Review paper

Genetic aspects of osteoporosis

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Abstract

Osteoporosis is a generalized or local metabolic bone disease characterized by the increased risk fracture, reduced bone mass and microarchitectural deterioration of bone tissue. The etiology of osteoporosis is multifactorial, where enviromental, genetic and hormonal factors modulate the risk fracture and affects bone moneral density (BMD), which is the most important predictor of osteoporotic fractures. Osteoporosis is one of the major and growing health care problem around the world, and affecting the elderly of both sexs, however women are affected five times more likely then men. Osteoporosis is generally considered to be polygenic, arising from interaction of multiple enviromental factors with polymorphic alleles at quantitative trai loci (QTL). Genetic factors play an important role not only in the regulation of BMD, but also in the regulation of bone mass, bone turnover, bone quality and other skeletal phenotypes essential to the pathogenesis of osteoporosis. Twin and family studies shown that the heritability of bone mass has been estimated range from 80-90%. However, the genetic determination of osteoporosis is difficult because several loci and candidate gene play a key role in the regulation of bone mass and in the pathogenesis of osteoporotic fractures. Mutation and variation in these genes control BMD, bone mass and bone turnover, but none of them have been replicated over all population and moreover their function is still unclear. An important aim of future work will be meeting and understanding function of these genes and how they cause osteoporosis in individual patients. When that aim will be achieved then choosing new methods of treatment and new therapeutic targets will be easier.

Key words: *osteoporosis, candidate genes, polymorphisms.*

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Introduction

Osteoporosis called also "silent epidemic" is a generalized or local metabolic bone disease characterized by the microarchitectural deterioration of bone tissue, low bone mass and reduction in bone mineral density (BMD) leading to increase in bone fragility and susceptibility to fractures [1-3]. Osteoporosis is a complex disease, involving a broad spectrum of enviromental, genetic and hormonal factors that may modulate the risk fracture and affects BMD [2, 3].

There are two categories of osteoporosis: primary and secondary osteoporosis. Primary osteoporosis can be divided into three types. Type 1 – postmenopausal osteoporosis, type 2 – age-associated osteoporosis and type 3 – idiopathic osteoporosis. Type 1 is characterized by the disproportional loss of trabecelular bone, type 2 affects all skeletal sites with both cancellous and cortical bone and type 3 affects premenopausal women and young men [4]. Secendary osteoporosis results from chronic conditions, which include exogenous and endogenous thyroxine excess, medications, malignancies, hyperparathyroidism and connective tissue disease, that contribute to significantly to accelerated bone loss. Osteoporotic fractures are associated with high morbidity, disability and even death. Most osteoporotic fractures appear at hip, knee, ankle, pelvis, lumbar and thoracic spine, and also distal and proximal humerus [5].

Epidemiology of osteoporosis

Osteoporosis is one of the major and growing health care problem around the world, affecting 75 milion person in the USA, Japan and Europe, including one third of postmenopausal women and most of the elderly people [6, 7]. The risk of osteoporosis increases with age, with a peak

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above the age of 50 however, it can also develop in young people, pregnant and lactacing women. Women are affected five times more likely then men, because women lose bone mass ealier and more rapidly for the sake of hormonal changes during menopause.

The greates risk of osteoporosis developing have Europeans, North Americans and Asians, and also people with the family history of the disease. Moreover, osteoporosis and osteoporotic fractures are more common in whites, Asians and Caucasians then in blacks and Hispanic-Americans and African-Americans. One possible reason is that blacks achieve higher peak bone density then whites. The difference in frequency between racial and ethnic groups is related not only to enviromental factors, but also may reflect inherited differences in susceptibility [7-9].

Ethiopathogenesis of osteoporosis

The etiology of osteoporosis is multifactorial. Interaction between genetic and non-genetic factors determinate the risk of osteoporotic fractures (figure 1) [1-3, 10]. Many of these factors are involved in the accumulation and maintenance of bone mass during adulthood and accelerate bone loss in persons during the sixth decade [1, 11]. The most important predictor of osteoporotic fractures is BMD, which is determined by the interaction of environmental and genetic factors [2, 12].

About 70% of cases of osteoporosis are probably the result of genetic predisposition, however 30% of cases of osteoporosis are probably triggered by environmental influences. Althought environmental factros such as nutrition and exercise, may account for only one –fourth of the variation in bone mass, they should not be ignored, because these factors are important to the development of peak bone mass. From a nutritional factors, calcium is an essential for developing and maintaining skeletal structure and it is necessary for numerous metabolic process [9].

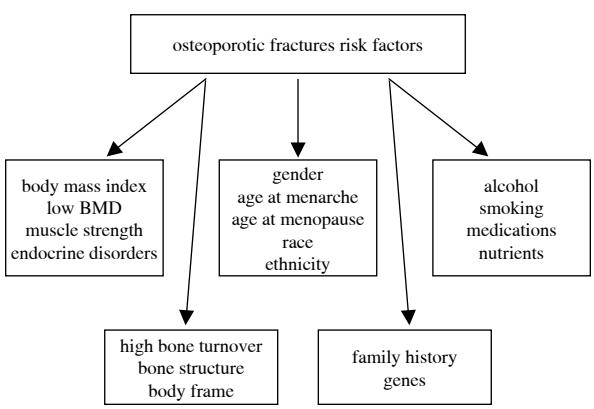

Fig. 1. Genetic and non-genetic risk factors of osteoportic factures

The risk of osteoporotic fractures is also determined by severity and concurrent presence of other polygenic disease such as neurological, cardiovascular, chronic disease of the lungs, kidneys and stomach [13]. The pathogenesis of fragility factrures often involves trauma and some of them are connected with bone mass reduction. Osteoporosis is generally considered to be polygenic, arising from interaction of multiple environmental factors with polymorphic alleles at quantitative trait loci (QTL) [14].

Genetic factors play an important role in inherent bone structural characteristics, regulation of BMD, bone mass determination and other skeletal phenotypes essential to the pathogenesis of osteoporosis [8, 10, 12]. The recent studies have shown that the genes determining risk of factures and bone fragility may be not identical with those associated with BMD. The heritability of the axial skeleton and femoral neck BMD has been estimated for 70-85%, whereas the peripheral skeleton BMD as between 50-60% [3, 15]. Twins studie shown that the heritability of bone mass has ben assesed for 80-90%, and there is much closer concordance of BMD in monozygotic as opposed to dizygotic twins [11, 16, 17]. Studies by Smith and co-workers [18] demonstrated that dizygotic twins have a significantly greater variation in interpair difference in bone width and bone mass compared with monozygotic twins of similar ages. Moreover the interpair variance of both bone mass and bone width was greater in the adult twins of both types then in the juvenile twins. These interpair differences suggesting that enviromental, as well genetic, interactions contribute to such observed variations in bone mass at large age. Their studies have shown that bone mass does have significant genetic factors, which alone or in conjunction with enviromental factors may predispose people to the development of osteoporosis [18, 19]. However, family studies have demonstrated that mothers with osteoporotic fractures have a doughters with reduced bone mass and lower site-specyfic bone density [8]. The genetic determination of osteoporosis is difficult by the fact that in the regulation of bone mass and the pathogenesis of osteoporotic fractures several loci and candidate genes are involved [20, 21].

The role of genes in the pathogenesis of osteoporosis

Bothe regulatory and structural genes have been implicated in the pathogenesis of osteoporosis. Among these genes we distinguish genes regulators of bone metabolism, such as bone matrix components, local regulators of bone metabolism, calciotrophic hormones and receptors and steroid receptors (tables 1, 2, 3) [2, 3, 10, 15]. Mutations and variations in these genes control bone turnover, bone mass and BMD, but none of them have been replicated over all population [13]. Heaney et al. [22] localized the genes responsible for autosomal recessive osteoporosis, which is characterized by deafness, osteosclerosis and severe ana-

Table 1. Candidate genes, mapped on chromosome form 1 to 6, associated with osteoporosis

Candidate genes	Name	Chromosome	Disease
MTHFR	methylenetetrahydrofolate reductase	1p36.3	adenoma, cancer, neural tube defects, psychiatric disorders
IL-1RN	interleukin 1 receptor antagonist	2q14.2	type 2 diabetes, rheumatoid arthritis
CASR	calcium-sensing receptor	3q21-q24	sporadic idiopathic hypoparathyroidism, chronic pancreatitis
AHSG	α2-HS-glycoprotein	3q27	type 2 diabetes, Alzheimer's disease
IL-4	interleukin 4	5q31.3	rheumatoid disease, ulcerative colitis, bronchial asthma
HLA DRB1	major histocompatibility complex, class 11,DR β1	6p21.3	type 1 diabetes, breaset cancer
ESR1	estrogen receptor-alpha	6q25.1	RA, autoimmune thyroid disease, breast cancer

Table 2. Candidate genes, mapped on chromosome form 7 to 13, associated with osteoporosis

Candidate genes	Name	Chromosome	Disease
CTR	calcitonin receptor	7q21.3	juvenile idiopathic arthritis
IL-6	interleukin 6	7p21	rheumatoid arthritis, Takayasu's arteritis, breast cancer
CA2	carbonic anhydrase II	8q22	tubules
OPG	osteoprotegerin	8q23-24	vascular disease
TCIRG1	T cell immune regulator	11q13.4--q13.5	autosomal recessive osteoporosis
P57, KIP2	cyclin-dependent kinase inhibitor 1	11p15.5	lymphoid malignancies, Beckwith-Wiedemann syndrome
LRP-5	receptor related protein 5	11q12-13	osteoporosis-pseudoglioma
VDR	vitamin D receptor	12q12-q14	hereditary hypocalcemic vitamin D-resistant rickets type II, breast and prostate cancer
IGFI	insulin-like growth factor	12q22-24	type 2 diabetes, metastatic prostate cancer, breast cancer

Table 3. Candidate genes, mapped on chromosome form 14 to 20, and chromosome X, associated with osteoporosis

Candidate genes	Name	Chromosome	Disease
ESR2	estrogen receptor-beta	14q22-q24	Alzheimer's disease
CYP19	aromatase (cytochrom P450)	15q21.1	breast cancer, metastatic prostate cancer, endometrial cancer
CYP1A1	cytochrome P450, superfamily I, polipeptyde 1	15q22-q24	breast cancer
CLCN7	chloride channel 7	16p13	autosomal recessive and dominant osteoporosis
SOST	sclerostin	17q12-q21	van Buchem disease, sclerosteosis
COLIA1	collagene type I α1 gene	17q21.31-q22	Ehlers-Danlos syndrome
TGF-β1	transforming growth factor β1	19q13	Camurati-Engelmann disease, spinal osteophytosis
Apo E	apolipoprotein E	19q13.2	cardiovascular disease, Alzheimer disease
BMP2	bone morphogenetic protein 2	20p12	pituitary hypoplasia, renal dysplasia
AR	androgen receptor	Xq11-q12	spinal and bulbar muscular atrophy, prostate cancer, OA

emia, on chromosome 11q12-13. Devoto et al. [23] identified three regions on chromosomes 1p36, 2p23-24, 4q32--34, which are connected with lumbar and neck bone mass. Similarly, Niu et al. [24] have shown the linkage between forearm BMD and loci on chromosome 2p21 and 3q34. However, Koller et al. [25, 26] mapped genes responsible for regulation bone mass on chromosome 1q21-23, 5q33-35, 6p11-12. They also have shown potential role of regions on chromosome 11q12-13 in BMD regulation. Moreover, Dunkan et al. [27] conducted a linkage study of 23 candidate genes implicated in the pathogenesis of osteoporosis and they have shown tha maximum lodscore was observed at

the parathyroid hormone receptor [3, 15]. A candidate gene is a gene, located in a particular chromosome region suspected of being involved in the disease, whose protein product may suggest that it could be the disease gene in question.

Vitamin (1, 25-dihydroxyvitamin) D receptor gene

Vitamin (1, 25-dihydroxyvitamin) D receptor (VDR) gene, which encodes the vitamin D receptor, is located on chromosome 12q12-q14 [28]. The vitamin D3 receptor is an intercellular polypeptides of 50-60kDa that specificially binds the biologically active form of the vitamin D and interact with target-cell nuclei to produce a variety of biologic effects. These receptor are characterized by highly conserved DNA-binding domain rich in arginine, cysteine and lysine residues and a carboxyl- terminal hybrophobic ligand-binding domain [29]. The receptor belongs to the superfamily of transcriptional regulatory factors that includes the thyroid and steroid hormone receptors. VDR consists of 11 exons and spans approximately 75 kb. Exons 7, 8, 9 are involved in ligand-binding domain however, exons 2 and 3 are involved in DNA- binding domain.

The vitamin D palys an important role in skeletal metabolism and maintenance of serum calcium homeostasis by binding to the VDR and regulation the expression of the response genes [3]. These genes stimulate differentiation and growth of bone, skin and cancer cells and differentiation of osteoblast. VDR paly a role in regulation of PTH secretion, intestinal calcium absorption and immune response. The vitamin D receptor gene has become one of the most extensively studied candidate gene for the regulation of bone mass [2, 10, 30].

Three polymorphisms in the 3' region of the VDR, which strongly correlate to ostecalcin level, were first described by Morrison et al. in 1994 [1, 10, 11, 20]. The allelic variation of this gene may account for up 75% of the genetic effect on BMD and that's way VDR is a major regulating gene in bone metabolism [2, 3, 11]. The relationship between BMD and VDR-3' genotype may be modified by high vitamin D and calcium intake. The observation have shown that postmenopausal women with low calcium intake and low fractional calcium absorption are at a significantly increased risk of hip fractures. Moreover, VDR-3' polymorphisms have been associated with BMD changes in response to vitamin D suplementiation in elderly women. These polymorphisms may be also associated with increase risk of osteoporotic fracture, but a possitive association between VDR genotype and fractures was found just only in an older women aged 75 years and above.

However, association between VDR-5' start codon polymorphism and BMD, at first observed in Japanese women, white premenopausal American women and postmenopausan Mexican-American women, has not been confirmed in postmenopausal and premenopausal European women. The VDR-5' polymorphism is associated with intestinal calcium absorption in children [3, 10, 21].

Another polymorphisms, which was found in exon 2 of the VDR gene, is a T to C transition. This polymorphism induces an alternative translation initiation start site, which changes the VDR protein structure by three amino acid and produce two isofors of the VDR protein [2, 3, 10]. This polymorphism may be also associated with regulation of bone mass and intestinal calcium absorption in chldren [2, 3].

The relation between VDR gene polymorphism and bone mineral mass may be modulating by the potential gene-enviromental interaction and gene-gene interaction. That's way VDR-3' and VDR-5' gene polymorphisms alone are possibly weak determinant of BMD and it is not clinically useful like genetic markers of osteoporosis risk in the eldery [1].

Estrogen receptor gene

The estrogen receptor (ER) is classified as a Class I nuclear receptor (NR). NRs are a superfamily of ligand-activated transcriptional factor, which contain some domains important for hormone binding and play a role in specific gene expression modulation [31]. The human estrogen receptor has a two isoforms – estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ), however the concentration of ERα is higher then ERβ in bone and osteoblasts at all stages of differentiation [31, 32]. Both receptors exhibit a specific tissue distribution and modulate activates of different estrogen responsive gene promotes in a different manner [32]. These receptors are encode by two different genes – ESR1 and ESR2. The gene ESR1 is located on chromosome 6p25.1, whereas the gene ESR2 is located on chromosome 14q22-q24. The ESR1 gene, which is strong candidate gene for osteoporosis, contains eight exons and is more then 140kb long [10, 32, 33]. ERα was found in ovarian stroma cells, endometrium breast cancer cells and the hypothalamus, and ERβ was found in kidney, lungs, heart, prostate, bone and endothelial cells. Estrogens play a role in the regulation on skeletal homeostasis in both women and men and they inhibit bone turnover by reducing osteoclast-mediated bone resorption and enhancing osteoblast-mediated bone formation [34].

Mutation and polymorphism on the ESR1 may be connected with some case of osteoporosis. ERα gene manifest two single nucleotide polymorphisms (SNPs) in the first intron and TA dinucleotide repeat in the promoter. These SNPs are associated with low BMD in postmenopausal and premenopausal women and they could be related to the acquisition of peak bone mass [2, 3, 35]. However, the molecular mechanism by which these polymorphisms influence bone mass are as yet unclear. Several authors suggested a significant gene-by-gene interaction between ESR1 and VDR gene polymorphisms and studies have shown that carrying VDR/ER polymorphisms had a significantly lower BMD at the lumbar spine compared with wild homozygotes [1].

Insulin-like growth factor I gene

Insulin-like growth factor I (IGF-I) is a ubiquitous polypeptide, which gene was mapped on chromosome 12q22--24 [36]. It consist of 70 amino acids in a single chain and it has a molecular weight of 7kDa. IGF-I is produced by the liver as an endocrine hormone and regulated by endocrine and autocrine factors. It stimulates growth, proliferation and differentiation of bone cell and also synthesis of type I collagen. IGF-I is essential not only for the neonatal development of the skeleton and growth in childhood, but it plays a key role also during adulthood in regulation of trabecular and cortical bone formation [2, 37]. The serum IGF-I concentration is associated with polymorphism in the IGF-I gene. IGF-I gene manifest a polymorphic CA dinucleotide repeat 1kb upstream from the transcription start. This polymorphism is associated with lower peak serum IGF-I, decrease BMD at the hip and the spine, incerase risk of osteoporotic fractures and lower femoral cross-sectional area in both men and women [1, 2, 37].

Low density lipoprotein receptor related protein 5

Low density lipoprotein receptor related protein 5 (LRP-5) gene, which maps to chromosome 11q12-q13 in humans, contains 23 exons. LRP-5 encodes a transmembrane protein, which is a member of the LDL receptor related family [28, 35, 38]. The LRP-5 contains three domain – extracellular domain, transmembrane domain and cytoplasmic domain. The extracellular domain starts with a signal peptide and four epidermal growth factor (EGF) repeats. The LRP-5 affects bone accrual during growth by Wnt-mediated (Wnt or wingless – family of gene in fruit flies) osteoblastic proliferation and differentiation and it is important for the establisment of peak bone mass.

The LRP-5 gene manifets some mutation and many SNPs. A missense substitution in exon 9 (G>A) and in exon 18 (C>T) of the gene are associaed with lumbar spine bone mass, bone area and lumbar spine BMD and they are more common in middle-age men with idiopathic osteoporosis then controls. Another mutations were found in exon 1, 10, 12, 14 and exon 19. The two missense mutation in exon 1 and 14 change the protein structure and result in a functionally abnormal protein. LRP-5 polymorphisms are BMD determinant and they could contribute to the risk of developing osteoporosis. However, it is not clear how these different mutations and polimorphisms affect the function and expression of the LRP-5 proteins [28, 35]. The LRP-5 allelic variation contributes to the determination of bone size and mass, mainly in white males. The LRP-5 may be an important genetic susceptibility factor for osteoporosis, because it plays a key role in bone metabilosm [38].

Parathyroid hormone gene

Parathyroid hormone (PTH) is an endocrine regulator of calcium, which gene contains 3 exons and was mapped on chromosome 11p15.3-15.1. The PTH gene stimulates calcium homeostasis and bone remodeling [39]. An intronic polymorphisms in the PTH gene are associeted with higher lumbar spine BMD [1, 3].

Osteoprotegerin gene

Osteoprotegerin (OPG) is a soluble protein receptor for RANKL, belonging to the tumor necrosis factor receptor superfamily [40]. OPG gene is located on chromosome 8q23-q24, contains 5 exons and spams 29kb. It is also known as osteoclastogenesis inhibitory factor (OCIF), folicular dendritic cell-derived receptor-1 (FDCR-1) or TNF receptor-related molecule-1 (TR1). The promoter region of OPG gene owns a binding site, which mediates the regulation of OPG gene expression by the bone morphogenetic protein-2, Cbfa-1 (osteblast-specyfic transcription factor) and TGF-β [13, 41]. OPG is produced by a variety of tissues including the heart, lungs, intestine, kidney, and bone, as well as immune and hematopoietic cells. The production and expression of this protein is regulated by many factors such as peptides, hormones (17β-estradiol), cytokines (TNF-α, IL-1α, IL-17 and BMP2) and drugs. OPG plays an important role in the control of bone resorption, osteoclast biology, inhibition of osteoclastogenesis and immune functions and the OPG gene is a good candidate gene for osteoporosis [41-43].

The OPG gene manifest some SNPs in the promotor region, exon and intron regions. The substitution in exon 1 (G1181C), which caused a change in the third amino acid from lysine to asparagine, is associated with the lumbar spine in BMD and increased risk of osteoporosis [40, 42, 44]. The polymorphism in the promoter region (G209A, T245G, C889T, T950C) are associated with lower BMD at lumbar spine and could be a risk factor for genetic susceptibility to osteoporosis and probably with higher bone mass [13, 40, 43]. Some studies suggest that polymorphisms of the OPG promoter may be one of the genetic determinants of bone mass and osteoporotic fractures [42, 43].

Collagen type I α gene

Collagen type I α (COLIA1) gene, which gene is located on chromosome 17q21.31-q22, encodes the alpha I chain of type 1 collage. The COLIA1 gene is one of the most important candidate gene for susceptibility to osteoporosis, since type I collagen is the major structural protein of bone and deletions and point mutations in this gene give rise severe osteoporotic phenotype in the osteogenesis imperfecta [3, 11, 28, 45]. The most interesting polymorphism of the COLIA1 gene is located in intron 1 (transition guanine to thymidyne) and affecting a binding site for transcription factor

SP1 [3, 28, 45]. This polymorphism is strongly associated with BMD at femoral neck and lumbar spine, bone mass and osteoporotic fractures, particularly verbetal fractures [11, 45, 46]. The COLIA1 Sp1 polymorphism is associated with the clinically important condition of osteoporotic fractures and it may have functional consequences for regulation of gene transcription [11]. This polymorphism is also associated with a reduction of BMD, higher levels of bone turnover, an increase fracture risk, increase bone loss, lower quantitative ultrasound (QUS) vaues and higher level of serum osteocalcin [3, 28, 45]. The COLIA1 Sp1 polymorphism may be a possible genetic risk factor related to disc degradation in older women and men [45].

Bone morphogenetic protein 2 gene

Bone morphogenetic protein 2 (BMP2), which gene is located on chromosome 20p12, belongs to a superfamily called transforming growth factor beta (TGF-beta). BMP2 plays a role in the differentiation of osteoblast located in the mature skeleton, early embriogenesis and bone and cartilage development [36, 47]. The SNPs, which was found in the BMP-2 gene, cause changes in amino acid sequences and they are a risk of osteoporosis. Two of them were found in exon 2 (T116G, G287T) and one of the SNPs was found in exon 3 (A224T). However, the most important is polymorphism at position T116G in exon 2, which changes amino acid in the precursor part of the protein and cause mdification of activation and secretion of the protein. This polymorphism is also associated with lumbar spine BMD and significant risk of osteoporosis. BMP2 gene may be useful as a factor of increased risk of osteoporosis and fractures [36, 47, 48].

Apolipoproteine E gene

Apolipoproteine E (ApoE) gene is a polymorphic, because three different isoforms of apolipoproteine are encode by three allelic variants E2, E3 and E4 [49]. This gene was mapped on chromosome 19q13.2. The mechanism by which ApoE alleles influence susceptibility to osteoporosis is still uncear, but it has been suggested that they play a role in the hydroxylation of osteocalcin indirectly by effect on vitamin K transport and concantration [10, 49]. However, recent studies have shown that just ApoE4 play a role in the pathogenesis of osteoporosis [50]. Postmenopausal women with the ApoE4 allele have a greater weight loss, faster rates of bone loss and higher prospective risk of hip fractures. The ApoE4 variant may be important in determining spine bone mass and hip fractures in postmenpausal women [49-51].

Androgene receptor gene

Androgene receptor (AR) gene is a member of the steroid receptor gene superfamily, which gene is located on X chromosome at Xq11.2-q12 and consist 8 exons. AR plays a role in some biological precesses such as spermatogenesis, sexual differentiation and maturation [52]. The (CAG)n trinucleotide repeat in the first exon of AR gene is associated with reduce transcriptional activity of the AR, increased risk of osteoporosis fractures and reduced bone mass in women with high levels of sex hormone-binding globulin (SHBG) [53, 54]. AR repeat polymorphism is associated with BMD and it may be a susceptibility gene for reduced BMD in premenopausal women [3, 55].

Arachidonate 15-lipoxygenase gene

Arachidonate 15-lipoxygenase (Alox15) gene is a one of several LOX isoforms and encodes an enzyme 12/15-lipoxygenase. This gene is located on chromosome 17p13.3 and has a 14 exons. Urano et al. described the SNPs in the Alox15 5'-flanking region, which is associated with low BMD in postmenopausal women [56]. However, Ichikawa et al. found that polymorphism in Alox12, but not Alox 15 is associated with high spine BMD in white women and men [57].

Cytochrome P450 gene

Cytochrome P450 (CYP1A1) gene, also called CYP1 or P1-450, encodes a member of the cytochrome-P450 superfamily of enzymes and it is located on chromosome 15q22--q24. Increased risk of osteoporosis may be connected with two variants of CYP1A1 gene, which occur in 19% people. The polymorphism at position C4887A play a role in regulation of estrogen metabolism and bone density [58].

Transforming growth factor beta gene

Transforming growth factor beta (TGF-β) gene is located on chromosome 19p13 and coding protein, which regulates osteoclast activity, that's way TGF-β gene is a strong candidate gene for regulation of BMD [10, 11]. In this gene a number of SNP have been identified, but few of them are associated with osteoporotic fractures, biochemical markers of bone turnover and BMD [10, 36]. The best functional candidate is polymorphism at position 10C/T in exon1, which is associated with circulating TGF-β levels and BMD [10].

Sclerostin gene

Sclerostin (SOST) gene, which gene is located on chromosome 17q12-q21, encodes a protein with a signal peptide for secrotion and a cysteine-knot motif. This gene is expressed most highly in cells involved in osteogenesis and it plays a role in genetic control of bone mass, bone formation and enhancing apoptosis of osteoblast [59, 60]. The SOST polymorphism (SRPs) is associated with some parameters of osteoporosis, such as BMD or risk fracture. The SRP3

and SRP4 polymorphisms seem to be the most important in osteoporosis. The SRPs (10565insGGA) is located in upstream of the SOST transcriptional site and influence for interaction of promoter region with the transcriptional factors and its connected with decrease BMD in older women and enhances expression of SOST mRNA. However, the effect of this polymorphism is modified by sex and age. The SRP9 at position A75707G is located on the VBD domain. The SRP9 changes the level of BMD and its effects ist modified by sex [59].

T-cell immune regulator 1 gene

T-cell immune regulator 1 (TCIRG1) gene was mapped at chromosome 11q13.4-13.5 and encodes the osteoblast-specific APT6i 116kDa submit, which is an integral component of the V-ATPase complex [61]. TCIRG1 gene plays a very important role in bone resorption in patients with autosomal recessive osteoporosis [36, 61]. Mutations and polymorphisms in this gene could change amino acid sequences. It may affect the ability of protons transport and modulates BMD [61]. The polymorphism which affects an AP1 binding site in the TCIRG1 promoter is strongly associated with BMD in perimenopausal women [36]. However, some studies have shown that this gene may be a strong candidate gene for BMD regulation in normal population, because polymorphisms in the TCIRG1 gene influence on subtle differences in gene expression [61].

Calcitonin receptor gene

Calcitonin receptor (CTR) gene is a member of seven transmembrane receptor superfamily and its located on chromosome 7q23.1. Calcitonin is a hormone, which regulates a bone resorption [62]. CTR gene polymorphisms have shown that these gene plays a role in the pathogenesis of osteoporosis, because it is associated with reduced BMD and predispose women to osteoporosis [62]. The polymorphisms at position 1377T/C in the 3' region of the CTR gene induce prolin transition to leucine at the amino sequence in the third intercellular domain of the protein [62, 64]. Postmenopausal women with these polymorphisms have a lower BMD at the lumbar spine and at the femoral neck [63, 64].

Interleukin 6 gene

Interleukin 6 (IL-6) is a pleiotropic cytokine, which gene was mapped on chromosome 7p21. This glycoprotein plays a central role in bone resorption, bone loss, hemopoiesis, immune and acute phase response, and some metabolic and endocrine diseases [35, 65]. Several SNPs, which have been identified in the IL-6 gene promoter region, are associated with IL-6 gene expression levels and C-reactive protein (CRP) levels. Common SNPs were identified at the position -174G/C, -572G/C and -634C/G [21, 35, 65]. The SNP at position -174 is associated with low serum levels of C-terminal cross-linking of type I collagen in postmenopausal women, decreased peak bone mass and low BMD in younger men and women. IL-6 -572 G/C polymorphism is connected with higher levels of CRP and c-terminal cross--linking type I collagen. All these variants may be a potential genetic susceptibility factors to the risk of osteoporosis [35, 65].

Chloride channel 7 gene

Chloride channel 7 (CLCN 7) gene was mapped on chromosome 16p13 in 1995. The polymorphisms (V418M), which was found in the CLCN7 gene, cause both autosomal recessive and autosomal dominant osteoporosis and it is associated with BMD in women [36].

Conclusion

Genetic factors play a central role in the pathogenesis of osteoporosis, because they are involved in the regulation of bone turnover, bone mineral density, bone fragility and bone geometry and quality. Many of the genes, which regulate BMD have been identified, but their function and influence is still unclear. Identifying the genetic factors of the osteoporosis and understanding their function, may have a diagnostic and therapeutic significance. Both genes and their protein products, which play a role in the regulation of bone mass and risk of osteoporotic fractures, are potentially important targets for new drugs development.

It is impossible to underestimate the predictive importance of the above mentioned genetic markers. The most promising marker is the COLIA1 polymorphism, which seems to be independent risk factor of osteoporosis. The assessment of genetic factors may appear to be crucial in the management of osteoporosis in the nearest future.

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