Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Chapter from the book Human Genetic Diseases
Downloaded from: http://www.intechopen.com/books/human-genetic-diseases

Interested in publishing with InTechOpen?
Contact us at book.department@intechopen.com
Osteoclast Genetic Diseases

Andrea Del Fattore¹ and Anna Teti²

¹Ospedale Pediatrico Bambino Gesù, Rome
²University of L’Aquila, L’Aquila
Italy

1. Introduction

Bone is a specialized connective tissue that performs many important functions: (i) mechanical, supporting the whole body and allowing the movements; (ii) protective, shielding many vital organs, such as brain, lung, heart and bone marrow; (iii) metabolic, regulating the homeostasis of calcium and phosphate (Baron, 1999); (iv) endocrine, regulating kidney function (Fukumoto & Martin, 2009; Mazzaferro et al., 2010) and contributing to global energy balance (Ducy et al., 1996; Ferron et al., 2010; Lee et al., 2007) and male fertility (Oury et al., 2011). Bone is a dynamic tissue, subjected to a continuous process of renewal and remodelling in which bone resorption by osteoclasts and bone formation by osteoblasts occur at the same site along the bone surface (Pogoda et al., 2005). About 10% of bone is replaced each year, with complete skeletal renewal every 10 years. An imbalance between osteoblast and osteoclast activities can cause serious consequences: if bone formation is enhanced or bone resorption is impaired, bone mass is increased, and vice versa (Parfitt, 1982; Pogoda et al., 2005). Often osteoclast diseases are monogenic, and in many of them the responsible gene and the respective function have been identified, while for other osteoclast diseases the causative gene has not been isolated or the exact function of the matching protein still remains unknown. In this review, a brief description of osteoclast biology will be provided and examples of genetic osteoclast diseases, including osteopetrosis, pycnodysostosis and Paget’s disease of bone, will be discussed.

2. Osteoclast

The osteoclast is the unique cell that is able to destroy the tissue to which it belongs (Teitelbaum, 2007). It is a giant cell with a diameter of 20-100 μm containing 4 to 50 nuclei, depending on the species (Roodman, 1996). The multinuclearity of osteoclast derives from the fusion of monocyte-macrophage mononuclear cells (Figure 1). In histological sections, osteoclasts appear variable in shape and size, adherent to the bone, within a small depression, called Howship’s lacuna, that is the result of their bone resorbing activity (Roodman, 1996). Osteoclasts are polarized cells (Takahashi et al., 2007). In fact, it is possible to identify a zone facing the bone matrix presenting a particular area of the plasma membrane, named ruffled border, composed by deep and irregular foldings that increase the size of the membrane located in front of the bone that will be resorbed (Stenbeck, 2002). The peripheral domain, named “sealing membrane”, represents the adhesion area by which the osteoclast attaches to the bone matrix around the site where it will be degraded. The
remaining membrane constitutes the basolateral domain containing proteins important for ion balance and response to regulatory stimuli. Opposite to the ruffled border domain, there is the apical domain, that is thought to be important for the transcytosis of bone resorption products from the resorbing lacuna to the extracellular fluids (Coxon & Taylor, 2008; Nesbitt & Horton, 1997; Peruzzi & Teti, 2011; Salo et al., 1996; Takahashi et al., 2007). Underneath the apical domain there are the nuclei that, under the light microscope, appear different in shape: some are round and euchromatic, others are irregular and more heterochromatic (Baron, 1989).

Fig. 1. Osteoclast differentiation. The cartoon illustrates the different phases of osteoclast differentiation, from the hematopoietic precursor to the mature multinuclear osteoclast. Some of the genes implicated in this process are indicated.

Moreover, ultrastructural studies showed Golgi complexes associated with each nucleus, many mitochondria and lysosomes (Baron et al., 1988; Stembeck, 2002). These latter organelles, approximately 0.5 μm in diameter, contain acid hydrolases, such as cathepsin K and Tartrate Resistant Acid Phosphatase (TRACP), representing markers of the osteoclast phenotype (Garnero, 1998; Sakigiyama et al., 2001). Mitochondria are very abundant, correlating with the high energy expenditure that is required for the degradation of bone matrix (Miyazaki et al., 2006).

2.1 The molecular mechanisms of bone resorption
Bone resorption is a complex process requiring two different phases, the acidification of the extracellular lacuna to dissolve the inorganic bone matrix and the secretion of proteolytic
enzymes to digest the organic components (Blair et al., 1986; Vaananen et al., 1998) (Figure 2). To achieve the acidification of the resorption lacunae and begin the process of bone demineralization, Carbonic Anhydrase II (CAII) generates carbonic acid from the hydration of CO\(_2\). Carbonic acid spontaneously dissociates in proton and bicarbonate (Bothwick et al., 2003; Boyle et al., 2003). The protons so generated are actively released in the resorbing lacuna through an osteoclast-specific vacuolar-type (V)-H\(^+\)-ATPase (Nishi & Forgac, 2002; Teitelbaum & Patrick, 2003). The excess of bicarbonate is removed by a bicarbonate/chloride exchanger, localised in the basolateral membrane (Baron, 1989; Teti et al., 1989). The chloride ion is then released in the bone resorption lacuna by a Cl\(^-\)/H\(^+\) antiport, CIC7, that, coupling with the proton pump activity, balances the ion charge across the membrane (Boyle et al., 2003; Graves et al., 2008; Teitelbaum & Patrick, 2003). The final goal of this process is to demineralise the bone and uncover the organic matrix ready to be digested by proteolytic enzymes, such as the metalloproteinase MMP9 released by endosomal vesicles, and the cathepsin K released by lysosomes (Blair et al., 1986; Bossard et al., 1996; Everts et al., 1992).

Fig. 2. The bone resorption process. The cartoon illustrates the molecular patterns involved in bone resorption by osteoclasts. See text for detailed description.

2.2 Osteoclastogenesis and regulation of osteoclast activity
Osteoclasts are cells that belong to the monocyte/macrophage lineage and derive from the fusion of monocuclear precursors (Teitelbaum, 2007) (Figure 1). In 1981, Marks and Walker showed, by experiments with parabiotic animals, that circulating blood contains cells able to differentiate into osteoclasts, thus identifying their haematogenous origin (Marks & Walker, 1981). Subsequently, in vitro studies with bone marrow-derived cells (Burger et al., 1989) suggested that osteoclasts arise from the differentiation of precursor cells of the CFU-M (Colony Forming Unit-Macrophage) lineage. This evidence suggested that osteoclasts present the same haematopoietic origin of antigen presenting cells and tissue macrophages. The pathway of osteoclast differentiation is now well characterized (Teitelbaum et al., 1997).
The PU.1 transcription factor is essential for the earliest phase of osteoclast differentiation, regulating the expression of the *c-fms* gene (Hayashi et al., 1998). *c-fms* encodes for the receptor of M-CSF (Macrophage-Colony Stimulating Factor), a cytokine crucial for the survival and the proliferation of early progenitors since it stimulates the cyclinD/CDK4 (Cyclin-Dependent Kinase 4) pathway (Mundy, 1993; So et al., 2003). Moreover, *c-fms* is able to stimulate the expression of PU.1 itself, establishing an amplification loop (Mundy, 1993). The essential role of PU.1 during osteoclast commitment is even due to its ability to regulate the expression of RANK (Receptor Activator of NF-κB) that, upon interaction of its ligand RANKL, is able to initiate the differentiation and the fusion of osteoclast precursors (Kwon et al., 2005). In fact, subsequent to RANKL-RANK interaction, TRAF6 (TNF Receptor-Associated Factor 6) is recruited and activates IκB and MAP kinases (Takayanagi et al., 2005), causing the nuclear translocation of NF-κB and of other transcription factors, including ATF2 (Activating Transcription Factor 2), *c-fos* and *c-jun*, required for the progression of osteoclast differentiation (Wada et al., 2006). Other two transcription factors important for osteoclast differentiation are MITF (Microphtalmia-associated Transcription Factor) (So et al., 2003) and NFATc1 (Nuclear Factor of Activated T-cells, cytoplasmic, calcineurin-dependent 1) (Takayanagi, 2007) that regulate the expression of osteoclast specific genes, like TRAcP, OSCAR (OSteoClast-Associated immunoglobulin-like Receptor), CTSK, CLC7 and OSTMI (OSteopetrosis associated TransMembrane protein) (Takayanagi, 2007; Meadows et al., 2007). The activation of RANK by RANKL is counterbalanced by the expression of a soluble decoy receptor, OPG (OsteoProteGerin), that is able to bind RANKL, preventing its interaction with RANK (Kong et al., 1999). The expression of RANKL by stromal cells and, during inflammation, by T cells and synovial fibroblasts, is regulated by hormones and local factors as it is stimulated by PTH (ParaThyroid Hormone), PGE$_2$ (ProstaGlandin E$_2$) and 1,25(OH)$_2$Vitamin D$_3$ (Lips, 2006; Parfitt, 1976; Takeda et al., 1999). According to other studies, osteoclast progenitors express 1,25(OH)$_2$Vitamin D$_3$ receptors and their activation could contribute to the induction of RANK (Blair & Zaidi, 2006). Even sex hormones regulate osteoclast differentiation and function (Manolagas et al., 2002). Estrogens and androgens are believed to attenuate the rate of osteoclast formation downregulating genes essential for osteoclastogenesis (Cheung et al., 2003; Girasole et al., 1992; Imai et al., 2009) and exerting a potent pro-apoptotic effect. Glucocorticoids are also thought to target the osteoclasts, preventing cell spreading and reducing their bone resorbing activity (Dempster et al., 1997; Kim et al., 2007). However, the use of glucocorticoids leads to a reduction of bone mass due to a direct negative effect on osteoblast activity and to inhibition of osteoclasts, that result in the interruption of the bone remodeling cycle (Dovio et al., 2004). Furthermore, osteoclasts are very sensitive to pH levels as it is known that systemic acidosis has detrimental effects on the skeleton and local acidosis is associated with bone destruction (Arnett, 2003; Krieger et al., 2004; Muzytak et al., 2007). It has been shown that the Ovarian cancer G-protein-coupled Receptor 1 (OGR1 or GPR68), a proton sensing receptor, is essential for osteoclast formation inducing RANKL-dependent osteoclastogenesis and activating NFATc1 (Iwai et al., 2007).

### 3. Osteopetrosis

Osteopetrosis is a rare (>1:100,000) genetic disorder characterized by an impaired osteoclast function that leads to pathological increase of bone mass and skeletal fragility. It was identified for the first time in 1904 by Albers-Scönberg, who described a patient...
with generalized sclerosis of the skeleton, suffering from several fractures (Albers-Schönberg, 1904). Subsequently, in 1926, Karshner denominated the syndrome “marble bone disease” or “osteopetrosis” (Karshner, 1926). Impaired bone resorption causes persistence of old bone, increase of bone mass and obstruction of cavities containing vital organs such as the bone marrow and the nervous system. Osteopetrotic patients usually suffer from pathological fractures, short stature and haematological and neural failures (Balemans et al., 2005; Del Fattore et al., 2008; Frattini et al., 2003; Loria-Cortes et al., 1977). Osteopetrosis is a heterogeneous disorder which includes several forms that differ on the basis of inheritance, severity and secondary clinical features (Balemans et al., 2005). So far, there is no effective cure for osteopetrosis (Del Fattore et al., 2010). Haematopoietic Stem Cell Transplantation (HSCT) is indicated only for some severe forms; however a large rate of unsuccessful engraftment and persistence of irreversible symptoms are frequently observed (Driesses et al., 2003).

### 3.1 Clinical features and genetic inheritance

The various forms of osteopetrosis are classified on the basis of clinical, radiological and inheritance features into three major groups (Balemans et al., 2005; Whyte, 2002): the Autosomal Recessive Osteopetrosis (ARO), the Intermediate autosomal Recessive Osteopetrosis (IRO) and the Autosomal Dominant Osteopetrosis (ADO). Although these forms display different symptoms, they share common clinical traits such as increase of bone density, spontaneous fractures and haematological failures (Del Fattore et al., 2008). ARO is the most severe form and it is commonly diagnosed soon after birth or within the first years of life. Patients display a generalised osteosclerosis, especially in skull, pelvis, spine and long bones (Frattini et al., 2000; Kornak et al., 2000; Loria-Cortes et al., 1977), which display the so-called “bone in bone” appearance (Figure 3). The poor development and/or compression of the bone marrow and the nervous system leads to severe anaemia, pancytopenia, hepatosplenomegaly, visual impairment, optic atrophy and deafness. Less common features are hydrocephaly, macrocephaly and strabismus. In a subtype of ARO primary degeneration of brain and retina are observed (Askmym et al., 2008). Unfortunately, a fatal outcome generally occurs in 75% of ARO patients, who die at 3–4 years of age because of haematological failure and recurrent infections (Balemans et al., 2005).

![Fig. 3. X-ray analysis illustrating generalized osteosclerosis in an ARO patient. The picture shows the extensive sclerosis of spine, ribs and skull.](www.intechopen.com)
IRO is milder than ARO and life expectancy is much longer. Typical symptoms of this form are generalized increase of bone density, osteomyelitis, short stature, dental malformations, and mild to moderate anaemia (Balemans et al., 2005; Bolt et al., 2005; Del Fattore et al., 2010; Sly et al., 1983). The Autosomal Dominant Osteopetrosis, also called Albers-Schönberg disease (Albers-Schönberg, 1904), was previously described inappropriately as the “benign form” but it is now accepted as an extremely heterogeneous osteopetrosis, ranging from asymptomatic to severe (Del Fattore et al., 2006; Frattini et al., 2003; Waguespack et al., 2007). This phenotypic variability is even observed within the same family (Letizia et al., 2004). ADO patients usually present with sclerosis of skull base, pelvis, and vertebral end-plates (Figure 4) (sandwich vertebrae or rugger-jersey spine), bone pain, osteomyelitis and frequent pathological fractures. Life expectancy is generally normal, but in some cases complications due to cranial nerve compression, a rather poor quality of life and death have been reported (Albers-Schönberg, 1904; Balemans et al., 2005; Del Fattore et al., 2006).

Fig. 4. X-ray analysis of an ADO patient showing sclerosis of vertebral end-plates (sandwich vertebrae) and pelvis.

Besides these classical forms, five male cases have been described so far with X-Linked Osteopetrosis (XLO) associated with lymphedema, anhidrotic ectodermal dysplasia, and immunodeficiency (so-called OL-EDA-ID syndrome). They died very young for severe phenotype and infection complications (Smahi et al., 2002).

3.2 Genetic features
The extreme phenotypic variability of osteopetrosis arises from the genetic heterogeneity. As shown in Table 1, in osteopetrotic patients mutations in genes encoding proteins essential for correct bone resorption or for osteoclast differentiation have been observed. As discussed above, these mutations can be inherited in an autosomal recessive, autosomal dominant or X-linked manner (Del Fattore et al., 2010). ARO, the most severe form, is due in more than 50% of cases to loss-of-function mutations of the TCIRG1 gene, encoding for the osteoclast-specific a3 subunit of V-H+-ATPase (Del Fattore et al., 2006; Frattini et al., 2000; Kornak et al., 2000; Taranta et al., 2003).
| Gene         | Protein                                           | Type of mutation      | Form of osteopetrosis |
|--------------|--------------------------------------------------|-----------------------|-----------------------|
| TCIRG1       | a3 subunit of vacuolar H⁺-ATPase                  | Loss-of-function      | ARO                   |
| TCIRG1/ATP6V1B1 | a3/B1 subunits of vacuolar H⁺-ATPase              | Loss-of-function      | ARO                   |
| CLC7         | Chloride/proton antiport                         | Loss-of-function      | ARO                   |
|              | Dominant negative                                |                       |                       |
| OSTM1        | Trasmembrane protein associated with ClC7 function| Loss-of-function      | ARO                   |
| PLEKHM1      | Protein with undefined function, probably associated with vesicular trafficking and acidification | Loss-of-function | IRO                   |
| CAII         | Carbonic anhydrase type II                       | Loss-of-function      | IRO                   |
| NEMO         | Regulatory subunit of IKK                        | Loss-of-function      | XLO                   |
| TNFSF11      | Receptor activator of NF-κB ligand (RANKL)        | Loss-of-function      | ARO                   |
| TNFRSF11A    | RANK                                             | Loss-of-function      | ARO                   |

Table 1. Genetic defects in human osteopetroses

The V-H⁺-ATPase is central to the mechanism of bone resorption because it is located in the osteoclast ruffled border membrane where it releases protons in the underneath resorbing lacuna (Nishi & Forgac, 2002). In rare cases, double mutations of the TCIRG1 gene and the ATP6V1B1 genes, this latter encoding the B1 subunit of V-H⁺-ATPase, were described (Bothwick et al., 2003). As shown in Table 1, other four genes are associated with ARO. About 10-15% of patients harbours mutations of the CLC7 gene (Frattini et al., 2003; Kasper et al., 2005; Kornak et al., 2001), encoding for the so called chloride channel type 7, recently reclassified as a Cl⁻/H⁺ antiport (Graves et al., 2008). This dimeric protein is located in lysosomes and osteoclast ruffled membrane where, as previously described, it is essential to restore the correct electrical potential altered by proton flux (Graves et al., 2008). So far, only 5 patients affected by ARO were found to harbour loss-of-function mutations of the OSTM1 gene, encoding for a protein whose role in bone resorption is still unknown (Chalhoub et al., 2003; Pangrazio et al., 2006). Ostm1 function is probably important for Cl⁻ conductance, because it was recently shown that the protein is involved in the stabilization and correct localization of the Cl⁻/H⁺ antiport (Lange et al., 2006). The correlated functions of ClC7 and Ostm1 proteins are demonstrated by the similar clinical features of patients harbouring mutations of the respective genes (Pangrazio et al., 2006). Primary retinal degeneration and lysosomal storage disease are observed in these patients, who are believed not to benefit from HSCT because it cannot cure the neural defects. Beside the types of AROs described above, so-called “osteoclast-rich” osteopetroses because in these forms osteoclasts form normally or are even increased in number, there is also a particularly rare form of ARO where the osteoclasts are absent (Helfrich, 2005). The patients affected by this “osteoclast-poor” osteopetrosis present mutations of the TNFSF11 (Sobacchi et al., 2007) or the TNFRSF11A (Guerrini et al., 2008) genes (Table 1), encoding the RANKL and its receptor
RANK, respectively. Both proteins are required for osteoclast differentiation. So far, only 6 patients have been described to carry mutations of the TNFSF11 gene. The importance of this discovery relies on the fact these patients could not be effectively treated with HSCT, because the genetic defect is not osteoclast-autonomous but rather relies on the inability of stromal/osteoblastic cells to produce RANKL. ADO, the most frequent osteopetrosis, is caused in about 70% of patients by heterozygous dominant negative mutations of the CLC7 gene (Bollerslev et al., 1988; Del Fattore et al., 2005; Frattini et al., 2003; Letizia et al., 2004; Waguespack et al., 2007). CLC7 gene mutations tend to affect the entire length of the gene, even if the most frequent mutations have been described in the regions encoding the C-terminal CBS (Cystathionine Beta Synthase) domains of the protein (Del Fattore et al., 2006; Waguespack et al., 2007). As described above, ADO is characterized by a phenotypic variability probably due to the incomplete penetrance of the mutant gene (Frattini et al., 2003; Letizia et al., 2004). No other genes are known so far to be correlated with ADO and about 30% of patients still lack a genetic diagnosis (Del Fattore et al., 2010). As in ADO, also in IRO a considerable clinical heterogeneity is observed. Presently, the two genes known to be associated with IRO are CAII (Bolt et al., 2005) and PLEKHM1 (Van Wesenbeeck et al., 2007), encoding the carbonic anhydrase type II and the Plekhm1 protein, respectively. Patients harbouring loss of function mutations of the CAII gene display, besides osteopetrosis, tubular acidosis, cerebral calcifications and mental retardation (Balemans et al., 2005). The novel gene recently associated with osteopetrosis, PLEKHM1, has been identified as the human homolog of the gene responsible of the incisor absent (ia) rat phenotype (Van Wesenbeeck et al., 2007). To date, only one female patient affected by IRO has been identified to harbour a mutation of the PLEKHM1 gene. The clinical features described in this patient were increased bone density, Erlenmeyer flask’ deformity of the distal femora and a chondrolysis of the left hip. The exact function of the Plekhm1 protein is not completely elucidated, but recent findings suggest that it is a member of Rab7-regulated proteins involved in late endosomal trafficking (Del Fattore et., 2008; Van Wesenbeeck et al., 2007), vesicular acidification and TRAcP release by osteoclasts (Del Fattore et al., 2008). As previously described, there is a XLO osteopetrosis, due to mutations of the NEMO (NF-kB Essential Modulator) gene, encoding the IxB regulatory subunit of IKK. The mutations described in the only 5 so far known patients cause the replacement of the NEMO stop codon with tryptophan, leading to the addition of 27 irrelevant residues that strongly destabilize the protein (Smahi et al., 2002). All other forms of osteopetrosis, about 30% of patients, still lack a recognized gene involved and much effort should be made to identify new genes associated with this disease.

4. Pycnodysostosis

Pycnodysostosis is a skeletal disorder also known as Toulouse-Lautrec disease because it is believed that the famous French painter Henri Toulouse-Lautrec (1864-1901) suffered from this syndrome (Maroteaux & Lamy, 1965). It is a rare monogenic disease (approximately 150 cases reported in the literature worldwide), first described in 1962 by Maroteaux and Lamy, who coined this term from the word of Greek origin puknos meaning “dense”, associated with the words dys meaning “defective” and ostosis meaning “condition of the bone”. Pycnodysostosis is characterised by a general osteosclerosis leading to short stature and increased bone mass. In fact, Schilling and coworkers analysed the volumetric bone density
in a cohort of pycnodysostosis patients and controls showing a value of 686 mg/cm in the
group of patients versus 290 mg/cm in the control group (Shilling et al., 2007). This disease
appears to be especially common among the Japanese, but many cases are even described in
Europe and United States (Muto et al., 1991).

4.1 Clinical features
The diagnosis of pycnodysostosis is usually performed during infancy or early childhood
because of increased bone mass, short stature and cranial dysplasia. Pycnodysostosis could
be confused with osteopetrosis, although it has peculiar features such as gracile clavicles
with hypoplastic ends, obtuse mandibular angle, enlarged skull with opened anterior
fontanel and cranial sutures, and acroosteolysis of distal phalanges (Soliman et al., 2001).
Moreover, in pycnodysostosis anaemia and hepatosplenomegaly have not been reported.
The exfoliation of deciduous teeth is usually altered, as well as the eruption of the
permanent dentition. Endobones and radiodense striations are absent. As in osteopetrosis,
pycnodysostosis patients may suffer from frequent fractures since the first year of life.
Moreover, fractures of the mandible during tooth extractions have been described. Lower
limbs seem to be particularly involved in fractures, resulting in genu valgum deformity. About
10% of the patients show mental retardation. Moreover, recurrent respiratory infections and
right heart failure have been described (Muto et al., 2005).

4.2 Genetic inheritance
Pycnodysostosis is an autosomal recessive disease caused by mutations of the CTSK gene.
In 1995, Gelb and coworkers first mapped the disease in a narrow region on chromosome
1q21 with a maximal lod score of 11.72 (Gelb et al., 1996). In 1996, they identified the
mutated gene, CTSK, encoding the cathepsin K, a cystein proteinase expressed in many
tissues such as bone, ovary, colon, skeletal muscle, placenta and small intestine (Zhao et al.,
2009). Cathepsin K is synthesized as an inactive precursor of 329 amino acids (aa). The N-
terminus pro-peptide of 99 aa is cleaved between Arg 114 and Ala 115 to supply the mature
cathepsin K of 215 aa (Bromme & Okamoto, 1995). In the bone, it plays an important role in
bone resorption since it cleaves, at acidic pH, collagen type I, osteopontin and other proteins
of the bone matrix (McQueney et al., 1997). Particularly, cathepsin K cuts triple-helical
collagen into small peptides. Cleavage occurs in its non collagenous termini (N- and C-
telopeptide regions). These fragments can be detected in urine and serum as markers of
bone resorption (Atley et al., 2000). Cathepsin K-deficient mice generated by inactivation of
the ctsk gene display an increase of bone mass as well as radiological and histological
abnormalities typical of pycnodysostosis (Gowen et al., 1999; Saftig et al., 1998). The analysis
of the genomic DNA indicated that the CTSK gene is composed by eight exons and seven
introns (Rood et al., 1997). Presently, 27 different types of mutations, spread throughout the
whole gene, have been described in 34 unrelated families (Helfrich, 2003; Toral-López et al.,
2011). According to bio-informatic analyses, all mutations seem to affect the protein folding,
destabilizing the whole structure or creating locally structural changes that could affect the
conformation of a small part of the protein (Donnarumma et al., 2007).

5. Paget’s disease of bone
Paget’s disease of bone is a common disorder characterized by increased bone turnover
within focal lesions throughout the skeleton. It was described for the first time in 1876 by Sir
James Paget as a disease that “begins in middle age or later . . . affects most frequently the long bones of the lower extremities and the skull”. Moreover, he stated that “the bones enlarge and soften, and those bearing weight yield and become unnaturally curved and misshapen” (Paget, 1876). Paget’s disease of bone affects both men and woman, with a slight predominance in males (van Staa et al., 2002). Although many patients are often asymptomatic, others have a poor quality of life, with bone pain, skeletal deformities and fractures (Selby et al., 2002). The estimated prevalence of Paget’s disease of bone in the world is about 1%, arising up to about 3% in North America, Great Britain, Australia and Western Europe. Conversely, this disease is very rare in Scandinavia and in the Indian subcontinent (Detheridge et al., 1982). These marked geographical differences in the prevalence strengthen the importance of genetic factors involved in the pathogenesis of Paget’s disease of bone, but some evidence suggests an important role also for environmental determinants.

5.1 Clinical features
Paget’s disease of bone is a disorder of bone remodelling. It is very important to underline the localized nature of the disease. It could affect a single bone or only a portion of it, or it could involve more bones (Ralston, 2008). As described above, many patients affected by Paget’s disease of bone are often asymptomatic and the diagnosis is usually performed incidentally on the basis of elevated serum alkaline phosphatase levels not correlated with other diseases, or of abnormal skeletal radiographs (Tiegs et al., 2000). Conversely, other patients suffer from mild to moderate bone ache that characteristically begins late in the clinical course (Ralston et al., 2008). The direct cause of pain could be difficult to explain, requiring a careful analysis. An increase of vascularity and consequent warmth usually occur in pagetic bones, leading to unpleasant sensation perceived by patients (Altman, 1980). Micro-fractures that frequently affect the diseased bone can contribute to discomfort. Another typical sign of the disease is skeletal deformity, usually of the femur or tibia, that could aid in the cause of pain onset (Ralston et al., 2008). Moreover, severe secondary osteoarthritis can be observed at joints close to pagetic bones. Patients affected by Paget’s disease of bone suffer from fractures that could be either traumatic or pathologic, particularly involving the long bones. The involvement of the skull in the disease complaints occurs in up to one third of the patients, and is characterized by macrocephaly, frontal bossing and hearing loss. Palsies of cranial nerves II, VI and VII could also be observed. Neoplastic degeneration, particularly osteogenic sarcoma involving the pelvis (although both fibrosarcoma and chondrosarcoma are also observed), develop in less than 1% of patients (Reddy et al., 2001).

5.2 Genetic inheritance
As aforementioned, both genetic and environmental factors can contribute to the pathogenesis of Paget’s disease of bone. In less than 15-40% of cases, this disease is inherited in an autosomal dominant manner, even if many patients do not have a family history (Haslam et al., 1998; Hocking et al., 2000). Seven different loci have been identified by locus linkage studies associated with the onset of the disease. They are located on chromosomes 2p36, 5q31, 5q35, 10p13, 18q21 and 18q23 (Good et al., 2002; Haslam et al., 1998; Hocking et al., 2001; Laurin et al., 2001; Tilyard et al., 1982). Other studies confute this linkage association, showing that the analysis may have false positives (Ralston, 2008).
Subsequently, Laurin et al. and Hocking et al. identified, by positional cloning studies on chromosome 5q35, the SQSTM1 gene as the most important cause of the disease (Hocking et al., 2002; Laurin et al., 2002). The SQSTM1 gene encodes the p62/sequestosome 1, an ubiquitously expressed adapter protein involved in several cellular activities, including regulation of NF-κB signalling, autophagy, sequestration of ubiquitinated proteins and inhibition of ERK-MAPK signalling (Mosca & Diaz-Meco, 2002) (Figure 5). Particularly, it was shown that p62 is able to bind TRAF6 and K48- and K63-linked ubiquitin chains via the UBA (UBiquitin-Associated) domain (Figure 5) (Seibenhener et al., 2004). It was shown that sequestosome 1 colocalizes with ubiquitinated protein aggregates, and it has been detected in protein aggregates typical of Alzheimer’s and Parkinson’s diseases (Paine et al., 2005). Moreover, most of the mutations found in Paget’s disease of bone are located in the UBA domains, preventing protein aggregation or, conversely, inducing the formation of aggregates larger than normal (Cavey et al., 2005; Cavey et al., 2006; Yip et al., 2006). However, it is not yet clear what role these aggregates might play in the pathogenesis of Paget’s disease of bone.

Fig. 5. Sequestosome/p62 pathway in osteoclasts. The binding of RANKL to the receptor RANK results in recruitment of TRAF6, p62 and aPKC (atypical Protein Kinase C). Moreover, the RANKL-RANK interaction leads to the phosphorylation of IKK (Inhibitor of kb kinase), that subsequently phosphorylates IκB (Inhibitor of κB). The phosphorylated IκB is degraded by the proteasome. NF-κB can translocate to the nucleus, inducing the expression of osteoclast specific genes. VCP (Valosin-Containing Protein) is involved in the regulation of IκB degradation by the proteasome.

The first mutation identified in French pagetic patients was the Proline-Leucine mutation affecting codon 392 (P392L) in the UBA domain (Laurin et al., 2002). A transgenic mouse carrying the P392L mutation under the control of the trACP promoter was generated and displayed an osteopenic phenotype, with increased number of osteoclasts, but no osteolytic lesions (Kurihara et al., 2000). Another animal model was generated by the group of Ralston, carrying a truncating mutation at serine 409, that developed focal lesions, representing the first true model of the disease (Rojas et al., 2007). Several other genes have been associated
with Paget’s disease of bone, such as TNFSF11, TNFRSF11A and TNFRSF11B, this latter particularly in juvenile disease. However, these association studies still lack a sample size large enough to enable to draw definitive conclusions on the involvement of these genes in the disease (Ralston, 2008).

6. Conclusions

Osteopetrosis, pycnodysostosis and Paget’s disease of bone are examples of genetic diseases that underlie the essential role of osteoclasts in the regulation of bone homeostasis. They have been instrumental for the understanding of the mechanisms by which osteoclasts form and resorb bone and contributed to shed light on the pathogenesis of more frequent bone diseases, including osteoporosis and bone inflammatory disorders, such as osteoarthritis and rheumatoid arthritis (Tanaka et al., 2005). Further investigation on osteoclast genetic diseases is expected to help increase our knowledge about the recently identified relationships between the bone and other systems, including the immune system (Takayanagi, 2010), the nervous system (Kumar et al., 2010), the endocrine system (Ferron et al., 2010; Fukumoto & Martin, 2009; Karsenty & Oury, 2010), the reproductive system (Oury et., 2011) and the skeletal muscle system (Rufo et al., 2011), in which osteoclasts may be implicated. Therefore, in the next future we are likely to assist to flourishing novel insights into the osteoclast biology, physiology and pathology, which could represent the basis for a better prophylaxis and more effective treatments of bone diseases.

7. Acknowledgments

We gratefully acknowledge the generous support provided by Telethon (grants GGP09018 and GGP06119) to AT and by the 2010 Gideon and Sevgi Rodan Fellowship provided by the International Bone and Mineral Society to ADF.

8. References

Albers-Schönberg, H.E. (1904). Röntgenbilder einer seltenen Knockenerkrankung. Munch Med Wochenschr, Vol.5, pp.365-368
Altman, R.D. (1980). Musculoskeletal manifestations of Paget's disease of bone. Arthritis Rheum, Vol.23, No.10, (October 1980), pp. 1121-1127
Arnett, T.R. (2008). Extracellular pH regulates bone cell function. J Nutr, Vol.138, No.2, (February 2008), pp. 415-418
Askmyr, M.K.; Fasth, A. & Richter, J. (2008). Towards a better understanding and new therapeutic of osteopetrosis. Br J Haematol., Vol.140, No.6, (March 2008), pp. 597-609
Atley, L.M.; Mort, J.S.; Lalumiere, M. & Eyre, D.R. (2000). Proteolysis of human bone collagen by cathepsin K: characterization of the cleavage sites generating by cross-linked N-telopeptide neoepitope. Bone, Vol.26, No.3, (March 2000), pp. 241-247
Balemans, W.; Van Wesenbeeck, L. & Van Hul, W. (2005). A clinical and molecular overview of the human osteopetroses. Calcif Tissue Int., Vol.77, No.5, (November 2005), pp. 263-274
Baron, R. (1989). Polarity and membrane transport in osteoclasts. Connect Tissue Res., Vol.20, pp. 109-12
Baron, R. (1999). Anatomy and Ultrastructure of Bone. In: Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism. Lippincott Williams & Wilkins, pp. 3-10, Philadelphia, PA

Baron, R.; Neff, L.; Brown, W.; Courtoy, P.J.; Louvard, D. & Farquhar, M.G. (1988). Polarized secretion of lysosomal enzymes: co-distribution of cation-independent mannose-6-phosphate receptors and lysosomal enzymes along the osteoclast exocytic pathway. J Cell Biol., (Jun 1988), Vol.106, No.6, pp. 1863-1872

Blair, H.C.; Kahn, A.J.; Crouch, E.C.; Jeffrey, J.J. & Teitelbaum, S.L. (1986). Isolated osteoclasts resorb the organic and inorganic components of bone. J Cell Biol., Vol.102, No.4, (April 1986), pp. 1164-1172

Blair, H.C. & Zaidi, M. (2006). Osteoclastic differentiation and function regulated by old and new pathways. Rev Endocr Metab Disord., Vol.7, No.1-2, (June 2006), pp. 23-32.

Bolt, R.J.; Wennink, J.M.; Verbeke, J.I.; Shah, G.N.; Sly, W.S. & Bokenkamp, A. (2005). Carbonic anhydrase type II deficiency. Am J Kidney Dis., Vol.46, No.5, (November 2005), pp. 71-73

Bossard, M.J.; Tomaszek, T.A.; Thompson, S.K.; Amegadzie, B.Y.; Hanning, C.R.; Jones, C.; Kurdyla, J.T.; McNulty, D.E.; Drake, F.H.; Gowen, M. & Levy, M.A. (1996). Proteolytic activity of human osteoclast cathepsin K. Expression, purification, activation, and substrate identification. J Biol Chem., Vol.271, No.21, (May 1996), pp. 12517-12524

Bothwick, K.J.; Kandemir, N.; Topaloglu, R.; Kornak, U.; Bakkaloglu, A.; Yordam, N.; Ozen, S.; Mocan, H.; Shah, G.N.; Sly, W.S. & Karet, F.E. (2003). A phenocopy of CAII deficiency: a novel genetic explanation for inherited infantile osteopetrosis with distal renal tubular acidosis. J Med Genet., Vol.40, No.2, (February 2003), pp. 115-121

Boyle, W.J.; Simonet, W.S. & Lacey, D.L. (2003). Osteoclast differentiation and activation. Nature, Vol.423, No.6937, (May 2003), pp. 337-342

Bromme, D. & Okamoto, K. (1995). Human cathepsin O2, a novel cysteine protease highly expressed in osteoclastomas and ovary molecular cloning, sequencing and tissue distribution. Biol Chem Hoppe Seyler., Vol.376, No.6 (June 1995), pp. 379-384

Burger, E.H.; Veldhuijzen, J.P.; Nulend, J.K. & Van Loon, J.J. (1989). Osteoclastic invasion and mineral resorption of fetal mouse long bone rudiments are inhibited by culture under intermittent compressive force. Connect Tissue Res., Vol.20, No.1-4, pp. 131-41

Cavey, J.R.;Ralston, S.H.; Hocking, L.J.; Sheppard, P.W.; Ciani, B.; Searle, M.S. & Layfield, R. (2005). Loss of ubiquitin-binding associated with Paget's disease of bone p62 (SQSTM1) mutations. J. Bone Miner. Res., Vol.20, No.4, (April 2005), pp. 619-624

Cavey, J.R.; Ralston, S.H.; Sheppard, P.W.; Ciani, B.; Gallagher, T.R.; Long, J.E.; Searle, M.S. & Layfield, R. (2006). Loss of ubiquitin binding is a unifying mechanism by which mutations of SQSTM1 cause Paget's disease of bone. Calcif. Tissue Int., Vol.78, No.5, (May 2006), pp. 271-277

Chalhoub, N.; Benachenhou, N.; Rajapurohitam, V.; Pata, M.; Ferron, M.; Frattini, A.; Villa, A. & Vacher, J. (2003). Grey-lethal mutation induces severe malignant autosomal recessive osteopetrosis in mouse and human. Nat Med., Vol.9, No.4, (April 2003), pp. 399-406

Cheung, J.; Mak, Y.T.; Papaioannou, S.; Evans, B.A.; Fogelman, I. & Hampson, G. (2003). Interleukin-6(IL-6), IL-1, receptor activator of nuclear factor kappa B ligand
(RANKL) and osteoprotegerin production by human osteoblastic cells: comparison of the effects of 17-beta oestradiol and raloxifene. *J Endocrinol.*, Vol.177, No.3, (June 2003), pp. 423-433

Coxon, FP. & Taylor, A. (2008). Vesicular trafficking in osteoclasts. *Semin Cell Dev Biol.*, Vol.19, No.5, (October 2008), pp. 424-433

Del Fattore, A.; Cappariello, M. & Rucci, N. (2010). Bone and bone marrow: the same organ. *Arch Biochem Biophys.*, Vol.1, No.503, (November 2010), pp 28-34

Del Fattore, A.; Cappariello, A. & Teti, A. (2008). Genetics, Pathogenesis and Complications of Osteopetrosis. *Bone*, Vol.42, No.1, (January 2008), pp. 19-29

Del Fattore, A.; Peruzzi, B.; Rucci, N.; Recchia, I.; Cappariello, A.; Longo, M.; Fortunati, D.; Ballanti, P.; Iacobini, M.; Luciani, M.; Devito, R.; Pinto, R.; Caniglia, M.; Lanino, E.; Messina, C.; Cesaro, S.; Letizia, C.; Bianchini, G.; Fryssira, H.; Grabowski, P.; Shaw, N.; Bishop, N.; Hughes, D.; Kapur, R.P.; Datta, H.K.; Taranta, A.; Fornari, R.; Migliaccio, S. & Teti, A. (2006). Clinical, genetic, and cellular analysis of 49 osteopetrotic patients: implications for diagnosis and treatment. *J Med Genet.*, Vol.43, No.4, (April 2006), pp. 315-325.

Del Fattore, A.; Van Wesenbeeck, L.; Fornari, R.; Peruzzi, B.; Cappariello, A.; Rucci, N.; Spera, G.; Helfrich, M.; Van Hul, M.; Migliaccio, S. & Teti, A. (2008). A new heterozygous mutation (R714C) of the osteopetrosis gene, pleckstrin homolog domain containing family M (with run domain) member 1 (PLEKHM1), impairs vesicular acidification and increases TRACP secretion in osteoclasts. *J Bone Miner Res.*, Vol.23, No.3, (March 2008), pp. 380-391

Dempster, D.W.; Moonga, B.S.; Stein, L.S.; Horbert, W.R. & Antakly, T. Glucocorticoids inhibit bone resorption by isolated rat osteoclasts by enhancing apoptosis. *J Endocrinol.*, Vol.154, No.3, (September 1997), pp. 397-406

Detheridge, F.M.; Guyer, P.B. & Barker, D.J. (1982). European distribution of Paget's disease of bone. *Br Med J.*, Vol.285, No.6347 (October 1982), pp. 1005-1008

Donnarumma, M.; Regis, S.; Tappino, B.; Rosano, C.; Assereto, S.; Corsolini, F.; Di Rocco, M. & Filocamo, M. (2007). Molecular analysis and characterization of nine novel CTSK mutations in twelve patients affected by pycnodysostosis. Mutation in brief #961. Online. *Hum Mutat.*, Vol.28, No.5, (May 2007), pp. 524

Dovio, A.; Perazzolo, L.; Osella, G.; Ventura, M.; Termine, A.; Milano, E.; Bertolotto, A. & Angeli, A. (2004). Immediate fall of bone formation and transient increase of bone resorption in the course of high-dose, short-term glucocorticoid therapy in young patients with multiple sclerosis. *J Clin Endocrinol Metab.*, Vol.89, No.10, (October 2004), pp. 4923-4928

Driessen, G.J.; Gerritsen, E.J.; Fischer, A.; Fasth, A.; Hop, W.C.; Veys, P.; Porta, F.; Cant, A.; Steward, C.G.; Vossen, J.M.; Uckan, D. & Friedrich, W. (2003). Long-term outcome of haematopoietic stem cell transplantation in autosomal recessive osteopetrosis: an EBMT report. *Bone Marrow Transplant.*, Vol.32, No.7, (October 2003), pp. 657-663

Ducy, P.; Desbois, C.; Boyce, B.; Pinero, G.; Story, B.; Dunstan, C.; Smith, E.; Bonadio, J.; Goldstein, S.; Gundberg, C.; Bradley, A. & Karsenty, G. (1996). Increased bone formation in osteocalcin-deficient mice. *Nature*, Vol.1, No.382, (August 1996), pp. 448-452

Everts, V.; Delaisse, J.M.; Korper, W.; Niehof, A.; Vaes, G. & Beertsen, W. (1992). Degradation of collagen in the bone-resorbing compartment underlying the
osteoclast involves both cysteine-proteinases and matrix metalloproteinases. J Cell Physiol., Vol.150, No.2, (February 1992), pp. 221-231

Ferron, M.; Wei, J.; Yoshizawa, T.; Del Fattore, A.; DePinho, R.A.; Teti, A.; Ducy, P. & Karsenty, G. (2010). Insulin signaling in osteoblasts integrates bone remodeling and energy metabolism. Cell., Vol.23, No.142, (July 2010), pp. 296-308

Frattini, A.; Orchard, P.J.; Sobacchi, C.; Giliani, S.; Abinun, M.; Mattsson, J.P.; Keeling, D.J.; Andersson, A.K.; Wallbrandt, P.; Zecca, L.; Notarangelo, L.D.; 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., Vol.25, No.3, (July 2000), pp. 343-346

Frattini, A.; Pangrazio, A.; Susani, L.; Sobacchi, C.; Mirolo, M.; Abinum, M.; Andolina, M.; Flanagan, A.; Horwitz, E.M.; Mihi, E.; Notarangelo, L.D.; Ramenghi, U.; Teti, A.; Van Hove, J.; Vujic, D.; Young, T.; Albertini, A.; Orchard, P.J.; Vezzoni, P. & Villa, A. (2003). Chloride channel ClCN7 mutations are responsible for severe recessive, dominant, and intermediate osteopetrosis. J Bone Miner Res., Vol.18, No.10, (October 2003), pp. 1740-1747

Fukumoto, S. & Martin, T.J. (2009). Bone as an endocrine organ. Trends Endocrinol Metab., Vol.20, No.5 (July 2009), pp. 230-236

Garnero, P.; Borel, O.; Byrjalsen, I.; Ferreras, M.; Drake, FH.; McQueney, MS.; Foged, NT.; Delmas, PD. & Delaisse, JM. (1998). The collagenolytic activity of cathepsin K is unique among mammalian proteinases. J Biol Chem., Vol.273, No.48, (November 1998), pp. 32347-32352

Gelb, B.D.; Shi, G.P.; Chapman, H.A. & Desnick, R.J. Pycnodysostosis, a lysosomal disease caused by cathepsin K deficiency. Science, Vol.273, No.5279, (August 1996), pp. 1236-1238.

Girasole, G.; Jilka, R.L.; Passeri, G.; Boswell, S.; Boder, G.; Williams, D.C. & Manolagas, S.C. (1992). 17 β-estradiol inhibits interleukin-6 production by bone marrow-derived stromal cells and osteoblasts in-vitro: a potential mechanism for the antosteoporotic effect of estrogens. J Clin Invest., Vol.89, No.3, (March 1992), pp. 883-891

Good, D.A.; Busfield, F.; Fletcher, B.H.; Duffy, D.L.; Kesting, J.B.; Andersen, J. & Shaw, J.T. (2002). Linkage of Paget disease of bone to a novel region on human chromosome 18q23. Am J Hum Genet., Vol.70, No2, (February 2002), pp. 517-525

Gowen, M.; Lazner, F.; Dodds, R.; Kapadia, R.; Feild, 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., Vol.14, No.10, (October 1999), pp. 1654-1663

Graves, A.R.; Curran, P.K.; Smith, C.L. & Mindell, J.A. (2008). The Cl-/H+ antiporter CIC-7 is the primary chloride permeation pathway in lysosomes. Nature, Vol.453, No.7196, (June 2008), pp. 788-792

Guerrini, M.M.; Sobacchi, C.; Cassani, B.; Abinun, M.; Kilic, S.S.; Pangrazio, A.; Moratto, D.; Mazzolari, E.; Clayton-Smith, J.; Orchard, P.; Coxon, F.P.; Helfrich, M.H.; Crockett, J.C.; Mellis, D.; Vellodi, A.; Tezcan, I.; Notarangelo, L.D.; Rogers, M.J.; Vezzoni, P.; Villa, A. & Frattini, A. (2008). Human osteoclast-poor osteopetrosis with hypogammaglobulinemia due to TNFRSF11A (RANK) mutations. Am J Hum Genet., Vol.83, No.1, (July 2008), pp. 64-76
Haslam, S.I.; Van Hul, W.; Morales-Piga, A.; Balemans, W.; San-Millan, J.L.; Nakatsuka, K.; Willems, P.; Haïtes, N.E. & Ralston, S.H. (1998). Paget's disease of bone: evidence for a susceptibility locus on chromosome 18q and for genetic heterogeneity. J Bone Miner Res., Vol.13, No.6, (June 1998), pp. 911-917

Hayashi, S.; Yamane, T.; Miyamoto, A.; Hemmi, H.; Tagaya, H.; Tanio, Y.; Kanda, H.; Yamazaki, H. & Kunisada, T. (1998). Commitment and differentiation of stem cells to the osteoclast lineage. Biochem Cell Biol., Vol.76, No.6, pp. 911-922

Helfrich, M.H. (2003). Osteoclast diseases. Microsc Res Tech., Vol. 61, No.15, (August 2003), pp. 514-32

Hocking, L.; Slee, F.; Haslam, S.I.; Cundy, T.; Nicholson, G.; Van Hul, W. & Ralston, S.H. (2000). Familial Paget's disease of bone: patterns of inheritance and frequency of linkage to chromosome 18q. Bone, Vol.26, No.6, (June 2000), pp. 577-580

Hocking, L.J.; Herbert, C.A.; Nicholls, R.K.; Williams, F.; Bennett, S.T.; Cundy, T.; Nicholson, G.C.; Wuys, W.; Van Hul, W. & Ralston, S.H. (2001). Genomewide search in familial Paget disease of bone shows evidence of genetic heterogeneity with candidate loci on chromosomes 2q36, 10p13, and 5q35. Am J Hum Genet., Vol.69, No.5, (November 2001), pp. 1055-1061

Hocking, L.J.; Lucas, G.J.; Daroszewska, A.; Mangion, J.; Olavesen, M.; Cundy, T.; Nicholson, G.C.; Ward, L.; Bennett, S.T.; Wuys, W.; Van Hul, W. & Ralston SH. (2002). Domain-specific mutations in sequestosome 1 (SQSTM1) cause familial and sporadic Paget's disease. Hum Mol Genet., Vol.11, No.22, (October 2002), pp. 2735-2739

Imai, Y.; Youn, M.Y.; Kondoh, S.; Nakamura, T.; Kouzmenko, A.; Matsumoto, T.; Takada, I.; Takaoka, K. & Kato, S. Estrogens maintain bone mass by regulating expression of genes controlling function and life span in mature osteoclasts. Ann N Y Acad Sci. Vol.1173, No.1, (September 2009), pp. 31-39

Iwai, K.; Koike, M.; Ohshima, S.; Miyatake, K.; Uchiyama, Y.; Saeki, Y. & Ishii, M. (2007). RGS18 acts as a negative regulator of osteoclastogenesis by modulating the acid-sensing OGR1/NFAT signaling pathway. J Bone Miner Res., Vol.22, No.10, (October 2007), pp. 1612-1620

Karsenty, G. & Oury, F. (2010). The central regulation of bone mass, the first link between bone remodeling and energy metabolism. J Clin Endocrinol Metab., Vol.95, No.11, (November 2010), pp. 4795-4801

Karshner, R.G. (1926). Osteopetrosis, Amer. J. Roentg., Vol.16, No.403

Kasper, D.; Planells-Cases, R.; Fuhrmann, J.C.; Scheel, O.; Zeitz, O.; Ruether, K.; Schmitt, A.; Poet, M.; Steinfeld, R.; Schweizer, M.; Kornak, U. & Jentsch, T.J. (2005). Loss of the chloride channel CIC-7 leads to lysosomal storage disease and neurodegeneration. EMBO J., Vol.24, No.5, (March 2005), pp.1079-1091

Kim, H.J.; Zhao, H.; Kitaura, H.; Bhattacharyya, S.; Brewer, J.A.; Muglia, L.J.; Patrick, R.F. & Teitelbaum, S.L. (2007). Glucocorticoids and the osteoclast. Ann N Y Acad Sci., Vol.1116, (November 2007), pp. 335-339

Kong, Y.Y.; Yoshida, H.; Sarosi, I.; Tan, H.L.; Timms, E.; Capparelli, C.; Morony, S.; Oliveira-dos-Santos, A.J.; Van, G.; Itie, A.; Khoo, W.; Wakeham, A.; Dunstan, C.R.; Lacey, D.L.; Mak, T.W.; Boyle, W.J. & Penninger, J.M. (1999). OPGL is a key regulator of osteoclastogenesis, lymphocyte development and lymph-node organogenesis. Nature, Vol.397, No.6717, (January 1999), pp. 315-323
Osteoclast Genetic Diseases

Kornak, U.; Kasper, D.; Bosl, M.R.; Kaiser, E.; Schweizer, M.; Schulz, A.; Friedrich, W.; Delling, G. & Jentsch, T.J. (2001). Loss of the ClC-7 chloride channel leads to osteopetrosis in mice and man. *Cell*, Vol.104, No.2, (January 2001), pp. 205-215

Kornak, U.; Schulz, A.; Friedrich, W.; Uhlhaas, S.; Kremens, B.; Voit, T.; Hasan, C.; Bode, U.; Jentsch, T.J. & Kubish, C. (2000). Mutations in the α3 subunit of the vacuolar H+-ATPase cause infantile malignant osteopetrosis. *Hum Mol Genet.*, Vol.9, No.13, (August 2000), pp. 2059-2063

Krieger, N.S.; Frick, K.K. & Bushinsky, D.A. (2004). Mechanism of acid-induced bone resorption. *Curr Opin Nephrol Hypertens.*, Vol.13, No.4, (July 2004), pp. 423-436

Kumar, K.K.; Tung, S. & Iqbal, J. (2010). Bone loss in anorexia nervosa: leptin, serotonin, and the sympathetic nervous system. *Ann N Y Acad Sci.*, Vol.1211, (November 2010), pp. 51-65

Kurihara, N.; Hiruma, Y.; Zhou, H.; Subler, M.A.; Dempster, D.W.; Singer, F.R.; Reddy, S.V.; Gruber, H.E.; Windle, J.J. & Roodman, G.D. Mutation of the sequestosome 1 (p62) gene increases osteoclastogenesis but does not induce Paget disease. *J Clin Invest.*, Vol.117, No.1, (January 2007), pp. 133-142

Kwon, O.H.; Lee, C.K.; Lee, Y.I.; Paik, S.G. & Lee, H.J. (2005). The hematopoietic transcription factor PU.1 regulates RANK gene expression in myeloid progenitors. *Biochem Biophys Res Commun.*, Vol.335, No.2, (September 2005), pp. 437-446

Lange, P.F.; Wartosch, L.; Jentsch, T.J. & Fuhrmann, J.C. (2006). ClC-7 requires Ostm1 as a beta-subunit to support bone resorption and lysosomal function. *Nature*, Vol.440, No.7081, (March 2006), pp. 220-223

Laurin, N.; Brown, J.P.; Lemainque, A.; Duchesne, A.; Huot, D.; Lacourcière, Y.; Drapeau, G.; Verreault, J.; Raymond, V. & Morissette, J. (2001). Paget disease of bone: mapping of two loci at 5q35-qter and 5q31. *Am J Hum Genet.*, Vol.69, No.6, (Jun 2002), pp. 1582-1588

Laurin, N.; Brown, J.P.; Morissette, J. & Raymond, V. (2002). Recurrent mutation of the gene encoding sequestosome 1 (SQSTM1/p62) in Paget disease of bone. *Am J Hum Genet.*, Vol.70, No.6, (Jun 2002), pp. 1582-1588

Lee, N.K.; Sowa, H.; Hinoi, E.; Ferron, M.; Ahn, J.D.; Confavreux, C.; Dacquin, R.; Mee, P.J.; McKee, M.D.; Jung, D.Y.; Zhang, Z.; Kim, J.K.; Mauvais-Jarvis, F.; Ducy, P. & Karsenty, G. (2007). Endocrine regulation of energy metabolism by the skeleton. *Cell*, Vol.10, No.3, (August 2010), pp. 456-469

Letizia, C.; Taranta, A.; Migliaccio, S.; Caliumi, C.; Diacinti, D.; Delfini, E.; D’Erasmo, E.; Iacobini, M.; Rognini, M.; Albagha, O.M.; Ralston, S.H. & Teti A. (2004). Type II Benign Osteopetrosis (Albers-Schönberg Disease) caused by a novel mutation in CICN7 presenting with unusual clinical manifestations. *Calcif Tissue Int.*, Vol.74, No.1, (January 2004), pp. 42-46

Lips, P. (2006). Vitamin D physiology. *Prog Biophys Mol Biol.*, Vol. 92, No.1, (September 2006), pp. 4-8

Loria-Cortes, R.; Quesada-Calvo, E. & Cordero-Chavarri, C. (1977). Osteopetrosis in children: a report of 26 cases. *J Pediatr.*, Vol.91, No.1, (July 1977), pp. 43-47

Manolagas, S.C.; Kousteni, S. & Jilka, R.L. (2002). Sex steroids and bone. *Recent Prog Horm Res.*, Vol.57, pp. 385-409
Marks, S.C. & Jr Walker, D.G. (1981). The hematogenous origin of osteoclasts: experimental evidence from osteopetrotic (microphthalmic) mice treated with spleen cells from beige mouse donors. *Am J Anat.*, Vol.161, No.1, (May 1981), pp. 1-10

Maroteaux, P. & Lamy, M. (1965). The malady of Toulouse-Lautrec. *JAMA*. Vol.191, pp. 715-717

Mazzaferro, S.; Pasquali, M.; Pirrò, G.; Rotondi, S. & Tartaglione L. (2010). The bone and kidney. *Arch Biochem Biophys.*, Vol.503, No.1 (July 2010), pp. 95-102

McQueney, M.S.; Amegadzie, B.Y.; D’Alessio, K.; Hanning, C.R.; McLaughlin, M.M.; McNulty, D.; Carr, S.A.; Ijames, C.; Kurdyla, J. & Jones, C.S. (1997). Autocatalytic activation of human cathepsin K. *J Biol Chem.*, Vol.272, No.21, (May 1997) pp. 13955-13960

Meadows, N.A.; Sharma, S.M.; Faulkner, G.J.; Ostrowski, M.C.; Hume, D.A. & Cassady, A.I. (2006). The expression of Clcn7 and Ostm1 in osteoclasts is coregulated by microphthalmia transcription factor. *J Biol Chem.*, Vol.282, No.3, (January 2006), pp. 1891-1904

Miyazaki, T.; Tanaka, S.; Sanjay, A. & Baron, R. (2006). The role of c-Src kinase in the regulation of osteoclast function. *Mod Rheumatol.*, Vol.16, No.2, (2006), pp. 68-74

Moscat, J. & Diaz-Meco, M.T. (2002). The atypical PKC scaffold protein P62 is a novel target for anti-inflammatory and anti-cancer therapies. *Adv Enzyme Regul.*, Vol.42, (2002), pp. 173-179

Mundy, G.R. (1993). Cytokines and growth factors in the regulation of bone remodeling. *J Bone Miner Res.*, Vol.8, No.2, (December 1993), pp. 505-10

Muto, T.; Michiya, H.; Taïra, H.; Murase, H. & Kanazawa, M. (1991). Pycnodysostosis. Report of a case and review of the Japanese literature, with emphasis on oral and maxillofacial findings. *Oral Surg Oral Med Oral Pathol.*, Vol.72, No.4, (October 1991), pp. 449-55

Muto, T.; Yamazaki, A.; Takeda, S.; Tsuji, Y. & Shibata, T. (2005). Pharyngeal narrowing as a common feature in pycnodysostosis--a cephalometric study. *Int J Oral Maxillofac Surg.*, Vol.34, No.6, (September 2005), pp. 680-685

Muzyk, M.; Arnett, T.R.; Price, J.S. & Horton, M.A. (2007). The in vitro effect of pH on osteoclasts and bone resorption in the cat: implications for the pathogenesis of FORL. *J Cell Physiol.*, Vol.213, No.1, (October 2007), pp. 144-150

Nesbitt, S.A. & Horton, M.A. (1997). Trafficking of matrix collagens through bone-resorbing osteoclasts. *Science.*, Vol.11, No.276, (April 1997), pp. 266-269

Nishi, T. & Forgac, M. (2002). The Vacuolar (H+) -ATPase. Nature’s most versatile proton pumps. *Nat Rev Mol Cell Biol.*, Vol.3, No.2, (February 2002), pp. 94-103

Oury, F.; Sumara, G.; Sumara, O.; Ferron, M.; Chang, H.; Smith, C.E.; Hermo, L.; Suarez, S.; Roth, B.L.; Ducy, P. & Karsenty, G. (2011). Endocrine regulation of male fertility by the skeleton. *Cell.*, Vol.144, No.5, (March 2011), pp. 796-809

Paget, J. (1876). On a form of chronic inflammation of bones (osteiti deformans). *Med-Chir Trans* ix:37-38

Paine, M.G.; Babu, J.R.; Seibenhener, M.L. & Wooten, M.W. (2005). Evidence for p62 aggregate formation: role in cell survival. *FEBS Lett.* Vol.579, No.22, (September 2005), pp. 5029-5034

Pangrazio, A.; Poliani, P.L.; Megarbane, A.; Lefranc, G.; Lanino, E.; Di Rocco, M.; Rucci, F.; Lucchini, F.; Ravanini, M.; Facchetti, F.; Abinun, M.; Vezzoni, P.; Villa, A. &
Frattini, A. (2006). Mutations in OSTM1 (grey lethal) define a particularly severe form of autosomal recessive osteopetrosis with neural involvement. *J Bone Miner Res.*, Vol.21, No.7, (July 2006), pp. 1098-1105

Parfitt, A.M. (1976). The actions of parathyroid hormone on bone: relation to bone remodeling and turnover, calcium homeostasis, and metabolic bone diseases. II. PTH and bone cells: bone turnover and plasma calcium regulation. *Metabolism*, Vol.25, No.9, (September 1976), pp. 1033-1069

Parfitt, A.M. (1982). The coupling of bone formation to bone resorption: a critical analysis of the concept and of its relevance to the pathogenesis of osteoporosis. *Metab Bone Dis Relat Res.*, Vol.4, No.1, pp. 1-6

Peruzzi, B. & Teti, A. (2011). The Physiology and Pathophysiology of the Osteoclast. *Clinic Rev Bone Miner Metab.*, (2011)

Pogoda, P.; Priemel, M.; Rueger, J.M. & Amling, M.; (2005). Bone remodeling: new aspects of a key process that controls skeletal maintenance and repair. *Osteoporos Int.*, Vol.16, No.2, (March 2005), pp. 18-24

Ralston, S.H. (2008). Pathogenesis of Paget's disease of bone. *Bone*, Vol.43, No.5, (November 2008), pp. 819-825

Ralston, S.H.; Langston, A.L. & Reid, I.R. Pathogenesis and management of Paget’s disease of bone. *Lancet*, Vol.372, No.9633, (July 2008), pp. 155-163

Reddy, S.V.; Kurihara, N.; Menaa, C.; Landucci, G.; Forthal, D.; Koop, B.A.; Windle, J.J. & Roodman, G.D. (2001). Osteoclasts formed by measles virus-infected osteoclast precursors from hCD46 transgenic mice express characteristics of pagetic osteoclasts. *Endocrinology*, Vol.142, No.7, (July 2001), pp. 2898-2905

Rojas, J.A.; Daroszewska, A.; Helfrich, M.; Layfield, R.; van't Hof, R. & Ralston, S.H. (2007). Mice with a truncation mutation affecting sequestosome 1 exhibit several phenotypic features in common with Paget's disease of bone. *Calcif Tiss Int.*, Vol.81, (2007), p. 149

Rood, J.A.; Van Horn, S.; Drake, F.H.; Gowen, M. & Debouck, C. (1997). Genomic organization and chromosome localization of the human cathepsin K gene (CTSK). *Genomics*. Vol.41, No.2, (April 1997), pp. 169-176

Roodman, G.D. (1996). Advances in bone biology: the osteoclast. *Endocr Rev.*, Vol.14, No.4, (August 1996), pp. 308-332

Rufo, A.; Del Fattore, A.; Capulli, M.; Carvello, F.; De Pasquale, L.; Ferrari, S.; Pierroz, D.; Morandi, L.; De Simone, M.; Rucci, N.; Bertini, E.; Bianchi, M.L.; De Benedetti, F. & Teti, A. (2011). Mechanisms inducing low bone density in Duchenne muscular dystrophy in mice and humans. (August 2011)

Saftig, P.; Hunziker, E.; Wehmeyer, O.; Jones, S.; Boyde, A.; Rommerskirch, W.; Moritz, J.D.; Schu, P. & von Figura, K. (1998). Impaired osteoclastic bone resorption leads to osteopetrosis in cathepsin-K-deficient mice. *Proc Natl Acad Sci USA*, Vol.95, No.23, (November 1998), pp. 13453-13458

Sakiyama, H.; Masuda, R.; Inoue, N.; Yamamoto, K.; Kuriiya, K.; Nakagawa, K. & Yoshida, K. (2001). Establishment and characterization of macrophage-like cell lines expressing osteoclast-specific markers. *J Bone Miner Metab.*, Vol.19, No.4, pp. 220-227
Salo, J.; Metsikko, K.; Palokangas, H.; Lehenkari, P. & Vaananen, H.K. (1996). Bone-resorbing osteoclasts reveal a dynamic division of basal plasma membrane into two different domains. J Cell Sci, Vol.109, No.2, (February 1996), pp. 301-317

Schilling, A.F.; Mullerhausen, C.; Lehmann, W.; Santer, R.; Schinke, T.; Rueger, J.M. & Amling, M. (2007). High bone mineral density in pycnodysostotic patients with a novel mutation in the propeptide of cathepsin K. Osteoporos Int., Vol.18, No.5, (May 2007), pp. 659-669

Seibenhener, M.L.; Babu, J.R.; Geetha, T.; Wong, H.C.; Krishna, N.R. & Wooten, M.W. (2004). Sequestosome 1/p62 is a polyubiquitin chain binding protein involved in ubiquitin proteasome degradation. Mol. Cell. Biol., Vol.24, No.18, (September 2004), pp. 8055-8068

Selby, P.L.; Davie, M.W.; Ralston, S.H. & Stone, M.D. (2002). Bone and Tooth Society of Great Britain; National Association for the Relief of Paget's Disease. Guidelines on the management of Paget's disease of bone. Bone, Vol.31, No.3, (September 2002), pp. 366-373

Sly, W.S.; Hewett-Emmett, D.; Whyte, M.P.; Yu, Y.S. & Tashjian, R.E. (1983). Carbonic anhydrase II deficiency identified as the primary defect in the autosomal recessive syndrome of osteopetrosis with renal tubular acidosis and cerebral calcification. Proc Natl Acad Sci USA, Vol.80, No.9, (May 1983), pp. 2752-2756

Smahi, A.; Courtois, G.; Rabia, S.H.; Doffinger, R.; Bodemer, C.; Munnich, A.; Casanova, J.L. & Israel, A. (2002). The NF-kappaB signalling pathway in human diseases: from incontinentia pigmenti to ectodermal dysplasias and immune-deficiency syndromes. Hum Mol Genet., Vol.11, No.20, (October 2002), pp. 2371-2375

So, H.; Rho, J.; Jeong, D.; Park, R.; Fisher, D.E.; Ostrowski, M.C.; Choi, Y. & Kim, N. (2003). Microphthalmia transcription factor and PU.1 synergistically induce the leukocyte receptor osteoclast-associated receptor gene expression. J Biol Chem., Vol.278, No.26, (June 2003), pp. 24209-24216

Sobacchi, C.; Frattini, A.; Guerrini, M.M.; Abinun, M.; Pangrazio, A.; Susani, L.; Bredius, R.; Mancini, G.; Cant, A.; Bishop, N.; Grabowski, P.; Del Fattore, A.; Messina, C.;Errigo, G.; Coxon, F.P.; Scott, D.I.; Teti, A.; Rogers, M.J.; Vezzoni, P.; Villa, A. & Helfrich, M.H. (2007). Osteoclast-poor human osteopetrosis due to mutations in the gene encoding RANKL. Nat Genet., Vol.39, No.8, (August 2007), pp. 960-962

Soliman, A.T.; Ramadan, M.A.; Sherif, A.; Aziz Bedair, E.S. & Rizk, M.M. (2001) Pycnodysostosis: clinical, radiologic, and endocrine evaluation and linear growth after growth hormone therapy. Metabolism, Vol.50, No.8, (August 2001), pp. 905-911

Stenbeck, G. (2002). Formation and function of the ruffled border in osteoclasts. Semin Cell Dev Biol., Vol.13, No.4, (August 2002), pp. 285-292

Takahashi, N.; Ejiri, S.; Yanagisawa, S. & Ozawa, H. (2007). Regulation of osteoclast polarization. Odontology, Vol.95, No.1, (July 2007), pp. 1-9

Takayanagi, H. (2007). The role of NFAT in osteoclast formation. Ann N Y Acad Sci., Vol.1116, (November 2007), pp. 227-37

Takayanagi, H. (2010). New immune connections in osteoclast formation. Ann N Y Acad Sci., Vol.1191, (March), pp. 117-123

Takayanagi, H.; Sato, K.; Takaoka, A. & Taniguchi, T. Interplay between interferon and other cytokine systems in bone metabolism. Immuno Rev., Vol.208, (December 2005), pp. 181-93
Takeda, S.; Yoshizawa, T.; Nagai, Y.; Yamato, H.; Fukumoto, S.; Sekine, K.; Kato, S.; Matsumoto, T. & Fujita, T. (1999) Stimulation of osteoclast formation by 1, 25-dihydroxyvitamin D requires its binding to vitamin D receptor (VDR) in osteoblastic cells: studies using VDR knockout mice. Endocrinology, Vol.140, No.2, (February 1999), pp. 1005-1008

Tanaka, Y.; Nakayamada, S. & Okada, Y. Osteoblasts and osteoclasts in bone remodeling and inflammation. Curr Drug Targets Inflamm Allergy, Vol.4, No.3 (June 2005), pp. 325-328

Taranta, A.; Migliaccio, S.; Recchia, I.; Caniglia, M.; Luciani, M.; De Rossi, G.; Dionisi-Vici, C.; Pinto, RM.; Francalanci, P.; Boldrini, R.; Lanino, E.; Dini, G.; Morreale, G.; Ralston, SH.; Villa, A.; Vezzoni, P.; Del Principe, D.; Cassini, F.; Palombo, G. & Teti A. (2003) Genotype-Phenotype relationship in Human ATP6i-Dependent Autosomal Recessive Osteopetrosis. Am J Pathol., Vol.162, No.1, (January 2003), pp. 57-68

Teitelbaum, S.L. & Ross, P. (2003). Genetic regulation of osteoclast development and function. Nat Rev Genet., Vol.4, No.8, (August 2003), pp. 638-649

Teitelbaum, S.L. (2007). Osteoclasts: what do they do and how do they do it? Am J Pathol., Vol.170, No.2, (February 2008), pp. 427-435

Tetri, A.; Blair, H.C.; Teitelbaum, S.L.; Kahn, A.J.; Konsek, J.; Zambonin-Zallone, A. & Schlesinger, P.H. (1989). Cytoplasmic pH regulation and chloride/bicarbonate exchange in avian osteoclasts. J Clin Invest, Vol.83, No.1 (January 1989), pp. 227-233

Tiegs, R.D.; Lohse, CM.; Wollan, P.C. & Melton, L.J. (2000). Long-term trends in the incidence of Paget's disease of bone. Bone, Vol.27, No.3, (September 2000), pp. 423-427

Tilyard, MW.; Gardner, R.J.; Milligan, L.; Cleary, T.A. & Stewart R.D. A probable linkage between familial Paget's disease and the HLA loci. Australian & New Zealand Journal of Medicine, Vol.12, No.5, (October 1982), pp. 498-500

Toral-López, J.; Gonzalez-Huerta, L.M.; Sosa, B.; Orozco, S.; González, H.P. & Cuevas-Covarrubias, S.A. (2011) Familial pycnodysostosis: identification of a novel mutation in the CTSK gene (cathepsin K). J Investig Med., Vol.59, No.2, (February 2011), pp. 277-280

Vaaninen, H.K.; Iu, Y.K.; Lehenkari, P. & Uemara, T. (1998). How do osteoclasts resorb bone? Mat Sci Eng C., Vol.6, pp. 205-209

van Staa, T.P.; Selby, P.; Leufkens, H.G.; Lyles, K.; Sprafka, J.M. & Cooper, C. (2002). Incidence and natural history of Paget's disease in England and Wales. J Bone Miner Res., Vol.17, No.3, (March 2002), pp. 465-471

Van Wesenbeeck, L.; Odgren, P.R.; Coxon, F.P.; Frattini, A.; Moens, P.; Perdu, B.; MacKay, C.A.; Van Hul, E.; Timmermans, J-P.; Vanhoenacker, F.; Jacobs, R.; Peruzzi, B.; Teti, A.; Helfrich, M.H.; Rogers, M.J.; Villa, A. & Van Hul, W. (2007) Involvement of PLEKHM1 in osteoclastic vesicular transport and osteopetrosis in incisors absent rats and humans. J Clin Invest., Vol.117, No.4, (April 2007), pp. 919-930
Wada, T.; Nakashima, T.; Hiroshi, N. & Penninger, J.M. (2006). RANKL-RANK signaling in osteoclastogenesis and bone disease. *Trends Mol Med.*, Vol.12, No.1, (January 2006), pp. 17-25

Waguespack, S.G.; Hui, S.L.; Dimeglio, L.A. & Econs, M.J. (2007) Autosomal dominant osteopetrosis: clinical severity and natural history of 94 subjects with a chloride channel 7 gene mutation. *J Clin Endocrinol Metab.*, Vol.92, No.3, (March 2007), pp. 771-778

Walker, D.G. (1981). Control of bone resorption by hematopoietic tissue. The induction and reversal of congenital osteopetrosis in mice through use of bone marrow and splenic transplants. *Am J Anat.*, Vol.161, No.1, (May 1981), pp. 1-10

Whyte, MP. (2002). Osteopetrosis. In: *Connective Tissue and Its Heritable Disorders: Medical, Genetic, and Molecular Aspects*. Royce, P.M., Steinman, B. New York, Wiley-Liss, Inc, pp. 753-770

Yip, KHM.; Feng, HT.; Pavlos, NJ.; Zheng, MH. & Xu JK. (2006). p62 Ubiquitin binding-associated domain mediated the receptor activator of nuclear factor-κB ligand-induced osteoclast formation – A new insight into the pathogenesis of Paget's disease of bone. *Am. J. Pathol.*, Vol.169, No.2, (August 2006), pp. 503–514

Zhao, Q.; Jia, Y. & Xiao, Y. (2009). Cathepsin K: a therapeutic target for bone diseases. *Biochem Biophys Res Commun.*, Vol.380, No.4, (March 2009), pp. 721-723
The genetics science is less than 150 years old, but its accomplishments have been astonishing. Genetics has become an indispensable component of almost all research in modern biology and medicine. Human genetic variation is associated with many, if not all, human diseases and disabilities. Nowadays, studies investigating any biological process, from the molecular level to the population level, use the “genetic approach” to gain understanding of that process. This book contains many diverse chapters, dealing with human genetic diseases, methods to diagnose them, novel approaches to treat them and molecular approaches and concepts to understand them. Although this book does not give a comprehensive overview of human genetic diseases, I believe that the sixteen book chapters will be a valuable resource for researchers and students in different life and medical sciences.

How to reference
In order to correctly reference this scholarly work, feel free to copy and paste the following:

Andrea Del Fattore and Anna Teti (2011). Osteoclast Genetic Diseases, Human Genetic Diseases, Dr. Dijana Plaseska-Karanfilska (Ed.), ISBN: 978-953-307-936-3, InTech, Available from: http://www.intechopen.com/books/human-genetic-diseases/osteoclast-genetic-diseases