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Perspective:

On Genetic Studies of Bone Loss

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BMD, a major determinant of fracture risk, depends not only on peak bone mass achieved during growth but also on bone loss rate in later life. A number of studies have attempted to dissect the genetic basis of bone loss rate.[1–3] However, cautions should be taken in performing and interpretation of such studies, particularly, in light of the presumption that bone loss rate can be treated as a phenotype independent of BMD for genetic studies.

First, there is no clear evidence that the variation of bone loss rate is under genetic control. Ovariectomized mice showed varied bone loss rates among strains, suggesting that the bone loss rate may be regulated by genetic factors[4]; however, little evidence is available in humans. Christian et al.[5] performed a 16-year longitudinal study in 25 monozygotic (MZ) and 21 dizygotic (DZ) aging male white twins and found no evidence of genetic influence on the loss of BMD/BMC. Kelly et al.[6] conducted a twin study on the rate of BMD change (rather than bone loss) in a cohort of 21 MZ and 19 DZ twins for a relatively short period (range, 1.1–5.5 years). Significant genetic effects on rate of BMD change were detected at lumbar spine and Ward's triangle but not at the femoral neck. However, this study has several apparent limitations, including small sample size, short follow-up study period, and a wide age range of the subjects (range, 24–75 years), which make it difficult to draw a definitive conclusion on the genetic determination of bone loss rate. Also, although bone turnover markers may be useful for predicting bone loss rate in some circumstances,[7] the sensitivity and specificity of the predictions are very limited.[8] In addition, the heritability of bone turnover markers is still controversial.[9,10] Thus, no studies have powerfully addressed the important question of whether the rate of bone loss is heritable.

Second, the rate of bone loss may be influenced by multiple environmental and physiological factors, such as age,[11] body composition,[12] and skeletal sites.[13] Lack of controlling these important factors may lead to adverse effects on genetic studies of bone loss. Notably, the variation of bone loss rate can never be independent of the variation of BMD. This is determined by the nature of bone loss rate measurement (i.e., computation) and can be easily shown by simple mathematic formulations:

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$$\text{Bone Loss Rate} = \frac{\text{BMD}_1 - \text{BMC}_2}{\Delta t},$$

$$\text{Var (Bone Loss Rate)} = \frac{\text{Var}(\text{BMD}_1) + \text{Var}(\text{BMD}_2) - 2\text{Cov}(\text{BMD}_1, \text{BMD}_2)}{\Delta t^2},$$

where BMD_1 and BMD_2 represent the baseline BMD and the follow-up BMD, respectively. Apparently, the variation of bone loss rate partially reflects the variation of baseline BMD, no matter whether there exists a true physiological connection between baseline BMD value and bone loss rate. Several empirical studies have also suggested that the rate of bone loss may vary depending on the baseline BMD, because women with higher BMD also tend to have faster bone loss.[14,15] In addition, the magnitude of the genetic correlation between bone loss rate and BMD is unknown. Without a clear depiction of the relation between BMD and the subsequent bone loss rate, it is hard to interpret the results of previous genetic studies on bone loss, because most of these studies, if not all of them, have not controlled the effects of baseline BMD on bone loss rate. Moreover, by reanalyzing the data in a 9.5-year longitudinal study,[13] we found that ~67% of postmenopausal BMD variation is attributable to the premenopausal BMD, whereas only ~29% to the bone loss rate. These results suggest that, compared with peak BMD, the contribution of bone loss rate to low BMD is fairly small and not of primary importance.

Another factor that also received less attention is measurement error. Bone loss is a relatively slow process. The estimated pre- and postmenopausal bone loss rates are ~0.3–1.5%/year, varying at different skeletal sites.[16,17] Even during the perimenopausal period when “rapid” bone loss occurs, the annual bone loss rate is only ~2% at the lumbar spine[18] and 0.6% at the femoral neck.[19] Given the fact that the CV for BMD measurement by current available instruments is ~1–2%, the estimated bone loss rate over a short period would be in low precision.[20] Although increasing the follow-up time may reduce the effects of measurement errors, it may not be the case all the time because the BMD data collected over an extended period of time are likely to be measured by different machines and/or different models, which may result in more severe measurement errors.[21]

Recently, a few groups conducted age-stratified subgroup linkage analyses on BMD variation[22,23] and identified several potential age-specific quantitative trait loci (QTLs) for BMD. On the one hand, stratification of samples on the basis of age may help to reflect genuine etiological heterogeneity[22] and shed light on the genetic mechanisms of BMD and bone loss variation. On the other hand, it should be pointed out that the QTLs identified specifically in the older subgroup may not necessarily be genuine bone loss-specific QTLs. This is because genes of differential effects in the two age groups (gene by age interaction, but not bone loss–specific gene) may also lead to differential detection in the subgroup analyses. In addition, these subgroup analyses may suffer from the problems of reduced statistical power and increased magnitude of multiple testing and thus may generate more false-positive results. Failing to detect a gene in a subgroup (one age group) does not mean the gene is not there. The existence of bone loss/age-specific genes should be ultimately tested, not just by the evidence of detecting a region in the older group and not being able to detect it in the younger group, but that we detect a region in the older group and also are able to exclude this region in the younger group.

Given the issues addressed above, claims of candidate genes or QTLs related to bone loss rate may be treated with caution. More care and thought should be taken to produce less biased findings.

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