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Chapter 2

Genetic Diseases Related with Osteoporosis

Margarita Valdés-Flores, Leonora Casas-Avila and
Valeria Ponce de León-Suárez

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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

Author details

Margarita Valdés-Flores*, Leonora Casas-Avila and Valeria Ponce de León-Suárez

*Address all correspondence to: mvaldes@inr.gob.mx

Genetics Unit. National Rehabilitation Institute. Ministry of Health, Mexico

References

[1] Kok C, Sambrook PN. Secondary osteoporosis in patients with an osteoporotic fracture. Best Pract Res Clin Rheumatol 2009;23(6):769-79. Review.

[2] Krall EA, Dawson-Hugues B. Hereditable and life-style determinants of bone mineral density. J Bone Miner 1993;8(1):1-9.

[3] Obermayer-Pietsch B, Chararas C, Kotschan S, Walter D, Leb G. Genetic background of osteoporosis. Acta Med Austriaca 2000;27(1):18-22.

[4] Stewart TL, Ralston SH. Role of genetics in the pathogenesis of osteoporosis. J of Endocrinology 2000;166(2):235-245.

[5] Slemenda CW, Turner CH, Peacock M, et al. The genetics of proximal femur geometry, distribution of bone mass and bone mineral density. Osteoporos Int 1996;6(2): 178-182.

[6] Arden NK, Baker J, Hogg C, Baan K, Spector TD. The heritability of bone mineral density, ultrasound of the calcaneus and hip axis length: a study of postmenopausal twins. J Bone Miner Res 1996;11(4):530-534.

[7] Koller DL, Liu G, Econs MJ, et al. Genome screen for quantitative trait loci underlying normal variation in femoral structure. J Bone Miner Res 2001;16(6):985-991.

[8] Flicker L, Faulkner KG, Hopper JL, et al. Determinants of hip axis length in women aged 10–89 years: A twin study. Bone 1996;18(1):41-45.

[9] Deng HW, Mahaney MC, Williams JT, et al. Relevance of the genes for bone mass variation to susceptibility to osteoporotic fractures and its implications to gene search for complex human diseases. Genet Epidemiol 2002;22(1):12-25.

[10] Slemenda CW, Christian JC, Williams CJ, Norton JA, Johnston CCJr. Genetic determinants of bone mass in adult women: a reevaluation of the twin model and the potential importance of gene interaction on heritability estimates. J Bone Miner Res 1991;6(6):561-567.

[11] Flicker L, Hopper JL, Rodgers L, Kaymakci B, Green RM, Wark JD. Bone density determinants in elderly women: A twin study. J Bone Miner Res 1995;10(11):1607-1613.

[12] Harris M, Nguyen TV, Howard GM, Kelly PJ, Eisman JA. Genetic and environmental correlations between bone formation and bone mineral density: a twin study. Bone 1998;22(2):141-145.

[13] Xiong DH, Shen H, Zhao LJ, et al. Robust and comprehensive analysis of 20 osteoporosis candidate genes by very high-density single-nucleotide polymorphism screen among 405 white nuclear families identified significant association and gene-gene interaction. J Bone Miner Res 2006;21(11):1678-1695.

[14] Liu YZ, Liu YJ, Recker RR, Deng HW. Molecular studies of identification of genes for osteoporosis: the 2002 update. J Endocrinol 2003;177(2):147-96.

[15] Arvidson K, Abdallah BM, Applegate LA, et al. Bone regeneration and stem cells. J Cell Mol Med 2011;15(4):718-746. Review.

[16] Valdés-Flores M, Casas-Avila L, Falcón-Ramírez E, Ponce-de-León-Suárez V. Genetic aspects of osteoporosis. Rev Invest Clin 2012;64(3):294-307.

[17] Ralston SH, de Crombrugghe B. Genetic regulation of bone mass and susceptibility to osteoporosis. Genes Dev 2006;15:20(18):2492-2506. Review

[18] Rivadeneira F, Styrkársdottir U, Estrada K, et al. Genetic Factors for Osteoporosis (GEFOS) Consortium. Twenty bone-mineral-density loci identified by large-scale meta-analysis of genome-wide association studies. Nat Genet 2009;41(11):1199-1206.

[19] Richards JB, Kavvoura FK, Rivadeneira F, et al. Genetic Factors for Osteoporosis Consortium. Collaborative meta-analysis: associations of 150 candidate genes with osteoporosis and osteoporotic fracture. Ann Intern Med 2009;20;151(8):528-537.

[20] Sadat-Ali M, Al-Turki HA. Genetic influence of candidate osteoporosis genes in saudi arabian population: a pilot study. J Osteoporos 2012; doi: 10.1155/2012/569145.

[21] Langdahl BL, Uitterlinden AG, Ralston SH, et al. APOSS investigators; DOPS investigators; EPOS investigators; EPOLOS investigators; FAMOS investigators; LASA investigators; ERGO investigators; GENOMOS Study. Large-scale analysis of association between polymorphisms in the transforming growth factor beta 1 gene (TGFB1) and osteoporosis: the GENOMOS study. Bone 2008;42(5):969-981.

[22] Ralston SH. Genetics of osteoporosis. Proc Nutr Soc 2007;66(2):158-65. Review.

[23] Albagha OM, Ralston SH. Genetics and osteoporosis. Rheum Dis Clin North Am 2006;32(4):659-680. Review.

[24] Magaña JJ, Gómez R, Cisneros B, et al. Association of the CT gene (CA) polymorphism with BMD in osteoporotic Mexican women. Clin Genet 2006;70(5):402-408.

[25] Gómez R, Magaña JJ, Cisneros B, et al. Association of the estrogen receptor alpha gene polymorphisms with osteoporosis in the Mexican population. Clin Genet 2007;72(6):574-581.

[26] Magaña JJ, Gómez R, Cisneros B, Casas L, Valdés-Flores M. Association of interleukin-6 gene polymorphisms with bone mineral density in Mexican women. Arch Med Res 2008;39(6):618-624.

[27] Wang JT, Guo Y, Yang TL, et al. Polymorphisms in the estrogen receptor genes are associated with hip fractures in Chinese. Bone 2008;43(5):910-914.

[28] Massart F, Marini F, Bianchi G, et al. Age-specific effects of estrogen receptors' polymorphisms on the bone traits in healthy fertile women: the BONTURNO study. Reprod Biol Endocrinol 2009;7:32.

[29] Lee YH, Woo JH, Choi SJ, Ji JD, Song GG. Associations between osteoprotegerin polymorphisms and bone mineral density: a meta-analysis. Mol Biol Rep 2010;37(1): 227-234.

[30] Seremak-Mrozikiewicz A, Tatuśko J, Drews K, et al. Polymorphism of osteoprotegerin gene and osteoporosis in postmenopausal women. Ginekol Pol 2009;80(5):354-360.

[31] Jones ET, Hensinger RN. Spinal deformity in idiopathic juvenile osteoporosis. Spine (Phila Pa 1976). 1981;6(1):1-4.

[32] Lorenc RS. Idiopathic juvenile osteoporosis. Calcif Tissue Int 2002;70(5):395-7. Review.

[33] Van Dijk FS, Pals G, Van Rijn RR, Nikkels PG, Cobben JM. Classification of Osteogenesis Imperfecta revisited. Eur J Med Genet 2010;53(1):1-5.

[34] Zhang ZL, Zhang H, Ke YH, et al. The identification of novel mutations in COL1A1, COL1A2, and LEPRE1 genes in Chinese patients with osteogenesis imperfecta. J Bone Miner Metab 2012;30(1):69-77.

[35] Pyott SM, Schwarze U, Christiansen HE, et al. Mutations in PPIB (cyclophilin B) delay type I procollagen chain association and result in perinatal lethal to moderate osteogenesis imperfecta phenotypes. Hum Mol Genet 2011;20(8):1595-1609.

[36] Meyer HJ. Atypical osteogenesis imperfecta: Lobstein's disease. Arch Pediat 1955;72(6):182-186.

[37] Brude E. Ocular osteogenesis imperfecta. (Letter) Clin Genet 1986;29(2):187.

[38] Beighton P, Winship I, Behari D. The ocular form of osteogenesis imperfecta: a new autosomal recessive syndrome. Clin Genet 1985;28(1):69-75.

[39] Frontali M, Stomeo C, Dallapiccola B. Osteoporosis-pseudoglioma syndrome: report of three affected sibs and an overview. Am J Med Genet 1985;22(1):35-47.

[40] Gong Y, Slee RB, Fukai N, et al. LDL receptor-related protein 5 (LRP5) affects bone accrual and eye development. Cell 2001;107(4):513-523.

[41] Gong Y, Vikkula M, Boon L, et al. Osteoporosis-pseudoglioma syndrome, a disorder affecting skeletal strength and vision, is assigned to chromosome region 11q12-13. Am J Hum Genet 1996;59(1):146-151.

[42] Gardner-Medwin D. The natural history of Duchenne muscular dystrophy. In: Wise G, Blaw M, Procopis PG, (eds.) Topics in Child Neurology. New York: Spectrum; 1983. p 17–29.

[43] Pareyson D, Marchesi C. Diagnosis, natural history, and management of Charcot-Marie-Tooth disease. Lancet Neurol 2009;8:654–667.

[44] Dubowitz V. Ramblings in the history of spinal muscular atrophy. Neuromuscul Disord 2009;19(1):69-73.

[45] Lee SJ, Lee DH, Yoo HW, Koo SK, Park ES, Park JW, Lim HG, Jung SC. Identification and functional analysis of cystathionine beta-synthase gene mutations in patients with homocystinuria. J Hum Genet 2005;50(12):648-654.

[46] Tyagi N, Kandel M, Munjal C, et al. Homocysteine mediated decrease in bone blood flow and remodeling: role of folic acid. J Orthop Res 2011;29(10):1511-1516.

[47] Cao A, Galanello R. Beta-thalassemia. Genet Med 2010;12(2):61-76.

[48] Chatterjee R, Katz M, Bajoria R. Use of hormone replacement therapy for correction of high turnover bone disease in hypogonadal β-Thalassemia major patients presenting with osteoporosis: comparison with idiopathic premature ovarian failure. Hemoglobin 2011;35(5-6):653-658.

[49] Javier RM, Hachulla E, Rose C, et al. Vertebral fractures in Gaucher disease type I: data from the French "Observatoire" on Gaucher disease (FROG). Osteoporos Int 2011;22(4):1255-1261.

[50] Wenstrup RJ, Roca-Espiau M, Weinreb NJ, Bembi B. Skeletal aspects of Gaucher disease: a review. Br J Radiol 2002;75(Suppl 1):A2-12.

[51] Germain DP, Benistan K, Boutouyrie P, Mutschler C. Osteopenia and osteoporosis: previously unrecognized manifestations of Fabry disease. Clin Genet 2005;68(1): 93-95.

[52] Mersebach H, Johansson JO, Rasmussen AK, et al. Osteopenia: a common aspect of Fabry disease. Predictors of bone mineral density. Genet Med 2007;9(12):812-818.

[53] Haworth CS, Selby PL, Webb AK, Adams JE. Osteoporosis in adults with cystic fibrosis. J R Soc Med. 1998;91 Suppl 34:14-18.

[54] Javier RM, Jacquot J. Bone disease in cystic fibrosis: what's new? Joint Bone Spine. 2011;78(5):445-450.

[55] Paccou J, Zeboulon N, Combescure C, Gossec L, Cortet B. The prevalence of osteoporosis, osteopenia, and fractures among adults with cystic fibrosis: a systematic literature review with meta-analysis. Calcif Tissue Int. 2010;86(1):1-7.

[56] Aris R, Lester G, Ontjes D. Treatment of bone disease in cystic fibrosis. Curr Opin Pulm Med. 2004;10(6):524-30.

[57] Pollex RL, Hegele RA. Hutchinson-Gilford progeria syndrome. Clin Genet 2004;66(5):375-381.

[58] Iglesias BP, Guijarro AG, Civantos MS, Vega PB, Pavón PI, Monereo MS. Complicated osteoporosis in progeroid syndrome: treatment with teriparatide. J Clin Densitom 2012;15(1):116-119.

[59] Laine CM, Koltin D, Susic M, et al. Primary osteoporosis without features of OI in children and adolescents: clinical and genetic characteristics. Am J Med Genet A 2012;158A(6):1252-1261.

[60] Wekre LL, Eriksen EF, Falch JA. Bone mass, bone markers and prevalence of fractures in adults with osteogenesis imperfecta. Arch Osteoporos 2011;6(1-2):31-38.

[61] Sakai H, Visser R, Ikegawa S, et al. Comprehensive genetic analysis of relevant four genes in 49 patients with Marfan syndrome or Marfan-related phenotypes. Am J Med Genet A 2006;140(16):1719-1725.

[62] Villamizar C, Regalado ES, Fadulu VT, et al. Paucity of skeletal manifestations in Hispanic families with FBN1 mutations. Eur J Med Genet 2010;53(2):80-84

[63] Stheneur C, Collod-Béroud G, Faivre L, et al. Identification of 23 TGFBR2 and 6 TGFBR1 gene mutations and genotype-phenotype investigations in 457 patients with Marfan syndrome type I and II, Loeys-Dietz syndrome and related disorders. Hum Mutat 2008;29(11):E284-E95.

[64] Kirmani S, Tebben PJ, Lteif AN, et al. Germline TGF-beta receptor mutations and skeletal fragility: a report on two patients with Loeys-Dietz syndrome. Am J Med Genet A 2010;152A(4):1016-1019.

[65] Ben Amor IM, Edouard T, Glorieux FH, et al. Low bone mass and high material bone density in two patients with Loeys-Dietz syndrome caused by transforming growth factor beta receptor 2 mutations. J Bone Miner Res 2012;27(3):713-718.

[66] Kiliç E, Alanay Y, Utine E, Ozgen-Mocan B, Robinson PN, Boduroğlu K. Arterial tortuosity and aneurysm in a case of Loeys-Dietz syndrome type IB with a mutation p.R537P in the TGFBR2 gene. Turk J Pediatr 2012;54(2):198-202.

[67] van de Laar IM, Oldenburg RA, Pals G, et al. Mutations in SMAD3 cause a syndromic form of aortic aneurysms and dissections with early-onset osteoarthritis. Nat Genet 2011;43(2):121-126.

[68] van de Laar IM, van der Linde D, Oei EH, et al. Phenotypic spectrum of the SMAD3-related aneurysms-osteoarthritis syndrome. J Med Genet 2012;49(1):47-57.

[69] Stanitski DF, Nadjarian R, Stanitski CL, Bawle E, Tsipouras P. Orthopaedic manifestations of Ehlers-Danlos syndrome. Clin Orthop Relat Res 2000;376:213-221.

[70] Mayer K, Kennerknecht I, Steinmann B. Clinical utility gene card for: Ehlers-Danlos syndrome types I-VII and variants - update 2012. Eur J Hum Genet 2012; doi: 10.1038/ejhg.2012.162.

[71] Myllyharju J, Kivirikko KI. Collagens and collagen-related diseases. Ann Med 2001;33(1):7-21.

[72] Duan Y, De Luca V, Seeman E. Parathyroid hormone deficiency and excess: similar effects on trabecular bone but differing effects on cortical bone. J Clin Endocrinol Metab 1999;84(2):718-722.

[73] Bastepe M. The GNAS locus and pseudohypoparathyroidism. Adv Exp Med Biol 2008;626:27-40.

[74] Thiele S, de Sanctis L, Werner R, et al. Functional characterization of GNAS mutations found in patients with pseudohypoparathyroidism type Ic defines a new subgroup of pseudohypoparathyroidism affecting selectively Gsα-receptor interaction. Hum Mutat 2011;32(6):653-660.

[75] de Nanclares GP, Fernández-Rebollo E, Santin I, et al. Epigenetic defects of GNAS in patients with pseudohypoparathyroidism and mild features of Albright's hereditary osteodystrophy. J Clin Endocrinol Metab 2007;92(6):2370-2373.

[76] Cao LH, Wang LB, Wang SS, Ma HW, Ji CY, Luo Y. Identification of novel and recurrent mutations in the calcium binding type III repeats of cartilage oligomeric matrix protein in patients with pseudoachondroplasia. Genet Mol Res 2011;10(2):955-963.

[77] Jackson GC, Mittaz-Crettol L, Taylor JA, et al. Pseudoachondroplasia and multiple epiphyseal dysplasia: a 7-year comprehensive analysis of the known disease genes identify novel and recurrent mutations and provides an accurate assessment of their relative contribution. Hum Mutat 2012;33(1):144-157.

[78] Sinnema M, Maaskant MA, van Schrojenstein Lantman-de Valk HM, et al. Physical health problems in adults with Prader-Willi syndrome. Am J Med Genet A 2011;155A(9):2112-2124.

[79] Vestergaard P, Kristensen K, Bruun JM, et al. Reduced bone mineral density and increased bone turnover in Prader-Willi syndrome compared with controls matched for sex and body mass index--a cross-sectional study. J Pediatr 2004;144(5):614-619.

[80] Isidor B, Lindenbaum P, Pichon O, et al. Truncating mutations in the last exon of NOTCH2 cause a rare skeletal disorder with osteoporosis. Nat Genet 2011;43(4): 306-308.

[81] Simpson MA, Irving MD, Asilmaz E, et al. Mutations in NOTCH2 cause Hajdu-Cheney syndrome, a disorder of severe and progressive bone loss. Nat Genet 2011;43(4): 303-305.

[82] Prié D, Beck L, Friedlander G, Silve C. Sodium-phosphate cotransporters, nephrolithiasis and bone demineralization. Curr Opin Nephrol Hypertens 2004;13(6):675-681.

[83] Scheinman SJ, Tenenhouse HS. Nephrolithiasis, osteoporosis, and mutations in the type 2a sodium-phosphate cotransporter. N Engl J Med 2003;348(3):264-265.

[84] Karim Z, Gérard B, Bakouh N, et al. NHERF1 mutations and responsiveness of renal parathyroid hormone. N Engl J Med 2008;359(11):1128-1135.

[85] Arrabal-Polo MA, Arrabal-Martin M, de Haro-Munoz T, et al. Mineral density and bone remodelling markers in patients with calcium lithiasis. BJU Int 2011;108(11): 1903-1908.

[86] Arrabal-Polo MA, Arrabal-Martin M, Girón-Prieto MS, et al. Osteopenia/osteoporosis in patients with calcium nephrolithiasis. Urol Res 2012; doi:10.1007/ s00240-012-0497-8.

[87] Norton N, Siegfried JD, Li D, Hershberger RE. Assessment of LMNA copy number variation in 58 probands with dilated cardiomyopathy. Clin Transl Sci 2011;4(5): 351-352.

[88] Sébillon P, Bouchier C, Bidot LD, et al. Expanding the phenotype of LMNA mutations in dilated cardiomyopathy and functional consequences of these mutations. J Med Genet 2003;40(8):560-567.

[89] Basel-Vanagaite L, Dokal I, Tamary H, et al. Expanding the clinical phenotype of autosomal dominant dyskeratosis congenita caused by TERT mutations. Haematologica 2008;93(6):943-934.

[90] Du HY, Pumbo E, Manley P, et al. Complex inheritance pattern of dyskeratosis congenita in two families with 2 different mutations in the telomerase reverse transcriptase gene. Blood 2008;111(3):1128-1130.

[91] Sasa GS, Ribes-Zamora A, Nelson ND, Bertuch AA. Three novel truncating TINF2 mutations causing severe dyskeratosis congenita in early childhood. Clin Genet 2012;81(5):470-478.

[92] Hofer AC, Tran RT, Aziz OZ, et al. Shared phenotypes among segmental progeroid syndromes suggest underlying pathways of aging. J Gerontol A Biol Sci Med Sci 2005;60(1):10-20.

[93] Groussin L, Jullian E, Perlemoine K, et al. Mutations of the PRKAR1A gene in Cushing's syndrome due to sporadic primary pigmented nodular adrenocortical disease. J Clin Endocrinol Metab 2002;87(9):4324-4329.

[94] Stratakis CA. New genes and/or molecular pathways associated with adrenal hyperplasias and related adrenocortical tumors. Mol Cell Endocrinol 2009;300(1-2):152-157.

[95] Horvath A, Boikos S, Giatzakis C, et al. A genome-wide scan identifies mutations in the gene encoding phosphodiesterase 11A4 (PDE11A) in individuals with adrenocortical hyperplasia. Nat Genet 2006;38(7):794-800.

[96] Carney JA, Gaillard RC, Bertherat J, Stratakis CA. Familial micronodular adrenocortical disease, Cushing syndrome, and mutations of the gene encoding phosphodiesterase 11A4 (PDE11A). Am J Surg Pathol 2010;34(4):547-555.

[97] Ihde LL, Forrester DM, Gottsegen CJ, et al. Sclerosing bone dysplasias: review and differentiation from other causes of osteosclerosis. Radiographics 2011;31(7): 1865-1882.

[98] van Egmond ME, Dikkers FG, Boot AM, van Lierop AH, Papapoulos SE, Brouwer OF. A rare cause of facial nerve palsy in children: Hyperostosis corticalis generalisata (Van Buchem disease). Three new pediatric cases and a literature review. Eur J Paediatr Neurol 2012; doi: 10.1016/j.ejpn.2012.03.002.

[99] Scopelliti D, Orsini R, Ventucci E, Carratelli D. Van Buchem disease. Maxillofacial changes, diagnostic classification and general principles of treatment. Minerva Stomatol 1999;48(5):227-234.

[100] van Wesenbeeck L, Cleiren E, Gram J, et al. Six novel missense mutations in the LDL receptor-related protein 5 (LRP5) gene in different conditions with an increased bone density. Am J Hum Genet 2003;72(3):763-771.

[101] Grodum E, Gram J, Brixen K, Bollerslev J. Autosomal dominant osteopetrosis: bone mineral measurements of the entire skeleton of adults in two different subtypes. Bone 1995;16(4):431-434.

[102] Bollerslev J, Nielsen HK, Larsen HF, Mosekilde L. Biochemical evidence of disturbed bone metabolism and calcium homeostasis in two types of autosomal dominant osteopetrosis. Acta Med Scand 1988;224(5):479-483.

[103] Bénichou O, Cleiren E, Gram J, Bollerslev J, de Vernejoul MC, Van Hul W. Mapping of autosomal dominant osteopetrosis type II (Albers-Schönberg disease) to chromosome 16p13.3. Am J Hum Genet 2001;69(3):647-654.

[104] Kantaputra PN, Thawanaphong S, Issarangporn W, et al. Long-term survival in infantile malignant autosomal recessive osteopetrosis secondary to homozygous p.Arg526Gln mutation in CLCN7. Am J Med Genet A 2012;158A(4):909-916.

[105] Lahera Vargas M, da Costa CV. Prevalence, etiology and clinical findings of Cushing's syndrome. Endocrinol Nutr 2009;56(1):32-39.

[106] Beauregard C, Dickstein G, Lacroix A. Classic and recent etiologies of Cushing's syndrome: diagnosis and therapy. Treat Endocrinol 2002;1(2):79-94.

[107] Heimall J, Freeman A, Holland SM. Pathogenesis of hyper IgE syndrome. Clin Rev Allergy Immunol 2010;38(1):32-38.

[108] Moneret-Vautrin DA, Kanny G, Thinus G. Hyperglobulinemia E syndrome with recurrent infections (Job's syndrome). Rev Med Interne 1999;20(2):133-140.

[109] Mani A, Radhakrishnan J, Wang H, et al. LRP6 mutation in a family with early coronary disease and metabolic risk factors. Science 2007;315(5816):1278-1282.

[110] van Meurs JB, Trikalinos TA, Ralston SH, et al. Large-scale analysis of association between LRP5 and LRP6 variants and osteoporosis. JAMA 2008;299(11):1277-1290.

[111] Ugwonali OF, Sarkissian H, Nercessian OA. Bilateral osteonecrosis of the femoral head associated with pregnancy: four new cases and a review of the literature. Orthopedics 2008;31(2):183.

[112] Zhao F, Li Z, Zhang N, et al. Differences between transient osteoporosis of the hip and bone marrow edema associated with osteonecrosis of the femoral head. Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi 2008;22(10):1157-1160.

[113] Boyden ED, Campos-Xavier AB, Kalamajski S, et al. Recurrent dominant mutations affecting two adjacent residues in the motor domain of the monomeric kinesin KIF22 result in skeletal dysplasia and joint laxity. Am J Hum Genet 2011;89(6):767-772. Erratum in: Am J Hum Genet 2012;90(1):170.

[114] Min BJ, Kim N, Chung T, et al. Whole-exome sequencing identifies mutations of KIF22 in spondyloepimetaphyseal dysplasia with joint laxity, leptodactylic type. Am J Hum Genet 2011;89(6):760-766.

[115] Dai J, Kim OH, Cho TJ, et al. Novel and recurrent TRPV4 mutations and their association with distinct phenotypes within the TRPV4 dysplasia family. J Med Genet 2010;47(10):704-709.

[116] Nishimura G, Dai J, Lausch E, et al. Spondylo-epiphyseal dysplasia, Maroteaux type (pseudo-Morquio syndrome type 2), and parastremmatic dysplasia are caused by TRPV4 mutations. Am J Med Genet A 2010;152A(6):1443-1449.

[117] Watanabe H, Hashimoto-Uoshima M, Goseki-Sone M, Orimo H, Ishikawa I. A novel point mutation (C571T) in the tissue-non-specific alkaline phosphatase gene in a case of adult-type hypophosphatasia. Oral Dis 2001;7(6):331-5.

[118] Sutton RA, Mumm S, Coburn SP, Ericson KL, Whyte MP. "Atypical femoral fractures" during bisphosphonate exposure in adult hypophosphatasia. J Bone Miner Res 2012;27(5):987-994.

[119] Wang GX, Sun RP, Song FL. A novel RUNX2 mutation (T420I) in Chinese patients with cleidocranial dysplasia. Genet Mol Res 2010;9(1):41-47.

[120] El-Gharbawy AH, Peeden JN Jr, Lachman RS, Graham JM Jr, Moore SR, Rimoin DL. Severe cleidocranial dysplasia and hypophosphatasia in a child with microdeletion of the C-terminal region of RUNX2. Am J Med Genet A 2010;152A(1):169-174.

[121] Shao C, Tian J, Shi DH, et al. A novel mutation in TPRS1 gene caused tricho-rhino-phalangeal syndrome in a Chinese patient with severe osteoporosis. Chin Med J (Engl) 2011;124(10):1583-1585.

[122] Gai Z, Gui T, Muragaki Y. The function of TRPS1 in the development and differentiation of bone, kidney, and hair follicles. Histol Histopathol 2011;26(7):915-921.

[123] Kitanaka S, Takeyama K, Murayama A, Kato S. The molecular bases of vitamin D-dependent rickets type I. Endocr J 2001;48(4):427-432.

[124] Portale AA, Miller WL. Human 25-hidroxyvitamin D-1alpha-hydroxilase: cloning, mutation and gene expression. Pediatr Nefrol 2000;14(7):620-625.

[125] Valenti L, Varenna M, Fracanzani AL, Rossi V, Fargion S, Sinigaglia L. Association between iron overload and osteoporosis in patients with hereditary hemochromatosis Osteoporos Int 2009;20(4):549–555.

[126] Nakchbandi IA, van der Merwe SW. Current understanding of osteoporosis associated with liver disease. Nat Rev Gastroenterol Hepatol 2009;6:660-670.

[127] Narumi S, Numakura C, Shiihara T, et al. Various types of LRP5 mutations in four patients with osteoporosis-pseudoglioma syndrome: identification of a 7.2-kb microdeletion using oligonucleotide tiling microarray. Am J Med Genet A 2010;152A(1): 133-140.

[128] Laine CM, Chung BD, Susic M, et al. Novel mutations affecting LRP5 splicing in patients with osteoporosis-pseudoglioma syndrome (OPPG). Eur J Hum Genet 2011;19(8):875-81.

[129] El Maghraoui A, Ghozlani I, Mounach A, et al. Homocysteine, folate, and vitamin b(12) levels and vertebral fracture risk in postmenopausal women. J Clin Densitom 2012;15(3):328-333.

[130] Bucciarelli P, Martini G, Martinelli I, et al. The relationship between plasma homocysteine levels and bone mineral density in post-menopausal women. Eur J Intern Med 2010;21(4):301-305.

[131] Takagi M, Ishii T, Barnes AM, et al. A novel mutation in LEPRE1 that eliminates only the KDEL ER- retrieval sequence causes non-lethal osteogenesis imperfecta. PLoS One 2012;7(5):e36809. doi: 10.1371/journal.pone.0036809.

[132] Willaert A, Malfait F, Symoens S, et al. Recessive osteogenesis imperfecta caused by LEPRE1 mutations: clinical documentation and identification of the splice form responsible for prolyl 3-hydroxylation. J Med Genet 2009;46(4):233-241.

[133] van Dijk FS, Nesbitt IM, Zwikstra EH, et al. PPIB mutations cause severe osteogenesis imperfecta. Am J Hum Genet 2009;85(4):521-527.

[134] Kraus JP, Spector E, Venezia S, et al. Mutation analysis in 54 propionic acidemia patients. J Inherit Metab Dis 2012;35(1):51-63.

[135] Pérez B, Angaroni C, Sánchez-Alcudia R, et al. The molecular landscape of propionic acidemia and methylmalonic aciduria in Latin America. J Inherit Metab Dis 2010;33(Suppl 2):S307-S314.

[136] Yen JL, Lin SP, Chen MR, Niu DM. Clinical features of Ehlers-Danlos syndrome. J Formos Med Assoc 2006;105(6):475-480.

[137] Uppal S, Diggle CP, Carr IM, et al. Mutations in 15-hydroxyprostaglandin dehydrogenase cause primary hypertrophic osteoarthropathy. Nat Genet. 2008;40(6):789-793. Erratum in: Nat Genet 2008;40(7):927.

[138] Shimizu C, Kubo M, Kijima Het al. A rare case of acromegaly associated with pachydermoperiostosis. J Endocrinol Invest 1999;22(5):386-389.

[139] Georgitsi M, Raitila A, Karhu A, et al. Molecular diagnosis of pituitary adenoma predisposition caused by aryl hydrocarbon receptor-interacting protein gene mutations. Proc Natl Acad Sci USA 2007;104(10):4101-4105.

[140] Minetto M, Reimondo G, Osella G, Ventura M, Angeli A, Terzolo M. Bone loss is more severe in primary adrenal than in pituitary-dependent Cushing's syndrome.Osteoporos Int 2004;15(11):855-861.

[141] Chong B, Hegde M, Fawkner M, et al. International Hyperphosphatasia Collaborative Group. Idiopathic hyperphosphatasia and TNFRSF11B mutations: relationships between phenotype and genotype. J Bone Miner Res 2003;18(12):2095-2104.

[142] Whyte MP, Singhellakis PN, Petersen MB, Davies M, Totty WG, Mumm S. Juvenile Paget's disease: the second reported, oldest patient is homozygous for the TNFRSF11B "Balkan" mutation (966_969delTGACinsCTT), which elevates circulating immunoreactive osteoprotegerin levels. J Bone Miner Res 2007;22(6):938-946.

[143] Yates CJ, Bartlett MJ, Ebeling PR. An atypical subtrochanteric femoral fracture from pycnodysostosis: a lesson from nature. J Bone Miner Res 2011;26(6):1377-1379.

[144] Toral-López J, González-Huerta LM, Sosa B, Orozco S, González HP, Cuevas-Covarrubias SA. Familial pycnodysostosis: identification of a novel mutation in the CTSK gene (cathepsin K). J Investig Med 2011;59(2):277-280.

[145] Hayashi YK, Matsuda C, Ogawa M, et al. Human PTRF mutations cause secondary deficiency of caveolins resulting in muscular dystrophy with generalized lipodystrophy. J Clin Invest 2009;119(9):2623-2633.

[146] Shastry S, Delgado MR, Dirik E, Turkmen M, Agarwal AK, Garg A. Congenital generalized lipodystrophy, type 4 (CGL4) associated with myopathy due to novel PTRF mutations. Am J Med Genet A 2010;152A(9):2245-2253.

[147] Desnick JP, Kim J, He X, Wasserstein MP, Simonaro CM, Schuchman EH. Identification and characterization of eight novel SMPD1 mutations causing types A and B Niemann-Pick disease. Mol Med 2010;16(7-8):316-321.

[148] Bachor E, Knop E, Karmody CS, Northrop C, Carranza A, Schuknecht HF. Temporal bone histopathology of Niemann-Pick disease type A. Am J Otolaryngol 1997;18(5): 349-362.

[149] Volders P, Van Hove J, Lories RJ, et al. Niemann-Pick disease type B: an unusual clinical presentation with multiple vertebral fractures. Am J Med Genet 2002;109(1): 42-51.

[150] Brunetti-Pierri N, Corso G, Rossi M, et al. Lathosterolosis, a novel multiple-malformation/mental retardation syndrome due to deficiency of 3beta-hydroxysteroid-delta5-desaturase. Am J Hum Genet 2002;71(4):952-958. Erratum in: Am J Hum Genet 2003;73(2):445.

[151] Rossi M, D'Armiento M, Parisi I, et al. Am J Med Genet A 2007;143A(20):2371-2381.

[152] Pajares S, Alcalde C, Couce ML, et al. Molecular analysis of mucopolysaccharidosis IVA (Morquio A) in Spain. Mol Genet Metab 2012;106(2):196-201.

[153] Tomatsu S, Montaño AM, Oikawa H, et al. Mucopolysaccharidosis type IVA (Morquio A disease): clinical review and current treatment. Curr Pharm Biotechnol 2011;12(6):931-945.

[154] Menkès CJ, Rondot P. Idiopathic osteonecrosis of femur in adult Morquio type B disease. J Rheumatol 2007;34(11):2314-2316.

[155] Krishnamurthy J, Dalal BS, Sunila, Gubanna MV. Juvenile hyaline fibromatosis. Indian J Dermatol. 2011;56(6):731-3.

[156] El-Kamah GY, Fong K, El-Ruby M, et al. Spectrum of mutations in the ANTXR2 (CMG2) gene in infantile systemic hyalinosis and juvenile hyaline fibromatosis. Br J Dermatol. 2010;163(1):213-215.

[157] Oz OK, Zerwekh JE, Fisher C, et al. Bone has a sexually dimorphic response to aromatase deficiency. J Bone Miner Res 2000;15(3):507-514.

[158] Vandenput L, Ohlsson C. Estrogens as regulators of bone health in men. Nat Rev Endocrinol 2009;5:437-443.

[159] Dwyer E, Hyland J, Modaff P, Pauli RM. Genotype-phenotype correlation in DTDST dysplasias: Atelosteogenesis type II and diastrophic dysplasia variant in one family. Am J Med Genet A 2010;152A(12):3043-3050.

[160] Forlino A, Piazza R, Tiveron C, et al. A diastrophic dysplasia sulfate transporter (SLC26A2) mutant mouse: morphological and biochemical characterization of the resulting chondrodysplasia phenotype. Hum Mol Genet 2005;14(6):859-871.

[161] Faivre L, Cormier-Daire V, Young I, et al. Long-term outcome in Desbuquois dysplasia: a follow-up in four adult patients. Am J Med Genet A 2004;124A(1):54-59.

[162] Faden M, Al-Zahrani F, Arafah D, Alkuraya FS. Mutation of CANT1 causes Desbuquois dysplasia. Am J Med Genet A 2010;152A(5):1157-1160.

[163] Mosig RA, Dowling O, DiFeo A, et al. Loss of MMP-2 disrupts skeletal and craniofacial development and results in decreased bone mineralization, joint erosion and defects in osteoblast and osteoclast growth. Hum Mol Genet 2007;16(9):1113-1123.

[164] Zankl A, Bonafé L, Calcaterra V, Di Rocco M, Superti-Furga A. Winchester syndrome caused by a homozygous mutation affecting the active site of matrix metalloproteinase 2. Clin Genet 2005;67(3):261-266.

[165] Newman WG, Clayton-Smith J, Metcalfe K, et al. Geroderma osteodysplastica maps to a 4 Mb locus on chromosome 1q24. Am J Med Genet A 2008;146A(23):3034-3037.

[166] Yildirim Y, Tolun A, Tüysüz B. The phenotype caused by PYCR1 mutations corresponds to geroderma osteodysplasticum rather than autosomal recessive cutis laxa type 2. Am J Med Genet A 2011;155A(1):134-140.

[167] Sebastio G, Sperandeo MP, Andria G. Lysinuric protein intolerance: reviewing concepts on a multisystem disease. Am J Med Genet C Semin Med Genet 2011;157(1): 54-62.

[168] Gömez L, García-Cazorla A, Gutiérrez A, et al. Treatment of severe osteoporosis with alendronate in a patient with lysinuric protein intolerance. J Inherit Metab Dis 2006;29(5):687.

[169] Briggs TA, Abdel-Salam GM, Balicki M, et al. Cerebroretinal microangiopathy with calcifications and cysts (CRMCC). Am J Med Genet A 2008;146A(2):182-190.

[170] Toiviainen-Salo S, Linnankivi T, Saarinen A, Mäyränpää MK, Karikoski R, Mäkitie O. Cerebroretinal microangiopathy with calcifications and cysts: characterization of the skeletal phenotype. Am J Med Genet A 2011;155A(6):1322-1328.

[171] Jiao X, Ventruto V, Trese MT, Shastry BS, Hejtmancik JF. Autosomal recessive familial exudative vitreoretinopathy is associated with mutations in LRP5. Am J Hum Genet 2004;75(5):878-884.

[172] Qin M, Hayashi H, Oshima K, Tahira T, Hayashi K, Kondo H. Complexity of the genotype-phenotype correlation in familial exudative vitreoretinopathy with mutations in the LRP5 and/or FZD4 genes. Hum Mutat 2005;26(2):104-112.

[173] Cabanillas R, Cadiñanos J, Villameytide JA, et al. Néstor-Guillermo progeria syndrome: a novel premature aging condition with early onset and chronic development caused by BANF1 mutations. Am J Med Genet A 2011;155A(11):2617-2625.

[174] Osorio FG, Ugalde AP, Mariño G, Puente XS, Freije JM, López-Otín C. Cell autonomous and systemic factors in progeria development. Biochem Soc Trans 2011;39(6): 1710-1714.

[175] Walne AJ, Vulliamy T, Marrone A, et al. Genetic heterogeneity in autosomal recessive dyskeratosis congenita with one subtype due to mutations in the telomerase-associated protein NOP10. Hum Mol Genet 2007;16(13):1619-1629.

[176] Vulliamy TJ, Dokal I. Dyskeratosis congenita: the diverse clinical presentation of mutations in the telomerase complex. Biochimie 2008;90(1):122-130.

[177] Basel-Vanagaite L, Sarig O, Hershkovitz D, et al. RIN2 deficiency results in macrocephaly, alopecia, cutis laxa, and scoliosis: MACS syndrome. Am J Hum Genet 2009;85(2):254-263.

[178] Syx D, Malfait F, Van Laer L, et al. The RIN2 syndrome: a new autosomal recessive connective tissue disorder caused by deficiency of Ras and Rab interactor 2 (RIN2). Hum Genet 2010;128(1):79-88.

[179] Sinibaldi L, Harifi G, Bottillo I, et al. A novel homozygous splice site mutation in the HPGD gene caused mild primary Hypertrophic osteoarthropathy. Clin Exp Rheumatol 2010;28(2):153-157.

[180] Sajnani AK, Yiu CK, King NM. Larsen syndrome: a review of the literature and case report. Spec Care Dentist 2010;30(6):255-260.

[181] Knoblauch H, Urban M, Tinschert S. Autosomal recessive versus autosomal dominant inheritance in Larsen syndrome: report of two affected sisters. Genet Couns 1999;10(3):315-320.

[182] Lindvall LE, Kormeili T, Chen E, et al. Infantile systemic hyalinosis: Case report and review of the literature. J Am Acad Dermatol 2008;58(2):303-307.

[183] Dowling O, Difeo A, Ramirez MC, et al. Mutations in capillary morphogenesis gene-2 result in the allelic disorders juvenile hyaline fibromatosis and infantile systemic hyalinosis. Am J Hum Genet 2003;73(4):957-966.

[184] Lussiana C, Guani B, Mari C, Restagno G, Massobrio M, Revelli A. Mutations and polymorphisms of the FSH receptor (FSHR) gene: clinical implications in female fecundity and molecular biology of FSHR protein and gene. Obstet Gynecol Surv 2008;63(12):785-795.

[185] Doherty E, Pakarinen P, Tiitinen A, Kiilavuori A, Huhtaniemi I, Forrest S, Aittomäki K. A Novel mutation in the FSH receptor inhibiting signal transduction and causing primary ovarian failure. J Clin Endocrinol Metab 2002;87(3):1151-1155.

[186] Delépine M, Nicolino M, Barrett T, Golamaully M, Lathrop GM, Julier C. EIF2AK3, encoding translation initiation factor 2-alpha kinase 3, is mutated in patients with Wolcott-Rallison syndrome. Nat Genet 2000;25(4):406-409.

[187] Liu J, Hoppman N, O'Connell JR, Wang H, Streeten EA, McLenithan JC, Mitchell BD, Shuldiner AR. A functional haplotype in EIF2AK3, an ER stress sensor, is associated with lower bone mineral density. J Bone Miner Res 2012;27(2):331-341.

[188] Jaakkola E, Mustonen A, Olsen P, et al. ERCC6 founder mutation identified in Finnish patients with COFS syndrome. Clin Genet. 2010;78(6):541-547.

[189] Natale V. A comprehensive description of the severity groups in Cockayne syndrome. Am J Med Genet A 2011;155A(5):1081-1095.

[190] Selimoglu MA, Ertekin V, Doneray H, Yildirim M. Bone mineral density of children with Wilson disease: efficacy of penicillamine and zinc therapy. J Clin Gastroenterol 2008;42(2):194-198.

[191] Hegedus D, Ferencz V, Lakatos PL, et al. Decreased bone density, elevated serum osteoprotegerin, and beta-cross-laps in Wilson disease. J Bone Miner Res 2002;17(11): 1961-1967.

[192] Ogata N, Shiraki M, Hosoi T, Koshizuka Y, Nakamura K, Kawaguchi H. A polymorphic variant at the Werner helicase (WRN) gene is associated with bone density, but not spondylosis, in postmenopausal women. J Bone Miner Metab 2001;19(5):296-301.

[193] Uhrhammer NA, Lafarge L, Dos Santos L, et al. Werner syndrome and mutations of the WRN and LMNA genes in France. Hum Mutat 2006;27(7):718-719.

[194] Mohaghegh P, Hickson ID. Premature aging in RecQ helicase-deficient human syndromes. Int J Biochem Cell Biol 2002;34(11):1496-1501.

[195] Mehollin-Ray AR, Kozinetz CA, Schlesinger AE, Guillerman RP, Wang LL. Radiographic abnormalities in Rothmund-Thomson syndrome and genotype-phenotype correlation with RECQL4 mutation status. AJR Am J Roentgenol 2008;191(2):W62-W66.

[196] Stum M, Davoine CS, Vicart S, et al. Spectrum of HSPG2 (Perlecan) mutations in patients with Schwartz-Jampel syndrome. Hum Mutat 2006;27(11):1082-1091.

[197] Mallineni SK, Yiu CK, King NM. Schwartz-Jampel syndrome: a review of the literature and case report. Spec Care Dentist 2012;32(3):105-111.

[198] Pierce SB, Walsh T, Chisholm KM, et al. Mutations in the DBP-deficiency protein HSD17B4 cause ovarian dysgenesis, hearing loss, and ataxia of Perrault Syndrome. Am J Hum Genet 2010;87(2):282-288.

[199] Jenkinson EM, Clayton-Smith J, et al. Perrault syndrome: further evidence for genetic heterogeneity. J Neurol 2012;259(5):974-976.

[200] Cabrera-Abreu J, Crabtree NJ, Elias E, Fraser W, Cramb R, Alger S. Bone mineral density and markers of bone turnover in patients with glycogen storage disease types I, III and IX. J Inherit Metab Dis 2004;27(1):1-9.

[201] Lee PJ, Patel JS, Fewtrell M, Leonard JV, Bishop NJ. Bone mineralisation in type 1 glycogen storage disease. Eur J Pediatr 1995;154(6):483-487.

[202] Zaffanello M, Diomedi-Camassei F, Melzi ML, Torre G, Callea F, Emma F. Sensenbrenner syndrome: a new member of the hepatorenal fibrocystic family. Am J Med Genet A 2006;140(21):2336-2340.

[203] Walczak-Sztulpa J, Eggenschwiler J, Osborn D, et al. Cranioectodermal Dysplasia, Sensenbrenner syndrome, is a ciliopathy caused by mutations in the IFT122 gene. Am J Hum Genet 2010;86(6):949-956.

[204] Gallus GN, Dotti MT, Mignarri A, et al. Four novel CYP27A1 mutations in seven Italian patients with CTX. Eur J Neurol 2010;17(10):1259-1262.

[205] Keren Z, Falik-Zaccai TC. Cerebrotendinous xanthomatosis (CTX): a treatable lipid storage disease. Pediatr Endocrinol Rev 2009;7(1):6-11.

[206] Dalal A, Bhavani G SL, Togarrati et al. Analysis of the WISP3 gene in Indian families with progressive pseudorheumatoid dysplasia. Am J Med Genet A 2012; doi:10.1002/ajmg.a.35620.

[207] Delague V, Chouery E, Corbani S, et al. Molecular study of WISP3 in nine families originating from the Middle-East and presenting with progressive pseudorheumatoid dysplasia: identification of two novel mutations, and description of a founder effect. Am J Med Genet A. 2005;138A(2):118-126.

[208] Penttinen M, Koillinen H, Niinikoski H, Mäkitie O, Hietala M. Genitopatellar syndrome in an adolescent female with severe osteoporosis and endocrine abnormalities. Am J Med Genet A 2009;149A(3):451-455.

[209] Campeau PM, Kim JC, Lu JT, et al. Mutations in KAT6B, encoding a histone acetyltransferase, cause Genitopatellar syndrome. Am J Hum Genet. 2012;90(2):282-289.

[210] Foulquier F, Amyere M, Jaeken J, et al. TMEM165 deficiency causes a congenital disorder of glycosylation. Am J Hum Genet 2012;91(1):15-26.

[211] Woods AG, Woods CW, Snow TM. Congenital disorders of glycosylation. Adv Neonatal Care 2012;12(2):90-95.

[212] Noordam C, Funke S, Knoers NV, et al. Decreased bone density and treatment in patients with autosomal recessive cutis laxa. Acta Paediatr 2009;98(3):490-494.

[213] Callewaert B, Su CT, Van Damme T, et al. Comprehensive clinical and molecular analysis of 12 families with type 1 recessive cutis laxa. Hum Mutat 2012; doi: 10.1002/humu.22165.

[214] Reversade B, Escande-Beillard N, Dimopoulou A, et al. Mutations in PYCR1 cause cutis laxa with progeroid features. Nat Genet 2009;41(9):1016-1021.

[215] Lin DS, Yeung CY, Liu HL, et al. A novel mutation in PYCR1 causes an autosomal recessive cutis laxa with premature aging features in a family. Am J Med Genet A. 2011;155A(6):1285-1289.

[216] Rodríguez-Pascau, L., Gort, L., Schuchman, et al. Identification and characterization of SMPD1 mutations causing Niemann-Pick types A and B in Spanish patients. Hum. Mutat 2009;30:1117–1122.

[217] Lambert WC, Gagna CE, Lambert MW. Trichothiodystrophy: Photosensitive, TTD-P, TTD, Tay syndrome. Adv Exp Med Biol 2010;685:106-110.

[218] Hashimoto S, Egly JM. Trichothiodystrophy view from the molecular basis of DNA repair/transcription factor TFIIH. Hum Mol Genet 2009;18(R2):R224-R230.

[219] Fukutake T. Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL): from discovery to gene identification. J Stroke Cerebrovasc Dis 2011 Mar-Apr;20(2):85-93.

[220] Hara K, Shiga A, Fukutake T, et al. Association of HTRA1 mutations and familial ischemic cerebral small-vessel disease. N Engl J Med 2009;360(17):1729-1739.

[221] Giordano N, Senesi M, Battisti E, Mattii G, Gennari C. Weill-Marchesani syndrome: report of an unusual case. Calcif Tissue Int 1997;60(4):358-360.

[222] Dagoneau N, Benoist-Lasselin C, Huber C, et al. ADAMTS10 mutations in autosomal recessive Weill-Marchesani syndrome. Am J Hum Genet 2004;75(5):801-806.

[223] Eshed V, Benbassat CA, Laron Z. Effect of alendronate on bone mineral density in adult patients with Laron syndrome (primary growth hormone insensitivity).Growth Horm IGF Res 2006;16(2):119-124.

[224] Benbassat CA, Eshed V, Kamjin M, Laron Z. Are adult patients with Laron syndrome osteopenic? A comparison between dual-energy X-ray absorptiometry and volumetric bone densities. J Clin Endocrinol Metab 2003;88(10):4586-4589.

[225] Agarwal AK, Kazachkova I, Ten S, Garg A. Severe mandibuloacral dysplasia-associated lipodystrophy and progeria in a young girl with a novel homozygous Arg527Cys LMNA mutation. J Clin Endocrinol Metab 2008;93(12):4617-4623.

[226] Kosho T, Takahashi J, Momose T, et al. Mandibuloacral dysplasia and a novel LMNA mutation in a woman with severe progressive skeletal changes. Am J Med Genet A 2007;143A(21):2598-2603.

[227] Cranenburg EC, VAN Spaendonck-Zwarts KY, Bonafe L, et al. Circulating matrix γ-carboxyglutamate protein (MGP) species are refractory to vitamin K treatment in a new case of Keutel syndrome. J Thromb Haemost 2011;9(6):1225-1235.

[228] Cranenburg EC, Schurgers LJ, Vermeer C. Vitamin K: the coagulation vitamin that became omnipotent. Thromb Haemost 2007;98(1):120-125.

[229] Goseki-Sone M, Sogabe N, Fukushi-Irie M, et al. Functional analysis of the single nucleotide polymorphism (787T>C) in the tissue-nonspecific alkaline phosphatase gene associated with BMD. J Bone Miner Res 2005;20(5):773-782.

[230] Girschick HJ, Schneider P, Kruse K, Huppertz HI. Bone metabolism and bone mineral density in childhood hypophosphatasia. Bone 1999;25(3):361-367.

[231] Grünert SC, Schwab KO, Pohl M, Sass JO, Santer R. Fanconi-Bickel syndrome: GLUT2 mutations associated with a mild phenotype. Mol Genet Metab 2012;105(3): 433-437.

[232] Pena L, Charrow J. Fanconi-Bickel syndrome: Report of life history and successful pregnancy in an affected patient. Am J Med Genet A 2011; 155(2):415-417.

[233] Obermayer-Pietsch BM, Gugatschka M, Reitter S, et al. Adult-type hypolactasia and calcium availability: decreased calcium intake or impaired calcium absorption? Osteoporos Int 2007;18(4):445-451.

[234] Honkanen R, Pulkkinen P, Järvinen R, et al. Does lactose intolerance predispose to low bone density? A population-based study of perimenopausal Finnish women. Bone 1996;19(1):23-28.

[235] Hartley JL, Zachos NC, Dawood B, et al. Mutations in TTC37 cause trichohepatoenteric syndrome (phenotypic diarrhea of infancy). Gastroenterology 2010;138(7): 2388-2398, 2398.e1-2.

[236] Fabre A, Martinez-Vinson C, Roquelaure B, et al. Novel mutations in TTC37 associated with tricho-hepato-enteric syndrome. Hum Mutat 2011;32(3):277-281.

[237] Digilio MC, Sarkozy A, Capolino R, et al. Costello syndrome: clinical diagnosis in the first year of life. Eur J Pediatr 2008;167(6):621-628.

[238] White SM, Graham JM Jr, Kerr B, et al. The adult phenotype in Costello syndrome. Am J Med Genet A 2005;136(2):128-135. Erratum in: Am J Med Genet A 2005;139(1): 55.

[239] Bachelot A, Chakhtoura Z, Samara-Boustani D, Dulon J, Touraine P, Polak M. Bone health should be an important concern in the care of patients affected by 21 hydroxylase deficiency. Int J Pediatr Endocrinol 2010;2010: 326275.

[240] Arlt W, Willis DS, Wild SH, et al. United Kingdom Congenital Adrenal Hyperplasia Adult Study Executive (CaHASE). Health status of adults with congenital adrenal hyperplasia: a cohort study of 203 patients. J Clin Endocrinol Metab 2010;95(11): 5110-5121.

[241] Francis F, Hennig S, Korn B, et al. A gene (PEX) with homologies to endopeptidases is mutated in patients with X–linked hypophosphatemic rickets. Nature Genet 1995;11(2):130-136.

[242] Sato K, Tajima T, Nakae J, et al. Three novel PHEX gene mutations in Japanese patients with X-linked hypophosphatemic rickets. Pediatr Res 2000;48(4):536-40.

[243] Boehmer AL, Brinkmann O, Brüggenwirth H, et al. Genotype versus phenotype in families with androgen insensitivity syndrome. J Clin Endocrinol Metab 2001;86(9): 4151-4160. Erratum in: J Clin Endocrinol Metab 2002;87(7):3109.

[244] Melo KF, Mendonca BB, Billerbeck AE, et al. Clinical, hormonal, behavioral, and genetic characteristics of androgen insensitivity syndrome in a brazilian cohort: five novel mutations in the androgen receptor gene. J Clin Endocrinol Metab 2003;88:3241-3250.

[245] D'Hulst C, Kooy RF. Fragile X syndrome: from molecular genetics to therapy. J Med Genet 2009;46(9):577-584.

[246] Hjalgrim H, Fisher Hansen B, Brondum-Nielsen K, Nolting D, Kjaer I. Aspects of skeletal development in fragile X syndrome fetuses. Am J Med Genet 2000;95(2): 123-129.

[247] Bazzocchi A, Femia R, Feraco P, Battista G, Canini R, Guglielmi G. Occipital horn syndrome in a woman: skeletal radiological findings. Skeletal Radiol 2011;40(11): 1491-1494.

[248] Dagenais SL, Adam AN, Innis JW, Glover TW. A novel frameshift mutation in exon 23 of ATP7A (MNK) results in occipital horn syndrome and not in Menkes disease. Am J Hum Genet 2001;69(2):420-427.

[249] Gérard-Blanluet M, Birk-Møller L, Caubel I, Gélot A, Billette de Villemeur T, Horn N. Early development of occipital horns in a classical Menkes patient. Am J Med Genet A 2004;130A(2):211-213. Review. Erratum in: Am J Med Genet A 2005;134(3):346.

[250] Kanumakala S, Boneh A, Zacharin M. Pamidronate treatment improves bone mineral density in children with Menkes disease. J Inherit Metab Dis 2002;25(5):391-398.

[251] Mason PJ, Bessler M. The genetics of dyskeratosis congenita. Cancer Genet 2011;204(12):635-645.

[252] Heiss NS, Knight SW, Vulliamy TJ, et al. X-linked dyskeratosis congenita is caused by mutations in a highly conserved gene with putative nucleolar functions. Nat Genet 1998;19(1):32-38.

[253] Scherleue A, Greenberg F, McCabe ERB. Dysmorphic features in patients with glycerol-kinase deficiency. J Pediatr 1995;126:764-767.

[254] Walker AP, Muscatelli F, Stafford AN, et al. Mutations and phenotype in isolated glycerol kinase deficiency. Am J Hum Genet 1996;58(6):1205-1211.

[255] Goswami D, Conway GS. Premature ovarian failure. Horm Res 2007;68(4):196-202.

[256] Persani L, Rossetti R, Cacciatore C. Genes involved in human premature ovarian failure. J Mol Endocrinol 2010;45(5):257-79. Review. Erratum in: J Mol Endocrinol 2010;45(6):405.

[257] Brunetti-Pierri N, Lachman R, Lee K, et al. Terminal osseous dysplasia with pigmentary defects (TODPD): Follow-up of the first reported family, characterization of the radiological phenotype, and refinement of the linkage region. Am J Med Genet A 2010;152A(7):1825-1831.

[258] Sun Y, Almomani R, Aten E, et al. Terminal osseous dysplasia is caused by a single recurrent mutation in the FLNA gene. Am J Hum Genet 2010;87(1):146-153.

[259] Hsu LY. Phenotype/karyotype correlations of Y chromosome aneuploidy with emphasis on structural aberrations in postnatally diagnosed cases. Am J Med Genet 1994; 53:108-40.

[260] Tuck-Muller CM, Chen H, Martinez JE, et al. Isodicentric Y chromosome: cytogenetic, molecular and clinical studies and review of the literature. Hum Genet 1995;96:119-29.

[261] Ksglaede L, Petersen JH, Main KM, Skakkebaek NE, Juul A. High normal Testosterone levels in infants with non-mosaic Klinefelter's syndrome. Eur J Endocrinol 2007;157:345-350.

[262] Corona G, Petrone L, Paggi F, et al. Sexual dysfunction in subjects with Klinefelter's syndrome. Int J Androl 2009a;32:1-8.

[263] Khosla S, Oursler MJ, Monroe DG. Estrogen and the skeleton. Trends Endocrinol Metab 2012;23(11):576-581.

[264] Delhon I, Gutzwiller S, Morvan F, et al. Absence of estrogen receptor-related-alpha increases osteoblastic differentiation and cancellous bone mineral density. Endocrinology 2009;150(10):4463-4472.

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