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Very important pharmacogene summary for VDR

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Introduction

The vitamin D receptor (VDR) binds the active form of vitamin D (1,25-dihydroxyvitamin D₃). It belongs to the family of *trans*-acting transcriptional regulatory factors and shows sequence similarity to the steroid and thyroid hormone receptors. The gene was cloned by Baker and colleagues in 1988 and maps to chromosome 12q13.11 [1]. It consists of nine exons with at least six isoforms of exon 1, spans 63.5 kb, and encodes a 427 amino acid protein [2]. Alternative splicing results in multiple transcript variants encoding the VDR protein of different lengths [3,4].

The interaction of 1,25-dihydroxyvitamin D₃ with VDR modulates many biological activities of the neural, immune, and endocrine systems, including calcium and phosphorous homeostasis, apoptosis, and cell differentiation (reviewed by Hewison and colleagues [5-7]).

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Conflicts of interest

There are no conflicts of interest.

Its pleiotropic property is reflected by the findings that VDR is expressed in at least 37 tissues, which can roughly be grouped into seven biological systems (calcium homeostasis, immune, pancreatic β cells, muscle, cardiovascular, brain, and lung) [8-10]. The most characterized mechanism is the binding of vitamin D₃ to nuclear VDR, which activates the receptor to form a heterodimer with the retinoid-X receptor and interacts with a specific DNA sequence on the gene promoter regions called the 'vitamin D response element' (VDRE). Transcription repressors occupying the VDRE are then replaced by transcription activators to initiate transcription of targeted genes. Microarray analyses using different human cell lines have identified over 100 genes with VDREs in the promoter regions, all potential targets of the 1,25-dihydroxyvitamin D₃-VDR complex [11-13]. In human oral squamous carcinoma SCC25 cells, genes with characterized VDREs and of which demonstrated greater than 10-fold increase after treatment with 1,25-dihydroxy-vitamin D₃ include 24-hydroxylase (*CYP24*), 17 β -hydroxy-steroid dehydrogenase (*HSD17B2*), CD14 (*CD14*), type XIII collagen (*COL13A1*), and 5-lipoxygenase (*ALOX5*) [13]. The effect of 1,25-dihydroxyvitamin D₃ by binding to VDR in the nucleus is often described as the slow-acting genomic effect; the effect will take days or hours to be noticed.

Alternatively, 1,25-dihydroxyvitamin D₃ can bind to VDR located in the caveolae in the plasma membrane to exert rapid responses through production of second messengers [14]. Pathways that have been shown to be activated by the 1,25-dihydroxyvitamin D₃-VDR_[memb] complex include mitogen-activated protein kinase-dependent [15], cAMP-dependent [16], phospholipase A₂-dependent [17], phospholipase C-dependent [18], phosphatidylinositol 3-kinase-dependent [19], and protein kinase C-dependent [20] pathways. Examples of such rapid response include rapid Ca²⁺ absorption in the duodenum [21,22], opening of Cl⁻ channels and secretion in osteoblasts, insulin secretion from pancreatic β -cells [23,24], and vascular smooth muscle cell migration [19].

VDR variations

Because of the pleiotropic effect exerted by the 1,25-dihydroxyvitamin D₃-VDR complex, its genetic variants have been found to be associated with a wide variety of diseases/phenotypes, including various types of cancer, tuberculosis, asthma, height, longevity/mortality, insulin-dependent diabetes mellitus, bone mineral density (BMD), and hyperparathyroidism, as reviewed comprehensively elsewhere [25,26]. This study focuses on clinically relevant associations between treatment responses in the presence of VDR genetic polymorphisms. Furthermore, although no VDR polymorphism has been reported to be associated with vitamin D treatment in cancer therapy, the findings that VDR expression is reduced in colon cancer and negatively correlated with progression imply a role of VDR protein expression in treatment response [27-29].

In a comprehensive study of the genetic architecture of VDR, areas of low linkage disequilibrium (LD) and areas of high LD were observed [30]. This study further noted that the number and size of LD blocks are different in whites, Han Chinese, and Africans. In whites, four blocks were found at the 5' end, and the largest block encompassed exons 4-9 and 3' UTR. The LD structure in Han Chinese is similar to that of whites but that of African Americans is substantially fragmented and different from that of whites and Han Chinese. The 5' promoter variants *Cdx2* and *GATA* reside in block 2, and the three widely studied 3' variants *BsmI*, *ApaI*, and *TaqI* are located in block 5; variant *FokI* does not reside in any block and is located between blocks 2 and 3. However, further analysis of this genomic area showed that the three variants do not capture all the information in the block [31]. (Note: In the nomenclature of the variants, the alleles are conventionally defined by capital letters in the absence of a restriction site and by small letters in the presence of a given restriction site; for example, *TaqI* T and C alleles are named T and t, respectively. To avoid confusion this

review will only use the allele corresponding to the nucleic acid.) This review highlights the pharmacogenetic effects of *VDR* polymorphisms in various biological systems. Table 1 summarizes the functional effect and associated phenotypes of genetic variants in the *VDR* gene.

Important variants

5' variants

VDR: rs11568820 (A > G, commonly known as Cdx2) and rs4516035 (T > C, commonly known as GATA)—Two functional variants lying in an LD block in the promoter region captured the genetic information around exons 1e and 1a and are often analyzed as a haplotype block [51]. These two variants are commonly known as *Cdx2* (rs11568820) and *GATA* (rs4516035). Variant rs11568820 resides in the binding site of transcription factor Cdx2, upstream of exon 1e. Functional analyses showed that the A to G base substitution (referring to the minus strand) eliminates the Cdx binding site and reduces transcriptional activity of VDR to 70% of the A allele [52,53]. The frequency of allele A ranges from 50% in Asians to 80% in Europeans to 98% in Sub-Saharan Africans, as estimated by the HapMap Project [54]. Downstream is variant rs4516035, which resides at the GATA binding site, and its C allele eliminates the GATA binding site and confers a lower VDR promoter activity [51]. The frequency of allele T ranges from 50% in Europeans to 98% in Asians to 99% in Sub-Saharan Africans [54]. Allele T of *GATA* is found to have a 1.9-fold higher VDR promoter activity compared with allele C [51]. In a study on 69 Dutch children with acute lymphoblastic leukemia, the effect of dexamethasone treatment on body composition was investigated. It was found that, during treatment, noncarriers of haplotype *Cdx2* allele A/*GATA* allele C had greater fat gain and higher BMD and apparent BMD of the lumbar spine compared with the carriers [32]. In another study that examined the effect of VDR polymorphisms on growth and treatment response of 1 α -hydroxyvitamin D3 derivatives, vitamin D3, and phosphates to X-linked hypophosphatemic rickets, patients who were treated with 1 α -hydroxyvitamin D3 since childhood experienced less growth defect compared with those not treated with 1 α -hydroxyvitamin D3 [33]. When the *Cdx2/GATA* haplotypes of these patients were considered, patients who had been treated with 1 α -hydroxyvitamin D3 since childhood and were carriers of *Cdx2* G/*GATA* C haplotype experienced less growth defect compared with noncarriers. In children receiving 1 α -hydroxyvitamin D3 and who were carriers of *Cdx2* G/*GATA* C haplotype, a lower urinary calcium/creatinine level was detected compared with noncarriers, suggesting that *Cdx2* G/*GATA* C may protect these children from developing hypercalciuria during treatment. Taken together, these studies showed that carriers of *Cdx2* G/*GATA* C and *Cdx2* G/*GATA* T haplotypes were at lower risk of having bone-related side effects from treatment with 1 α -hydroxyvitamin D3 and dexamethasone.

In a recent study that examined the effect of *VDR* genotypes, calcium intake, and prostate cancer in African Americans, carriers of the *Cdx2* GG genotype were found to be at a lower risk (roughly 40% of men of AA genotype) of developing advanced cancer, and such risk was further reduced (8% of men of AA genotype) when coupled with a low-calcium diet [34]. The authors noted that the same association was not observed with localized prostate cancer, suggesting that high calcium intake is not involved in the initiation but progression of prostate cancer.

VDR: rs2228570 (T > C, commonly known as FokI)—At the translation start site of *VDR*, a T > C base change of variant rs2228570 eliminates the translation start site in exon 2, and the encoded protein is shortened by three amino acids [55]. The frequency of allele T ranges from 40% in whites and Asians to 20% in Sub-Saharan Africans [54]. The smaller protein exhibits greater transcription activity because of its greater binding efficiency to

transcription factor IIB [56]. In immune cells, transcripts with the C allele (often referred to as allele F of *FokI* polymorphism) demonstrated stronger transcriptional effect of VDR target genes [57]. Given the pivotal role of 1,25-dihydroxyvitamin D₃ and calcium absorption, variant *FokI* has been studied for its association with calcium absorption, BMD, and other anthropometric measures. In an association study of calcium absorption kinetics, bone mineralization rates, and *VDR* polymorphisms in early pubertal adolescents, individuals with the TT genotype had less total calcium absorption, and less calcium accretion to the skeleton [36]. In an earlier study, children with the TT genotype were found to have lower calcium absorption and lower BMD, after adjusting for age, ethnicity, BMI, and puberty status [37]. In a study on 36 white postmenopausal women with osteoporosis or osteopenia who were treated with calcium and vitamin D supplements for 3 months, the *FokI* TC genotype was more common in responders compared with nonresponders [38].

In a study that examined the genotypic effect of *VDR* polymorphism and calcipotriol response in white psoriasis patients, variant *FokI* alone was not associated with any significant effect; however, when analyzed in combination with variant *Cdx2*, patients with the *Cdx2* AA/*FokI*CC genotype combination were four times more likely to respond to calcipotriol [35]. Furthermore, additional variant combinations found to be associated with calcipotriol response were *Cdx2* AA/*TaqI* TT and *FokI* CC/*TaqI* TT. A similar association with positive response to calcipotriol in psoriasis patients was detected in a Turkish population [42].

In a study that examined the VDR genetic effect on treatment response of antimycobacterial chemotherapy against tuberculosis in Peruvian patients, carriers of the *FokI* CC genotype had faster conversion of sputum mycobacterial culture from positive to negative compared with non-CC genotype carriers [39].

In an in-vitro study on thyroid cancer, thyroid cancer cell lines that had significant decrease in cell viability after VDR agonist treatment were found to be those carrying the *FokI* TT genotype, whereas those of CC genotype were resistant [40]. Further analysis of the mRNA level of 1 α -hydroxylase (*CYP27B1*) and 24-hydroxylase (*CYP24A1*) suggested that the C allele may confer resistance by upregulation of 24-hydroxylase and subsequent suppression on VDR activation. However, in an in-vitro study on breast cancer, carriers of the CC genotype were found to have the greatest growth inhibition compared with the TT genotype and vector control after treatment with 1,25-dihydroxy-vitamin D₃ [41]. VDR protein level was found to be elevated in the CC, TT genotype carriers and vector control, with CC genotype carriers exhibiting the highest elevation. *CYP24A1*, a downstream target gene, was upregulated at both the mRNA and protein levels after 1,25-dihydroxyvitamin D₃ treatment, with the CC genotype carriers exhibiting the greatest elevation. In contrast, the protein level of another downstream target, estrogen receptor α (*ESR1*), was downregulated after treatment, and cells with the CC genotype exhibited the greatest protein suppression. Furthermore, estrogen-induced cell growth was inhibited by 1,25-dihydroxyvitamin D₃ in the cells with the CC genotype but not in the TT genotype counterparts. In the same study the authors demonstrated greater VDR protein stability and longer half-life after 1,25-dihydroxy-vitamin D₃ treatment in cells carrying the CC genotype compared with vector control and the TT counterparts.

3' variants

VDR: rs1544410 (C > T, commonly known as BsmI)—This variant is commonly known as *BsmI* and is located in intron 8 (allele C is commonly referred to as allele b and allele T is referred as allele B). No known functional consequence of this variant has been described; however, a few studies have found that it is associated with antiresorptive treatment responses [40,41,47,48]. In a study on the effectiveness of antiresorptive treatment

in postmenopausal women, treatment outcomes (i.e. BMD, bone formation and bone resorption) were found to be influenced by treatment arms, genotype at variant *BsmI* and treatment arms \times genotype interactions [47]. Women with the CC genotype had greater improvement in BMD after treatment compared with those with the TT genotype, regardless of the treatment arms. Decrease in bone formation after treatment was the least in CC women compared with their CT and TT counterparts. Homozygous CC women also demonstrated the least decrease in bone resorption compared with the other two genotype groups. In a pilot study on antiresorptive treatment (oral alendronate vs. subcutaneous teriparatide) in postmenopausal women, women who received alendronate and had at least one allele C had greater BMD at their lumbar spine compared with those with the TT genotype [48]. In addition to a genotypic effect toward antiresorptive treatment, *BsmI* is also associated with response to calcium and vitamin D supplementation in healthy adolescent girls [58]. In a study on 167 adolescent girls from Lebanon, placebo and vitamin D supplements were given randomly for a year, and bone mineral content (BMC), BMD, and lean mass were measured as outcomes [45]. In the treatment group, percentage change in BMC of the total body, hip, and trochanter were significantly greater in CT heterozygous individuals compared with CT nontreated controls. A similar trend was observed in CC girls, although it did not reach statistical significance. In a study that investigated the effect of longterm antiepileptic treatment on BMD in men and premenopausal women, those with the CC genotypes had higher BMD, higher serum level of 25-hydroxyvitamin D₃, and lower level of parathormone, compared with those with the CT and TT genotypes [49].

VDR: rs7975232 (C > A, commonly known as *Apal*)—This variant is commonly known as *Apal* and is located in intron 8 (allele A is often referred to as allele A and allele C is allele a). At present, no known functional consequence of this variant has been described. In a study that investigated the effect of dairy intake and colorectal cancer recurrence, an interaction between *Apal* genotype and dairy product intake was detected [50]. In particular, individuals with at least one copy of allele A and who consumed a large amount of dairy products had the lowest risk of colorectal cancer recurrence compared with CC genotype carriers who consumed lower amounts of dairy products.

VDR: rs731236 (T > C, commonly known as *TaqI*)—This variant is commonly known as *TaqI* and is located in exon 9 (allele T is often referred to as allele T, and allele C is allele t). In a study on tuberculosis susceptibility, it has been demonstrated in lymphoblastoid cell lines that this variant resides on a CpG island and the C allele is always methylated, and that interactions exist between *TaqI* polymorphism, methylation levels, ethnicities, and tuberculosis susceptibility [43].

In a multivariate study investigating the interaction between therapy and VDR variants, allele C confers increased risk to new fracture in postmenopausal women treated with calcium supplement in Australia [44]. Healthy adolescent girls with the TT genotype had greater spine and femoral neck BMC and femoral neck area when given vitamin D supplement, compared with the CC group [45]. In a study using narrowband ultraviolet light to treat chronic plaque psoriasis, individuals with the CC genotype had the shortest remission period compared with the other genotypes [46]. In another study that examined the VDR genetic effect on treatment response of antimycobacterial chemotherapy against tuberculosis in Peruvian patients, variant *FokI* CC and *TaqI* CT genotypes were both found to be associated with faster conversion of sputum mycobacterial culture from positive to negative [39].

Conclusion

The pleiotropic effects of 1,25-dihydroxyvitamin D₃ on a wide range of physiological systems render its receptor VDR an attractive candidate for investigation in disease mechanism and therapeutic responses. Of the six conventionally investigated variants, those at the 5' end have the biological consequence of the base change characterized. Recently, the biological effect of the base change at the *TaqI* variant was also characterized as aforementioned. It is likely that the associations observed for variants *BsmI* and *ApaI* are due to linkage disequilibrium with the causative variant(s). Given the vast number of genes whose transcription can be upregulated or downregulated by VDR, an allele may be a risk factor for one trait and a protective one for another. Although the scientific community agrees that the present guidelines for vitamin D intake must be augmented, one must take into account the differential activity of the VDR protein as partially dictated by variations in the *VDR* gene.

This PharmGKB summary briefly discusses the very important pharmacogene VDR and its variants that can influence drug responses. A fully interactive version of this short review, with links to individual paper and detailed mapping information, can be found at <http://www.pharmgkb.org/search/annotatedGene/vdr/index.jsp>.

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Table 1The functional effect and associated phenotype of genetic variants in the *VDR* gene

SNP	Functional consequence	Medical condition	Treatment	Associated phenotypes
rs11568820	A >G eliminates Cdx binding site	Childhood acute lymphoblastic leukemia	Dexamethasone	Fat gain, BMD, and apparent BMD of the lumbar spine [32]
		X-linked hypophosphatemic ricket patients	1 α -Hydroxyvitamin D ₃	Growth defect and urinary calcium/keratinise levels [33]
		Prostate cancer risk	Low-calcium diet	Prostate cancer risk [34]
		Psoriasis	Calcipotriol	Calcipotriol response [35]
rs4516035	T >C eliminates GATA binding site	Childhood acute lymphoblastic leukemia	Dexamethasone	Fat gain, BMD and apparent BMD [32]
		X-linked hypophosphatemic ricket patients	1 α -Hydroxyvitamin D ₃	Growth defect and urinary calcium/keratinise levels [33]
rs2228570	T >C eliminates translation start site	Puberty	Not applicable	Calcium absorption and calcium accretion to skeleton [36]
		Childhood	Not applicable	Calcium absorption and BMD [37]
		Osteoporosis or osteopenia	Calcium and vitamin D	Vitamin D and parathyroid hormone levels [38]
		Psoriasis	Calcipotriol	Calcipotriol response [35]
		Tuberculosis	Antimycobacterial chemotherapy	Sputum mycobacterial culture conversion [39]
		Thyroid cancer	VDR agonist	Cell viability [40]
		Breast cancer	1,25-Dihydroxyvitamin D ₃	Growth inhibition [41]
rs731236	T >C methylation site	Psoriasis	Calcipotriol	Calcipotriol response [42]
		Tuberculosis	Not applicable	Tuberculosis susceptibility [43]
		Postmenopausal women	Calcium supplement	New fracture [44]
		Adolescent girls	Vitamin D supplement	Spine and femoral neck BMC and femoral neck area [45]
		Chronic plaque psoriasis	Narrowband ultraviolet light	Remission period [46]
rs1544410	C >T, unknown functional consequence	Postmenopausal women	Antiresorptive treatment	BMD, bone formation and bone resorption [47]
		Postmenopausal women	Antisorptive treatment	BMD [48]
		Adolescent girls	Vitamin D supplement	BMC [45]
		Epilepsy	Antiepileptic treatment	BMD, serum 25-hydroxyvitamin D ₃ level and parathormone level [49]
rs7975232	C >A, unknown functional consequence	Colorectal cancer	Dairy product intake	Colorectal cancer recurrence [50]

BMD, bone mineral density; SNP, single nucleotide polymorphism; VDR, vitamin D receptor.