Marcella D. Walker

Abstract
Osteoporosis is characterized by low bone mineral density (BMD) and microstructural deterioration. While BMD has high heritability, genetic testing for variants associated with osteoporosis or fracture plays no role in the clinical assessment of bone health. Most of the genetic variance of BMD has yet to be accounted for. Attempts to address this issue have been impeded by the genetic approaches utilized and the skeletal outcomes assessed. Genome-wide association studies (GWASs) cannot identify rare variants. Such rare variants, which can be identified by whole exome sequencing (WES), often have large functionally important effects. Moreover, rare variants are relevant to common, polygenic conditions. Some of the "missing heritability" of osteoporosis is likely due to unidentified rare variants. Further most GWASs have assessed genetic associations with "bone mineral density" (BMD) or "fracture", both outcomes of heterogeneous pathogenic processes. To overcome these limitations, we will use WES to assess specific skeletal traits, such as microstructure or matrix properties, that predispose to or protect from fracture. Such traits are less genetically heterogeneous and more amenable to genetic analysis. Thus, tools other than DXA, such as high resolution peripheral quantitative computed tomography (HRpQCT) and impact microindentation (IMI) that can measure specific skeletal elements contributing to fracture are useful to identify osteoporosis genes. With HRpQCT, we have made progress by identifying in minorities, novel imaging-based bone phenotypes conferring greater bone strength despite lower or similar BMD by DXA. Using WES, we have begun to study the genetics of these racial differences. Our data indicate this is a powerful approach to identify genetic contributors to microstructure. The goal of this project is to phenotype a large, population-based, multi-ethnic cohort with existing WES data using HRpQCT and IMI in order identify genes regulating bone microstructure and matrix properties. In doing so, we can assess how racial differences in causal variant allele frequencies dictate racial differences in these traits. Lastly, we will assess if identified variants are associated with fractures. A major strength of this study is the availability of WES data, which in contrast to GWAS, allows for the identification of both common and rare coding variants. Our gene-based statistical approach is a powerful method, making this approach feasible with our sample size. These methods have been used to identify new disease-causing genes (not found with GWAS) that regulate lipids, height, infectious susceptibility, epilepsy and other conditions. It has only begun to be explored in osteoporosis, but offers a way to identify novel genes with important biological effects not detected by GWAS. The overarching hypothesis is that skeletal microstructure and matrix properties are under genetic regulation and genes underlying them can be identified using WES. Ultimately, identification of such genes may enhance understanding of skeletal regulators, which may lead to the development of gene