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Osteoporosis is a very common disorder characterized by low bone mineral density (BMD) and microarchitectural deterioration of the skeleton that predisposes to fracture. The diagnosis of osteoporosis and assessment of fracture risk rely heavily upon the measurement of BMD by dual x-ray absorptiometry (DXA). The diagnosis of osteoporosis is currently made, and treatment recommended, when a fragility (or low-trauma) fracture is present or when the DXA-derived T-score is ≤ -2.5. Unfortunately greater than one-third of patients who experience a fragility fracture do not have osteoporosis by DXA, which makes it unlikely that they will be diagnosed and treated before that first fracture occurs. This arises because the currently available diagnostic tools, such as DXA, do not capture information on the internal bone microstructure, a system that contributes to bone strength and fracture independently of BMD. While BMD is known to have strong genetic component, genetic testing for variants associated with low BMD or fracture plays no role in the clinical assessment of skeletal health. In part, this is because very little of the genetic variation in BMD has been accounted for to date. Attempts to address this issue have been hampered by assessing genetic associations with "osteoporosis" or "fracture" which are the endpoints of heterogeneous pathophysiological processes. Instead, a more fruitful approach might be to assess more specific skeletal traits, which are more likely to share the same genetic basis. Thus technologies other than DXA that can characterize specific skeletal elements contributing to fracture may be useful in identifying such genes. Using a new imaging technology known as high resolution peripheral quantitative computed tomography, we have recently identified a novel bone microstructural phenotype (the plate-like trabecular phenotype) that confers greater bone strength despite lower BMD by DXA. This proposal will use an interdisciplinary team of metabolic bone disease specialists, geneticists and bioengineers to identify genetic variants associated with this novel trait. Using whole exome sequencing, our goal is to begin elucidating the genetic underpinnings of skeletal fragility. The absence of genetic insight in this area to date has hampered our ability to prevent disease, adequately understand each individual's unique disease pathophysiology, sufficiently risk stratify, choose treatments based on individual pathogenesis and has greatly impaired the development of new therapies for osteoporosis. Identification of genes associated with skeletal fragility could eventually lead to the development of genetic tests to assess for the predisposition to osteoporosis and may point to new biological targets for drug development and therapy. This project may yield results that contribute to a new era of personalized medicine in the field of osteoporosis. Ultimately, this shift from a "one size fits all" approach for osteoporosis patients will enable us to develop more effective and tailored diagnostic and therapeutic strategies while avoiding unnecessary treatment and adverse effects.