Molecular Epidemiology of Vitamin D Receptor Gene Variants

Joseph M. Zmuda,1 Jane A. Cauley,1 and Robert E. Ferrell2

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 12q21 (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).


Abbreviations: Cl, 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.

1 Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA.
2 Human Genetics, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA.

Reprint requests to Dr. Joseph M. Zmuda, Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, 130 Desoto Street, Pittsburgh, PA 15261 (e-mail: epidjmz@pitt.edu).

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.hgmd.cf.ac.uk/ac/fmg.php).

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 FokI restriction endonuclease (11). Individuals with the C allele (designated F) initiate translation at the second ATG site and lack the three NH2-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).

BsmI (14) and Apal (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 TaqI. The BsmI and FokI alleles do not appear to be in linkage disequilibrium (11, 13, 17, 18), whereas a strong concordance exists between the absence of the BsmI (B allele) and presence of the TaqI (t allele) sites (19), and these sites show significant linkage disequilibrium with the Apal polymorphism. Hustmyer et al. (16) detected a rare third allele by Apal digestion in African Americans, but more recent PCR-based typing of the Apal 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 EcoRV-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
assays have not genotyped this variation. Because few studies of the EcoRV polymorphism are available, we have not reviewed this variant.

The BsmI 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 TaqI genotypes in these populations is similar to BsmI genotype frequencies. The ApaI 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 (A13-A17) or long (A18-A24) 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 (A23-A24) in that study were found only among African Americans, whereas the shortest allele (A13) was found only among Hispanics (24).

Linkage disequilibrium has been reported between the poly(A) and BsmI alleles, such that the short poly(A) and BsmI B alleles (BS haplotype) and the long poly(A) and BsmI 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 FokI 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 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 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 FokI 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 BsmI 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, I) 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 TaqI 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 FokI 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 FokI 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 FokI 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 BB haplotype had 11 percent lower (69) and postmenopausal women had 37 percent lower (68) calcium absorption compared with women with the BB haplotype (pp < 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 FokI 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

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Design</th>
<th>No. of cases</th>
<th>No. of controls</th>
<th>Genotype or haplotype</th>
<th>OR*</th>
<th>95% CI*</th>
<th>Comments</th>
<th>Reference no.</th>
</tr>
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<tbody>
<tr>
<td>Caucasian</td>
<td>43–69</td>
<td>Female</td>
<td>Case-control (nested)</td>
<td>54 (hip)</td>
<td>108</td>
<td>BbBb</td>
<td>1.0</td>
<td>Referent</td>
<td>Cases and controls matched</td>
<td>74</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BB</td>
<td>2.4</td>
<td>1.1, 5.2</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>bb</td>
<td>38</td>
<td>Referent</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Bb</td>
<td>43</td>
<td>Referent</td>
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<td></td>
<td></td>
<td>BB</td>
<td>18</td>
<td>Referent</td>
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<td></td>
<td></td>
<td></td>
<td>0</td>
<td>1.0</td>
<td>0.4, 2.5</td>
<td>Similar results for spine and nonspine fracture</td>
<td>75</td>
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<tr>
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<td></td>
<td></td>
<td>1</td>
<td>1.8</td>
<td>0.6, 5.0</td>
<td>Association independent of bone mineral density</td>
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<td></td>
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<td>2</td>
<td>2.6</td>
<td>1.4, 5.0</td>
<td></td>
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<tr>
<td>Caucasian</td>
<td>45–88</td>
<td>Female</td>
<td>Case-control</td>
<td>44 (spine)</td>
<td>44</td>
<td>bb</td>
<td>36</td>
<td>Referent</td>
<td>No adjustments made</td>
<td>77</td>
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<td></td>
<td></td>
<td>Bb</td>
<td>43</td>
<td>Referent</td>
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<td></td>
<td>BB</td>
<td>20</td>
<td>Referent</td>
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<tr>
<td>Caucasian</td>
<td>65</td>
<td>Female</td>
<td>Prospective</td>
<td>19 (nonspine)</td>
<td>30</td>
<td>bb</td>
<td>37</td>
<td>Referent</td>
<td>No adjustments made</td>
<td>78</td>
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<td></td>
<td>Bb</td>
<td>42</td>
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<td></td>
<td></td>
<td>BB</td>
<td>21</td>
<td>Referent</td>
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<tr>
<td>Caucasian</td>
<td>55–80</td>
<td>Female</td>
<td>Case-control (nested)</td>
<td>52 (nonspine)</td>
<td>900</td>
<td>baT haplotype (alleles)</td>
<td></td>
<td></td>
<td>Similar results for other fracture types. Adjusted for age and weight</td>
<td>76</td>
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<td></td>
<td></td>
<td>aTt</td>
<td>1.0</td>
<td>Referent</td>
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<td></td>
<td>AATt</td>
<td>0.7</td>
<td>0.4, 1.3</td>
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<td></td>
<td>AATi</td>
<td>0.9</td>
<td>0.5, 1.5</td>
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<td></td>
<td></td>
<td>AAtt</td>
<td>0.8</td>
<td>0.4, 1.4</td>
<td></td>
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</tr>
</tbody>
</table>

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

The relation between the FokI 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 BsmI 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 I 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 BsmI 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 FokI 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 TaqI 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 BsmI 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 BsmI 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 Apal (101), FokI (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 BsmI 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

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>No. of cases</th>
<th>No. of controls</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>95 consecutive prostatectomy cases identified at hospitals.</td>
<td>162 urology clinic patients presenting with BPH* or impotence and no history of cancer other than nonmelanoma skin cancer. Age not specified.</td>
<td>TT/Tt 1.0 Referent</td>
<td>No exposures assessed. Genotype not correlated with age, stage, or age at diagnosis</td>
</tr>
<tr>
<td>Caucasian</td>
<td>57 cases diagnosed between 1991 and 1992 identified by SEER* registry. Mean age = 58 years.</td>
<td>169 controls enrolled in a bladder cancer study. Mean age = 58 years.</td>
<td>LL 1.0 Referent</td>
<td>No exposures assessed.</td>
</tr>
<tr>
<td>Caucasian (90%)</td>
<td>41 cases of fatal, metastatic PCa* (20 hereditary) Mean age at diagnosis = 64 years</td>
<td>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 = 82 years.</td>
<td>TT/Tt 1.0 Referent</td>
<td>No exposures assessed.</td>
</tr>
<tr>
<td>Caucasian (92%)</td>
<td>372 cases in the Physicians Health Study ascertained by questionnaire and confirmed by medical chart review. Age 40–64 years.</td>
<td>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, 40–64 years.</td>
<td>BB 1.0 Referent</td>
<td>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 Taql).</td>
</tr>
<tr>
<td>Caucasian (92%)</td>
<td>77 biopsy-proven cases identified through urology and radiation oncology practices. Age ≥50 years.</td>
<td>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.</td>
<td>TT 1.0 Referent</td>
<td>Similar results for nonhereditary cases.</td>
</tr>
<tr>
<td>African-American</td>
<td>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)</td>
<td>105 controls without evidence of PCa on PSA tests and DRE. Mean age = 71 years (range, 64–86 years).</td>
<td>TT 1.0 Referent</td>
<td>No exposures assessed. No association with Fokl genotype.</td>
</tr>
<tr>
<td>African-American</td>
<td>151 new diagnosed cases in the Hawai'i-Los Angeles Multi-Ethnic cohort were ascertained through linkage to the SEER registry. Mean age ≥67 years.</td>
<td>174 nondiseased cohort members were randomly selected as controls. Mean age = 64 years.</td>
<td>BB 1.0 Referent</td>
<td>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.</td>
</tr>
<tr>
<td>Japanese</td>
<td>66 cases. Ascertainment methods not described. Mean age = 68 years (range, 57–84).</td>
<td>60 urology patients without evidence of PCa on PSA tests and DRE. Mean age = 71 years (range, 64–86 years).</td>
<td>TT/Tt 1.0 Referent</td>
<td>No exposures assessed. Men with metastatic disease and T allele had better progression-free survival than men with the T allele.</td>
</tr>
</tbody>
</table>

*No. Cl* = 95% confidence interval

**OR** = Odds Ratio

<table>
<thead>
<tr>
<th>Genotype</th>
<th>OR*</th>
<th>95% Cl*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TT/Tt</td>
<td>1.0</td>
<td>Referent</td>
</tr>
<tr>
<td>t</td>
<td>0.3</td>
<td>0.1, 0.7</td>
</tr>
<tr>
<td>TT/TT</td>
<td>1.0</td>
<td>Referent</td>
</tr>
<tr>
<td>t</td>
<td>1.4</td>
<td>0.4, 4.5</td>
</tr>
<tr>
<td>LL/LS</td>
<td>1.0</td>
<td>Referent</td>
</tr>
<tr>
<td>SS</td>
<td>1.3</td>
<td>0.4, 4.3</td>
</tr>
<tr>
<td>bb</td>
<td>1.0</td>
<td>Referent</td>
</tr>
<tr>
<td>Bb</td>
<td>0.9</td>
<td>0.7, 1.2</td>
</tr>
<tr>
<td>BB</td>
<td>0.9</td>
<td>0.6, 1.3</td>
</tr>
<tr>
<td>TT</td>
<td>1.0</td>
<td>Referent</td>
</tr>
<tr>
<td>T1</td>
<td>0.9</td>
<td>0.7, 1.3</td>
</tr>
<tr>
<td>t</td>
<td>0.9</td>
<td>0.6, 1.4</td>
</tr>
<tr>
<td>TT</td>
<td>1.0</td>
<td>Referent</td>
</tr>
<tr>
<td>T1</td>
<td>0.6</td>
<td>0.3, 1.2</td>
</tr>
<tr>
<td>t</td>
<td>0.9</td>
<td>0.4, 2.0</td>
</tr>
<tr>
<td>LL</td>
<td>1.0</td>
<td>Referent</td>
</tr>
<tr>
<td>LS</td>
<td>0.7</td>
<td>0.3, 1.4</td>
</tr>
<tr>
<td>SS</td>
<td>1.0</td>
<td>0.4, 2.0</td>
</tr>
<tr>
<td>TT</td>
<td>1.0</td>
<td>Referent</td>
</tr>
<tr>
<td>Tt</td>
<td>0.5</td>
<td>0.3, 0.9</td>
</tr>
<tr>
<td>t</td>
<td>1.2</td>
<td>0.5, 2.7</td>
</tr>
<tr>
<td>LL</td>
<td>1.0</td>
<td>Referent</td>
</tr>
<tr>
<td>LS</td>
<td>2.3</td>
<td>1.0, 5.0</td>
</tr>
<tr>
<td>SS</td>
<td>1.6</td>
<td>0.7, 2.6</td>
</tr>
<tr>
<td>bb</td>
<td>1.0</td>
<td>Referent</td>
</tr>
<tr>
<td>Bb</td>
<td>1.0</td>
<td>0.5, 2.1</td>
</tr>
<tr>
<td>BB</td>
<td>0.9</td>
<td>0.4, 1.8</td>
</tr>
<tr>
<td>LL</td>
<td>1.0</td>
<td>Referent</td>
</tr>
<tr>
<td>LS</td>
<td>1.4</td>
<td>0.6, 3.1</td>
</tr>
<tr>
<td>SS</td>
<td>1.1</td>
<td>0.5, 2.4</td>
</tr>
<tr>
<td>TT</td>
<td>1.0</td>
<td>Referent</td>
</tr>
<tr>
<td>Tt</td>
<td>0.8</td>
<td>0.3, 1.6</td>
</tr>
</tbody>
</table>

**Notes:**
- PCa: Prostate cancer
- BPH: Benign prostatic hyperplasia
- DRE: Digital rectal examination
- 25(OH)D: 25-hydroxyvitamin D
Vitamin D Receptor Gene Polymorphisms

vitamin D receptors are expressed in chondrocytes (109), a cellular component of osteophytes (110). In contrast to these findings, the TaqI T allele was associated with a decreased risk of spine osteoarthritis (111), and the BsmI 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 BsmI (122, 123) and Apal (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 Bangladeshis 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

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>No. of cases</th>
<th>No. of controls</th>
<th>Genotype</th>
<th>OR*</th>
<th>95% CI*</th>
<th>Comments</th>
<th>Reference no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japanese</td>
<td>60 cases. Age not reported.</td>
<td>120 age-matched controls. Age not reported.</td>
<td>BB/Bb 1.0</td>
<td>Referent</td>
<td>1.6, 9.3</td>
<td>No exposures assessed.</td>
<td>105</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>bb 3.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>102 cases. Age not reported.</td>
<td>155 randomly sampled controls from cohort. Age not reported.</td>
<td>Ff/FI 1.0</td>
<td>Referent</td>
<td>0.2, 0.7</td>
<td>No exposures assessed.</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>FI 0.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>68 consecutive cases recruited through radiation oncology center. 50 were newly diagnosed 38 were recurrent cases. Age not reported.</td>
<td>167 women in an osteoporosis prevention trial in same geographic area as cases. Age not reported.</td>
<td>BB 1.0</td>
<td>Referent</td>
<td>0.9, 15.4</td>
<td>No exposures assessed.</td>
<td>103</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Primary cases bb 0.9</td>
<td></td>
<td>0.4, 1.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Metastatic cases bb 3.8</td>
<td></td>
<td>0.9, 15.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>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).</td>
<td>110 women without a personal or family history of any cancer were recruited from the same community. Mean age = 50 years (range, 20–61 years).</td>
<td>AA 1.0</td>
<td>Referent</td>
<td>1.5, 2.5</td>
<td>No exposures assessed.</td>
<td>101</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Aa 1.5</td>
<td></td>
<td>0.8, 2.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>aa 2.5</td>
<td></td>
<td>1.2, 5.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>111 women aged 24–36 years (median, 34) diagnosed with BrCa between 1990 and 1993.</td>
<td>130 female blood donors aged 19–64 years (median, 37 years).</td>
<td>tt 16.2</td>
<td>Referent</td>
<td>17.7</td>
<td>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).</td>
<td>104</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tt 53.2</td>
<td></td>
<td>50.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TT 30.6</td>
<td></td>
<td>31.5</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>p = NS*</td>
<td></td>
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<tr>
<td>Caucasian</td>
<td>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)</td>
<td>627 randomly selected women from the European Prospective investigation of Cancer (EPIC) cohort. Mean age = 51 years (range, 40–76 years).</td>
<td>tt 1.0</td>
<td>Referent</td>
<td>0.8, 1.2</td>
<td>No exposures assessed. Similar results for analyses stratified by recruitment source.</td>
<td>102</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tt 1.0</td>
<td></td>
<td>0.8, 1.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TT 1.9</td>
<td></td>
<td>0.8, 1.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latina</td>
<td>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 years).</td>
<td>300 women without BrCa in cohort were randomly sampled. Mean age = 65 years (range, 45–75 years).</td>
<td>BB 1.0</td>
<td>Referent</td>
<td>0.4, 0.9</td>
<td>No exposures assessed. No association with FokI genotype.</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bb 0.6</td>
<td></td>
<td>0.2, 1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>bb 0.4</td>
<td></td>
<td>0.2, 1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LL 1.0</td>
<td></td>
<td>Referent</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LS 1.5</td>
<td></td>
<td>1.0, 1.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SS 3.2</td>
<td></td>
<td>1.5, 6.9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 mononuclear cells in vitro (136). Bellamy et al. (137) reported that the TaqI 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 FokI ff genotype and vitamin D status was also observed. Roy et al. (139) also found that the TaqI 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 Apal 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 BsmI 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 BsmI 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 homozgyous presence of the VDR FokI 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), 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 Apal and BsmI 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-
been associated with significantly lower VDR mRNA levels in the baT haplotype in transfected human osteoblast and luciferase activity with reporter gene constructs containing or containing the baT haplotype had significantly lower function. Morrison et al. (19) showed that COS-7 and rat BsmVApaVTaql haplotypes and VDR 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 Bsml 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 Fokl 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
Nevertheless, understanding the potential role of gene mental effects during the later stages of life (169). Alleles with beneficial effects early in life will have decreased risk of late-in-life diseases is consistent with the alleles with high bone mass yet VDR with high bone mass (168), raising the possibility of a tent with the increased rates of breast cancer among women both increased bone mass and breast cancer risk is consistent with antagonistic pleiotropy theory of aging, which proposed that variation in these other common, chronic conditions may suggest new approaches to their prevention and treatment.

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 BsmI 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.

ACKNOWLEDGMENTS

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