Chapter 2

Genetic Diseases Related with Osteoporosis

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Additional information is available at the end of the chapter

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1. Introduction

Osteoporosis is a disease entity characterized by the progressive loss of bone mineral density (BMD) and the deterioration of bone microarchitecture, leading to the development of fractures. Its classification encompasses two large groups, primary and secondary osteoporosis [1].

Primary osteoporosis is the disease's most common form and results from the progressive loss of bone mass related to aging and unassociated with other illness, a natural process in adult life; its etiology is considered multifactorial and polygenic. This form currently represents a growing worldwide health problem due in part, to the contemporary environmental conditions of modern civilization. Risk factors that are considered as "modifiable" also play an important role and include physical activity, dietary habits and eating disorders. Furthermore, there is another group of associated risk factors that are considered "non-modifiable", including gender, age, race, a personal and/or family history of fractures that in turn, indirectly reflect the degree of genetic susceptibility to this disease [2-4]. Secondary osteoporosis encompasses a large heterogeneous group of primary conditions favoring osteoporosis development. Table 1 summarizes some of the disease entities associated to primary and secondary osteoporosis.

1.1. Genetic aspects of primary osteoporosis

This form of osteoporosis results from the interaction of several environmental and genetic factors, leading to difficulties in its study. It is not easy to define the magnitude of the effect of genetic susceptibility since it is a trait determined by multiple genes whose products affect the bone phenotype; moreover, the environmental factors compromising bone mineral density are also difficult to analyze. However, in spite of these barriers, research suggests that inherited factors affect BMD in ranges between 40 – 70% in the spine, 70 – 85% in the hip and 50 – 60%

Type of osteoporosis	Causes
Primary	Multifactorial, polygenic. Senile/Involutional
Secondary	Drugs compromising bone quality: anticonvulsants, antidepressants, anticoagulants, antacids with aluminum, aromatase inhibitors, barbiturates, cimetidine, corticosteroids, glucocorticoids, birth control pills, cancer drugs, gonadotropin releasing hormone (GnRH), loop diuretics, methotrexate, phenobarbital, phenothiazines, among others.
	Other entities: nephropathies, malabsorption syndromes, neoplasias, rheumatoid arthritis, ankylosing spondylitis, multiple sclerosis, any process leading to decreased mobility or prolonged immobility.
	Metabolic diseases: diabetes, hyperthyroidism, hyperparathyroidism.
	Hypogonadism: Turner and Klinefelter syndromes.
	Behavioral disorders: anorexia nervosa, depression, prolonged physical inactivity, malnutrition, high caffeine intake, smoking and/or chronic alcoholism.
	Monogenic diseases: osteogenesis imperfecta, glioma syndrome, osteoporosis.

Table 1. Osteoporosis classification.

in the wrist. Bone density studies in monozygotic (MZ) and dizygotic (DZ) twins suggest that spinal and femoral neck BMD concordance is higher (6-8:1) in MZ versus DZ twins. Other studies have estimated that fracture predisposition heritability per se ranges between 25 – 35% and up to 40% of patients with osteoporotic fractures have a positive family history of fractures, thus reflecting the great influence of genetic factors in this disease. On the other hand, the geometry and length of the femoral neck, the bone's properties on ultrasound, growth speed and bone remodeling variations are also dependent on genetic factors. The genes associated with the bone phenotype are distributed throughout the human genome and located in practically all chromosomes; their products fulfill specific functions and contribute in different manners to the genetic control of the bone tissue phenotype [5-12]. Some of these genes and their products are presented in Table 2 [13-23].

It is important to mention that the mechanisms conditioning the hereditary susceptibility to osteoporosis are determined, among other factors, by the presence of mutations or genetic polymorphisms (natural genomic variations) in one or several genes involved in bone phenotype genetic control. These polymorphisms follow a well-defined inheritance pattern and their distribution is different among racial groups and populations. There are several reports in the world literature, of associations between specific genetic variants and

osteoporosis development or the risk of fractures; these risks may vary according to the fractures' anatomic location [3, 4, 24-30]

Product Function	Genes
Matrix components	COL1A1, COL1A2, OPN
Hormones and their receptors	ESR1, ESR2, AR, VDR, PTHR1, CASR, PTH, CYP1A1, PRL, LEP, LEPR, INS, INSR
Participants in osteoblastogenic proccesses	ALOX12, ALOX15, BMP4, BMP7, IGF-1 LRP5, LRP6, SOST
Participants in osteoclastogenic proccesses	P53, RANK, RANK-L
Citokines and their receptors	IL1α, IL1β, IL6, TNF, TNFR2
Other	MTHFR, APOE

Table 2. Genes involved in bone metabolism.

2. Mendelian diseases and osteoporosis

The description in the literature of some genetic diseases of monogenic inheritance and whose phenotype includes the loss or increase in bone mineral density and even fractures, has suggested and even proved that bone phenotype has an important genetic component. These diseases include idiopathic osteoporosis, osteogenesis imperfecta in all its variants, osteopetrosis, pycnodysostosis and the osteoporosis syndrome associated to pseudoglioma, among others. In some cases of severe osteoporosis, mutations in the estrogen and even the androgen receptor genes have been detected.

2.1. Idiopathic juvenile osteoporosis

This is an unusual variety of osteoporosis whose frequency has not been precisely determined. This disease may develop in females and males, usually around 7 – 10 years of age; children present difficulty in gait, pain in the lower extremities, ankles, knees, occasionally in the hip and fractures tend to develop particularly in long bones. Radiologically, it is characterized by diffuse osteopenia, metaphyseal fractures – especially of the femur -, and vertebral collapse that may lead to severe kyphoscoliosis or collapse of the thoracic cage. This disease is considered potentially reversible whereby in most cases, there is almost complete recovery of the bone tissue; growth, however, may be compromised.

In these patients, it is important to exclude other disease entities or conditions manifesting secondarily as osteoporosis. A differential diagnosis must be made with other genetic diseases, particularly the different variants of osteogenesis imperfecta; this is relatively easy

due to its clinical characteristics, lacking in idiopathic osteoporosis. The genetic basis of this disease has of yet, not been established but it is possible that genetic mutations with preferential tissue expression in bone and with great impact on the tissue's phenotype, may explain some of these cases [31, 32].

2.2. Osteogenesis imperfecta

Osteogenesis imperfecta, also known as "brittle bone disease", has an estimated incidence of approximately 1 in 20 000 births. It has great phenotypic variability, different patterns of inheritance and a wide clinical spectrum ranging from very mild forms of the disease to severe cases with an unfavorable prognosis. It is caused by the defective synthesis of one of the two alpha chains of type I collagen (COL1A1 and COL1A2), leading to anomalies in these protein's structure; it is normally constituted by 3 coiled sub-units, two α1 chains and one α2 chain. This type of collagen is considered the most abundant component of structural protein in bone as well as in ligaments, tendons, sclerae and skin. Quantitative or qualitative defects in this protein lead to bone fragility and hence, to an increased risk of fractures.

The genes encoding the α1 and α2 chains are located in the 17q21.31-q22 and 7q22.1 chromosomes, respectively. Aside from brittle bones, these patients may also present long bones with no curvatures, severe deformities preventing appropriate gait and even standing, conductive deafness due to malformations of the auditory canal, dentinogenesis imperfecta, joint hyperlaxity and intervertebral disc herniation. Patients with severe forms of the disease have a long history of fractures on mild impact and variable bone deformities. The most severe variants may even lead to fractures in utero and pre or perinatal death. Tables 3 and 4 shows different forms of the disease [33-35].

2.3. Osteoporosis – Pseudoglioma Syndrome (OPPG)

This syndrome is an autosomal recessive disease characterized by bone and visual abnormalities including short stature, osteoporosis development during infancy, spontaneous fractures, scoliosis, platyspondyly and long bone deformities. A crucial associated finding is the presence of pseudoglioma that may be associated to microcephaly, blindness during childhood, cataracts and iris atrophy. Occasionally, some patients present interventricular septal defects and mental retardation. This disease is conditioned by mutations of the LRP5 gene, located on chromosome 11q13.4 and that encodes the low-density lipoprotein receptor-related protein 5 (LRP5). It was initially believed that this entity was another variant of osteogenesis imperfecta (OI) but the study of collagen in patients with OPPG established that this protein was normal and the hypothesis was discarded; however, this is still the most relevant differential diagnosis [36-41].

2.4. Neuromuscular disorders

Muscular dystrophies, peripheral neuropathies and muscle atrophies of hereditary origin, represent broad groups of diseases that aside from their characteristic clinical stigmata, can be associated with osteoporosis as one of their complications. As the disease progresses in these

patients, there is increased difficulty and limitation in walking and periods of immobility become progressively more prolonged leading to the gradual loss of the mechanical stimuli that bone needs to maintain its strength and hence, favoring the development of osteoporosis. As all Mendelian diseases, these neuromuscular abnormalities follow different inheritance patterns and present phenotypic variability [42-44].

2.5. Inborn errors of metabolism

This group of genetic diseases encompasses a great number of inborn defects with repercussions in several aspects of carbohydrate, amino acid, protein, vitamin, mineral, complex molecule, neurotransmitter and energy metabolism. The genetic basis of most of these entities hinges on gene mutations encoding proteins, particularly enzymes, leading to partial or complete blockade of one or several metabolic processes. In these diseases, symptoms arise for different reasons, including: a deficit of the products generated by the compromised enzymatic reaction, accumulation of the precursor immediate to the defect, an increase in alternative products due to increased activation of alternate metabolic pathways or inhibition of these alternate pathways due to the accumulated substrate. In most cases, inheritance of these diseases is autosomal recessive and less frequently, X-linked recessive.

In cases of metabolic errors, osteoporosis tends to develop for different reasons: in some cases, it is secondary to nutritional deficiencies, progressive neurologic or muscular impairment or as a consequence of the therapeutic measures taken in the management of the primary disease: their secondary effects directly compromise bone quality (steroids, antiseizure drugs, etc.). The number of monogenic diseases whose phenotype may include osteoporosis is large and are shown in Tables 3-5, according to their Mendelian inheritance pattern [45-56].

Disease	Gene	Product	Genomic Location	Reference
Hutchinson-Gilford progeria syndrome; HGPS	LMNA	Prelamin-A/C precursor (LMNA)	1q22	57, 58
Osteogenesis imperfecta, Type I; OI1	COL1A1	Collagen, type I, alpha 1 (COL1A1)	17q21.33	33, 34
Osteogenesis imperfecta, Type II; OI2	COL1A1	Collagen, type I, alpha 1 (COL1A1)	17q21.33	33, 59
	COL1A2	Collagen, type I, alpha 2 (COL1A2)	7q21.3	
Osteogenesis imperfecta, Type III; OI3	COL1A1	Collagen, type I, alpha 1 (COL1A1)	17q21.33	33, 60
	COL1A2	Collagen, type I, alpha 2 (COL1A2)	7q21.3	
Marfan syndrome; MFS	FBN1	Fibrillin 1 (FBN1)	15q21.1	61, 62

Disease	Gene	Product	Genomic Location	Reference
Loeys-Dietz syndrome, Type 1A; LDS1A	TGFBR1	Transforming growth factor-beta receptor, Type I (TGFBR1)	9q22.33	63, 64
Loeys-Dietz syndrome, Type 1B; LDS1B	TGFBR2	Transforming growth factor-beta receptor, Type II (TGFBR2)	3p24.1	65, 66
Loeys-Dietz syndrome, Type 2B; LDS2B	TGFBR2	Transforming growth factor-beta receptor, Type II (TGFBR2)	3p24.1	63, 65
Loeys-Dietz syndrome, Type 3; LDS3	MADH3/ SMAD3	Mothers against decapentaplegic homolog 3 (Drosophila) (SMAD3)	15q22.33	67, 68
Ehlers-Danlos syndrome, Type I	COL5A2	Collagen, type V, alpha 2 (COL5A2)	2q32.2	69, 70
	COL5A1	Collagen, type V, alpha 1 (COL5A1)	9q34.3	
	COL1A1	Collagen, type I, alpha 1 (COL1A1)	17q21.33	
Ehlers-Danlos syndrome, Type II	COL5A1	Collagen, type V, alpha 1 (COL5A1)	9q34.3	70, 71
	COL5A2	Collagen, type V, alpha 2 (COL5A2)	2q32.2	
Pseudohypoparathyroidism, Type IA; PHP1A	GNAS	GNAS complex locus (GNAS) [Gs, alpha subunit, included]	20q13.32	72, 73
Pseudohypoparathyroidism, Type IC; PHP1C	GNAS	GNAS complex locus (GNAS) [Gs, alpha subunit, included]	20q13.32	73, 74
Pseudopseudohypopara-thyroidism; PPHP	GNAS	GNAS complex locus (GNAS) [Gs, alpha subunit, included]	20q13.32	73, 75
Epiphyseal dysplasia, multiple, 1; EDM1	COMP	Cartilage oligomeric matrix protein (COMP)	19p13.11	76, 77

Disease	Gene	Product	Genomic Location	Reference
Prader-Willi syndrome; PWS	NDN SNRPN /PWCR	Necdin homolog (mouse) (NDN) Small nuclear ribonucleoprotein-associated protein N (SNRPN/PWCR)	15q11.2 15q11.2	78, 79
Hajdu-Cheney syndrome; HJCYS	NOTCH2	Neurogenic locus Notch homolog protein 2 (NOTCH2)	1p12-p11	80, 81
Nephrolithiasis/osteoporosis, hypophosphatemic, 1; NPHLOP1	SLC34A1	Sodium-dependent phosphate transport protein 2A (SLC34A1/ .NPT2A)	5q35.3	82, 83
Nephrolithiasis/osteoporosis, hypophosphatemic, 2; NPHLOP2	SLC9A3R1/ NHERF	Na(+)/H(+) exchange regulatory cofactor NHE-RF1 (SLC9A3R1/ NHERF)	17q25.1	84-86
Cardiomyopathy, dilated, with hypergonadotropic hypogonadism	LMNA	Prelamin-A/C precursor (LMNA)	1q22	87, 88
Dyskeratosis congenita, autosomal dominant, 1; DKCA1	TERC	Telomerase RNA component (TERC) (RNA)	3q26.2	87, 88
Dyskeratosis congenita, autosomal dominant, 2; DKCA2	TERT	Telomerase reverse transcriptase (TERT)	5p15.33	89, 90
Dyskeratosis congenita, autosomal dominant, 3; DKCA3	TINF2	TERF1-interacting nuclear factor 2 (TINF2)	14q12	91, 92
Pigmented nodular adrenocortical disease, primary, 1; PPNAD1	PRKAR1A	cAMP-dependent protein kinase type I-alpha regulatory subunit (PRKAR1A/ TSE1)	17q24.2	93, 94
Pigmented nodular adrenocortical disease, primary, 2; PPNAD2	PDE11A	Dual 3',5'-cyclic-AMP and -GMP phosphodiesterase 11A (PDE11A)	2q31.2	95, 96
Hyperostosis corticalis generalisata, benign form of worth, with torus palatinus	LRP5	Low density lipoprotein receptor-	11q13.2	97, 98

Disease	Gene	Product	Genomic Location	Reference
		related protein 5 (LRP5)		
Van Buchem disease, Type 2; HVB2	LRP5	Low density lipoprotein receptor-related protein 5 (LRP5)	11q13.3	99, 100
Osteopetrosis, autosomal dominant 1; OPTA1	LRP5	Low density lipoprotein receptor-related protein 5 (LRP5)	11q13.3	101, 102
Osteopetrosis, autosomal dominant 2; OPTA2	CLCN7	H(+)/Cl(-) exchange transporter 7 (CLCN7)	16p13.3	103, 104
ACTH-independent macronodular adrenal hyperplasia; AIMAH	GNAS	GNAS complex locus (GNAS) [Gs, alpha subunit, included]	20q13.32	105, 106
Hyper-IgE recurrent infection syndrome, autosomal dominant	STAT3	Signal transducer and activator of transcription 3 (STAT3)	17q21.2	107, 108
Coronary artery disease, autosomal dominant 2; ADCAD2 or CADO	LRP6	Low density lipoprotein receptor-related protein 6 (LRP6)	12p13.2	109, 110
Avascular necrosis of femoral head, primary; ANFH	COL2A1	Collagen, type II, alpha 1 (COL2A1)	12q13.11	111, 112
Spondyloepimetaphyseal dysplasia with joint laxity Type 2; SEMDJL2	KIF22	Kinesin-like protein KIF22 (KIF22)	16p11.2	113, 114
Spondyloepiphyseal dysplasia, Maroteaux type (pseudo-Morquio syndrome, Type 2)	TRPV4	Transient receptor potential cation channel, subfamily V, member 4 (TRPV4)	12q24.11	115, 116
Hypophosphatasia, adult	ALPL	Alkaline phosphatase, liver/bone/kidney or alkaline phosphatase, tissue-nonspecific isozyme (ALPL)	1p36.12	117, 118

Disease	Gene	Product	Genomic Location	Reference
Cleidocranial dysostosis; CLCD	RUNX2	Runt-related transcription factor 2 (RUNX2)	6p21.1	119, 120
Trichorhinophalangeal syndrome, type I; TRPS1	TRPS1	Zinc finger transcription factor Trps1(TRPS1)	8q23.3	121, 122

Table 3. Autosomal dominant diseases with bone mineral density loss.

Disease	Gene	Product	Genomic location	Reference
Vitamin D hydroxylation-deficient rickets, Type 1A; VDDR1A	CYP27B1	25-hydroxy-vitamin D-1 alpha hydroxylase, mitochondrial (CYP27B1)	12q13	123, 124
Hemochromatosis; HFE	HFE (C282Y y H63D)	Hereditary hemochromatosis protein (HFE)	6p22.2	125, 126
	BMP2 [HFE hemochromatosis, modifier of]	Bone morphogenetic protein 2 (BMP2)	20p12.3	
Beta-Thalassemia	beta-Thalassemia:HBB	Hemoglobin subunit beta (HBB)	11p15.4	47, 48
	Thalassemia, Hispanic gamma-delta-beta: LCRB	Locus control region, beta (LCRB)	11p15.5	
Osteoporosis-pseudoglioma syndrome; OPPG	LRP5	Low density lipoprotein receptor-related protein 5 (LRP5)	11q13.2	127, 128
Homocystinuria due to cystathionine beta-synthase deficiency	CBS/HIP4	Cystathionine beta-synthase (CBS)	21q22.3	45, 46
Homocysteinemia	MTHFR (C677T)	Methylenetetrahydrofolate reductase (MTHFR)	1p36.6	129, 130
	CBS	Cystathionine beta-synthase (CBS)	21q22.3	
	MS/MTR	Methionine synthase (MTR/METH)	1q23	

Disease	Gene	Product	Genomic location	Reference
Homocysteinemia	MTHFR (C677T)	Methylenetetrahydrofolate reductase (MTHFR)	1p36.6	33, 131, 132
	CBS	Cystathionine beta-synthase (CBS)	21q22.3	
	MS/MTR	Methionine synthase (MTR/METH)	1q23	
Osteogenesis imperfecta, Type IX; OI9 [Osteogenesis imperfecta type II-B, III or IV PPIB related]	PPIB	Peptidyl-prolyl cis-trans isomerase B (PPIB)	15q22.31	35, 133
Propionic acidemia	PCCA	Propionyl-CoA carboxylase alpha chain, mitochondrial (PCCA)	13q32.3	134, 135
	PCCB	Propionyl-CoA carboxylase beta chain, mitochondrial (PCCB)	3q22.3	
Ehlers-Danlos syndrome, type VI; EDS6	PLOD1	Procollagen-lysine,2-oxoglutarate 5-dioxygenase 1 (PLOD1)	1p36.22	69, 136
Hypertrophic osteoarthropathy, primary, autosomal recessive, 1; PHOAR1	HPGD	15-hydroxy-prostaglandin dehydrogenase [NAD+] (HPGD)	4q34.1	137, 138
Pituitary adenoma, ACTH-secreting; CUDP	AIP	AH receptor-interacting protein (AIP)	11q13.2	139, 140
Gaucher disease, Type I; GDI	GBA	Glucosylceramidase (GLCM/GBA)	1q22	49, 50
Paget disease, juvenile; JPD	TNFRSF11B	Tumor necrosis factor receptor superfamily, member 11b (TNFRSF11B)	8q24.12	141, 142
Pycnodysostosis; PKND	CTSK	Cathepsin K	1q21.3	143, 144
Lipodystrophy, congenital generalized, type 4; CGL4	PTRF	Polymerase I and transcript release factor (PTRF)	17q21.2	145, 146

Disease	Gene	Product	Genomic location	Reference
Niemann-Pick disease, Type A	SMPD1	Sphingomyelin phosphodiesterase 1, acid lysosomal (SMPD1/ASM)	11p15.4	147, 148
Niemann-Pick disease, Type B	SMPD1	Sphingomyelin phosphodiesterase 1, acid lysosomal (SMPD1/ASM)	11p15.4	147, 149
Lathosterolosis	SC5DL	Lathosterol oxidase (SC5DL)	11q23.3	150, 151
Mucopolysaccharidosis Type IVA (Morquio syndrome A)	GALNS	N-acetyl-galactosamine-6-sulfatase (GALNS)	16q24.3	152-154
Mucopolysaccharidosis Type IVB (Morquio syndrome B)	GLB1	Beta-galactosidase1 (BGAL)	3p22.3	
Fibromatosis, juvenile hyaline; JHF	ANTXR2	Anthrax toxin receptor 2 (ANTXR2)	4q21	155, 156
Aromatase deficiency	CYP19A1	Cytochrome P450 19A1 (CYP19A1)	15q21.2	157, 158
Diastrophic dysplasia	SLC26A2	Sulfate transporter 2 (S26A2)	5q32	159, 160
Desbuquois dysplasia; DBQD	CANT1	Soluble calcium-activated nucleotidase 1 (CANT1)	17q25.3	161, 162
Torg-winchester syndrome	MMP2	72 kDa type IV collagenase (MMP2)	16q12.2	163, 164
Geroderma osteodysplasticum; GO	GORAB	RAB6-interacting golgin (GORAB)	1q24.2	165, 166
Lysinuric protein intolerance; LPI	SLC7A7	Y+L amino acid transporter 1 (YLAT1)	14q11.2	167, 168
Cerebroretinal microangiopathy with calcifications and cysts; CRMCC	CTC1	CST complex subunit CTC1	17p13.1	169, 170
Exudative vitreoretinopathy 4; EVR4	LRP5	Low density lipoprotein receptor-related protein 5 (LRP5)	11q13.2	171, 172
Nestor-Guillermo progeria syndrome; NGPS	BANF1	Barrier to autointegration factor 1 (BANF1)	11q13.1	173, 174

Disease	Gene	Product	Genomic location	Reference
Dyskeratosis congenita, autosomal recessive, 1; DKCB1	NOLA3 / NOP10	H/ACA ribonucleoprotein complex subunit 3 (NOP10/ NOLA3)	15q14	175, 176
Macrocephaly, alopecia, cutis laxa, and scoliosis	RIN2	Ras and Rab interactor 2 (RIN2)	20p11.23	177, 178
Hypertrophic osteoarthropathy, primary, autosomal recessive, 1; PHOAR1	HPGD	15-hydroxyprostaglandin dehydrogenase [NAD+] (PGDH)	4q34.1	137, 179
Multiple joint dislocations, short stature, craniofacial dysmorphism, and congenital heart defects	B3GAT3	Galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferase 3 (B3GAT3)	11q12.3	180, 181
Hyalinosis, infantile systemic; ISH	ANTXR2	Anthrax toxin receptor 2 (ANTXR2)	4q21.21	182, 183
Ovarian dysgenesis 1; ODG1	FSHR	Follicle stimulating hormone receptor (FSHR)	2p16.3	184, 185
Epiphyseal dysplasia, multiple, with early-onset diabetes mellitus	EIF2AK3	Eukaryotic translation initiation factor 2 alpha kinase 3 (EIF2AK3)	2p11.2	186, 187
Cerebrooculofacioskeletal syndrome 1; COFS1	ERCC6	DNA excision repair protein ERCC-6	10q11.23	188, 189
Wilson disease; WND	ATP7B	Copper-transporting ATPase 2 (ATP7B)	13q14.3	190, 191
Werner syndrome; WRN	WRN/RECQL2	Werner syndrome ATP-dependent helicase (WRN / RECQL2)	8p12	192, 193
Rothmund-thomson syndrome; RTS	RECQL4	ATP-dependent DNA helicase Q4 (RECQL4)	8q24.3	194, 195
Schwartz-Jampel syndrome, Type 1; SJS1	HSPG2	Basement membrane-specific heparan sulfate proteoglycan core protein (HSPG2)	1p36.12	196, 197

Disease	Gene	Product	Genomic location	Reference
Perrault syndrome; prlts	HSD17B4	Peroxisomal multifunctional enzyme type 2 (HSD17B4)	5q23.1	198, 199
Glycogen storage disease Ia; GSD1A	G6PC	Glucose-6-phosphatase, catalytic subunit (G6PC)	17q21.31	200, 201
Glycogen storage disease Ib; GSD1B	SLC37A4	Glucose-6-phosphate translocase (SLC37A4)	11q23.3	200, 201
Cranioectodermal dysplasia 1; CED1	IFT122	Intraflagellar transport protein 122 homolog (IFT122)	3q21.3	202, 203
Cerebrotendinous xanthomatosis; CTX	CYP27A1	Sterol 26-hydroxylase, mitochondrial (CYP27A1/CP27A)	2q35	204, 205
Arthropathy, progressive pseudorheumatoid, of childhood; PPAC	WISP3	WNT1-inducible-signaling pathway protein 3 (WISP3)	6q21	206, 207
Genitopatellar syndrome; GTPTS	KAT6B	Histone acetyltransferase KAT6B	10q22.2	208, 209
Congenital disorder of glycosylation, Type IIk; CDG2K	TMEM165	Transmembrane protein 165 (TMEM165/TM165)	4q12	210, 211
Cutis laxa, autosomal recessive, Type IA; ARCL1A	FBLN5	Fibulin-5 (FBLN5)	14q32.12	212, 213
Cutis laxa, autosomal recessive, Type IIB; ARCL2B	PYCR1	Pyrroline-5-carboxylate reductase 1, mitochondrial (PYCR1/P5CR1)	17q25.3	166, 214
Cutis laxa, autosomal recessive, Type IIIB; ARCL3B	PYCR1	Pyrroline-5-carboxylate reductase 1, mitochondrial (PYCR1/P5CR1)	17q25.3	212, 215
Niemann-Pick disease, Type B	SMPD1	Sphingomyelin phosphodiesterase (SMPD1)	11p15.4	149, 216
Trichothiodystrophy, photosensitive; TTDP	ERCC3	TFIIH basal transcription factor	2q14.3	217, 218

Disease	Gene	Product	Genomic location	Reference
		complex helicase XPB subunit (ERCC3)		
	GTF2H5	General transcription factor IIH, subunit 5 (GTF2H5)	6q25.3	
	ERCC2	TFIIH basal transcription factor complex helicase XPD subunit (ERCC2)	19q13.32	
Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy; CARASIL	HTRA1	Serine protease HTRA1	10q26.13	219, 220
Weill-Marchesani syndrome 1; WMS1	ADAMTS10	A disintegrin and metalloproteinase with thrombospondin motifs 10 (ADAMTS10/ATS10)	19p13.2	221, 222
Laron syndrome	GHR	Growth hormone receptor (GHR)	5p13-p12	223, 224
Mandibuloacral dysplasia with type A lipodystrophy; MADA	LMNA	Prelamin-A/C precursor (LMNA)	1q22	225, 226
Keutel syndrome	MGP	Matrix Gla protein (MGP)	12p12.3	227, 228
Hypophosphatasia, childhood	ALPL	Alkaline phosphatase, liver/bone/kidney or alkaline phosphatase, tissue-nonspecific isozyme (ALPL / PPBT)	1p36.12	229, 230
Fanconi-Sickel syndrome; FBS	SLC2A2	Solute carrier family 2, facilitated glucose transporter member 2 (SLC2A2 / GTR2)	3q26.2	231, 232
Lactose intolerance, adult type	MCM6	DNA replication licensing factor MCM6	2q21.3	233, 234
Trichohepatoenteric syndrome 1; THES1	TTC37	Tetratricopeptide repeat domain 37 (TTC37)	5q15	235, 236
Costello syndrome	HRAS	GTPase HRas (HRAS/ RASH) (HRAS / RASH)	11p15.5	237, 238

Disease	Gene	Product	Genomic location	Reference
Adrenal hyperplasia, congenital, due to 21-hydroxylase deficiency	CYP21A2	Steroid 21-hydroxylase (CYP21A2)	6p21.33	239, 240

Table 4. Autosomal recessive diseases with bone mineral density loss.

Disease	Gene	Product	Genomic location	Reference
Hypophosphatemic rickets, X-linked dominant; XLHR or HYP	PHEX	Phosphate-regulating neutral endopeptidase (PHEX/PEX)	Xp22.11	241, 242
Androgen insensitivity syndrome; AIS	AR	Androgen receptor (AR)	Xq12	243, 244
Fragile X mental retardation syndrome	FMR1	Fragile X mental retardation protein 1 (FMR1)	Xq27.3	245, 246
Fabry disease	GLA	Galactosidase, alpha (AGAL)	Xq22.1	51, 52
Occipital horn syndrome; OHS	ATP7A	Copper-transporting ATPase 1 (ATP7A)	Xq21.1	247, 248
Menkes disease	ATP7A	Copper-transporting ATPase 1 (ATP7A)	Xq21.1	249, 250
Dyskeratosis congenita, X-linked; DKCX	DKC1	H/ACA ribonucleoprotein complex subunit 4 (DKC1)	Xq28	251, 252
Hyperglycerolemia (glycerol kinase deficiency; GKD)	GK	Glycerol kinase (GK)	Xp21.2	253, 254
Premature ovarian failure 2B; POF2B	FLJ22792 / POF1B	Protein POF1B	Xq21.1-q21.2	255, 256
Terminal osseous dysplasia; TOD or ODPF	FLNA	Filamin-A (FLNA)	Xq28	257, 258

Table 5. X-linked recessive diseases with bone mineral density loss.

2.6. Genetic diseases of chromosomal origin and osteoporosis

Within the different categories of genetic diseases, we can include numeric or structural chromosomal abnormalities. Two of the most common chromosomal diseases are Turner's syndrome and Klinefelter's syndrome, both associated to X chromosome aneuploidy; in the first case, there is complete or partial absence of an X chromosome and less frequently, it can be caused by structural anomalies in the short arms of the X chromosome. In Klinefelter's syndrome, there is an additional X chromosome and occasionally, there may be more than one

extra X chromosome. In both syndromes, the phenotypic spectrum includes gonadal dysgenesis, in Turner's syndrome there are fibrous bands instead of ovaries and in Klinefelter's, the testicles are hypoplastic, leading in both cases to hypogonadism and a partial or complete deficit in the sex hormones that would normally be produced by the ovaries and testicles. Due to their lack, the development of normal secondary sexual characteristics is stunted and the various metabolic processes dependent on the hormones are also compromised. One of these metabolic processes occurs in bone [259-262].

Undoubtedly, bone metabolism is complex and the processes of osteoblastogenesis, osteoclastogenesis and remodeling must occur in a balanced manner; it is important to mention that the entire family of steroid hormone receptors (estrogen, androgen, vitamin D and retinoids), are expressed in bone, both in osteoblasts and osteoclasts as well as in chondrocytes. Within this microenvironment, the action of these hormones on their receptors is key to appropriate skeletal development; as a matter of fact, individuals with genetic mutations encoding any of these receptors develop, among other manifestations, bad quality bone mass. These hormones and their receptors play a pivotal role in female and male bone growth and may also favor epiphyseal closure at the end of the growth period. It is known that one of effects of steroid hormones on bone metabolism is resorption inhibition since they promote osteoclast apoptosis and decrease the frequency of remodeling unit activation. Therefore, the integral treatment of both entities includes hormone replacement that to a certain extent, will improve bone mass and will prevent or delay the development of osteoporosis [263, 264].

3. Conclusion

Bone metabolism and the large amount of processes that it involves, such as osteoblastogenesis, osteoclastogenesis and bone remodeling, must be kept in constant balance. Each one of these aspects of the physiology of bone shows a particular gene expression patterns, which may even differ according to conditions and tissue needs. As previously mentioned the number of genes involved is very large and sometimes their expression might be modified by multiple environmental conditions. It is important to mention that the expression of these genes is ubiquitous and is not restricted to the bone tissue, which explains why the phenotypic characteristics of a large number of monogenic and some polygenic entities include alterations on bone mineral density and on the microarchitecture of this tissue; this includes several degrees of osteopenia,osteoporosis or increased bone mineral density. Even a good number of these genes have been identified through the study of human disease whose phenotype includes altered bone mineral density. Without a doubt, the investigation of several processes that regulate bone metabolism will continue generating new knowledge that will allow better understanding of bone physiology and physiopathology of multiple diseases and possibly new therapeutic options in diseases which compromise the quality and function of the bone.

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Nomenclature

OPN-Osteopontin

ESR1-Estrogen Receptor Alpha

ESR2-Estrogen Receptor Beta

AR-Androgen Receptor

VDR-Vitamin D Receptor

PTHR1-Parathohormone Receptor

PTH-Parathormone

CASR-Calcium Sensing Receptor

CYP1A1-Cytochrome P450, Subfamily A, Polypeptide 1

PRL-Prolactin

LEP-Leptin

LEPR-Leptin Receptor

INS-Insulin

INSR-Insulin Receptor

ALOX12-Arachidonate 12-Lipoxygenase

ALOX15-Arachidonate 15-Lipoxygenase

BMP4-Bone Morphogenetic Protein 4

BMP7-Bone Morphogenetic Protein 7

IGF-1-Insulin-Like Growth Factor 1 (Somatomedin C)

SOST-Sclerostin

P53-Protein 53

RANK-Receptor Activator Of Nf-Kb2

RANK-L.-Receptor Activator Of Nf-Kb2 Ligand

IL1β-Interleucin 1 Beta

IL6-Interleucin 6

TNF-Tumor Necrosis Factor

TNFR2-Tumor Necrosis Factor Receptor

APOE-Apolipoprotein E

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