**1,25-DIHYDROXYVITAMIN D3 RECEPTOR**

**VITAMIN D HORMONE RECEPTOR**

**Gene map locus 12q12**

**TEXT**

**DESCRIPTION**

The vitamin D3 receptor (VDR) is an intracellular hormone receptor that specifically binds the active form of vitamin D (1,25-dihydroxyvitamin D3 or calcitriol) and interacts with target-cell nuclei to produce a variety of biologic effects (Baker et al., 1988).

**CLONING**

Baker et al. (1988) isolated a cDNA corresponding to the human vitamin D receptor from a human intestinal cDNA library. The deduced 427-amino acid protein has a calculated molecular mass of 48.3 kD and belongs to the superfamily of trans-acting transcriptional regulatory factors, including the steroid and thyroid hormone receptors. The VDR protein contains a zinc-finger DNA-binding and transcriptional activation domain and a ligand-binding domain. VDR is closely related to the thyroid hormone receptors. RNA blot hybridization indicated a single RNA species of about 4.6 kb.

**GENE STRUCTURE**

Miyamoto et al. (1997) determined that the VDR gene contains 11 exons and spans approximately 75 kb. The noncoding 5-prime end of the VDR gene includes exons 1A, 1B, and 1C, while its translated product is encoded by 8 additional exons (2-9). Three unique mRNA isoforms are produced as a result of the differential splicing of exons 1B and 1C. The DNA sequence upstream to exon 1A is GC-rich and does not contain an apparent TATA box. Several potential binding sites for the transcription factor SP1 (189906) and other activators were noted. An intron fragment 3-prime of exon 1C conferred retinoic acid responsivity when fused to a reporter gene plasmid.

Exons 2 and 3 of the VDR gene are involved in DNA binding, and exons 7, 8, and 9 are
involved in binding to vitamin D (Hughes et al., 1988).

**GENE FUNCTION**

Using mutation analysis, Jurutka et al. (2000) characterized arg18/arg22, VDR residues immediately N-terminal of the first DNA-binding zinc finger, as vital for contact with the general transcription factor IIB (TFIIB; 189963). A natural polymorphic variant of VDR, termed F/M4 (missing a FokI restriction site), which lacks only the first 3 amino acids (including glu2), interacted more efficiently with TFIIB and also possessed elevated transcriptional activity compared with the full-length (f/M1) receptor. The authors concluded that the functioning of positively charged arg18/arg22 as part of a VDR docking site for TFIIB is influenced by the composition of the adjacent polymorphic N terminus. Increased transactivation by the F/M4 neomorphic VDR was hypothesized to result from its demonstrated enhanced association with TFIIB.

Makishima et al. (2002) demonstrated that the vitamin D receptor also functions as a receptor for the secondary bile acid lithocholic acid, which is hepatotoxic and a potential enteric carcinogen. The vitamin D receptor is an order of magnitude more sensitive to lithocholic acid and its metabolites than are other nuclear receptors. Activation of the vitamin D receptor by lithocholic acid or vitamin D induced expression in vivo of CYP3A (124010), a cytochrome P450 enzyme that detoxifies lithocholic acid in the liver and intestine. Makishima et al. (2002) suggested a mechanism that may explain the proposed protective effect of vitamin D and its receptor against colon cancer.

Kitagawa et al. (2003) identified a human multiprotein complex that directly interacts with VDR through the WSTF gene (BAZ1B; 605681). They designated the complex WINAC (WSTF-including nucleosome assembly complex) and determined that it contains at least 13 components. WINAC has ATP-dependent chromatin-remodeling activity and contains both SWI/SNF components and DNA replication-related factors. WINAC mediates the recruitment of unliganded VDR to its target sites in promoters, while subsequent binding of coregulators requires ligand binding. This recruitment order exemplifies that an interaction of a sequence-specific regulator with a chromatin-remodeling complex can organize nucleosomal arrays at specific local sites in order to make promoters accessible for coregulators. Overexpression of WSTF restored the impaired recruitment of VDR to vitamin D-regulated promoters in fibroblasts from patients with Williams syndrome (194050). This finding suggested that WINAC dysfunction may contribute to the phenotypic variability of Williams syndrome.

Using retroviral transduction, Palmer et al. (2004) generated human SW480-ADH colon cancer cells that ectopically express mouse hemagglutinin-tagged Snai1 (604238) protein (SNAIL-HA). Overexpression of Snai1 in these cells resulted in lower vitamin D receptor mRNA and protein expression and inhibited induction of E-cadherin (192090) and VDR by 1,25(OH)2D3. A 1,25(OH)2D3 analog inhibited tumor growth in immunodeficient mice injected with mock cells, but not in those injected with SNAIL-HA cells. In 32 paired samples of normal colon and tumor tissue from patients undergoing colorectal surgery, Palmer et al. (2004) found that high SNAI1 expression in tumor tissue correlated with downregulation of VDR and E-cadherin (p = 0.007 and 0.0073, respectively). Palmer et al. (2004) concluded that the balance between VDR and SNAI1 expression is critical for E-cadherin expression, which influences cell fate during colon cancer progression.

Healy et al. (2005) administered human PTH (168450) over 48 hours to wildtype mice and observed a 15% reduction in renal VDR levels (p less than 0.03). When the authors similarly administered PTH to CYP27B1 (609506)-null mice, which are incapable of
endogenously producing vitamin D hormone, they observed a 29% reduction in VDR levels (p less than 0.001). Healy et al. (2005) concluded that PTH is a potent downregulator of VDR expression in vivo. Shah et al. (2006) stated that the signaling and oncogenic activity of beta-catenin (CTNNB1; 116806) can be repressed by activation of VDR. Conversely, high levels of beta-catenin can potentiate the transcriptional activity of 1,25-dihydroxyvitamin D3. Shah et al. (2006) showed that the effects of beta-catenin on VDR activity are due interaction between the activator function-2 domain of VDR and the C terminus of beta-catenin.

Using DNA microarray and quantitative PCR analyses, Liu et al. (2006) found that activation of TLR2 (603028) and TLR1 (601194) by a mycobacterial ligand upregulated expression of VDR and CYP27B1, the vitamin D 1-hydroxylase that catalyzes the conversion of vitamin D to its active form, in monocytes and macrophages, but not dendritic cells. Intracellular flow cytometric and quantitative PCR analyses showed that treatment of monocytes with vitamin D upregulated expression of CYP24 (CYP24A1; 126065), the vitamin D 24-hydroxylase, and cathelicidin (CAMP; 600474), an antimicrobial peptide, but not DEFB4 (602215). Confocal microscopy demonstrated colocalization of CAMP with bacteria-containing vacuoles of vitamin D-treated monocytes, and vitamin D treatment of M. tuberculosis-infected macrophages reduced the number of viable bacilli. Ligand stimulation of TLR2 and TLR1 upregulated CYP24 and CAMP in the presence of human serum, but not bovine serum, and CAMP upregulation was more efficient in Caucasian than in African American serum, in which vitamin D levels were significantly lower. Vitamin D supplementation of African American serum reversed the CAMP induction defect. Liu et al. (2006) proposed that vitamin D supplementation in African and Asian populations, which may have a reduced ability to synthesize vitamin D from ultraviolet light in sunlight, might be an effective and inexpensive intervention to enhance innate immunity against microbial infection and neoplastic disease.

MAPPING

Faraco et al. (1989), who identified an ApaI dimorphism at the VDR locus, assigned the VDR gene to chromosome 12 by somatic cell hybrid studies. By study of rat/human somatic cell hybrids, Szpirer et al. (1991) showed that the VDR gene is located on 12q in the human and chromosome 7 in the rat. Labuda et al. (1991) assigned the VDR gene to 12q12-q14 by in situ hybridization. No recombination was found between VDR and COL2A1 (120140; lod = 1.94) or ELA1 (130120; lod = 0.98) on 12q13. The COL2A1 and VDR loci are separated by less than 740 kb, with VDR distal to COL2A1 (Pedeutour et al., 1994).

MOLECULAR GENETICS

**Vitamin D-Dependent Rickets Type II**

In 2 patients with vitamin D-dependent rickets type II (VDDR II; 277440), Hughes et al. (1988) identified 2 different mutations in the VDR gene (601769.0001 and 601769.0002). Hughes et al. (1988) suggested that this was the first molecular identification of a disease-producing mutation in a steroid hormone receptor gene. (Mutations were found at about the same time in the androgen receptor; see 313700.)

Saijo et al. (1991) noted that different mutations in the VDR gene have been specific for particular ethnic groups: Arabian (601769.0002 and 601769.0003), Haitian (601769.0001), North African (601769.0004), and Japanese (601769.0005).
Miller et al. (2001) reported a patient with type II vitamin D-resistant rickets who was compound heterozygous for 2 mutations in the VDR gene (601769.0013, 601769.0014). Similar to patients with mutations in HR (602302), follicular remnants in this patient's skin appeared to possess hair follicle stem cells, some of which generated cutaneous cysts. These and other findings suggested that VDR and HR, which are both zinc finger proteins, may be in the same genetic pathway that controls postnatal cycling of the hair follicle.

**Role in Bone Mineral Density (BMD) and Osteoporosis**

Studies on the role of polymorphisms in the VDR gene in the determination of bone mineral density have been conflicting. Most of the studies (see below) identified the restriction fragment length polymorphisms (RFLPs) Bb, Tt, Aa, and Ff, as defined by the endonucleases BsmI, TaqI, and Apal, FokI, respectively. The lowercase allele contains the restriction site, whereas the uppercase allele does not.

Calcitriol, the active hormonal form of vitamin D, acts through the vitamin D receptor and a specific vitamin D-responsive element to induce the synthesis of osteocalcin (BGLAP; 112260), the most abundant noncollagenous protein in bone. In studies of twins, variation in serum osteocalcin levels was shown to have a major genetic component (Kelly et al., 1991) and to be closely correlated with the genetic diversity in bone density (Pocock et al., 1987). Morrison et al. (1992) presented evidence suggesting that VDR polymorphisms may influence serum levels of osteocalcin.

Among 311 healthy women from Sydney, 207 of whom were postmenopausal, Morrison et al. (1994) found an association between the BB VDR genotype and lower bone mineral density. However, Hustmyer et al. (1994) found no relationship between several VDR polymorphisms and bone mineral density at spine, femur, and forearm among 86 monozygotic and 39 dizygotic adult female twin pairs. In Korea, Lim et al. (1995) found that no patients with osteoporosis had the BB genotype. In a study in the northeast of Scotland, Houston et al. (1996) found that individuals with the BB genotype had a higher femoral neck bone density than individuals with the bb genotype, the opposite of the finding in the study of Morrison et al. (1994). Among 44 patients with severe osteoporosis with vertebral compression fractures, Houston et al. (1996) found no association with the VDR genotype.

Garnero et al. (1996) found no relationship between VDR genotype and bone mass, bone turnover, or bone loss among 268 untreated postmenopausal women. Ensrud et al. (1999) found no association between VDR genotype and fracture risk among 9,704 women aged 65 years or older.

Among a group of prepubertal American girls of Mexican descent, Sainz et al. (1997) found that girls with the aa and bb genotypes had 2 to 3% higher femoral bone density and an 8 to 10% higher vertebral bone density than girls with AA and BB genotypes. However, there was no association between the cross-sectional area of the vertebrae or the cross-sectional or cortical area of the femur and the vitamin D receptor genotype. Riggs (1997) quoted a remark by Charles Dent of University College, London, that 'senile osteoporosis is a pediatric disease.'

Among healthy prepubertal white Australian children aged 7 years, Tao et al. (1998) found that females homozygous for the t Taq1 allele had lower BMD than TT homozygotes in certain bone regions; tt homozygotes were also significantly shorter and lighter. These effects were not observed in males. The authors suggested that the VDR may play a more important role in trabecular bone than in cortical bone, and that VDR allelic variation might
be responsible for some of the variation in BMD and postnatal growth in prepubertal girls.

In a group of men, Ferrari et al. (1999) found that BB homozygotes had significantly lower BMD only in subjects also carrying the f allele at the VDR 5-prime polymorphic site (FokI). Serum PTH levels were significantly higher in the BB genotype at baseline and remained so under either a low or a high calcium-phosphorus diet. Moreover, on the low calcium-phosphorus diet, BB subjects had significantly decreased tubular Pi reabsorptive capacity and plasma Pi levels. The authors emphasized the importance of identifying multiple single-base mutation polymorphisms, and suggested a role for environmental/dietary factor interactions with VDR gene polymorphisms in peak bone mineral mass in men.

Uitterlinden et al. (2001) found that a haplotype represented by polymorphisms in the VDR gene and the presence of the COL1A1 gene Sp1-binding site polymorphism 2046G-T (120150.0051) exhibited a combined influence on osteoporotic fracture risk, independent of BMD.

Among 426 Italian postmenopausal women, Gennari et al. (1998) found an association between certain VDR polymorphisms and lumbar spine BMD as well as the development of osteoporosis. Colin et al. (2003) studied the combined influence of polymorphisms in both the estrogen receptor gene (ESR1; 133430) and the VDR gene on the susceptibility to osteoporotic vertebral fractures in 634 women aged 55 years and older. Three VDR haplotypes (1, 2, and 3) of the BsmI, ApaI, and TaqI RFLPs and 3 ESR1 haplotypes (1, 2, and 3) of the PvuII and XbaI RFLPs were identified. ESR1 haplotype-1 was dose-dependently associated with increased vertebral fracture risk corresponding to an odds ratio of 1.9 (95% CI, 0.9-4.1) per copy of the risk allele. VDR haplotype-1 was also overrepresented in vertebral fracture cases. These associations were independent of BMD.

Nejentsev et al. (2004) studied population differences in single-nucleotide polymorphisms (SNPs) of the VDR gene. Fang et al. (2005) determined sequence variation across the major relevant parts of VDR, including construction of linkage disequilibrium blocks and identification of haplotype alleles. They analyzed 15 haplotype-tagging SNPs in relation to 937 clinical fractures recorded in 6,148 elderly whites over a follow-up period of 7.4 years. Haplotype alleles of the promoter region and of the 3-prime untranslated region (UTR) was strongly associated with increased fracture risk. For the 16% of subjects who had risk genotypes at both regions, their risk increased 48% for clinical fractures (P = 0.0002), independent of age, sex, height, weight, and bone mineral density. The population-attributable risk varied between 1% and 12% for each block and was 4% for the combined VDR risk genotypes. Fang et al. (2005) showed further a 30% increased mRNA decay in an osteoblast cell line for a construct carrying the 3-prime-UTR risk haplotype (P = 0.02). This comprehensive candidate gene analysis demonstrated that the risk allele of multiple VDR polymorphisms results in lower VDR mRNA levels. This could impact the vitamin D signaling efficiency and might contribute to the increased fracture risk observed for these risk haplotype alleles.

In a multicenter large-scale association study of over 26,000 individuals enrolled from 9 European teams, Uitterlinden et al. (2006) found no association between bone mineral densities at the lumbar spine and femoral neck or fracture risk and the FokI, BsmI, ApaI, or TaqI VDR polymorphisms. There was a modest risk reduction (9%) for vertebral fractures associated with the Cdx2 promoter A allele (rs11568820).

Garnero et al. (2005) investigated the relationships between VDR genotypes and fracture
risk. A total of 589 postmenopausal women (mean age, 62 years) were followed prospectively during a median (interquartile) of 11 (1.1) years. VDR allele B was significantly and dose dependently overrepresented in women who fractured, including 34 and 86 women with first incident vertebral and nonvertebral fragility fractures, respectively. This corresponded to an odds ratio of 1.5 (95% confidence interval, 0.95-2.40) for heterozygous carriers (bB, n = 286) and 2.10 (95% confidence interval, 1.16-3.79) for homozygous carriers (BB, n = 90) of the B allele, compared with women with the bb genotype (n = 213). The authors concluded that VDR genotypes are associated with the risk of fracture in postmenopausal women independently of BMD, rate of postmenopausal forearm BMD loss, bone turnover, and endogenous hormones.

Role in Height and Overall Growth

Among 589 healthy 2-year-old infants, Suarez et al. (1997) found that homozygous BB girls had higher length, weight, and body surface area, and inversely, BB boys had lower weight, body mass index, and body surface area, than their respective bb counterparts. As a result, gender-related differences were observed in Bb and bb, but not in BB populations. These associations with VDR genotype were also observed at birth and at 10 months of age in the longitudinal analysis of 145 selected full-term babies homozygous for the BsmI polymorphism. The authors concluded that the VDR genotype may influence intrauterine and early postnatal growth.

Among 90 healthy Caucasian males, Lorentzon et al. (2000) found that boys with the BB VDR genotype were shorter at birth and grew less from birth until after puberty than their Bb and bb counterparts. The BB boys had lower bone area of the humerus, femur, and total body (p less than 0.05) than the Bb and bb boys; however, the VDR polymorphisms were not related to BMD at any site. The authors concluded that a prediction model including parental height, birth height, birth weight, and VDR alleles could predict up to 39% of the total variation in adult height in their study population. The VDR allelic variants alone contributed to 8% of the total variation. See STQTL3 (606257).

In a study of 1,873 white subjects from 406 nuclear families, Xiong et al. (2005) found within-family associations with height at BsmI and TaqI loci (p = 0.048 and 0.039, respectively). Analyses based on BsmI/TaqI haplotypes showed linkage (p = 0.05) and association (p = 0.001) with height. The bT haplotype had the most significant and consistent total and within-family associations (p = 0.0006 and 0.033, respectively), and subjects with the bT haplotype were an average of 1% (1.6 cm) taller than those without it (p = 0.003). The authors noted that this association might be female-specific and influenced by menstrual status. Xiong et al. (2005) suggested that VDR may be linked to and associated with adult height variation in white populations.

Role in Hyperparathyroidism

Among 206 Caucasian patients with sporadic primary hyperparathyroidism (see 145000), Carling et al. (1997) found that the VDR b, a, and T alleles were overrepresented in 100 menopausal females with sporadic hyperparathyroidism equivalent. Hyperparathyroidism appeared to be unrelated to the VDR polymorphisms in patients with hyperparathyroidism of multiple endocrine neoplasia type I (MEN1; 131100) and patients with hyperparathyroidism of uremia. By in vitro studies of parathyroid adenomas, Carling et al. (1997) found an association between calcium-mediated PTH secretion and inhibition suppression and VDR genotype. Carling et al. (1998) found that parathyroid tumors from patients homozygous for the VDR b, a, or T alleles showed significantly lower VDR and higher PTH mRNA levels than those from patients with BB, AA, or tt genotypes (p less than
0.0001-0.02), whereas those from heterozygotes had intermediate values. A similar discrepancy was found when comparing the baT and non-baT haplotypes (0.042 +/- 0.005 vs 0.064 +/- 0.004 for VDR; 34.4 +/- 3.7 vs 21.6 +/- 2.2 for PTH; both p less than 0.005). The authors concluded that the lower VDR mRNA levels associated with the b, a, and T alleles may affect the calcitriol-mediated control of parathyroid function and thereby contribute to the development of sporadic primary hyperparathyroidism.

**Correa et al. (1999)** found no association between the VDR FokI polymorphism and the development of sporadic primary hyperparathyroidism among 182 postmenopausal women compared to controls. There were no significant associations with age, serum calcium, serum PTH, BMD, or parathyroid tumor weight. The authors concluded that the FokI polymorphism has at most a minor pathogenic importance in the development of the disorder.

**Other Disease Associations**

**Uitterlinden et al. (1997)** found overrepresentation of 1 VDR haplotype and radiographic osteoarthritis and osteophytes at the knee. Adjustment for bone density at the femoral neck did not change these results, indicating that the association was not mediated by bone density. The authors raised the possibility of linkage disequilibrium with the closely situated COL2A1 gene, which encodes cartilage collagen.

Among 104 Korean patients with psoriasis (177900), **Park et al. (1999)** found a significant increase in the frequency of the VDR A polymorphism compared to controls. This tendency was more marked in early-onset psoriasis. Derived allele frequencies on the basis of Hardy-Weinberg equilibrium for A and a were 0.317 and 0.683 in the psoriasis group and 0.168 and 0.832 in the control group, respectively, while in the early-onset group, A increased to 0.354.

**Ban et al. (2000)** presented evidence suggesting an association between the VDR B polymorphism and Japanese patients with Graves disease (275000).

**Motohashi et al. (2003)** found a significantly higher frequency of the VDR B allele among 203 patients with acute onset of type I diabetes (222100) compared with 222 controls (p = 0.0010).

**Selvaraj et al. (2004)** presented evidence suggesting that polymorphisms in the VDR gene may predispose to spinal tuberculosis (see 607948).

**ANIMAL MODEL**

**Yoshizawa et al. (1997)** found that VDR-null mice displayed no defect in development and growth before weaning, irrespective of reduced expression of vitamin D target genes. After weaning, however, mutants failed to thrive, with appearance of alopecia, hypocalcemia, and infertility, and bone formation was severely impaired as a typical feature of vitamin D-dependent rickets type II. Unlike humans with this disease, most of the VDR-null mice died within 15 weeks after birth, and uterine hypoplasia with impaired folliculogenesis was found in female reproductive organs. These defects, such as alopecia and uterine hypoplasia, were not observed in vitamin D-deficient animals. Uterine hypoplasia was shown to be due to lack of estrogen synthesis in the mutant ovaries; the uterus in these animals responded normally to administration of estrogen. Male reproductive organs appeared normal in VDR-null mice. Uterine hypoplasia, infertility, and early lethality are not pronounced in patients with vitamin D-dependent rickets type II, possibly because of therapy with calcium.
supplements. The higher content of calcium in murine milk than in human milk may keep serum calcium levels normal, thereby ensuring normal growth of VDR-null mice before weaning. The findings of Yoshizawa et al. (1997) established a critical role for VDR in growth, bone formation, and female reproduction in the postweaning stage.

The active metabolite of vitamin D, 1,25(OH)2D3, modulates the immune response in Th1-related diseases. Using an experimental allergic asthma model, Wittke et al. (2004) found that, apart from upregulation of 2 Th2-related genes, 1,25(OH)2D3 had no affect on asthma severity in wildtype mice. Asthma-induced Vdr-deficient mice, however, failed to develop airway inflammation, airway hyperresponsiveness, or eosinophilia, despite high IgE concentrations and elevated Th2 cytokines. Wittke et al. (2004) suggested that the vitamin D endocrine system has an important role in the development of Th2-driven inflammation in the lung.

During development and postnatal growth of the endochondral skeleton, proliferative chondrocytes differentiate into hypertrophic chondrocytes, which subsequently undergo apoptosis and are replaced by bone. Donohue and Demay (2002) found that Vdr-null mice who developed rickets had expansion of hypertrophic chondrocytes due to impaired apoptosis of these cells. Sabbagh et al. (2005) showed that institution of a rescue diet that restored mineral ion homeostasis in Vdr-null mice prevented the development of rachitic changes, indicating that mineral ion abnormalities, not ablation of the Vdr gene, were the cause of impaired chondrocyte apoptosis. Similarly, 'Hyp' mice with rickets due to mutation in the Phex gene (300550) also showed impaired apoptosis of hypertrophic chondrocytes, and the decreased apoptosis was correlated with hypophosphatemia. Wildtype mice rendered hypercalcemic and hypophosphatemic by dietary means also developed rickets. In vitro studies showed that the apoptosis was mediated by caspase-9 (CASP9; 602234). Sabbagh et al. (2005) concluded that hypophosphatemia was the common mediator of rickets in these mice. The findings indicated that normal phosphorus levels are required for growth plate maturation and that circulating phosphate is a key regulator of hypertrophic chondrocyte apoptosis.

Masuyama et al. (2006) generated mice with conditional inactivation of Vdr in chondrocytes. Growth-plate chondrocyte development was not affected by lack of Vdr, but vascular invasion was impaired, and osteoclast number was reduced in juvenile mice, resulting in increased trabecular bone mass. Vdr signaling in chondrocytes directly regulated osteoclastogenesis by inducing Rankl (TNFSF11; 602642) expression. Mineral homeostasis was also affected in mutant mice. In vivo and in vitro analysis indicated that Vdr inactivation in chondrocytes reduced expression of Fgf23 (605380) by osteoblasts and consequently led to increased renal expression of 1-alpha-hydroxylase (CYP27B1) and sodium/phosphate cotransporter type IIA (SLC34A1; 182309). Masuyama et al. (2006) concluded that VDR signaling in chondrocytes is required for timely osteoclast formation during bone development and for endocrine action of bone in phosphate homeostasis.

Froicu et al. (2006) compared mice lacking Il10 (124092), which develop inflammatory bowel disease (IBD; see 266600), with double-knockout (DKO) mice lacking Il10 and Vdr. They observed normal thymic development and peripheral T-cell numbers in DKO mice up to 3 weeks of age. However, following onset of IBD, the thymus became dysplastic with reduced cellularity and increased apoptosis. Spleen weight increased due to red blood cell accumulation, but there was a 50% reduction in lymphocytes. In contrast, mesenteric lymph nodes of DKO mice were enlarged and had increased lymphocyte numbers. DKO T cells were hyporesponsive. RT-PCR detected overexpression of inflammatory cytokines (e.g., IL1B; 147720) in DKO colon. Froicu et al. (2006) concluded that Vdr expression is required for T-cell control of inflammation in Il10-deficient mice.
ALLELIC VARIANTS
(selected examples)

.0001 VITAMIN D-DEPENDENT RICKETS, TYPE II [VDR, GLY33ASP]

In 2 affected sisters from a black Haitian family with vitamin D-dependent rickets type II (277440), Hughes et al. (1988) identified a G-to-A transition in exon 2 of the VDR gene, resulting in a gly30-to-asp (GLY30ASP) substitution near the tip of the first zinc finger. Based on corrected sequencing, the mutation is gly33 to asp.

.0002 VITAMIN D-DEPENDENT RICKETS, TYPE II [VDR, ARG73GLN]

In 2 affected brothers from an Arab family living in the Middle East with vitamin D-dependent rickets type II (277440), Hughes et al. (1988) identified a mutation in the VDR gene, resulting in an arg70-to-gly (ARG70GLY) substitution at the tip of the second zinc finger of the vitamin D receptor. Based on corrected sequencing, the mutation is arg73 to gln.

.0003 VITAMIN D-DEPENDENT RICKETS, TYPE II [VDR, TYR292TER]

In 4 affected children from 3 related Middle Eastern Arabic families with a classic form of vitamin D-dependent rickets type II (277440) and absence of detectable binding of vitamin D to the vitamin D receptor in cultured fibroblasts or lymphoblasts, Ritchie et al. (1989) identified a 970C-A transversion in exon 7 of the VDR gene, resulting in a tyr292-to-ter (Y292X) substitution. The Y292X mutation caused a truncation of the VDR protein, thereby deleting a large portion of the steroid hormone-binding domain (amino acids 292-424). The 4 parents tested showed both wildtype and mutant alleles. Also see Malloy et al. (1990).

.0004 VITAMIN D-DEPENDENT RICKETS, TYPE II [VDR, ARG77GLN]

In 2 unrelated patients with vitamin D-dependent rickets type II (277440), Sone et al. (1990) identified a homozygous 327G-A transition in exon 3 of the VDR gene, resulting in an arg77-to-gln (R77Q) substitution at a highly conserved residue. In vitro functional expression studies showed that the R77Q mutant receptor bound 1,25-dihydroxyvitamin D3 with normal affinity, but displayed weak affinity for the nuclear fraction and for heterologous DNA. Significantly, the protein was inactive in promoting transcription in a cotransfection assay using a chloramphenicol acetyltransferase gene reporter fused downstream of the VDR-inducible osteocalcin gene promoter-enhancer. The patients were of North African ancestry.

.0005 VITAMIN D-DEPENDENT RICKETS, TYPE II [VDR, ARG47GLN]

Takeda et al. (1989) described 2 sibs, children of first-cousin parents, with vitamin D-dependent rickets with alopecia (277440). In these 2 sibs and in another patient with VDDR type II, Saijo et al. (1991) identified a 140G-A transition in exon 3 of the VDR gene, resulting in an arg47-to-gln (R47Q) substitution between 2 zinc fingers. The affected residue is conserved in all steroid hormone receptors. Single-strand conformation polymorphism analysis of amplified DNA confirmed that all 3 patients were homozygous and that parents from 1 family were heterozygous carriers.

.0006 VITAMIN D-DEPENDENT RICKETS, TYPE II [VDR, GLN149TER]
In a child of Middle Eastern origin with vitamin D-dependent rickets type II (277440), Kristjansson et al. (1993) identified a C-to-T transition in the VDR gene, resulting in a gln149-to-ter (Q149X) substitution in the hinge region of the protein. The child was born of consanguineous parents. Functional expression analyses showed that the Q149X mutant receptor was unable to induce transcription of the osteocalcin hormone gene response element at low levels of vitamin D.

**0007 VITAMIN D-DEPENDENT RICKETS, TYPE II [VDR, ARG271LEU]**

In a child of Middle Eastern origin with vitamin D-dependent rickets type II (277440), Kristjansson et al. (1993) identified a G-to-T transversion in the VDR gene, resulting in an arg271-to-leu (R271L) substitution in the steroid-binding domain of the receptor. Functional expression studies showed that although the R271L mutation was unable to induce transcription of the osteocalcin hormone gene response element at low levels of vitamin D, it showed normal transcription responses in the presence of 1,000-fold higher vitamin D concentrations than needed for the wildtype receptor. This showed that arginine-271 directly affects the affinity of VDR for its ligand, and its conversion to leucine decreases its affinity for vitamin D by a factor of 1,000. Arginine-271 is located immediately 3-prime to a 30-amino acid segment that is conserved among members of the steroid/thyroid/retinoid hormone receptor superfamily.

**0008 VITAMIN D-DEPENDENT RICKETS, TYPE II [VDR, GLY46ASP ]**

In a Saudi Arabian child with vitamin D-resistant rickets type II (277440) with consanguineous parents, Lin et al. (1996) identified a G-to-A transition in exon 2 of the VDR gene, resulting in a gly46-to-asp (G46D) substitution. Functional expression studies showed that the mutant receptor displayed normal binding affinity for 1,25-(OH)2D3, but had reduced affinity for DNA binding. The mutant VDR was unable to activate gene transcription in cells treated with up to 100 nmol/L of 1,25-(OH)2D3. Thus this mutation, which occurs in the first zinc finger of the DNA-binding domain of the receptor, blocks 1,25-(OH)2D3 action.

**0009 VITAMIN D-DEPENDENT RICKETS, TYPE II [VDR, HIS305GLN]**

Van Maldergem et al. (1996) reported an 8.5-year-old Turkish boy, born of first-cousin parents, who had 3 different disorders: congenital lipoatrophic diabetes (269700), persistent Mullerian ducts (261550), and vitamin D-dependent rickets type II (277440). In this boy, Malloy et al. (1997) identified a homozygous mutation in the VDR gene, resulting in a his305-to-gln (H305Q) substitution in the ligand-binding domain of the vitamin D receptor. The mutation caused hereditary vitamin D-resistant rickets due to decreased affinity for 1,25(OH)2D3. The disorder could be effectively treated with extremely high doses of hormone. As pictured by Van Maldergem et al. (1996) in their Figure 2, the patient did not have alopecia but was hirsute, with hypertrichosis of the face and acanthosis nigricans and pachydermia in the axillae. The hands suggested acrogeria, and in general the patient had a prematurely aged appearance.

**0010 VITAMIN D-DEPENDENT RICKETS, TYPE II [VDR, ILE314SER ]**

In a patient with vitamin D-dependent rickets type II (277440), Whitfield et al. (1996) identified a mutation in the VDR gene, resulting in an ile314-to-ser (I314S) substitution in the hormone-binding domain of the protein. The mutation caused decreased 1,25-(OH)2D3-dependent transactivation of the VDR and impaired heterodimeric interaction with the retinoid X receptor (RXR; 180245). However, the transactivation ability of the I314S mutant
receptor could be partially restored by providing excess 1,25-(OH)2D3; clinically, the patient had a nearly complete response to pharmacologic doses of a vitamin D derivative.

**0011 VITAMIN D-DEPENDENT RICKETS, TYPE II [VDR, ARG391CYS]**

In a patient with vitamin D-dependent rickets type II (277440), Whitfield et al. (1996) identified a mutation in the VDR gene, resulting in an arg391-to-cys (R391C) substitution in the hormone-binding domain of the protein. The mutation caused decreased 1,25-(OH)2D3-dependent transactivation of the VDR and impaired heterodimeric interaction with the retinoid X receptor (RXR; 180245). The patient responded only partially to pharmacologic doses of a vitamin D derivative.

**0012 VITAMIN D-DEPENDENT RICKETS, TYPE II [VDR, ARG30TER]**

In affected patients from a Brazilian family with vitamin D-dependent rickets type II with alopecia (277440), Mechica et al. (1997) identified a homozygous 88C-T transition in exon 2 of the VDR gene, resulting in an arg30-to-ter (R30X) substitution in the first zinc finger of the DNA-binding domain, truncating the VDR by 397 residues. The mutation occurred at a CpG dinucleotide. The propositus, a 12-year-old boy born to first-cousin parents, had early-onset rickets, total alopecia, convulsions, hypocalcemia, secondary hyperparathyroidism, and elevated 1,25-dihydroxyvitamin D3 serum levels. His younger sister also developed clinical and biochemical features of the disorder at 1 month of age but died at 4 years of age.

Zhu et al. (1998) described a C-to-T transition at nucleotide 218 (as opposed to nucleotide 88 cited by Mechica et al., 1997) of the VDR cDNA of a French Canadian boy with vitamin D-dependent rickets type II born to nonconsanguineous parents. The single-base substitution changed the codon for arginine (CGA) to an opal stop codon (TGA), resulting in the truncation of the VDR protein at amino acid 30. The result was truncation of 398 amino acids including most of the zinc fingers as well as the entire ligand-binding domain. Both parents were heterozygous for the mutant allele. The child showed early-onset rickets, hypocalcemia, secondary hyperparathyroidism, and elevated 1,25-dihydroxyvitamin D levels as well as total alopecia. (The other stop codons are referred to as amber (TAG) and ochre (TAA). See 141900.0312 for an account of the history of this colorful system of designation.)

**0013 VITAMIN D-DEPENDENT RICKETS, TYPE II [VDR, 1-BP DEL, 366C ]**

In a patient with vitamin D-dependent rickets type II with alopecia (277440), Miller et al. (2001) identified compound heterozygosity for 2 mutations in the VDR gene: a 1-bp deletion (366delC) in exon 4, resulting in premature termination, and a 985G-A transition in exon 8, resulting in a glu329-to-lys (E329K; 601769.0014) substitution. Miller et al. (2001) characterized the alopecia associated with the disorder as clinically and pathologically indistinguishable from that seen in generalized atrichia with papular lesions (209500).

**0014 VITAMIN D-DEPENDENT RICKETS, TYPE II [VDR, GLU329LYS ]**

See 601769.0013 and Miller et al. (2001).

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