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Genetic control of bone mass

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ABSTRACT

Bone mineral density (BMD) is a quantitative traits used as a surrogate phenotype for the diagnosis of osteoporosis, a common metabolic disorder characterized by increased fracture risk as a result of a decreased bone mass and deterioration of the microarchitecture of the bone. Normal variation in BMD is determined by both environmental and genetic factors. According to heritability studies, 50–85% of the variance in BMD is controlled by genetic factors which are mostly polygenic. In contrast to the complex etiology of osteoporosis, there are disorders with deviating BMD values caused by one mutation with a large impact. These mutations can result in monogenic bone disorders with either an extreme high (sclerosteosis, Van Buchem disease, osteopetrosis, high bone mass phenotype) or low BMD (osteogenesis imperfecta, juvenile osteoporosis, primary osteoporosis). Identification of the disease causing genes, increased the knowledge on the regulation of BMD and highlighted important signaling pathways and novel therapeutic targets such as sclerostin, RANKL and cathepsin K. Genetic variation in genes involved in these pathways are often also involved in the regulation of normal variation in BMD and osteoporosis susceptibility. In the last decades, identification of genetic factors regulating BMD has proven to be a challenge. Several approaches have been tested such as linkage studies and candidate and genome wide association studies. Although, throughout the years, technological developments made it possible to study increasing numbers of genetic variants in populations with increasing sample sizes at the same time, only a small fraction of the genetic impact can yet be explained. In order to elucidate the missing heritability, the focus shifted to studying the role of rare variants, copy number variations and epigenetic influences. This review summarizes the genetic cause of different monogenic bone disorders with deviating BMD and the knowledge on genetic factors explaining normal variation in BMD and osteoporosis risk.

1. Introduction

Bone mineral density (BMD, g/cm^2) is a skeletal trait subjected to both environmental and genetic influences and is widely used as a surrogate phenotype for several common and rare bone disorders. As a continuous parameter, BMD is often interpreted through T- and Z-scores. The T-score is the number of standard deviations above or below the peak bone mass of young adults. This peak bone mass is bone mass at its highest level, which is reached approximately between the age of 20–30 years. It's suggested that the lower a persons' peak bone mass, the higher the risk for bone fragility later on in life (Bachrach, 2001). Furthermore, a T-score between +1 and −1 is considered normal or healthy, while a T-score below or equal to −2.5 indicates severe bone fragility (Siris et al., 2001). The Z-score is the number of standard deviations above or below the BMD value of an average person of the same age (and eventually the same body size, gender, ethnic background etc.) (Bhalla, 2010). At 20–30 years of age, T- and Z-scores of a normal, healthy population exhibit a Gaussian distribution with the majority of people having a T-score between −1 and +1 and a mean of zero. At older age, the mean of this Gaussian distribution will shift to a negative value, since the majority will then have a suboptimal bone mass. In fact, from the moment peak bone mass is reached, bone mass will only decrease in the following years due to the combination of environmental factors and general aging-related changes. For example, lifestyle can influence bone mass either detrimentally or beneficially. Sufficient intake of vitamin D, calcium and fruits containing high amounts of antioxidants has an advantageous effect, while smoking and excessive intake of alcohol adversely impact bone mass. Moreover, in women there is a sudden drop in bone mass mainly explained by sex steroid deficiency

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during menopause, since sex steroids contribute to the balance between bone formation and resorption. Also, in both sexes aging is associated with deviations in physiological mechanisms like oxidative stress, apoptosis and macroautophagy resulting in unfavorable effects on bone mass (Hendrickx et al., 2015).

Next to these environmental and aging-related factors, the genetic background is an essential determinant of BMD, making it a classic complex trait. Based on the results from twin and family studies, the general genetic character of the variance in bone mineral density was initially estimated between 50 and 85% (Gueguen et al., 1995; Krall and Dawson-Hughes, 1993; Slemenda et al., 1996; Smith et al., 1973). Depending on the site in the body and the investigated population, heritability varies between and around these two ranges, as demonstrated in Table 1. It is clear that in most studies, males tend to have higher heritability values than females. Also, heritability values clearly vary among different skeletal sites and between different studies. Inter-study variance can be attributed to dissimilar study designs, for example by using monozygous or dizygous twins or a family-based approach or by correcting for disparate covariates. Variance in the heritability of BMD of different skeletal sites is possibly due to dissimilar external forces placed on certain bones of the skeleton. For example, Tse and colleagues observed the greatest degree of BMD heritability in both genders at the level of the head (male, $h^2 = 0.951$; female, $h^2 = 0.976$), which is supported by anatomical studies which document that the head is the most anatomically conserved region of the body (Relethford, 1994; Tse et al., 2009). The general interindividual differences in BMD can be explained by genetic variations with small effects. This observation is in line with the findings from the genome-wide association studies (GWAS), where small effects from many common variants in or near genes were detected. The past decade, these GWAS have been an essential tool in exploring the complex genetic character of BMD, making it an emergent surrogate phenotype for common and multifactorial bone disorders like osteoporosis (Duncan et al., 2011; Estrada et al., 2012; Medina-Gomez et al., 2012; Richards et al., 2008; Rivadeneira et al., 2009; Styrkarsdottir et al., 2010; Zhang et al., 2014). Nevertheless, severe osteoporosis, bone fragility or an abnormally high bone mass may also be inherited as the result of rare mutations in single genes (Hendrickx et al., 2015; Fijalkowski et al., 2014; Ralston and Uitterlinden, 2010). For disorders with both a monogenic and complex genetic background, identifying the disease-causing genes might improve the understanding of the pathogenesis of these bone disorders and can pinpoint important pathways in bone homeostasis. This is how, the past 20–30 years, genetic research reinforced the importance of the WNT signaling pathway, RANK/RANKL/OPG pathway and pathways regulating endochondral ossification in the determination and maintenance of (peak) bone mass (Hendrickx et al., 2015; Fijalkowski et al., 2014). Moreover, identifying new genes or new pathways that influence BMD can create possibilities to modulate these in light of prevention or therapeutic intervention of bone disorders.

This review summarizes the main heritable factors contributing to an abnormal BMD, with a monogenic and multifactorial nature. Monogenic disorders with abnormal high and low BMD will be discussed. The complex genetic architecture of bone mass reviewed in this article focusses on the results of GWAS with the aim to not only explain the heritability of BMD as a trait, but also as a contributor to complex bone disorders like osteoporosis. Subsequently, possible explanations of the current missing heritability of BMD (and complex traits in general) and perspectives on the role of genetic testing in conditions with abnormal bone density are discussed in this review.

2. Monogenic diseases with abnormal BMD

Monogenic bone disorders are the most extreme illustrations of genetic determination of BMD. In such conditions, disruption of the carefully maintained balance between bone formation and resorption occurs as the result of a mutation in a single gene. For this reason, monogenic conditions have been of great importance in highlighting genes and pathways involved in bone metabolism and contributed significantly to our understanding of the tissue biology. Depending on the nature of the genetic variation and the function of the genes involved, a full spectrum of phenotypes is observed ranging from severe bone loss to pathogenic bone overgrowth. A division can be made based on BMD resulting from these conditions.

3. Monogenic diseases with increased BMD

Sclerosing bone dysplasias are a heterogeneous group of rare, monogenic disorders characterized by increased BMD at one or multiple skeletal sites. This can be due to impaired bone resorption, increased bone formation or increased bone turnover rates.

3.1. Impaired bone resorption

The osteopetroses illustrate the first deteriorating scenario as mutations in multiple genes involved in osteoclastic differentiation and function have been identified as the underlying cause (Table 2). The most common, autosomal recessive type of the disease (ARO) is characterized by generalized increase in BMD, “Erlenmeyer flask”

Table 1
Heritability of BMD of different skeletal sites across different studies.

Study	Subjects	Ethnicity	TH-BMD ($h^2 \pm$ SE)	LS-BMD ($h^2 \pm$ SE)
Deng et al, 2000 [a]	Families	European/Caucasian	♀ 0.680 ± 0.15 ♂ 0.858 ± 0.276	♀ 0.639 ± 0.126 ♂ 0.684 ± 0.212
Yang et al, 2006 [b]	Families	European/Caucasian	♀ 0.71 ± 0.05 ♂ 0.74 ± 0.06	♀ 0.63 ± 0.04 ♂ 0.76 ± 0.06
Hernandez-de Sosa et al, 2014 [c]	Families	Spanish	0.427 ± 0.101	0.414 ± 0.100
Ng et al., 2006 [d]	Families	Southern Chinese	♀ 0.68 ± 0.04 ♂ 0.80 ± 0.12	♀ 0.73 ± 0.09 ♂ 0.73 ± 0.13
Arden et al., 1996 [e]	MZ and DZ twins	English	♀ 0.67	♀ 0.78
Tse et al., 2009	MZ twins	Unknown	♀ 0.488 ♂ 0.873	♀ 0.595 ♂ 0.926

Abbreviations: TH-BMD, total hip bone mineral density; LS-BMD, lumbar spine bone mineral density; h^2, heritability; SE, standard error; MZ, monozygous: DZ, dizygous.
[a] Corrected for age, age^2, weight, height, menopausal status, smoking, alcohol consumption, exercise.
[b] Corrected for age, age^2, weight, height, menopausal status, hormone replacement therapy use.
[c] Corrected for age, age^2, gender, body weight index, age at menopause, smoking, alcohol consumption, osteoporosis-related medication use.
[d] Corrected for age, age^2, weight, height.
[e] Corrected for age, weight, years since menopause, hormone replacement therapy use.

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