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REVIEW

Osteoporosis: A Silent Disease with Complex Genetic Contribution

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ABSTRACT

Osteoporosis is the most common multifactorial metabolic bone disorder worldwide with a strong genetic component. In this review, the evidence for a genetic contribution to osteoporosis and related phenotypes is summarized alongside with methods used to identify osteoporosis susceptibility genes. The key biological pathways involved in the skeleton and bone development are discussed with a particular focus on master genes clustered in these pathways and their mode of action. Furthermore, the most studied single nucleotide polymorphisms (SNPs) analyzed for their importance as genetic markers of the disease are presented. New data generated by next-generation sequencing in conjunction with extensive meta-analyses should contribute to a better understanding of the genetic basis of osteoporosis and related phenotype variability. These data could be ultimately used for identifying at-risk patients for disease prevention by both controlling environmental factors and providing possible therapeutic targets.

KEYWORDS: Osteoporosis; Bone mineral density; Regulatory pathways; Single nucleotide polymorphisms

INTRODUCTION

Osteoporosis is a common metabolic bone disorder with a strong genetic influence. It is characterized by decrease in bone mass and defects in bone tissue, which weaken bone strength and lead to increased risk of fragility fractures (Kanis et al., 1994; Kamel, 2006). Osteoporosis affects one third of women and one out of eight men over the age of 50 (Li et al., 2010). As bone mass decreases with age during adulthood, osteoporosis is considered as a common disease of the elderly people, also known as a silent disease due to the absence of significant signs before the occurrence of fractures. Conclusively, spinal fractures cause pain and most commonly, deformity, loss of height and disability with an increased risk of future fractures (Nevitt et al., 1998), while hip fractures are more painful and often require hospitalization. Susceptibility to osteoporosis results from many different genetic variations and their interaction with environmental factors (Ralston and Uitterlinden, 2010). Correspondingly, up to 60%−80% of

Abbreviations: ALDH, aldehyde dehydrogenase; APC, adenomatous polyposis coli; APOE, apolipoprotein E; BMD, bone mineral density; CBFA1, core-binding factor A1; CGAS, candidate gene association study; COL1A1, collagen type I α1; CRFs, clinical risk factors; CTNNB1, catenin β1; CYP, cytochrome P450; DBP, vitamin D binding protein; DKK1, Dickkopf1; DMP1, dentin matrix acidic phosphoprotein 1; ER, estrogen receptor; GRP177, G-protein-coupled receptor 177; GWAS, genome-wide association study; HDAC, histone deacetylase; hMSC, human mesenchymal stem cells; IBSP, Integrin-binding sialoprotein; IGF, insulin-like growth factor; IL, interleukin; LRP, low-density lipoprotein receptor-related protein; LS, linkage study; MEF2C, myocyte enhancer factor 2C; OPG, osteoprotegerin; RSPO, R-spondin; PTH, parathyroid hormone; RANKL, receptor activator of NF-κB ligand; RUNX2, runt-related transcription factor 2; SNP, single nucleotide polymorphism; SOST, sclerostin; SOX, sex-determining region Y-box; Sp1, specificity protein 1; TCF/LEF, T cell factor/lymphoid enhancer factor; TGF β, transforming growth factor β; TNFRS11B, tumor necrosis factor receptor superfamily, member 11B; UGT2B17, UDP-glucuronosyl transferase 2B17; VDR, vitamin D receptor.

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bone loss acceleration is due to genetic factors (Ralston and de Crombrugghe, 2006).

More than 66 bone mineral density (BMD) loci have been studied in genome wide association studies (GWASs), confirming the highly polygenic nature of BMD variation. Although there has been significant progress in identifying genes and loci involved in BMD, fracture and other related phenotypes over the past two to three decades, most of the genetic variants remain to be uncovered. In this review, we first describe evidences for a genetic contribution to osteoporosis and related phenotypes, then discuss about the methods used to identify osteoporosis susceptibility genes, and present the key biological pathways involved in skeleton and bone development alongside with genes clustered in each pathway.

PHENOTYPE AND HERITABILITY

The recent WHO and European guidelines for the management of osteoporosis contributed to identifying clinical risk factors (CRFs) and the use of BMD determination in order to estimate the individual probability of a fragility fracture. Remarkably, among those CRFs, the maternal history of fracture seems to be important (Kanis and Reginster, 2008). BMD is highly correlated between mothers and daughters. It is obvious that this fact is mostly due to the inheritance of bone phenotypes that determine osteoporosis (NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy, 2001). Twin and family studies have shown that 50%−85% of inter-individual variation in BMD is genetically determined (Krall and Dawsonhughes, 1993; Gueguen et al., 1995). Recent studies performed on twins or multigenerational families also confirmed that differences in bone microarchitecture and remodeling markers are mainly due to genetic factors rather than environmental factors (Liu et al., 2012; Stone et al., 2015; Bjørnerem et al., 2015).

Several studies conducted mainly on women in the Middle Eastern countries like Lebanon (Maalouf et al., 2000; El-Hajj Fuleihan et al., 2002), Saudi Arabia (El-Desouki, 2003; Ardawi et al., 2005), Kuwait (Dougherty and Al-Marzouk, 2001) and Qatar (Hammoudeh et al., 2005) showed BMDs lower than the Western population standard. However, lower BMD values in women from Middle Eastern countries could be mainly due to the dressing style imposing reduced exposition to sunlight and subsequent reduced vitamin D activation rather than genetic factors alone. Despite these differences among populations, it is of great importance to investigate the relationship between BMD and fracture risk in order to establish local standards in populations.

Although there is a high risk of fracture and low BMD in the offspring of parents with fracture (Soroko et al., 1994), as osteoporosis fractures are mainly fragility fractures principally not depending on falling but caused by low-level or even no trauma, BMD appears an appropriate marker for genetic analyses of osteoporosis. Moreover, as BMD alone appears to be a poor predictor of fragility fractures in some patients, during the last decade a range of skeletal and non-skeletal factors affecting bone regeneration and osteointegration are used to assess fracture risk (Fini et al., 2010). However, further calibration studies are still necessary to prove the robustness of those tools (Aspray, 2015). BMD is still considered as an effective way of osteoporosis diagnosis by many researchers.

Considerably, as the age at menopause is determined by multiple genes, and estrogen deficiency after menopause is an important determinant of bone loss, it seems to be logical that bone loss might be determined at least partially by genetic factors (Snieder et al., 1998). The heritability of fracture is 25%−48% (Deng et al., 2000). A family history of fracture is suggested to be a risk factor for fracture occurrence independent of BMD (Cummings et al., 1995; Torgerson et al., 1996). To date, only one GWAS of fracture performed in elderly Chinese subjects has been published (Guo et al., 2010).

METHODS FOR IDENTIFYING OSTEOPOROSIS SUSCEPTIBILITY GENES

Linkage and association genetic mapping studies are generally performed for analyzing complex traits and disease. Linkage analysis is the classical approach for gene discovery in an inherited monogenic Mendelian human disease. There are two main subtypes of linkage analysis: parametric (specifying a model of inheritance in a family) and nonparametric (no inheritance model) (Ralston and Uitterlinden, 2010). The latter method has been more widely used for analysis of complex traits.

Linkage studies in animal models provide another possible way of identifying genes that regulate BMD and other relevant phenotypes. Noticeably, this approach relies on the assumption that there are at least some orthologous genes with homologous nucleotide sequences and/or biological functions in animals and humans. More than a dozen genome-wide linkage scans have been performed on BMD and other related phenotypes of osteoporosis (Wilson et al., 2004), but even in very large meta-analyses, linkage studies did not yield any genome-wide significant loci for BMD (Ioannidis et al., 2007), possibly because common variants regulating BMD have modest effects which are difficult to be detected reproducibly by conventional linkage analysis (Zheng et al., 2011).

Given the failure of linkage studies, researchers turned their focus to candidate gene studies. However, results often appeared to be non-replicative, probably due to the statistical power, sample size, lack of standardized phenotype and genotype, limited number of gene variants assessed and difficulties in matching cases and controls. An example of such limitations is a large-scale collaborative meta-analysis performed in 2009 (Richards et al., 2009). This study, which assessed all common SNPs in 150 candidate genes for osteoporosis, found only nine genes associated with BMD regulation. Significantly, GWAS has identified many genome-wide significant loci. GWAS is a powerful tool allowing the investigation of genetic contribution to complex diseases in a specific population composed of unrelated subjects through the analysis of a panel of SNPs surrounding a limited number of candidate genes (Hardy and Singleton, 2009; Manolio et al., 2009). The major benefit of GWASs over candidate gene