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Original Article

Individualized Assessment of Fracture Risk: Contribution of "Osteogenomic Profile"

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Abstract

Over the past decade, several genetic variants or genes for osteoporosis have been identified through genome-wide association studies and candidate gene association studies. These genetic variants are common in the general population but have modest effect sizes, with odds ratio ranging from 1.1 to 1.5. Thus, the utility of any single variant is limited. However, theoretical and empirical studies have suggested that a profiling of multiple variants that are associated with bone phenotypes (i.e., "osteogenomic profile") can improve the accuracy of fracture prediction and classification beyond that obtained by conventional clinical risk factors. These results support the view that an osteogenomic profile, when integrated into existing models, can help clinicians and patients alike to better assess the risk fracture for an individual, and raise the possibility of personalized osteoporosis care.

Key Words: Fracture; genetic profiling; osteoporosis; polygenic risk score; risk assessment.

Introduction

Until now, the assessment of fracture risk is largely suboptimal. Clinical guidelines for the prevention and treatment of osteoporosis in postmenopausal women and older men are mostly based on the concept of risk grouping. In risk grouping thinking, the estimate of risk is applicable to a group of individuals rather than to an individual despite the fact that medical practice is concerned with an individual. For example, the dichotomization of bone mineral density (BMD) measurement into osteoporosis vs nonosteoporosis categorizes 2 women with *T*-scores of –2.50 and –2.45 into 2 distinct groups despite the trivial numerical and biological difference, and despite the plausibility that the 2 women may have a comparable risk of fracture if other risk factors are considered. The risk grouping approach is conceptually simple and sometimes useful in clinical practice, but its predictive value is often poor. In recent years, predictive models incorporating BMD and non-BMD risk factors have been developed and introduced into the clinical setting *(1–4)*, but these models have modest discrimination and poor calibration. Thus, there is an urgent need for more accurate and reliable models for fracture risk assessment.

The relevance of fracture risk assessment models lies in the fact that osteoporotic fracture is a major public health burden worldwide. From the age of 50, the residual lifetime risk of fracture is ~50% in women and ~30% in men *(5)*. A not-commonly known fact is that the lifetime risk of hip fracture is equivalent to or higher than the risk of invasive breast cancer *(5,6)*. Moreover, in men, the lifetime risk of hip and vertebral fractures (17%) is comparable to the lifetime risk of being diagnosed with prostate cancer *(6,7)*. With the rapid aging of the population, it is projected that fractures not only will become simply a public health problem but also will impose a great demand on medical services in the near future.

It is now well recognized that fracture contributes to the loss of human life. A pre-existing fracture is associated with reduced life expectancy *(8)*, and the relative risk of death in men (1.8-fold) is significantly greater than that in women (1.4-fold) *(8,9)*. Among those survivors of a fracture, their

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risk of refracture is substantially increased *(9,10)*. A lower BMD, a more rapid bone loss, weight loss, and weight fluctuation are significant predictors of all-cause mortality in men and in women, independent of age and concomitant diseases *(11)*. However, the sequential consequences of fracture, recurrent fracture, and mortality are highly heterogeneous among individuals. Indeed, not all individuals with an initial fracture will sustain another fracture, and not all fractures or recurrent fractures are associated with premature mortality.

The risk of fracture is determined by multiple factors. At the population level, fracture cases are clustered in postmenopausal women and in elderly men with low BMD, low body weight, a personal history of fracture, a history of fall, prolonged use of corticosteroids, and histories of smoking and alcohol consumption *(12,13)*. Based on those risk factors, predictive models have been developed for estimating the probability of fracture within a 5- or 10-yr period. Currently, there are 2 main predictive models for assessing the absolute risk of fracture for an individual, namely, the Garvan Fracture Risk Calculator *(1,2)*, the Fracture Risk Assessment Tool (FRAX) *(3)*, and QFract *(4)*. Although these tools are helpful in the identification of high-risk individuals, their predictive value is not perfect. In external validation studies, the area under the receiver operating characteristic curve (AUC) of the Garvan and FRAX models ranged between 0.61 and 0.85 *(14–17)*. Thus, there is room for further improvement in fracture prediction.

Identification of Genetic Variants

One of the factors that can improve the accuracy of fracture risk assessment is genetic factors, because fracture has a hereditary component. Women with a family history of hip fracture have a 2-fold increase in the risk of hip fracture *(18)*. Moreover, twin and family studies have estimated that approximately 25%–35% of the variance in the liability to fracture is attributable to genetic factors *(19,20)*. Genetic factors also account for a large proportion of variance in risk factors for fracture, such as BMD *(21)*, bone loss *(22)*, quantitative ultrasound *(23)*, and bone turnover markers *(24)*. Taken together, these data show that heredity is an important nonmodifiable risk factor for osteoporosis and fracture risk.

During the past 2 decades or so, intensive efforts have been made to determine specific loci that are associated with BMD and fracture risk. Statistically, genes can be identified by either association or linkage analysis. Association analysis tests for the association between 1 or more genetic variants and the occurrence of a phenotype in unrelated populations. Linkage analysis tracks the dependence between genetic variants transmitted from parents to offsprings for genes near each other on a chromosome. Each of the analyses can be applied to either a candidate gene or a genome-wide approach *(25)*. 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 single gene, the genome approach scans the entire genome, and usually uses hundreds of thousands of common single-nucleotide polymorphisms (SNPs) to identify chromosomal regions harboring genes likely to influence a trait. Conceptually, the genome-wide approach is a hypothesis-free approach because it makes no assumptions about the location and the functional significance of associated loci or their products *(26)*. In each of the approaches, either association or linkage analysis can be used to identify putative genes. The 2 approaches, particularly the genome-wide approach, have been useful in finding genes for bone phenotypes.

Using the candidate gene association approach, several gene polymorphisms have been identified to be associated with BMD or fracture risk. These genes, 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 identified *(27)*. However, findings from candidate gene studies have poor replicability, with ongoing conflicting findings. The poor replicability is mainly due to the lack of statistical power *(28)* and false positives *(29)*.

Nevertheless, linkage analysis of well-characterized families seems to help. Indeed, by using linkage analysis of data from a family with an osteoporosis-pseudoglioma syndrome (OPS), a disorder characterized by a severely low bone mass and eye abnormality, investigators were able to localize the OPS locus to the chromosomal region 11q12-13 *(30)*. 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) has suggested that the HBM locus is also located within the 30-cM region of the same locus *(31)*. 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 *(32–34)*. The discovery of the *LRP5* gene has, in many ways, inspired a new phase in the search for genes in osteoporosis.

That new phase is genome-wide association studies (GWAS). The earliest genome-wide association study in osteoporosis examined the association between 71,000 genetic variants in the form of SNPs and found 40 variants associated with BMD. Although the study was then considered to be underpowered, several SNPs identified in this study were located in potential osteoporosis-associated genes, such as the *MTHFR*, *ESR1*, *LRP5*, *VDR*, and *COL1A1* genes *(35)*. Another genome-wide association study 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 a genome-wide threshold ($p < 5 \times 10^{-8}$) *(36)*. This study also suggested some loci associated with fracture risk, including variants in the 1p36, 2p16, *OPG*, *MHC*, *LRP4*, and *RANK*.