Pharmacogenetics of osteoporosis and the prospect of individualized prognosis and individualized therapy

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Purpose of review

Description of recent progress in genetics and pharmacogenetics of osteoporosis.

Recent findings

Osteoporosis and its consequence of fragility fracture are characterized by highly complex phenotypes, which include bone mineral density, bone strength, bone turnover markers, and nonskeletal traits. Recent developments in the genome-wide studies using high-throughput single-nucleotide polymorphisms have yielded reliable findings. Four genome-wide studies have identified 40 single-nucleotide polymorphisms in various chromosomes that were modestly associated with either bone mineral density or fracture risk. Clinical response, including adverse reactions, to antiosteoporosis therapy (such as bisphosphonates and selective estrogen receptor modulators) is highly variable among treated individuals. Candidate gene studies have found that common polymorphic variations within the collagen I alpha 1 and vitamin D receptor genes were associated with variability in response to antiosteoporosis treatment. Moreover, a recent genome-wide study identified four single-nucleotide polymorphisms that were associated with bisphosphonate-related osteonecrosis of the jaw with relative risk being between 10 and 13.

Summary

The evaluation of osteoporosis and fracture risk is moving from a risk stratification approach to a more individualized approach, in which an individual's absolute risk of fracture is evaluable as a constellation of the individual's environmental exposure and genetic makeup. Therefore, the identification of gene variants that are associated with osteoporosis phenotypes or response to therapy can eventually help individualize the prognosis, treatment and prevention of fracture and its adverse outcomes.

Keywords

genome-wide association, linkage, osteonecrosis of the jaw, osteoporosis, pharmacogenetics

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Introduction

The current prevailing concept of osteoporosis is that it is a result of impaired bone strength leading to an increased risk of fragility fracture [1]. The 'bone strength' component in this concept reflects the integration of bone mass, estimated by bone mineral density (BMD) and bone quality. Bone quality is a generic term that refers to the constellation of bone architecture, bone turnover, and damage accumulation and mineralization. Although a precise definition of bone quality is still lacking, a prior fracture is considered a clinically relevant indicator of a deterioration of bone quality. Thus, the current concept recognizes that osteoporosis is a complex, multifactorial disease, in the sense that the osteoporosis phenotype is not a single entity, but it encompasses a set of dynamic parameters.

The phenotypic complexity of osteoporosis is a problem for genetic dissection of the disease. Fragility fracture is considered an outcome of osteoporosis. Therefore, it is logical to consider fracture a phenotype of osteoporosis. However, fracture is age dependent such that the risk of fracture increases exponentially with advancing age. Theoretically, if the life expectancy of a population were infinite, then the lifetime risk of fracture would be 100%. Therefore, a genetic analysis of fracture as a single and categorical phenotype may not adequately capture the dynamic of osteoporosis.

Genetic studies of osteoporosis have mainly focused on BMD as a phenotype, because it is the single most powerful predictor of fracture risk and is the most accessible measure of skeletal health for an individual. A BMD measurement is actually a composite index reflecting the

size, shape, and geometry of the bones. Therefore, a BMD measurement at a skeletal site is the sum of many different combinations of these traits, each making an independent contribution to the strength of bone and its resistance to fracture, and each potentially subject to different regulatory processes and genetic influences. For any population and at any given age, BMD varies continuously between individuals, but the variation follows a normal distribution with a constant variance. This distribution of BMD is a typical manifestation of a polygenic trait, determined by the actions of and interactions between multiple genes and environments.

Although BMD is the primary determinant of fracture risk, it accounts for a modest proportion of fractures. Indeed, recent studies have suggested that more than 50% of women and 70% of men who fracture do not have BMD below the osteoporosis threshold [2]. Moreover, the antifracture efficacy observed in randomized controlled clinical trials exceeds the expected magnitude of association between BMD and fracture risk [3]. It has been estimated that change in BMD induced by antiresorptive drugs explained only approximately 15% of the reduction in fracture risk [4]. Therefore, genetic determinants of BMD may not necessarily translate to determinants of the liability of fracture.

Bone structure is a net result of two counteracting processes of bone resorption and bone formation, often referred to as bone remodeling. Bone remodeling is a normal, natural process that maintains skeletal strength, enables repair of microfractures and is essential for calcium homeostasis. During the remodeling process, osteoclasts produce bone degradation products that are also released into the circulation and are eventually cleared through the kidney. These include both enzymes and nonenzymatic peptides derived from cellular and noncellular compartments of bone. Similarly, osteoblasts produce a number of cytokines, peptides, and growth factors that are released into the circulation. Their concentration thus reflects the rate of bone formation. It has been possible to measure bone formation and bone resorption by serum or urinary biochemical markers [5]. These markers include serum osteocalcin, bone-specific alkaline phosphatase and procollagen I carboxyterminal propeptide (PICP) and urinary excretion of hydroxyproline, pyridinoline, deoxypyridinoline, collagen type I cross-linked N telopeptide (NTX), and collagen type I cross-linked C telopeptide (CTX). Markers of bone formation and resorption have been shown to be associated with bone loss; higher rates of bone resorption being associated with rapid bone loss and fracture risk [6–8]. However, few genetic studies of osteoporosis have utilized bone turnover markers as phenotypes [9,10].

Thus, the osteoporosis phenotype is not a single entity but rather a set of parameters. The universe of parameters constituting osteoporosis phenotype is diverse including cellular bone remodeling, bone strength, bone mass, and bone size. Although fracture is a direct consequence of bone fragility and is therefore a key component of an osteoporosis phenotype, fracture is also a function of nonskeletal factors, such as fall propensity that is affected by neuromuscular function, muscle strength, and postural sway. Many of these nonskeletal traits are also determined by genetic factors. The liability to fracture is therefore a complex phenotype, in the sense that it is a constellation of bone strength and nonskeletal factors, and each of these factors may be determined by specific genes or sets of genes [11] acting together and interacting with environmental factors.

Through several twin and family studies, it is now clear that the risk of fracture segregates within families, but the segregation is not consistent with the Mendelian law seen in single-gene disorders [12]. Women whose mother had had a hip fracture had a two-fold increase in risk of hip fracture compared with controls [13], but the penetrance is not complete. Indeed, approximately 25–35% of the variance in the liability to fracture has been attributed to genetic factors [14,15]. Moreover, genetic factors account for a large proportion of variance in risk factors of fracture such as BMD [11], bone loss [16], quantitative ultrasound [17], and bone turnover markers [9].

Candidate genes

The recognition that various bone-related traits are largely determined by genetic factors has led to an intensive search for specific genes linked to these quantitative traits or fracture risk. The search for genes that are involved in the regulation of a trait is mainly based on linkage or association or both. Linkage analysis tracks the inheritance of a trait and identifies chromosomal regions that deviate from independent segregation with the trait. Association analysis determines whether the genetic make up in those with and without the trait is different and seeks to identify specific DNA loci (or gene variants) that are responsible for the difference [18]. Either linkage or association analysis uses two major approaches for gene search: candidate gene and genome-wide screening [19]. The candidate gene approach is based on a priori knowledge of the potential function of the gene involved and takes advantage of the relevant and known biochemical pathway of bone physiology. In the genome-wide scan, a set of markers on a genome map are selected on the basis of utility without any a priori hypothesis (so-called hypothesis-free research) for analysis of association with a phenotype [20,21].

On the basis of the candidate gene approach, Morrison *et al.* [22,23] first demonstrated a linkage and association between variation in BMD and common variation in

polymorphic sites located in exons 8 and 9 at the 3' end of the VDR gene (detected by BsmI, TaqI, and ApaI restriction enzymes). Despite there being a problem of genotyping in the sample, the association between BsmI genotypes and BMD was still significant [23]. Subsequent to the discovery of the VDR gene, several studies have attempted to validate the association with contradictory findings [24]. A meta-analysis of 75 studies published between 1994 and 1998 concluded that there was a positive association between VDR genotypes and BMD though the magnitude of association was lower than the initial report [25]. Moreover, the VDR was one of the genetic loci identified, albeit with lower power, in the largest genome-wide scan of osteoporosis genetics to date [46].

Following the identification of the VDR gene, numerous candidate gene studies have yielded a list of genes that may be associated with BMD or fracture risk [26] (Table 1). These genes include collagen type Iα1, osteocalcin, IL-1 receptor antagonist, calcium-sensing receptor, α2HS glycoprotein, osteopontin, osteonectin, estrogen receptor α, IL-6, calcitonin receptor, collagen type Iα2, parathyroid hormone, and transforming growth factor α1. Among these genes, the collagen type Iα1 gene has been reported to be largely consistently associated with BMD [27] and fracture risk [28]. However, the enthusiasm surrounding the early studies of allelic variation has faded in a proliferation of conflicting studies and lack of independent replication, mainly due to lack of statistical power [29] and false positive [30], and this gene was not identified in either of the large genome-wide scans reported to date [39,46].

Linkage analysis of data from a family with osteoporosis–pseudoglioma syndrome (OPS), a disorder characterized by severely low bone mass and eye abnormality, localized the OPS locus to chromosomal region 11q12-13 [31]. At the same time, a genome-wide linkage analysis of an extended family with 22 members among whom 12 had very high bone mass (HBM) suggested that the HBM locus also located within 30cM region of the same locus [32]. In follow-up studies using the positional candidate approach, both research groups found that a gene encoding the LDL receptor-related protein 5 (LRP5) was linked to both OPS and HBM [33–35]. The finding that LRP5 gene is linked to HBM was subsequently confirmed in a family study which included individuals with exceptionally high BMD but were otherwise phenotypically normal [34]. This study showed that a missense mutation (G171V) was found in high-BMD individuals (25). A recent family study further identified six novel mutations in LRP5 among 13 confirmed polymorphisms that were associated with different conditions with increased BMD [36].

Table 1 Some candidate genes implicated in the association with osteoporosis

Candidate gene	Physiological function
Vitamin D receptor	Calcium absorption; osteoblast/ osteoclast activity
Estrogen receptor α	Osteoblast/osteoclast activity
Estrogen receptor β	Osteoblast/osteoclast activity
Collagen 1 alpha 1	Matrix component
Transforming growth factor β1	Osteoblast/osteoclast activity
Androgen receptor	Osteoblast function
IL-6	Osteoclast activity
Apolipoprotein E	Vitamin K transport
Parathyroid hormone receptor	Calcium homeostasis; osteoblast/ osteoclast activity
Calcitonin receptor	Osteoblast function
Peroxisome proliferator-activated receptor γ	Adipocyte differentiation
Osteocalcin	Matrix component
Calcium-sensing receptor	Regulation of calcium homeostasis
Methylenetetrahydrofolate reductase	Homocysteine metabolism
Metalloproteinase-1 gene	Matrix component

A meta-analysis on 37 534 individuals from 18 study populations in Europe and North America found that two common variants (Val667Met and Ala1330Val) within the LRP5 gene were associated with BMD and fracture risk (38). For example, carriers of the *MetMet* genotype of the Val667Met variant were associated with 20 mg/cm^2 lower in lumbar spine BMD ($P = 3.3 \times 10^{-8}$) and 11 mg/cm^2 lower in femoral neck BMD ($P = 3.8 \times 10^{-5}$) compared with those with *MetVal* and *ValVal* genotypes. The *ValVal* genotype within the Ala1330Val variant was associated with 16 mg/cm^2 lower in lumbar spine BMD ($P = 3.4 \times 10^{-9}$) and 10 mg/cm^2 lower in femoral neck BMD ($P = 9.9 \times 10^{-7}$) compared with those with *AlaVal* and *AlaAla* genotypes. These results are comparable with a recent genome-wide association (GWA) study, in which the Ala1330Val (rs3736228) was associated with BMD with an effect size of 0.13 standard deviation and P value of 6.3×10^{-12} (39). In a summary-based meta-analysis [37•], using the Bayesian approach, the probability that the effect size (AlaAla vs. AlaVal/ValVal) of more than 0.1 SD (each SD was 0.12 g/cm^2) was only 34% for femoral neck BMD and 56% for lumbar spine BMD (0.15 g/cm^2), and there is a 100% chance that the effect size was less than 0.25 SD. Taken together, these latest data clearly show that the gene variant Ala1330Val within the LRP5 gene is modestly associated with BMD. Nevertheless, the identification of the LRP5 gene can be considered a genuine progress in the search for genes that are actually associated with osteoporosis.

Genome-wide studies

Following the completion of the Human Genome Project and the HapMap Project [38], the search for osteoporosis genes shifted from the investigation of single genes by candidate gene association studies to the discovery-oriented approach in which hundreds of thousands of

gene variants are analyzed simultaneously without any *a priori* hypothesis. It would be ideal if one could scan the whole genome to pinpoint the relevant genes of osteoporosis, but such an effort is not practical or not necessary. Although there are 3 billion genetic variants [38], most of these are rare, with only approximately 10 million variants being common (those in which each allele has a frequency of at least 1%). On average, more than 90% of the differences between any two individuals are due to common variants [39]. Therefore, it has been hypothesized that the susceptibility to common diseases such as osteoporosis is caused by a relatively small number of common genetic variants with low effect size (i.e., the 'common gene–common variant' hypothesis) [40].

Under this hypothesis, it has been estimated that the number of genetic variants that are associated with a common disease is about 100 or less [41]. Therefore, it may be reasonable to assume that the prior probability that a randomly selected common variant is associated with an osteoporosis trait is 1/100 000 or 0.000001. With such low prior odds, an observed association with P values ranging from 0.001 and 0.05 can be expected to be almost always false positive, even in well powered studies with 10 000 participants in each group. A finding of association in lower powered studies with 200–500 cases and 200–500 controls, even with P values less than 10^{-8}, can still be more likely false than true. However, a study of 1000 cases and 1000 controls observing an association with P values less than 10^{-8} is more likely to be true than false [39].

During the last few months, results of four GWA studies in the osteoporosis field [42••–45••] have been reported. The single-nucleotide polymorphisms (SNPs) identified by the Framingham group [45••] were largely independent from the multicenter study [42••]. About 40 gene variants have been identified to be associated with BMD or fracture. These gene variants were found in chromosomes 1, 2, 4, 5, 6, 7, 8, 11, 12, 13, 16, 18, 19, and 21, with minor allele frequencies ranging between 3 and 49% (Table 2). It seems, the common gene–common variant

Table 2 Gene variants identified from genome-wide association to be associated with bone mineral density or fracture

Chromosome	Gene variant (SNP)	Gene/close to gene	Location	Physical position	Base change	MAF (HapMap-CEU)
1	rs6696981	ZBTB40, WNT4	1p36	22 575 445	G/T	0.04
1	rs7524102	ZBTB40, WNT4	1p36	22 571 034	A/G	0.13
1	rs7544774	XPR1	1q25	179 024 251	C/T	0.17
1	rs7554650	Unknown	1q42	232 941 363	C/G	0.48
2	rs11898505	SPTBN1	2p16	54 538 061	A/G	0.38
2	rs1261226	Unknown	2p12	79 019 951	C/T	0.41
2	rs2380707	Unknown	2p24	15 930 081	A/G	0.18
2	rs7584788	Unknown	2p25	6 686 769	C/T	0.17
4	rs10520437	Unknown	4q34	181 000 963	A/G	0.24
4	rs922028	Unknown	4q34	181 024 748	A/G	0.22
4	rs9312601	Unknown	4q34	177 604 036	A/T	0.41
5	rs1479679	CDH9	5p33	26 917 842	C/T	0.1
5	rs16882423	ARL15	5q11	53 527 854	A/C	0.26
6	rs1038304	ESR1, C6orf97	6q24	151 974 868	A/G	0.48
6	rs1999805	ESR1	6q25	152 110 057	C/T	0.42
6	rs3130340	MHC	6p21	32 352 605	C/T	0.21
6	rs4870044	ESR1, C6orf97	6q25	151943102	C/T	0.35
6	rs6929137	ESR1, C6orf97	6q25	151 978 370	A/G	0.31
6	rs9479055	ESR1, C6orf97	6q25	151 889 660	A/C	0.42
7	rs10486135	THSD7A	7p21	11 495 025	A/C	0.41
7	rs10486301	Unknown	7p21	18 376 306	A/G	0.23
7	rs1557978	Unknown	7p21	9 932 437	A/G	0.39
8	rs1156075	CSMD3	8q23	114 092 330	A/G	0.47
8	rs4355801	OPG	8q23	119 993 054	A/G	0.47
8	rs6469804	OPG	8q24	120 114 010	A/G	0.49
8	rs6993813	OPG	8q24	120 121 419	C/T	0.45
11	rs2306033	LRP4	11p11	46 854 022	A/G	0.05
11	rs3736228	LRP5	11q12	67 957 871	C/T	0.12
11	rs4988321	LRP5	11q12	67 930 765	A/C/G	0.03
11	rs546809	MTMR2	11q21	95 219 586	C/T	0.34
11	rs7935346	LRP4	11p11	46 964 955	A/G	0.16
12	rs10507180	CHST11	12q23	103 548 535	C/T	0.37
12	rs2302685	LRP6	12p12	12 193 165	C/T	0.18
13	rs9594738	RANKL	13q14	41 850 145	C/T	0.42
13	rs9594759	RANKL	13q14	41 930 593	C/T	0.49
16	rs8051539	Unknown	16q23	76 268 225	C/T	0.20
18	rs3018362	RANK	18q21	58 233 073	A/G	0.37
18	rs768207	DCC	18q21	48 132 968	G/T	0.23
19	rs1465434	ZNF569	19q13	42 607 072	C/T	0.17
21	rs1209926	C21orf24, ETS2	21q21	39 078 994	C/T	0.27

MAF, minor allele frequency; SNP, single-nucleotide polymorphism.

hypothesis is consistent with the observed data. However, only a few gene variants met the *P* value threshold of less than 10^{-8} for BMD, and none of the gene variants reported to be associated with fracture risk passed this threshold. Taken together, these latest findings suggest that BMD is determined by multiple genes, with each gene polymorphism conferring a small-to-modest effect.

Osteoporosis pharmacogenetics

During the past two decades, major advances in the treatment of osteoporosis have been made, with more therapeutic options now being available than any time before. Antiosteoporosis therapies can be broadly divided into two groups: antiresorptive and bone-forming (anabolic) agents [46]. The former decreases bone resorption (and overall turnover), whereas the latter increases bone formation. The antiresorptive agents include bisphosphonates (e.g. alendronate, risedronate, clodronate, etidronate, ibandronate, zoledronic acid), raloxifene, and calcitonin. Anabolic agents include teriparatide [recombinant human parathyroid hormone (1–34)] and strontium ranelate, which has been suggested to induce a combination of modest effects on formation and resorption.

All these antiresorptive and anabolic agents have been shown to reduce fracture risk for some, though not necessarily all, fragility fractures [47]. In most clinical trials with fracture being the primary outcome, the relative risk reduction of fracture incidence was approximately 50% with high variability in the response to treatment. In terms of BMD change induced by antiresorptive drugs, the variability (e.g. standard deviation) of change in BMD is up to twice the mean rate of change. As a result, whereas the majority of patients experience an increase in BMD, a small proportion (perhaps up to 10%) of patients apparently still lose BMD [48]. Thus, though very few patients experience absolutely no therapeutic effect following typical antiresorptive treatment, no current treatment completely prevents bone loss or prevents all fractures.

Although patients' characteristics such as age, sex, ethnicity, concomitant diseases, and environmental factors (such as diet, alcohol consumption, and cigarette smoking) can affect drug response, genetic factors may also determine an individual's response to pharmacological therapy for each specific drug [49–51]. Genetic information can, thus, potentially be used to identify patients who likely respond (or do not respond) to pharmacological therapy. Some drugs used in osteoporosis therapy, bisphosphonates, for example, are not subject to metabolism, but others are metabolized to active components or as part of their elimination pathway. Despite the evidence of genetic effects on the variation in efficacy and safety of pharmacological agents in other diseases, these are still largely untested in the treatment of osteoporosis.

However, recent evidence suggests that genetic factors may mediate the response to drug treatment [52] and modify the dynamic association bone turnover markers and bone density. A recent series of studies by Palomba *et al.* [53–55] suggested that among postmenopausal women who were on alendronate and hormone replacement therapy (HRT) treatments, the *b* allele of the VDR BsmI polymorphism exhibited a greater increase in BMD than those carriers of the *B* allele. However, by contrast, those patients on raloxifene the *B* allele carriers had a greater increase in BMD than the *b* allele carriers. As a result of these opposing effects, among those on combined alendronate and raloxifene, there was no significant association between VDR polymorphisms and BMD change. These results strongly support the concept of an interaction between VDR polymorphisms and antiresorptive drug therapies in BMD change.

Polymorphism of the collagen I alpha 1 (COLIA1) gene has also been shown to be associated with response to antiosteoporosis therapy in terms of BMD change [56]. In a study on 108 perimenopausal women with osteopenia, randomized to receive either cyclical etidronate (a bisphosphonate drug) or placebo, femoral neck BMD was increased in carriers of the Sp1 (dbSNP rs1800012) SS genotype (~64% in the population) but was decreased in those carrying the *s* allele (Ss and ss genotypes) [56]. The Sp1 polymorphism has also been shown to be associated with the dose of human growth hormone (hGH) in men and women with growth hormone deficiency [57•]. Individuals with the SS genotype required a higher subcutaneous dose than those with the ss genotype [57•]. However, because these studies were based on relatively small sample sizes and the confidence intervals of effect size were wide, no definitive conclusion on the association between the Sp1 polymorphism and drug response can be inferred. Moreover, there have been no attempts to expand these studies to examine the efficacy and cost-effectiveness in a broader clinical setting.

Apart from antiosteoporosis therapy, bisphosphonates are commonly used in the management of patients with advanced cancers that have metastasized to bone, high risk of bone pain, and fractures. Several cancers can involve or metastasize to the bone, including lung, breast, prostate, multiple myeloma, and others. In cancer chemotherapy, bisphosphonates are given intravenously and usually for long duration. In these patients with cancers, there is a low but significant risk of osteonecrosis of the jaw (ONJ). Over the past 20 years, 368 cases of ONJ reported to be associated with bisphosphonate treatment; among whom approximately 95% occurred in patients

with myolema and breast cancer [58]. In a study on more than 260 000 patients with cancers of the breast, lung, and prostate, patients who had been on bisphosphonates, the investigators found 224 ONJ cases; an incidence of 0.3% [59]. The risk of bisphosphonate-related ONJ has also been associated with genetic factors. In a GWA study on 22 cases of ONJ and 65 age-matched controls, by screening more than 500 000 SNPs, the investigators found four SNPs (rs1934951, rs1934980, rs1341162, and rs17110453) mapped within the cytochrome P450-2C gen (CYP2C8) to be associated with the risk of ONJ [60••]. The relative risk of ONJ associated with each of the SNPs ranged between 10 and 13 [60••].

Toward the individualization of prognosis and therapy

A major priority in osteoporosis research at present is the translation of risk factors into simple and accurate prognostic models to identify individuals who are at high risk of fractures in the future and to treat them appropriately so that their fracture risk can be reduced [61]. The prognosis of fracture risk has until now been largely based on the measurement of BMD and a history of prior fracture. This is logical, as there is a strong association between BMD and the risk of fracture [62–64]. Furthermore, a history of postmenopausal fracture is also a strong risk factor of subsequent fracture [65]. The National Osteoporosis Foundation guidelines recommend treatment to be considered for women with BMD *T*-scores below −2 with no risk factors or women with BMD *T*-scores below −1.5 and one or more risk factors for fracture (including a prior fracture), or women with a prior vertebral or hip fracture. This strategy is based on evidence obtained from randomized clinical trials in which treatment of these patients did reduce fracture risk [46,47].

However, there is a problem of treatment initiation based on a BMD cut-off value. Although the risk of fracture is directly related to BMD at all levels, there is no threshold value for BMD that accurately separates those who will from those who will not sustain a fracture. In fact, more than half of fractures occurred in individuals with BMD above the −2.5 SD cut-off (e.g. 'osteoporosis'). In other words, treatment of individuals with osteoporosis is expected to reduce only a modest number of fractures in the general population. Thus, important changes in thinking are needed for that majority of individuals whose BMD measurements are at or near, below and above, the current threshold of osteoporosis. As outlined above, osteoporosis or low BMD is only one, if a major one, of many risk factors of fracture. At any given level of BMD, fracture risk varied widely in relation to the burden of other risk factors, such as advancing age, sex, genetics, family history of fracture, increased bone loss, low body weight, fall propensity, and smoking behavior. For any one individual, the likelihood of fracture depends on a combination of these risk factors [63]. This means that two individuals, both with 'osteoporosis' by BMD, can have very different risks of fracture because they have different non-BMD risk factors. On the contrary, an osteoporotic individual can have the same risk of fracture as a nonosteoporotic individual due to the difference in constellation of risk factors between the two individuals. Thus, the prognosis and treatment of fracture should be individualized by using an individual's unique risk profile.

The approach of individualized prognosis must be distinguished from the approach of risk stratification. In risk stratification, the estimate of risk is applicable to a group of individuals rather than to an individual. For example, the stratification of BMD measurement into osteoporosis against nonosteoporosis based on the *T*-score treats two women with *T*-scores of −2.4 and −2.6 into two distinct groups despite the modest numerical and biologically relevant difference; two women, who may have comparable risk of fracture if other risk factors are considered. In contrast to the risk-grouping approach, the individualized prognosis approach recognizes the different fracture risks as one would logically expect. Although this risk-grouping approach is simple and sometimes useful in clinical practice, its predictive value is poorer than the individualized approach due to the arbitrariness of any cut-off values [66].

Imparting of prognosis and decision of treatment are both concerned with an individual. Each individual is a unique case, because there exists no 'average individual' in the population. The uniqueness of an individual can be defined in terms of the individual's environmental and genetic factors. The knowledge of genetics, in combination of environmental factors, can shift beyond our current risk stratification approaches to a more individualized evaluation and treatment of osteoporosis. Given the large variability in response to antiresorptive therapies, and there is currently no measurement to guide osteoporosis therapy selection, the use of genetic variants that are associated with drug response may help select suitable individuals for optimal treatment.

The challenge is to identify all gene variants that are associated with osteoporosis phenotypes and response to antiosteoporosis therapy. Through the recent genome-wide studies, it is now clear that osteoporosis is partially determined by many genes, each with a modest effect size. This is perhaps not surprising given the number of complex phenotypes and the number of regulatory and structural proteins involved in calcium, collagen, bone metabolism, bone strength, and bone size. There is no reason to think that genes exert their effects on bone

phenotypes independently. Considering the complex phenotypes of osteoporosis, it would be expected that the effect of a certain gene is in part dependent on other genes and environments (i.e. gene and gene–environment interactions). However, identification of these interactions is difficult, because the current linear statistical genetic methods used for analyzing and detecting gene–phenotype association in human populations are not sensitive enough to detect nonlinear interacting effects due to the combinatorial complexity of gene–gene and gene–environment interactions.

Conclusion

The exponential progress driven by the Human Genome Project and technological advances continues to provide ever more powerful analytical technologies and opportunities for gaining a better understanding of complex diseases, including osteoporosis. The success of finding osteoporosis genes should clearly be based on a collection of large cohorts of well characterized individuals. It is expected that with large-scale studies, many, if not all, of the genes that contribute to interindividual variation in osteoporosis phenotypes and influence therapeutic responses will be identified. The next challenge will be to ascertain the pathophysiological mechanisms of these newly discovered gene variants, to assess the extent of gene–gene and gene–environment interactions, and to identify pathways of effect that will be valid targets for intervention. Osteoporosis research is entering a stage in which large-scale population-based studies incorporating multiplicity of data on genetics and environment are not only necessary, but also the appropriate approach in translating advances in genetic research into knowledge of direct clinical and public health relevance. With the recent genuine advance in the genome-wide studies, there is reason to be optimistic that the transnational collaboration and collection and analyses of multidimensional data in the coming years will have the potential to revolutionize the approaches to the prognosis, treatment, and prevention of fracture and its adverse outcomes.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 554).

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