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Genetics of Osteoporosis

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I. Introduction

OSTEOPOROSIS is a common disease affecting the majority of older women and a significant minority of older men. It is defined as the gradual reduction in bone strength with advancing age, particularly in women post menopause, such that bones fracture with minimal trauma (1–4). Although fractures of the hip, wrist, and spine are often focused upon, almost any bone can fracture (5–21). Age *per se* is the strongest risk factor for osteoporotic fracture; however, the variance in bone density is similar across all ages. A range of hormonal and environmental factors heighten the risk of osteoporosis, yet together these risk factors explain only a small proportion of the overall risk. Trauma is an important factor with the event of fracture often the result of a relatively weak bone being subjected to force, such as in a fall. Any bone will fracture if subjected to excessive force, *e.g.*, in a motor vehicle accident. However weakened, osteoporotic bones can fracture without any obvious antecedent trauma. This complete spectrum in bone strength is the focus of this review, particularly the genetic factors that may influence sensitivity to environmental and hormonal factors. These factors and their interactions contribute to the end result of bone strength in later adult life when the risk for osteoporotic fractures rises.

Osteoporosis is one of the major and growing health care problems around the world largely related to the general aging of societies with improvement in public and preventive health and delay in mortality. In a recent community-based study in an Australian country town, it was estimated that for a 60-yr-old Caucasian woman the remaining life-time risk of an osteoporotic fracture was about 60% and almost 30% for a man of the same age (5). Moreover, the prevalence of vertebral deformities and fractures, including those in men, appears to have been underestimated (8, 12, 17, 18, 22–24). Based on the Australian population mentioned above, the overall direct costs, including rehabilitation, of osteoporosis in both men and women were estimated to be about 30 million US$ per million of population annually (25). A similar population-based analysis in the United States in 1995 estimated 52.5 million US$ per million (26). The age-adjusted incidence of hip fractures is reported to be lower in Asian than Caucasian populations, but there are wide differences in the incidence of hip fractures even across various Caucasian communities (14, 24, 27–30). However, osteoporosis is becoming a major problem even in developing countries and, by the middle of the next century, more hip fractures are predicted in the populous Asian countries than in the rest of the world combined (7, 14, 18, 24, 27–30). The difference in incidence between ethnic and racial groups may relate to environmental factors, but also may reflect inherited differences in susceptibility. Thus osteoporosis affects both women and men and has an impact comparable to, if not greater than, the major health problems, such as cardiovascular disease and malignancy. Given the increased mortality associated with major osteoporotic fractures (6, 31, 32), the impact of this disease on mortality also cannot be ignored. Understanding the inherited factors involved and their potential interaction with environmental factors may hold the key to better prevention and treatment.

The likelihood of a fracture event relates to the forces applied and the strength of the bone (33) and of course to the duration of observation. Fractures without major trauma, *e.g.*, falls from standing height or less, suggest inadequate structural integrity of the bone. Falls are important contributors to fracture risk; however, their causes are beyond the scope of this review. Bone strength relates to the total amount of bone and to its structural and microstructural integrity. These latter components are measured to some extent independently of bone size by quantitative ultrasound, which is also predictive of fracture risk independent of bone density (34–37). Bone strength depends upon the total amount of bone, size, and density as well as its structural and material properties. The bone mass of an individual at any time in their life depends upon the amount of bone formed and

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consolidated by the late teens or early twenties and the subsequent loss with aging and postmenopause (38–48). The determinants of peak bone mass, turnover, and loss are a major focus of osteoporosis research. The role of genetic factors as a determinant of these phenotypic characteristics is the subject of this review.

II. Determinants of Bone Mass

The assessment of bone structure is particularly important in relation to genetic studies. The tools used over the past few decades have advantages over earlier invasive measurements, which were not readily applicable for large population studies. The new noninvasive techniques include the radiological measures of quantitative computerized tomography and more recently dual photon absorptiometry or dual energy x-ray absorptiometry. However, these techniques do not completely correct for bone size, which may itself be under genetic control. Quantitative ultrasound has also been shown to provide comparable predictive power for osteoporotic fracture risk in some epidemiological studies (34, 35). Although there is debate about the best parameter (*e.g.*, ultrasound velocity or broad band attenuation) or site of measurement (*e.g.*, heel, digit) this approach has the potential advantage of lesser influence from bone and body size. Each of the densitometric and ultrasound techniques has particular advantages and disadvantages but their safety and noninvasive nature have allowed rapid expansion of knowledge of the behavior of bone and the prediction of fracture risk. Bone phenotype measured by any of these techniques remains the most powerful predictor of subsequent fracture risk.

Peak bone mass achieved by late childhood-early adulthood appears to be under genetic control but also is influenced by life-style factors such as physical loading and calcium intake. With puberty, bone mass increases about 3-fold over just a few years (46, 49–51) and remains relatively stable thereafter until the late forties or early fifties after which it starts to decline in both men and women. There is accelerated bone loss with sex hormone deficiency after the onset of menopause and for 10–15 yr after (13, 40, 44, 48, 52–54). This also occurs with estrogen deficiency of any cause, *e.g.*, due to anorexia. Bone loss continues and actually accelerates with aging in both men and women (55). Thus, bone mass in later life depends upon peak bone mass achieved and subsequent loss due to natural aging processes and various hormone-deficiency and disease-related insults (Fig. 1). Androgen deficiency is also associated with osteoporosis in men (56–58). Importantly, sex hormone deficiency-related bone loss can be prevented and at least partially reversed by estrogen replacement (44, 54, 59–61) and to a somewhat lesser extent by treatment with selective estrogens (62).

Medical diseases, including malabsorption, renal dysfunction, respiratory diseases, immobilization, rheumatoid arthritis, immunological disorders, and hematopoietic malignancies, can have a major impact on bone in individuals. In these situations the underlying disease and its associated morbidity and mortality are usually more important than the effect on bone, but treatment, particularly with corticosteroids, can have a major effect on bone, and corticosteroid-associated osteoporosis is a major side effect. Interestingly, some people seem more (or less) sensitive to the effects of corticosteroids. This may reflect gene-environment interactions and, although little is known is this area, it will likely be an important area for future research.

Before considering the effect of inherited factors on bone mass, it is necessary to consider the effects of lifestyle and hormonal factors. The actual effect of these factors may relate to underlying inherited susceptibilities or resistances. Lifestyle factors include diet, exercise, alcohol intake, and to-

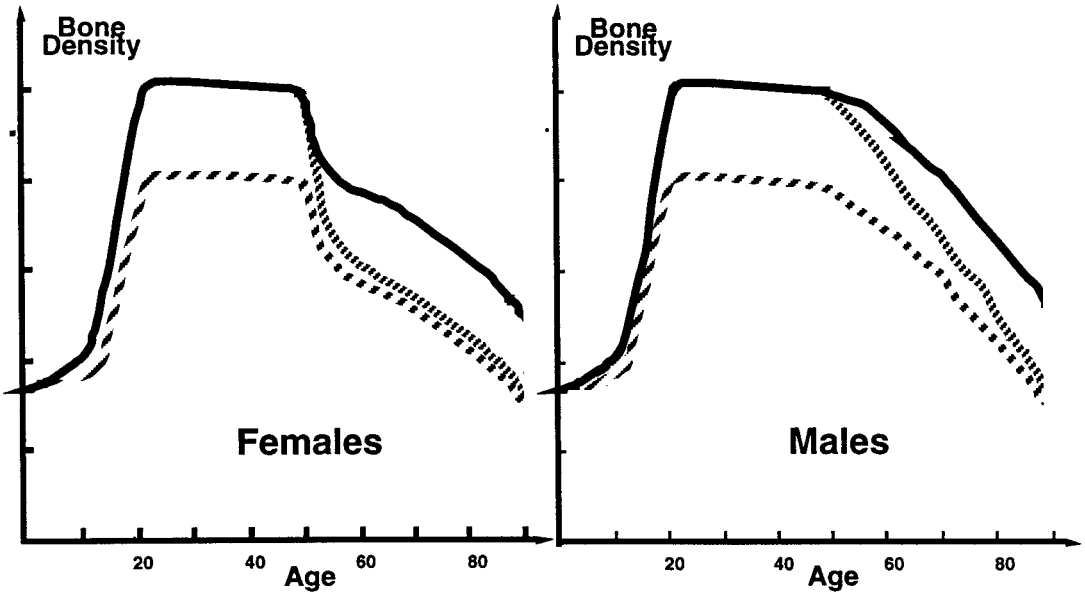

FIG. 1. Bone density change with age in women and men. Bone density (*solid lines*) follows a gradual decline from the peak values achieved by early adulthood in both women (*left panel*) and men (*right panel*). In women there is additional loss due to menopause. Low bone density in later life thus can result from achievement of a relatively low peak bone density (*dashed line*) or excessive bone loss (*dotted line*) with advancing age in both men and women. Both adverse patterns may coexist in some individuals.

bacco use among a range of others that are less well characterized. Excessive intake of common salt (NaCl), phosphate, caffeine, and excessive use of tobacco and alcohol have been associated with increased fracture incidence in epidemiological studies (1, 11, 60, 63–66). Dietary intake of calcium has been a major focus. Although dietary calcium is considered an important component of skeletal development, there is considerable disagreement about what is "adequate" (1, 30, 45, 46, 50, 51, 54, 63, 67–76). Intakes of 1,200–1,500 mg/day have been recommended around puberty and after menopause and 800–1,000 mg/day suggested for other life stages. The rationale for such figures is difficult to establish. In many countries, particularly those with little dairy intake for cultural reasons, the average dietary calcium intake is considerably below those figures, yet the age-adjusted incidence of osteoporotic fracture is not notably increased. Such discrepancies may relate to ethnic or racial differences in sensitivity to these environmental factors or to bone size or geometry or be confounded by other lifestyle factors (77, 78). Interestingly, lactase deficiency, which could be expected to result in lower calcium intake by limiting dairy intake, was not associated with differences in bone density in one mid-Western United States twin study (79). These apparent discrepancies between dietary calcium intake and osteoporotic fracture incidence may also relate to inherited components of calcium handling, which will be addressed below.

Physical loading on the skeleton has a role in maintaining bone mass. This effect is most apparent in studies of immobilization and micro-gravity, which result in rapid bone loss in animal as well as human models (44, 46, 49, 80–87). In athletes, increased loading has been shown to be associated with increased bone mass often localized to the sites of loading (88–90). Life-long loading may be central to such effects in view of limited evidence of beneficial bone effect of achievable physical exercise levels and duration in older people. The "dose-response" between bone mass and physical loading over the physiologically relevant range is shallow and variable. It is unclear to what extent genetic factors may have an impact on that relationship.

Hormonal factors include sex hormone deficiency as well as excesses of glucocorticoids, T_4, and PTH. Certainly the best characterized effect on the skeleton is the accelerated loss that occurs in relation to sex hormone deficiency and continues for at least 10–15 yr after menopause. The rate and extent of this bone loss vary widely between individuals, leading to categorization of slow and fast losers. The mechanisms for these differences are unexplained but appear to depend in part upon inherited factors. Glucocorticoid excess, either endogenous as in Cushing's disease or from exogenous sources for therapeutic reasons, results in significant bone loss (91, 92). A limiting factor for long-term use of glucocorticoids can be their effects on bone mass resulting in severe osteoporosis. Nevertheless, there is no clear relationship between the level of glucocorticoid exposure and the resultant loss of bone. This also indicates the possible operation of inherited factors relating to the sensitivity of bone to glucocorticoids. Similar variability of effects on bone can be seen for thyroid hormone excess (2, 11). Finally, the effect of PTH excess on bone mass, particularly of cortical bone mass, has been reported in hyperparathyroidism (92a, 92b). However, PTH has anabolic effects on bone and therapy with PTH has been associated with increases in bone mass. For this hormone the final effect may relate to its competing effects on bone formation and resorption, and genetic factors may modulate the development and/or progression of hyperparathyroidism.

III. Inherited Predisposition For and Against Osteoporosis

Several key studies have focused on the inheritance of the predisposition to development of osteoporotic fractures. Although not always considered, inherited factors are logically as likely to operate to protect against as to predispose to the development of osteoporosis. Generally, epidemiological studies have examined family history of osteoporotic fracture as a risk factor for the development of osteoporotic fracture (3, 4, 46–48, 93–102). In such epidemiological studies, which necessarily examine this relationship on a group rather than an individual basis, family history of fractures and indeed specific types of fractures are consistent with an inherited component (3, 93, 96–98). Importantly, any apparent inherited predisposition to fracture would not necessarily be related to inherited alterations in bone strength. For example, predisposition to falling and, for that matter, longevity *per se* would increase the apparent risk obtained from a family history. However, family studies have demonstrated that mothers with osteoporotic fractures have daughters with lower bone density. Interestingly, the bone density "deficit" seems to be relatively specific for skeletal sites (3, 93, 96–98). Thus, it seems that a large part of the inherited predisposition to osteoporotic fractures is due to inherited factors in bone mass, density, and/or material quality of bone. The concept of inherited predisposition in terms of bone mass leads naturally to the question of how such an inherited predisposition could be mediated. The assumption has been that it would be the result of the interaction between a relatively large number of genes, *i.e.*, complex multifactorial genetic factors.

Child-parent resemblances are taken for granted in terms of externally obvious and less obvious traits, such as personality. Yet relatively little is known about the mediation of such apparently genetically determined traits. Indeed the degree of physical resemblance varies widely, yet such resemblances relate to a range of structural parameters, such as height and build. Presumably, bone mass is one of these genetically modulated parameters. Groups involved in osteoporosis research have been particularly interested in addressing how the familial similarity in various anthropomorphic features could translate to similarities in bone density.

A number of family (and animal) studies of bone density have now shown apparently high levels of heritability of bone phenotype, as assessed by bone densitometry (3, 4, 46, 83, 86, 94–98, 100, 101, 103–112). Other studies of familial association have shown similarly high degrees of heritability for other parameters such as quantitative ultrasound (105, 113). Overall these studies suggest that 60–80% of variance in bone phenotype measurement at any age or group is

genetically determined. One interesting study of young girls and their mothers indicated half-heritability contributions of 23–35%. This would be equivalent to 46–70% heritability from both parents if, as suggested from other studies, there are similar contributions from both parents (114). Moreover, this heritability, which was comparable to that for height (38%), was apparent in these girls before puberty, and the correlation changed little as they progressed through puberty (114). These data are consistent with genetic factors playing a major role in inherent bone structural characteristics and skeletal size and that these heritable effects are already programmed before puberty. Recent studies have started to address the extent to which other anthropomorphic parameters segregate with bone density and other bone phenotypes. They suggest that a significant part of the heritability is related to shared genetic contributions to skeletal size and body composition. These studies also suggest that there are both shared and distinct genetic factors contributing to the determination of bone density at different skeletal sites. These data are yet to be extended to examine differences between ethnic and racial groups.

IV. Genetic Factors in Bone Phenotype

Family-based studies can be confounded by the inevitable comparisons of individuals of widely different ages and year-of-birth cohorts and by familial similarities in lifestyle choices (46–48, 66, 86, 94, 95, 104). Heritability has been investigated using the twin model by studying the relative degree of the difference between monozygotic (identical) and same-sex dizygotic (nonidentical) twins. These analyses make the assumption that twin pairs of the same age and sex share their environments and other lifestyle factors to a similar extent whether they are mono- or dizygotic. This assumption can be and usually is examined for many external factors that could impact on bone phenotype. Incidentally, monozygotic twins can be used to examine the impact of various environmental and lifestyle factors since the twin pairs are of the same age, sex, and genetic make-up (66, 115, 116).

Using this approach we (see Fig. 2) and others have shown that both lumbar spine and femoral neck bone density are more similar in monozygotic than in dizygotic twins (39, 66, 105, 107–112, 118–120). This genetic effect appeared to be greater at some sites than others, however it is not clear whether this relates to real differences in genetic *vs.* environmental effects or to the relative precision of measurement at any site or even side-to-side differences (37). Overall, however, several studies suggest that different genes may regulate bone density at different skeletal sites as measured by different modalities such as densitometry and ultrasound (105, 109, 110, 112, 113). More recent studies have shown similar genetic determination of bone parameters assessed by quantitative ultrasound and bone geometry (66, 105, 108, 120, 121). In several such studies 50–80% of the age-related variability of bone phenotypic parameters appeared to be genetically determined.

The concept of genetic effects on bone would have relatively little clinical utility, if it were not possible to relate such genetic factors to identification of high-risk groups or to the better understanding of cause-and-effect leading to improved interventions. To understand and apply these concepts, it is useful to consider the difference between continuous and discontinuous models of genetic effects (Fig. 3). Clinicians are familiar with the discontinuous model of genetic "disease" due to loss-of-function or, less commonly, gain-of-function mutation of a gene or genes. This model is entirely appropriate to disorders of bone structure and function such as osteogenesis imperfecta or osteopetrosis with major effects on structural components of bone (*e.g.*, collagen), or on the normal development of bone cells (*e.g.*, osteoclasts). However, these are clinical entities distinct from the clinical disease of osteoporosis that affects such a high proportion of elderly men and women. Less severe mutations in these pathways could be associated with less severe disease, and indeed individuals with premature osteoporosis

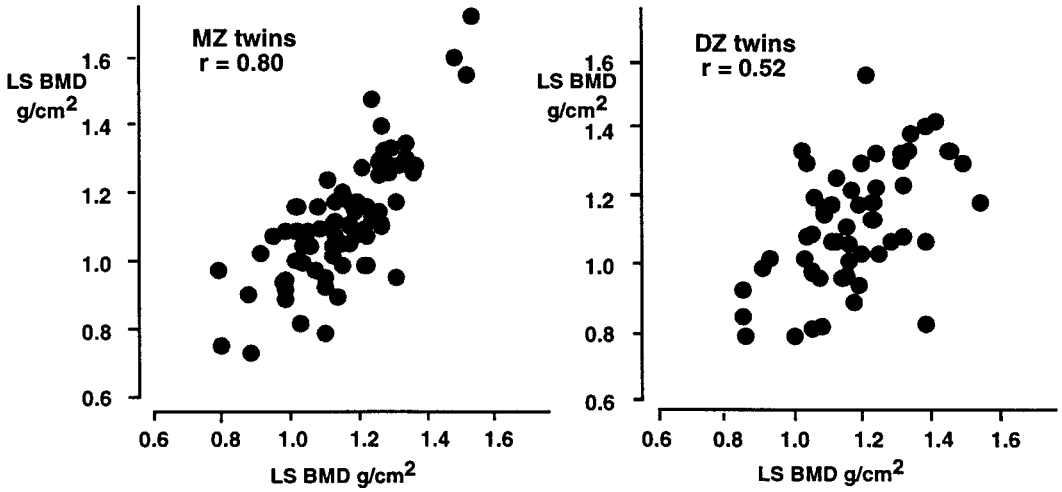

FIG. 2. Similarity of bone density in monozygotic and dizygotic twins. Lumbar spine bone density is more similar between monozygotic twins, who are genetically identical, than between dizygotic twins, who share on average half their genes. Analysis of these data suggests that 75–80% of the variance in bone density in individuals matched for age, sex, and general health is genetically determined. [Derived from Ref. 117.]

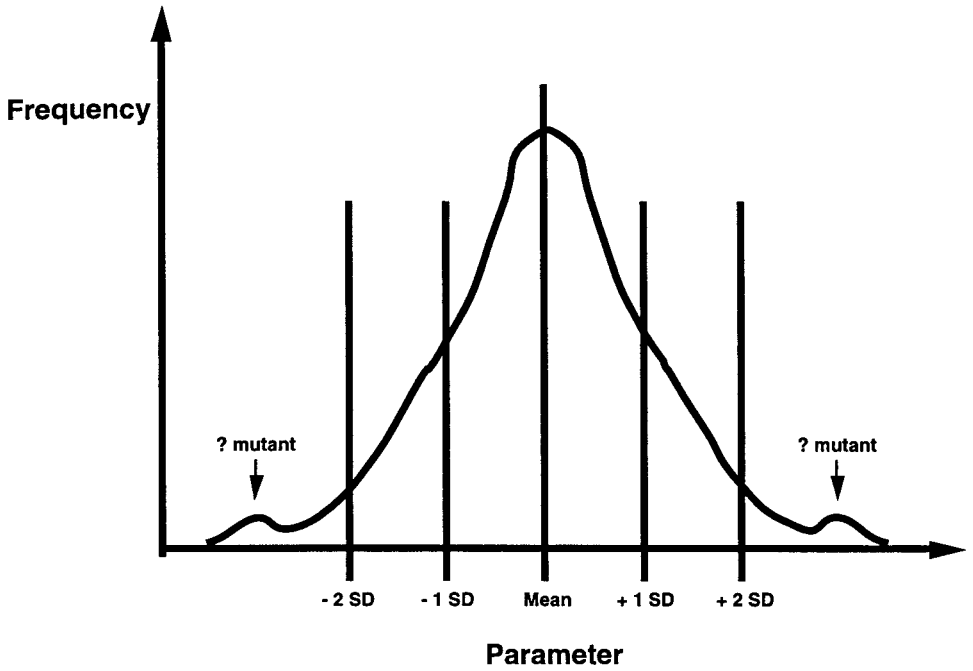

FIG. 3. Normal and mutational variation in bone density. Bone density, as for any physiological parameter, has a normal "mean" with a distribution around that age-matched mean. This distribution can be conceptualized as above with some extreme outliers distinct from the "normal" population but related to mutations, which cause very weak (*e.g.*, osteogenesis imperfecta) or very dense bones (*e.g.*, osteopetrosis). Fracture risk increases with age as the age-matched mean declines relative to the young normal mean. With advancing age many within the normal age-matched range, *i.e.*, within 2 SD of the mean, will fall more than 2 SD below young normal mean and are thus likely to suffer such fractures. The high lifetime risk of osteoporotic fractures indicates that many more people from within the normal range will suffer fractures compared with the small numbers with extreme mutations. Thus, genetic changes, which could result in shifts in bone density within that normal range, are of considerable importance for the targeting and prevention of osteoporosis from a public health point of view.

have been reported to be heterozygotes for some forms of osteogenesis imperfecta (122–124). Some studies have identified structurally relevant mutations in the collagen 1α1 gene in familial forms of osteoporosis as distinct from osteogenesis imperfecta (122–126). In one of these studies almost one in five subjects of a selected group had such mutations (123). However, given that osteoporosis affects more than half of the normal older female population, such collagen mutations probably explain only a relatively minor part of the entire osteoporosis spectrum. Differences in the regulatory regions of the collagen genes could be of greater frequency and biological relevance (see *Section VI*).

If structural gene mutations are relevant to the "mutation" model of the relatively uncommon extreme abnormal bone phenotype, the majority of "osteoporosis" cases would seem to require other genetic explanations. In fact most individuals with osteoporosis lie close to the normal distribution of bone density, *i.e.*, in the range of 2–3 SD below the mean of YOUNG normal; this is mostly within the expected range of age-matched normal (*i.e.*, mean $\pm$ 2 SD). Indeed, using the World Health Organization definition that relates osteoporotic fracture risk to difference from young normal, the majority of the elderly population are expected to be "osteoporotic."

The concept of inherited components to the risk of development of osteoporosis could lead to a negative approach in relation to osteoporosis prevention, since any inherited factor would by its very genetic nature be "immutable." This may be true for mutations in a structural gene or for mutations associated with gross loss- or gain-of-function. However, this may not be relevant to less severely modified forms of genes where the normal physiological counter-regulatory systems could overcome minor "deficiencies" in their function. This concept is central to the understanding of the possibility of "normal" genetic variability and its exploitation for better understanding of genetic predisposition to disease and in response to therapy. Indeed, it was found that genetic factors contribute to the determination of bone turnover as assessed by various biochemical indices. This indicates that the genetic factors may be modulating bone turnover and thus mediating their effects on bone mass through changes in this normal bone regulation of bone. On the other hand, it is important to recognize that bone turnover is itself related to environmental and other genetic factors. Thus genetic variants could be expected to have distinctly different effects on physiological parameters and phenotypic expression of bone depending upon the genetic as well as the environmental background (66, 110, 112, 119, 127).

V. Vitamin D Receptor (VDR) Gene Polymorphisms and Bone Phenotype

A. VDR gene polymorphisms and bone phenotype

One of the first genes to be associated with the common form of osteoporosis is that for the VDR. In the first set of studies, common polymorphic alleles in the VDR gene were reported to be linked with different serum levels of a marker

of bone turnover, osteocalcin (128). Osteocalcin, the functions of which are still poorly understood, is produced almost exclusively by osteoblasts and is the most common protein in bone after collagen. In earlier twin studies it had been shown to be under strong genetic "control" (119, 129). Other markers, *e.g.*, the procollagen type I propeptide, cleaved and released when collagen is produced, were also shown to be genetically linked in some (130) but not all studies (131–133). The reasons for these differences may be similar to those related to the differences observed in relationships between candidate genes and bone density in various ethnic and environmental backgrounds as discussed below.

In the earlier twin studies the linkage in bone turnover markers were shown to be related to differences in bone density, so it was reasonable to examine various samples for a linkage between the VDR gene alleles and bone density. In the first such study a strong relationship was reported between common VDR alleles and bone density in twin and nontwin Caucasian populations in Australia (134). We subsequently reported problems in our original genotyping of the dizygotic twin part of the study, such that the heritability component attributable to this gene is somewhat less (135, 136). Our initial population data had suggested a difference between the extreme homozygote genotypes of up to 1 SD unit (~10%) in bone density, while later twin studies have found weak effects on bone density (137, 138) or no effect on either bone density or ultrasound characteristics (131, 138). This work generated much interest resulting in a large number of follow-up studies and considerable controversy. Several population studies have shown a weak effect, perhaps 0.3–0.5 SD unit (4–13%), in several Caucasian and Asian populations (130, 139–158). However others, including some large carefully performed studies, have found no discernible effect in various Caucasian and Asian populations (131–133, 138, 156, 159–168). Among those studies that did find a VDR bone density relationship, a Dutch study (144) has reported a VDR gene allele effect in a sample of several thousand elderly individuals; however, the effect is in the opposite direction to the previous studies. Another smaller Scottish study and a US study have reported similar findings (146, 151). The conflicting findings have been reviewed (169–171), and two meta-analyses suggest that the VDR effect is real and likely to account for about 0.3 SD between alternate homozygotes (172, 173). Reasons for the differences in apparent effect of the VDR alleles remain uncertain; however, it is likely that differences in genetic (racial/ethnic) background and possibly environmental factors may alter the expression of subtle genetic differences. Interaction of the VDR gene allelic differences with the genetic background may relate to differences noted between Asian and Caucasian studies. However, positive and negative studies have been observed in both Asian and Caucasian cohorts.

In addition to the original polymorphisms in the 3′-region of the VDR gene, a start codon polymorphism has been reported. It has been reported to be associated with differences in bone density in different population groups, particularly Mexican-American groups (142, 143, 174) and in Japanese women (175), although not in a study of premenopausal French women (159). Interestingly, in one of these Mexican-American study groups (141), the allelic sites further 3′ in the gene were associated with differences in bone density, which were not statistically significant but of the same magnitude, 0.25–0.5 SD suggested from the earlier meta-analysis (172).

B. VDR gene polymorphisms and calcium homeostatic responses

Gene-environment interaction has been examined for VDR alleles and dietary calcium intakes, which have varied widely across studies with mean intakes from 300–400 mg/day to more than 1,000 mg/day. A possible relationship between VDR genotype and calcium homeostasis via calcium intake has been addressed in two longitudinal studies (176, 177). In the Ferrari study there were genotype-related differences in change in bone density over time, such that the "Bb" heterozygotes responded to calcium intake while the "bb" maintained and "BB" lost bone density over time irrespective of calcium intake. In the Krall study there appeared to be genotype-related differences such that at low dietary calcium intakes the "BB" genotype subjects responded best to calcium supplementation. In a further short-term study, intestinal calcium absorption was studied at low (<300 mg/day) and high (1,500 mg/day) calcium intakes (178). The BB genotype subjects did not increase their intestinal calcium absorption at lower calcium intake as well as the bb genotype subjects. There have been variable findings of differences in calcium handling and bone responses to calcium therapy with respect to VDR genotype in some (113, 152, 178–181) but not all (162, 163, 182, 183) studies. In a study in Thai women, VDR genotype was not associated with differences in bone density but was associated with urinary calcium excretion, which presumably reflects differences in efficiency of gut calcium absorption (160). In this study, urinary calcium excretion was 38% greater in "bb" than "Bb" genotype subjects. As in other studies in Asian subjects the frequency of "BB" genotype was too low for meaningful analysis. However, in another study in young children, the VDR gene start codon polymorphism (Fok1) was associated with major differences in calcium absorption (42% between extreme homozygotes) as well as in bone density (184). In relation to gut calcium absorption, two separate but small studies did not identify any genotype-related difference in intestinal VDR level (147, 183, 185) suggesting that the intestine is not the primary mediator of any genotype-related differences. In fact, VDR polymorphisms have been reported to have effects on parathyroid gland regulation (186–189). This suggests differences in PTH regulation as a possible pathway for subtle differences in vitamin D regulation of bone and calcium homeostasis.

The various studies of calcium absorption and response to calcium intake suggest that any potential VDR genotype effect would be largely masked at high effective calcium intakes. Looked at another way, this would suggest that VDR genotype could be considered as a guide to the identification of individuals in whom calcium supplementation could be expected to be most efficacious. Thus calcium supplementation would be most effective (and justifiable) in "BB" and possibly in "Bb" genotype subjects with little if any value in "bb" genotype subjects. Despite some conflicting data, which

may relate to ethnic and environmental heterogeneity, it seems clear that polymorphisms of the VDR gene are associated with differences in bone density, bone size, gut calcium absorption, and bone turnover. These data provide a basis for understanding the studies of differential bone density responses of the different VDR genotype subjects not only to long-term calcium supplementation but also to vitamin D intake and treatment with "active" vitamin D compounds, as considered below.

Several Japanese studies have reported differences in bone density response to 1α-hydroxylated vitamin D metabolites or analogs (129, 190, 191). The "bb" genotype, which is most common in Japanese cohorts (~75% of the subjects), was more responsive to the vitamin D compounds compared with the "Bb" genotype, which either did not respond as well or actually worsened with the treatment. Given that the "Bb" genotype is the most common (~50%) in Caucasian populations, VDR genotype differences could contribute to the variable and generally less impressive responses to vitamin D metabolites and analogs in Caucasian as opposed to Japanese studies. A Dutch study of simple vitamin D supplementation in the prevention of hip fracture found that the bone density response to the supplement varied according to VDR genotype (161). In this relatively small study, bone density increased significantly in the "BB" and "Bb" genotype subjects (>4%) but not in "bb" genotype subjects (−0.3%). These two groups of studies, albeit in different racial groups, suggest that "BB" and "Bb" subjects may respond positively to simple vitamin D but not to 1α-hydroxylated vitamin D. By contrast, "bb" subjects may respond positively to 1α-hydroxylated vitamin D but not to simple vitamin D.

These data suggest that some of the differences observed in relation to VDR alleles and bone density end-points may relate to their environment. For example, any differences between "BB" and "bb" genotypes could be expected to be least apparent in a population with relatively high calcium or relatively high vitamin D intake and amplified in those with low calcium and thus habitually relatively high 1,25-dihydroxyvitamin D levels. However, it remains to be shown in prospective randomized studies if VDR genotype-related differences do determine bone density responses.

C. VDR gene polymorphisms, body size, and development

Body size, as measured by body weight, lean mass, fat mass, or height, has one of the strongest associations with bone density and bone mass in a wide range of studies (3, 49, 80, 86, 104, 107, 109, 112, 147, 192–195). Depending upon the parameter used, it has been argued that fat mass or lean mass is the stronger predictor (116, 192–194), particularly of spine bone mass or density. In this regard some studies suggest a relationship between body size and VDR genotypes. One study in 589 French children reported that at 2 yr, body length and weight were greater in "BB" than "bb" girls but less in "BB" than "bb" boys. They noted the same relationships at birth and 2 yr in longitudinal studies of 145 infants (196). This is consistent with a retrospective study in infant health records of 66 postmenopausal British women in whom those with the BB genotype had 7% higher weight than "bb" cohorts at 1 yr of age (197). Higher weight and higher bone mineral content in "bb" genotype subjects was found in another small study of 32 premenopausal women (147). Another study in 146 men over a wide age range suggested that lower forearm bone mineral density in "BB" than "Bb" or "bb" individuals was due to larger bone area for the same bone mineral content (198). Another large study found bone density was associated with VDR genotype in nonobese (body mass index < 30 kg/m^2) older women (140). Importantly, this association appeared to be driven by an interaction between VDR and muscle strength (153). A Japanese study found an association between bone density and VDR genotype that was possibly due to an effect on age at menarche (199). These relationships between bone density and bone and body size and development may explain some of the differences observed between studies. Relationships between VDR genotypes and insulin secretion (200, 201) and between serum insulin levels and bone density (202) may underlie some of these effects.

D. Potential mechanisms for VDR allelic associations

The association or linkage of the VDR with bone or body phenotype could be due to the linkage of these polymorphisms to differences in a nearby gene or genes or to a functional or regulatory change in the VDR gene itself. Although changes in nearby genes cannot be excluded, the studies, indicative of variations in various aspects of bone and calcium homeostasis in relation to VDR genotypes, suggest that the changes are related in some way to functions of the vitamin D endocrine system. Any functional difference in the vitamin D-endocrine system could be due to a coding region mutation resulting in an altered receptor protein or due to an altered regulatory mechanism resulting in an altered amount of normal receptor protein produced in different tissues. Importantly, the initially described polymorphisms do not produce any coding region differences, and even the start codon polymorphism, which encodes a VDR protein shorter by three amino acids, may not generate any functional differences. In Japanese women, the start codon polymorphism has been reported to be associated with bone density and to be associated with a 70% difference in efficiency of transcriptional responses to 1,25-dihydroxyvitamin D *in vitro* (175). By contrast, two other studies found no relationship of VDR protein level in relation to BsmI genotypes in monocytic cells and skin fibroblasts, respectively (203, 204). Although the original report of the VDR gene alleles and bone density suggested that the 3′-untranslated region altered stability of heterologous gene transcripts, a more recent study found no effect of these regions on mRNA stability of heterologous gene transcripts *in vitro* (134, 206). In a recent development, the single human VDR gene has been reported to have multiple promoters resulting in multiple transcripts with evidence for tissue specificity of promoter activities and encoded receptor proteins, differing by up to 10% in size (207). Subtle differences in the balance of these different isoforms within and between tissues could mediate bone and calcium homeostatic differences. As yet no functional differences have been ascribed to the distinct VDR protein isoforms nor have any differences in these distinct

promoter regions been linked to any of the previously described polymorphisms. Further studies on these alternative transcripts will be of considerable interest.

VI. Collagen Iα1 Gene

The collagen Iα1 gene is another most interesting gene to emerge in the search for candidate genes in the determination of osteoporosis risk. In the initial studies a polymorphism in intron 1 of the collagen Iα1 gene was shown to be associated with differences in bone density (151, 208). In subsequent studies this effect has been noted to be of varying strength or absent in various studies (48). In particularly interesting recent studies, the collagen Iα1 alleles have been associated with risk of nonvertebral fractures in the large Dutch population study (209) and for vertebral but not hip fractures, respectively, in smaller Danish and Swedish studies (210, 211). In a French study in healthy premenopausal women (212) there was a relationship between the collagen gene alleles and bone density but not after adjustment for height. This suggests that the collagen gene effects may be related to body size as has been suggested for the VDR gene alleles (see *Section V.C.* above). In the Dutch study the effect on bone density was not particularly strong in 50- to 80-yr-old women, and the association with fracture was most marked in the relatively small number of older subjects (209). It remains to be seen whether there is a stronger and unequivocal effect in older old (80+ year old) subjects, among whom the majority of hip fractures occur. An effect in older subjects could suggest that the collagen gene alleles affect bone turnover and loss; however, there were only weak or no relationships with biochemical markers of bone turnover in the French study (212).

In studies of possible functional differences, the intron 1 polymorphism has been reported to involve a consensus binding site for a transcriptional regulator, SpI. The polymorphism associated with lower bone density appears to result in less efficient transcription (208). This could be a causative pathway analogous with the effects of collagen gene mutations in osteogenesis imperfecta.

The collagen Iα1 gene polymorphisms are unique in the genetics of osteoporosis in that they have been associated, at least in some studies, with fracture risk. However, the overall strength of this effect is still modest, and it is not clear whether any effect is direct on bone density or on other characteristics of the bone phenotype.

VII. Other Candidate Genes and Chromosomal Loci

Although both the VDR and collagen Iα1 gene polymorphisms have been associated with bone density, it is clear that a large number of other genes with modest effects and possibly some major effect genes remain to be identified. Several studies suggest that other genes involved in homeostasis of bone density, including potential regulators of bone cell function and calcium homeostasis, may be determinants of bone phenotype. Genome screening in human linkage studies and mouse models is now providing exciting results.

Polymorphisms of another steroid receptor gene, the estrogen receptor gene, have been associated with differences in bone density. These results initially reported in Japanese women (213) have been found in other (150, 191, 214–216) but not all studies (217). Interactions between estrogen receptor and VDR polymorphisms on bone density (150) and of estrogen receptor gene polymorphisms' effects on calcium homeostasis in postmenopausal women with parathyroid gland dysfunction (218) suggest potential gene-gene interactions.

Polymorphisms of genes for cytokines and factors involved in regulation of bone cell function have been involved in bone phenotypic differences in human and mouse models. Interleukin-6 gene polymorphisms were associated with a relatively large difference in bone density between one homozygote and the heterozygote (219) and according to a CA repeat polymorphism (220). Interleukin-6 may also be associated with bone density in a mouse model of accelerated senescence (221). The interleukin-1 receptor antagonist gene allelic variation has been reported to be associated with bone loss at the spine in women within 5 yr of the menopause (222). However, allele selection appeared to be made *post-hoc,* which can lead to type 2 statistical errors particularly in small studies. Moreover, in these studies there was no clear effect in the alternate homozygote, suggesting that some of the differences could relate to sampling biases. The interleukin 6 (and 4) genes have also been linked to bone density in a family linkage study (223). The transforming growth factor (TGF) pathway has also been implicated with bone density being associated with alleles of the TGF receptor gene (224) and weakly linked and associated with polymorphisms of the TGFβ1 gene (225). The insulin-like growth factor-I pathway has also been associated with bone density in some human studies (226, 227) as well as in mouse models (228–230).

Calcitonin and PTH receptor gene alleles have been associated with bone density. In an Italian study a calcitonin receptor gene polymorphism was associated with lumbar spine bone density (231). In another study based on linkage in more than 600 family members, a number of candidate loci (*i.e.*, collagen Iα1, collagen IIα1, epidermal growth factor, and interleukins 4 and 6) were shown to have weak linkage to bone density (223). However, in that study, the strongest linkage was with the PTH receptor gene, consistent with the central regulatory role of this pathway in bone and calcium homeostasis.

In Japanese women, phenotypes of the apolipoprotein E have been reported to be associated with differences in bone density (191). However, another recent US study found no relationship of apolipoprotein E polymorphisms with bone density or hip fracture incidence (232). Interestingly, in the Japanese population sample, the estrogen receptor and VDR genotypes had similar effects to the apolipoprotein E polymorphisms of about 0.5 SD between extreme homozygotes. The role of the apolipoprotein E in transport of vitamin K and hence in γ-carboxylation of both osteocalcin and matrix γ-carboxylated proteins is suggestive of a bone-regulatory role. Another small Japanese study has identified an HLA type as being associated with bone density (233).

A recent US family linkage study has identified a region of chromosome 11q12–13 associated with very high bone

density (234). The gene(s) involved are expected to be identified and reported in the near future (235). The genome screening approach being pursued in determination of bone density in extended family groups has confirmed a chromosome 11q locus and identified other candidate chromosomal loci at 1p36, 2p23–24, and 4qter and chromosomes 2 and 13 in various studies (124, 236, 237). The genome screening approach seems likely to surpass and replace the candidate gene approach (238). This approach is strongly supported and complemented by breeding and genome screening studies in mouse models of high and low bone mass (106, 239–241) and of early senescence (221, 242, 243).

VIII. Gene-Environment Interaction

A large number of studies on the VDR polymorphisms have found effects on bone phenotype or calcium homeostasis (139, 140, 142, 145, 147–150, 152, 157, 174, 176–178, 181, 190, 198, 244–247). Nevertheless, a number of carefully conducted studies in similar ethnic and racial groups have not found such effects (48, 131–133, 138, 141, 159, 162–165, 168, 175, 183, 248). Some of the reported differences in the apparent strength and even direction of the vitamin D allelic effects may relate to the genetic backgrounds in different studies and environmental factors such as calcium and vitamin D intakes, as discussed above. For example, in two recent studies a VDR association with bone density was apparent only in a subgroup selected according to estrogen receptor genotype (150, 156). It may well be that allelic differences beneficial in one environmental or lifestyle context are detrimental in another (Fig. 4). This is not an unusual suggestion given that even some of the most clearly deleterious mutations in human disease have been proposed to offer some benefit under some circumstances, *e.g.*, hemoglobinopathies and malarial resistance. That potentially adverse and beneficial effects coexist in relation to allelic differences, such as for the VDR gene alleles, is a plausible hypothesis but yet to be formally tested. However, one recent large case-control study in Africa found that the tt (equivalent to the BB) genotype of the VDR was underrepresented in individuals with chronic infections, *i.e.*, tuberculosis and hepatitis B but not malaria (249).

Bone density at any age is the end result of peak bone density and subsequent loss and thus reflects the sum of responses to various environmental exposures. If genetic factors modulate those responses to environments, these gene-environment interactions presumably also accumulate over time with aging. In individuals with rheumatoid arthritis, rate of loss was found to be related to VDR genotype (250). Another interesting insight into aging in relation to VDR gene alleles and bone density comes from a Mayo clinic study (148). In that study a VDR gene effect was apparent in younger subjects from their population sample but was not in the older subjects. These age-related differences imply that any allelic effect is modified by an accumulation of age-related environmental exposures. Osteoarthritis and related bone changes, which confound analyses at some skeletal sites, particularly the lumbar spine, may reflect cohort differences in environmental exposures, particularly work history, during critical ages and stages of development and growth. However, degenerative changes in the spine (251) as well as knee osteoarthritis (252, 253) have been reported to be associated with VDR genotype. Another smaller study of osteoarthritis of the hip found no relationship with VDR alleles or with collagen gene (Iα1 or IIα1) alleles (254).

An important corollary of any VDR gene effect on bone density could be an influence on the frequency of osteoporosis or its age of onset. Two small studies seeking a difference in VDR gene allele frequencies between osteoporotic and "control" subjects found no VDR genotype effects (151, 255). A larger case-control cohort study based on the Study of Osteoporotic Fractures found no association of any fracture type with VDR genotype even after adjustment for age, bone density, or calcium intake (255a). By contrast, a recent nested case-control study in the Nurse Health Study found a greater than 2-fold increased risk for hip fracture associated with the BB genotype, and the risk increased with age, leanness, inactivity, and lower calcium intake (256). The need for

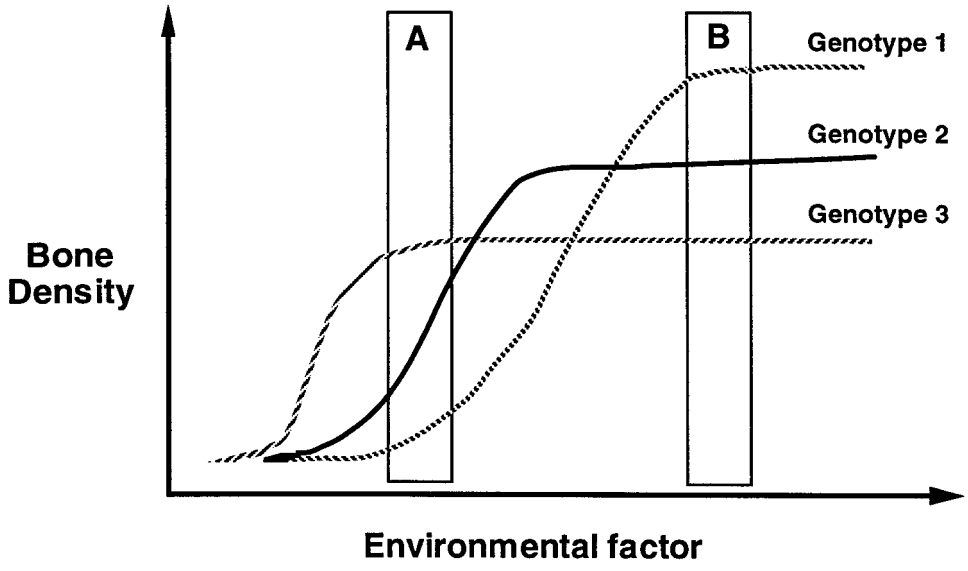

FIG. 4. Gene-environment interaction. The concept that a gene variant could be an advantage under one set of conditions and a disadvantage under another is depicted. Under conditions A, individuals with genotype 1 would be worse off compared with those with genotype 2 or 3. However, under conditions B, the reverse order would apply. For the VDR gene alleles, the environmental factors expected to impact in this way would include dietary calcium and vitamin D availability. For the estrogen receptor gene alleles, these conditions would include estrogen exposure. Importantly, these environmental factors could change at different ages.

large samples has been analyzed in relation to adequacy of statistical power to identify or exclude a biologically relevant effect (257, 258).

Several studies have examined whether VDR alleles might be related to postmenopausal bone loss. Some studies (130, 190) suggested differences in rate of bone loss in Japanese women according to VDR gene alleles. However, other studies in Caucasian women have not found a similar effect (131–133, 248). In studies in young children with calcium supplementation, an improvement was seen in bone density in prepubertal children but not in those going through puberty (51). Also increase in forearm density in peripubertal children and young adults was not associated with VDR genotype (182). These studies suggest that the major effects of introduction (puberty) or removal (menopause) of sex hormones overwhelm other effects. In that regard it is interesting that the inherited bone density similarity of daughters and their parents was already apparent before puberty (114), although in one study VDR genotype was associated with age of menarche (199). Given that sex hormone effects are so great, VDR alleles might not be expected to alter the major changes of sex hormone withdrawal associated with postmenopausal bone loss. In any case, the issue of genetic effect on rates of bone loss remains uncertain. A genetic effect on change of bone density over time was reported in one short-term study in women (118) but not in longer term studies in men, where shared environment appeared to be more important than genetic predisposition (13, 84). Heaney and co-workers have been studying bone density and size in relation to calcium intake in a large group of nuns for more than 20 yr (258a). They have found a VDR genotype effect on femoral shaft cortical area, suggesting that any gene effect could be on material or structural characteristics as well as on bone turnover and density. This may be similar to the relationships mentioned above in relation to body and bone size, which may be central in studying and understanding genetic effects on bone structure.

Interestingly, associations have now been reported between VDR gene alleles and PTH function in primary (186–188) and secondary (189) hyperparathyroidism. This has also been linked with changes in bone density over time in subjects with renal disease (259, 260) and rheumatoid arthritis (250). These findings are consistent with these alleles of the VDR being linked to subtly altered physiological regulatory processes. For example, the initially described 3′-alleles of the VDR, but not the more 5′-start codon polymorphism, has been associated with altered VDR levels and differences in PTH mRNA and calcium-sensing receptor mRNA levels (261–263).

The examples of gene-environment interaction for the VDR gene have been described since such effects in bone and calcium homeostasis have been addressed largely in relation to allelic differences in that gene. However, these reports should only be seen as examples of what will presumably be identified for many different genes. This area of "pharmacogenetics" will undoubtedly be one of the major new areas for therapeutic advance in which different genetic (and ethnic) backgrounds will be shown to determine responses to different modalities of therapy. Understanding of such differences in relation to drug metabolism already can influence drug dose in chemotherapy. Knowledge of gene allelic differences in type of response could underpin targeted selection of optimal therapy according to genetic background.

IX. Summary

There is clear evidence of genetic modulation of bone phenotype parameters including bone density, quantitative ultrasound, bone size, and bone turnover. At any particular age and phase of life, genetic factors explain about 70% of the variance in bone phenotype after adjustment for major medical and disease factors. Hormonal factors, diet, and lifestyle interact with those genetic factors over time.

Common allelic variation in the VDR was the first of several genes and now chromosomal loci to be implicated in the genetic determination of bone phenotype. The VDR polymorphisms have an effect weaker than originally reported, and part of the allelic effects may be mediated by effects on body size and development and even other hormonal regulators such as PTH or insulin. Irrespective of the strength or mechanism of these associations, these initial findings on the VDR stimulated the field of the genetics of osteoporosis with targeted genetic studies and now genome scan approaches.

Intronic polymorphisms of the collagen Iα1 gene have been shown to be related to bone density and to fracture risk in several studies, although not all findings concur. Common allelic variations have now been associated with bone density for the estrogen receptor, TGFβ receptor, and TGFβ1, for the insulin-like growth factor-I pathway, for interleukin-4 and -6 and the interleukin-1 receptor antagonist, for calcitonin and the PTH receptors and for apolipoprotein E. Of considerable interest, chromosomal loci, notably 11q 12–13, have now been linked to bone phenotypes in human and mouse studies. The mouse strain studies seem likely to be powerful tools providing insight to important human loci based on the mouse-human chromosomal synteny.

Variability of genetic findings across studies seems to be the rule rather than the exception. This variability may relate to interaction of particular loci with specific environmental or even other genetic loci. The importance of genetic heterogeneity, including ethnicity, as well as environmental and hormonal confounders, such as calcium and vitamin D intake, hormonal status and skeletal and body size, will need to be taken into account in future gene search approaches. Genome scans in relation to bone density and fracture endpoints will need to account for such important potential confounders in each target population.

Interactions between genetic and environmental factors, including lifestyle, have been investigated initially for the VDR polymorphisms in relation to the response of bone density and turnover to calcium intake and treatment with simple vitamin D and active vitamin D compounds. Gene-gene and gene-environment interactions in human and animal models will be critical targets for future research. Further genes with positive and negative effects on bone phenotype are certain to be identified in the near future. Each of these will need to be evaluated in relation to potential environmental modulators in pharmacogenetic models. Understanding the molecular physiology of such gene effects is

likely to lead to more specific treatments and to allow the selection of more appropriate and effective treatment options.

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