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Molecular Epidemiology of Vitamin D Receptor Gene Variants

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INTRODUCTION

The vitamin D receptor (VDR) is a ligand-activated transcription factor that mediates the genomic effects of 1,25-dihydroxyvitamin D in a wide variety of tissues. The gene encoding the VDR is located on chromosome 12q and has several common allelic variants. The individual allelic variants and their haplotypes have been widely studied as markers of susceptibility to osteoporosis, a prevalent metabolic bone disease characterized by reduced bone mass and a resultant increased susceptibility to fracture. More recent attention has focused on the possible role of *VDR* gene variation in the development of other diseases, including breast and prostate cancer, osteoarthritis, atherosclerotic coronary artery disease, diabetes, primary hyperparathyroidism, susceptibility to infection, and psoriasis. In this paper, we review the evidence for a role of common molecular variation in the *VDR* gene in osteoporosis and other diseases and discuss areas in need of further investigation.

VITAMIN D RECEPTOR GENE

Genomic organization

The VDR belongs to the steroid and thyroid hormone receptor family of ligand-activated transcription factors. The VDR mediates the effects of 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) on gene expression (1). The gene encoding the VDR is located on chromosome 12cen-q12 (2), contains 14 exons (3), and spans approximately 75 kilobases of genomic DNA (4). Exons IA through IF encode the 5′ untranslated region, exons II and III encode the DNA-binding domain, and exons IV-IX encode the ligand-binding region (3, 5). The expression of the human VDR is under complex transcriptional control by multiple tissue-specific promoters (3).

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Abbreviations: CI, confidence interval; $1,25(OH)_2D$, 1,25-dihydroxyvitamin D; mRNA, messenger RNA; PTH, parathyroid hormone; SD, standard deviation; TDT, transmission disequilibrium test; VDR, vitamin D receptor.

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Allelic variants

At least 22 unique loss-of-function mutations in the *VDR* gene have been reported (6, 7). Single nucleotide changes producing amino acid substitutions in the DNA- and ligand-binding domains are the predominate type of mutation found (6). Less frequent mutations, including premature stop codons, cryptic splice sites, and a partial gene deletion, have also been described (6, 8, 9). These mutations cause hereditary vitamin D-resistant rickets, a rare autosomal recessive disease resulting from target organ resistance to $1,25(OH)_2D$ (6). An updated database of rare *VDR* mutations can be found on the Human Gene Mutation Database (http://www.uwcm.ac.uk/uwcm/mg/hgmd0.html).

Several common allelic variants have also been identified in the *VDR* gene and are the focus of the present review (figure 1). The presence of a T/C transition polymorphism (ATG to ACG) at the first of two potential translation initiation sites in exon II (10) has been defined using the *Fok*I restriction endonuclease (11). Individuals with the C allele (designated F) initiate translation at the second ATG site and lack the three NH_2– terminal amino acids of the full-length VDR protein (12). In contrast, individuals with the T allele (designated f) initiate translation at the first ATG site and synthesize the full-length (427 amino acids) VDR protein (12). The ff genotype frequency was 4 percent among African Americans and 13–18 percent among Asians and Caucasians in one report (13).

*Bsm*I (14) and *Apa*I (15) restriction site polymorphisms occur in the intron separating exons VIII and IX (figure 1). A T/C nucleotide substitution (ATT to ATC) leading to a synonymous change at codon 352 (isoleucine) in exon IX has also been described (16) and is detected by the restriction enzyme *Taq*I. The *Bsm*I and *Fok*I alleles do not appear to be in linkage disequilibrium (11, 13, 17, 18), whereas a strong concordance exists between the absence of the *Bsm*I (B allele) and presence of the *Taq*I (t allele) sites (19), and these sites show significant linkage disequilibrium with the *Apa*I polymorphism. Hustmyer et al. (16) detected a rare third allele by *Apa*I digestion in African Americans, but more recent PCR-based typing of the *Apa*I polymorphism has not detected the presence of this allele. Morrison et al. (14) reported a fifth restriction site polymorphism, detected by southern blot analysis of *Eco*RV digested genomic DNA probed with a *VDR* complementary DNA probe, and Hustmyer et al. (16) showed that the frequency of the two alleles at this locus varied among Caucasians, African Americans, and Asians. The molecular basis of this polymorphism is unknown, and recent studies using PCR-based

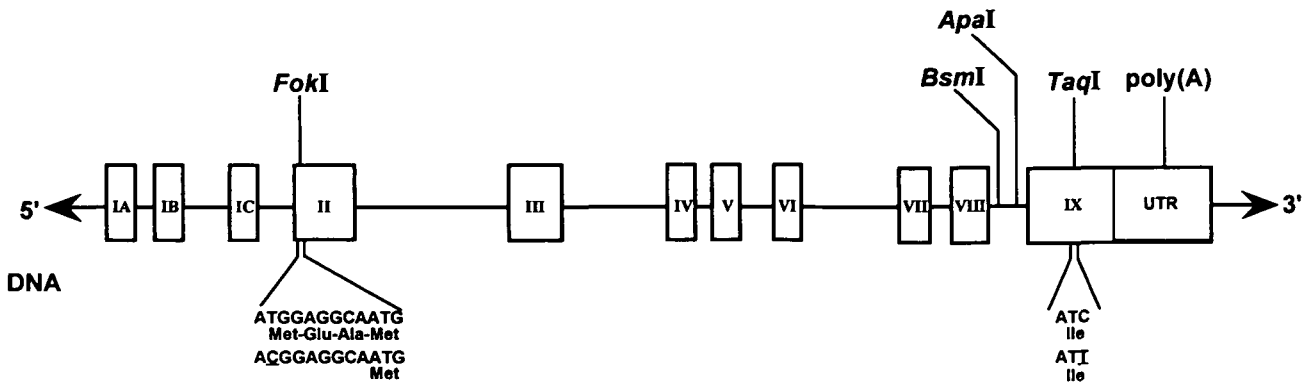

FIGURE 1. Schematic diagram of the human vitamin D receptor gene and the location of its naturally occurring polymorphisms.

assays have not genotyped this variation. Because few studies of the *Eco*RV polymorphism are available, we have not reviewed this variant.

The *Bsm*I bb genotype frequency was 2 percent among Asians, 5 percent among African Americans, and 17 percent among Caucasians in a meta-analysis (20). The frequency of *Taq*I genotypes in these populations is similar to *Bsm*I genotype frequencies. The *Apa*I AA genotype frequency is 9 percent among Asians (21), 28 percent among Caucasians (22), and 44 percent among African Americans (23).

A mononucleotide repeat [(A)n] polymorphism that varies in length from 13 to 24 adenosines (12 alleles) (poly(A)) occurs in the 3′ untranslated region of the VDR gene (24). The distribution of allele size is bimodal, such that individuals can be classified as having short (A_{13}-A_{17}) or long (A_{18}-A_{24}) alleles (24). The frequency of short alleles in one study was 5–10 percent among Asians, 32 percent among African Americans, and 41 percent among Caucasians (24). The longest alleles (A_{23}-A_{24}) in that study were found only among African Americans, whereas the shortest allele (A_{13}) was found only among Hispanics (24).

Linkage disequilibrium has been reported between the poly(A) and *Bsm*I alleles, such that the short poly(A) and *Bsm*I B alleles (BS haplotype) and the long poly(A) and *Bsm*I b alleles (bL haplotype) are coupled. Linkage disequilibrium is nearly complete among Caucasian Americans (disequilibrium coefficient, 0.96) and Japanese Americans (disequilibrium coefficient, 0.90), but is less pronounced among African Americans (disequilibrium coefficient, 0.53) (24). Poly(A) and *Fok*I alleles do not appear to be in linkage disequilibrium (25, 26).

VITAMIN D RECEPTOR ALLELIC VARIANTS AND OSTEOPOROTIC RISK

Early infant growth and skeletal size

Vitamin D regulates the differentiation and proliferation of cells responsible for skeletal and overall somatic growth (27), and mice lacking the *VDR* gene experience severe growth retardation (28). Several reports demonstrate that common *VDR* gene variants are associated with early infant growth and skeletal size, although these findings have been inconsistent, possibly because of the relatively small sample size of these studies. For example, girls aged 7 years with the TT genotype were 3.9 kg heavier ($p = 0.03$) and 4.1 cm taller ($p = 0.008$) than were those with the tt genotype in one study (29), whereas in another self-reported body weight at age 1 year was significantly *lower* among adult women with the TT genotype (30). Differences in age or ethnicity might also explain the conflicting findings of these studies.

Girls aged 2 years with the BB genotype were taller ($p < 0.05$) and heavier ($p < 0.01$) than were girls with the bb genotype (31). In contrast, boys with the BB genotype weighed less ($p < 0.01$) than those with the bb genotype, an effect that was also observed at birth (31). Lower height at birth, decreased growth during adolescence, and shorter adult stature has been confirmed among boys with the BB genotype (32). The decreased body size among male infants with the BB genotype in another study was confined to those who were also homozygous for a PvuII site in intron one of the estrogen receptor gene (33). Although less well studied, the *Fok*I variant has also been associated with stature in Japanese girls (34). These data raise the possibility that molecular variation in the *VDR* gene influences intrauterine, early postnatal, and adolescent growth and that the effect may be modified by allelic variation in other growth-regulating genes and by gender.

Bone mass, postmenopausal bone loss, and osteoporotic risk

Growth in infancy is associated with skeletal size and mass in adulthood (35) and may contribute to the development of osteoporosis, a prevalent metabolic bone disease characterized by low bone mass and a resultant increased susceptibility to fracture. The risk of fracture increases by as much as 2.5- to 3.0-fold with each standard deviation (SD) reduction in bone mass (36). Bone mass and osteoporotic risk are under strong genetic control (37), and the *VDR* gene has been studied widely as an osteoporosis candidate gene.

Most reports have examined the association between the *Bsm*I polymorphism and bone mass. An initial study by

Morrison et al. (19, 20, 38) documented about 0.5 SD or 8 percent lower ($p < 0.01$) spine bone mass in a sample of pre- and postmenopausal Australian women with the BB compared with bb genotypes. These findings were confirmed in some, but not all, subsequent studies (37). In a meta-analysis of 16 reports published through July 1996 and involving over 3,600 subjects, the BB genotype was associated with 0.2 SD or 2.4 percent lower hip ($p = 0.03$) and 0.2 SD or 2.5 percent lower spine ($p = 0.06$) bone mass compared with the bb genotype (20). More recently, Gong et al. (39) performed a qualitative meta-analysis of 75 reports and abstracts published up to January 1997 and involving more than 14,000 individuals. They concluded that *VDR* alleles (B, A, t) were associated with lower hip and spine bone mass more often than the expected 5 percent false-positive rate under the null hypothesis (39). Studies were more likely to find a significant association between *VDR* alleles and bone mass among premenopausal than postmenopausal women or pre- and postmenopausal women combined and less likely to find a significant association if they included osteoporotic subjects. This suggests that the major effect of *VDR* genotype may be on peak bone mass rather than on age- or menopause-related bone loss.

Bone mass in the elderly is a product of both peak skeletal mass achieved during the first 3 decades of life and subsequent age- and menopause-related rates of bone loss. Although less well studied, allelic variants of the *VDR* gene have not been consistently associated with rates of bone loss among postmenopausal women. Three (40–42) of eight studies (22, 23, 40–45) have found significantly greater postmenopausal bone loss associated with the B allele. Three studies did not find a significant association between the *Taq*I polymorphism and bone loss (22, 44, 46), although we documented a significantly greater rate of hip bone loss among older (≥70 years), but not younger (<70 years), African-American women with the tt genotype (23). Most studies had fewer than 100 subjects and less than 2 years of follow-up and may have lacked adequate statistical power to detect differences between genotypes. For example, a more than twofold greater rate of spinal bone loss among postmenopausal women ($n = 109$) with the BB or tt genotype did not achieve statistical significance in one study (22). Postmenopausal Mexican-American women with the *Fok*I ff genotype experienced significantly greater hip bone loss compared with women with either the Ff or FF genotypes (11), although this finding was not confirmed in a subsequent study of Caucasian-American women (47).

Two (48, 49) of eight studies (48–55) have demonstrated a significant difference in *VDR* genotype or haplotype distribution between osteoporotic patients and controls. Most studies included fewer than 100 cases, so it is possible that small differences in genotype frequencies were missed. The largest study to date (49) found that the homozygous BAt haplotype was significantly more prevalent among 176 osteoporotic Italian women compared with 144 controls (24 vs. 8 percent, respectively; $p < 0.01$), whereas the homozygous baT haplotype was less common among osteoporotic women (7 vs. 18 percent, respectively; $p < 0.01$).

More recent studies have focused on the *Fok*I variant in exon 2. Initial reports of this polymorphism found 11–12 percent (approximately 1 SD) lower bone mass at the hip and spine in Japanese (12), Mexican-American (11), and Caucasian-American (56) women with the ff compared with FF genotypes. Subsequent reports have not confirmed significant associations between the *Fok*I variant and bone mass, and differences between homozygous genotypes have generally been much smaller (approximately 2–5 percent or <0.3 SD) (13, 17, 18, 57–61). Most studies have lacked sufficient statistical power to detect differences of this magnitude. Moreover, ethnic (genetic) background may modify the effects of this polymorphism (56). There may also be effect modification by unlinked loci (modifier genes) (62) and environmental factors such as dietary calcium intake (42, 63–65) that remain to be fully explored.

The physiologic mechanisms mediating the associations between *VDR* gene variants and bone mass are unclear but are probably due to established actions of vitamin D on calcium homeostasis. For example, $1,25(OH)_2D$ and its receptor mediates active intestinal calcium absorption (66), and calcium absorption has been reduced in subjects with the BB genotype (23, 67, 68) and homozygous BAt haplotype (68, 69). These associations may be more pronounced among subjects with low dietary calcium intake (67). Premenopausal women with the BAt haplotype had 11 percent lower (69) and postmenopausal women had 37 percent lower (68) calcium absorption compared with women with the baT haplotype ($p < 0.05$). Thus, the effect of *VDR* gene variation on calcium absorption may also be modified by age or hormonal status. An additive effect of *Fok*I alleles on calcium absorption has also been demonstrated among children (70). Calcium absorption was 41.5 percent greater in children who were FF than ff homozygotes and was 17 percent greater in heterozygotes (70). However, associations between *VDR* genotype and calcium absorption have not been confirmed in all studies (71–73). Nevertheless, these results suggest that there may be *VDR* genotype-dependent differences in intestinal sensitivity to $1,25(OH)_2D$.

Osteoporotic fracture

There have been relatively few studies of *VDR* gene variants and the risk of osteoporotic fractures (table 1). An ecologic analysis of 14 published studies suggested that higher population frequencies of the TT genotype are associated with lower, age-adjusted hip fracture rates (79), consistent with studies showing that this polymorphism is associated with greater bone mass. Feskanich et al. (74) found a 2.4-fold greater risk (95 percent confidence interval (CI): 1.1, 5.2) of hip fracture associated with the BB compared with the Bb or bb genotypes in a nested case-control study of Caucasian-American women aged 43–69 years. The increased risk of fracture associated with the BB genotype in this study is much greater than that expected based on the small differences in bone mass associated with this polymorphism. Uitterlinden et al. (75) documented a relation between the number of baT haplotypes and the risk of spine and nonspine fractures in a nested

TABLE 1. Summary of studies examining the association between vitamin D receptor genotype or haplotype and osteoporotic fracture

Ethnicity	Age (years)	Gender	Design	No. of cases	No of controls	Results			Comments	Reference no.
						Genotype or haplotype	OR*	95% CI*		
Caucasian	43–69	Female	Case-control (nested)	54 (hip)	108	Bb/bb	1.0	Referent	Cases and controls matched	74
						BB	2.4	1.1, 5.2		
						No. of cases	%	No. of controls (%)		
Caucasian	45–88	Female	Case-control	44 (spine)	44	bb	38	36	No adjustments made	77
						Bb	43	43		
						BB	18	20		
						p = NS*				
						Cases	(%)	Controls (%)		
Caucasian	65	Female	Prospective	19 (nonspine)	30	bb	37	37	No adjustments made	78
						Bb	42	37		
						BB	21	27		
						p = NS				
						baT haplotype (alleles)				
Caucasian	55–80	Female	Case-control (nested)	52 (nonspine)	900	0	1.0	Referent	Similar results for spine and nonspine fracture	75
						1	1 8	1.0, 3.3		
						2	2.6	1.4, 5.0	Association independent of bone mineral density	
						Hip fracture				
Caucasian	>65	Female	Case-cohort (nested)	163 (hip)	622	aaTT	1.0	Referent	Similar results for other fracture types. Adjusted for age and weight	76
				112 (spine)	435	AaTT	0.7	0.4, 1.3		
				174 (other)	322	AaTt	0.9	0.6, 1.5		
						AATt	0.8	0.4, 1.4		
						AAtt	0.9	0.5, 1.5		

* OR, odds ratio; CI, confidence interval; NS, not significant.

case-control study of older Caucasian-European women. The risk of both fractures was 80 percent greater (95 percent CI: 1.0, 3.3) among heterozygous women and 2.6-fold greater (95 percent CI: 1.4, 5.0) among homozygous women. The direction of the association conflicts with that found by Feskanich et al. (74) and suggests that different alleles may be associated with fracture in different populations (i.e., allelic heterogeneity). Interestingly, the increased risk of fracture associated with the baT haplotype was independent of bone mass, raising the possibility that factors other than low bone mass explain the association between *VDR* haplotype and fracture risk (75). Nevertheless, in the largest study to date, we were unable to confirm a relation between the *Taq*I and *Apa*I variants, either alone or in combination, and the incidence of hip, spine, or other fractures in a case-cohort study nested within a prospective study of 9,704 Caucasian-American women aged 65 years and older (76). Analyses stratified by age (<75 vs. ≥75 years), calcaneal bone mass (<0.40 vs. ≥0.40 mg/cm^2), and dietary calcium intake (<640 vs. ≥640 mg/day) produced similar results.

The relation between the *Fok*I variant and fracture risk has been less well studied. Gennari et al. (61) found that the ff genotype was overrepresented among postmenopausal women with vertebral fractures (25 percent) compared with controls (11 percent), equivalent to an odds ratio of 2.6 (95 percent CI: 1.4, 4.9). These findings have not been replicated in other populations yet.

Gene-environment interactions

The risk of osteoporosis associated with *VDR* genotype may be modified by age, diet, and other lifestyle factors. Failing to account for such interactions may mask an association with *VDR* genotype. For instance, an increased risk of hip fracture associated with the BB genotype was greatest among women who were older, leaner, and less active and among those with lower dietary calcium intake in one study (74). Other small clinical trials found that VDR genotype is associated with the bone mass response to vitamin D supplementation (80, 81). Two exercise

intervention studies (82, 83) did not find significant *VDR* genotype differences in changes in bone mass, perhaps because of their small sample size (<35 subjects). Larger trials will be necessary to convincingly demonstrate that *VDR* genotype influences the response to dietary or lifestyle modifications. Nevertheless, research addressing the influence of gene-environment interactions may suggest novel strategies for preventing or delaying the onset of this disease.

Gene-gene interactions

The association between *VDR* gene variation and risk of osteoporosis may also be modified by allelic variation in other candidate genes. For example, Willing et al. (62) found that the *Bsm*I polymorphism alone was not significantly associated with bone mass at the spine among premenopausal Caucasian women. However, bone mass was 15 percent, or more than 1 SD, lower among women with the BB genotype who were also homozygous for the absence of a PvuII variant in intron one of the estrogen receptor alpha gene ($p < 0.05$ for interaction). In another report, a complex interaction between the two-locus *VDR*-estrogen receptor alpha genotype and hormone replacement therapy in modifying calcaneal ultrasound measures was documented (84). These interactions are biologically plausible because estrogen can increase the number and expression of VDR in osteoblast (85, 86) and duodenal mucosa cells (87). The risk of fracture per copy of the baT haplotype was 1.1 (95 percent CI: 0.7, 1.6) among women with the G/G genotype at an Sp1 binding site in the type Iα1 collagen gene and 2.6 (95 percent CI: 1.6, 4.5) among those with the G/T or T/T genotype ($p < 0.05$ for interaction) (75). Thus, the influence of *VDR* genotype on osteoporotic risk may depend on the presence or absence of allelic variants at other unlinked loci.

Summary

Bone mass is under strong genetic control, but the specific genes and allelic variants contributing to bone mass and osteoporotic risk are not well defined (37). The *VDR* gene has been widely studied as an osteoporosis candidate gene during the past several years, with most reports focusing on a *Bsm*I restriction fragment length polymorphism in intron 8. The homozygous absence of this site has been associated with a small decrease (2 percent) in bone mass in a large meta-analysis and with an increase in hip fracture risk in one study, although attempts to replicate these later findings have been unsuccessful. A potentially functional *Fok*I polymorphism in exon 2 has also been associated with modest differences in bone mass in some studies and with vertebral fracture risk in one report, although, again, these findings have been inconsistent. The strength of association with *VDR* polymorphisms has been modified by molecular variation in other genes and other risk factors such as age and dietary calcium intake in some reports. This suggests that *VDR* allelic effects may be context dependent and that there may be larger *VDR* effects in certain subgroups in the population.

VITAMIN D RECEPTOR ALLELIC VARIANTS AND OTHER DISEASES

Cancer

Vitamin D can inhibit cancer cell growth, angiogenesis, and metastasis (88), and recent reports suggest that common *VDR* gene variants may be associated with the risk of prostate and breast cancer. At least 10 published reports have examined the relation between *VDR* allelic variants and prostate cancer (table 2). Initial reports found a 70–80 percent lower risk of prostate cancer associated with the *Taq*I tt genotype (89) or short poly(A) alleles (90). Subsequent studies have been inconsistent and generally have not confirmed an association between these polymorphisms and the overall risk of prostate cancer (91–93, 96, 98). However, associations were stronger for more advanced disease in some reports (90, 91), suggesting that *VDR* allelic variants may influence the progression, rather than initiation, of prostate cancer.

Vitamin D may also play a role in normal prostate growth (99), and one recent study demonstrated an association between the *VDR Bsm*I polymorphism and risk of benign prostatic hypertrophy (97). Thus, inclusion of men with benign prostatic hypertrophy as controls may have masked or attenuated an association between *VDR* polymorphisms and prostate cancer in some studies.

At least seven studies have examined the association between *VDR* allelic variants and breast cancer risk (table 3). An initial report found nearly fourfold greater risk of breast cancer associated with the homozygous presence of the *Bsm*I site among Japanese women (105), which is consistent with the threefold increases in prostate cancer risk among Japanese men with this *VDR* genotype (97). Subsequent reports have demonstrated similar (more than twofold) increases in breast cancer risk among women homozygous for the presence of the *Apa*I (101), *Fok*I (26), or short poly(A) alleles (100), although these findings have not been universal (100, 101), and in one study, the homozygous presence of the *Bsm*I site was associated with a *decreased* risk of breast cancer among Latina women (100). In two studies, an association was found for *VDR* genotype and metastatic, but not overall, disease risk (103, 104), suggesting that *VDR* allelic variants may influence tumor progression rather than development.

Osteoarthritis

Vitamin D receptor allelic variants have also been associated with prevalent osteoarthritis in some studies. The presence of the baT haplotype (106) or T allele (107) was associated with an approximately 2.5-fold increase in the risk of knee osteoarthritis, which was independent of age, body mass index, and bone mass in two case-control studies. This relation was explained largely by an association with osteophytes rather than joint space narrowing in one study (106), suggesting that *VDR* genotype may influence particular features of osteoarthritis. Biologic support for this association comes from studies showing that serum levels of vitamin D are related to the progression of knee osteoarthritis (108) and that

TABLE 2. Summary of studies examining the association between vitamin D receptor genotype and prostate cancer

Ethnicity	No. of cases	No. of controls	Results			Comments	R	e
			Genotype	OR*	95% CI*			
Caucasian	95 consecutive prostatectomy cases identified at hospitals. Age not specified	162 urology clinic patients presenting with BPH* or impotence and no history of cancer other than nonmelanoma skin cancer. Age not specified.	TT/Tt tt	1.0 0.3	Referent 0.1, 0.7	No exposures assessed. Genotype not correlated with age, stage, or age at diagnosis		
Caucasian	57 cases diagnosed between 1991 and 1992 identified by SEER* registry. Mean age = 58 years.	169 controls enrolled in a bladder cancer study. Mean age = 58 years.	LL LS SS	1.0 0.2 0.2	Referent 0.1, 0.8 0.1, 0.8	No exposures assessed Stronger association with advanced cancer.		
Caucasian (90%)	41 cases of fatal, metastatic PCa* (20 hereditary) Mean age at diagnosis = 64 years	41 urology patients who participated in a screening program for PCa. No evidence of PCa on PSA* tests. DRE* and/or needle biopsy Mean age = 62 years.	TT/Tt tt LL/LS SS	1.0 1.4 1.0 1.3	Referent 0.4, 4.5 Referent 0.4, 4.3	No exposures assessed. Similar results for hereditary and non-hereditary cases.		
Caucasian (>95%)	372 cases in the Physicians Health Study ascertained by questionnaire and confirmed by medical chart review. Age 40–84 years.	591 controls selected from the same cohort who had not had a prostatectomy and not developed PCa at the time the case was diagnosed. Cases and controls were matched on age and smoking status. Age, 40–84 years.	bb Bb BB TT Tt tt	1.0 0.9 0.9 1.0 0.9 0.9	Referent 0.7, 1.2 0.6, 1.3 Referent 0.7, 1.3 0.6, 1.4	57% (95% CI, 0.19, 0.98) reduction in risk for the BB vs. bb genotype among men with low 25(OH)D* levels ($p = 0.04$ for interaction for TaqI.		
Caucasian (92%)	77 biopsy-proven cases identified through urology and radiation oncology practices. Age ≥50 years.	183 community controls matched on age, race, and zip code. Men with history of cancer (other than nonmelanoma skin cancer), prostate disease, or prostate surgery were excluded. Age ≥50 years.	TT Tt tt LL LS SS	1.0 0.6 0.9 1.0 0.7 1.0	Referent 0.3, 1.2 0.4, 2.0 Referent 0.3, 1.4 0.4, 2.0	No exposures assessed. Similar results for advanced PCa.		
Caucasian	132 histologically confirmed cases of PCa identified consecutively at two hospitals. Cases were considered sporadic if they did not have an affected first-degree relative and had ≤1 affected distant relative. Mean age = 68 years (range, 46–90 years)	105 controls without evidence of PCa on PSA tests and DRE. Mean age = 71 years (range, 64–86 years).	TT Tt tt LL LS SS	1.0 0.5 1.2 1.0 2.3 1.6	Referent 0.3, 0.9 0.5, 2.7 Referent 1.0, 5.0 0.7, 2.6	No exposures assessed. No association with FokI genotype.		
African-American	151 new diagnosed cases in the Hawaii-Los Angeles Multi-Ethnic cohort were ascertained through linkage to the SEER registry. Mean age ≤67 years.	174 nondiseased cohort members were randomly selected as controls. Mean age = 64 years.	bb Bb BB LL LS SS	1.0 1.0 0.9 1.0 1.4 1.1	Referent 0.5, 2.1 0.4, 1.8 Referent 0.6, 3.1 0.5, 2.4	No exposures assessed. BB genotype associated with a 2.6-fold (1.0, 6.7) greater risk of advanced PCa compared with bb genotype. BsmI genotype not associated with localized PCa.		
Japanese	66 cases. Ascertainment methods not described. Mean age = 68 years (range, 57–84).	60 urology patients without evidence of PCa on PSA tests and DRE. Mean age = 71 years (range, 64–86 years).	TT Tt/tt	1.0 0.8	Referent 0.3, 1.6	No exposures assessed. Men with metastatic disease and t allele had better progression-free survival than men with the T allele.	94	

Japanese	222 histologically confirmed cases treated at community hospitals. Mean age = 72 years.	128 patients admitted to community hospitals because of nonurologic diseases. None had voiding symptoms or prostate enlargement by DRE, and all had normal serum PSA levels. Mean age = 74 years.	bb Bb/BB	1.0 0.3	Referent 0.2, 0.5	No exposures assessed. ApaI and TaqI genotype were not associated with PCa.	97
Japanese	100 patients with biopsy confirmed PCa identified through hospitals. Mean age = 73 years.	202 patients with BPH, PCa excluded by serologic, physical, and/or histologic examination. Mean age = 71 years.	TT Tt tt LL LS SS	1.0 1.0 0.6 1.0 1.0 0.6	Referent 0 6, 1.9 0.2, 2.6 Referent 0.6, 1.9 0.2, 2.6	No exposures assessed. Analyses stratified by stage of disease produced similar results.	98

* OR, odds ratio; CI, confidence interval; BPH, benign prostatic hypertrophy; SEER, Surveillance, Epidemiology, and End Results; PCa, prostate cancer; PSA, prostate-specific antigen; DRE, digital rectal examination; 25(OH)D, 25-hydroxyvitamin D.

vitamin D receptors are expressed in chondrocytes (109), a cellular component of osteophytes (110). In contrast to these findings, the *Taq*I T allele was associated with a *decreased* risk of spine osteoarthritis (111), and the *Bsm*I variant was not significantly associated with hip osteoarthritis (total hip replacement) (112) in other studies. These studies are limited by their cross-sectional design, small sample size, and focus on Caucasian subjects. Prospective studies in larger and more diverse populations are needed to test whether *VDR* genotypes and haplotypes are associated with the incidence and progression of radiographically defined osteoarthritis.

Hyperparathyroidism

The vitamin D receptor mediates the inhibitory effects of vitamin D on parathyroid hormone (PTH) secretion (113) and parathyroid cell proliferation (114, 115). Recent studies suggest that *VDR* gene variants may be associated with primary hyperparathyroidism (116–120), a common disease often caused by benign parathyroid adenoma or parathyroid hyperplasia and accompanied by excessive PTH secretion (121). Carling et al. (116, 118) found that the b, a, and T alleles were significantly more common among patients with primary hyperparathyroidism than among age-matched controls. The estimated risk of primary hyperparathyroidism was 2.5-fold greater (95 percent CI: 1.3, 5.1) among women with the baT haplotype compared with those without this haplotype (118). Consistent with these findings, PTH messenger RNA levels were nearly 60 percent higher among patients with the baT haplotype compared with those with other haplotypes (119). The presence of the *Bsm*I (122, 123) and *Apa*I (124) restriction sites has also been associated with elevated PTH levels in patients with end-stage renal disease, suggesting that *VDR* gene variants may influence the development or severity of secondary hyperparathyroidism in such patients.

Diabetes

Transmission disequilibrium testing in 93 Indian families revealed that the b allele and bT and bAT haplotypes are preferentially transmitted from parents to offspring affected with type I diabetes (125). Insulin secretion was 30–50 percent lower ($p < 0.05$) in nondiabetic Bangladeshi Asians with the bb, aa, or TT genotypes compared with the BB, AA, or tt genotypes, respectively (126). These results are consistent with the presence of vitamin D receptors in pancreatic β-cells (127) and with studies showing that vitamin D deficiency impairs insulin secretion (128) and that vitamin D treatment prevents the development of type I diabetes in the nonobese diabetic mouse model (129).

Coronary artery disease

The risk of prevalent electrocardiogram-confirmed myocardial infarction increased by 20 percent (95 percent CI: 1.0, 1.5) per copy of the baT haplotype in a population-based study of men and women aged 55–80 years (130). This association was independent of traditional risk factors for myocardial infarction, including age, obesity, and serum

TABLE 3. Summary of studies examining the association between vitamin D receptor genotype and breast cancer

Ethnicity	No. of cases	No. of controls	Results			Comments	Reference no.
			Genotype	OR*	95% CI*		
Japanese	60 cases. Age not reported.	120 age-matched controls. Age not reported.	BB/Bb bb	1.0 3.9	Referent 1.6, 9.3	No exposures assessed.	105
African American	102 cases. Age not reported.	155 randomly sampled controls from cohort. Age not reported.	ff/Ff Ff	1.0 0.4	Referent 0.2, 0.7	No exposures assessed.	26
Caucasian	88 consecutive cases recruited through radiation oncology center. 50 were newly diagnosed 38 were recurrent cases. Age not reported.	167 women in an osteoporosis prevention trial in same geographic area as cases. Age not reported.	BB Primary cases bb Metastatic cases bb	1.0 0.9 3.8	Referent 0.4, 1.8 0.9, 15.4	No exposures assessed.	103
Caucasian	135 women previously diagnosed with BrCa* and without a known family history of BrCa were recruited through a pathology department. Mean age = 60 years (range, 31–88 years).	110 women without a personal or family history of any cancer were recruited from the same community. Mean age = 50 years (range, 20–81 years).	AA Aa aa	1.0 1.5 2.5	Referent 0.8, 2.8 1.2, 5.4	No exposures assessed.	101
			Cases (%)		*Controls*		
Caucasian	111 women aged 24–36 years (median, 34) diagnosed with BrCa between 1980 and 1993.	130 female blood donors aged 19–64 years (median, 37 years).	tt Tt TT	16.2 53.2 30.6	17.7 50.8 31 5	No exposures assessed. No overall association with TaqI genotype. TT genotype associated with increased risk of lymph node *metastases* (1.8; 95% CI: 1.3, 2.6).	104
			p = NS*				
Caucasian	951 women with BrCa identified through 2 sources: incident patients attending hospital (mean age = 53 years; range, 29–71); retrospectively ascertained patients identified through cancer registry (mean age = 47 years; range, 25–55 years)	627 randomly selected women from the European Prospective investigation of Cancer (EPIC) cohort. Mean age = 51 years (range, 40–76 years).	tt Tt TT	1 0 1.0 1.9	Referent 0.8, 1.2 0.8, 1.4	No exposures assessed. Similar results for analyses stratified by recruitment source.	102
Latina	143 women with newly diagnosed BrCa ascertained through linkage of the Hawaii Los Angeles *Multi-Ethnic Cohort to the* SEER* registry. Mean age = 65 years (range, 45–75).	300 women without BrCa in cohort were randomly sampled. Mean age = 63 years (range, 45–75 *years*).	BB Bb bb LL LS SS	1.0 0.6 0.4 1.0 1.5 3.2	Referent 0.4, 0.9 0.2, 1.0 Referent 1.0, 2 3 1.5, 6.9	No exposures assessed. No association with FokI genotype.	100

* OR, odds ratio; CI, confidence interval; BrCa, breast cancer; NS, nonsignificant; SEER, Surveillance, Epidemiology, and End Results.

levels of total and high-density lipoprotein cholesterol. Consistent with these findings, patients ($n = 41$) with the bb genotype undergoing open-heart surgery were four times more likely (95 percent CI: 0.8, 22.5, $p = 0.09$) to have severe coronary artery stenosis compared with those with the Bb or BB genotypes (131). Biologic support for these associations comes from studies demonstrating that vitamin D receptors are present in aortic endothelial (132) and vascular smooth muscle (133) cells.

Infectious diseases

The immune system is a well-known target of vitamin D (134), and children with hereditary vitamin D- resistant rickets may have impaired phagocytosis and neutrophil motility and an increased number and severity of infections (135). Moreover, administration of $1,25(OH)_2D$ inhibits growth of *Mycobacterium tuberculosis* in human macrophages and monocytic cells in vitro (136). Bellamy et al. (137) reported that the *Taq*I tt genotype was significantly underrepresented in patients infected with pulmonary tuberculosis (6.6 percent) and hepatitis B (7.3 percent) compared with controls (12 percent and 14 percent, respectively). A smaller, subsequent study also noted a lower frequency of the tt genotype among tuberculosis patients (6 percent) compared with their uninfected contacts (11 percent), although this difference did not achieve statistical significance ($p = 0.49$) (138). However, there was significant interaction between 25-hydroxycholecalciferol status and *VDR* genotype (138). The combination of the TT/Tt genotypes and 25-hydroxycholecalciferol deficiency was associated with a 2.8-fold (95 percent CI: 1.2, 6.5) increased risk of tuberculosis. A similar interaction between the *Fok*I ff genotype and vitamin D status was also observed. Roy et al. (139) also found that the *Taq*I polymorphism is associated with susceptibility to *Mycobacterium leprae* infection in general and also to leprosy type. The estimated risk of tuberculoid leprosy was threefold greater (95 percent CI: 1.5, 7.1) among Bengali subjects with the tt compared with TT genotypes. In contrast, there was a 67 percent increase (95 percent CI: 1.02, 2.75) in the risk of lepromatous leprosy in subjects with the TT compared with tt genotypes. The possibility that common molecular variation in the *VDR* gene makes a broader contribution to host susceptibility to infectious diseases merits further investigation.

Psoriasis

Psoriasis is a chronic skin disease characterized by hyperproliferation of keratinocytes and inflammation (140). The observations that keratinocytes contain receptors for $1,25(OH)_2D$ (141) and that active metabolites of vitamin D inhibit proliferation of these cells (142) prompted recent studies of the association between *VDR* allelic variants and psoriasis (143–145). The frequency of *Apa*I A allele was significantly more common among 104 psoriatic Korean patients (0.317) compared with 104 controls (0.168), equivalent to a 2.4-fold (95 percent CI: 1.3, 4.3) increase in disease risk among subjects with the Aa genotype and fivefold (95 percent CI: 1.3, 19.1) increase in risk among those with the AA genotype (143). The age of onset of psoriasis was 19.1 years in patients with the AA genotype compared with 21.5 years in heterozygous subjects and 29.3 years in those with the aa genotype ($p < 0.05$). However, Mee and Cork (146) did not demonstrate an association between the *Bsm*I polymorphism and psoriasis (175 cases) or response to calcipotriol in 92 patients with chronic psoriasis. Likewise, Kontula et al. (145) were unable to document a difference in *Bsm*I allele and genotype distribution between psoriatic patients who did ($n = 10$) and those who did not ($n = 9$) respond to topical calcipotriol treatment.

Summary

In addition to bone mass and osteoporotic risk, *VDR* polymorphisms have been associated with several other diseases, including breast and prostate cancer, osteoarthritis, hyperparathyroidism, coronary artery disease, psoriasis, and infection. More recent reports also suggest a possible association between molecular variation in the *VDR* gene and multiple sclerosis (147), sarcoidosis (148), early-onset periodontal disease (149), and nephrolithiasis (150), although these later studies have included few cases, and replication of these findings in larger populations and other ethnic groups is clearly needed.

There is also a need to explore the relation between *VDR* genotype and other malignancies. For instance, the homozygous presence of the *VDR Fok*I site was recently associated with a 70 percent increase (95 percent CI: 1.1, 2.6) in the risk of malignant melanoma (151), consistent with the expression of VDR in normal and malignant melanocytes and the antiproliferative effects of $1,25\ (OH)_2$ vitamin D on these cells in vitro (88). Vitamin D influences the proliferation and differentiation of other malignant cell lines, including colon and leukemia (88). Thus, investigations of *VDR* genotype and the development and progression of these other malignancies may be an important future endeavor.

The effect of *VDR* polymorphisms on disease risk may be context dependent, and few studies to date have examined possible interactions between *VDR* polymorphisms and environmental exposures. The Physicians Health Study, for example, found a significant reduction in prostate cancer risk associated with the *VDR* BB or tt genotypes, but only among men with the lowest serum 25(OH) vitamin D levels (92). Thus, future investigations of *VDR* genotypes and disease risk may need to assess and stratify by serum vitamin D levels. It will also be important to test for possible interactions between *VDR* alleles and molecular variation in other candidate genes.

FUNCTIONAL CONSEQUENCES OF VDR ALLELIC VARIANTS

The possible functional consequences of *VDR* alleles remain unclear. The *Apa*I and *Bsm*I variants are unlikely to have functional consequences, since both sites are located in the intron between exons VIII and IX and neither variant is near the intron-exon boundaries or known to produce splic-

ing errors. Moreover, several studies have found similar VDR protein (73, 152, 153) and messenger RNA (mRNA) levels (152, 154), ligand-binding affinity (152), DNA binding (152), and transactivation function (152) between *Bsm*I genotypes, although these observations have not been universal (119). The *Taq*I polymorphism is also unlikely to directly affect *VDR* function, since both alleles code for isoleucine at amino acid 352.

Several studies have also examined the association between the common *Bsm*I/*Apa*I/*Taq*I haplotypes and VDR function. Morrison et al. (19) showed that COS-7 and rat osteosarcoma cells transfected with reporter gene constructs containing the baT haplotype had significantly lower luciferase activity than did those with the BAt haplotype. Consistent with these observations, the baT haplotype has been associated with significantly lower VDR mRNA levels in parathyroid adenomas of patients with primary hyperparathyroidism (119). In contrast to these studies, Beaumont et al. (155) recently demonstrated significantly *greater* luciferase activity with reporter gene constructs containing the baT haplotype in transfected human osteoblast and osteosarcoma cell lines. One possible explanation for these inconsistent findings may be that the effect of *VDR* allelic variants on VDR function is tissue and/or species specific.

The *Fok*I variant remains a candidate functional polymorphism. Colin et al. (156) found that phytohemoglutinin-stimulated growth of peripheral blood monocytes differs by *Fok*I genotype. They demonstrated that the one-half maximal concentration for $1,25(OH)_2$ vitamin D inhibition of phytohemoglutinin-stimulated growth was significantly higher for cells containing the full-length VDR isoform (i.e., Ff and ff genotypes) than for those with the shorter isoform (FF genotype). Interestingly, there were no genotype-related differences in maximal inhibition of growth, raising the possibility that genotypic effects may be most apparent among individuals with low $1,25(OH)_2$ vitamin D levels. Transfection experiments in COS-7, HeLa, and fibroblast cell lines have also shown that the full-length VDR isoform has a decreased ability to induce transcriptional activation of reporter genes in response to $1,25(OH)_2D$ compared with the shorter F allele isoform (12, 25), although these observations were not confirmed in another study (157). The f allele isoform interacts with the basal transcription factor IIB less efficiently than does the F allele isoform, providing a possible mechanism for the reduced transactivation associated with this allele (158). The 3′ poly(A) allelic variants do not appear to alter VDR mRNA stability (159).

Summary

The 3′ *Bsm*I, *Apa*I, and *Taq*I polymorphisms do not appear to alter *VDR* gene expression or VDR function. Disease associations with these polymorphisms are therefore most likely due to linkage disequilibrium with other functional variation within the *VDR* gene or with another closely linked gene or genes. The 5′ *Fok*I polymorphism remains a potentially functional variant, but does not appear to be in linkage disequilibrium with the *Bsm*I, *Apa*I, or *Taq*I polymorphisms in most populations studied thus far. This raises the possibility that there may be additional functional polymorphisms in the *VDR* gene that remain to be characterized.

CONCLUSIONS AND FUTURE DIRECTIONS

The possible role of *VDR* gene variation in osteoporosis susceptibility has been a subject of intense investigation during the past several years. Numerous studies have found that the homozygous absence of a *Bsm*I restriction site in intron 8 is associated with a modest reduction in bone mass and possible increase in the risk of fracture; however, others have found no such associations. Conflicting results are not unexpected in association studies and may arise for several reasons, including differences in ethnic (genetic) background, gene-gene and gene-environment interactions, and the definition of the phenotype. Inappropriate selection of controls is the major confounding factor in association studies, however, and differences in subject ascertainment may also contribute to discrepant and sometimes spurious results. For instance, the distribution of *VDR* genotypes was not in Hardy-Weinberg equilibrium (i.e., genotype frequencies were not predicted by allele frequencies) in some studies. Departures from Hardy-Weinberg equilibrium may arise for several reasons apart from genotyping errors, including chance fluctuations due to small samples, nonrandom mating, migration into or out of the population, selective survivorship among genotypes, population stratification, and admixture of different ethnic groups (160). Deviations from Hardy-Weinberg equilibrium can bias the type I error rate such that the chance of a false-positive association increases substantially if the proportion of homozygotes with the high-risk allele is more common in the general population than predicted by Hardy-Weinberg equilibrium (161). Appropriate selection of controls is thus essential in association studies, but can be difficult due to *unrecognized* confounding by ethnic, ancestry, or admixture differences between cases and controls. Family-based association tests, such as the transmission-disequilibrium test (TDT), avoid confounding due to population stratification or admixture (162–164), but have rarely been used in studies of *VDR* alleles (125). The TDT test compares allele frequencies in cases with the frequencies of nontransmitted alleles in parents, thereby eliminating the need for ethnically matched controls. Recent modifications to the TDT make it a more practical tool for the study of quantitative traits such as bone mass (165). Future investigations of *VDR* gene variation should use family-based association methods to validate the results of population-based studies.

A major difficulty in accepting the hypothesis that known *VDR* allelic variants are directly responsible for the observed associations is that none of the variants, with the possible exception of the *Fok*I polymorphism, have consistently altered VDR expression or function in vitro. The inconsistent study results and doubtful functional significance of several known *VDR* gene variants suggest that other DNA sequence variation within the coding or regulatory regions of the *VDR* gene should be sought. Identifying the functional variant(s) will be a challenging task. Sequencing the *VDR* gene in subjects with contrasting levels of bone mass might maximize the

chances of detecting new functional variation. Sequencing studies in populations with different evolutionary histories may also help to localize the major functional variation. Such studies will also provide a more complete picture of the nucleotide diversity and structure of linkage disequilibrium across the *VDR* gene. Statistical approaches for identifying the probable functional variation or at least reducing the number of candidates requiring further investigation, such as multiple DNA variant association (166) and cladistic (167) analysis, are available and may help to localize the functional variation.

Interest in identifying novel functional variation at the *VDR* locus is strengthened by the possible association of *VDR* alleles with several major diseases. Interestingly, the allele associated with potentially beneficial effects on bone mass at the *Bsm*I site (b allele) has also been associated with an increased risk of breast and prostate cancer, atherosclerotic coronary artery disease, and primary hyperparathyroidism in some studies. An association of the b allele with both increased bone mass and breast cancer risk is consistent with the increased rates of breast cancer among women with high bone mass (168), raising the possibility of a genetic link between these common conditions. The paradoxical association of *VDR* alleles with high bone mass yet increased risk of late-in-life diseases is consistent with the antagonistic pleiotropy theory of aging, which proposed that alleles with beneficial effects early in life will have detrimental effects during the later stages of life (169). Nevertheless, understanding the potential role of *VDR* gene variation in these other common, chronic conditions may suggest new approaches to their prevention and treatment.

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A summary of *VDR* allele and genotype frequencies in various ethnic and racial groups can be obtained from the authors and has been published on the Centers for Disease Control and Prevention, Office of Genetics and Disease Prevention, Human Genome Epidemiology web site (http://www.cdc.gov/genetics/.).

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