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BONE GENETICS (S FERRARI, SECTION EDITOR)

Genetics and the Individualized Prediction of Fracture

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Abstract Recent genome-wide association studies have identified many genetic variants associated with fracture risk. These genetic variants are common in the general population but have very modest effect sizes. A remaining challenge is to translate these genetic variant discoveries to better predict the risk of fracture based on an individual's genetic profile (ie, individualized risk assessment). Empirical and simulation studies have shown that 1) the utility of a single genetic variant for fracture risk assessment is very limited; but 2) a profile of 50 genetic variants, each with odds ratio ranging from 1.02 to 1.15, can improve the accuracy of fracture prediction and classification beyond that obtained by conventional clinical risk factors. These results are consistent with the view that genetic profiling, when integrated in existing risk assessment models, can inform a more accurate prediction of fracture risk in an individual.

Keywords Genetics · Individualized prediction · Fracture · Osteoporosis · Genome-wide association studies · GWAS · Single nucleotide polymorphism · SNP · Genes · Bone mineral density · BMD

Introduction

Fragility fracture is common among the elderly. Data from the Dubbo Osteoporosis Epidemiology Study showed that from the age of 50 years, the residual lifetime risk of fracture is ~50 % in women and ~30 % in men [1]. In women, the lifetime risk of hip fracture is equivalent to or higher than the risk of invasive breast cancer [1, 2]. In men, the lifetime risk of hip and vertebral fractures (17 %) is comparable to the lifetime risk of being diagnosed with prostate cancer [2, 3]. With the rapid aging of the population, it is projected that fracture will become not simply a public health problem, but also impose a great demand on medical services.

There is convincing evidence that fracture contributes to the loss of human life. A pre-existing fracture is associated with an increased risk of subsequent fracture [4, 5]. Moreover, a pre-existing fracture is associated with reduced life expectancy [6]. Individuals with osteoporosis, fracture, and recurrent fracture have a greater risk of mortality than those with an initial fracture, which is greater than for those without a fracture. Furthermore, numerous data, including our own, accumulated during the past three decades have consistently shown that the relative risk of death in men with fracture (1.8-fold) is significantly greater than that in women (1.4-fold) [4, 6].

Genetics of Fracture Susceptibility

That genetic factors affect the risk of fragility fracture is well established. Daughters of mothers with a history of hip fracture have lower bone mineral density (BMD) than those whose mothers do not have a fracture [7]. Moreover, women with a familial history of hip fracture have a twofold increase in the risk of hip fracture [8]. Twin and family studies have further provided estimates of the extent of genetic effects on fracture susceptibility. Approximately 25 %–35 % of the variance in the liability to fracture is attributable to genetic factors [9, 10]. Moreover, genetic factors also account for a large proportion of variance in risk factors for fracture such as BMD [11], bone loss [12], quantitative ultrasound [13], and bone turnover markers [14]. It can be

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stated that heredity is an important risk factor for osteoporosis and fracture risk.

While the demonstration of a genetic effect on fracture is relatively uncomplicated, the identification of specific genes that are associated with fracture has proven to be a formidable task. The difficulty lies, not just in the phenotype, but also in the analytic strategy. Fracture is a clinical event, but can also be viewed as a trait, in the sense that it is a discrete characteristic of an organism. As a discrete trait, fracture is an ultimate consequence of cumulative deterioration in bone strength and disturbances in bone remodeling. As a result, fracture is a heterogeneous phenotype, not just in clinical manifestations, but also in risk factors. For instance, while fall is a major risk factor for hip fracture, it contributes little to the risk of vertebral fracture. Moreover, femoral neck BMD is better than lumbar spine BMD as a predictor of hip fracture risk. This heterogeneity has major implication in the search for osteoporosis genes. A "fracture gene," or perhaps more accurately, a gene that influences the risk of fracture, could be the gene that affects BMD, bone structure, or muscle strength, that increases the likelihood of fall. Furthermore, a gene that is associated with hip fracture may not be predictive of vertebral fracture.

Apart from the difficulty in the definition of phenotype, there are also technical and methodologic difficulties in the search for genes. Basically, gene-search strategies have been based on the two major approaches of candidate gene and genome-wide association analysis [15]. 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. Instead of focusing on a biologically plausible candidate gene, the genome-wide association study (GWAS) scans the entire genome, usually used hundreds of thousands common single nucleotide polymorphisms (SNPs; minor allele frequency>5 %), to identify chromosomal regions harboring genes likely to influence a trait. GWAS is essentially is a hypothesis-free approach, because it makes no assumptions about the location and functional significance of associated loci or their products [16]. Although it is a hypothesis-free approach, GWAS has been highly successful in unraveling the genetic contribution to complex traits.

Identification of Genes

Based on the candidate gene approach, several gene polymorphisms (including vitamin D receptor, collagen type Iα1, osteocalcin, interleukin-1 receptor antagonist, calcium-sensing receptor, α2HS glycoprotein, osteopontin, osteonectin, estrogen receptor α, interleukin-6, calcitonin receptor, collagen type Iα2, parathyroid hormone, and transforming growth factor-α1) have been proposed [17]. However, the blossomed decade of candidate gene association studies has been accompanied by increasing frustration with ongoing conflicting findings and lack of replication, mainly due to lack of statistical power [18] and false-positives [19]. Until 1996 no clear and relevant genes or loci have emerged by the less common alternative approach of genome-wide scan. By using linkage analysis of data from a family with osteoporosis-pseudoglioma syndrome (OPS), a disorder characterized by severe low bone mass and eye abnormality, investigators were able to localize the OPS locus to chromosomal region 11q12-13 [20]. 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 was also located within a 30-cM region of the same locus [21]. In follow-up studies using the positional candidate approach both research groups found that a gene encoding the low-density lipoprotein receptor-related protein 5 (*LRP5*) was linked to both OPS and HBM [22–24]. The finding that the *LRP5* gene is linked to HBM was subsequently confirmed in a family study that included individuals with exceptionally high BMD but were otherwise phenotypically normal [23]. The discovery of the *LRP5* gene has, in many ways, initiated a new phase in the search for genes in osteoporosis.

That new phase is GWAS. The earliest GWAS study in osteoporosis examined the association between 71,000 genetic variants and BMD measured at different skeleton sites, and found evidence of association for 40 SNPs. Although the study was then considered to be underpowered, several SNPs identified in this study were located in potential osteoporosis-associated genes, such as *MTHFR*, *ESR1*, *LRP5*, *VDR*, and *COL1A1* genes [25]. Another GWAS screened 300,000 variants in an Icelandic population, and found that variants in the *ZBTB40*, *ESR1*, *OPG*, and *RANKL* genes, and those in a novel region 6p21 were significantly associated with BMD at genome-wide threshold ($P<5\times10^{-8}$) [26]. This study also suggested some loci associated with fracture risk, including variants in the 1p36, 2p16, *OPG*, *MHC*, *LRP4*, and *RANK*. In the meantime, a GWAS in the UK and Rotterdam cohorts found that variants in the *TNFRSF11B* and *LRP5* genes were associated with BMD, whereas the *LRP5* gene was also associated with fracture risk [27].

Two meta-analyses of GWAS showed that variants in the *ZBTB40*, *ESR1*, *LRP4*, *LRP5*, *TNFSF11*, *SOST,* and *TNFRSF11A* genes were associated with BMD [28, 29], and that variants in the *LRP5*, *SOST*, and *TNFSF11A* were associated with fracture risk [29]. Overall, results from GWAS and meta-analyses indicate that genes involved in the RANK-RANKL-OPG pathway (*TNFRSF11B*, *TNFRSF11A*, and *TNFSF11* genes), the Wnt-β-catenin pathway (*LRP5*, *LRP4,* and *SOST* genes), the estrogen

endocrine pathway (*ESR1* gene), and the 1p36 region (*ZBTB40* gene) were those strongly associated with osteoporosis. The latest meta-analysis, which involved 81,949 cases and 102,444 controls, identified 56 loci that are associated with BMD and 13 SNPs that are associated with fracture [30]. Several of these loci or SNPs cluster within or near the RANK-RANKL-OPG system, mesenchymal stem cell differentiation, endochondral ossification, and Wnt signaling pathways. The updated list of SNPs that have been shown to be associated with fracture is shown in Table 1.

Translation of Discovery

The genes listed in Table 1 are unlikely the final list, as ongoing studies are going to identify more genetic variants that contribute to the susceptibility to fracture. However, the genes provide an opportunity to examine their potential utility in the prediction of fracture. In fact, the potential application of genes for prediction and prognosis of complex diseases, including fragility fracture, has been anticipated before the advance of GWAS. In relation to the translational genetics of osteoporosis, at present, there are some questions of interest, including: 1) How can we make use of the genetic data to predict an individual risk of fracture?; 2) Can genetic variants alone identify individuals at high risk of fracture?; and 3) Can the genetic variants improve the prediction accuracy of fracture beyond that obtained with conventional clinical risk factors? Addressing these questions will help advance the individualization of fracture risk.

However, the translation of genetic discoveries into clinical applications remains a challenge. The issue is how to

Table 1 Genes or SNPs are associated with fracture risk through GWAS studies

SNP	Position	Gene	Allele	Allele frequency	OR and 95 % CI	*P*-value
rs7524102	1p36		A	0.83	1.12 (1.05-2.30)	8.4×10^{-4}
rs6696981	1p36		G	0.87	1.15 (1.07-1.25)	2.4×10^{-4}
rs3130340	6p21	*MHC*	T	0.80	1.09 (1.02-1.16)	0.008
rs9479055	6q25	*ESR1*	C	0.36	1.05 (1.00-1.11)	0.06
rs4870044	6q25	*ESR1*	T	0.28	1.02 (0.97-1.09)	0.14
rs1038304	6q25	*ESR1*	G	0.47	1.04 (0.99-1.10)	0.11
rs6929137	6q25	*ESR1*	A	0.30	1.05 (0.99-1.10)	0.12
rs1999805	6q25	*ESR1*	C	0.44	1.03 (0.97-1.08)	0.35
rs6993813	8q24	*OPG*	C	0.51	1.06 (1.00-1.11)	0.04
rs6469804	8q24	*OPG*	A	0.52	1.05 (1.00-1.11)	0.052
rs9594738	13q14	*RANKL*	T	0.57	1.04 (0.98-1.11)	0.23
rs9594759	13q14	*RANKL*	T	0.63	1.02 (0.97-1.07)	0.52
rs11898505	2p16		G	0.69	1.11 (1.05-1.17)	1.8×10^{-4}
rs3018362	18p21	*RANK*	A	0.37	1.08 (1.02-1.14)	0.005
rs2306033	11p11	*LRP4*	G	0.87	1.11 (1.03-1.19)	0.007
rs7935346	11p11	*LRP4*	G	0.78	1.08 (1.01-1.14)	0.02
rs4233949	2p16.2	*SPTBN1*	G	0.63	1.06 (1.04-1.08)	2.6×10^{-8}
rs6532023	4q22.1	*MEPE/SPP1*	G	0.67	1.06 (1.04-1.09)	1.7×10^{-8}
rs4727338	7q21.3	*SLC25A13*	G	0.32	1.08 (1.05-1.10)	5.9×10^{-11}
rs1373004	1q21.1	*MBL2/DKK1*	T	0.13	1.10 (1.06-1.13)	9.0×10^{-8}
rs3736228	11q13.2	*LRP5*	T	0.15	1.09 (1.06-1.13)	1.4×10^{-8}
rs4796995	18p11.21	*FAMB210A*	G	0.39	1.08 (1.06-1.10)	8.8×10^{-13}
rs6426749	1p36.12	*ZBTB40*	G	0.83	1.07 (1.04-1.10)	3.6×10^{-6}
rs7521902	1p36.12	*WNT4*	A	0.27	1.09 (1.06-1.13)	1.4×10^{-7}
rs430727	3p22.1	*CTNNB1*	T	0.47	1.06 (1.03-1.08)	2.9×10^{-7}
rs6959212	7p14.1	*STARD3NL*	T	0.33	1.05 (1.02-1.07)	7.2×10^{-5}
rs3801387	7q31.31	*WNT16*	A	0.74	1.06 (1.04-1.08)	2.7×10^{-7}
rs7851693	9q34.11	*FUBP3*	G	0.37	1.05 (1.02-1.07)	3.5×10^{-5}
rs163879	11p14.1	*DCDC5*	T	0.36	1.05 (1.03-1.07)	3.3×10^{-5}
rs1286083	14q32.12	*RPS6KA5*	T	0.81	1.05 (1.03-1.08)	7.2×10^{-5}
rs4792909	17q21.31	*SOST*	G	0.62	1.07 (1.04-1.10)	6.9×10^{-6}
rs227584	17q21.31	*C17orf53*	A	0.67	1.05 (1.03-1.07)	4.1×10^{-5}

This list was compiled from a previous GWAS [26] and the recent meta-analysis of GWAS [30]

GWAS genome-wide association studies, *SNP* single nucleotide polymorphism

assess the utility of genes in fracture prediction, and what metrics are suitable for the assessment. It is now well known that simple measure of association such as odds ratio (OR) is not adequate to gauge the utility of a genetic variant [31]. The utility of a genetic variant should be assessed in terms of discrimination, and more importantly, reclassification.

Discrimination measures how well a genetic variant can separate individuals who will have a fracture from those will not [32]. The primary metric of discrimination is the area under the receiver operating characteristic curve (AUC), which can be interpreted as the probability that in a set of randomly selected pairs of fracture and non-fracture, the test result will be higher in fracture patients than in non-fracture individuals. In reality, AUC is a compromise between sensitivity and specificity, and is thus a global estimate of prognostic accuracy. However, AUC is a rather insensitive measure to change (ie, a meaningful difference in prognostic value between two predictive models is not necessarily reflected by the AUC) [33]. Moreover, the AUC has no direct clinical meaning, and is therefore not helpful for clinical decision.

A clinically meaningful metric of usefulness of a marker is risk reclassification [34]. For a given threshold of risk, an individual can be classified as "high risk" or "low risk." With additional risk factors (eg, genetic variant) the individual may change risk category from one to another. Consider a predictive model with clinical risk factors, and a model with predictive factors plus genetic variants. If genetic variants are useful, then the addition of those genetic variants should result in more individuals with fracture being classified into the high-risk group than to the low-risk group; conversely, among those without a fracture, more are classified into the low-risk group than the high-risk group. The net difference between the two proportions of reclassification is referred to as net reclassification improvement (NRI) [35]. Thus, when treatment decision is based on risk threshold, the NRI can be helpful for making clinical decision concerning an individual.

Utility of a Single Gene

Conceptually, the utility of a gene in predicting fracture is a function of several parameters. Apart from the 5-year incidence of fracture in the general population, the risk threshold for treatment affects the NRI metric. Moreover, the frequency of high-risk allele of the genetic variant in the general population, and the OR of association between the genetic variant and fracture, are important factors that affect the clinical usefulness.

Assuming that the 5-year incidence of fracture is 10 %, and that the risk threshold for treatment decision is 20 % (ie, individuals with predicted risk >20 % are considered "high risk"), then it can be shown by simulation [36] that a genetic variant with OR between 1.1 and 1.4 is associated with an AUC of between 0.52 and 0.55, and almost zero NRI. In the above scenario, a genetic variant that confers an OR of 3 can result in an AUC of 0.76 and NRI of 20 %.

The relative risk of fracture associated with hip fracture for the COLIA1 genotype was 3.7. The AUC for a model including age and BMD was 0.83, but when COLIA1 genotype was added into the model, the AUC increased to 0.85 [37], a very modest improvement. None of the genetic variants identified by GWAS achieved that magnitude of association (eg, OR>1.5). Collectively, this suggests that the contribution of any single gene to fracture prognosis, no matter how large the effect size, is likely limited and would not be useful particularly in clinical setting.

Genetic Profiling

It is now clear that the susceptibility to fracture is affected by multiple genetic variants. It is not clear whether genetic profiling could enhance the predictive accuracy of fracture prediction because there is lack of empirical data. In the absence of data, we have conducted simulation studies to study the usefulness of genetic profiling using the methodology described by Pepe et al. [36], and the results can be summarized in Fig. 1. For a given OR, the discriminatory power and NRI increase proportionally to the number of genetic variants. With 50 genetic variants, each with an OR of ~1.1, the AUC value is expected to be 0.63; however, the NRI is approximately 5 %. However, in genetic profiling with 50 genetic variants, each with OR being ~1.3, the AUC is expected to be 0.80, and NRI of 15 %.

Estimation of an individual's risk of fracture, based on clinical risk factors (eg, Garvan Fracture Risk Calculator or nomogram [38, 39] and FRAX [40]), has increasingly become established as a means of targeting preventive interventions to those at highest risk. These risk assessment models were based on demographic, anthropometric, and clinical information. The prognostic performance of these models has been mixed, with AUCs ranging between 0.65 and 0.80, depending on type of fracture and populations. Thus, there is room for further improvement.

None of the existing predictive models has included genetic or genomic data for predicting fracture risk. Therefore, the question remains whether combining susceptibility genetic variants in risk model could provide added value on fracture risk for an individual. This question has been investigated by a partially simulated study, in which a set of 50 independent genetic variants (with allelic frequency being 0.01-0.60) were simulated so that ORs for fracture ranged between 1.01 and 3.0 [41] in the Dubbo Osteoporosis Epidemiology Study. Adding a simulated genetic profiling

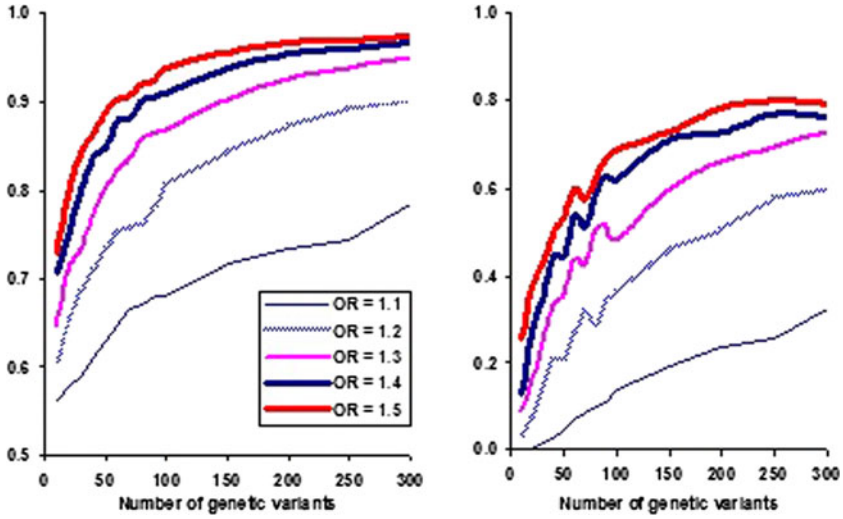

Fig. 1 Area under the receiver operating characteristic curve (*left*) and percentage net reclassification improvement (*right*) as a function of the number of genes and magnitude of association (odds ratio [OR]=1.1, 1.2, 1.3, 1.4, and 1.5). Data were obtained by simulation with the following parameters: gene frequency=0.5, risk threshold=0.2, and 5-year incidence of fracture=0.1

(in the form of a simple risk score) to the usual clinical risk factor model, the AUC increased from 0.77 to 0.88, with most of the improvement being in specificity, not sensitivity [41]. These results suggest that genetic profiling could enhance the predictive accuracy of fracture prediction.

However, the study [41] was based on some rather "optimistic" assumptions, which could overestimate the contribution of genes to fracture prediction. All SNPs identified by GWAS (Table 1) have a very modest association—albeit statistically significant—with fracture, with ORs ranging from 1.05 to 1.15. Assuming that there are 50 SNPs with such magnitudes of association, it is expected that the AUC value is ~0.72, which is significantly lower than that of the model with existing clinical risk factors (age, BMD, prior fracture, and fall; AUC=0.77). However, when the 50 genetic variants are added to the model with the clinical risk factors, the AUC value was increased to 0.83, and the NRI value is 21 %. Thus, the integration of genetic variants (in the form of genetic profiling) can improve the accuracy of fracture prediction beyond that obtained with conventional clinical risk factors. More importantly, the incorporation of genetic profiling into the current prognostic models could significantly improve the "correct" reclassification of fracture risk for an individual, and thus help improve treatment decision.

Perspectives: Toward Individualized Prediction

During the past three decades or so, epidemiologic studies have identified several risk factors for fracture. These risk factors, including anthropometric, demographic, clinical, physical, and behavioral factors, explain a modest proportion of variance in fracture susceptibility. It is here that genetics and genomics may have an important role in fracture risk assessment. A large twin study reported that almost 50 % of the variance in liability to fracture was attributable to genetic factors [10].

The recognition that fracture liability is partly due to genetic factors has led to intense efforts to search for specific genetic variants for fracture. After decades of confusion and disappointment with the candidate gene approach, the search for genes using GWAS has been highly successful. The hypothesis behind the GWAS approach is that between-individual variation in the susceptibility to common diseases such as osteoporosis is attributable in part to allelic variants present in 1 %–5 % of the population (ie, the so-called "common disease–common variant" hypothesis [42]). This hypothesis-free and unbiased approach has identified several genetic variants relevant to fracture risk. The discovery of these genetic variants has generated opportunities for translational research. At the heart of this research is the creation of a genetic/genomic profile for individualizing risk prediction for clinical purpose. Genetic profiling can help individualize fracture risk [43], which is a key component of personalized medicine.

The translation of GWAS discoveries to clinical application has proved to be a difficult process, because it requires the accumulation and synthesis of knowledge in many fields, including observational epidemiology and genetics. However, recent studies have shown that the predictive value of a single gene is very limited, and this can been entirely expected by simple epidemiologic principles [44]. Nevertheless, we have shown that a combination of multiple genetic variants in the form of genetic profiling could be useful for fracture prediction. Even with 50 SNPs, each may have only a modest effect size (ie, OR=1.1–1.2), and can yield an AUC of 0.72. It should be noted that the AUC value for genetic variants has an upper limit. Wray et al. [45] have elegantly shown that the AUC value for genetic profiling is a function of disease prevalence and heritability of the disease. For example, for hip fracture, the heritability index

is 30 % [9, 10], and if the 10-year incidence of fracture is 20 %, the maximum AUC value is approximately 0.80. Therefore, it can theoretically be speculated that the maximum discrimination of fracture by genes cannot be more than 0.80.

Perhaps, more importantly, a recent study and simulation have shown that genetic profiling could increase the accuracy—mostly improved specificity—of fracture prediction over and above that of conventional risk factors [41]. The integration of genetic variants can also have meaningful impact on the risk classification for an individual. If this finding is validated in independent populations, it opens a new opportunity for integrating genetic data into the existing fracture risk assessment models, which usher toward the era of individualized risk assessment.

The approach of individualized risk assessment or 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 [46]. For example, the stratification of BMD measurement into osteoporosis versus non-osteoporosis based on the T-score splits two women with T-scores of -2.45 and -2.50 into two distinct groups despite the trivial numerical and biologic difference, and despite the plausibility that the two women may have comparable risk of fracture if other risk factors are considered. Moreover, because of the broad categories, such a stratification approach classifies an 80-year-old women with T-score of -2.5 and a 70-year-old women with T-score of -3.0 into a single group, despite the fact that the two women have very different risk profiles. In contrast to the risk grouping approach, the individualized prediction approach recognizes that the four individuals are different, and that they should have different fracture risks as one would logically expect. Thus, although the risk grouping approach is conceptually simple and sometimes useful in clinical practice, its predictive value is poorer than the individualized approach due to the arbitrariness of any numerical cutoff value [47].

The assessment of fracture risk has until now been largely based on the measurement of BMD and a history of prior fracture. This is appropriate, since there is a strong association between BMD and the risk of fracture [48–50]. Furthermore, a history of fracture is also a strong risk factor of subsequent fracture [51]. In the past, treatment initiation was based on BMD measurement or the presence of a pre-existing low trauma fracture. This strategy appears to be logical and evidence-based because results from randomized clinical trials show that treating these patients (eg, with osteoporosis and/or a prior fracture) did reduce their fracture risk [49, 52]. However, it has recently been recognized that 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. Even at the lowest BMD range, only some individuals will sustain a fracture; on the other hand, a high BMD does not confer total protection against a fracture. It has been shown that more than 50 % of women and 70 % of men who sustained a fracture had not had osteoporosis [53] as defined by bone density criteria alone. Therefore, the dichotomization of BMD into osteoporosis versus non-osteoporosis by a threshold can be ineffective at the population level, because treatment of individuals with osteoporosis by bone density definition will not reach the majority of men likely to fracture in the general population.

Important changes are needed for that majority of individuals whose BMD measurements are at or near, on both sides, the current threshold of osteoporosis. At any given level of BMD, fracture risk varies widely in relation to the burden of other risk factors, such as advancing age, gender, genetics, family history of fracture, falls, and lifestyle factors. Thus, for any one individual, the likelihood of fracture depends on a combination of these and other risk factors [49]. This means that two individuals, both with "osteoporosis," can have different risks of fracture because they have different genetic risk profile. Similarly, an osteoporotic individual can have the same risk of fracture as a non-osteoporotic individual due to the difference in genetic profiles between the two individuals. In other words, the prediction of fracture risk can and should be individualized by using an individual's unique risk profile.

Medical practice is concerned with an individual, and each individual is unique, because there exists no "average individual" in the population. Individualized assessment of risk—or the prediction of risk for an individual given a risk profile—is fundamentally important. The more risk factors that are considered, the greater the likelihood of uniqueness of an individual's profile being defined. Therefore, genetic profiling can define the uniqueness of an individual, and thus better predict the risk for the individual.

There are some major advantages of using genetic variants as a prognostic factor of fracture risk. Since an individual's genetic profile is time-invariant, the risk of fracture for the individual can be predicted at younger ages, well before the conventional risk factors become apparent. Although there is no "genetic" therapy for individuals at high risk of fracture, the use of genetic variants could help segregate individuals at high risk from those with low risk of fracture, and help counseling services.

Individualized Risk Assessment

It is appropriate that individuals with high risk of fracture, regardless of their BMD levels, should be considered for treatment because there is evidence that treating these individuals could yield clinical benefit. However, what level

(or levels) of risk should be regarded as "high risk," so that an intervention can be considered cost-effective? The individualization of fracture risk can help select patients suitable for intervention. In a recent analysis, it was suggested that treatment is cost-effective (based on the criteria of £30,000 per quality-adjusted life-year gained) if an individual's 10-year risk of hip fracture is between 1.2 % and 9.0 %, dependent on age [54]. It has been estimated that for a 50-year-old Australian, treatment would be considered cost-effective if his 10-year risk of hip fracture is at least 1.93 % [54]. However, for a 90-year-old man, the treatment would only be cost-effective if his 10-year risk is 10.8 % or higher. Thus, the incorporation of genetic variants into an existing predictive model can help improve the cost-effectiveness of fracture management.

The individualization of fracture prediction can also be used to optimize the number needed to treat (NNT). In several randomized clinical trials the NNT to reduce one vertebral fracture (compared to the untreated group) ranged between 8 and 83 [55]. For hip fracture, the NNT ranged between 91 and 250 [55, 56]. The NNT varies inversely with the background risk, such that treatment of high-risk individuals inherently yields lower NNT. The large variability in the NNTs among trials is assumed to be due to the variability in fracture rates among the study samples, despite the fact that patients were selected on the basis of having osteoporosis and/or a prevalent vertebral fracture. However, the variability is expected given the multiple risk factors, including genetic variants, that affect the risk of fracture. In the presence of such variability, selecting patients based on their unique clinical and genetic profile (rather than based on a BMD threshold value) may improve the consistency of therapeutic efficacy and efficiency of trials.

Trials specifically testing the efficacy of multivariable risk-based therapy have not been done. As a result, it is not known whether treatment of individuals selected on the basis of absolute risk of fracture will result in reduced fracture risk. One clinical trial [57] randomized 5212 women aged 75 years and older into two groups: placebo receiving calcium and vitamin D, and the treatment group receiving clodronate (800 mg daily po). Ten-year probability of fracture was computed for each woman using baseline clinical risk factors including body mass index, prior fracture, glucocorticoid use, parental hip fracture, smoking, alcohol, and secondary osteoporosis. In women in the top 25th percentile of fracture probability (average probability of 24 %), treatment reduced the risk of fracture by 23 % over 3 years (hazards ratio [HR] 0.77, 95 % CI 0.63–0.95). Importantly, among those in the top 10 % percentile (average fracture probability of 30 %), treatment reduced the fracture risk by 31 % (HR 0.69, 0.53–0.90) [57]. These data are consistent with the hypothesis that treating individuals at high risk or moderate risk could reasonably be expected to reduce fractures.

Problems with Current Models

However, it should be noted that all models considered so far are somewhat simplistic. These models have assumed that genetic variants are inherited independently, and that their effects on fracture are independent of each other (ie, no interaction effect or epistasis). While no gene-gene interaction effect has been identified, such effect is likely to be identified in the future when data are adequately accumulated. At the individual level, the gene-gene interaction predicts that two individuals can have different fracture risk even if they share the same genotype at one locus. At the population level, epistasis suggests that a heterogeneity and incomplete penetrance of fracture is expected. However, the gene-gene interaction has not been taken into account in virtually all studies, and that could partly explain the phenomenon of "missing heritability" [58, 59].

Of course, genetics is unlikely the only factor that affects the risk of fragility fracture. Environmental factors, including hormones and behavioral factors, also contribute to fracture susceptibility [8, 60–62]. It can therefore be hypothesized that the risk of fragility fracture is a function of interaction between the time-invariant genes, and exposure to environmental factors. Consequently, the risk of fracture for an individual has to be considered not just in terms of gene-gene interactions, but also in terms of environmental context (ie, gene-environment interactions). However, virtually all genetic analyses of osteoporosis have not considered these interactions, and that could partly account for the incomplete prediction.

Conclusions

The assessment of fracture risk for an individual is currently based on conventional clinical risk factors. However, recent GWAS have identified several common genetic variants that are moderately associated with fracture risk. Moreover, simulation studies have shown that these genetic variants, despite their modest effect sizes, can yield predictive value beyond conventional clinical risk factors when integrated into existing fracture risk assessment tools such as the Garvan Fracture Risk Calculator [38, 39]. These genetic variants, together with established clinical risk factors, can provide a useful index of risk for an individual. This individualized index will potentially helps clinicians to tailor treatment to an individual and to make informed choices relating to lifestyle and preventive intervention. However, the incomplete discrimination and accuracy of

prediction—most likely related to the incomplete coverage of relevant variants and failure to take into account the gene-gene and gene-environment interactions [59]—remains a major challenge. With a rapid improvement in genotyping technology, the next generation of GWAS will be adding more variants at a low frequency to cover as many SNPs as possible. Advances in modeling approaches will refine the genetic profiling and allow a better assessment of fracture risk and individualized fracture prevention.

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