Osteoporos Int (2015) 26:2529–2558
DOI 10.1007/s00198-015-3188-9

ORIGINAL ARTICLE

Taxonomy of rare genetic metabolic bone disorders

L. Masi[1] · D. Agnusdei[2] · J. Bilezikian[3] · D. Chappard[4] · R. Chapurlat[5] · L. Cianferotti[1] · J.-P. Devolgelaer[6] · A. El Maghraoui[7] · S. Ferrari[8] · M. K. Javaid[9] · J.-M. Kaufman[10] · U. A. Liberman[11] · G. Lyritis[12] · P. Miller[13] · N. Napoli[14] · E. Roldan[15] · S. Papapoulos[16] · N. B. Watts[17] · M. L. Brandi[1]

Received: 10 October 2014 / Accepted: 26 May 2015 / Published online: 13 June 2015

Abstract

Summary This article reports a taxonomic classification of rare skeletal diseases based on metabolic phenotypes. It was prepared by The Skeletal Rare Diseases Working Group of the International Osteoporosis Foundation (IOF) and includes 116 OMIM phenotypes with 86 affected genes.

Introduction Rare skeletal metabolic diseases comprise a group of diseases commonly associated with severe clinical consequences. In recent years, the description of the clinical phenotypes and radiographic features of several genetic bone disorders was paralleled by the discovery of key molecular pathways involved in the regulation of bone and mineral metabolism. Including this information in the description and classification of rare skeletal diseases may improve the recognition and management of affected patients.

Electronic supplementary material The online version of this article (doi:10.1007/s00198-015-3188-9) contains supplementary material, which is available to authorized users.

✉ M. L. Brandi
marialuisa.brandi@unifi.it

[1] Metabolic Bone Diseases Unit, Department of Surgery and Translational Medicine, University Hospital of Florence, University of Florence, Florence, Italy

[2] Eli Lilly and Co., Florence, Italy

[3] College of Physicians and Surgeons, Columbia University, New York, NY, USA

[4] GEROM Groupe Etudes Remodelage Osseux et bioMatériaux-LHEA, IRIS-IBS Institut de Biologie en Santé, LUNAM Université, Angers, France

[5] INSERM UMR 1033, Department of Rheumatology, Université de Lyon, Hospices Civils de Lyon, Lyon, France

[6] Departement de Medicine Interne, Cliniques Universitaires UCL de Saint Luc, Brussels, Belgium

[7] Service de Rhumatologie, Hôpital Militaire Mohammed V, Rabbat, Morocco

[8] Division of Bone Diseases, Faculty of Medicine, Geneva University Hospital, Geneva, Switzerland

[9] Oxford NIHR Musculoskeletal Biomedical Research Unit, University of Oxford, Oxford, UK

[10] Department of Endocrinology, Ghent University Hospital, Gent, Belgium

[11] Department of Physiology and Pharmacology and the Felsenstein Medical Research Center, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

[12] Laboratory for the Research of Musculoskeletal System, University of Athens, Athens, Greece

[13] Colorado Center for Bone Research, University of Colorado Health Sciences Center, Lakewood, CO, USA

[14] Division of Endocrinology and Diabetes, Università Campus Bio-Medico di Roma, Rome, Italy

[15] Department of Clinical Pharmacology, Gador SA, Buenos Aires, Argentina

[16] Center for Bone Quality, Leiden University Medical Center, Leiden, The Netherlands

[17] Mercy Health Osteoporosis and Bone Health Services, Cincinnati, OH, USA

Methods IOF recognized this need and formed a Skeletal Rare Diseases Working Group (SRD-WG) of basic and clinical scientists who developed a taxonomy of rare skeletal diseases based on their metabolic pathogenesis.
Results This taxonomy of rare genetic metabolic bone disorders (RGMBDs) comprises 116 OMIM phenotypes, with 86 affected genes related to bone and mineral homeostasis. The diseases were divided into four major groups, namely, disorders due to altered osteoclast, osteoblast, or osteocyte activity; disorders due to altered bone matrix proteins; disorders due to altered bone microenvironmental regulators; and disorders due to deranged calciotropic hormonal activity.
Conclusions This article provides the first comprehensive taxonomy of rare metabolic skeletal diseases based on deranged metabolic activity. This classification will help in the development of common and shared diagnostic and therapeutic pathways for these patients and also in the creation of international registries of rare skeletal diseases, the first step for the development of genetic tests based on next generation sequencing and for performing large intervention trials to assess efficacy of orphan drugs.

Keywords Bone metabolism · Genetic bone diseases · Metabolic bone diseases · Rare bone diseases · Taxonomy

Introduction

A disease or disorder is defined as rare or "orphan" when it affects less than 5 in 10,000 individuals or has a prevalence of <7.5/100,000 [1–3]. More than 6000 rare disorders have been described affecting approximately 30 million individuals in the USA and 27–36 million in the EU [1, 4–6; http://www.fda.gov/; http://ec.europa.eu/research/fp7/index_en.cfm; http://www.ema.europa.eu/pdfs/human/comp/29007207en.pdf), with almost half affecting children [7]. Many of these conditions are complex, severe, degenerative, and chronically debilitating [1, 7], and there is a need for recognition, diagnosis, and treatment of affected individuals. Due to the rarity of these disorders, international cooperation and coordination of research and funding are essential [7–18].

Genetic disorders involving primarily the skeletal system represent a considerable portion of the recognized rare diseases, and more than 400 different forms of skeletal dysplasia have been described [19]. Accumulating evidence of the clinical and genetic heterogeneity of skeletal disorders has led to different classifications of these disorders based on their clinical and radiological features and, subsequently, their molecular and embryological features [20–24]. In 2011, Warman et al. [25] proposed a classification of rare skeletal disorders based on four criteria: (1) significant skeletal involvement, corresponding to the definition of skeletal dysplasia, metabolic bone disorders, dysostoses, and skeletal malformation and/or reduction syndromes; (2) publication and/or listing in MIM (meaning that observations should not find their way into the nosology before they achieve peer-reviewed publication status); (3) genetic basis proven by pedigree or very likely based on homogeneity of phenotype in unrelated families; and (4) nosology au-

USA-based reference websites for rare diseases

- National Center for Biotechnology Information, Online Mendelian Inheritance in Men and GeneReviews databases: http://www.ncbi.nlm.nih.gov , http://www.ncbi.nlm.nih.gov/omim and http://www.ncbi.nlm.nih.gov/books/NBK1116/
- *Genetic and Rare Diseases Information Center (GARD) by National Institutes of Health: http://rarediseases.info.nih.gov/gard/browse-by-first-letter/a*
- Rare Disease Database by the National Organization for Rare Disorders (NORD, https://www.rarediseases.org/rare-disease-information/rare-diseases
- OMIM, www.omim.org

Europe-based reference websites for rare diseases

- Orphanet, European database dedicated to information on rare diseases and orphan drugs: www.orpha.net
- Swedish rare disease database: http://www.socialstyrelsen.se/rarediseases

Fig. 1 Main English websites on rare diseases with constantly updated databases (as most recently accessed in January 2015)

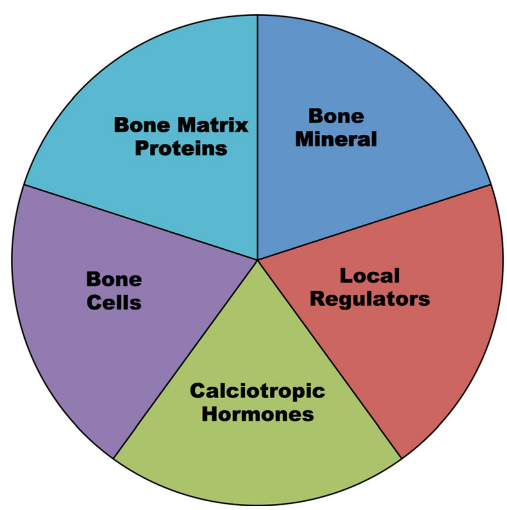


Fig. 2 The bone metabolic machinery

tonomy confirmed by molecular or linkage analysis and/ or by the presence of distinctive diagnostic features and of observation in multiple individuals or families. Using these criteria, the authors identified 456 different conditions which they classified in 40 groups. Of these conditions, 316 were associated with one or more of 226 different gene defects [25, 26]. Nowadays, several websites, mainly focusing on genetics, are available (Fig. 1) and can be used as reference once a rare disease is identified.

Bones are formed during embryonic development through two major mechanisms: endochondral and intramembranous ossification. This process, called modeling, begins in utero and continues throughout adolescence until skeletal maturity. Following skeletal maturity, bone continues to be broken down and rebuilt (remodeling) throughout life and adapts its material to the mechanical demands. Remodeling has the function of the control of mineral homeostasis and of maintaining the biomechanical competence of the skeleton. The

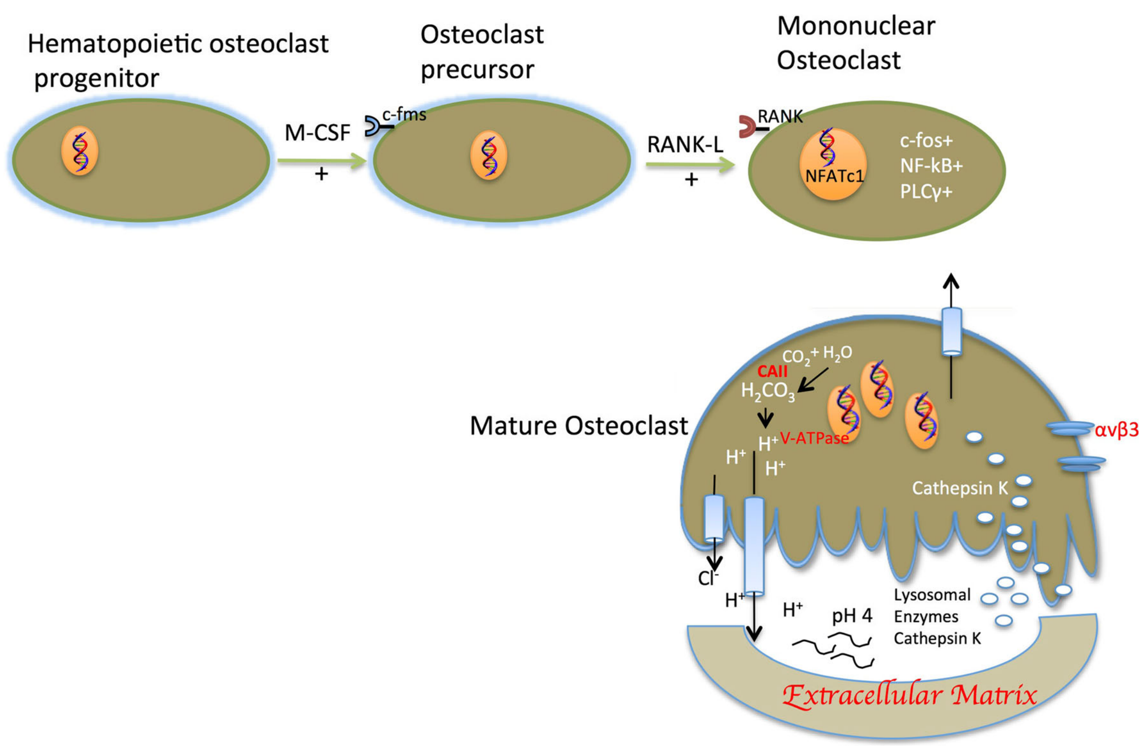


Fig. 3 Osteoclasts (OCs), the bone-resorbing cells, are multinucleated cells originating from precursor cells derived from the mononuclear myeloid lineage, which also give rise to macrophages [42]. The main regulators of osteoclastogenesis are cells of the osteoblastic lineage, through the release in the bone microenvironment of important chemokines, as macrophage-colony stimulating factor (M-CSF) and receptor activator of NF-κB ligand (RANKL), both active on the OC precursors (OCPs) [42]. M-CSF binds to its receptor, c-fms, on OCPs and activates signaling through MAP kinases and ERKs during the early phase of OCP differentiation [43]. RANKL binds to its receptor, RANK, on the surface of OCPs, activating signaling through NF-κB, c-Fos, phospholipase Cγ (PLCγ), and nuclear factor of activated T cells c1 (NFATc1), to induce differentiation of OCPs into mature osteoclasts [44]. Osteoprotegerin (OPG), also secreted by osteoblasts in response to several local and systemic factors, functions as a decoy receptor that binds RANKL and prevents it from interacting with RANK, limiting OC formation, activity, and survival [45]. In pathological conditions, remodeling/modeling activity can be increased or decreased. The bone resorption process is complex; two phases in this pathway can be recognized, namely acid secretion and proteolysis [46]. The model of bone degradation clearly depends on physical intimacy between the osteoclast and bone matrix, a role provided by integrins. Integrins, alpha beta (αvβ3) heterodimers, are the principal cell matrix attachment molecules and they mediate osteoclastic bone recognition creating a sealing zone, into which hydrochloric acid and acidic proteases such as cathepsin K are secreted [47]. Acid secretion is initiated through the active secretion of protons through a vacuolar type ATPase (V-ATPase) and passive transport of chloride through a chloride channel [48, 49], with a final dissolution of the inorganic bone matrix [50]. Acid production is accompanied by an increased chloride transport [46, 51–55] and the involvement of the enzyme carbonic anhydrase II (CAII), which catalyzes conversion of CO_2 and H_2O into H_2CO_3, thereby providing the protons for the V-ATPase [56]. Proteolysis of the type I collagen matrix in bones is mainly mediated by the cysteine proteinase, cathepsin K, which is active at low pH in the resorption lacunae [46, 50, 57, 58]. Products of bone metabolism can be measured, with fragments of collagen type I being the most direct indicators of the osteoclastic activity [59–61]

components of the metabolic bone tissue machinery are depicted in Fig. 2. The cells involved in the metabolic activity of the skeleton are osteoclasts (OCs), osteoblasts (OBs), and osteocytes [27]. The bone extracellular matrix (ECM), known as osteoid, is a complex of self-assembled macromolecules composed predominantly of collagens (~90 % of the matrix proteins), noncollagenous glycoproteins, hyaluronan, and proteoglycans. The osteoid and its local modulating factors are also primary factors in the metabolic performance of bone tissue. The mineral is another important component of the metabolic machinery of bone tissue. The metabolic activity of bone is controlled by systemic and local factors and mechanical signals depicted in Figs. 3, 4, 5, 6, and 7 [28–41].

The major advances in our understanding of the regulation of bone metabolism in recent years allow a different approach to the classification of rare skeletal diseases based on their metabolic pathogenesis. Such approach cannot only improve the recognition and diagnosis of affected patients but can also lead to identification of new targets for therapeutic interventions. In addition, it can

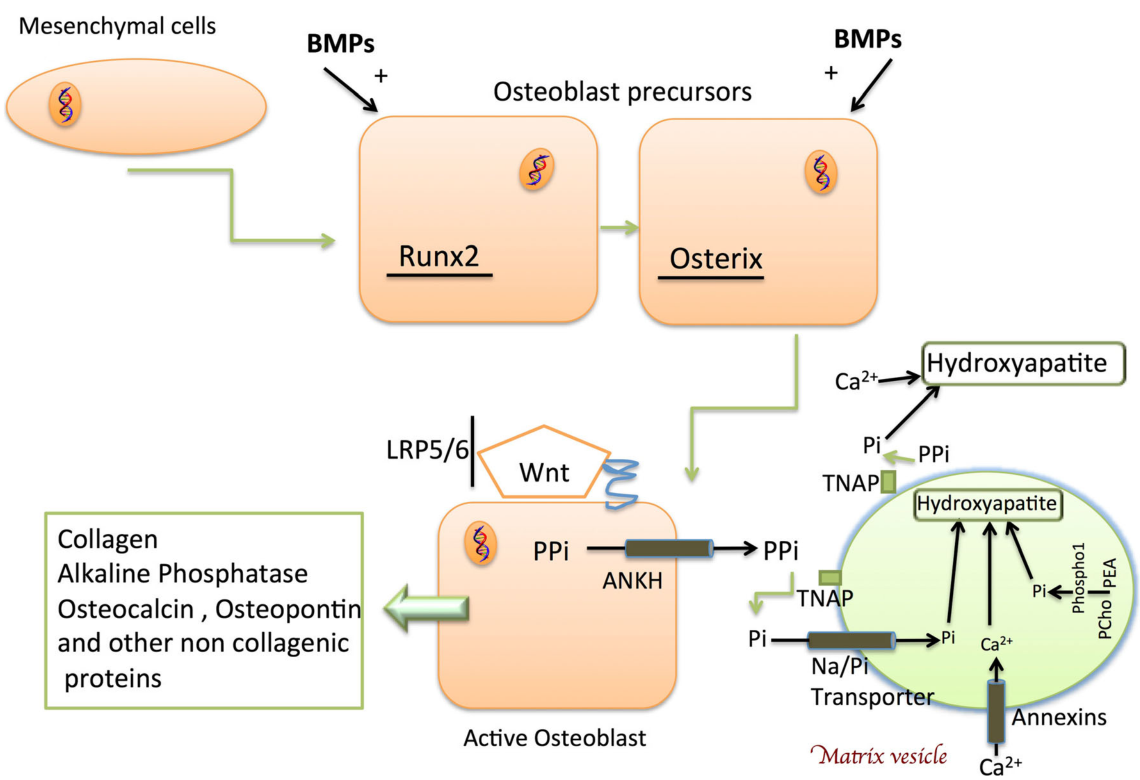


Fig. 4 Osteoblasts (OBs) are bone-forming cells that originate from mesenchymal stem cells (MSCs). The complexities of bone formation are immediately apparent in the embryo, where different regions of the skeleton arise either from intramembranous bone formation or from the endochondral sequence. Osteogenesis is regulated by many molecules, including transcription factors, growth factors, cytokines, and hormones, acting through paracrine, autocrine, and endocrine mechanisms [27], with axial and appendicular-derived osteoblasts exhibiting different responses to hormones [24, 62, 63]. Factors critical in osteoblastogenesis and in mature OBs function are represented by Runx2, Osterix, Wingless (Wnt), lipoprotein receptor-related protein 5 and 6 (Lrp5/6), and bone morphogenetic proteins (BMPs) [27]. OBs are responsible for the deposition of bone extracellular matrix (osteoid), which become mineralized, by deposition of calcium hydroxyapatite, giving the bone rigidity and strength. Biomineralization is characterized by development of matrix extracellular vesicles that are formed by polarized budding from the surface membrane of OBs [64]. The mineralization begins with the formation of hydroxyapatite crystals [calcium (Ca) and inorganic phosphate (Pi)] within matrix vesicles. Ca is incorporated in vesicles by annexin Ca channel, Ca-binding phospholipids calbindins and sialoprotein. Pi is provided by type III Na/Pi cotransporter, by PHOSPHO1, and from the activity of tissue-nonspecific alkaline phosphatase that hydrolyzes pyrophosphate (PPi) [64]. This process is followed by propagation of hydroxyapatite through the membrane into the extracellular matrix in clusters around matrix vesicles and fills the space between collagen fibrils in the skeletal matrices. PPi inhibits the formation of hydroxyapatite. The ratio of Pi to PPi that is mediated by alkaline phosphatase activity is crucial in this step of mineralization [64]. Markers of bone formation are measurable, some being enzymes or proteins produced by osteoblasts (i.e., alkaline phosphatase and osteocalcin) [60, 65–69], while others derive from type I collagen metabolism (i.e., procollagen type I propetides) [60]

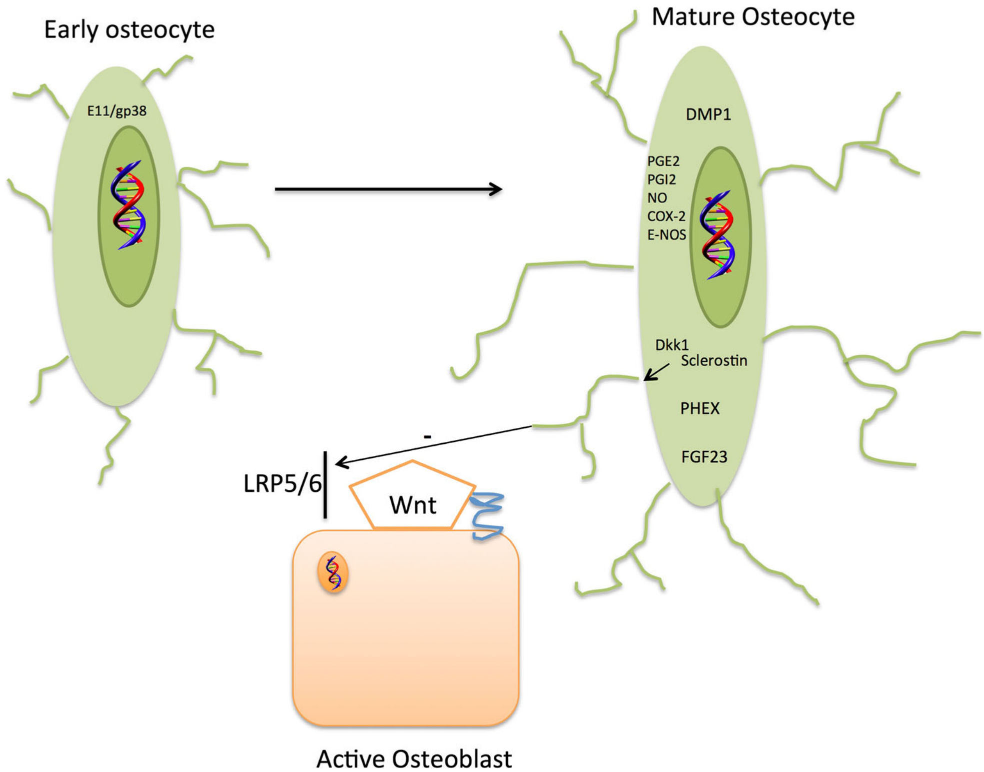


Fig. 5 In the adult skeleton, osteocytes make up 90–95 % in volume of all bone cells compared with 4–6 % osteoblasts and 1–2 % osteoclasts [70]. Osteocytes establish an extensive intercellular communication system via gap-junction-coupled cell processes, also extended to OBs and OCs on the bone surface and, therefore, represent an ideal mechanosensory system. Various authors have identified several transitional stages between osteoblasts and osteocytes. In their review article, Franz-Odendaal et al. [71] combined these observations to propose eight recognizable transitional stages from the osteoblast to the osteocyte. These authors favor an embedding mechanism in which a subpopulation of osteoblasts on the bone surface slows down matrix production relative to adjacent cells and becomes "buried alive" under the matrix produced by neighboring osteoblasts. Sclerostin, the *SOST* gene protein product, is specifically expressed in osteocytes and inhibits osteoblast function and bone formation by antagonizing canonical Wnt signaling through binding to Wnt coreceptor Lrp5 and Lrp6, with *Sost*-deficient mice being resistant to bone loss at unloading [72]. In addition, Dickkopf (in particular Dkk-1) protein, expressed in many cell types, is highly expressed in osteocytes [73] and has also been shown to bind to Lrp5/6 and a transmembrane protein, Kremen, inhibiting canonical Wnt activation pathway [74]. The function of osteocytes in bone formation is still a matter of debate. Under in vitro application of mechanical stimuli, osteocytes activate bone formation through the release of anabolic factors [i.e., prostaglandin E2 (PGE2), prostaglandin I2 (PGI2), nitric oxide (NO), cyclooxygenase-2 (COX-2), and endothelial nitric oxide synthase (eNOS)] [72], with bone formation being severely inhibited after osteocyte ablation [75]. Within the past two decades, several markers of osteocytes have been identified [74, 76, 77]. It is known that there is a heterogeneity in gene expression in osteocytes within bone. For example, early embedding osteoid osteocytes and young osteocytes express high levels of E11/gp38 (also known as podoplanin), while more mature, deeply embedded osteocytes express high levels of sclerostin [78]. Moreover, several proteins that are osteocyte specific, or selectively expressed in osteocytes, play critical roles in phosphate homeostasis. These include phosphate-regulating gene with homologies to endopeptidases on the X chromosome (PHEX), matrix extracellular phosphoglycoprotein (MEPE), dentin matrix protein 1 (DMP1), and fibroblast growth factor 23 (FGF23) [79]. Compared to OBs, osteocytes also appear to be enriched in proteins associated with resistance to hypoxia [80] due to their embedded location within bone, as expected [79]. Another important category of factors whose expression is different in osteocytes compared to OBs is molecules involved in cytoskeletal function and cell motility (destrin, CapG, cdc42, and E11/gp38) [79, 80]

provide bone specialists the background for the diagnostic evaluation of biochemical alterations in individual patients and can contribute to their better understanding of the etiology of the disease.

The aim of the present article, resulted from the work of the members of the Skeletal Rare Diseases Working Group (SRD-WG) of the International Osteoporosis Foundation (IOF), is to classify rare skeletal disorders according to alterations of specific genes encoding proteins involved in the activity of bone cells, bone matrix proteins, microenvironmental regulators essential for bone physiology, or response to calciotropic hormones.

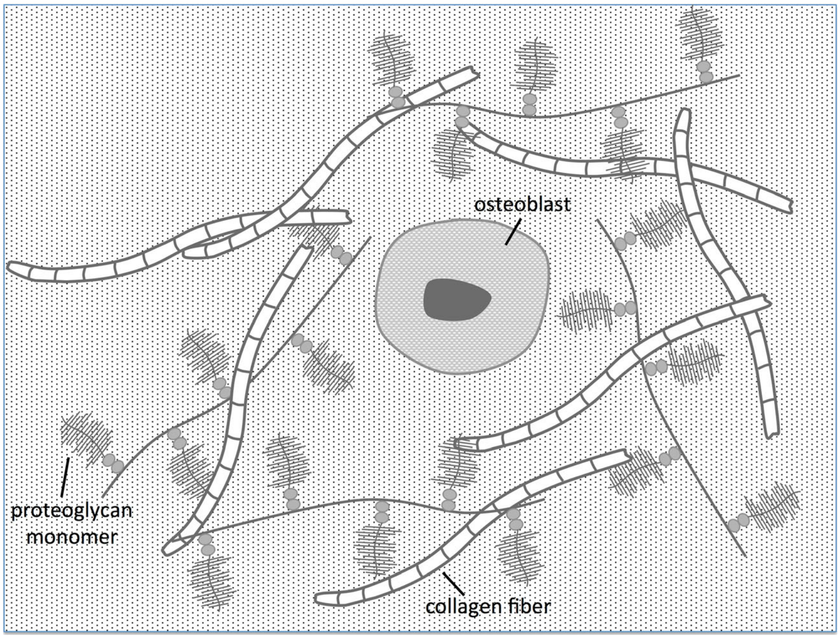


Fig. 6 Bone ECM is not only a scaffold for the cells, but also serves as a reservoir for growth factors and cytokines, and modulates bone turnover and mineral deposition [81, 82]. Type I collagen, synthesized by the OBs, is the most abundant extracellular protein of bone tissue (85–90 %), being essential for bone strength. The molecules of mature collagen spontaneously assemble into fibrils, and cross links form to increase the tensile strength of the fibrils [83]. Different cytokines, inflammatory mediators, matrix-degrading enzymes, hormones, and growth factors can modify the synthesis and degradation of type I collagen, within well-orchestrated autocrine and paracrine anabolic and catabolic pathways [81–83]. Noncollagenous proteins (NCPs) compose 10–15 % of the total bone protein content. These proteins are multifunctional, having roles in organizing the extracellular matrix, coordinating cell-matrix and mineral-matrix interaction, and regulating the mineralization process. [82]. The NCP molecules can be classified into four groups: (1) proteoglycans, (2) glycosylated proteins, (3) glycosylated proteins with potential cell adhesion properties, and (4) γ-carboxylated (gla) proteins [28, 82–85]. Since mutations in these proteins cause mainly skeletal dysplasia, they have not been considered in the proposed classification

Material and methods

In 2012, the IOF recognized the need for identifying and managing patients with rare skeletal diseases and established a working group (SRD-WG) of experts in diseases of bone metabolism to address this issue. The members of the group, after reviewing existing literature information and consulting other physicians involved in the management of patients with rare skeletal diseases, concluded that classification of these diseases according to their metabolic pathogenesis was more appropriate and prepared the first draft of the manuscript. The criteria used to include different disorders were as follows: skeletal involvement as linked to major alterations of bone metabolism, publication and/or listing in the Online Mendelian Inheritance in Man (OMIM) system, and nosologic autonomy (literature updated with PubMed database searches up to January 2015). The SRD-WG considered abnormalities of all elements known to influence bone metabolism and included disorders that are rare, metabolic, and skeletal in origin whose genetic basis is proven or suspected on the basis of the phenotype. This classification does not, therefore, include skeletal dysplasias due to altered morphogenesis during embryonic development. In addition, we did not include in the classification rare diseases in which alterations in the actors of bone metabolism are not the primary cause of the syndrome and bone is only secondarily involved (e.g., storage disorders). This manuscript is the result of several discussions and revisions of the original draft and represents the consensus reached by the members of the group.

Acronyms for the disorders described, phenotype, and gene/locus numbers are presented according to the nomenclature of the OMIM database, as most recently accessed in January 2015 (http://www.ncbi.nlm.nih.gov/omim). An OMIM entry preceded by a number sign (#) indicates the phenotype and specific OMIM entries for the genes/loci whose mutations have been shown as responsible for that phenotype (http://web.udl.es/dept/

cmb/biomatica/OMIM.PDF). The names of genes/loci are those approved by HGNC (HUGO Gene Nomenclature Committee, http://www.genenames.org). Diseases for which the OMIM classification leads to a confounding numbering system (e.g., osteogenesis imperfecta) have been listed into grouping in phenotypes according recently to suggested taxonomies. Diseases for which a specific OMIM phenotype has been described, but for which the genetic alteration has not yet been detected (e.g., Gorham-Stout disease), have in any case been included in the tables. For diseases for which locus heterogeneity has been recognized (e.g., Camurati-Engelmann disease), the main genetic alteration has been herein reported. A brief description of the phenotype and altered biomarkers, when available, has been reported for each rare metabolic bone disease, in order to focus on the metabolic phenotype, even for cases for which this latter information is indicated as “NR” (*not reported*). In Fig. 8, the available nondisease-specific screening/diagnostic assays, which could be of use to further refine the diagnosis, have been listed.

Some diseases/phenotypes overlap in two or more tables because of multiple alterations in bone metabolism (e.g., a pure osteoblast defect can manifest into a disorder of bone matrix). Following a metabolic-based taxonomy, these specific disorders have to be indicated in more than one table. Thus, a disease resembling a phenotype due, for example, to an alteration of collagen metabolism, but due to a primitive alteration in osteoblast (e.g., osteogenesis imperfecta type IV due to mutations of SP7 or PLS3) has been primarily inserted in Tables 1, 2, 3, and 4, encompassing the alterations in osteoblasts, which indeed ultimately lead to collagen metabolism alteration, and secondarily in Tables 5 and 6, since they resemble a disorder in bone matrix (and referred to as “see Tables 1, 2, 3, and 4”).

Results

Rare genetic metabolic bone disorders (RGMBDs) were classified in four major groups according to their primary pathogenetic mechanism: altered osteoblast, osteoclast, or osteocyte function; altered bone matrix proteins; altered bone microenvironmental regulators; and altered calciotropic hormonal activity. We report 116 disease-related OMIM phenotypes with 86 affected genes, and we include genetic causes (germ line mutations, postzygotic somatic mutations, mitochondrial DNA) where known, as well as general and bone-specific features and biochemical alterations.

Altered osteoblast, osteoclast, or osteocyte function

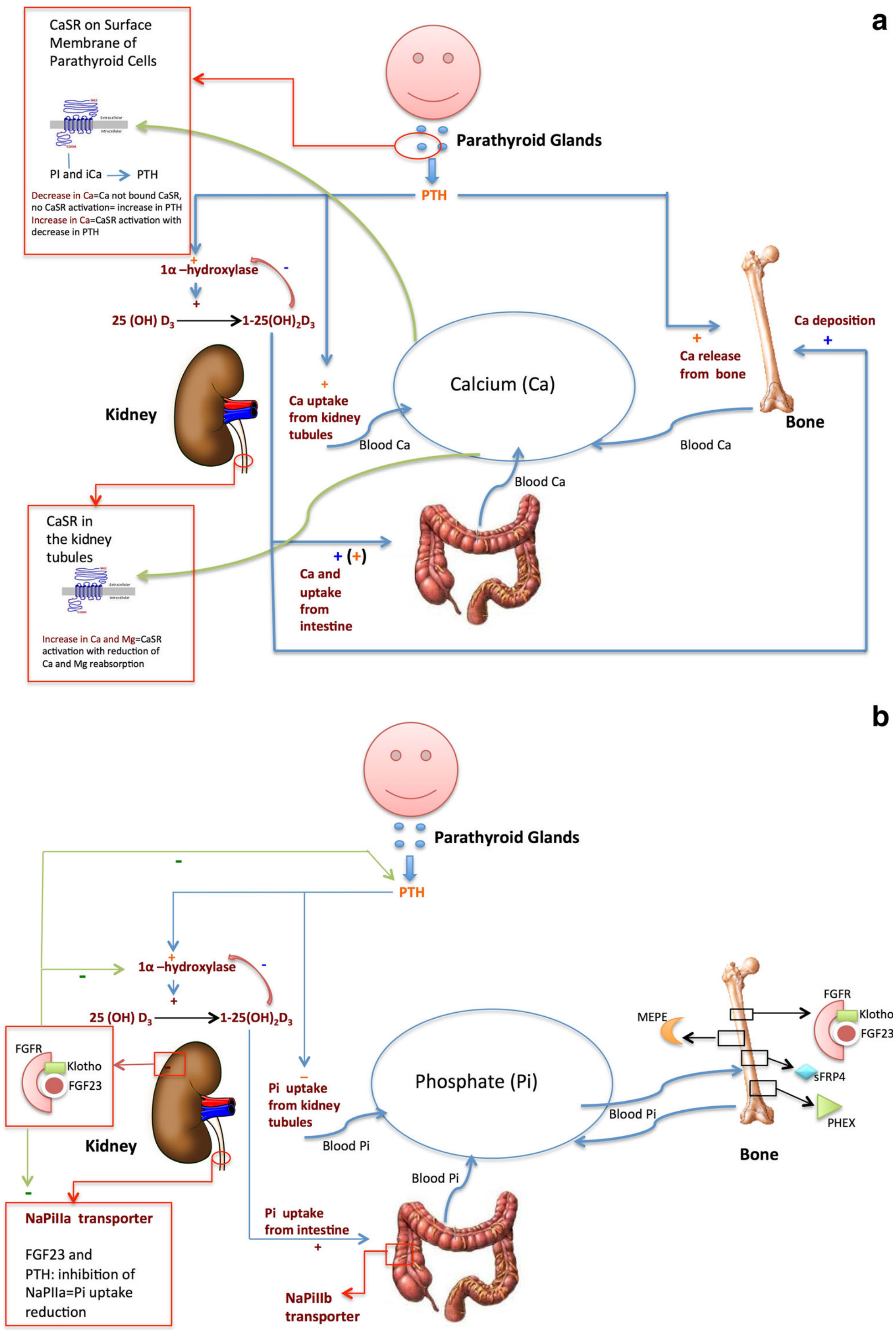
Tables 1, 2, 3, and 4 describe diseases due to an alteration in the activity of bone cells (osteoclasts, osteoblasts, and osteocytes) resulting in an increase or decrease in either bone formation or bone resorption. The four main groups identified include 38 different phenotypes. Disorders characterized by high bone resorption are shown in Table 1, while those associated with low bone resorption are shown in Table 2. These disorders are generally caused by mutations in genes encoding osteoclastic functional proteins. Table 3 depicts disorders characterized by high bone formation. These are caused by mutations in genes encoding proteins involved in osteoblastogenesis and mature osteoblast function or proteins produced by osteocytes involved in differentiation and life span of osteoblasts. Finally, diseases characterized by low bone formation are shown in Table 4; these are caused by mutations in genes encoding proteins involved in the formation and function of osteoblasts.

Altered bone matrix proteins

Tables 5 and 6 describe diseases where the characteristics of matrix proteins are altered. Three major groups were identified, with 28 different phenotypes (five overlapping with the forms listed in Tables 1, 2, 3, and 4). Regarding the diseases related to proteoglycan alterations, only the forms where the large proteoglycans are involved in the pathogenesis were included. Mutations in genes encoding type I collagen and collagen-related bone matrix proteins have been primarily listed in rare skeletal disorders characterized by altered collagen metabolism (Table 5). Alkaline phosphatase is one of the main enzymes involved in bone mineralization. Disorders causing altered production of alkaline phosphatase have been described primarily in Table 6.

Altered bone microenvironmental regulators

Tables 7, 8, 9, and 10 depict diseases caused by mutation of genes encoding for proteins involved in the regulation of bone turnover. Four major groups were recognized with 13 different phenotypes (12 overlapping with the forms listed in Tables 1, 2, 3, and 4 or 5 and 6).


a
CaSR on Surface Membrane of Parathyroid Cells
PI and iCa → PTH
Decrease in Ca=Ca not bound CaSR, no CaSR activation= increase in PTH
Increase in Ca=CaSR activation with decrease in PTH
Parathyroid Glands
PTH
1α –hydroxylase
25 (OH) D3
1-25(OH)2D3
Kidney
CaSR in the kidney tubules
Increase in Ca and Mg=CaSR activation with reduction of Ca and Mg reabsorption
Ca uptake from kidney tubules
Blood Ca
Calcium (Ca)
Ca release from bone
Ca deposition
Bone
Blood Ca
Blood Ca
+ (+)
Ca and uptake from intestine
b
Parathyroid Glands
PTH
1α –hydroxylase
25 (OH) D3
1-25(OH)2D3
FGFR
Klotho
FGF23
Kidney
NaPiIIa transporter
FGF23 and PTH: inhibition of NaPIIa=Pi uptake reduction
Pi uptake from kidney tubules
Blood Pi
Phosphate (Pi)
Blood Pi
Blood Pi
Pi uptake from intestine
NaPiIIb transporter
MEPE
FGFR
Klotho
FGF23
sFRP4
PHEX
Bone

◀ **Fig. 7** Calciotropic hormones are defined on the basis of their capability to modulate Ca/Pi metabolism, and all of them directly and indirectly modulate bone metabolism. Ca and Pi are essential to many vital physiological processes [29] and their regulation involves a concerted action among the digestive system, kidneys, and skeleton via the action of calciotropic hormones. Disturbances in calciotropic hormone homeostasis have been linked to several pathophysiological disorders, including bone abnormalities [29, 30]. Among the hormones that control Ca and Pi metabolism, parathyroid hormone (PTH) and calcitriol [1-25$(OH)_2D_3$] are the most documented. PTH inhibits renal Pi reabsorption and increases Ca reabsorption, indirectly increasing intestinal Ca and Pi absorption by stimulating the synthesis of calcitriol. Conversely, Ca and Pi modulate the synthesis and secretion of PTH from parathyroid cells [31]. Homeostasis of calcium is represented in **a**. The symbol *orange* + indicates the direct PTH stimuli and *orange (+)* indicates the PATH indirect stimuli. The symbol *blue* + indicates the vitamin D stimuli. Parathyroid cells respond to decreases in extracellular calcium concentration by means of the calcium-sensing receptor (CaSR), a cell surface receptor that alters phosphatidylinositol turnover and intracellular calcium, ultimately determining an increase in PTH secretion [31]. In addition to parathyroid tissue, the receptor is also expressed in the regions of the kidney involved in the regulation of Ca and magnesium (Mg) reabsorption [32] and in many different tissues throughout the body [33]. Conversely, calcitriol increases both intestinal Ca and Pi absorption and renal Pi reabsorption [34, 35]. In addition, PTH-related peptide (PTHrP), first discovered as the major cause of the humoral hypercalcemia of malignancy [36], is evolutionarily and functionally related to PTH and also functions as mineral metabolism regulator. It is expressed by a variety of fetal and adult tissues, having a prominent role in the regulation of endochondral bone formation [37] and in the organogenesis of several epithelial tissues (i.e., skin, mammary gland, teeth) [38]. The most recently identified calciophosphotropic hormones are the phosphatonins [29, 31] (**b**). The term phosphatonins is used to describe factors responsible for the inhibition of Pi renal reabsorption by cotransporter and for the modulation of the 1-alpha-hydroxylase levels [29]. These molecules include FGF23, PHEX, matrix extracellular phosphoglycoprotein (MEPE), secreted frizzled related protein 4 (sFRP4), and fibroblast growth factor 7 (FGF7) [36, 37, 76]. Most of the studies indicate FGF23 as the most important phosphatonin. Functional in vitro studies show that FGF23 activity is regulated by proteases and its specific receptors [38]. Mature FGF23 is degraded to two small fragments by the furin family proteases [39]. Moreover, the tissue-specific activity of FGF23 can be explained on the basis of the need for the presence of both fibroblast growth factor receptors (FGFRs) and Klotho (KL), a coreceptor for FGF23 that increases the affinity of FGF23 for FGFRs [40]. In bone tissue, Ca and Pi interact with cells of the bone-forming lineage and with the extracellular matrix proteins to control the osteoid mineralization [32], while deposition of minerals in soft tissues is prevented through less well-understood factors [41]. The "bone" hormones measurable in serum include intact PTH (iPTH), calcidiol [25$(OH)D_3$], calcitriol [1-25$(OH)_2D_3$], intact FGF23 (iFGF23), C-terminal FGF23, and α-Klotho

Altered calciotropic hormonal activity

Tables 11, 12, 13, and 14 describe diseases with bone involvement due to congenital alterations of the function of hormones involved in the regulation of calciotropic hormones. Four major groups were described with 54 different phenotypes. Disorders due to parathyroid hormone excess or deficiency are listed in Table 11, while diseases caused by altered parathyroid hormone (PTH) signaling and abnormal vitamin D metabolism and action are shown in Tables 12 and 13, respectively. Table 14 displays disorders due to altered phosphate metabolism.

Discussion

We propose here for the first time a classification system for rare skeletal bone diseases based on a metabolic approach, selecting from this large number of disorders those due to an abnormality of the actors of bone metabolism: bone cells, bone matrix, and local and systemic regulators. The primary aim of this taxonomy is to provide a reference list on a metabolic basis, and only secondarily to help in the diagnostic workup. For this reason, the information regarding family history, genetic evaluation, and management of the different disorders reported was not included in the classification. We acknowledge further that this classification is arbitrary, but it has the strength that is based on actual, known findings that will encourage clinicians to perform proper metabolic evaluation of patients in order to plan targeted suitable treatment. It should be also noted that some level of arbitrary judgment is always compatible with a taxonomy process, and the same criticism can be posed toward a radiological classification that does not encompass information that we consider relevant for the clinical management of such difficult patients. In addition, such evaluation can be of clinical relevance in targeting appropriate treatment, when available, that generally is not timely and appropriately prescribed in the majority of patients. Finally, this metabolic taxonomy does not undermine the importance of previous classifications on this subject, which still constitute a reference list for these disorders [25].

To date, the diagnosis of rare skeletal diseases is based on clinical phenotype and radiographic features. A classification system based on measurement of bone mineral density (BMD) or assessment of skeletal fragility is not feasible because in the majority of these disorders, systematic evaluation of BMD by DXA has not yet been performed, and the long-term incidence of fracture is unknown. Classification of "local" or "systemic" disorders is also not feasible, because in apparently localized disorders, a systemic alteration in

Biochemical Markers

- Serum Calcium
- Urinary Calcium
- Serum Phosphate
- Urinary Phosphate
- Serum Magnesium
- Urinary Magnesium
- Parathyroid hormone (PTH)
- Fibroblast growth factor 23 (FGF23)
- 25 hydroxyvitamin D_3 [25(OH)D_3]
- 1,25 dihydroxyvitamin D_3 [1-25(OH)$_2$$D_3$]
- Bone Formation Markers:
  Total Alkaline Phosphatase, Bone Alkaline Phosphatase, Osteocalcin, Procollagen 1 N-terminal Propeptide (P1NP), Procollagen 1 C-terminal Propeptide (P1CP)
- Bone Resorption Markers:
  Hydroxyproline, Pyridinoline and Deoxypiridinoline, Cross-linked N-telopeptide of type I collagen (NTX), Cross-linked C-telopeptide of type I collagen (CTX)
- Bone Mineralization Markers:
  Pyridoxal-5′-phosphate
  Urinary 4-pyridoxic acid
- Bone Microenvironment Products:
  Sclerostin, RANK-ligand, Osteoprotegerin

Instrumental exams

- DEXA: Lumbar Spine, hip, wrist, total body
- Ultrasound (US): heel, finger
- Peripheral Quantitative Computed Tomography (pQCT): leg, wrist
- Quantitative Computed Tomography (QCT): spine
- X-rays
- Radiographic vertebral morphometry
- DEXA: Vertebral Fracture Assessment (VFA)
- Bone scintigraphy
- Positron Emission Tomography (PET)
- Magnetic Resonance Imaging (MRI)

Bone Biopsy

- Histology
- Histomorphometry

In vitro assays

Fig. 8 Biochemical/instrumental exams and in vitro tests for characterizing metabolic bone diseases. Measurements of biochemical indexes and hormones regulating mineral homeostasis can help in confirming or excluding systemic bone metabolic disorders. The assessment of bone turnover is important in order to plan further therapeutic approaches. Bone quantity and quality appraisal and prevalent vertebral fracture assessment may help to refine the metabolic framing of the disease, manifesting with an otherwise evident bone phenotype, and is crucial in the follow-up of the treated patient. Bone biopsy is critical in selected cases for the identification and for differential diagnosis. In vitro assays can be useful to identify supposed functional abnormalities of bone cells and/or matrix proteins (e.g., in collagen-related disorders)

bone metabolism can be present (e.g., tumoral calcinosis) or maybe have not yet been assessed. For the majority of the listed disorders, biochemical features are not available, which underlines the need for a better metabolic characterization. Determination of biomarkers related to mineral metabolism as well as systematic assessment of BMD and quality of bone by improved diagnostic tools is, therefore, needed. However, these investigations are not disease-specific and are not commonly employed, unless patients are evaluated in referral centers by bone specialists with expertise in rare skeletal disorders. In selected cases, bone biopsy and in vitro assays can help to further refine the metabolic diagnosis. Many of the bone marker tests, not available at the time of the first description of these diseases, are now routinely used, encouraging the biochemical/metabolic characterization of disorders potentially characterized by metabolic fingerprints.

The metabolic framing of a rare skeletal disease is of paramount importance for therapeutics and can guide the clinician in the choice of the most appropriate pharmacological intervention. Indeed, the characterization of a rare bone disease for the bone-forming or bone-resorbing phenotype will lead to different therapeutic approaches (e.g., anabolics or antiresorptives). In this respect, an example is hypophosphatasia, the only rare bone disease, due to a specific metabolic enzymatic alteration, for which a targeted therapy (asfotase alpha) has recently been developed and for which an antiresorptive therapy is contraindicated. However, other rare genetic metabolic bone disorders are often treated with the available antiosteoporotic agents which are given without being included in their approved indications (*off-label* prescription). In such cases, knowledge of the bone metabolic and structural profile can help in choosing the most suitable therapy for a given clinical case.

Table 1 Altered osteoclast, osteoblast, or osteocyte activity: low bone resorption

Disease	OMIM phenotype number	OMIM gene/locus number	Gene	Chromosome location	Phenotype	Main biochemical alterations
Osteopetrosis due to altered osteoclast function					Entities characterized by an increased bone density (sclerosis) and generalized high bone mass, depending on decreased bone resorption due to decreased osteoclast function, with high fracture rate in severe recessive forms; additional signs for each phenotype:	Adult/intermediate forms: high CK-BB, high bone ALP Infantile/severe forms: low Ca, high PTH, high 1,25(OH)2D, high CK-BB, high AP, anemia
• Autosomal dominant 2 (OPTA2)/Albers-Schonberg disease	#166600	602727	*CLCN7*	16p13.3	Asymptomatic, bone sclerosis, fractures, dental abscesses, osteomyelitis of the mandible	
• Autosomal recessive 1 (OPTB1)	#259700	604592	*TCIRG1*	11q13.2	Severe, loss of trabecular structure, poor/no definition between cortical and medullary bone, macrocephaly, frontal bossing, blindness, deafness, facial palsy, genu valgum, dental defects, bone marrow insufficiency	
• Autosomal recessive 2 (OPTB2)	#259710	602642	*TNFSF11*	13q14.11	Intermediate, osteoclast-poor, fractures, genu valgum, hepatosplenomegaly, dental defects, osteomyelitis of the mandible	
• Autosomal recessive 3 (OPTB3)	#259730	611492	*CA2*	8q21.2	Intermediate, renal tubular acidosis, early fractures, short stature, mental retardation, dental malocclusion, visual impairment	+ Metabolic acidosis
• Autosomal recessive 4 (OPTB4)	#611490	602727	*CLCN7*	16p13.3	Severe, loss of trabecular structure, poor/no definition between cortical and medullary bone, fractures, hepatosplenomegaly, mild optic nerve atrophy	
• Autosomal recessive 5 (OPTB5)	#259720	607649	*OSTM1*	6q21	Severe, loss of trabecular structure, poor/no definition between cortical and medullary bone, hydrocephaly, microcephaly, fractures, osteosclerosis, hepatosplenomegaly, visual impairment, bone marrow insufficiency	
• Autosomal recessive 6 (OPTB6)	#611497	611466	*PLEKHM1*	17q21.31	Intermediate, bone deformities, pain, chondrolysis, dense metaphyseal bands	
• Autosomal recessive 7 (OPTB7)	#612301	603499	*TNFRSF11A*	18q21.33	Severe, osteoclast-poor, hypogammaglobulinemia	
• Autosomal recessive 8 (OPTB8)	#615085	614780	*SNX10*	7p15.2	Severe, loss of trabecular structure, poor/no definition between cortical and medullary bone, macrocephaly, failure to thrive, optic nerve atrophy, nasal stuffiness due to fully ossified sinuses, bone marrow insufficiency	
• Ectodermal dysplasia, anhidrotic, immunodeficiency, osteopetrosis, lymphedema (OLEDAID)	#300301	300248	*IKBKG*	Xq28	Lymphedema, anhidrotic ectodermal dysplasia, immunologic alterations	
• Osteopetrosis and infantile neuroaxonal dystrophy	#600329	–	–	–	Severe, OPTB1 phenotype, agenesis of the corpus callosum	
Osteopetrosis due to altered osteoclast number						
• Dysosteosclerosis (DSS)	#224300	612373	*SLC29A3*	10q22.1	Platyspondyly and metaphyseal osteosclerosis with relative radiolucency of widened diaphyses, dense but brittle skeleton, short stature and fractures, failure of tooth eruption, developmental delay, seizures, skin findings such as red-violet macular atrophy, at the histopathological level paucity of osteoclasts	Low total and bone ALP, low TRAP5b, low Ur DPD/Cr
Pycnodysostosis (PYCD)	#265800	601105	*CTSK*	1q21.3	Generalized high bone mass, bone fragility, short stature, clavicular dysplasia, obtuse angle of mandible, short terminal phalanges	Low GH, low IGF1

Table 2 Altered osteoclast, osteoblast, or osteocyte activity: high bone resorption

Disease	OMIM phenotype number	OMIM gene/locus number	Gene	Chromosome location	Phenotype	Main biochemical alterations
Cystic angiomatosis of bone/Gorham-Stout disease (GSD)	#123880	–	–	–	Inherited osteolysis disorder characterized by destruction and resorption of affected bones with subsequent skeletal deformities and functional impairment. Early-onset progressive osteolysis of one or more bones always associated with an angiomatosis of blood vessels and sometimes of lymphatics, history of fragility fractures, and vascular malformations in the affected bones or surrounding soft tissues, multiple dilated vascular spaces replacing normal bone marrow elements, disseminated multifocal vascular lesions of the skeleton with possible visceral involvement, bony deformities, muscular weakness and localized pain	High IL-6 (not always), high serum fibrinogen, high serum D-dimer, high ESR, high CD105/endoglin
Cystic angiomatosis (CA)	#123880	–	–	–	Multifocal hemangiomatous and/or lymphangiomatous lesions of the skeleton with possible visceral organ involvement	High OPG, high OPN, high IL-6
Familial hydiopatic hyperphosphatasia/ juvenile Paget's disease of bone	#239000	602643	*TNFRSF11B*	8q24.12	Retinal degeneration in some individuals, angioid streaks, muscular weakness, deafness in infancy, osteoporosis, expanded long bones, bowed long bones, fragile bones, increased bone formation and destruction, progressive skeletal deformity, short stature, mild involvement of cranial bones, islands of increased skull bone density	High Pi, normal Ca, markedly high ALP, high acid phosphatase, high uric acid
Familial expansile osteolysis (FEO)	#174810	603499	*TNFRSF11A*	18q21.33	Deafness and loss of dentition, focal skeletal changes, with predominantly peripheral distribution, progressive osteoclastic resorption accompanied by medullary expansion led to severe, painful, disabling deformity and a tendency to pathologic fracture	High ALP, high Ur OHP, possible high Ca

Table 3 Altered osteoclast, osteoblast, or osteocyte activity: high bone formation

Disease	OMIM phenotype number	OMIM gene/ locus number	Gene	Chromosome location	Phenotype	Main biochemical alterations
• High bone mass (HBM)	#607634	603506	*LRP5*	11q13.2	Increased bone density, mostly asymptomatic (rarely bone pain)	NR
• Van Buchem disease type 2, autosomal dominant (VBCH2)	#607636	603506	*LRP5*	11q13.2	Increased bone density, mostly asymptomatic, associated with osteosclerosis of the skull, enlarged and squared jaw (decreased gonial angle), cranial nerve compression, sensorineural hearing loss (otopharyngeal exostosis)	
• Osteosclerosis/endosteal hyperostosis, autosomal dominant	#144750	603506	*LRP5*	11q13.2	See above + cortical thickening of the long bones, torus palatinus	High ALP
• Hyperostosis corticalis generalisata/Van Buchem disease (VBD)	#239100	605740	*SOST*	17q21.31	Progressive skeletal overgrowth (especially skull) and cortical thickening and generalized osteosclerosis, enlargement of the jaw with wide angle, flat nasal bridge, frontal prominence, pain of long bone with applied pressure, no fragility fractures, hypertelorism, proptosis, multiple cranial nerve involvement with recurrent facial nerve palsy, deafness, optic atrophy from narrowing of cranial foramina, associated with:	High bone ALP, high P1NP, decreased sclerostin in VBD, undetectable sclerostin in SOST1 and CDD
• Sclerosteosis 1, autosomal recessive (SOST1)	#269500	605740	*SOST*	17q21.31	Symmetric cutaneous syndactyly, excessive height and weight	
• Sclerosteosis 2, autosomal dominant/recessive (SOST2)	#614305	604270	*LRP4*	11p11.2	Syndactyly/brachyphalangy with nail dysplasia	
• Craniodiaphyseal dysplasia, autosomal dominant (CDD)	#122860	605740	*SOST*	17q21.31	Leonine facies	
Osteopathia striata						NR
• Without cranial sclerosis (OS)	#300373	–	–	–	Striations in the ileum, intestinal malrotation (rare, in males), anal stenosis (rare in males), anal atresia (rare, in males), gastroesophageal reflux, linear striations at the ends of long bones, bilateral fibula aplasia (always)	
• With cranial sclerosis (OSCS)	#300373	300647	*AMER1*	Xq11.2	Females: see above + mild learning disabilities, macrocephaly, cleft palate, mild learning disabilities, sclerosis of the long bones and skull, cleft palate, long straight clavicole and striations visible on radiographs of the long bones, pelvis, and scapulae Males: fetal or neonatal lethality	
• Focal dermal hypoplasia (FDH)/Goltz syndrome	#305600	300651	*PORCN*	Xp11.23	Females: heart defects, gastrointestinal malformations, linear areas of dermal hypoplasia through which adipose tissue can herniate and a variety of bone defects in the limbs (striated bones) Males: utero lethality	
Osteopoikilosis/Buschke-Ollendorff syndrome (BOS)	#166700	607844	*LEMD3*	12q14.3	Asymptomatic, disseminated connective tissue nevi with both elastic-type nevi (juvenile elastoma) and collagen type nevi (dermatofibrosis lenticularis disseminate), osteosclerotic foci in epimetaphyseal regions of long bones	NR
Melorheostosis (associated with osteopokilosis)	#155950	607844 –	*LEMD3* *unknown gene(s)*	12q14.3 –	Joint contractures, sclerodermatous skin lesions, muscle atrophy, hemangiomas, lymphedema, bone deformities with linear hyperostosis of the cortex of long bones reminiscent of dripping candle wax	
Craniometaphyseal dysplasia, autosomal dominant (CMD)	#123000	605145	*ANKH*	5p15.2		NR

Table 3 (continued)

Disease	OMIM phenotype number	OMIM gene/ locus number	Gene	Chromosome location	Phenotype	Main biochemical alterations
					Impaired vision, hearing loss, and facial nerve paralysis, metaphyseal flaring, hyperostosis and sclerosis of the cranial bones, thick bony wedge over the bridge of the nose and glabella (first sign)	
Craniometaphyseal dysplasia, autosomal recessive (CMDR)	#218400	121014	*GJA1*	6q22.31	Hyperostosis and sclerosis of the craniofacial bones and abnormal modeling of the metaphyses, sclerosis of the skull, asymmetry of the mandible, cranial nerve compression with hearing loss and facial palsy	
Camurati-Engelmann disease (CAEND)	#131300	190180	*TGFB1* *unknown gene(s)*	19q13.2	Leg pain, muscular atrophy and weakness, diaphyseal dysplasia, hyperostosis of the skull base, cortical bone thickening and sclerosis of the diaphysis of the long tubular bones by both endosteal and periosteal bone proliferation. The extreme variability in phenotypical expression, both between families sharing the same mutation and among members of the same family, makes it difficult to detect possible genotype-phenotype correlations. The most severely affected individuals have progression of mild skull hyperostosis to severe skull thickening and cranial nerve compression	Anemia, high P1NP, N/high bone ALP
Camurati-Engelmann disease type 2	#606631	190180	*TGFB1*	19q13.2	Marfanoid habitus, waddling gait, muscular weakness, intense leg pain, flexion contracture of the hip and knee joints, delayed sexual development, cortical thickening of the diaphyses. Metaphyseal expansion of the long bones, coarse and thick trabeculae of the long and short tubular bones, striations in the spinal, pelvic, and long bones, and cranial sclerosis restricted to the petromastoid regions	High ALP, high ESD

NR not reported

Table 4 Altered osteoclast, osteoblast, or osteocyte activity: low bone formation

Disease	OMIM phenotype number	OMIM gene/locus number	Gene	Chromosome location	Phenotype	Main biochemical alterations
Osteoporosis-pseudoglioma syndrome, autosomal recessive (OPPG)	#259770	603506	*LRP5*	11q13.1	Blindness, microphthalmia, vitreoretinal abnormalities, cataract, phthisis bulbi, absent anterior eye chamber, iris atrophy, pseudoglyoma, muscle hypotonia, obesity, mental retardation (in some cases), ligament laxity, severe osteoporosis, multiple fractures, short stature, kyphoscoliosis, hyperextensible joints, wide metaphyses	NR
Familial exudative vitroretinopathy (FEVR)	#601813	603506	*LRP5*	11q13.1	Decreased visual acuity, blindness, falciform retinal folds, tractional retinal detachment, macular ectopia, retinal exudates, vitreous detachment, subcapsular opacities peripheral retinal avascularization, neovascularization, vitreous hemorrhage, horizontal pendular nystagmus, decreased bone mineral density	NR
OI type IV, common variable OI with normal sclerae					Moderate, some cases indistinguishable from type III, adult hearing loss, variable phenotype, osteoporosis, bone fractures, short stature, vertebral deformity and scoliosis, triangular face, normal sclerae, hypermobility of the joints, mild dentinogenesis imperfecta in some cases	
	#613849	606633	*SP7*	12q13.13		NR
	#300910	300131	*PLS3*	Xq23		NR
OI type V, with calcification in interosseous membranes	#610967	614757	*IFITM5*	11p15.5	Moderate-severe, similar to type IV, but without dentinogenesis imperfecta and blue sclerae, calcification of intraosseus membranes in the forearm and hyperplastic callus formation, metaphyseal bands adjacent to growth plate (distal femora, proximal tibia, distal radii), histological mesh-like or irregular bone pattern	High ALP, high NTX
Cleidocranial dysplasia (CCD)	#119600	600211	*RUNX2*	6p21	Skeletal dysplasia characterized by abnormal clavicles (hypoplastic clavicles, aplastic clavicles) short ribs, cervical ribs, patent sutures and fontanelles, supernumerary teeth, short stature, and a variety of other skeletal changes	NR
• Forme fruste, with brachydactyly					See above + brachydactyly	
• Forme fruste, dental anomaly only					See above + delayed eruption of permanent teeth, supernumerary teeth	
Hajdu-Cheney syndrome	#102500	#600275	*NOTCH2*	1p12p11	Short stature, coarse and dysmorphic facies, bowing of the long bones, vertebral anomalies Facial features include hypertelorism, bushy eyebrows, micrognathia, small mouth with dental anomalies, low-set ears, and short neck Progressive focal bone destruction, including acroosteolysis and generalized osteoporosis Additional and variable features include hearing loss, renal cysts, and cardiovascular anomalies	NR
Winchester-Torg syndrome	#259600	#120360	*MMP2*	16q12.2	Torg syndrome: multiple, painless, subcutaneous nodules (interphalangeal joints, knees, feet, elbows, pretibial), mild to moderate osteoporosis and osteolysis usually limited to the hands and feet, widening of the metacarpal and metatarsal bones Winchester syndrome: subcutaneous nodules are characteristically absent, severe osteolysis in the hands and feet, and various additional features including coarse face, corneal opacities, gum hypertrophy, and EKG coarse face	High ANA, high IL-6, high IL-1β

NR not reported

Table 5 Altered bone matrix proteins: disorders in collagen metabolism

Disease	OMIM phenotype number	OMIM gene/locus number	Gene	Chromosome location	Phenotype (systemic and bone-specific signs)	Main biochemical alterations
Osteogenesis imperfecta (OI)					Also known as *brittle bone disease*, it is a genetically determined bone disorder in which either defective or insufficient quantities of collagen molecules are produced Common clinical signs: increased bone fractures. Secondary features such as short stature, blue sclerae, dentinogenesis imperfecta and hearing loss may also exist in affected individuals	
• Nondeforming, with blue sclerae (OI type I)					Mildest form of OI, due to 50 % reduction of the amount of collagen type I; blue sclerae, joint hyperextensibility, normal tooth (OI type IA, with a reduction in the amount of normal collagen) or dentinogenesis imperfecta (OI type IB, with abnormal collagen), hearing loss (onset usually around 20 years), mitral valve prolapse, thin skin, increased fracture rate throughout childhood (ensues when child begins to walk, decreases after puberty, then increases after menopause and in men aged 60–80 years), biconcave flattened vertebrae	
	#166200	120150	*COL1A1*	17q21.33		No specific alterations in bone markers (low sclerostin, low PINP and PICP have been reported)
	#166200	120160	*COL1A2*	7q21.3		
• Perinatally lethal (OI type II)					Most severe form of OI, neonatal lethality, born prematurely and small for gestational age, multiple neonatal fractures, shortening and bowing of long bones with severe under modeling leading to crumpled long bones, all vertebrae hypoplastic/crushed, hip abducted and knees flexed, severe osteoporosis with intrauterine fractures and abnormal modeling, skull with severe undermineralization with wide-open anterior and posterior fontanels, white or blue sclerae, death for respiratory insufficiency and pneumonias	
– Type II-A	#166210	120150	*COL1A1*	17q21.33		NR
	#166210	120160	*COL1A2*	7q21.3		NR
– Type II-B	#610682	605497	*CRTAP*	3p22.3		NR
	#610915	610339	*LEPRE1*	1p34.2		NR
	#259440	123841	*PPIB*	15q22.31		NR
• Progressively deforming (OI type III)					Severe, progressive with age, born prematurely and small for gestational age, marked impairment of linear growth, progressive deformity of long bones and spine, blue/gray or white sclerae, dentinogenesis imperfecta, severe bone dysplasia, severe osteoporosis with multiple fractures and bone deformities (more than 3 prepubertal fractures per annum), soft and shorter long bones, joint laxity, chronic bone pain, triangular face with frontal bossing, dentinogenesis imperfecta in some cases	
	#259420	120150	*COL1A1*	17q21.33		NR
	#259420	120160	*COL1A2*	7q21.3		NR
	#614856	112264	*BMP1*	8p21.3		Normal to slightly high ALP; in some patients: low P1CP and/or high Ur DPD/Cr
	#610682	605497	*CRTAP*	3p22.3		NR
	#610968	607063	*FKBP10*	17q21.2		High AP

Table 5 (continued)

Disease	OMIM phenotype number	OMIM gene/locus number	Gene	Chromosome location	Phenotype (systemic and bone-specific signs)	Main biochemical alterations
	#259450	607063	*FKBP10*	17p21.2	+ Congenital joint contracture (elbow and knees) (Bruck syndrome type 1)	High Ur OHP
	#610915	610339	*LEPRE1*	1p34.2	+ Specific radiological sign ("popcorn" epiphyses)	NR
	#609220	601865	*PLOD2*	3q24	+ Congenital joint contracture (elbow and knees) (Bruck syndrome type 2)	High Ur OHP
	#259440	123841	*PPIB*	15q22.31		NR
	#613982	172860	*SERPINF1*	17p13.3	+ Specific histological sign (fish-scale lamellar appearance)	NR
	#613848	600943	*SERPINH1*	11q13.5		NR
	#615066	611236	*TMEM38B*	9q31.2		NR
	#615220	164820	*WNT1*	12q13.12	+ Developmental delay, brain malformation, unilateral cerebellar hypoplasia, congenital absence of the vermis, pontine hypoplasia, hypoplasia of the mesencephalic tectum, small anterior commissure, hypoplasia of the optic chiasm, hypoplasia of the hypothalamus, closed-lip schizencephaly, type 1 Chiari malformation	NR
• Common variable moderate OI with normal sclerae (OI type IV)					Moderate, some cases indistinguishable from type III, adult hearing loss, variable phenotype, osteoporosis, bone fractures, short stature, vertebral deformity and scoliosis, triangular face, normal sclerae, hypermobility of the joints, mild dentinogenesis imperfecta in some cases	
	#166220	120150	*COL1A1*	17q21.33		NR
	#166220	120160	*COL1A2*	7q21.3		NR
	#615220	164820	*WNT1*	12q13.12	+ Developmental delay, brain malformation, unilateral cerebellar hypoplasia, congenital absence of the vermis, pontine hypoplasia, hypoplasia of the mesencephalic tectum, small anterior commissure, hypoplasia of the optic chiasm, hypoplasia of the hypothalamus, closed-lip schizencephaly, type 1 Chiari malformation	NR
	#610682	605497	*CRTAP*	3p22.3		NR
	#259440	123841	*PPIB*	15q22.31		NR
	#613849	606633	*SP7*	12q13.13	See Table 4	
	#300910	300131	*PLS3*	Xq23	See Table 4	
OI with calcification in interosseous membranes and/or hypertrophic callus (OI type V)	#610967	614757	*IFITM5*	11p15.5	See Table 4	
Unclassified OI-like disorders:					Disorders with a phenotype similar to OI	
• Osteoporosis-pseudoglioma syndrome (OPPG)	#259770	603506	*LRP5*	11q13.1	See Table 4	
• Cole-Carpenter syndrome type 1	#112240	176790	*P4HB*	17q25.3	Craniosynostosis, ocular proptosis, hydrocephalus, distinctive facial features, bone phenotype similar to OI type IV with recurrent diaphyseal fractures	NR
• Cole-Carpenter syndrome type 2	#616294	607186	*SEC24D*	4q26	See above	

NR not reported

Table 6 Altered bone matrix proteins: disorders of alkaline phosphatase

Disease	OMIM phenotype number	OMIM gene/locus number	Gene	Chromosome location	Phenotype (systemic and bone-specific signs)	Main biochemical alterations
Hypophosphatasia (HPP)		171760	*ALPL*	1p36.12	Inborn error of bone and mineral metabolism caused by various defects in tissue-nonspecific alkaline phosphatase (TNSALP(ALPL) gene	**Low ALP**
• Perinatal	#241500				Almost always fatal, irritability, periodic apnea with cyanosis, bradycardia, unexplained fever, myelophthisic anemia (due to excess osteoid and unmineralized cartilage), intracranial hemorrhage, profound bone hypomineralization with bone deformities, fractures, craniosynostosis, osteochondral spurs that may pierce the skin and protrude laterally from midshaft of the ulnas and fibulas, dental abnormalities with deciduous teeth poorly formed	See exam in bold + high Ca
• Infantile	#241500				Postnatal but before 6 months of age, failure to thrive, hypotonia, bulging of the anterior fontanel, raised intracranial pressure and papilledema, proptosis, mild hypertelorism, brachycephaly, sclera may be blue, vitamin B_6-responsive seizures, rickets	See exam in bold + high Ca, high Ur Ca, high Pi (in heterozygotes), high Pi, high Ur Pi
• Childhood	#241500				After 6 months of age, premature loss of primary teeth (before 5 years) without tooth root resorption, non progressive myopathy, rickets, radiographic focal defect if cartilage that project from the growth plates into the metaphyses (tongues of radiolucency)	See exam in bold + normal Ca, high Pi due to high TmP/GFR, high Pi, high Ur PPi
• Adult	#146300				Premature loss of primary and secondary teeth, severe dental caries, decreased alveolar bone, enlarged pulp chamber; osteomalacia recurrent fractures, long bone pseudofractures, calcium pyrophosphate arthropathy, chondrocalcinosis metatarsal stress fracture	See exam in bold + normal Ca, high Pi due to high TmP/GFR
• Odontohypophosphatasia	#146300				Very mild form, early-onset periodontitis	NR
Hyperphosphatasia						**High ALP**
• Familial hydiopatic hyperphosphatasia/juvenile Paget's disease	#239000	602643	*TNFRS11B*	8q24.12	See Table 2	
• Hyperphosphatasia with mental retardation syndrome 1 (HPMRS1)	#239300	610274	*PIGV*	1p36.11	Mental retardation, various neurologic abnormalities such as seizures and hypotonia, facial dysmorphism, variable degrees of brachytelephalangy	See exam in bold + high Pi, normal Ca, markedly high ALP, high acid phosphatase, high uric acid
• Hyperphosphatasia with mental retardation syndrome 2 (HPMRS2)	#614749	614730	*PIGO*	9p13.3	Moderately to severely delayed psychomotor development, mental retardation, various neurologic abnormalities such as seizures and hypotonia, hypoplasic nails, long palpebral fissures, facial dysmorphism; variable degrees of brachytelephalangy	See above
• Hyperphosphatasia with mental retardation syndrome 3 (HPMRS3)	#614207	615187	*PGAP2*	11p15.4	Mild (in some patients), delayed psychomotor development, mental retardation, severe, intellectual disability, hypotonia, seizures, disorder in sleep pattern (in some patients), cerebral atrophy (in some patients), microcephaly	See above
• Hyperphosphatasia with mental retardation syndrome 4 (HPMRS4)	#615716	611801	*PGAP3*	17q12	Severely delayed psychomotor development with mental retardation, seizures, and dysmorphic facial features	See above

NR not reported

Table 7 Mutated bone microenvironment regulators (cytokines and growth factors): disorders of the RANK/RANKL/OPG system

Disease	OMIM phenotype number	OMIM gene/locus number	Gene	Chromosome location	Phenotype (systemic and bone-specific signs)	Main biochemical alterations
Hereditary familial expansile polyostotic osteolytic dysplasia (FEO)	#174810	603499	*TNFRSF11A*	18q21.33	See Table 2	
Osteopetrosis severe	#259710	602642	*TNFSF11*	13q14.11	See Table 1	
	#612301	603499	*TNFRSF11A*	18q21.33		
Juvenile Paget's disease	#239000	602643	*TNFRSF11B*	8q24.12	See Table 2	

Table 8 Mutated bone microenvironment regulators (cytokines and growth factors): disorders of the glycosylphosphatidylinositol biosynthetic pathway

Disease	OMIM phenotype number	OMIM gene/locus number	Gene	Chromosome location	Phenotype (systemic and bone-specific signs)	Main biochemical alterations
Hyperphosphatasia with mental retardation syndrome 1 (HPMRS1)	#239300	610274	*PIGV*	1p36.11	See Table 6	
Hyperphosphatasia with mental retardation syndrome 2 (HPMRS2)	#614749	614730	*PIGO*	9p13.3	See Table 6	
Hyperphosphatasia with mental retardation syndrome 3 (HPMRS3)	#614207	615187	*PGAP2*	11p15.4	See Table 6	
Hyperphosphatasia with mental retardation syndrome 4 (HPMRS4)	#615716	611801	*PGAP3*	17q12	See Table 6	

Table 9 Mutated bone microenvironment regulators (cytokines and growth factors): disorders of the LRP5

Disease	OMIM phenotype number	OMIM gene/locus number	Gene	Chromosome location	Phenotype (systemic and bone-specific signs)	Main biochemical alterations
Van Buchem disease type 2, autosomal dominant (VBCH2)	#607636	610274	*LRP5*	1p36.11	See Table 3	
High bone mass (HBM)	#607634	614730	*LRP5*	9p13.3	See Table 3	
Osteoporosis-pseudoglioma syndrome, autosomal recessive (OPPG)	#259770	603506	*LRP5*	11q13.1	See Table 4	
OI type III	#615220	164820	*WNT1*	12q13.12	See Table 5	

Table 10 Mutated bone microenvironment regulators (cytokines and growth factors): disorders of the bone morphogenetic protein receptor (BMPPR)

Disease	OMIM phenotype number	OMIM gene/locus number	Gene	Chromosome location	Phenotype (systemic and bone-specific signs)	Main biochemical alterations
Fibrodysplasia ossificans progressiva (FOP)	#135100	102576	*ACVR1*	2q24.1	Sporadic episodes of painful soft tissue swellings, occur which are often precipitated by soft tissue injury, intramuscular injections, viral infection, muscular stretching, falls or fatigue, sensorineural hearing loss, conductive hearing loss, widely spaced teeth, mental retardation, respiratory failure, intermittently progressive ectopic ossification and malformed big toes which are often monophalangic (hallux valgus, malformed first metatarsal, and/or monophalangism), flat, broad mandibular condyles, scoliosis, small cervical vertebral bodies, proximal medial tibial osteochondromas	High ALP, high Ur OHP

Table 11 Deranged calciotropic hormonal activity: parathyroid hormone excess or deficiency

Disease	OMIM phenotype number	OMIM gene/locus number	Gene	Chromosome location	Phenotype (systemic and bone-specific signs)	Main biochemical alterations
Primary hyperparathyroidism					Endocrine disorder resulting from a persistent hypercalcemia supported by an inadequate secretion of PTH; rarely it occurs in familial syndromes. Systemic signs: renal (polyuria, hypercalciuria, nephrolithiasis) skeletal, neuromuscular (myopathy, chondrocalcinosis, arthritis), central nervous system (fatigue, cognitive changes), gastrointestinal (peptic ulcer, pancreatitis), cardiovascular (hypertension, reduction QT interval), bone-specific signs: osteoporosis with a reduction of bone mineral density mainly of the cortical bone, osteitis fibrosa cystica in severe cases (subperiostal resorption of the phalange, salt and pepper appearance of the skull, bone cysts, brown tumors of the long bones)	**High Ca, low Pi, high Ur Pi, high Ur Ca, high PTH:**
• Multiple endocrine neoplasia type I (MEN 1)	#131100	613733	MEN1	11q13.1	Enteropancreatic endocrine tumors, anterior pituitary tumors	See exams in bold + other pituitary and/or enteropancreatic hormone alterations
• Multiple endocrine neoplasia type II (MEN2)	#171400	164761	RET	10q11.21	Medullary thyroid carcinoma, pehochromocytoma	See exams in bold (not always) + high calcitonin (always), high catecholamine/catecholamine metabolites
• Multiple endocrine neoplasia type IV (MEN4)	#610755	600778	CDKN1B	12p13.1	Enteropancreatic endocrine tumors, anterior pituitary tumors	See exams in bold + other pituitary and/or enteropancreatic hormone alterations
• Hereditary hyperparathyroidism jaw-tumor syndrome (HPT-JT)	#145001	607393	HRPT2	1q31.2	Fibro-osseous tumors of the jaw, benign and/or malignant lesions over the course of the lifetime (most common: Wilms' tumor, papillary renal carcinoma), polycystic kidney disease	See exams in bold
• Familial isolated primary hyperparathyroidism (FIHP)	#145000	613733 601199 607393	MEN1 CaSR HRPT2	11q13.1 3q21.1 1q31.2		See exams in bold
• Neonatal severe hyperparathyroidism (NSHPT)	#239200	601199	CaSR	3q21.1	Life-threatening, severe osteoporosis	Extremely high Ca, high Ur Ca, low Pi, high Ur Pi, high PTH
• Familial hypocalciuric hypercalcemia type I (HHC1)	#145980	601199	CaSR	3q21.1	Usually asymptomatic, rare bone involvement, pancreatitis and chondrocalcinosis	High Ca, low Ur Ca, CaCl/CrCl<0.01, high Mg, normal/high normal PTH
• Familial hypocalciuric hypercalcemia type II (HHC2)	#145981	139313	GNA11	19p13.3	See above	
• Familial hypocalciuric hypercalcemia type III (HHC3)	#600740	602242	AP2S1	19q13.32	See above	
Hypoparathyroidism					Endocrine deficiency disorder characterized by low serum calcium, elevated serum phosphorus, and absent or inappropriately low levels of parathyroid hormone, systemic signs: increases neuromuscular irritability (cramping, tetany, seizures) ocular (cataracts), cardiovascular (prolongation QT interval), soft tissue calcifications; bone-specific signs: increase in cancellous bone volume and cortical thickness	**Low Ca, high Pi, low/undetectable PTH, low 1,25(OH)$_2$D**

Table 11 (continued)

Disease	OMIM phenotype number	OMIM gene/locus number	Gene	Chromosome location	Phenotype (systemic and bone-specific signs)	Main biochemical alterations
Isolated hypoparathyroidism						
• Autosomal dominant hypocalcemia with hypercalciuria type 1 (HYPOC1)/Bartter syndrome subtype V	#601198	601199	CaSR	3q21.1	Mild or asymptomatic hypocalcemia, symptomatic hypocalcemia, rarely hypercalciuria, kidney stones and nephrocalcinosis, ectopic and basal ganglia calcifications, if associated with Bartter syndrome: hypokalemic metabolic alkalosis, high renin and aldosterone	See exams in bold + low-normal Mg, high-normal Ur Ca, low K (rare), high renin and aldosterone (rare)
• Autosomal dominant hypocalcemia with hypercalciuria type 2 (HYPOC2)	#615361	139313	GNA11	19p13.3	Mild or asymptomatic hypocalcemia, symptomatic hypocalcemia, rarely hypercalciuria, kidney stones and nephrocalcinosis, ectopic and basal ganglia calcifications	See exams in bold + low-normal Mg, high-normal Ur Ca
• Familial isolated hypoparathyroidism (FIH), autosomal dominant/autosomal recessive	#146200	168450 603716	PTH GCMB	11p15.2 6p24.2	Severe, early-onset (congenital), life-threatening hypocalcemia, neonatal seizures, parathyroid hypoplasia/aplasia	See exams in bold
Familial isolated hypoparathyroidism, X-linked recessive (HYPX)	#307700	–	SOX3	Xq26-q27	Severe, early-onset (congenital), life-threatening hypocalcemia, neonatal seizures, parathyroid hypoplasia/aplasia	See exams in bold
Hypoparathyroidism in complex disorders						
• DiGeorge syndrome type 1 (DGS1)	#188400	602054	TBX1	22q11.2	Thymic hypoplasia with T-cell deficiency, often early-onset, congenital hypocalcemia, with cardiac defects, craniofacial deformities	Neonates: low Ca Adults: low Ca in 65 % of cases, low PTH
• DiGeorge syndrome type 2 (DGS2)	#601362	–	NEBL	10p14-p13	Thymic hypoplasia with T-cell deficiency, often early-onset, congenital hypocalcemia, cardiac defects, craniofacial deformities	See exams in bold
• Hypoparathyroidism, sensorineural deafness, renal disease (HDR)	#146255	131320	GATA3	10p14	Early-onset, congenital and severe hypocalcemia, deafness, renal anomalies	See exams in bold
• Kenny-Caffey syndrome type 1 (KCS1)	#244460	604934	TBCE	1q42.3	Early-onset hypocalcemia, basal ganglial calcification, nanophthalmos and hyperopia, dental abnormalities; medullary stenosis of long bones, short stature, osteosclerosis, cortical thickening of the long bones, delayed closure of the anterior fontanel	See exams in bold + anemia, low/normal Mg
• Kenny-Caffey syndrome type 2 (KCS2)	#127000	615292	FAM111A	11q12.1	See above	Anemia (not always), low Ca (transient), high Pi (transient), low PTH, low/normal Mg
• Hypoparathyroidism, retardation, dysmorphism syndrome (HRD)	#241410	604934	TBCE	1q42.3	Early-onset hypocalcemia, deep-set eyes, microcephaly, thin lips, depressed nasal, bridge, posteriorly rotated ears, tetany, mental retardation, growth retardation	See exams in bold
• Gracile bone dysplasia (GCLEB)	#602361	615292	FAM111A	11q12.1	Severe hypoparathyroidism with high perinatal lethality, thin long bones, premature closure of basal cranial sutures, stenosis the medullary cavity of the long bones, microphthalmia, triangular face with frontal bossing	See exams in bold
• Autoimmune hypoparathyroidism polyendocrine syndrome type 1 (APS1)	#240300	607358	AIRE	21q22.3	Hypoparathyroidism (100 %), chronic mucocutaneous candidiasis, autoimmune adrenal insufficiency	See exams in bold + other hormone alterations

Table 11 (continued)

Disease	OMIM phenotype number	OMIM gene/locus number	Gene	Chromosome location	Phenotype (systemic and bone-specific signs)	Main biochemical alterations
• Autoimmune hypoparathyroidism polyendocrine syndrome type 2 (APS2)	#269200	142860	HLA haplotype DR3 DR4	6p21.32	Hypoparathyroidism, autoimmune Addison's disease, insulin-dependent diabetes, primary hypergonadotropic hypogonadism, autoimmune thyroid disease, pernicious anemia, alopecia, vitiligo chronic autoimmune hepatitis, hypophysitis, myasthenia gravis, rheumatoid arthritis, Sjögren's syndrome, thrombocytic purpura	See exams in bold + other hormone alterations
Mitochondrial diseases:					Severe multiorgan conditions, with high perinatal lethality, sometimes associated with hypoparathyroidism	See exams in bold + high CSF proteins (>100 mg/dl), low CSF folic acid, lactic acidosis, low serum and muscle coenzyme Q
• Kearns-Sayre syndrome (KSS)	#530000	–	mitoc.DNA			
• Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS)	#540000	–	mitoc.DNA			
• Mitochondrial trifunctional protein deficiency (MTPD)	#609015	600890 143450	HADHA/ HADHB	2p23.3 2p23.3		
Medium chain acylCoA dehydrogenase deficiency (ACADMD)	#201450	607008	ACADM	1p31.1		+ Low plasma carnitine levels

Table 12 Deranged calciotropic hormonal activity: abnormal parathyroid hormone receptor signaling

Disease	OMIM phenotype number	OMIM gene/locus number	Gene	Chromosome location	Phenotype (systemic and bone-specific signs)	Main biochemical alterations
Gsα abnormalities						
• Pseudohypoparathyroidism					Increased neuromuscular irritability (spasms, tetany, seizures) ocular (cataracts), cardiovascular (prolongation QT interval), soft tissue calcifications	**Low Ca, high Pi, high PTH, low/normal 1-25(OH)$_2$D$_3$**
- Type Ia (PHP1A)	#103580	139320	GNAS (maternal)	20q13.32	Albright hereditary osteodystrophy (obesity, round face, mild mental retardation, basal nuclei calcifications) with multihormonal resistance (to TSH, gonadotropins, GHRH), increase in cancellous bone volume and cortical thickness, short stature, premature closure of growth plate, brachydactyly (IV metacarpal), ectopic ossifications	See exams in bold + low Ur cAMP in response to PTH + multiple hormone resistance
- Type Ib (PHP1B)	#603233	603666 610540 139320	STX16 GNASAS1 GNAS	20q13.32 20q13.32 20q13.32	Resistance to PTH without multihormonal resistance	See exams in bold + low Ur cAMP in response to PTH
- Type Ic (PHPIC)	#612462	139320	GNAS	20q13.32	Resistance to PTH usually not associated to other hormonal resistance, hyperparathyroid bone disease (in some cases osteitis fibrosa cystica)	See exams in bold + low Ur cAMP in response to PTH
- Type II (PHP2)	#203330	–	–	–	Resistance to PTH usually not associated to resistance to other hormones	See exams in bold + normal Ur cAMP in response to PTH
• Pseudo-pseudohypoparathyroidism (PPHP)	#612463	139320	GNAS (paternal)	20q13.32	Albright hereditary osteodystrophy (obesity, round face, mild mental retardation, basal nuclei calcifications) without multihormonal resistance	Normal Ca, normal Pi, normal PTH
• Acrodysostosis 1 (ACRDYS1)	#101800	188830	PRKAR1A	17q24.2	Form of skeletal dysplasia characterized by brachydactyly, short stature, obesity, facial dysostosis and nasal hypoplasia (features of Albright hereditary osteodystrophy)	Low or normal Ca and Pi, low or normal PTH, ± multiple hormone resistance
• Acrodysostosis 2 (ACRDYS2)	#614613	600129	PDE4D	5q12	See above	See above
• Progressive osseous heteroplasia (POH)	#166350	139320	GNAS (paternal)	20q13.32	Autosomal dominant disorder characterized by heterotopic ossifications in the dermis (osteoma cutis) with possible extension to deep tissues, intramembranous ossification; rarely Albright hereditary osteodystrophy	Normal Ca, normal Pi, normal PTH
• McCune-Albright syndrome (MAS)	#174800	139320	GNAS	20q13.32	Disorder that affects the bones, skin (café-au-lait pigmentation), and several endocrine tissues with possible precocious puberty, hyperthyroidism, excessive secretion of growth hormone, Cushing syndrome, polyostotic fibrous dysplasia (scar-like/fibrous tissue in the bones, often confined to one side of the body), some cases of hypophosphatemic osteomalacia, craniofacial hyperostosis	Normal-high Ca, normal-low Pi, normal-high PTH, normal/high 1-25(OH)$_2$D$_3$ + other endo-crine abnormalities
PTH/PTHrP receptor abnormalities						
• chondrodysplasias with mineral ion homeostasis abnormalities					Chondrodysplasias with mineral ion homeostasis abnormalities due to alterations of the PTH/PTHrP receptor gene (PTHR1) gene, which usually mediates the actions of the two ligands: PTH and PTH-related peptide	

Table 12 (continued)

Disease	OMIM phenotype number	OMIM gene/locus number	Gene	Chromosome location	Phenotype (systemic and bone-specific signs)	Main biochemical alterations
- Metaphyseal chondrodysplasia Jansen type (JMC)	#156400	168468	PTHR1	3p21.31	High skull vault, flattening of the nose and forehead, low-set ears, hypertelorism, high arched palate, micrognathia, retrognathia, kyphoscoliosis with bell-shaped thorax and widened costochondral junctions, metaphyseal enlargement of the joints, frontonasal hyperplasia, short legs and relatively long arms; in younger patients: enlargement of metaphyses with a wide zone of irregular calcifications (lesions similar to rickets) *At puberty:* partially calcified cartilage that protrude into diaphysis *Late adolescence:* cartilaginous tissue in the metaphysis disappears, sclerosis and thickening of the base of skull with cranial auditory and optical nerve compression	High Ca, low Pi, high Ur Pi, high Ur Ca, high Ur cAMP, suppressed/low-normal PTH
- Chondrodysplasia Blomstrand type (BOCD)	#215045	168468	PTHR1	3p21.31	Early lethality, defects of mammary gland and of tooth development, hypoplasia of nasal, mandibular and facial bones, short thick ribs, hypoplasia of the vertebrae, hyperdensity of the whole skeleton, markedly advanced ossification *Long bones:* extremely short and poorly modeled, no zones of chondrocyte proliferation and of column formation are lacking	Low Ca, high PTH, low Ur Pi, high Ur cAMP
- Eiken familial skeletal dysplasia	#600002	168468	PTHR1	3p21.31	Multiple epiphyseal dysplasia	Normal-high PTH
- Multiple enchondromatosis, Ollier type	#166000	168468 147700 147650	PTHR1 IDH1 IDH2	3p21.31 2q34 15q26.1	Soft tissue hemangiomas (Maffucci syndrome), multiple enchondromas with skeletal deformities and potential risk for malignant change to chondrosarcoma	Slightly high PTH

Table 13 Deranged calciotropic hormonal activity: disorders of vitamin D metabolism and action

Disease	OMIM phenotype number	OMIM gene/ locus number	Gene	Chromosome location	Phenotype (systemic and bone-specific signs)	Main biochemical alterations
Disorders of vitamin D metabolism					Alteration of vitamin D metabolism causes defects in the growth plate and bone demineralization that is called rickets in children and osteomalacia in adults	**Low Ca, low Pi, high bone ALP**
• Vitamin D hydroxylation-deficient rickets type 1A (VDDR1A)	#264700	609506	*CYP27B1*	12q14.1	Growth retardation, muscle weakness, irritability, congenital rickets with enlarged costochondral junctions of the ribs, pectus carinatum, metaphyseal flaring of the wrists or ankles, genus varus, frontal bossing enlarges sutures and fontanels or craniotabes, long bone deformities	See exams in bold + low 1,25(OH)$_2$D, normal 25 OH D, slightly high PTH, generalized aminoaciduria
• Vitamin D hydroxylation-deficient rickets type 1B (VDDR1B)	#600081	608713	*CYP2R1*	11p15.2	Hypotonia, muscle weakness, difficulty in walking, difficulty in standing, congenital rickets with fractures, bone pain, sparse bone trabeculae, thin bony cortex, delayed opacification of the epiphyses, widened, distorted epiphyses, frayed, irregular metaphyses, lower limb deformities, bowing of the legs	See exams in bold + normal 1,25(OH)$_2$D, decreased 25 OH D
Disorders of vitamin D action						
• Vitamin D-dependent rickets type 2A (VDDR2A)	#277440	601769	*VDR*	12q13.11	Growth retardation, muscle weakness, convulsion for hypocalcemia, bone pain at the lower extremities that delays their development of walking, dental caries or hypoplasia of the teeth, scalp and total alopecia, mild deafness, congenital rickets with fracture and pseudofractures, sparse bone trabeculae, thin bony cortex, delayed opacification of the epiphyses, widened, distorted epiphyses, frayed, irregular metaphyses, lower limb deformities, bowing of the legs, curvatures of the femur, tibia, fibula, enlargement of the wrists, enlargement of the ankles, subperiosteal erosions due to secondary hyperparathyroidism	High 1,25(OH)$_2$D normal 25 OH D, markedly high PTH, markedly high bone ALP
• Vitamin D-dependent rickets type 2B (VDDR2B)	#600785	–	–	–	See above	

Table 14 Deranged calciotropic hormonal activity: disorders of phosphate homeostasis

Disease	OMIM phenotype number	OMIM gene/locus number	Gene	Chromosome location	Phenotype (systemic and bone-specific signs)	Main biochemical alterations
Hypophosphatemic disorders					Group of disorders with similar clinical and biochemical features represented by hypophosphatemia, hyperphosphaturia	
Phosphatonin-related disorders:						**High Ur P, low Pi, low renal TmP/GFR, normal Ca, low-normal Ur Ca, normal 25 OH D; low-normal 1,25(OH)$_2$D, high bone ALP**
• Autosomal dominant hypophosphatemic rickets (ADHR)	#193100	605380	*FGF23*	12p13.32	Fatigue and muscle weakness, short stature, *early onset* (1–3 years): severe bowing of lower extremities, rickets with enlarged costochondral junctions of the ribs; *late onset* (puberty): bone pain (no bowing of lower extremities)	See exams in bold + high intact FGF23, normal PTH
• X-linked, dominant, hypophosphatemic rickets (XLHR)	#307800	300550	*PHEX*	Xp22.11	Late dentition, tooth abscesses secondary to poor mineralization, bowing of lower extremities, enlarged costochondral junctions of the ribs, pectum carinatum, metaphyseal flaring of the wrists or ankles, genus varus, frontal bossing enlarges sutures and fotanels or craniotabes	See exams in bold + high intact FGF23, normal PTH, rarely low GH
• Osteoglophonic dysplasia (OGD)	#166250	136350	*FGFR1*	9p11.23-p11.22	Macroglossia, hypertrophy of the gums, severe dwarfism, mandibular prognathism, frontal bossing, and proptosis; rickets/osteomalacia, severe craniofacial abnormalities, bone dysplasia	See exams in bold + high/normal intact FGF23, normal PTH
• Autosomal recessive hypophosphatemic rickets type 1 (ARHR1)	#241520	600980	*DMP1*	4q22.1	Short stature; limited movement of spine and hip, calcification of the ligaments at the bony insertions sites, high bone density at the base of skull, clavicle and rib anomalies, enthesopathies	See exams in bold + high intact FGF23, normal PTH
• Autosomal recessive hypophosphatemic rickets type 2 (ARHR2)	#613312	173335	*ENPP1*	6q23.2	See above	
• Arterial calcification of infancy	#208000	173335	*ENPP1*	6q23.2	Short stature, deafness, conductive (in some patients), angioid retinal streaks (in some patients), coronary and generalized artery calcification, cardiac dysfunction, periarticular calcification, hypophosphatemic rickets, pseudoxanthoma	Low Pi
• Hypophosphatemic rickets with hyperparathyroidism (HRH)	#612089	604824	*KLOTHO*	13q13.1	Kidney stones, rickets	See exams in bold + high PTH (normal intact FGF23)
Phosphatonin-unrelated disorders:						**High Ur P, low Pi, low renal TmP/GFR, normal calcium, high Ur Ca, low/normal PTH, normal 25 OH D, high 1,25(OH)$_2$D, high bone ALP**
• Hereditary hypophosphatemic rickets with hypercalciuria (HHRH)	#241530	609826	*SLC34A3 (NPTIIc)*	9q34.3	Kidney stone, nephrocalcinosis, rickets/osteomalacia	See exams in bold + normal/high Ca, normal intact FGF23

Table 14 (continued)

Disease	OMIM phenotype number	OMIM gene/locus number	Gene	Chromosome location	Phenotype (systemic and bone-specific signs)	Main biochemical alterations
• Hypophosphatemia nephrolithiasis osteoporosis type 1 (NPHLOP1)	#612286	182309	*SLC34A1 (NPTIIa)*	5q35.3	Kidney stones, nephocalcinosis, osteoporosis	See exams in bold + normal Ca, normal intact FGF23
• Hypophosphatemia nephrolithiasis osteoporosis type 2 (NPHLOP2)	#612287	604990	*SLC9A3R1*	17q25.1	See above	
Hyperphosphatemic disorders						
Tumoral calcinosis						
• Hyperphosphatemic familial tumoral calcinosis (HFTC)/hyperostosis hyperphosphatemia syndrome (HHS)	#211900	605380 601756 604824	*FGF23* *GALNT3* *KLOTHO*	12p13.32 2q24.3 13q13.1	Periarticular cystic and solid tumoral calcifications with hyperphosphatemia and hypophosphaturia and elevated serum of calcitriol, soft tissue masses around major joints, dental abnormalities, ocular involvement with range from angioid streaks to corneal calcification deposits and neuronal calcifications, altered skeletal mineralization, low/normal bone mass	Low Ur P, high Pi, high TmP/GFR, normal Ca, normal Ur Ca, normal PTH, normal 25 OH D, high 1,25$(OH)_2$D, low intact FGF23
Normophosphatemic disorders resembling hyperphosphatemic disorders						
• Normophosphatemic familial tumoral calcinosis (NFTC)	#610455	610456	*SAMD9*	7q21.2	Reddish to hyperpigmented skin lesions, soft tissue masses at the extremities, severe conjunctivitis, severe gingivitis, no altered skeletal mineralization	Normal Pi, normal Ur P

Conclusions

In conclusion, with the present report, the IOF's SRD-WG provides for the first time a metabolic classification for RGMBDs. Surprisingly perhaps, bone remodeling phenotype is not known for all diseases of metabolic origin. However, knowledge of the metabolic pathway that characterizes a given disorder may help in the management of such patients. Indeed, for the majority of these disorders, disease-targeted therapies are still missing, restricting the choice between antiresorptive and anabolic agents in complicated syndromes, often in children. The metabolic profile may help in selecting the most appropriate pharmacological treatment in patients affected by RGMBDs. It is intended that this taxonomic paper will provide the core and the structural framework for the development of a web-based atlas for rare metabolic skeletal diseases by the International Osteoporosis Foundation with a detailed description and a guided diagnostic workup for each disease, leading to a targeted therapeutic approach on the basis of the available metabolic hallmarks and structural phenotypes.

Acknowledgments This paper was supported by the *IOF*.

Conflicts of interest None.

References

1. (2013) Report on the state of the art of rare disease activities in Europe; European Union Committee of Expert on Rare Disease. Overview of rare disease activities in Europe. Part I; pp. 1–78 http://www.eucerd.eu/upload/file/Reports/2013ReportStateofArtRDActivities.pdf
2. Ayme S, Schmidtke J (2007) Networking for rare diseases: a necessity for Europe. Bundesgesundheitsbl Gesundheitsforsch Gesundheitsschutz 50:1477–1483
3. Available from: National Organization for Rare Diseases (NORD) of the United States: www.rarediseases.org. Accessed Jan 2015
4. Haffner ME, Whitley J, Moses M (2002) Two decades of orphan product development. Nat Rev Drug Discov 10:821–825
5. Braun MM, Farag-El-Massah S, Xu K, Coté TR (2010) Emergence of orphan drugs in the United States: a quantitative assessment of the first 25 years. Nature Reviews Drug Discovery 9:519–522
6. For a list of rare diseases and their prevalence, please consult the Orphanet Reports Series "Prevalence of rare diseases: bibliographic data", Orphanet Report Series, Rare Diseases collection, Number 1: Listed in alphabetical order of diseases, http://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf. Accessed Jan 2015
7. Villa S, Compagni A, Reich MR (2009) Orphan drug legislation: lessons for neglected tropical diseases. Int J Health Plann Manage 24:27–42
8. (2010) 5th European conference on rare diseases. European reference networks & centers of expertise for rare diseases, pp. 1–75
9. Available from: EUROPLAN website: www.europlanproject.eu. Accessed Jan 2015
10. Commission Regulation (EC) No 847/2000 of 27 April 2000; OJ L 103, 28.4.2000
11. Macarthur D (2011) Orphan drugs in Europe: pricing, reimbursement, funding & market access issues, Edition www.justpharmareports.com
12. Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products. Revision 2005, http://ec.europa.eu/health/files/orphanmp/doc/inventory_2006_08_en.pdf. Accessed Jan 2015
13. Available from: Orphabioetic foundation: www.orphanbiotec-foundation.com. Accessed Jan 2015
14. Commission Regulation (EC) No 847/2000 of 27 April 2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concepts 'similar medicinal product' and 'clinical superiority'. Off J Eur Commun 103/5-103/8
15. Available from: Orphanet Activity Report 2012, http://www.orpha.net/orphacom/cahiers/docs/GB/ActivityReport2012.pdf. Accessed Jan 2015
16. Thorat C, Xu K, Freeman SN, Bonnel RA, Joseph F, Phillips MI, Imoisili MA (2012) What the Orphan Drug Act has done lately for children with rare diseases: a 10-year analysis. Pediatrics 129:516–521
17. Forman J, Taruscio D, Llera VA, Barrera LA, Coté TR, Edfjall C, Gahved D, Haffner ME, Nishimura Y, Posada M, Tambuyzer E, Groft SC, Henter J-I (2012) The need for world-wide policy and actions plans for rare diseases. Acta Pediatr 101:805–807
18. Roldán EJA (2013) Proceedings from the VIII International Conference on Rare Diseases and Orphan Drugs (ICORD), St Petersburg (Russia). Rare J 1(suppl 1):1–48
19. Mäkitie O (2011) Molecular defects causing skeletal dysplasias. Camacho-Hübner C, Nilsson O, SŠvendahl L (eds) Cartilage and bone development and its disorders. Endocr Dev. Basel, Karger, vol 21, pp 78–84
20. (1970) International nomenclature of constitutional diseases of bones. Ann Radiol (Paris) 13(7):455–464
21. (1971a) A nomenclature for constitutional (intrinsic) diseases of bones. J Pediatr 78(1):177–179
22. (1971b) International nomenclature of constitutional bone diseases. Constitutional bone diseases without known pathogenesis. Arch Fr Pediatr 28(5):553–557
23. Nomenclature for constitutional (intrinsic) diseases of bones. (1971c) Pediatrics 47(2):431–344. Nomenclature for the constitutional (intrinsic) diseases of bone. Radiology. 1971d; 99(3):699–702
24. McKusick VA, Scott CI (1971) A nomenclature for constitutional disorders of bone. J Bone Joint Surg Am 53(5):978–986
25. Warman ML, Cormier-Daire V, Hall C, Krakow D, Lachman R, LeMerrer M, Mortier G, Mundlos S, Nishimura G, Rimoin DL, Robertson S, Savarirayan R, Sillence D, Spranger J, Unger S, Zabe B, Superti-Furga A (2011) Nosology and classification of genetic skeletal disorders—2010 revision. Am J Med Genet A 155A(5):943–968
26. Superti-Furga A, Unger S (2007) Nosology and classification of genetic skeletal disorders: 2006 revision. Am J Med Genet A 143(1):1–18
27. Boyce BF, Zuscik MJ, Xing L (2013) Biology of bone and cartilage. In: Thakker RV, Whyte MP, Eisman JA, Igarashi T (eds) 1 edn. Genetics of bone biology and skeletal diseases. Ch. 1 pp. 3–24
28. Pagani F, Francucci CM, Moro L (2005) Markers of bone turnover: biochemical and clinical perspectives. J Endocrinol Invest 28:8–13
29. Berndt TJ, Schiavi S, Kumar R (2005) Phosphatonins and the regulation of phosphorus homeostasis. Am J Renal Physiol 289:1170–1182
30. Kumar R, Riggs R (1980) Pathologic bone physiology. In: Urist MR (ed) Fundamental and clinical bone physiology. Lippincott, Philadelphia, pp 394–406

31. Schiavi SC, Moe OW (2002) Phosphatonins: a new class of phosphate regulating proteins. Curr Opin Nephrol Hypertens 11:423–430
32. Brown EM, MacLeod RJ (2001) Extracellular calcium sensing and extracellular calcium signaling. Physiol Rev 81:239–297
33. Alfadda TI, Saleh AM, Houllier P, Gaidel JP (2014) Calcium-sensing receptor 20 years later. Am J Physiol 307(3):C221–C231
34. Kumar R (1990) Vitamin D metabolism and mechanisms of calcium transport. J Am Soc Nephrol 1:30–42
35. Fleisch H (1980) Homeostasis of inorganic phosphate. In: Urist MR (ed) Fundamental and clinical bone physiology. Lippincott, Philadelphia, pp 268–282
36. Burtis WJ, Wu T, Bunch C, Wysolmerski JJ, Insogna KL, Weir EC, Broadus AE, Stewart AF (1987) Identification of a novel 17,000-dalton parathyroid hormone-like adenylate cyclase-stimulating protein from a tumor associated with humoral hypercalcemia of malignancy. J Biol Chem 262:7151–7156
37. Kronenberg HM (2003) Developmental regulation of the growth plate. Nature 2423:332–336
38. Juppner H, Silve C (2013) Genetic disorders affecting PTH/PTHrP receptor function. In: Thakker RV, Whyte MP, Eisman JA, Igarashi T (eds) Genetics of bone biology and skeletal diseases. Ch. 28, pp. 441–457
39. Qin C, Baba O, Butler WT (2004) Post-translational modifications of sibling proteins and their roles in osteogenesis and dentinogenesis. Crit Rev Oral Biol Med 15:126–136
40. Econs MJ, Drezner MK (1994) Tumor induced osteomalacia unveiling a new hormone. N Engl J Med 330:1679–1681
41. Quarles LD (2003) FGF23, PHEX, and MEPE regulation of phosphate homeostasis and skeletal mineralization. Am J Physiol Endocrinol Metab 285:E1–9
42. Boyce BF, Yao Z, Zing L (2009) Osteoclasts have multiple roles in bone in addition to bone resorption. Crit Rev Eukaryot Gene Expr 19:171–80
43. Fukuchi M, Fukai Y, Masuda N, Miyazaki T, Nakajima M, Sohda M, Manda R, Tsukada K, Kato H, Kuwano H (2002) High-level expression of the Smad ubiquitin ligase Smurf2 correlates with poor prognosis in patients with esophageal squamous cell carcinoma. Cancer Res 62:7162–7165
44. Takayanagi H (2007) Osteoimmunology: shared mechanisms and crosstalk between the immune and bone systems. Nat Rev Immunol 7:292–304
45. Hofbauer LC, Kühne CA, Viereck V (2004) The OPG/RANKL/RANK system in metabolic bone diseases. J Musculoskelet Neuronal Interact 4:268–75
46. Henriksen K, Bollerslev J, Everts V, Karsdal MA (2011) Osteoclast activity and subtypes as a function of physiology and pathology—implications for future treatments of osteoporosis. Endocrine Reviews 32:31–63
47. Ross PF (2013) Osteoclast biology and bone resorption. In: Primer on the metabolic bone diseases and disorders of mineral metabolism. Official publication of the American Society for Bone and Mineral Research (ASBMR) 8 edn Ch. 3 pp.25–33
48. Blair HC, Teitelbaum SL, Ghiselli R, Gluck S (1989) Osteoclastic bone resorption by a polarized vacuolar proton pump. Science 245: 855–857
49. Blair HC, Teitelbaum SL, Tan HL, Koziol CM, Schlesinger PH (1991) Passive chloride permeability charge coupled to H(+)-ATPase of avian osteoclast ruffled membrane. Am J Physiol 260: C1315–C1324
50. Josephsen K, Praetorius J, Frische S, Gawenis LR, Kwon TH, Agre P, Nielsen S, Fejerskov O (2009) Targeted disruption of the Cl/HCO3 exchanger Ae2 results in osteopetrosis in mice. Proc Natl Acad Sci USA 106:1638–1641
51. Baron R, Neff L, Louvard D, Courtoy PJ (1985) Cell-mediated extracellular acidification and bone resorption: evidence for a low pH in resorbing lacunae and localization of a 100-kD lysosomal membrane protein at the osteoclast ruffled border. J Cell Biol 101: 2210–2222
52. Frattini A, Orchard PJ, Sobacchi C, Giliani S, Abinun M, Mattsson JP, Keeling DJ, Andersson AK, Wallbrandt P, Zecca L, Notarangelo LD, Vezzoni P, Villa A (2000) Defects in TCIRG1 subunit of the vacuolar proton pump are responsible for a subset of human autosomal recessive osteopetrosis. Nat Genet 25:343–346
53. Karsdal MA, Henriksen K, Sørensen MG, Gram J, Schaller S, Dziegiel MH, Heegaard AM, Christophersen P, Martin TJ, Christiansen C, Bollerslev J (2005) Acidification of the osteoclastic resorption compartment provides insight into the coupling of bone formation to bone resorption. Am J Pathol 166:467–47
54. Henriksen K, Gram J, Schaller S, Dahl BH, Dziegiel MH, Bollerslev J, Karsdal MA (2004) Characterization of osteoclasts from patients harboring a G215R mutation in ClC-7 causing autosomal dominant osteopetrosis type II. Am J Pathol 164: 1537–1545
55. Arnett TA (2008) Extracellular pH regulates bone cell function. J Nutr 138:415S–418S
56. Tolar J, Teitelbaum SL, Orchard PJ (2004) Osteopetrosis. N Engl J Med 351:2839–2849
57. Jansen ID, Mardones P, Lecanda F, de Vries TJ, Recalde S, Hoeben KA, Schoenmaker T, Ravesloot JH, van Borren MM, van Eijden TM, Bronckers AL, Kellokumpu S, Medina JF, Everts V, Oude Elferink RP (2009) Ae2a, b-deficient mice exhibit osteopetrosis of long bones but not of calvaria. FASEB J 23:3470–3481
58. Gowen M, Lazner F, Dodds R, Kapadia R, Field J, Tavaria M, Bertoncello I, Drake F, Zavarselk S, Tellis I, Hertzog P, Debouck C, Kola I (1999) Cathepsin K knockout mice develop osteopetrosis due to a deficit in matrix degradation but not demineralization. J Bone Miner Res 14:1654–1663
59. Calvo MS, Eyre DR, Gundberg CM (1996) Molecular basis and clinical application of biological markers of bone turnover. Endocr Rev 17:333–368
60. Singer FR, Eyre MD (2008) Using biochemical markers of bone turnover in clinical practice. Cleveland Clinic Journal of Medicine 75:739–750
61. Bergmann P, Body JJ, Boonen S, Boutsen Y, Devogelaer JP, Goemaere S, Kaufman JM, Rozenberg S, Reginster JY (2009) Evidence-based guidelines for the use of biochemical markers of bone turnover in the selection and monitoring of bisphosphonate treatment in osteoporosis: a consensus document of the Belgian Bone Club. Int J Clin Pract 63:19–26
62. Suwanwalaikorn S, Van Auken M, Kang MI, Alex S, Braverman LE, Baran DT (1997) Site selectivity of osteoblast gene expression response to thyroid hormone localized by in situ hybridization. Am J Physiol 272(2 Pt 1):E212–217
63. Kasperk C, Wergedal J, Strong D, Farley J, Wangerin K, Gropp H, Ziegler R, Baylink DJ (1995) Human bone cell phenotypes differ depending on their skeletal site of origin. J Clin Endocrinol Metab 80(8):2511–2517
64. Orimo H (2010) The mechanism of mineralization and the role of alkaline phosphatase in health and disease. J Nippon Med Sch 77: 4–12
65. Mortland M, Robison R (1929) The preparation and use of the phosphatase. Biochem J 23:237–242
66. Seibel MJ (2005) Biochemical markers of bone turnover: part I: biochemistry and variability. Clin Biochem Rev 26:97–122
67. Gundberg CM, Markowitz ME, Mizruchi M, Rosen JF (1985) Osteocalcin in human serum: a circadian rhythm. J Clin Endocrinol Metab 60:736–739
68. Delmas PD, Wilson DM, Mann KG, Riggs BL (1983) Effect of renal function on plasma levels of bone Gla-protein. J Clin Endocrinol Metab 57:1028–1030

69. Bergmann P, Body JJ, Boonen S, Boutsen Y, Devogelaer JP, Goemaere S, Kaufman JM, Reginster JY, Gangji V, Members of Advisory Board on Bone Markers (2009) Evidence-based guidelines for the use of biochemical markers, bone turnover: biomarkers of bone turnover. Int J Clin Pract CME 63(1):19–26
70. Keen RW (2013) Sclerosing and displastic bone diseases. In: Primer on the metabolic bone diseases and disorders of mineral metabolism. 8 edn, Wiley, Ames, section VIII, pp 767–842
71. Franz-Odendaal TA, Hall BK, Witten PE (2006) Buried alive: how osteoblasts become osteocytes. Dev Dyn 235:176–190
72. Burger EH, Klein-Nulend J (1999) Mechanotransduction in bone—role of the lacuno-canalicular network. FASEB J 13(Suppl):S101–112
73. Li X, Liu P, Liu W, Maye P, Zhang J, Zhang Y, Hurley M, Guo C, Boskey A, Sun L, Harris SE, Rowe DW, Ke HZ, Wu D, Liu LX (2005) Dkk2 has a role in terminal osteoblast differentiation and mineralized matrix formation. Nat Genet 37:945–952
74. Bonewald LF, Johson ML (2008) Osteocytes, mechanosensing and Wnt signaling. Bone 42:606–615
75. Tatsumi S, Ishii K, Amizuka N, Li M, Kobayashi T, Kohno K, Ito M, Takeshita S, Ikeda K (2007) Targeted ablation of osteocytes induces osteoporosis with defective mechanotransduction. Cell Metabolism 5:464–475
76. Moriishi T, Fukuyama R, Ito M, Miyazaki T, Maeno T, Kawai Y, Komori H, Komori T (2012) Osteocyte network; a negative regulatory system for bone mass augmented by the induction of Rankl in osteoblasts and Sost in osteocytes at unloading. PLoS ONE 7(6): e401–443
77. Bonewald LF (2007) Osteocytes as dynamic multifunctional cells. Ann N Y Acad Sci 1116:281–290
78. Kneissel M (2009) The promise of sclerostin inhibition for the treatment of osteoporosis. IBMS BoneKEy 6:259–264
79. Dalla SL, Bonewald LF (2010) Dynamics of the transition from osteoblast to osteocyte. Ann N Y Acad Sci 1192:437–443
80. Guo D et al (2006) Identification of proteins involved in cytoskeletal rearrangement, anti-hypoxia and membrane channels in osteocytes over osteoblasts. J Bone Miner Res 21:S168
81. Gentili C, Cancedda R (2009) Cartilage and bone extracellular matrix. Curr Pharm Des 15:1334–1348
82. Robey PG, Boskey AL. The composition of bone. In: Primer on the bone metabolic diseases and disorders of mineral metabolism. Seventh ed. Official publication of the American Society for Bone and Mineral Research Ch. 6 pp. 32–38
83. Rossert J, de Crombrugghe B (1996) Type I collagen: structure, synthesis, and regulation. In: JP Bilezikian, Raisz LC, Rodan Ga (eds) Principle of bone biology. 1st edn. Ch. 10 pp. 127–142
84. Lian JB, Stein GS (2006) The cells of bone. In: Seibel MJ, Robins S, Bilezikian JP (eds) Dynamics of bone and cartilage metabolism. Academic, San Diego
85. Lee NK, Sowa H, Hinoi E, Ferron M, Ahn JD, Confavreux C, Dacquin R, Mee PJ, McKee MD, Jung DY, Zhang Z, Kim JK, Mauvais-Jarvis F, Ducy P, Karsenty G (2007) Endocrine regulation of energy metabolism by the skeleton. Cell 130:456–469