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PHARMACOGENETICS OF THE VITAMIN D RECEPTOR AND OSTEOPOROSIS

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ABSTRACT:

Osteoporosis is a major health care problem internationally with important implications for health care costs, morbidity, and mortality. Bone density, an important predictor of osteoporotic fracture risk, is affected by hormonal and environmental factors. However, in twin and family studies most of its age-specific variance is genetically determined. Common allelic variations in the vitamin D receptor (VDR) gene were the first to be linked to bone density. Recently, other candidate genes, notably oestrogen receptor, collagen 1αI, and PTH receptor genes and a chromosome 11 locus, have been associated with bone density and fracture. Polymorphisms in adjacent regulatory regions may be important mechanisms since functional coding region mutations have not been defined. For example, the polymorphic region in the collagen 1αI gene alters a SpI binding site and may alter collagen gene expression. At the pharmacogenetic level, VDR alleles predict differences in gut calcium absorption and long-term bone density response to calcium intake and active vitamin D analog treatment. Understanding the mechanisms underlying these allelic differences in relation to diet and lifestyle factors as well as response to therapy could aid selection of optimal therapy for osteoporosis prevention and treatment.

Osteoporosis is a common problem affecting older women and a large number of older men. In a recent community-based Australian study, the remaining lifetime risk for a 60-year-old woman was 56% and 29% for a man of the same age (Jones et al., 1994b). The prevalence of vertebral deformities and fractures in older men has now been shown to be similar to that in women (Cooper et al., 1992a; Cooper and Melton, 1992; Jacobsen et al., 1992; Kanis and McCloskey, 1992; Melton et al., 1993; Spector et al., 1993; Jones et al., 1996). The health care costs are estimated at 30 to 50 million dollars per year per million of population across many developed countries (Randell et al., 1995; Ray et al., 1997). There is also increased risk of death in both men and women with all types of osteoporotic fractures (Cooper et al., 1993; Browner et al., 1996; Center and Eisman, 1997; Center et al., 1999). Epidemiological data suggest important ethnic/racial differences, e.g., wide differences in age-adjusted incidence of hip fractures across various Caucasian populations and between Asian and Caucasian populations (Kanis, 1991, 1993, 1997; Kanis and McCloskey, 1992; Elffors et al., 1994; Gullberg et al., 1997).

Osteoporosis occurs when bones become fragile such that they can break when relatively minor force is applied to them. Although these osteoporotic bone fractures heal normally, significant morbidity and even mortality is associated with these fractures. Some, such as of the spine, leave deformity and contribute to long-term disability and even pain. The weaker bones, susceptible to fracture, are the result of the peak bone mass and size achieved in late childhood or early adulthood and the inevitable loss that occurs after menopause and with advancing age (Hui et al., 1990; Kelly et al., 1990b; Kroger et al., 1992, 1994; Johnston and Slemenda, 1993, 1994; Eisman et al., 1993; Teegarden et al., 1995; Lonzer et al., 1996; Lysen and Walker, 1997; Willing et al., 1997). A range of hormonal and environmental factors affects the risk of osteoporosis, and genetic factors may influence sensitivity to environmental and hormonal factors. The ethnic and racial differences in incidence may relate to genetic or environmental factors, but it has also been suggested to reflect inherited differences in susceptibility to environmental factors. Understanding how inherited factors interact with environmental factors may hold the key to better prevention and treatment.

[1] Abbreviation used is: VDR, vitamin D receptor.

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Genetics of Osteoporosis

Noninvasive techniques for assessment of bone structure, including radiological measures of quantitative computerized tomography and more recently dual photon absorptiometry or dual energy X-ray absorptiometry and quantitative ultrasound, have facilitated studies of genetics in osteoporosis. Bone phenotype measured by any of these techniques is the most powerful predictor of subsequent fracture risk. Peak bone mass measured by these tools seems to be under genetic control. This has been most clearly shown in studies of monozygotic and dizygotic twins (Slemenda et al., 1991a, 1996; Kelly et al., 1993, 1995; Johnston and Slemenda, 1994; Flicker et al., 1996; Seeman et al., 1996; Arden et al., 1996a; Arden and Spector, 1997; Harris et al., 1998; Hopper et al., 1998; Nguyen et al., 1998). Overall 45 to 80% of the age-corrected variability of bone phenotypic parameters can be explained by genetic factors with site-to-site differences in heritability (Slemenda et al., 1990b, 1991a, 1996; Flicker et al., 1996; Arden et al., 1996a; Arden and Spector, 1997; Harris et al., 1998; Nguyen et al., 1998; Howard et al., 1997, 1998a).

In addition, bone mass is also influenced by hormonal changes, such as puberty and menopause, and by lifestyle factors such as physical loading and calcium intake. Total bone mass increases about 3-fold over just a few years just before puberty (Johnston et al., 1992; Slemenda et al., 1994; Lonzer et al., 1996; Weaver et al., 1996). Bone mass remains stable until the onset of menopausal bone loss and

age-related bone loss. The latter type of bone loss may start in the early 40s in both men and women and accelerates with aging (Hui et al., 1990; Johnston and Slemenda, 1992; Tuppurainen et al., 1993; Kroger et al., 1994; Jones et al., 1994a; Nguyen et al., 1995; Harris and Dawson-Hughes, 1996; Willing et al., 1997). Younger men also lose bone with androgen deficiency (Seeman, 1995; Soule et al., 1995; Slemenda et al., 1997). There is considerable and as yet unexplained variation in the rate of postmenopausal bone loss. Similarly, corticosteroid excess can have a major adverse effect on bone, but there is a wide range of sensitivity to these effects. These variations in hormonal sensitivity, which may reflect gene-environment interactions, are the focus of this review.

Family history of osteoporotic fracture has been found to be a risk factor for the development of osteoporotic fracture in numerous epidemiological studies (Sowers et al., 1992; Krall and Dawson-Hughes, 1993, 1995; Seeman et al., 1994; Seeman, 1994; Soroko et al., 1994; McKay et al., 1994; Gueguen et al., 1995; Lonzer et al., 1996; Torgerson et al., 1996; Lysen and Walker, 1997; Willing et al., 1997; Diaz et al., 1997; Lips, 1997; Evans et al., 1998). Even specific types of fractures seem to be related to inherited differences in bone density, e.g., mothers with osteoporotic fractures have daughters with lower site-specific bone density (Evans et al., 1988; McKay et al., 1994; Seeman, 1994; Seeman et al., 1994; Soroko et al., 1994). These findings lead to questions regarding the mechanisms of such an inherited predisposition. One obvious mechanism would be gene-gene interaction for a relatively large number of genes, i.e., complex multifactorial genetic factors. An alternative and complementary mechanism could involve gene-environment interactions.

Human and animal studies have shown high levels of heritability (45–80% of variance) of bone density and structure for any age or group (Sowers et al., 1992; Krall and Dawson-Hughes, 1993, 1995; Seeman et al., 1994, 1996; Seeman, 1994; Soroko et al., 1994; McKay et al., 1994; Garabedian, 1995; Jouanny et al., 1995; Lonzer et al., 1996; Slemenda et al., 1996; Arden et al., 1996a; Torgerson et al., 1996; Salamone et al., 1996b; Ulrich et al., 1996; Beamer et al., 1996; Arden and Spector, 1997; Diaz et al., 1997; Harris et al., 1998; Hopper et al., 1998; Nguyen et al., 1998; Howard et al., 1998a; Ferrari et al., 1998b). This heritability being apparent before puberty suggests that genetic factors program inherent bone structural characteristics. However, these family-based studies compare individuals of widely different ages and do not assess the effects of age cohorts and familial environment and lifestyle similarities (Slemenda et al., 1991a; Sowers et al., 1992; Krall and Dawson-Hughes, 1993; Jouanny et al., 1995; Lonzer et al., 1996; Ulrich et al., 1996; Lysen and Walker, 1997; Willing et al., 1997). These data are yet to be extended to examine differences between ethnic and racial groups.

Although the twin model has been used to assess heritability, twin studies, particularly in monozygotic twins, can also be used to investigate the impact of environments and other lifestyle factors (Pocock et al., 1989b; Slemenda et al., 1991a; Young et al., 1995). Several environmental aspects have been shown to affect bone density. These include skeletal loading, calcium intake, smoking, and alcohol use (Slemenda et al., 1990a, 1991a; Cooper et al., 1992b; Nieves et al., 1992; Blaauw et al., 1994; Cummings et al., 1995; Massey and Whiting, 1996). It is unclear to what extent genetic factors may affect these relationships. Physical loading on the skeleton, ranging from immobilization and microgravity to loading in elite athletic sports, has been shown to affect bone mass (Pocock et al., 1989a; Sessions et al., 1989; Kroger et al., 1994; Lonzer et al., 1996; Slemenda et al., 1991b, 1992, 1994; Recker et al., 1992; Slemenda and Johnston, 1993; Khan et al., 1996; Salamone et al., 1996b; Ulrich et al., 1996; Ensrud et al., 1997a,b).

There is considerable debate about what is appropriate calcium intake ranging from 800 to over 1000 mg/day (Kelly et al., 1990a; Kanis and Passmore, 1990; Kanis, 1991, 1994a,b; Johnston et al., 1992; Tuppurainen et al., 1993; Blaauw et al., 1994; Teegarden et al., 1995; Weaver et al., 1995, 1996; Lonzer et al., 1996; Massey and Whiting, 1996; Dawson-Hughes et al., 1996, 1997; Wastney et al., 1996; Nordin, 1997; Jackman et al., 1997). In Asian cultures with little dairy intake and thus dietary calcium intakes closer to 400 mg/day, osteoporotic fracture incidence is unexpectedly lower than in comparable Caucasian populations (Nakamura et al., 1994; Xu et al., 1996). Although other lifestyle factors may be important, this may also relate to ethnic or racial differences in calcium absorption, an example of gene-environment interactions.

The accelerated bone loss for 10 to 15 years post menopause varies widely among individuals, leading to categorization of slow and fast losers (Riis et al., 1996). Although there is some debate on this point, some “fast losers” remain so over 15 years of follow-up (Riis et al., 1996). Similar differences have been shown in individuals exposed to excessive levels of glucocorticoid or thyroid hormone (Sambrook et al., 1989, 1990; Cummings et al., 1995; Orwoll et al., 1996). The reasons for these interindividual differences have not been adequately defined. However, inherited and other environmental factors and gene-environment interactions would seem to be a logical mechanism.

An important concept in studying a disease such as osteoporosis is the high prevalence of the disease in the overall community. Gene mutations can be important factors in rare diseases such as osteogenesis imperfecta, an extreme form of osteoporosis that can result in lethality in utero, or osteopetrosis, wherein the bones are so dense that normal marrow space can not develop, leading to aplastic anemia. From the current World Health Organization definition of osteoporosis, relating to difference from young normal, the majority of the elderly population would be “osteoporotic”. It seems inherently unlikely that this common problem with such high heritability could be caused by “extreme” mutations; rather, it seems that it would be caused by a number of small effect-size changes (allelic polymorphisms) shifting bone density within the normal range.

Genes and Bone Mass

Polymorphic alleles of the vitamin D receptor gene were the first to be associated with bone turnover and bone density in a nonstructural gene (Morrison et al., 1992, 1994, 1997; Barger-Lux et al., 1995; Riggs et al., 1995; Fleet et al., 1995; Eisman, 1996). A number of subsequent studies have identified weaker (Morrison et al., 1992, 1994, 1997; Arden et al., 1996b; Grosset al., 1996; Uitterlinden et al., 1996; Tokita et al., 1996; Viitanen et al., 1996; Salamone et al., 1996a; Houston et al., 1996; Zmuda et al., 1997; Vandevyver et al., 1997; McClure et al., 1997; Harris et al., 1997; Kiel et al., 1997; Geusens et al., 1997; Lazaretti-Castro et al., 1997; Tamai et al., 1997; Gennari et al., 1998; Willing et al., 1998; Ferrari et al., 1998a; Hauache et al., 1998) or no effects (Hustmyer et al., 1994; Garnero et al., 1995, 1996; Lim et al., 1995; Arden et al., 1996b; Garnero et al., 1995, 1996; Tsai et al., 1996; Spotila et al., 1996b; Boschitsch et al., 1996; Ongphiphadhanakul et al., 1997; Graafmans et al., 1997; Francis et al., 1997; Rauch et al., 1997; Alahari et al., 1997; Willing et al., 1998; Eccleshall et al., 1998). However two meta-analyses, recently published, support a role for the vitamin D receptor gene alleles, albeit with somewhat less strength than originally reported (Cooper and Umbach, 1996; Gong et al., 1999). An additional start codon polymorphism of the vitamin D receptor gene has been associated with differences in bone density in some but not all population groups (Gross et al., 1996; Arai et al., 1997; McClure et al., 1997; Harris et al., 1997; Sainz et al., 1997; Eccleshall et al., 1998). Markers of bone

turnover, e.g., the procollagen type I propeptide cleaved and released when collagen is produced, have also been shown to be genetically linked in some (Tokita et al., 1996) but not all (Hustmyer et al., 1994; Garnero et al., 1995, 1996) studies.

Some studies suggest relationships between the vitamin D receptor alleles and risk of fracture (Feskanich et al., 1998), but others found no such relationship (Looney et al., 1995; Houston et al., 1996; Ensrud et al., 1999). Some of these differences may relate to statistical power (Nguyen et al., 1994, 1996) and to differing ethnic and environmental backgrounds.

Several other "candidate" gene loci have been associated with bone density or fractures. These include hormone receptor genes, such as the oestrogen receptor gene (Qi et al., 1995; Kobayashi et al., 1996; Mizunuma et al., 1997; Han et al., 1997; Carling et al., 1997b; Shiraki et al., 1997; Gennari et al., 1998) and the calcitonin and parathyroid hormone receptors (Duncan et al., 1998, 1999; Masi et al., 1998). Genes for various cytokines have also been implicated, e.g., interleukins 6 and 4 (Kajkenova et al., 1997; Murray et al., 1997; Duncan et al., 1998; Tsukamoto et al., 1999), the interleukin-1 receptor antagonist gene (Keen et al., 1998b), TGF receptor and TGF-β1 gene (Langdahl et al., 1997; Keen et al., 1998a), as well as the insulin-like growth factor-I gene (Kurland et al., 1997; Rosen et al., 1997, 1998a,b; Rosen and Donahue, 1998) and the apolipoprotein E gene (Shiraki et al., 1997; Kiel et al., 1998), and even an HLA type (Tsuji et al., 1998). In each of these cases initial positive (association) results have been counter-balanced by some if not several negative (no association) studies. This wide variation across studies and populations suggests ethnic (presumably genetic) and/or environmental determinants of the expression of these gene effects. As mentioned above these may also relate in part to statistical power issues (Nguyen et al., 1994, 1996).

Less severe mutations in structural genes, e.g., collagen 1 α1 gene, identified in these severe diseases have already been related to bone density differences in familial forms of osteoporosis (Spotila et al., 1991, 1994, 1996a; Shapiro et al., 1992; Paterson and Mole, 1994). Moreover, a polymorphism affecting an SpI binding site in the first intron of the collagen 1 α1 gene has now been associated with differences in bone density and fracture risk in a large number of osteoporosis studies (Houston et al., 1996; Grant et al., 1996; Garnero et al., 1998; Langdahl et al., 1998; Liden et al., 1998; Uitterlinden et al., 1998). As for other studies of particular genes or genetic loci, this effect has varied in size in different studies (Willing et al., 1997).

The genome screening approach has recently defined a chromosomal locus (11q12–13) associated with very high bone density (Johnson et al., 1997, 1998). The original affected family members had bone densities 4 to 5 standard deviations away from their age-corrected means and some suggestion of abnormal long bone marrow space development. Other family studies have also identified a chromosome 11q locus as well as other loci at 1p36, 2p23–24, 4qter, and chromosome 13 (Spotila et al., 1996a; Devoto et al., 1998; Niu et al., 1999). The genome-screening approach, applied in mouse and baboon studies, is helping to identify other loci (Beamer et al., 1996; Jilka et al., 1996; Kajkenova et al., 1997; Beamer et al., 1998; Orwoll et al., 1998; Young et al., 1998; Benes et al., 1998; Zmuda et al., 1999), which should lead to human loci from synteny with the human genome.

The concept of inheritance and disease could lead to the misunderstanding that the disease process could not be changed except perhaps via gene therapy. While this may be true for structural gene mutations, it is less relevant to changes in genes that may result in differences in the normal physiological regulatory systems. Indeed these sorts of changes are likely to interact with physiological stresses being expressed as the phenotypic outcome. This concept underlies the idea of normal genetic variability and the new field of pharmacogenetics. In relation to osteoporosis, it is important to remember the bone turnover itself is related to both environmental and genetic factors. Genetic variation could be expected to explain some of the widely observed differences in bone responses to various hormonal and environmental insults (Kelly et al., 1991, 1995; Slemenda et al., 1991a; Harris et al., 1998; Nguyen et al., 1998).

Dietary Calcium Intake and Vitamin D Receptor Gene Alleles

Dietary calcium intake is an obvious factor that may affect responsiveness of vitamin D receptor genes. This commonly ranges from less than 400 to over 1000 mg/day in different population groups. In some studies, genotype related differences in calcium handling have been observed. In one study the "BB" subjects did not increase their gut calcium absorption on lower dietary calcium intakes, as did the "bb" subjects and, in another, urinary calcium excretion was higher in the "bb" subjects (Dawson-Hughes et al., 1995; Ongphiphadhanakul et al., 1997). Another recent study found a 42% difference in gut calcium absorption between alternate homozygotes for the vitamin D receptor start codon polymorphism (Ames et al., 1999). As with other studies of bone and genetics, a number of studies have found positive relationships between the vitamin D receptor gene alleles and calcium homeostasis (Howard et al., 1995, 1998a,b; Dawson-Hughes et al., 1995; Kiel et al., 1997; Wishart et al., 1997; Ames et al., 1999), while other studies have been negative (Francis et al., 1997; Gunnes et al., 1997; Kinyamu et al., 1997a; Rauch et al., 1997).

Similarly longitudinal studies have shown differences of the bone density response to calcium intake according to vitamin D receptor genotype. In one study, the vitamin D receptor heterozygotes responded to calcium intake while the alternate homozygotes either gained or lost bone irrespective of calcium intake (Ferrari et al., 1995). By contrast in a second study the "BB" homozygotes gained some bone when supplemented from a very low basic calcium intake (Krall et al., 1995).

Interestingly, despite apparent differences in gut calcium absorption, several studies have not found any difference in intestinal vitamin D receptor level (Barger-Lux et al., 1995; Kinyamu et al., 1997a,b). By contrast, differences in parathyroid gland regulation have been related to vitamin D receptor polymorphisms (Carling et al., 1995, 1997a,c; Yokoyama et al., 1998).

Another potential gene-environment interaction for the vitamin D receptor gene would be in relation to simple vitamin D itself or the active hormonal forms of vitamin D. Differences in response of bone density to the vitamin D metabolites and analogs have been reported according to the vitamin D receptor genotypes, particularly in Japanese studies (Tokita et al., 1994; Yamagata et al., 1994; Shiraki et al., 1997). The more common "bb" genotype in Japanese cohorts (about 75% of the subjects) was more responsive compared with the heterozygotes, who did not respond well or actually worsened. Given that the heterozygote is the most common genotype in most Caucasian groups, these differences have an intriguing parallel to the differences that have been observed in response to the active vitamin D compounds in clinical studies of osteoporosis between Japanese and Caucasian groups. In another study, the response to simple vitamin D varied according to vitamin D receptor genotype (Graafmans et al., 1997).

Relationships between vitamin D receptor and bone mass may also not be simple. In fact, there is now evidence that the vitamin D receptor gene alleles are associated with body weight (Barger-Lux et al., 1995; Suarez et al., 1997), which is one of the strongest predictors of bone density in all studies. There is considerable debate whether

this strong effect is via differences in lean mass or fat mass (Reid et al., 1992a,b, 1994; Young et al., 1995). In this regard several studies suggest a relationship between components of body size and vitamin D receptor genotypes. In some of these, body weight in infancy or early childhood was greater in "BB" subjects (Keen et al., 1997a; Suarez et al., 1997). In another study in older men, differences in forearm density were apparently due to differences in bone size, with greater bone size in the "BB" homozygotes (Need et al., 1996). In two other studies, a vitamin D receptor effect was not apparent in obese individuals (Vandevyver et al., 1997) and was associated with muscle strength (Geusens et al., 1997). It is possible that some of these relationships between vitamin D receptor genotypes, bone size, and bone mass may be mediated through insulin or insulin-like growth factor pathways (McDermott et al., 1997; Hitman et al., 1998), which have also been linked to bone density (Reid et al., 1993).

The mechanism by which any changes in the vitamin D receptor alleles may account for changes in calcium and bone homeostasis is not clear. At a simple level it is possible that subtle differences may exist in the regulation of the gene or in the stability of the mRNA product. Some initial in vitro studies suggested that change in stability of mRNA product (Morrison et al., 1994; Arai et al., 1997); however, other studies did not confirm this affect (Mocharla et al., 1997; Gross et al., 1998; Durrin et al., 1999). Another mechanism may relate to changes in alternative transcripts from the recently reported multiple promoters of single human vitamin D receptor gene (Crofts et al., 1998).

The differences in the vitamin D allelic effects may relate to genetic backgrounds and/or environmental factors such as calcium and vitamin D intakes. Genetic backgrounds may relate to other allelic gene effects, e.g., the oestrogen receptor genotype (Willing et al., 1998; Gennari et al., 1998). By this mechanism, allelic effects could differ between environments. Some effects could be quite unexpected; for example, the apparent protection against some chronic infections reported in a recent African study (Bellamy et al., 1999) and relationship to risk of osteoarthritis of spine and hip (Keen et al., 1997b; Uitterlinden et al., 1997; Jones et al., 1998).

Despite some continuing controversy over the strength of the vitamin D receptor gene associations, these initial findings stimulated the field of the genetics of osteoporosis toward targeted genetic studies and now genome scan approaches. The various examples of possible gene-environment interaction for the vitamin D receptor gene alleles include dietary calcium intake, simple vitamin D intake, and responses to therapy with active vitamin D compounds as well as more complex interactions with body growth patterns. The allelic variation in the vitamin D receptor is one of what seem likely to be a wide range of genes and chromosomal loci to be implicated in the genetic determination of response to therapy. This is perhaps most important in situations where long periods of time, often years, must elapse before the response to a therapy can be adequately assessed. In the sense that this information could guide selection of therapy in individuals, this could be seen as an example of pharmacogenetics, and similar information could soon be applicable for many different genes and therapies. Variability of genetic findings, which seems to be the rule rather than the exception, across studies, may reflect false positives. However, others appear to relate to interaction of loci with specific environmental and hormonal factors and other genetic loci, which includes genetic heterogeneity and differing ethnicity. Understanding how these different genetic (and ethnic) backgrounds combine with different environments to explain responses to therapy could underpin targeted selection of optimal therapy on an individual basis.

References

Alahari KD, Lobaugh B and Econs MJ (1997) Vitamin D receptor alleles do not correlate with bone mineral density in premenopausal Caucasian women from the southeastern United States. [i]Metab Clin Exp **46:**224–226.

Ames S, Ellis K, Gunn S, Copeland K and Abrams S (1999) Vitamin D receptor gene Fok1 polymorphism predicts calcium absorption and bone mineral density in children. *J Bone Miner Res* **14:**740–746.

Arai H, Miyamoto K, Taketani Y, Yamamoto H, Iemori Y, Morita K, Tonai T, Nishisho T, Mori S and Takeda E (1997) A vitamin D receptor gene polymorphism in the translation initiation codon: Effect on protein activity and relation to bone mineral density in Japanese women. *J Bone Miner Res* **12:**915–921.

Arden NK, Baker J, Hogg C, Baan K and Spector TD (1996a) The heritability of bone mineral density, ultrasound of the calcaneus and hip axis length: A study of postmenopausal twins. *J Bone Miner Res* **11:**530–534.

Arden NK, Keen RW, Lanchbury JS and Spector TD (1996b) Polymorphisms of the vitamin D receptor gene do not predict quantitative ultrasound of the calcaneus or hip axis length. *Osteoporos Int* **6:**334–337.

Arden NK and Spector TD (1997) Genetic influences on muscle strength, lean body mass and bone mineral density: A twin study. *J Bone Miner Res* **12:**2076–2081.

Barger-Lux MJ, Heaney RP, Hayes J, DeLuca HF, Johnson ML and Gong G (1995) Vitamin D receptor gene polymorphism, bone mass, body size and vitamin D receptor density. *Calcif Tissue Int* **57:**161–162.

Beamer WG, Donahue LR, Rosen CJ and Baylink DJ (1996) Genetic variability in adult bone density among inbred strains of mice. *Bone* **18:**397–403.

Beamer WG, Rosen CJ, Donahue LR, Frankel WN, Churchill GA, Shultz KL, Baylink DJ and Pettis JL (1998) Location of genes regulating volumetric bone density in C57BL/6J (low) and C3H/HeJ (high) inbred strains of mice. *Bone* **23 (Suppl 5):**S162.

Bellamy R, Ruwende C, Corrah T, McAdam KP, Thursz M, Whittle HC and Hill AV (1999) Tuberculosis and chronic hepatitis B virus infection in Africans and variation in the vitamin D receptor gene. *J Infect Dis* **179:**721–724.

Benes H, Dennis R, Zheng W, Kang P, Weinstein RS, Shelton R, Robertson P, Jilka RL, Manolagas SC and Shmookler RJ (1998) Detection and confirmation of osteopenia-associated loci in two independent crosses between closely related mouse strains with differing bone densities. *Bone* **23 (Suppl 5):**S274.

Blaauw R, Albertse EC, Beneke T, Lombard CJ, Laubscher R and Hough FS (1994) Risk factors for the development of osteoporosis in a South African population. A prospective analysis. *S Afr Med J* **84:**328–332.

Boschitsch E, Suk EK, Mayr WR, Lang T, Schwartz WM and Panzer S (1996) Genotypes of the vitamin-D-receptor gene and bone mineral density in Caucasoid postmenopausal females [published erratum appears in *Maturitas* (1996) **25:**84]. *Maturitas* **24:**91–96.

Browner WS, Pressman AR, Nevitt MC and Cummings SR (1996) Mortality following fractures in older women. The study of osteoporotic fractures. *Arch Intern Med* **156:**1521–1525.

Carling T, Kindmark A, Hellman P, Holmberg L, Akerstrom G and Rastad J (1997a) Vitamin D receptor alleles b, a, and T: Risk factors for sporadic primary hyperparathyroidism (HPT) but not HPT of uremia or MEN 1. *Biochem Biophys Res Commun* **231:**329–332.

Carling T, Kindmark A, Hellman P, Lundgren E, Ljunghall S, Rastad J, Akerstrom G and Melhus H (1995) Vitamin D receptor genotypes in primary hyperparathyroidism [see comments]. *Nat Med* **1:**1309–1311.

Carling T, Rastad J, Kindmark A, Lundgren E, Ljunghall S and Akerstrom G (1997b) Estrogen receptor gene polymorphism in postmenopausal primary hyperparathyroidism. *Surgery* **122:**1101–1105; discussion 1106.

Carling T, Ridefelt P, Hellman P, Rastad J and Akerstrom G (1997c) Vitamin D receptor polymorphisms correlate to parathyroid cell function in primary hyperparathyroidism. *J Clin Endocrinol Metab* **82:**1772–1775.

Center J and Eisman J (1997) The epidemiology and pathogenesis of osteoporosis. *Baillieres Clin Endocrinol Metab* **11:**23–62.

Center J, Nguyen T, Schneider D, Sambrook P and Eisman J (1999) Mortality after all major types of osteoporotic fracture in men and women: An observational study. *Lancet* **353:**878–892.

Cooper C, Atkinson EJ, Jacobsen SJ, O'Fallon WM and Melton LJD (1993) Population-based study of survival after osteoporotic fractures. *Am J Epidemiol* **137:**1001–1005.

Cooper C, Atkinson EJ, Kotowicz M, O'Fallon WM and Melton LJD (1992a) Secular trends in the incidence of postmenopausal vertebral fractures. *Calcif Tissue Int* **51:**100–104.

Cooper C, Atkinson EJ, Wahner HW, O'Fallon WM, Riggs BL, Judd HL and Melton LJD (1992b) Is caffeine consumption a risk factor for osteoporosis? *J Bone Miner Res* **7:**465–471.

Cooper C and Melton LJ (1992) Vertebral fractures (Editorial) [see comments]. *Br Med J* **304:**793–794.

Cooper GS and Umbach DM (1996) Are vitamin D receptor polymorphisms associated with bone mineral density? A meta-analysis [see comments]. *J Bone Miner Res* **11:**1841–1849.

Crofts L, Hancock M, Morrison N and Eisman J (1998) Multiple promoters direct the tissue-specific expression of novel N-terminal variant human vitamin D receptor gene transcripts. *Proc Nat Acad Sci USA* **95:**10529–10534.

Cummings SR, Nevitt MC, Browner WS, Stone K, Fox KM, Ensrud KE, Cauley J, Black D and Vogt RM (1995) Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group [see comments]. *N Engl J Med* **332:**767–773.

Dawson-Hughes B, Fowler SE, Dalsky G and Gallagher C (1996) Sodium excretion influences calcium homeostasis in elderly men and women. *J Nutr* **126:**2107–2112.

Dawson-Hughes B, Harris SS and Finneran S (1995) Calcium absorption on high and low calcium intakes in relation to vitamin D receptor genotype. *J Clin Endocrinol Metab* **80:**3657–3661.

Dawson-Hughes B, Harris SS, Krall EA and Dallal GE (1997) Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older [see comments]. *N Engl J Med* **337:**670–676.

Devoto M, Shimoya K, Caminis J, Ott J, Tenenhouse A, Whyte MP, Sereda L, Hall S, Considine E, Williams CJ, Tromp G, Kuivaniemi H, Ala-Kokko L, Prockop DJ and Spotila LD (1998) First-stage autosomal genome screen in extended pedigrees suggests genes predisposing to low bone mineral density on chromosomes 1p, 2p and 4q. *Eur J Hum Genet* **6:**151–157.

Diaz MN, O'Neill TW and Silman AJ (1997) The influence of family history of hip fracture on

the risk of vertebral deformity in men and women: The European Vertebral Osteoporosis Study. *Bone* **20:**145–149.
Duncan E, Brown M, Sinsheimer J, Bell J, Wordsworth B and Wass J (1999) Suggestive linkage of the parathyroid receptor type I to osteoporosis. *J Bone Miner Res* **14:**1993–1999.
Duncan EL, Brown MA, Sinsheimer JS, Carr JA, Wordsworth BP and Wass JAH (1998) Candidate gene linkage screen in osteoporosis. *Bone* **23 (Suppl 5):**S160.
Durrin LK, Haile RW, Ingles SA and Coetzee GA (1999) Vitamin D receptor 3′-untranslated region polymorphisms: Lack of effect on mRNA stability. *Biochim Biophys Acta* **1453:**311–320.
Eccleshall TR, Garnero P, Gross C, Delmas PD and Feldman D (1998) Lack of correlation between start codon polymorphism of the vitamin D receptor gene and bone mineral density in premenopausal French women: The OFELY study. *J Bone Miner Res* **13:**31–35.
Eisman J (1996) Genetics of osteoporosis, in *Osteoporosis 1996* (Papapoulos SEA ed), pp 131–135, Elsevier Science Publishing Co., Inc., New York.
Eisman JA, Kelly PJ, Morrison NA, Pocock NA, Yeoman R, Birmingham J and Sambrook PN (1993) Peak bone mass and osteoporosis prevention. *Osteoporos Int* **1:**56–60.
Elffors I, Allander E, Kanis JA, Gullberg B, Johnell O, Dequeker J, Dilsen G, Gennari C, Lopes Vaz AA, Lyritis G, et al. (1994) The variable incidence of hip fracture in southern Europe: The MEDOS Study. *Osteoporos Int* **4:**253–263.
Ensrud KE, Cauley J, Lipschutz R and Cummings SR (1997a) Weight change and fractures in older women. Study of Osteoporotic Fractures Research Group. *Arch Intern Med* **157:**857–863.
Ensrud KE, Lipschutz RC, Cauley JA, Seeley D, Nevitt MC, Scott J, Orwoll ES, Genant HK and Cummings SR (1997b) Body size and hip fracture risk in older women: A prospective study. Study of Osteoporotic Fractures Research Group. *Am J Med* **103:**274–280.
Ensrud K, Stone K, Cauley J, White C, Zmuda J, Nguyen T, Eisman J and Cummings S (1999) Vitamin D receptor gene polymorphisms and the risk of fractures in older women. *J Bone Miner Res* **14:**1637–1645.
Evans RA, Marel GM, Lancaster EK, Kos S, Evans M and Wong SY (1988) Bone mass is low in relatives of osteoporotic patients. *Ann Intern Med* **109:**870–873.
Ferrari S, Rizzoli R, Chevalley T, Slosman D, Eisman JA and Bonjour JP (1995) Vitamin-D-receptor-gene polymorphisms and change in lumbar-spine bone mineral density [see comments]. *Lancet* **345:**423–424.
Ferrari S, Rizzoli R, Manen D, Slosman D and Bonjour JP (1998a) Vitamin D receptor gene start codon polymorphisms (FokI) and bone mineral density: Interaction with age, dietary calcium and 3′-end region polymorphisms. *J Bone Miner Res* **13:**925–930.
Ferrari S, Rizzoli R, Slosman D and Bonjour JP (1998b) Familial resemblance for bone mineral mass is expressed before puberty. *J Clin Endocrinol Metab* **83:**358–361.
Feskanich D, Hunter DJ, Willett WC, Hankinson SE, Hollis BW, Hough HL, Kelsey KT and Colditz GA (1998) Vitamin D receptor genotype and the risk of bone fractures in women. *Epidemiol* **9:**535–539.
Fleet JC, Harris SS, Wood RJ and Dawson-Hughes B(1995) The BsmI vitamin D receptor restriction fragment length polymorphism (BB) predicts low bone density in premenopausal black and white women. *J Bone Miner Res* **10:**985–990.
Flicker L, Faulkner KG, Hopper JL, Green RM, Kaymacki B, Nowson CA, Young D and Wark JD (1996) Determinants of hip axis length in women aged 10–89 years: A twin study. *Bone* **18:**41–45.
Francis RM, Harrington F, Turner E, Papiha SS and Datta HK (1997) Vitamin D receptor gene polymorphism in men and its effect on bone density and calcium absorption. *Clin Endocrinol* **46:**83–86.
Garabedian M (1995) Genetic aspects of osteoporosis [Review]. *Curr Opin Rheumatol* **7:**237–239.
Garnero P, Borel O, Grant SF, Ralston SH and Delmas PD (1998) Collagen Ialpha1 Sp1 polymorphism, bone mass and bone turnover in healthy French premenopausal women: The OFELY study. *J Bone Miner Res* **13:**813–817.
Garnero P, Borel O, Sornay-Rendu E, Arlot ME and Delmas PD (1996) Vitamin D receptor gene polymorphisms are not related to bone turnover, rate of bone loss, and bone mass in postmenopausal women: The OFELY Study. *J Bone Miner Res* **11:**827–834.
Garnero P, Borel O, Sornay-Rendu E and Delmas PD (1995) Vitamin D receptor gene polymorphisms do not predict bone turnover and bone mass in healthy premenopausal women. *J Bone Miner Res* **10:**1283–1288.
Gennari L, Becherini L, Masi L, Mansani R, Gonnelli S, Cepollaro C, Martini S, Montagnani A, Lentini G, Becorpi AM and Brandi ML (1998) Vitamin D and estrogen receptor allelic variants in Italian postmenopausal women: Evidence of multiple gene contribution to bone mineral density. *J Clin Endocrinol Metab* **83:**939–944.
Geusens P, Vandevyver C, Vanhoof J, Cassiman JJ, Boonen S and Raus J (1997) Quadriceps and grip strength are related to vitamin D receptor genotype in elderly nonobese women. *J Bone Miner Res* **12:**2082–2088.
Gong G, Stern H, Cheng S, Fong N, Mordeson J, Deng H and Recker R (1999) The association of bone mineral density with vitamin D receptor gene polymorphisms. *Osteoporos Int* **9:**55–64.
Graafmans WC, Lips P, Ooms ME, van Leeuwen JP, Pols HA and A.G. Uitterlinden AG (1997) The effect of vitamin D supplementation on the bone mineral density of the femoral neck is associated with vitamin D receptor genotype. *J Bone Miner Res* **12:**1241–1245.
Grant SF, Reid DM, Blake G, Herd R, Fogelman I and Ralston SH (1996) Reduced bone density and osteoporosis associated with a polymorphic Sp1 binding site in the collagen type I alpha 1 gene. *Nat Genet* **14:**203–205.
Gross C, Eccleshall TR, Malloy PJ, Villa ML, Marcus R and D. Feldman D (1996) The presence of a polymorphism at the translation initiation site of the vitamin D receptor gene is associated with low bone mineral density in postmenopausal Mexican-American women [see comments]. *J Bone Miner Res* **11:**1850–1855.
Gross C, Musiol IM, Eccleshall TR, Malloy PJ and Feldman D (1998) Vitamin D receptor gene polymorphisms: Analysis of ligand binding and hormone responsiveness in cultured skin fibroblasts. *Biochem Biophys Res Commun* **242:**467–473.
Gueguen R, Jouanny P, Guillemin F, Kuntz C, Pourel J and Siest G (1995) Segregation analysis and variance components analysis of bone mineral density in healthy families. *J Bone Miner Res* **10:**2017–2022.
Gullberg B, Johnell O and Kanis JA (1997) World-wide projections for hip fracture. *Osteoporos Int* **7:**407–413.
Gunnes M, Berg JP, Halse J and Lehmann EH (1997) Lack of relationship between vitamin D receptor genotype and forearm bone gain in healthy children, adolescents, and young adults. *J Clin Endocrinol Metab* **82:**851–855.
Han KO, Moon IG, Kang YS, Chung HT, Min HK and Han IK (1997) Nonassociation of estrogen receptor genotypes with bone mineral density and estrogen responsiveness to hormone replacement therapy in Korean postmenopausal women [see comments]. *J Clin Endocrinol Metab* **82:**991–995.
Harris M, Nguyen TV, Howard GM, Kelly PJ and Eisman JA (1998) Genetic and environmental correlations between bone formation and bone mineral density: A twin study. *Bone* **22:**141–145.
Harris SS and Dawson-Hughes B (1996) Weight, body composition, and bone density in postmenopausal women. *Calcif Tissue Int* **59:**428–432.
Harris SS, Eccleshall TR, Gross C, Dawson-Hughes B and Feldman D (1997) The vitamin D receptor start codon polymorphism (FokI) and bone mineral density in premenopausal American black and white women. *J Bone Miner Res* **12:**1043–1048.
Hauache OM, Lazaretti-Castro M, Andreoni S, Gimeno SG, Brandao C, Ramalho AC, Kasamatsu TS, Kunii I, Hayashi LF, Dib SA and Vieira JG (1998) Vitamin D receptor gene polymorphism: Correlation with bone mineral density in a Brazilian population with insulin-dependent diabetes mellitus. *Osteoporos Int* **8:**204–210.
Hitman GA, Mannan N, McDermott MF, Aganna E, Ogunkolade BW, Hales CN and Boucher BJ (1998) Vitamin D receptor gene polymorphisms influence insulin secretion in Bangladeshi Asians. *Diabetes* **47:**688–690.
Hopper JL, Green RM, Nowson CA, Young D, Sherwin AJ, Kaymakci B, Larkins RG and Wark JD (1998) Genetic, common environment, and individual specific components of variance for bone mineral density in 10- to 26-year-old females: A twin study [see comments]. *Am J Epidemiol* **147:**17–29.
Houston LA, Grant SF, Reid DM and Ralston SH (1996) Vitamin D receptor polymorphism, bone mineral density, and osteoporotic vertebral fracture: Studies in a UK population. *Bone* **18:**249–252.
Howard G, Nguyen T, Morrison N, Watanabe T, Sambrook P, Eisman J and Kelly PJ (1995) Genetic influences on bone density: Physiological correlates of vitamin D receptor gene alleles in premenopausal women. *J Clin Endocrinol Metab* **80:**2800–2805.
Howard GM, Nguyen TV, Harris M, Kelly PJ and Eisman JA (1998a) Genetic and environmental contributions to the association between quantitative ultrasound and bone mineral density measurements: A twin study. *J Bone Miner Res* **13:**1318–1327.
Howard GM, Nguyen T, Morrison N, Watanabe T, Sambrook P, Eisman J and Kelly P (1998b) Genetic influences on bone density: Physiological correlates of vitamin D receptor gene alleles in premenopausal women. Notification of genotype corrections [Letter]. *J Clin Endocrinol Metab* **83:**1043.
Howard GM, Nguyen TV, Pocock NA, Kelly PJ and Eisman JA (1997) Influence of handedness on calcaneal ultrasound: Implications for assessment of osteoporosis and study design. *Osteoporos Int* **7:**190–194.
Hui SL, Slemenda CW and Johnston CC Jr (1990) The contribution of bone loss to postmenopausal osteoporosis. *Osteoporos Int* **1:**30–34.
Hustmyer FG, Peacock M, Hui S, Johnston CC and Christian J (1994) Bone mineral density in relation to polymorphism at the vitamin D receptor gene locus. *J Clin Invest* **94:**2130–2134.
Jackman LA, Millane SS, Martin BR, Wood OB, McCabe GP, Peacock M and Weaver CM (1997) Calcium retention in relation to calcium intake and postmenarcheal age in adolescent females. *Am J Clin Nutr* **66:**327–333.
Jacobsen SJ, Cooper C, Gottlieb MS, Goldberg J, Yahnke DP and Melton LDJ (1992) Hospitalization with vertebral fracture among the aged: A national population-based study, 1986–1989 [see comments]. *Epidemiol* **3:**515–518.
Jilka RL, Weinstein RS, Takahashi K, Parfitt AM and Manolagas SC (1996) Linkage of decreased bone mass with impaired osteoblastogenesis in a murine model of accelerated senescence. *J Clin Invest* **97:**1732–1740.
Johnson ML, Gong G, Kimberling W, Recker SM, Kimmel DB and Recker RB (1997) Linkage of a gene causing high bone mass to human chromosome 11 (11q12–13) [see comments]. *Am J Hum Genet* **60:**1326–1332.
Johnson ML, Lappe M, Gong G, Recker RB, Little R, Del Mastro R, Osborne M, Tulig C and Carulli J (1998) Physical mapping and characterization of the high bone mass (HBM) gene region. *Bone* **23 (Suppl 5):**S161.
Johnston CC Jr and Slemenda CW (1992) Changes in skeletal tissue during the aging process. *Nutr Rev* **50:**385–387.
Johnston CC Jr and Slemenda CW (1993) Determinants of peak bone mass. *Osteoporos Int* **3:**54–55.
Johnston CC Jr and Slemenda CW (1994) Peak bone mass, bone loss and risk of fracture. *Osteoporos Int* **4:**43–45.
Johnston CJ, Miller JZ, Slemenda CW, Reister TK, Hui S, Christian JC and Peacock M (1992) Calcium supplementation and increases in bone mineral density in children [see comments]. *N Engl J Med* **327:**82–87.
Jones G, Nguyen T, Sambrook P, Kelly PJ and Eisman JA (1994a) Progressive loss of bone in the femoral neck in elderly people: Longitudinal findings from the Dubbo osteoporosis epidemiology study. *Br Med J* **309:**691–695.
Jones G, Nguyen T, Sambrook PN, Kelly PJ, Gilbert C and Eisman JA (1994b) Symptomatic fracture incidence in elderly men and women: The Dubbo Osteoporosis Epidemiology Study (DOES). *Osteoporos Int* **4:**277–282.
Jones G, White C, Nguyen T, Sambrook PN, Kelly PJ and Eisman JA (1996) Prevalent vertebral deformities: Relationship to bone mineral density and spinal osteophytosis in elderly men and women. *Osteoporos Int* **6:**233–239.
Jones G, White C, Sambrook P and Eisman J (1998) Allelic variation in the vitamin D receptor, lifestyle factors and lumbar spinal degenerative disease. *Ann Rheum Dis* **57:**94–99.
Jouanny P, Guillemin F, Kuntz C, Jeandel C and Pourel J (1995) Environmental and genetic factors affecting bone mass. Similarity of bone density among members of healthy families. *Arthritis Rheum* **38:**61–67.
Kajkenova O, Lecka-Czernik B, Gubrij I, Hauser SP, Takahashi K, Parfitt AM, Jilka RL, Manolagas SC and Lipschitz DA (1997) Increased adipogenesis and myelopoiesis in the bone marrow of SAMP6, a murine model of defective osteoblastogenesis and low turnover osteopenia. *J Bone Miner Res* **12:**1772–1779.
Kanis JA (1991) Calcium requirements for optimal skeletal health in women. *Calcif Tissue Int* **49:**S33–S41.
Kanis JA (1993) The incidence of hip fracture in Europe. *Osteoporos Int* **3:**10–15.

Kanis JA (1994a) Calcium nutrition and its implications for osteoporosis. Part I. Children and healthy adults [see comments]. *Eur J Clin Nutr* **48:**757–767.

Kanis JA (1994b) Calcium nutrition and its implications for osteoporosis. Part II. After menopause [see comments]. *Eur J Clin Nutr* **48:**833–841.

Kanis JA (1997) Osteoporosis: A view into the next century. *Neth J Med* **50:**198–203.

Kanis JA and McCloskey EV (1992) Epidemiology of vertebral osteoporosis. *Bone* **13:**S1–S10.

Kanis JA and Passmore R (1990) Calcium supplementation of the diet [Letter] [see comments]. *Br Med J* **300:**1523.

Keen RW, Egger P, Fall C, Major PJ, Lanchbury JS, Spector TD and Cooper C (1997a) Polymorphisms of the vitamin D receptor, infant growth, and adult bone mass. *Calcif Tissue Intl* **60:**233–235.

Keen RW, Hart DJ, Lanchbury JS and Spector TD(1997b) Association of early osteoarthritis of the knee with a Taq I polymorphism of the vitamin D receptor gene. *Arthritis Rheum* **40:**1444–1449.

Keen RW, Snieder H, Daniels J, Davies H, Chiano M, MacGregor AJ, Gewert D and Spector TD (1998a) A novel TGF-?1 gene polymorphism is linked and associated with hip BMD in female twins. *Bone* **23 (Suppl 5):**S161.

Keen RW, Woodford-Richens KL, Lanchbury JS and Spector TD (1998b) Allelic variation at the interleukin-1 receptor antagonist gene is associated with early postmenopausal bone loss at the spine. *Bone* **23:**367–371.

Kelly PJ, Hopper JL, Macaskill GT, Pocock NA, Sambrook PN and Eisman JA (1991) Genetic factors in bone turnover. *J Clin Endocrinol Metab* **72:**808–813.

Kelly PJ, Morrison NA, Sambrook PN, Nguyen TV and Eisman JA (1995) Genetic influences on bone turnover, bone density and fracture. *Eur J Endocrinol* **133:**265–271.

Kelly PJ, Nguyen T, Hopper J, Pocock N, Sambrook P and Eisman J (1993) Changes in axial bone density with age: A twin study. *J Bone Miner Res* **8:**11–17.

Kelly PJ Pocock NA, Sambrook PN and Eisman JA (1990a) Dietary calcium, sex hormones, and bone mineral density in men. *Br Med J* **300:**1361–1364.

Kelly PJ Twomey L, Sambrook PN and Eisman JA (1990b) Sex differences in peak adult bone mineral density. *J Bone Miner Res* **5:**1169–1175.

Khan KM, Green RM, A. Saul, Bennell KL, Crichton KJ, Hooper JL and Wark JD (1996) Retired elite female ballet dancers and nonathletic controls have similar bone mineral density at weightbearing sites. *J Bone Miner Res* **11:**1566–1574.

Kiel DP, Cupples LA, Myers RH, Hannan MT, Tucker KL, Booth SL, Ordovas J, Gagnon DR and Wilson PWF (1998) Bone mineral density (BMD), hip fracture and apolipoprotein E (ApoE) genotype. *Bone* **23 (Suppl 5):**S278.

Kiel DP, Myers RH, Cupples LA, Kong XF, Zhu XH, Ordovas J, Schaefer EJ, Felson DT, Rush D, Wilson PW, Eisman JA and Holick MF (1997) The BsmI vitamin D receptor restriction fragment length polymorphism (bb) influences the effect of calcium intake on bone mineral density. *J Bone Miner Res* **12:**1049–1057.

Kinyamu HK, Gallagher JC, Knezetic JA, DeLuca HF, Prahl JM and Lanspa SJ (1997a) Effect of vitamin D receptor genotypes on calcium absorption, duodenal vitamin D receptor concentration, and serum 1,25 dihydroxyvitamin D levels in normal women. *Calcif Tissue Int* **60:**491–495.

Kinyamu HK, Gallagher JC, Prahl JM, DeLuca HF, Petranick KM and Lanspa SJ (1997b) Association between intestinal vitamin D receptor, calcium absorption, and serum 1,25 dihydroxyvitamin D in normal young and elderly women. *J Bone Miner Res* **12:**922–928.

Kobayashi S, Inoue S, Hosoi T, Ouchi Y, Shiraki M and Orimo H (1996) Association of bone mineral density with polymorphism of the estrogen receptor gene. *J Bone Miner Res* **11:**306–311.

Krall EA and Dawson-Hughes B (1993) Heritable and life-style determinants of bone mineral density. *J Bone Miner Res* **8:**1–9.

Krall EA and Dawson-Hughes B (1995) Soft tissue body composition: Familial resemblance and independent influences on bone mineral density. *J Bone Miner Res* **10:**1944–1950.

Krall EA, Parry P, Lichter JB and Dawson-Hughes B (1995) Vitamin D receptor alleles and rates of bone loss: Influences of years since menopause and calcium intake. *J Bone Miner Res* **10:**978–984.

Kroger H, Heikkinen J, Laitinen K and Kotaniemi A (1992) Dual-energy X-ray absorptiometry in normal women: A cross-sectional study of 717 Finnish volunteers. *Osteoporos Int* **2:**135–140.

Kroger H, Tuppurainen M, Honkanen R, Alhava E and Saarikoski S (1994) Bone mineral density and risk factors for osteoporosis: A population-based study of 1600 perimenopausal women. *Calcif Tissue Int* **55:**1–7.

Kurland ES, Rosen CJ, Cosman F, McMahon D, Chan F, Shane E, Lindsay R, Dempster D and Bilezikian JP (1997) Insulin-like growth factor-I in men with idiopathic osteoporosis [see comments]. *J Clin Endocrinol Metab* **82:**2799–2805.

Langdahl BL, Knudsen JY, Jensen HK, Gregersen N and Eriksen EF (1997) A sequence variation: 713–8delC in the transforming growth factor-beta 1 gene has higher prevalence in osteoporotic women than in normal women and is associated with very low bone mass in osteoporotic women and increased bone turnover in both osteoporotic and normal women. *Bone* **20:**289–294.

Langdahl BL, Ralston SH, Grant SF and Eriksen EF (1998) An Sp1 binding site polymorphism in the COLIA1 gene predicts osteoporotic fractures in both men and women. *J Bone Miner Res* **13:**1384–1389.

Lazaretti-Castro M, Duarte-de-Oliveira MA, Russo EM and Vieira JG (1997) Vitamin D receptor alleles and bone mineral density in a normal premenopausal Brazilian female population. *Brazil J Med Biol Res* **30:**929–932.

Liden M, Wilen B, Ljunghall S and Melhus H (1998) Polymorphism at the Sp 1 binding site in the collagen type I alpha 1 gene does not predict bone mineral density in postmenopausal women in Sweden. *Calcif Tissue Int* **63:**293–295.

Lim SK, Park YS, Park JM, Song YD, Lee EJ, Kim KR, Lee HC and Huh KB (1995) Lack of association between vitamin D receptor genotypes and osteoporosis in Koreans [see comments]. *J Clin Endocrinol Metab* **80:**3677–3681.

Lips P (1997) Epidemiology and predictors of fractures associated with osteoporosis. *Am J Med* **103:**3S–8S; discussion 8S–11S.

Lonzer MD, Imrie R, Rogers D, Worley D, Licata A and Secic M (1996) Effects of heredity, age, weight, puberty, activity, and calcium intake on bone mineral density in children. *Clin Pediatr (Phila)* **35:**185–189.

Looney JE, Yoon HK, Fischer M, Farley SM, Farley JR, Wergedal JE and Baylink DJ (1995) Lack of a high prevalence of the BB vitamin D receptor genotype in severely osteoporotic women. *J Clin Endocrinol Metab* **80:**2158–2162.

Lysen VC and Walker R (1997) Osteoporosis risk factors in eighth grade students. *J Sch Health* **67:**317–321.

Masi L, Becherini L, Colli E, Gennari L, Mansani R, Falchetti A, Becorpi AM, Cepollaro C, Gonnelli S, Tanini A and Brandi ML (1998) Polymorphisms of the calcitonin receptor gene are associated with bone mineral density in postmenopausal Italian women. *Biochem Biophys Res Commun* **248:**190–195.

Massey LK and Whiting SJ (1996) Dietary salt, urinary calcium, and bone loss [see comments]. *J Bone Miner Res* **11:**731–736.

McClure L, Eccleshall TR, Gross C, Villa ML, Lin N, Ramaswamy V, Kohlmeier L, Kelsey JL, Marcus R and Feldman D (1997) Vitamin D receptor polymorphisms, bone mineral density, and bone metabolism in postmenopausal Mexican-American women. *J Bone Miner Res* **12:**234–240.

McDermott MF, Ramachandran A, Ogunkolade BW, Aganna E, Curtis D, Boucher BJ, Snehalatha C and Hitman GA (1997) Allelic variation in the vitamin D receptor influences susceptibility to IDDM in Indian Asians. *Diabetologia* **40:**971–975.

McKay HA, Bailey DA, Wilkinson AA and Houston CS (1994) Familial comparison of bone mineral density at the proximal femur and lumbar spine. *Bone Miner* **24:**95–107.

Melton LJD, Lane AW, Cooper C, Eastell R, O'Fallon WM and Riggs BL (1993) Prevalence and incidence of vertebral deformities. *Osteoporos Int* **3:**113–119.

Mizunuma H, Hosoi T, Okano H, Soda M, Tokizawa T, Kagami I, Miyamoto S, Ibuki Y, Inoue S, Shiraki M and Ouchi Y (1997) Estrogen receptor gene polymorphism and bone mineral density at the lumbar spine of pre- and postmenopausal women. *Bone* **21:**379–383.

Mocharla H, Butch AW, Pappas AA, Flick JT, Weinstein RS, De Togni P, Jilka RL, Roberson PK, Parfitt AM and Manolagas SC (1997) Quantification of vitamin D receptor mRNA by competitive polymerase chain reaction in PBMC: Lack of correspondence with common allelic variants. *J Bone Miner Res* **12:**726–733.

Morrison NA, Qi JC, Tokita A, Kelly PJ, Crofts L, Nguyen TV, Sambrook PN and Eisman JA (1994) Prediction of bone density from vitamin D receptor alleles [see comments]. *Nature (Lond)* **367:**284–287.

Morrison NA, Qi JC, Tokita A, Kelly PJ, Crofts L, Nguyen TV, Sambrook PN and Eisman JA (1997) Prediction of bone density from vitamin D receptor alleles [Correction]. *Nature (Lond)* **387:**106.

Morrison NA, Yeoman R, Kelly PJ and Eisman JA (1992) Contribution of trans-acting factor alleles to normal physiological variability: Vitamin D receptor gene polymorphism and circulating osteocalcin. *Proc Natl Acad Sci USA* **89:**6665–6669.

Murray RE, McGuigan F, Grant SF, Reid DM and Ralston SH (1997) Polymorphisms of the interleukin-6 gene are associated with bone mineral density. *Bone* **21:**89–92.

Nakamura T, Turner CH, Yoshikawa T, Slemenda CW, Peacock M, Burr DB, Mizuno Y, Orimo H, Ouchi Y and Johnston CJ (1994) Do variations in hip geometry explain differences in hip fracture risk between Japanese and white Americans? *J Bone Miner Res* **9:**1071–1076.

Need AG, Horowitz M, Stiliano A, Scopacasa F, Morris HA and Chatterton BE (1996) Vitamin D receptor genotypes are related to bone size and bone density in men. *Eur J Clin Invest* **26:**793–796.

Nguyen TV, Howard GM, Kelly PJ and Eisman JA (1998) Bone mass, lean mass, and fat mass: Same genes or same environments? [see comments]. *Am J Epidemiol* **147:**3–16.

Nguyen TV, Jones G, Sambrook PN, White CP, Kelly PJ and Eisman JA (1995) Effects of estrogen exposure and reproductive factors on bone mineral density and osteoporotic fractures. *J Clin Endocrinol Metab* **80:**2709–2714.

Nguyen TV, Kelly PJ, Morrison NA, Sambrook PN and Eisman JA (1994) Vitamin D receptor genotypes in osteoporosis [Letter]. *Lancet* **344:**1580–1581.

Nguyen TV, Morrison NA, Sambrook PN, Kelly PJ and Eisman JA (1996) Vitamin D receptor gene and osteoporosis [Letter]. *J Clin Endocrinol Metab* **81:**1674–1675.

Nieves JW, Grisso JA and Kelsey JL (1992) A case-control study of hip fracture: Evaluation of selected dietary variables and teenage physical activity. *Osteoporos Int* **2:**122–127.

Niu T, Chen C, Cordell H, Yang J, Wang B, Wang Z, Fang Z, Schork NJ, Rosen CJ and Xu X (1999) A genome-wide scan for loci linked to forearm bone mineral density. *Hum Genet* **104:**226–233.

Nordin BE (1997) Calcium and osteoporosis. *Nutrition* **13:**664–686.

Ongphiphadhanakul B, Rajatanavin R, Chanprasertyothin S, Chailurkit L, Piaseu N, Teerarungsikul K, Sirisriro R, Komindr S and Puavilai G (1997) Vitamin D receptor gene polymorphism is associated with urinary calcium excretion but not with bone mineral density in postmenopausal women. *J Endocrinol Invest* **20:**592–596.

Orwoll E, Belknap J, Phillips T and Kelin R (1998) Gender differences in bone mass are genetically determined: Quantitative trait loci analyses. *Bone* **23 (Suppl 5):**S275.

Orwoll ES, Bauer DC, Vogt TM and Fox KM (1996) Axial bone mass in older women. Study of Osteoporotic Fractures Research Group. *Ann Intern Med* **124:**187–196.

Paterson CR and Mole PA (1994) Bone density in osteogenesis imperfecta may well be normal [see comments]. *Postgrad Med J* **70:**104–107.

Pocock N, Eisman J, Gwinn T, Sambrook P, Kelly P, Freund J and Yeates M (1989a) Muscle strength, physical fitness, and weight but not age predict femoral neck bone mass. *J Bone Miner Res* **4:**441–448.

Pocock NA, Eisman JA, Kelly PJ, Sambrook PN and Yeates MG (1989b) Effects of tobacco use on axial and appendicular bone mineral density. *Bone* **10:**329–331.

Qi J, Morrison N, Nguyen T, White C, Kelly P, Sambrook P and Eisman J (1995) Estrogen receptor genotypes and bone mineral density in women and men. *J Bone Miner Res* **10 (Suppl 1):**S170.

Randell A, Sambrook PN, Nguyen TV, Lapsley H, Jones G, Kelly PJ and Eisman JA (1995) Direct clinical and welfare costs of osteoporotic fractures in elderly men and women. *Osteoporos Int* **5:**427–432.

Rauch F, Radermacher A, Danz A, Schiedermaier U, Golucke A, Michalk D and Schonau E (1997) Vitamin D receptor genotypes and changes of bone density in physically active German women with high calcium intake. *Exp Clin Endocrinol Diabetes* **105:**103–108.

Ray NF, Chan JK, Thamer M and Melton LJR (1997) Medical expenditures for the treatment of osteoporotic fractures in the United States in 1995: Report from the National Osteoporosis Foundation. *J Bone Miner Res* **12:**24–35.

Recker RR, Davies KM, Hinders SM, Heaney RP, Stegman MR and Kimmel DB (1992) Bone gain in young adult women [see comments]. *J Am Med Assoc* **268:**2403–2408.

Reid IR, Ames R, Evans MC, Sharpe S, Gamble G, France JT, Lim TM and Cundy TF (1992a)

Determinants of total body and regional bone mineral density in normal postmenopausal women: A key role for fat mass. *J Clin Endocrinol Metab* **75:**45–51.
Reid IR, Evans MC and Ames RW (1994) Volumetric bone density of the lumbar spine is related to fat mass but not lean mass in normal postmenopausal women. *Osteoporos Int* **4:**362–367.
Reid IR, Evans MC, Cooper GJ, Ames RW and Stapleton J (1993) Circulating insulin levels are related to bone density in normal postmenopausal women. *Am J Physiol* **265:**E655–E659.
Reid IR, Plank LD and Evans MC (1992b) Fat mass is an important determinant of whole body bone density in premenopausal women but not in men. *J Clin Endocrinol Metab* **75:**779–782.
Riggs BL, Nguyen TV, Melton LJR, Morrison NA, O'Fallon WM, Kelly PJ, Egan KS, Sambrook PN, Muhs JM and Eisman JA (1995) The contribution of vitamin D receptor gene alleles to the determination of bone mineral density in normal and osteoporotic women. *J Bone Miner Res* **10:**991–996.
Riis B, Hansen M, Jensen A, Overgaard K and Christiansen C (1996) Low bone mass and fast rate of bone loss at menopause: Equal risk factors for future fracture: A 15-year follow-up study. *Bone* **19:**9–12.
Rosen C, Beamer W and Donahue L (1998a) Assessing IGF-I dependent and independent loci that regulate femoral bone density by development of congenic little mice. *Bone* **23 (Suppl 5):**S162.
Rosen CJ, Dimai HP, Vereault D, Donahue LR, Beamer WG, Farley J, Linkhart S, Linkhart T, Mohan S and Baylink DJ (1997) Circulating and skeletal insulin-like growth factor-I (IGF-I) concentrations in two inbred strains of mice with different bone mineral densities [see comments]. *Bone* **21:**217–223.
Rosen CJ and Donahue LR (1998) Insulin-like growth factors and bone: The osteoporosis connection revisited. *Proc Soc Exp Biol Med* **219:**1–7.
Rosen CJ, Kurland ES, Vereault D, Adler RA, Rackoff PJ, Craig WY, Witte S, Rogers J and Bilezikian JP (1998b) Association between serum insulin growth factor-I (IGF-I) and a simple sequence repeat in IGF-I gene: Implications for genetic studies of bone mineral density. *J Clin Endocrinol Metab* **83:**2286–2290.
Sainz J, Van Tornout JM, Loro ML, Sayre J, Roe TF and Gilsanz V (1997) Vitamin D-receptor gene polymorphisms and bone density in prepubertal American girls of Mexican descent [see comments]. *N Engl J Med* **337:**77–82.
Salamone LM, Ferrell R, Black DM, Palermo L, Epstein RS, Petro N, Steadman N, Kuller LH and Cauley JA (1996a) The association between vitamin D receptor gene polymorphisms and bone mineral density at the spine, hip and whole-body in premenopausal women [published erratum appears in *Osteoporos Int* (1996) **6:**187–188]. *Osteoporos Int* **6:**63–68.
Salamone LM, Glynn NW, Black DM, Ferrell RE, Palermo L, Epstein RS, Kuller LH and Cauley JA (1996b) Determinants of premenopausal bone mineral density: The interplay of genetic and lifestyle factors. *J Bone Miner Res* **11:**1557–1565.
Sambrook P, Birmingham J, Kempler S, Kelly P, Eberl S, Pocock N, Yeates M and Eisman J (1990) Corticosteroid effects on proximal femur bone loss. *J Bone Miner Res* **5:**1211–1216.
Sambrook PN, Cohen ML, Eisman JA, Pocock NA, Champion GD and Yeates MG (1989) Effects of low dose corticosteroids on bone mass in rheumatoid arthritis: A longitudinal study. *Ann Rheum Dis* **48:**535–538.
Seeman E (1994) Reduced bone density in women with fractures: Contribution of low peak bone density and rapid bone loss. *Osteoporos Int* **4:**15–25.
Seeman E (1995) The dilemma of osteoporosis in men. *Am J Med* **98:**76S–88S.
Seeman E, Hooper JL, Young NR, Formica C, Goss P and Tsalamandris C (1996) Do genetic factors explain associations between muscle strength, lean mass, and bone density? A twin study. *Am J Physiol* **270:**E320–E327.
Seeman E, Tsalamandris C, Formica C, Hooper JL and McKay J (1994) Reduced femoral neck bone density in the daughters of women with hip fractures: The role of low peak bone density in the pathogenesis of osteoporosis. *J Bone Miner Res* **9:**739–743.
Sessions ND, Halloran BP, Bikle DD, Wronski TJ, Cone CM and Morey-Holton E (1989) Bone response to normal weight bearing after a period of skeletal unloading. *Am J Physiol* **257:**E606–E610.
Shapiro JR, Stover ML, Burn VE, McKinstry MB, Burshell AL, Chipman SD and Rowe DW (1992) An osteopenic nonfracture syndrome with features of mild osteogenesis imperfecta associated with the substitution of a cysteine for glycine at triple helix position 43 in the pro alpha 1(I) chain of type I collagen. *J Clin Invest* **89:**567–573.
Shiraki M, Shiraki Y, Aoki C, Hosoi T, Inoue S, Kaneki M and Ouchi Y (1997) Association of bone mineral density with apolipoprotein E phenotype. *J Bone Miner Res* **12:**1438–1445.
Slemenda CW, Christian JC, Reed T, Reister TK, Williams CJ and Johnston CC Jr (1992) Long-term bone loss in men: Effects of genetic and environmental factors. *Ann Intern Med* **117:**286–291.
Slemenda CW, Christian JC, Williams CJ, Norton JA and Johnston CC Jr (1991a) Genetic determinants of bone mass in adult women: A reevaluation of the twin model and the potential importance of gene interaction on heritability estimates. *J Bone Miner Res* **6:**561–567.
Slemenda CW, Hui SL, Longcope C, Wellman H and Johnston CC Jr (1990a) Predictors of bone mass in perimenopausal women. A prospective study of clinical data using photon absorptiometry. *Ann Intern Med* **112:**96–101.
Slemenda CW, Hui SL, Williams CJ, Christian JC, Meaney FJ and Johnston CC Jr (1990b) Bone mass and anthropometric measurements in adult females. *Bone Miner* **11:**101–109.
Slemenda CW and Johnston CC (1993) High intensity activities in young women: Site specific bone mass effects among female figure skaters. *Bone Miner* **20:**125–132.
Slemenda CW, Longcope C, Zhou L, Hui SL, Peacock M and Johnston CC (1997) Sex steroids and bone mass in older men. Positive associations with serum estrogens and negative associations with androgens. *J Clin Invest* **100:**1755–1759.
Slemenda CW, Miller JZ, Hui SL, Reister TK and Johnston CC Jr (1991b) Role of physical activity in the development of skeletal mass in children. *J Bone Miner Res* **6:**1227–1233.
Slemenda CW, Reister TK, Hui SL, Miller JZ, Christian JC and Johnston CC Jr (1994) Influences on skeletal mineralization in children and adolescents: Evidence for varying effects of sexual maturation and physical activity. *J Pediatr* **125:**201–207.
Slemenda CW, Turner CH, Peacock M, Christian JC, Sorbel J, Hui SL and Johnston CC (1996) The genetics of proximal femur geometry, distribution of bone mass and bone mineral density. *Osteoporos Int* **6:**178–182.
Soroko SB, Barrett-Connor E, Edelstein SL and Kritz-Silverstein D (1994) Family history of osteoporosis and bone mineral density at the axial skeleton: The Rancho Bernardo Study. *J Bone Miner Res* **9:**761–769.
Soule SG, Conway G, Prelevic GM, Prentice M, Ginsburg J and Jacobs HS (1995) Osteopenia as a feature of the androgen insensitivity syndrome. *Clin Endocrinol* **43:**671–675.
Sowers MR, Boehnke M, Jannausch ML, Crutchfield M, Corton G and Burns TL (1992) Familiality and partitioning the variability of femoral bone mineral density in women of child-bearing age. *Calcif Tissue Int* **50:**110–114.
Spector TD, McCloskey EV, Doyle DV and Kanis JA (1993) Prevalence of vertebral fracture in women and the relationship with bone density and symptoms: The Chingford Study. *J Bone Miner Res* **8:**817–822.
Spotila LD, Caminis J, Devoto M, Shimoya K, Sereda L, Ott J, Whyte MP, Tenenhouse A and Prockop DJ (1996a) Osteopenia in 37 members of seven families: Analysis based on a model of dominant inheritance. *Mol Med* **2:**313–324.
Spotila LD, Caminis J, Johnston R, Shimoya KS, O'Connor MP, Prockop DJ, Tenenhouse A and Tenenhouse HS (1996b) Vitamin D receptor genotype is not associated with bone mineral density in three ethnic/regional groups. *Calcif Tissue Int* **59:**235–237.
Spotila LD, Colige A, Sereda L, Constantinou-Deltas CD, Whyte MP, Riggs BL, Shaker JL, Spector TD, Hume E, Olsen N, et al. (1994) Mutation analysis of coding sequences for type I procollagen in individuals with low bone density. *J Bone Miner Res* **9:**923–932.
Spotila LD, Constantinou CD, Sereda L, Ganguly A, Riggs BL and Prockop DJ (1991) Mutation in a gene for type I procollagen (COL1A2) in a woman with postmenopausal osteoporosis: Evidence for phenotypic and genotypic overlap with mild osteogenesis imperfecta. *Proc Natl Acad Sci USA* **88:**5423–5427.
Suarez F, Zeghoud F, Rossignol C, Walrant O and Garabedian M (1997) Association between vitamin D receptor gene polymorphism and sex-dependent growth during the first two years of life. *J Clin Endocrinol Metab* **82:**2966–2970.
Tamai M, Yokouchi M, Komiya S, Mochizuki K, Hidaka S, Narita S, Inoue A and Itoh K (1997) Correlation between vitamin D receptor genotypes and bone mineral density in Japanese patients with osteoporosis. *Calcif Tissue Int* **60:**229–232.
Teegarden D, Proulx WR, Martin BR, Zhao J, McCabe GP, Lyle RM, Peacock M, Slemenda C, Johnston CC and Weaver CM (1995) Peak bone mass in young women. *J Bone Miner Res* **10:**711–715.
Tokita A, Kelly PJ, Nguyen TV, Qi JC, Morrison NA, Risteli L, Risteli J, Sambrook PN and Eisman JA (1994) Genetic influences on type I collagen synthesis and degradation: Further evidence for genetic regulation of bone turnover. *J Clin Endocrinol Metab* **78:**1461–1466.
Tokita A, Matsumoto H, Morrison NA, Tawa T, Miura Y, Fukamauchi K, Mitsuhashi N, Irimoto M, Yamamori S, Miura M, et al. (1996) Vitamin D receptor alleles, bone mineral density and turnover in premenopausal Japanese women [see comments]. *J Bone Miner Res* **11:**1003–1009.
Torgerson DJ, Campbell MK, Thomas RE and Reid DM (1996) Prediction of perimenopausal fractures by bone mineral density and other risk factors. *J Bone Miner Res* **11:**293–297.
Tsai KS, Hsu SH, Cheng WC, Chen CK, Chieng PU and Pan WH (1996) Bone mineral density and bone markers in relation to vitamin D receptor gene polymorphisms in Chinese men and women. *Bone* **19:**513–518.
Tsuji S, Munkhbat B, Hagihara M, Tsuritani I, Abe H and Tsuji K (1998) HLA-A*24-B*07-DRB1*01 haplotype implicated with genetic disposition of peak bone mass in healthy young Japanese women. *Hum Immunol* **59:**243–249.
Tsukamoto K, Yoshida H, Watanabe S, Suzuki T, Miyao M, Hosoi T, Orimo H and Emi M (1999) Association of radial bone mineral density with CA repeat polymorphism at the interleukin 6 locus in postmenopausal Japanese women. *J Hum Genet* **44:**148–151.
Tuppurainen M, Honkanen R, Kroger H, Saarikoski S and Alhava E (1993) Osteoporosis risk factors, gynaecological history and fractures in perimenopausal women: The results of the baseline postal enquiry of the Kuopio Osteoporosis Risk Factor and Prevention Study. *Maturitas* **17:**89–100.
Uitterlinden AG, Burger H, Huang Q, Odding E, Duijn CM, Hofman A, Birkenhager JC, van Leeuwen JP and Pols HA (1997) Vitamin D receptor genotype is associated with radiographic osteoarthritis at the knee. *J Clin Invest* **100:**259–263.
Uitterlinden AG, Burger H, Huang Q, Yue F, McGuigan FE, Grant SF, Hofman A, van Leeuwen JP, Pols HA and Ralston SH (1998) Relation of alleles of the collagen type Ialpha1 gene to bone density and the risk of osteoporotic fractures in postmenopausal women [see comments]. *N Engl J Med* **338:**1016–1021.
Uitterlinden AG, Pols HA, Burger H, Huang Q, Van Daele PL, Van Duijn CM, Hofman A, Birkenhager JC and Van Leeuwen JP (1996) A large-scale population-based study of the association of vitamin D receptor gene polymorphisms with bone mineral density. *J Bone Miner Res* **11:**1241–1248.
Ulrich CM, Georgiou CC, Snow-Harter CM and Gillis DE (1996) Bone mineral density in mother-daughter pairs: Relations to lifetime exercise, lifetime milk consumption and calcium supplements. *Am J Clin Nutr* **63:**72–79.
Vandevyver C, Wylin T, Cassiman JJ, Raus J and Geusens P (1997) Influence of the vitamin D receptor gene alleles on bone mineral density in postmenopausal and osteoporotic women. *J Bone Miner Res* **12:**241–247.
Viitanen A, Karkkainen M, Laitinen K, Lamberg-Allardt C, Kainulainen K, Rasanen L, Viikari J, Valimaki MJ and Kontula K (1996) Common polymorphism of the vitamin D receptor gene is associated with variation of peak bone mass in young Finns. *Calcif Tissue Int* **59:**231–234.
Wastney ME, Ng J, Smith D, Martin BR, Peacock M and Weaver CM (1996) Differences in calcium kinetics between adolescent girls and young women. *Am J Physiol* **271:**R208–R216.
Weaver CM, Martin BR, Plaweck KL, Peacock M, Wood OB, Smith DL and Wastney ME (1995) Differences in calcium metabolism between adolescent and adult females. *Am J Clin Nutr* **61:**577–581.
Weaver CM, Peacock M, Martin BR, Plaweck KL and McCabe GP (1996) Calcium retention estimated from indicators of skeletal status in adolescent girls and young women. *Am J Clin Nutr* **64:**67–70.
Willing M, Sowers M, Aron D, Clark MK, Burns T, Bunten C, Crutchfield M, D'Agostino D and Jannausch M (1998) Bone mineral density and its change in white women: Estrogen and vitamin D receptor genotypes and their interaction. *J Bone Miner Res* **13:**695–705.
Willing MC, Torner JC, Burns TL, Segar ET and Werner JR (1997) Determinants of bone mineral density in postmenopausal white Iowans. *J Gerontol A Biol Sci Med Sci* **52:**M337–M342.
Wishart JM, Horowitz M, Need AG, Scopacasa F, Morris HA, Clifton PM and Nordin BE (1997) Relations between calcium intake, calcitriol, polymorphisms of the vitamin D receptor gene and calcium absorption in premenopausal women. *Am J Clin Nutr* **65:**798–802.
Xu L, Lu A, Zhao X, Chen X and Cummings SR (1996) Very low rates of hip fracture in Beijing, People's Republic of China the Beijing Osteoporosis Project. *Am J Epidemiol* **144:**901–907.
Yamagata Z, Miyamura T, Iijima S, Asaka A, Sasaki M, Kato J and Koizumi K (1994) Vitamin

D receptor gene polymorphism and bone mineral density in healthy Japanese women [Letter]. *Lancet* **344:**1027.

Yokoyama K, Shigematsu T, Tsukada T, Ogura Y, Takemoto F, Hara S, Yamada A, Kawaguchi Y and Hosoya T (1998) Apa I polymorphism in the vitamin D receptor gene may affect the parathyroid response in Japanese with end-stage renal disease. *Kidney Int* **53:**454–458.

Young D, Hooper JL, Nowson CA, Green RM, Sherwin AJ, Kaymakci B, Smid M, Guest CS, Larkins RG and Wark JD (1995) Determinants of bone mass in 10- to 26-year-old females: A twin study. *J Bone Miner Res* **10:**558–567.

Young T, Villagomez S, Yershov Y, Gupta R, Martin ML, Paschalis EP, Demant P, Bockman RS and Blank RD (1998) Bone strength segregates in HcB/Dem recombinant congenic mouse strains. *Bone* **23 (Suppl 5):**S277.

Zmuda JM, Cauley JA, Danielson ME, Wolf RL and Ferrell RE (1997) Vitamin D receptor gene polymorphisms, bone turnover and rates of bone loss in older African-American women. *J Bone Miner Res* **12:**1446–1452.

Zmuda J, Cauley J and Ferrell R (1999) Recent progress in understanding the genetic susceptibility to osteoporosis. *Genet Epidemiol* **16:**356–367.