EuroSciCon

Annual Summit on
Surgery

August 06-07, 2018
Prague, Czech Republic

J Univer Surg 2018, Volume: 6
DOI: 10.21767/2254-6758-C1-003

CHALLENGES AND OPPORTUNITIES FOR THE DISCOVERY OF OSTEOPOROSIS GENES

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Osteoporosis, the silent killer most prevailing metabolic bone disease worldwide, is a polygenic disorder associated with impaired bone matrix mineralization that leads to low bone mineral density and deterioration of bone microarchitecture with increased chance of bone fractures. However, bone mineral density is a complex phenotype because it is the outcome of the balance between bone resorption and formation during cyclic bone remodeling. Although extracellular matrix mineralization and osteoporosis are closely related, the mineralization of bone matrix is almost a forgotten facet in the pathogenesis of metabolic bone disease. Genetic linkage analysis first developed to map gene alterations causing monogenic bone disorders appears to lack the sensitivity to define genes underlying bone polygenic diseases. In fact, genetic linkage analysis has ultimately failed to identify the causative genes of a complex genetic disorder such as osteoporosis. Decades of osteoporosis research have identified few causative genes, but much less is known about the signaling pathways at which they are affiliated. The complex processes of bone matrix mineralization, bone resorption, and bone remodeling are tightly regulated by several transcription factors and signal transduction pathways. However, signal transduction pathways occur at protein level that depends not only on mRNA transcriptional regulation but also on a multitude of translational and posttranslational controls. Also, proteomic alterations in bone tissue due to disease may occur in several ways that are not predictable from either genome or transcriptome analysis, and it is obvious that a deeper view of these alterations will impact medicine in the field of metabolic bone disease. The strategy to combine proteomics with RNA interference, CRISPR/Cas9 or gene knockout animal models would greatly improve the efficiency of gene discovery and divulge the molecular pathways involved in osteoporosis pathogenesis.

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