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Review

Genetics of osteoporosis

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ABSTRACT

Osteoporosis is a skeletal disease characterized by low bone mineral density (BMD) and microarchitectural deterioration of bone tissue, which increases susceptibility to fractures. BMD is a complex quantitative trait with normal distribution and seems to be genetically controlled (in 50–90% of the cases), according to studies on twins and families. Over the last 20 years, candidate gene approach and genome-wide association studies (GWAS) have identified single-nucleotide polymorphisms (SNPs) that are associated with low BMD, osteoporosis, and osteoporotic fractures. These SNPs have been mapped close to or within genes including those encoding nuclear receptors and WNT-β-catenin signaling proteins. Understanding the genetics of osteoporosis will help identify novel candidates for diagnostic and therapeutic targets.

Contents

1. Introduction

Osteoporosis, a skeletal disease characterized by low bone mineral density (BMD) and microarchitectural deterioration of bone tissue, leads to decreased skeletal strength and increased susceptibility to fractures [1]. Osteoporosis and osteoporotic fractures are strongly associated with mortality and morbidity in developing as well as developed countries [2].

BMD is a complex quantitative trait with normal distribution and is thought to be genetically controlled (in 50–90% of the cases), according to twin and family studies [3–6]. Variations in BMD are associated with polymorphisms in several genes [6]. In this review, we have briefly summarized current literatures on genetic factors that are specifically associated with the pathogenesis of osteoporosis and fractures.

2. Polymorphisms in nuclear receptor genes and osteoporosis

Among the several candidate genes, the vitamin D receptor (VDR) gene encoding a nuclear hormone receptor was the first to be proposed as a major locus for its genetic control of BMD. In 1994, a single nucleotide polymorphism (SNP) in intron 8 (IVS8 + 284A > G, rs1544410) of the *VDR* gene was reported to be associated with BMD [7]. The VDR plays an important role in regulating calcium homoeostasis through the binding of the ligand

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$1\alpha,25(OH)_2D_3$, increasing the absorption of calcium [8]. Several SNPs within the *VDR* gene are associated with variations in BMD, and fractures [9]. An Australian study based on twins and the general population demonstrated that SNPs in intron 8 and the 3′-untranslated region (3′-UTR) were associated with BMD in a twin and general population study from Australia [7]. The presence of the homozygous G allele (bb genotype) characterized by the absence of the restriction site for *Bsm*I endonuclease is related to the highest BMD values, while the A allele (BB genotype) is typical in women with a BMD value below the threshold for risk of osteoporotic fractures. Three meta-analyses incorporating the results from major VDR studies have also confirmed the contribution of the IVS8 + 284A > G polymorphism (*Bsm*I) to the variation in BMD values [9–12].

Estrogen deficiency is another risk factor for postmenopausal osteoporosis [13]. Two estrogen receptors (ESRs), namely ESR1 (ERα) and ESR2 (ERβ), encoded by different genes, have been described in mammals [14–18]. ERα primarily mediates the action of estrogen in the bone [19–21]. Genetic screening of the *ESR1* gene locus revealed the existence of several polymorphic sites [21]. In 1995 and 1996, we reported the correlation between BMD and the TA variable number of tandem repeats (VNTR) within the *ESR1* promoter region [22] and also between BMD and the IVS1 − 397T > C SNP (rs2234693, detected by *Pvu*II endonuclease) in the *ESR1* gene [23]. Subsequently, many other studies have also demonstrated the role of the TA VNTR of the *ESR1* promoter region, IVS1 − 397T > C SNP, and IVS1 − 351A > G SNP (rs9340799, detected by *Xba*I endonuclease), in BMD [21,24]. These two SNPs that lie in the introns of *ESR1* are in strong linkage disequilibrium. Those SNP alleles P and X (characterized by the absence of the restriction sites) as well as alleles p and x (with the presence of the restriction sites) are strongly associated with each other. Although haplotype pX was not detected in most of the studies, the haplotype Px was detected at a low frequency, indicating that the disequilibrium is not complete. The IVS1 − 397T > C transition associated with the loss of the *Pvu*II site (P allele) results in a potential binding site for the transcription factor *myb*, followed by *in vitro* transcriptional changes, indicating that the presence of the P allele may amplify *ESR1* transcription [25]. VNTR polymorphisms in the vicinity of certain gene promoters can have a significant impact on transcriptional regulation [26]. Allelic variation arising from different TA repeat lengths can also affect promoter activity.

3. Genetic regulation of bone metabolism by WNT signaling genes

The WNT signaling pathway plays an important role in cell proliferation, differentiation, morphogenesis, and oncogenesis [27–29]. Studies using Drosophila, Xenopus, and mammalian models have established the canonical signaling pathway in which WNT proteins bind Frizzled (FZ) proteins and inhibit glycogen synthase kinase 3 (GSK3)-dependent phosphorylation and stabilization of β-catenin. Evidence from both genetic and biochemical experiments indicates that FZ proteins function as WNT receptors. In addition, low-density lipoprotein receptor-related proteins 5 and 6 (LRP5 and LRP6) also act as WNT co-receptors in the WNT-β-catenin signaling pathway (Fig. 1A). In 2001, Gong et al. reported that the WNT-β-catenin signaling pathway plays a pivotal role in regulating bone density through LRP5 [30]. The authors show that inactivating mutations in the human *LRP5* gene decrease the bone mass and cause an autosomal recessive disorder called osteoporosis-pseudoglioma syndrome (Fig. 1B). Moreover, activating mutations in *LRP5* lead to autosomal-dominant high bone mass traits (Fig. 1C) [31,32]. These data suggest that LRP5 controls the *in vivo* bone metabolism in humans. Additional studies have also reported that mutations in *LRP5* lead to osteoporosis-pseudoglioma syndrome and autosomal-dominant high bone mass traits (Fig. 2) [33,34].

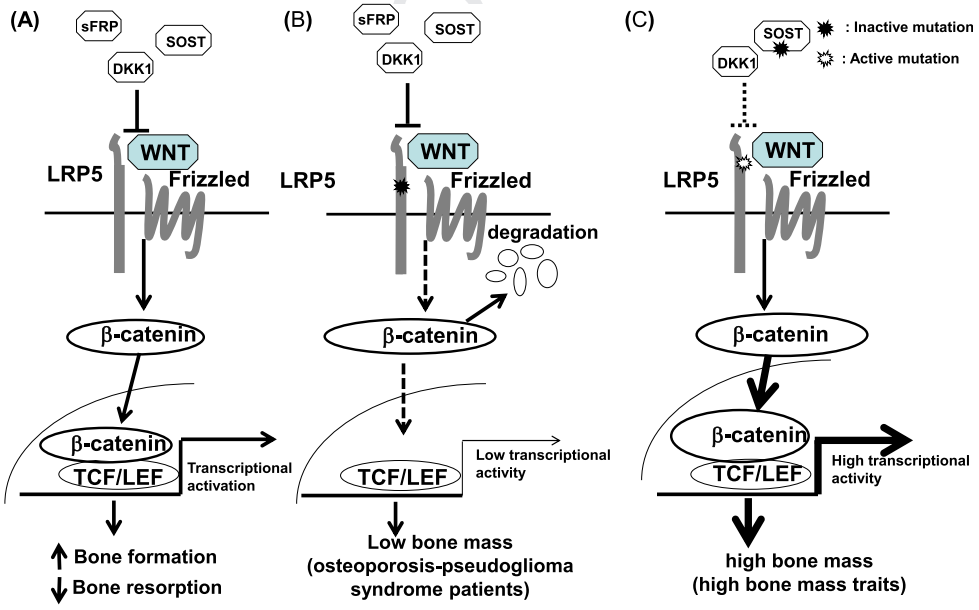

Fig. 1. Canonical WNT signaling pathway in the bone metabolism. (A) Binding of canonical Wnt ligands to a dual-receptor complex comprising the WNT co-receptor LRP5 and one of the seven transmembrane receptors of the Frizzled family initiates WNT-β-catenin signaling. The activation of WNT signaling inhibits the phosphorylation of β-catenin and its proteosomal degradation. β-Catenin accumulates in the cytoplasm and translocates into the nucleus, where it associates with members of the TCF/LEF transcription factors. Activation of the canonical WNT signaling pathway affects the entire osteoblastic lineage and increases bone formation. WNT-β-catenin signaling in osteoblasts and osteocytes indirectly represses osteoclast differentiation and bone resorption. Sclerostin (SOST), dickkopf 1 (DKK1), and secreted Frizzled-related protein (sFRP) act by inhibiting the interaction between the Frizzled family members, LRP5 and WNT. (B) In patients with osteoporosis-pseudoglioma syndrome, loss of function mutations in the *LRP5* gene lead to the destabilization of β-catenin and decrease in bone formation. (C) In high bone mass traits, gain of function mutations in the *LRP5* gene prevent the inhibition of WNT signaling by DKK1, resulting in increased WNT-β-catenin signaling and bone formation. Inactivating mutations of *SOST* also present with high bone mass traits. SOST: Sclerostin, DKK1: dickkopf 1, SFRP: secreted Frizzled-related protein.

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