Case-control study	A significant association with *BsmI* and *ApaI* were confirmed	103
	BsmI, FokI, ApaI, TaqI	Turkey	Case-control study	*FokI* and *ApaI* showed a significant association	145
(f) Enveloped viral infection	*Cdx-2, BsmI, ApaI, FokI, TaqI, A1012G*	India, China, South Africa, Spain, Canada, Netherlands, Gambia	Meta-analysis	*FokI* showed a significant relationship with viral infection	54
Cardiovascular diseases	*ApaI, TaqI*	Egyptian	Case-control study	Both polymorphism failed to show any association with the pathogenesis of disease	146
	Tru9I, ApaI, TaqI, FokI	Han Chinese	Case-control study	Only *FokI* reported to be associated with risk of disease	81
	ApaI, TaqI, BsmI, FokI	Caucasian and East Asian	Meta-analysis	No significant association was observed	82

CT+CC genotypes[154]. In another cohort study of adults and children in United Kingdom, three SNPs of VDR (rs4334089, rs11568820 and rs7970314) were found to increase the risk of upper respiratory tract infections. Thus, it is assumed that these SNPs might be involved in influencing the risk of developing COVID-19 infection[155].

Recent findings and large number of clinical data indicate the predominance of vitamin D in patients with severe implications of COVID-19[156–158]. More controlled randomized studies and large disease population studies are needed to further validate the role of vitamin D and VDR polymorphism in COVID-19 progression and to propose its therapeutic potential in reducing or treating the disease.

3. Conclusions

Since the discovery and cloning of VDR, the receptor has been extensively studied for its involvement in diverse cellular and physiological functions, as well as in its genetic implications. VDR has now been identified as a central regulator of a variety of processes in the human body, including both calcemic and non-calcemic functions. Although the structure, receptor localization, and functions of VDR are relatively well studied, the next phase about which less is known, involves VDR polymorphism. Though VDR polymorphisms have been explored to some extent in several disease states, there is barely any knowledge about their implications on molecular mechanism of actions and functional consequences. Currently, there is need to elucidate and classify the possible involvements of VDR polymorphism in receptor functionality and its inter-molecular interactions in different disease states. Further research in this area will aid in our understanding of VDR polymorphism-related diseases that will subsequently help in designing novel receptor modulators thereby leading to the modification in therapeutics and clinical applications.

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