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Genetics and Osteoporosis

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1. Introduction

Osteoporosis is a multifactorial disease influenced by multiple factors and characterized by an imbalance in the regulation of bone remodeling that cause microarchitectural deterioration which compromises the bone strength and leads to bone fragility increasing the fracture risk. Since several years ago, the World Health Organization has considered osteoporosis as one of the most important public health issues worldwide, with a great repercussion in patients' life quality and in their familiar, social and work environments. Osteoporosis is an important problem in Latin America, currently its prevalence is similar to that in South Europe and slightly lower than in North Europe and among white population in the USA; World Health Organization estimates that in the forthcoming 50 years, osteoporosis prevalence will increase in Latin America until reach those of the currently observable in Europe and USA (World Health Organization [WHO], 1994; National Institute of Health [NIH], 2001 Consensus Development Panel on Osteoporosis Prevention, Diagnosis and Therapy; Cole ZA et al., 2008). During the last decades, the life expectancy has been increased notoriously and the number of subjects older than 60 years old has been increased. This situation in combination with the adverse environmental conditions and the life style, will cause a notorious increment in the incidence of chronic-degenerative diseases in the next decades, as will occur with osteoporosis. Certainly, primary osteoporosis use to be more frequent in posmenopausal women (Greespan et al., 1993); however occasionally it appears in premenopausal women which present several risk factors and even males may be affected by this disorder. It is important to mention that the actual life style favours the inadequate bone quality of children and young people (Asociación Mexicana de Metabolismo Óseo y Mineral, 2001). There are two forms of osteoporosis; primary OP, named posmenopausal or senile form and secondary OP, which is related to diverse endocrine, renal, rheumatic and genetic diseases, and with the prolonged administration of some drugs which induce bone loss (Riggs et al., 1986; Elliot-Gibson et al., 2004). Discussing about osteoporosis it is necessary to mention the term "peak bone mass" (PBM), which refers to the maximum bone mass that an individual reaches in his life and it occurs between 20-30 years old approximately. PBM is the result of the interaction of multiple genetic and environmental factors; upon the PBM is reached, progressive loss of bone mass occurs naturally, depending on the magnitude and speed of subsequent bone loss (Burclar et al., 1989; Kanis et al., 1994; Guéguen et al., 1995.). The annual average bone loss in posmenopausal women is estimated in 1-2%, and 0.2-0.5 % in males. It is considered that

about 30% of women at this phase shows an accelerated bone loss (approximately 5% per year) during the first 5 years after menopause, which represents higher risk to suffer osteoporotic fractures at this moment of their lives (Elliot –Gibson V et al., 2004).

Osteoporosis has been characterized for having a very discrete clinic behavior; it is practically “silent” remaining latent for years or could get worsen without causing significant symptoms. Nevertheless, one of the most frequent clinic manifestations is the back chronic pain, which may be attributed to the presence of vertebral micro-fractures, frequently it can be noted progressive height loss due to vertebral compression and/or slimming; this anomalies can be heterogeneous and cause loss of the spine natural conformation causing abnormal curvatures and scoliosis (Ismail et al., 1999). Fractures are the most frequent and dangerous complication of osteoporosis and may occur practically in all bones, even with a discrete trauma and spontaneously. As has been documented in LAVOS (*Latin American Vertebral Osteoporosis Study*) (Clark et al., 2009). and EVOS (European Vertebral Osteoporosis Study) (Raspe et al., 1998) studies, the spine is the most common site in which fracture occur. Booth studies showed that, the frequency of these fractures are related to gender and age, but also to races geographic distribution. Apparently they are more common in Scandinavian and North American population, whereas they are less frequent in South of Europe. Interestingly, the frequency is higher in urban areas than in rural ones, which outstands the importance of environmental factors in this disease besides of the genetic predisposition. After vertebral fractures, hip fractures occur, followed by forearm. It is estimated that about 25% of individuals showing this kind of fractures die due to complications, and other 25% (even the after the surgery), never recover the life quality they have before the fracture. On the other hand, patients who have suffered one or more fractures (in any place) predispose to have new fractures, independently of their bone mineral density (BMD). The risk for new fractures is higher in individuals who have suffered first fractures at early age and in those who have higher number of previous fractures.

2. Genetic susceptibility in osteoporosis

There are several elements that suggest that bone phenotype is under of an important genetic influence. The first observation is the familial aggregation detected in the clinical practice, in which can be observed the segregation of some phenotypic characteristics, like family history of bad bone quality of osteoporotic fractures (Guéguéz et al 1995; Fox et al., 1998; Kannus et al., 1999). On the other hand, description in literature of several diseases of genetic origin with monogenetic inheritance, which phenotype includes the loss or gain of mineral bone density, supports the hypothesis that bone phenotype has an important genetic component. Some of the most studied diseases are the different forms of osteogenesis imperfecta, the diverse varieties of osteopetrosis, pyknodisostosis, sclerostenosis and osteoporosis syndrome accompanied by pseudoglioma (Barros et al., 2007), among others. Besides, there are reports of severe osteoporosis cases in which mutations have been detected in genes which have been previously associated with the genetic control of mineral bone density, as the genes for estrogens receptors 1 and 2 (ESR1, ESR2), androgens receptor (AR) and vitamin D receptor (VDR). Changes in the normal sequence of those genes could cause osteoporosis. However, the primary osteoporosis represents the most common form in all populations (Duncan et al., 2005, 2008, 2010). Primary osteoporosis has a multi-factorial and polygenic origin and the evidences that it shows clearly genetic susceptibility are family history of bad bone quality and fractures,

familial or demographic similarity during the natural history development of the disease or even differences in the pharmacological management response. In accordance to National Osteoporosis Foundation (IOF) 2008 statements, fractures family history represents an important risk factor independently of the bone mineral density and the presence of osteoporosis in first degree relatives has been related to the decrease in peak bone mass.

The analysis of genetic susceptibility to osteoporosis has been complicated because it is caused by the effect of multiple genes that exert their effect on the bone phenotype, taking in account that a great number of environmental factors acting on BMD are involved; however, despite all these difficulties, a large amount and variety of worldwide investigations suggest that BMD heritability ranges between 40-70% in spine, between 70-85% in hip and between 50-60% in wrist (Andrew et al., 2005; Michaelsson et al 2005; Deng et al., 2002). Densitometric studies in monozygotic twins (MC) and dicygotic twins (DC) have revealed that spine and femoral neck BMD consistency is higher (6-8:1) in MC twins than in DC twins. Family studies have estimated that fractures heritability ranges between 20-60%, depending on the anatomic region where those occur (Michaelsson et al 2005; MacGregor et al., 2000; Deng et al., 2002). In these cases, classic segregation studies have facilitated identifying new genes related to the BMD genetic control.

In the other hand, association studies have also been very helpful to associate particular phenotypic characteristics, such as bone mineral density or the occurrence of fractures, with very specific genetic variants (gene polymorphisms, specially single nucleotide variants). Besides, there are other bones characteristics with evident heritable component, among them are: geometry and length of the femoral neck, bone ultrasonic properties (which represent the trabecular interconnectivity degree), growth and speed of bone remodeling, bone dimensions and other conditions that have an impact on bone quality (Slemenda et al., 1996; Arden et al., 1996); for example body mass index and age at which menopause occurs. It is convenient to mention that family history of hip fractures has consistently been shown to be a risk factor for osteoporosis(Andrew et al., 2005).

The functioning of osteoarticular system is extremely dynamic and complex, it is constantly under remodeling and it have multiple and varied mechanisms to maintain homeostasis; therefore, its genetic regulation mechanisms are also complex to understand and integrate. Genes that have been linked with BMD genetic control are distributed along all the human genome and, they are in practically all chromosomes, each of them fulfills different functions and contributes in a different way to the genetic control of bone phenotype (Stewart et al., 2006; Xiong et al., 2006; Marini et al., 2010). There are some genes with important roles in bone homeostasis because their products are involved in elemental functions related to bone structure and metabolism (formation, growth, differentiation, resorption, maintenance, etc.) (Ralston et al., 2002; Williams et al., 2006).

Since long time ago, we know that bone metabolism has a great hormonal influence; therefore, genes that encode for its receptors are elemental in bone metabolism genetic regulation, among them we have genes ESR1 and ESR2 which encode for estrogens α and β receptors and are expressed in various bone cells types (osteoblasts, oocyteocytes and osteoclasts), both receptor types show a different expression pattern in the cortical and trabecular bones. Estrogens represent one of the most important regulators for bone metabolism, they regulate bone growth and maturation, and they also influence the differences between bone maturation and bone consolidation in men and women. These hormones have the capacity to block the osteoclastogenesis process, can interfere with the function of osteoclasts, induce them to

apoptosis, and may also modify the expression of genes involved in the bone remodeling process (Slemenda et al., 1996; Kameda et al., 1997; Cummings et al., 1998)). Moreover, hormones contribute to down the expression of the Tumoral Necrosis Factor (TNF), and thereby reducing osteoclasts response to the RANK and RANKL activity (the ligand binding to the activator receptor for the kappa B factor and its ligand) (Hughes et al., 1996).

It is already known that vitamin D, through the interaction with its receptor, plays an important role in calcium homeostasis for the regulation of growth and differentiation of bone cells; that is the reason why the gene that encodes for the vitamin D receptor (VDR) is quite important in bone metabolism. Another important gene is IL6, which codifies for interleukin 6, which is a proinflammatory cytokine that has been related to several biologic processes, as bone resorption, osteoporosis and other diseases as rheumatoid arthritis, diabetes mellitus, cardiovascular diseases, cancer, etc. LRP5 gene, which encodes for protein 5 related to the low density lipoprotein receptor that participates in the development and maintenance of several tissues and represent one of the regulators for the development and proliferation of the osteoblasts (Gong et al., 2001). Other genes relevant for bone metabolism are RANK, RANK-L and OPG which encode for key proteins for bone remodeling process (Capellen et al., 2002). Other genes with higher impact on bone phenotype is the COL1A1 gene, which encodes for one of the most abundant structural proteins in bone (collagen 1A1). A great number of investigations have analyzed the association among osteoporosis and allelic and genotypic variants of these genes (Ralston et al., 2002).

There are some characteristics, for example the body mass index, that could have an impact on bone phenotype. These traits are also under genetic influence so we found genes that are related with more than one phenotype. Since several years ago it is clear that there is an important relation between bone mineral density and body mass, we already know that overweight individuals should support higher weight opposite to individuals with a lower body weight, therefore, bone mineral density is higher in overweight subjects, while thinner subjects, including the ones with alimentary disorders as anorexia or malnutrition, could present low bone quality. Some of the genes with impact on these phenotypes are ESR1, ESR2, VDR, LRP5, IL6 and OPG between others (Deng et al., 2002; Jie et al., 2009; Frenkel et al., 2010). During the last years, the leptin gene and its receptor (LEP and LEPR) have been revealed as an important hormonal factors for the regulation of appetite and energetic metabolism; besides, leptin has an osteogenic effect by stimulating osteoblasts formation and plays a direct osteogenic role on bone marrow stromal cells, which allows its differentiation and maturation to osteoblasts (Estepman et al., 2000).

Other important genes in both phenotypes are the proinsulin gene (INS), its receptor (INSR), and probably too the gene family of growth factors similar to insulin, since apparently insulin exerts a mitogenic effect on osteoblasts, which could partially explain bone mass increment that is usually noticed in obese individuals.

Table 1 depicts some of the genes related to the bone phenotype and the function that has been attributed to their products. It is evident the genetic influence on different aspects of metabolism and homeostasis of bone tissue (structure, formation, resorption and remodeling) and the number of genes involved is large and their functions are diverse. In the case of bone structure highlights the COL1A1 and COL1A2 genes which code for the type I collagen protein, which represents over 90% of the organic matrix of bone. The osteocalcin and osteopontin are also important, the first one is a calcium binding protein which is secreted by osteoblasts and is encoded by the gene OC, while the phosphoprotein known as osteopontin, encoded by the gene OPN, is essential in the mineralization process.

<i>Hormones and their receptors</i>		
Gene	Chromosomal location	Product
ESR α	6q25	Estrogens receptor α
ESR β	14q22	Estrogens receptor β
AR	Xq11	Androgens receptor
VDR	12q12	D vitamin receptor
PTH	11p15	Paratohormone
PTHr1	3p22	Paratohormone receptor 1
CT	11p15	Calcitonin
CTR	7p21	Calcitonin receptor
CYP1A1	15q21	Aromatase
CASR	3q13	Receptor sensitive to calcium
ADPN	3q27	Liponectin
GR	5q31	Glucocorticoids receptor
PRL	6p22	Prolactin
LEP	7q31	Leptine
LEPR	1p31	Leptine receptor
INS	11p15	Insulin
INSR	19p13	Insulin receptor
<i>Matrix components</i>		
COL1A1	17p21	Collagen 1A1
COL1A2	7q22	Collagen 1A2
OC	1q25	Osteocalcin
OPN	4q21	Osteopontin
<i>With participation in osteoblastogenic processes</i>		
ALOX12	17p13	Araquinodate 12 lipoxigenase
ALOX15	17p13	Araquinodate 15 lipoxigenase
BMP2	20p12	Morphogenetic protein of bone 2
BMP4	14q22	Morphogenetic protein of bone 4
BMP7	20q13	Morphogenetic protein of bone 7
IGF-1	12q22	Growth factor similar to insulin
LRP5	11q13	Receptor related to lipoprotein of low density 5
LRP6	12p13	Receptor related to lipoprotein of low density 6
SOST	17q12	Sclerotin
NOG	17q22	Protein antagonist of morphogenetic proteins

<i>With participation in osteoclastogenesis processes</i>		
Gene	Chromosomal location	Product
P53	17p13	Tumor suppressor P53 protein
CPK	1q21	Catepsine K
OC	1q25	Osteocalcin
OPN	4q21	Osteopontin
OPG	8q24	Osteoprotegerin
RANK	18q22	Receptor activator of NF-KAPPA-B
RANK-L	13q14	Ligand of the receptor activator of NF-KAPPA-B
CLC7	16p13	Chlorine channel 7
<i>Cytokines and their receptors</i>		
IL1 α	2q14	Interleukin 1A
IL1 β	2q14	Interleukin 1B
IL6	7p21	Interleukin 6
TNF	6p21	Tumoral necrosis factor
TNFR2	1p36	Tumoral necrosis factor receptor 2
<i>Others functions</i>		
MTHFR	1p36	5,10-Methylenetetrahydrofolate reductase
APOE1	19q13	Apolipoprotein E
MMP-1	11q22	Metalloproteinase
MMP-2	16q13	Metalloproteinase
MMP-9	20q11	Collagenase
PON-1	7q21	Esterase
SHH	7q36	Hedgehog protein (it participates in skeleton embryogenesis)

Table 1. Genes related to bone phenotype, their chromosomal location and their products

The osteoclastogenesis and the osteoblastogenesis are fundamental processes for the homeostasis of bone tissue as the speed and intensity of bone formation and bone resorption depending on several conditions. Both mechanisms show a significant genetic influence, so the amount of genes and therefore of proteins with participation in both processes is very significant. Among them are genes that encode for the family of bone morphogenetic proteins (BMP's), the LRP5 and LRP6 genes that code for receptors for low density lipoproteins, which are involved in the osteoblastogenesis most likely to regulate the level of bone mineralization. The osteoclastogenesis is determined by the differential expression of genes of the RANK/RANK-L/OPG route. The P53 oncogene which product is very important for multiple biological processes and the cathepsin K gen (CPK) wich codes for a

collagenase with preferential expression in osteoblasts, indubitably play a crucial role in bone resorption.

Different hormones involved in the bone formation and remodeling, including the sex hormones (estrogen, progesterone, androgens), growth hormone, insulin, parathyroid hormone, calcitonin, cortisol and thyroid hormones. These hormones are implicated in different ways in bone metabolism according to the different stages, including intrauterine life, in such a way that the different hormones impact on linear growth of bones, bone maturation, bone homeostasis and the size that will be achieved in adulthood. That's why there are hormonal conditions such as hypothyroidism, hyperthyroidism, postmenopause, andropause and glucocorticoid prolonged intake which are capable to impact on the quality of the bone. Finally we can not ignore that various interleukins, growth factors and their receptors have been identified and the participation in the genetic control of bone mineral density of other proteins are still under study, as in the case of IL α , IL β , IL6, TNF, TNFR2 among others.

On the other hand, it is important to mention that during the last years some investigations have pointed out that some of the genes related with bone phenotype have been related to other disorders as cardiovascular diseases; for example, genes such as osteoprotegerin (OPG), the receptor activator for nuclear factor kappa B ligand (RANKL) and bone morphogenetic protein 2 (BMP) have been associated with osteoporosis and with cardiovascular diseases, particularly atherosclerosis, which suggest that products of these genes take part in the calcification process (Collin-Osdoby et al., 2004; Marini et al., 2010).

3. Linkage analysis as strategy in the study of osteoporosis

Linkage studies are well validated for identification of responsible genes in monogenic diseases, since the inheritance of marker alleles is related to the inheritance of a bone trait within family members. Combining the use of statistical approaches in quantitative trait loci (QTL) and genome-wide association studies (GWAS), it is possible to establish a strategy to identify chromosomal regions which contain regulating genes of some important traits in complex polygenic diseases with genetically heterogeneous traits as osteoporosis, making possible to evaluate how many of the hundreds of proposed candidate genes are really associated. Most of linkage studies in osteoporosis selected the bone mineral density as the trait of interest; however regions that regulate other relevant phenotypes, such as bone mass and skeletal geometry, have been investigated.

Former studies identified important loci linked to bone mass and geometry. A genome search study in sib pairs recruited from families with a history of osteoporosis, obtained data suggestive of linkage of 1p36, 2p23-24 and 4q32-34 with spine and hip BMD (Devoto et al., 1998; Devoto et al., 2001). Studies with healthy female sib pairs demonstrated linkage of locus 11q12-13 with BMD variation (Koller et al., 1998) and evidence suggestive of linkage of 1q21-23, 5q33-35 and 6p1-12 to femoral neck or lumbar spine BMD was obtained in a genome-wide search study performed in Caucasian and African-American healthy female sib pairs (Koller et al., 2000). Other study identified loci in 5q and 4q that showed linkage to regulation of important aspects of femoral neck geometry (Koller et al., 2001). A QTL not previously described in 22q11 showed suggestive linkage in a study with families from Belgium and France (Kaufman et al., 2008). The presence of genes controlling BMD on 1p36 was suggested too in a multivariate linkage analysis in osteoporosis pedigrees (Zhang et al., 2009). One genome-wide scan for bone loss showed that change in femoral neck BMD in Mexican-American families is significantly linked to 1q23 (Shaffer et al., 2009). Interestingly

a study with pairs of brothers suggested that QTL on 7q34, 14q32 and 21q21 were male-specific (Peacock et al., 2009) and other report provides evidence of gender specific QTL on 10q21 and 18p11 (Ralston et al., 2005). Suggestive evidence of linkage of novel regions related with BMD and hip geometry on chromosomes 4, 5, 11, 16 and 20 was obtained in a sample of Caucasian Europeans (Karasik et al., 2010).

Two important large scale studies with a cohort of more than 19,000 european subjects, identified SNPs in previously proposed osteoporosis candidate genes and in regions not previously associated with femoral neck and lumbar spine BMD. SNPs from ESR1, LRP4, ITGA1, LRP5, SOST, SPP1, TNFRSF11A, TNFRSF11B AND TNFSN11 associated with either femoral neck or lumbar spine BMD in a cohort of more than 19,000 subjects. In the same study, SNPs from LRP5, SOST, SPP1 and TNFSF11A, were associated with fracture risk (Richards et al., 2009). The other study, confirmed the significant association of previously known BMD loci: ESR1, TNFRSF11B, LRP5, SP7, ZBTB40, TNFSF11 and TNFRSF11A, but interestingly they identified several loci in regions not previously associated with BMD (Rivadeneira et al., 2009). Recently, variants in CATSPERB (Koller et al., 2010), MATN3, IGF1 (Li et al., 2011), SOD2 (Deng et al., 2011) and FONG (Kou et al., 2011) genes between many others, have been involved in BMD regulation and in the pathogenesis of osteoporosis. Evidences for genes or loci association with BMD are controversial in many cases (Ralston & Uterlinden, 2010). Further large scale studies will be necessary to address the role of gene variants on BMD and osteoporosis, but the importance of this studies lies in the potential uses and clinical implications since, besides of differences in the effect of variants, the identified genes might be important for drugs design to prevention and treatment of osteoporosis.

4. Association studies

During the last years, association studies among natural variations of our genome (gene polymorphisms) and particular phenotypic characteristics such as OP, have shown that the mechanisms that condition this heritable susceptibility are defined by the presence of mutations or polymorphisms in one or several genes that influence bone phenotype. In this case, it is important clarifying that the term polymorphism refers to the presence of two or more gene variants in the same allele, in such a way that the less common variant must have a frequency equal or higher on 1% of the population, otherwise, the variation is considered as a mutation. These changes in the normal sequence may involve several bases, as in case mini-satellites or VNTR (*variable number of tandem repeat*), where the size of repeated fragments range from 15 to 70 pairs of bases in tandem. Other kind of polymorphisms are of micro-satellite also known as STR (*short tandem repeats*), which characterize for showing variations in the nucleotide number (2-6 base pairs). Recently, single nucleotide variations also known as SNPs (*single nucleotide polymorphisms*) have been analyzed; in this case, the analysis of these variations represents a very commonly used tool in studies that intend associating certain allelic variants with phenotypic characteristics, specially the ones attributed to polygenic diseases (multi-factorial and complex). Table 2 shows several single nucleotide polymorphisms studied in relation to osteoporosis and bone mineral density. It can be observed that some polymorphisms have been consistently studied with respect to particular bone traits, such as BMD in specific anatomic regions and in some cases with fracture risk.

Polymorphisms in genes as ER α and β , IL6, VDR, Aromatase (CYP19), COL IA1, RANK and RANKL are between the most studied. There are several polymorphic sites which association with BMD or with osteoporosis has been demonstrated in many different

populations. The results in many cases have been controversial, for example the SNP G/A in ER α gene exon 8, have been associated with osteoporosis in Thailander (Ongphiphadhanakul et al., 2001) and in Mexican women (Gómez et al., 2007), but association was denied when it was studied in Spanish women (Riancho et al., 2006), in spite all three investigations were performed with postmenopausal women. The T/C SNP of ER α gene was associated with low BMD in Japanese women, but not in Afro-American, Caucasian or Chinese women and the A/G SNP of the same gene, was associated with low BMD only in Afro-American Women, but not in Caucasian, Chinese nor in Japanese women (Greendale et al., 2006). The differences between studies results might be due to the genetic background of studied populations, which emphasize the importance of performing studies to explore the polymorphisms in specific groups with the same characteristics to avoid the incorrect use of genetic markers. Differences between races were evident too in studies with the IL6 G572C polymorphism in which the results in Korean (Chung et al., 2003) and Japanese (Ota et al., 2001) populations were consistent associating the G allele with low BMD, meanwhile in the study performed with Caucasian US women (Ferrari et al., 2003), the G allele appears as a protective factor from bone resorption.

Discordances can certainly be seen due to the frequencies of some alleles in different populations. It is important to determine the frequency of the polymorphism in a general population study before to perform a case-control study, since some genetic sites could be not polymorphic in some populations or the variant might be present in very low frequencies and their analysis could give spurious or no association results. An example of a SNPs which could not be used as osteoporosis genetic markers in Korean population are the G174C and G/A polymorphisms in the promoter of the IL6 gene because they show a very low frequency of this polymorphisms which difficult to found associations (Chung et al., 2003). However, the same G174C SNP was analyzed in Caucasian American healthy women (Ferrari et al., 2003) and in Mexican osteoporotic and non osteoporotic women as well as in general population (Magaña, et al., 2008), obtaining that the C allele is a protective factor from bone resorption and from osteoporosis respectively. However, most of the VDR gene SNPs showed in table 2, were consistently associated with low BMD or with osteoporosis in a great variety of populations. SNPs in intron 10, exon 2 and promoter of the gene, have resulted associated in European (Bustamante et al., 2007b; Utterlinden et al., 2001) American (Kiel et al., 2007; Pérez et al., 2008; Moffet et al., 2007) and Asiatic (Mencej et al., 2009) populations and even in large scale studies with world's population (Morrison, 2004). The collagen IA1 is one of the most studied genes involved in osteoporosis. Many SNPs have been consistently associated with BMD and osteoporosis in several populations in this gene. The G/T change has been associated with osteoporosis in almost all studied populations, for example in Mexican (Falcón-Ramírez et al., 2011) and in British (Stewart et al., 2006). Not all the polymorphisms have a functional effect on bone traits, but the presence of the polymorphism G/T in Sp1 site, alters the recognition of the Sp1 factor having effects on transcription, protein production and mechanical strength of bone.

The appropriate expression of the genes of the route of signaling RANK/RANK-L/OPG is essential in osteoclastogenesis process, and makes them some of the most investigated genes performing studies with specific allelic, genotypic and haplotypic variants in this genes searching for associations with bone mineral density. In this case, variations of a single nucleotide in the intron 1, 9, and others located in the 3' del region gene RANK have consistently shown their association with low bone mineral density in spine and hip in European populations (Paternoster et al., 2010; Stykarsdottir et al., 2009, Xiong et al., 2006).

GEN	POLYMORPHISM	LOCATION	REFERENCES	OU
CALCR	C/T C/T	Exon 13 Intron 12	Xiong et al., 2006.	Associated with spine osteoporosis
ER α	G/A	Exon 8	Ongphiphadhanakul et al., 2001. Riancho et al., 2006 Gómez et al., 2007.	Associated with osteoporosis in Not associated with BMD in postmenopausal women Associated with spine osteoporosis in Chinese women
	C/T	Intron 1	Ongphiphadhanakul et al., 1998. Wang et al., 2008.	Associated with high BMD of spine No association in Chinese of both sexes
	C/T	rs2234693	Greendale et al., 2006. Bustamante et al., 2007b	Low BMD in spine in Afro-American women Low BMD in femoral neck in Spanish women
	C/G	rs1884052	Kiel et al., 2007.	Associated with hip/spine osteoporosis
	C/T	rs3778099		geometry in US families of European descent
	C/T	rs3020314	Wang et al., 2008.	Associated with hip fracture in Chinese women
	C/T	rs1884051		
	T/C	3' UTR	Greendale et al., 2006.	Low BMD in hip and/or spine in Chinese women, respectively.
	A/G	rs728524		
	C/A	rs726282	Limer et al., 2009.	Low BMD in European males.
C/G	rs1801132			
ER β	G/C	Intron 3	Wang et al., 2008.	Associated with hip fracture in Chinese women
	G/A	Intron 8	Massart et al., 2009.	AA and AC genotypes associated with low BMD in Chinese women
	C/T	Intron 2	Greendale et al., 2006.	Associated with low spine BMD in Chinese women.
	C/A	Intron 8		
	T/C	Intron 3	Rivadeneira et al., 2006.	Vertebral fracture risk in carrier status in Chinese population.
	C/T	Intron 8		
	C/T	Intron 7	Shearman et al., 2004.	Low hip BMD in US population
	T/C	Promoter	Ichikawa et al., 2005.	Associated with spine BMD normal in men and women.
A/G	Promoter			
IL-6	G/C (G572C)	Promoter	Chung et al., 2003.	C allele and increased BMD in postmenopausal women
			Ota et al., 2001.	G allele associated with low BMD in Chinese women
			Ferrari et al., 2003	women
			G allele as protective factor from osteoporosis in Caucasian US women older than 65 years	
			Magaña et al., 2008.	

GEN	POLYMORPHISM	LOCATION	REFERENCES	OU
IL-6	G/C (G174C)	Promoter	Chung et al., 2003. Ferrari et al., 2003. Magaña et al., 2008.	No association with BMD of Korea its low frequency among Korean The C allele as a protective factor Caucasian US women older than The C allele is associated as a pro
	G/A	Promoter	Chung et al., 2003.	Korean premenopausal women. low frequency among Korean pe
IL6R	C/T G/A A/C	Promoter Promoter Exon 9	Bustamante et al., 2007a.	C/T and G/A polymorphisms a body mass ratio; A/C associated postmenopausal women.
VDR	C/T	3' UTR	Kiel et al., 2007.	Associated with low BMD of fem population (Framingham).
	A/C	Intron 10	Bustamante et al., 2007b. Kiel et al., 2007.	Associated with low BMD in Spa Associated with low BMD femor (Framingham).
	A/C	Intron 10	Morrison, 2004. Bustamante et al., 2007b. Uitterlinden et al., 2001.	Associated with low BMD. Worl Associated with low BMD in Spa Not associated with BMD or frac population.
	A/G	Intron 10	Kiel et al., 2007. Bustamante et al., 2007b. Morrison, 2004. Pérez et al., 2008.	Associated with osteoporosis an US population (Framingham). Associated with low BMD in Spa Associated with osteoporosis. W
	C/T	Exon 2	Bustamante et al., 2007b. Pérez et al., 2008.	Low BMD in spine and/or femo menopausal Argentinean wome Associated with BMD; not clearl
	A/C/G/T	Exon 2	Kiel et al., 2007. Morrison, 2004. Moffett et al., 2007.	Low BMD in spine and/or femo menopausal Argentinean wome Associated with osteoporosis an US population (Framingham). Associated with osteoporosis. W
				C/C genotype Associated with l Caucasian postmenopausal US w

GEN	POLYMORPHISM	LOCATION	REFERENCES	OU
VDR	C/T	Exon 2	Uitterlinden et al., 2001.	Associated with a larger number of fractures in men and women. Significant differences as risk factor for fractures in women.
	A/G	Promoter	Kiel et al., 2007. Morrison, 2004. Mencej et al., 2009.	Associated with osteoporosis and fractures in a US population (Framingham). Associated with osteoporosis. Weakly associated with osteoporosis in men.
	A/G	Promoter region	Uitterlinden et al., 2001.	Associated with fractures but not with osteoporosis.
	A/C	rs2189480	Kiel et al., 2007. Bustamante et al., 2007b.	Associated with low BMD of femoral neck in a population (Framingham). Associated with low BMD of femoral neck in postmenopausal Spanish women.
CYP19	ins/del TTC	Intron 4	Limer et al., 2009.	Low heel BMD with 1 or 2 copies in men of many countries.
			Riancho et al., 2005. Mendoza et al., 2006.	Low hip and spine BMD with TT genotype in men. Low hip and spine BMD with TT genotype in women.
			Riancho et al., 2007. Riancho et al., 2009.	Associated with higher vertebral fracture risk. Associated with low hip and spine BMD in men.
	T/C	Exon 3	Riancho et al., 2007. Riancho et al., 2009.	Associated with higher vertebral fracture risk. Associated with low hip and spine BMD in men.
			Riancho et al., 2009.	Associated with low hip and spine BMD in men.
	C/T	3' UTR	Limer et al., 2009. Mendoza et al., 2006.	Low heel BMD in males of many countries. Low hip and spine BMD in Spanish men.
	C/G	5' UTR	Riancho et al., 2007. Riancho et al., 2009.	Associated with vertebral fracture risk. Higher hip BMD with GG genotype.
	C/T	Exon I.6	Riancho et al., 2009.	Associated with high hip BMD with GG genotype.
	A/G	Between exons I.2 y I.6	Riancho et al., 2007.	Associated with vertebral fracture risk.
	C/G	3' UTR	Kiel et al., 2007.	Associated with osteoporosis and fractures in men of European origin (Framingham).
	G/A	Intron 2	Xiong et al., 2006.	Associated with hip/spine osteoporosis in men.
	C/T	3' UTR	Xiong et al., 2006.	Associated with hip/spine osteoporosis in men.
T/C	Intron 8	Xiong et al., 2006.	Associated with hip/spine osteoporosis in men.	
C/T	Intron 2		Associated with hip/spine osteoporosis in men.	

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GEN	POLYMORPHISM	LOCATION	REFERENCES	OU
CYP19	T/C G/A C/T	Intron 3 Intron 4 Intron 5	Hong et al., 2007.	Associated with low (T/C) and Chinese men.
PTHR1	A/T C/T A/G T/C	Intron 1 Intron 2 Intron 8 Intron 10	Vilariño-Güell et al., 2007.	As haplotype, they are associated and/or loss of BMD in spine and (FAMOS), in Caucasian and Bri
OPG	G/A G/C A/G	3' UTR Exon 1 5' proximal region	Richards et al., 2008. Paternoster et al., 2010. García-Unzueta et al., 2008. Kim et al., 2008. Lee et al., 2010. Geng et al., 2007.	Associated with low BMD in spi (Rotterdam study). Associated with low BMD cortic Kingdom (ALSPAC) and Swedis High BMD with CC genotype in High BMD with CC genotype; d women. Low spine BMD in European and BMD high con AA genotype in C
ITGA1	C/T T/G A/C	Exon 3 Intron 5 Intron 28	Lee et al., 2007.	Associated as alleles and also as Korean women.
COL1A1	G/T G/T Ins/del T C/A	Intron 1 Promoter Promoter Intron 11	Stewart et al., 2006. Jin et al., 2009. Falcón-Ramírez et al., 2011. Stewart et al., 2006. Stewart et al., 2006. Jin et al., 2009. Kiel et al., 2007.	Low BMD with haplotype -19970 spine in British women. Low BMD and increment of fract women. Associated with spine osteoporc Low BMD in hip and spine of Br haplotype with other SNPs of th Low BMD in hip and spine in Br Low BMD and increment of hip women. Associated with the width of the

GEN	POLYMORPHISM	LOCATION	REFERENCES	OU
RUNX2	A/T	Intron 3	Ermakov et al., 2006.	Associated with anthropometric in Israel.
	A/T	Intron 4		
	T/C	Intron 4		
	C/T	Promoter 2	Lee et al., 2009.	CC genotype shows a low BMD in spine and hip.
	A/G	Exon 2	Vaughan et al., 2002.	The A allele was associated with women.
Unknown gene	G/T	rs6696981	Styrkarsdottir et al., 2008.	Associated with hip and spine for Danish women.
	A/G	rs7524102		
RANK		rs3018362	Paternoster et al., 2010.	Associated with low cortical BMD in the United Kingdom (ALSPAC) and Swedish populations. Associated with low BMD in hip and spine in European families. Analyzed as haplotypes, these 17 polymorphisms showed a strong association with osteoporosis and fracture in European families.
	A/G	Intron 1	Styrkarsdottir et al., 2009.	
	A/G	Intron 1	Xiong et al., 2006.	
	A/C	Intron 1		
	C/G	Intron 1		
	A/G	Intron 1		
	A/G	Intron 2		
	A/T	Intron 3		
	G/T	Intron 3		
	A/T	Intron 4		
	C/T	Intron 7		
	A/G	Intron 7		
	G/T	Intron 9		
	G/T	Intron 9		
	C/T	Intron 9		
	C/G	Intron 9		
	G/T	3' region		
	C/T	3' region		
	A/G	Intron 6	Koh et al., 2007.	

GEN	POLYMORPHISM	LOCATION	REFERENCES	OU
RANKL	C/T	Intron 1	Xiong et al., 2006. Mencej et al., 2006.	Associated with hip BMD decrease in CC genotype Associated with a Slovenia women.
	C/T	Intron 2	Mencej et al., 2008. Mencej et al., 2009	Associated with low spine BMD Associated with spine BMD decrease women.
	C/T	Intron 1	Xiong et al., 2006.	Associated with hip BMD decrease
	C/G	Intron 1	Mencej et al., 2006. Mencej et al., 2008.	CC genotype associated with low postmenopausal Slovenia women Association to low spine BMD of
	C/T C/T	rs9594738 rs9594759	Mencej et al., 2008. Styrkarsdottir et al., 2008.	Associated with a BMD decrease Slovenia women. Associated with low spine BMD fractures, in Australian, Danish a
HDC	C/T	3' region	Xiong et al., 2006.	Polymorphisms associated with families.
	A/C	3' region		
	A/C	5' region		
	C/T	5' region		
ADCY10	G/A	Exon 7	Ichikawa et al., 2009.	Positive association to spine BMD spine of US population (sisters s
	C/T	Intron 14	Ichikawa et al., 2009.	US men presented association to spine BMD.
TWIST1	A/G	3' region	Hwang et al., 2010.	Associated with osteoporosis in

Table 2. Gene polymorphisms associated with osteoporosis and bone mineral density.

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Other variations of a single nucleotide in intron 1 of the RANK-L gene have repeatedly been associated with low BMD of hip and spine in European, Asiatic and European populations (Xiong et al., 2006; Mencej et al., 2006; Mencej et al., 2008; Styrkarsdottir et al., 2008). The presence of these polymorphisms on human genome, are relatively easy to identify since birth or even in prenatal stage. These polymorphisms show a well defined inheritance pattern and their distribution may show differences not only among family groups but among populations and ethnic groups. However, in this kind of studies, we must be extremely careful and constantly consider the potentially confusing effect of some variables, such as: heterogeneity of populations, caused by genetic admixture, specially product of population's migration, the number of individuals included in studies is very important as well as the proper selection of cases and controls, and finally, the method to analyze data (Spencer et al., 2009; Duncan et al., 2002; Macarty et al., 2008). Not considering these elements in association studies would easily led us to establish spurious associations (Koller et al., 2004). Defining the genetic basis of primary osteoporosis in any population is not a simple task, we face a multi-factorial and polygenic entity present in populations that may have a great genetic heterogeneity; however the exploration of bone structure and metabolism genetic control, would allow to know the molecular basis of diseases such as osteoporosis, which represents a new window to explore therapeutic opportunities that would facilitate management of bone disorders.

5. Epigenetics and osteoporosis

During the last years attempts have been made to analyze the relation between environmental and genetic factors in the so called "complex diseases" using epigenetic studies. Epigenetics studies causal interactions among "genes" and their "products" which give place to the "phenotype", which represents the body manifestation of a specific genetic profile. Epigenetics analyzes hereditary changes in the gene expression without changes in the DNA sequence, thus representing an important nexus between genotype, environment and the presence of a disease (Dupont et al., 2009). In osteoporosis, as a polygenic entity in which environmental component plays a determinant role, several risk conditions of maternal origin as bad nutrition of the mother, particularly the lack of vitamin D, habits as smoking and exposition to chemical agents (possibly including some drugs that impact bone quality), have the capacity to induce hereditary changes on future generations, which may occur in very early stages of the embrionary development, even during the neonatal period and they can generate an "imprinting" in the pattern of gene expression; this pattern is hereditary and "semi-permanent" because epigenetic modifications are reversible (Jiang et al., 2004; Dupont et al., 2009). On the other hand, apparently there is a relationship between low weight and size at time of birth and a higher risk of osteoporotic fractures during adult stage. Then we should understand that besides genetic and environmental factors, "epigenetic" can influence genome expression, so the prevention of some maternal conditions represents a valuable opportunity to develop preventative strategies aimed to improve bone quality in future generations.

6. Conclusion

Increment in life expectancy in some populations, ageing, changes in life style, especially the ones related to nutrition quality and physical activity, plus the vertiginous technological

development are characteristics of modern civilizations. This fact generates without a doubt a glaring increment in the incidence of several chronic degenerative diseases which may become crippling as occurs with osteoporosis, where the complications directly or indirectly cause great social and economic costs; thereby, they represent a social and health services challenge. Considering environment effects on the bone phenotype and the modifications in life style of populations in present time, osteoporosis could be in the future a disorder that occurs in younger population, rather than preferentially in elder people. This situation could overpass the medical services answer capacity and the governmental budget assigned to the medical care and rehabilitation of these patients; so it is important to intensify the investigations leading to elucidate the physiopathology of this disorder and the most relevant processes in bone metabolism.

Genetic association studies enable identification of new genes related to bone metabolism. Knowledge of the function of its products will allow us attaining a better understanding of some aspects of bone metabolism not entirely explored yet and will open new opportunities for therapeutic development in osteoporosis. On the other hand, clinical research from which results association studies, makes possible to identify and associate genotypic profiles (haplotypes) of risk in families and populations and even in ethnic groups. There is no doubt that progress in this scientific knowledge field, technological progress and especially the various preventative strategies at different stages of life, including prenatal stage through the integral care of maternal health, will surely contribute to achieve a better understanding of the disease, a better care and especially a better prevention.

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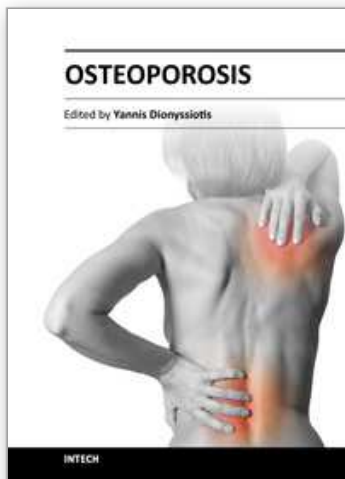
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Osteoporosis is a public health issue worldwide. During the last few years, progress has been made concerning the knowledge of the pathophysiological mechanism of the disease. Sophisticated technologies have added important information in bone mineral density measurements and, additionally, geometrical and mechanical properties of bone. New bone indices have been developed from biochemical and hormonal measurements in order to investigate bone metabolism. Although it is clear that drugs are an essential element of the therapy, beyond medication there are other interventions in the management of the disease. Prevention of osteoporosis starts in young ages and continues during aging in order to prevent fractures associated with impaired quality of life, physical decline, mortality, and high cost for the health system. A number of different specialties are holding the scientific knowledge in osteoporosis. For this reason, we have collected papers from scientific departments all over the world for this book. The book includes up-to-date information about basics of bones, epidemiological data, diagnosis and assessment of osteoporosis, secondary osteoporosis, pediatric issues, prevention and treatment strategies, and research papers from osteoporotic fields.

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