Post-GWAS Polygenic Risk Score: Utility and Challenges

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ABSTRACT
Over the past decade, through genome-wide association studies, more than 300 genetic variants have been identified to be associated with either BMD or fracture risk. These genetic variants are common in the general population, but they exert small to modest effects on BMD, suggesting that the utility of any single variant is limited. However, a combination of effect sizes from multiple variants in the form of the polygenic risk score (PRS) can provide a useful indicator of fracture risk beyond that obtained by conventional clinical risk factors. In this perspective, we review the progress of genetics of osteoporosis and approaches for creating PRSs, their uses, and caveats. Recent studies support the idea that the PRS, when integrated into existing fracture prediction models, can help clinicians and patients alike to better assess the fracture risk for an individual, and raise the possibility of precision risk assessment. © 2020 The Authors. JBMR Plus published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research.

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Consider the following two 70-year-old women. Case 1 has femoral neck BMD of 0.72 g/cm² (e.g., nonosteoporosis), has no prior fracture, but fell once over the past 12 months. Case 2 has femoral neck BMD of 0.65 g/cm² (e.g., osteoporosis), has no prior fracture, and had no fall during the past 12 months. If the two women have genotypes that are associated with an osteoporosis phenotype, how can the genetic data help inform their fracture risk? Below, we review the genetic influence on osteoporosis phenotypes and the generation, as well as the application of the polygenic risk score (PRS) in individualized fracture risk assessment.

The Genetics of Osteoporosis

The genetics of osteoporosis has, over the past five decades, evolved through five paradigms: heritability study, candidate gene study, genome-wide association study (GWAS), and recently, the PRS and whole-genome sequencing. Twin studies in the 1980s and 1990s showed that up to 80% of the variance in BMD was attributable to genetic factors.1,2 Twin studies also showed that between 25% to 35% of the variance in the liability to fracture isheritable,3,4 consistent with the observation that women with a familial history of hip fracture have a twofold increase in the risk of hip fracture.5 Moreover, genetic factors account for a large proportion of variance in recognized risk factors for fracture such as bone loss,6 quantitative ultrasound,7 and bone turnover markers.8 These lines of evidence have established that heredity is an important risk factor for osteoporosis and fracture risk.

Although the demonstration of hereditary effect on osteoporosis risk is relatively easy, the identification of specific genes that contribute to the risk has proven to be a formidable task. After a series of candidate gene studies, a number of “osteoporosis genes” (including, but not limited to, vitamin D receptor [VDR], collagen type 1 alpha 1 genes) have been identified.9 However, these candidate gene studies were marred by conflicting findings, limited reproducibility, and possibly false-positives,10 which were perhaps based mainly on the lack of statistical power.11

Instead of focusing on a biologically plausible candidate gene, a GWAS offers a hypothesis-free method of searching for putative genes in the entire genome without any assumptions about the location and functional significance of loci or their products.12 The thinking behind a GWAS is actually the “common disease–common variant” hypothesis, which postulates that the genetic component of common diseases (such as osteoporosis) is made up of a large number of putative alleles that are common (>5%) in the general population.13 Although it is a hypothesis-free approach, a GWAS has been successful in identifying multiple variants that are associated...
with BMD or fracture risk. A significant breakthrough was reported in a seminal study that analyzed 301,019 variants in ~14,000 individuals of White background, and discovered 77 variants that were associated with BMD at the genome-wide significance level. Some of these variants are located close to or within genes that are known to have important biologic roles in bone metabolism, such as RANK, RANKL, osteoprotegerin (OPG), estrogen receptor 1 (ESR1), and zinc finger and BTB domain containing 40 (ZBTB40). Apart from those variants, the study also identified several variants in and around the VDR and low-density lipoprotein receptor-related protein 5 (LRPS) genes that had been intensively examined in candidate gene studies.

Another seminal study comprised of 81,949 cases and 102,444 controls, largely of White background, identified 56 loci that were associated with BMD and 13 SNPs associated with fracture. Several of these loci or SNPs also cluster within or near the RANK–RANKL–OPG system, mesenchymal stem cell differentiation, endochondral ossification, and Wnt signaling pathways. A more recent study using the resource of UK Biobank identified 518 loci associated with heel ultrasound measurements, of which 301 were new loci. The list of genetic variants identified so far is unlikely the final list, as ongoing studies are likely to identify more variants that contribute to the susceptibility to osteoporosis and fracture.

The identified variants have two common characteristics: They are carried by a large proportion of people, and they confer modest effect sizes. Indeed, the frequency of the minor allele for all variants discovered so far ranged mostly between 5% and 45% in the general population. Moreover, the strength of association between these variants and traits is modest or very modest. Most of the variants that are associated with fracture risk had modest odds ratios (ORs; ie, <1.2). For example, the 77 variants in the first major GWAS accounted for only 3% of the total variance in hip and spinal BMD, and the 518 variants in the UK Biobank study accounted for 20% of the variance in heel ultrasound measurement. In terms of fracture association, virtually all variants confer modestly increased odds of fracture by a few percentage points, mostly closer to 5% and albeit some rare loci up to 20%.

The modest effect size of genetic variants implies that the predictive value of any single genetic variant is likely limited; this is entirely expected by simple epidemiologic principle. For instance, for a genetic variant with OR between 1.1 and 1.2, and assuming that the 5-year incidence of fracture is 10%, the area under the ROC curve (AUC) associated with this genetic variant is expected to be 0.52 to 0.55. Thus, any single variant of and by itself is unlikely to be useful for prediction.

On the other hand, a combination of multiple genetic variants, even with modest effect sizes, could be useful. Theoretically, it can be shown that for a given number of variants, the discriminatory power (eg, AUC) increases proportionally to the effect sizes. For example, for a combination of 50 genetic variants, each with an OR = 1.1, the AUC value is expected to be 0.63; however, if each variant has an OR = 1.2, the AUC is expected to be 0.73. From this simulation, it can also be inferred that a model with 500 variants, each with OR = 1.1, can yield an AUC >0.80 (Table 1). The idea of combining multiple variants gives rise to a construct known as the polygenic risk score, which is poised to improve patient outcomes via precision medicine, but raises concerns of health disparity between ethnicities.

The Polygenic Risk Score

The PRS can be defined as a quantitative index of the genetic burden related to a specific disorder and is specific to an individual. Operationally, there are several ways to create a PRS. The simplest approach is to assign a risk value of 0 if an individual is a noncarrier of a risk allele, 0.5 or 1 if a carrier, and 1 or 2 if homozygous for that allele, and then sum the score across variants for the individual. This simple approach implicitly assumes that all variants contribute equally to the trait variation, which is unlikely true in most real-world situations. Therefore, a better approach is to sum the trait-associated alleles weighted by their effect sizes. The trait-associated or risk allele is defined as an allele that is more common in cases than controls. The effect size can be a regression coefficient (for quantitative trait) or log OR (for categorical traits). In either approach, because the PRS is aggregated from multiple variants and effect sizes, it is likely to be unique to an individual. Moreover, given its aggregation nature, the PRS can be seen as an index of an individual’s genetic liability to develop a disorder.

Statistically, the PRS tends to show a normal or approximately normal distribution in the general population. The difference in the PRS between those with and without a disorder is mainly governed by the mean, not the variance of the distribution.

The number of variants can range between a few and millions that are identified across loci from GWASs. Intuitively, only variants that are statistically robust at genome-wide significance level should be included in the derivation of the PRS because variants that do not reach the significance level are unlikely to contribute to the variation in the trait of interest. However, in reality, some PRSs were constructed from many variants (eg, hundreds of thousands of variants) across the genome, even though they show very weak association with a trait. This practice of including a large number of variants is based on the view that many genuine associations are potentially missed because of inadequate power in the original GWAS.

Another approach to construct the PRS is to use knowledge of biological pathways or processes to select relevant variants. For example, one can select all variants that are involved with protein–protein interactions or involvement in signaling pathways. However, it remains to be shown whether pathway-based PRSs can predict phenotypic variation more robustly than the “traditional” PRS, which is based on the totality of disease risk.

What Can the Polygenic Risk Score Be Used For?

An obvious application of a PRS in clinical osteoporosis care is fracture risk assessment. At present, the assessment of fracture risk for an individual is primarily done using tools such as the Garvan fracture risk calculator, the fracture risk assessment tool (FRAX) and QFract software. Although these tools have proven useful for identifying high-risk individuals, their predictive performance is a matter for improvement. In external validation studies, the AUC of the Garvan and FRAX models ranged between 0.61 and 0.85, with average being ~0.70, a modest discrimination. Ideally, to be useful, predictive capacity would need to be high predictive (AUC ~0.80). Furthermore, FRAX tends to underestimate the risk of fracture by as much as 50% in part because factors that are associated with higher risk are also associated with earlier mortality for which the estimated risk was discounted. Thus, there is room for further improvement in

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fracture prediction, and genetic factors have emerged as an important for fracture risk prediction.

Although none of the existing fracture prediction tools incorporates genetic data, recent studies have suggested that the PRS can be a useful addition. We have created a PRS called osteogenic profile, which is based on 62 variants that are associated with BMD. We found that each unit increase in the PRS was associated with a hazard ratio of 1.20 (95% CI, 1.04–1.38) for fracture, independent of age, prior fracture, and falls. Importantly, when the PRS was included in the existing Garvan fracture risk calculator model, the reclassification of fracture versus nonfracture was significantly improved. In the MrOS (Osteoporotic Fractures in Men study) cohort, a PRS constructed from 63 genetic BMD-associated variants was also associated with the risk of total fracture. In postmenopausal women of Korean background, a PRS constructed from 39 variants improved the precision of nonvertebral fracture prediction in the general population, as well as in patients on bisphosphonate. QUS is associated with fracture, and the PRS generated from QUS can also help identify individuals at risk of fracture or osteoporosis. Taken together, a PRS constructed from BMD-associated variants could be used as a genetic factor for fracture prediction.

The PRS can also be used for assessing bone loss in an individual. Bone loss is highly variable between individuals, not simply because of measurement error, but also because of genetic factors. Although specific genes for bone loss have not been identified, a PRS has been shown to be associated with bone loss in postmenopausal women. In a longitudinal study in which BMD of 860 postmenopausal women had been monitored for up to 20 years, each unit higher PRS was associated with a 0.21% (standard error, 0.10) higher annual rate of bone loss at the femoral neck. Of note, this association was independent of PRS

| Number of variants | OR = 1.10 | OR = 1.15 | OR = 1.20 | OR = 1.25 | OR = 1.30 |
|--------------------|----------|----------|----------|----------|----------|
| 10                 | 0.557    | 0.586    | 0.611    | 0.635    | 0.659    |
| 50                 | 0.630    | 0.682    | 0.733    | 0.769    | 0.805    |
| 100                | 0.682    | 0.743    | 0.794    | 0.841    | 0.870    |
| 500                | 0.830    | 0.898    | 0.936    | 0.953    | 0.967    |
| 1000               | 0.895    | 0.943    | 0.966    | 0.977    | 0.983    |

Notes. Results were obtained by simulation with the following parameters: gene frequency = 0.5, risk threshold = 0.2, and 5-year incidence of fracture = 0.1. AUC = Area under the receiver operating characteristic curve; OR = odds ratio.

The PRS is not a diagnostic test. Like other risk assessment tools, the PRS can only indicate the risk of fracture, but cannot categorically establish whether an individual will or will not have a fracture. However, the advantage of risk assessment via the PRS is that it allows a life-time prediction well before the onset of fracture. Although there is no “genetic therapy” for individuals at high risk of fracture, this salient lifetime prediction may raise immediacy of primary and secondary prevention behaviors in those at heightened genetic risk.

The PRS alone is not informative of fracture status. That is, it cannot reliably discriminate between those who will from those who will not have a fracture. The PRS must and should be used in conjunction with established risk factors (eg, BMD, fall, personal history of fracture) for assessing fracture risk. Still, the PRS could be useful for the stratification of individuals in the general population, which can be useful for public health intervention.

Any scientifically useful measure should satisfy two basic criteria: content validity and criterion validity. Content validity refers to the extent to which the measure is representative of the entire domain or content the measure seeks to reflect. Criterion validity is the correlation between the new measure and an established method (eg, the gold standard). Any use or interpretation of the PRS must be considered in the context of these two types of validity.

In the PRS context, genetic liability is the domain. The PRS, which is constructed from a selected set of genetic variants, could not capture the totality of genetic liability. As mentioned above, different PRSs have been constructed using different approaches and criteria. The selection of variants has largely been based on P-value thresholds, so it is unlikely that they capture the totality of genetic liability. Logically, the more variants to be included in the PRS (usually by relaxing P-value criteria) the better content validity it is, and this has been shown in simulation as well as empirical studies. Moreover, rare variants (ie, allelic frequencies <1%) that are not currently identified by GWASs may account for a significant proportion of variance in BMD, but they are not included in the derivation of the PRS. At present, most PRSs account for a small proportion of genetic variance of BMD or fracture risk, and their content validity is an open question.

Table 1. Utility of Genetic Profiling in Terms of AUC and Percentage of Net Reclassification Improvement

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The criterion validity of the PRS also requires more consideration. BMD has been the gold standard for assessing fracture risk, and BMD has been shown to be valid in terms of measured content and its biology criterion. In the PRS context, the correlation between a PRS and BMD is low, with most correlation coefficients being <0.20, suggesting that PRSs have a low level of criterion validity.

The PRS is, as expected from the operational definition, sensitive to allele frequency and effect size of variants. Allele frequency is known to be different between ethnicities, such that an allele may be common in one ethnicity, yet may be rare in another ethnicity. Furthermore, the effect size associated with an allele can be different between ethnicities because of interaction with environmental factors. Furthermore, population history (eg, effective population size, immigration, and inbreeding) and inheritance patterns may be different between ethnic groups. Thus, a PRS constructed from an ethnicity may not be applicable to another ethnicity. At present, most PRSs in the field of osteoporosis were derived from White populations, and these PRSs may not be applicable to non-White populations.

It is now increasingly recognized that many chronic diseases are biologically linked such that they form a network. The diseases within a network may share common sets of genetic variants. For instance, osteoporosis and obesity are known to be linked, and eight genetic variants at the TBX15 gene were associated with both body mass and estimated BMD. It has been suggested that genes associated with morphological phenotypes, such as bone structure, evolve more slowly than those associated with physiological phenotypes, such as bone turnover markers. The implication of these complex relationships is that the regression weight associated with a variant may be different across diseases and environmental factors, but this possibility is not captured by a phenotype-specific PRS.

Another caveat of the PRS is its assumption of additive effects. Because the PRS is the sum of weighted effect alleles, it implicitly assumes that the effects of all variants are additive. However, there is no logical reason to suggest that the effects are independent; it is highly likely that the effect of one variant is dependent on the other’s effect (ie, epistatic effects or gene–gene interaction), and this would introduce bias into the risk estimates. However, current methodology and sample size do not allow a complete dissection of higher-order gene–gene interactions between genes. Nevertheless, in the presence of gene–gene interactions, the simple additive PRS can be biased.

Another concern with the PRS is its cost effectiveness. Although there have been no studies of the economic cost of PRS in osteoporosis, studies in the field of cancer and cardiovascular disease suggest that the PRS is cost effective in the prevention or improved management of disease. At present, it is quite feasible to generate the PRS with hundreds of thousands or even millions of SNPs for less than $100. Thus, in the long run, the implementation of the PRS into clinical practice will be technically and economically feasible.

Back to the two cases, what can the PRS contribute to the prediction of their fracture risk. The Garvan fracture risk calculator predicts that the two women have the same 10-year risk of fracture (24%), which may not be indicated for treatment. However, if both women have a PRS in the top 5% percentile, then their 10-year risk of fracture is now 32%, which may be indicated for treatment. Thus, knowing their genetic information in the form of a PRS can potentially change the indication of treatment.

In summary, the PRS has emerged as a useful measure of genetic propensity to a trait at the individual level that has multiple applications. In the field of osteoporosis, the PRS could be used for individualized fracture risk assessment in conjunction with existing prediction tools, prediction of bone loss, and as a quantitative index of family history. The PRS could also be used for risk stratification in the general population. However, the application of the PRS has to be considered in the context of its potential limitations concerning content and criterion validity and underlying assumption of additive effects. In the era of post-GWAS, when health care will be strongly influenced by genomics and big data, the PRS, as a proxy measure of genetic liability, will likely have a place in clinical decision and precision medicine.

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