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Feature Review

# Osteoporosis and Bone Mass Disorders: From Gene Pathways to Treatments

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**Genomic technologies have evolved rapidly contributing to the understanding of diseases. Genome-wide association studies (GWAS) and whole-exome sequencing have aided the identification of the genetic determinants of monogenic and complex conditions including osteoporosis and bone mass disorders. Overlap exists between the genes implicated in monogenic and complex forms of bone mass disorders, largely explained by the clustering of genes encoding factors in signaling pathways crucial for mesenchymal cell differentiation, skeletal development, and bone remodeling and metabolism. Numerous of the remaining discovered genes merit functional follow-up studies to elucidate their role in bone biology. The insight provided by genetic studies is serving the identification of biomarkers predictive of disease, redefining disease, response to treatment, and discovery of novel drug targets for skeletal disorders.**

## Trends

GWAS and whole-exome sequencing studies have revolutionized the identification of genetic determinants of monogenetic and complex conditions including osteoporosis and bone mass disorders.

GWAS pinpoint factors in pathways crucial to bone biology (WNT, NOTCH, INDIAN HEDGEHOG signaling), which are currently targets of drug compounds for the treatment of osteoporosis and bone mass disorders.

Given the hypothesis-free nature of these genomic screens, functional follow-up of the numerous remaining discovered genes will be necessary to elucidate their role in bone biology.

The considerable overlap in factors and biologic pathways underlying common and monogenetic forms of osteoporosis and bone mass disorders opens new avenues for diagnosis and personalized medicine.

The emerging discovery of novel skeletal biology by genetic studies is of huge potential for the identification of novel drug targets for skeletal disorders.

## Introduction

Musculoskeletal conditions are the most common causes of severe short and long-term pain and physical disability, affecting hundreds of millions of people across the world, with costs approaching 3% of gross national product globally [1] and constituting the second greatest contributor to years lived with disability worldwide [2]. One of the diseases with greatest burden is osteoporosis, affecting one in three women and one in five men globally. This debilitating condition presents with a high incidence of low-trauma hip, spine, and other fractures, leading to immobility, associated comorbidity, and early death [1]. About 43 000 deaths occur each year in Europe as a direct consequence of hip or spine fractures, where approximately 20% of senior citizens who suffer a hip fracture die within a year [3]. Those who survive the fracture are often significantly disabled and have a reduced life-expectancy [1].

In this review we provide a succinct overview of the main molecular pathways governing bone metabolism, with an overlay of the genes that underlie monogenic conditions and complex forms (Box 1) presenting with low bone mass. We evaluate the genetic determinants of some forms of monogenic skeletal disorders with abnormalities in bone matrix, mineralization, or homeostasis, together with those implicated in the pathogenesis of adult-onset osteoporosis and fracture. We place particular emphasis on GWAS findings on bone mineral density (BMD) and associated phenotypes to show that, despite incomplete scrutiny, there is an important overlap in the genes and pathways underlying both mono- and poly-/multigenic conditions. We end by discussing the implications for diagnosis and particularly treatment of skeletal conditions.

## Key Aspects of Skeletal Metabolism

### Integrity and Function of the Skeletal System

The primary function of the skeleton is to provide structural support for the soft tissues of the body. The skeleton also has a metabolic function to provide a mineral reservoir, primarily for

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## Box 1. Genetic Architecture of Monogenic and Complex Diseases, and Approaches to Identify Genes

*Allele Frequency and Effect Size of Underlying Genetic Variants*

The genetic architecture of genetic traits and conditions can be categorized as a function of the properties intrinsic to the underlying variants, namely the minor allele frequency (MAF) and the effect size on the outcome of study (Figure I). Typically, variants of very rare frequency (usually called mutations) underlying monogenic traits have large effects (harboring very little influence of the environment) on the outcome and usually cluster within families. The search for such rare variants has been very successfully performed by genome-wide linkage studies in pedigrees of affected individuals [4]. More recently, exome-wide sequencing studies (studying the coding variation of the genome) have proved successful in identifying several 'unsolved' monogenic conditions, and are currently the main approach used to investigate these types of traits [5,6,7]. At the other end of the spectrum, involving relatively common genetic variants (MAF >10%) with very weak (but real) effects [8] and a prominent influence of the environment, are the so-called 'complex' traits and the underlying susceptibility (risk) to multifactorial diseases. It has become evident that, for most complex traits and common diseases [9–11], the underlying genetic architecture comprises hundreds (if not thousands) of variants. From this perspective, well-powered studies incorporating several independent populations (for replication), scrutinizing a well-defined selection of polymorphisms and gene regions, while employing a robust control for multiple hypotheses testing in the analysis, is the setting suited to identify genuine genetic effects [12]. There are relatively few examples of common variants that exert large effects on complex traits (e.g., *CFH* in myopia, *APOE* in Alzheimer), and it is unlikely that others of this type remain to be identified. In addition, rare variants of small effect probably exist but are unlikely to be identified by current methods and approaches in human populations. On the other hand, less-frequent variants (in the 0.5–5% MAF spectrum) are the current objective of GWAS using increasingly larger and diverse sequenced references (1000 Genomes Project, UK10K), facilitated by the increasing performance of imputing techniques to call confidently these types of variants. One final distinction between Mendelian disorders and complex traits is that the former are usually caused by mutations that primarily affect the coding sequence, while the latter usually involve common variants that map to regulatory elements, for example DNase I hypersensitivity sites [13].

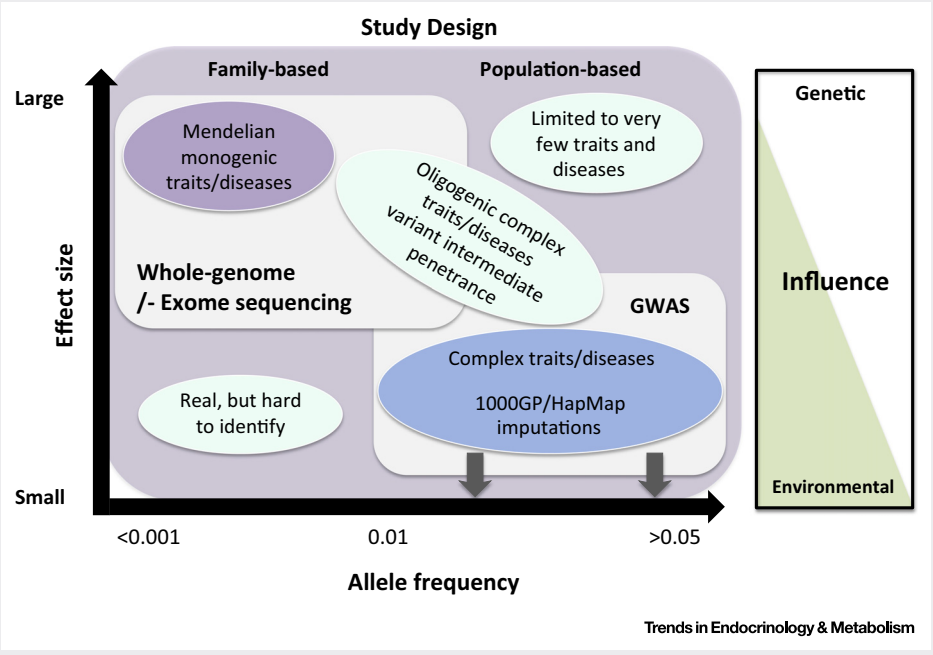


Figure I. Genetic Architecture of Traits and Diseases. The allele frequency and effect size spectrum of the underlying variants will shape the genetic architecture of a given trait or condition. Mendelian/monogenic diseases (purple balloon) were in the past mapped in familial collections employing linkage approaches; these have been recently replaced by whole-exome and whole-genome sequencing studies to identify rare variants (mutations with allele frequency <1%) exerting large effects on the phenotype. Complex traits and diseases (blue balloon) are usually common and are found through the study of large populations; genome-wide association studies employing imputation from sequenced reference sets are used to identify the typically rare (between 1% and 5%) and more common (>5%) variants with weak effects. Mendelian/monogenic traits usually have a large genetic influence with little contribution of the environment. By contrast, large environmental influences underlie the presentation of complex traits and diseases. Genes can harbor both mutations of large effect, causing Mendelian/monogenic diseases, and (low-frequency and common) polymorphisms causing complex diseases (for the overlap in such genes see, Table 4).

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