European Journal of Medical Genetics 69 (2024) 104936

Contents lists available at ScienceDirect

European Journal of Medical Genetics

journal homepage: www.elsevier.com/locate/ejmg

Osteopetrosis and related osteoclast disorders in adults: A review and knowledge gaps On behalf of the European calcified tissue society and ERN BOND

Thomas Funck-Brentano [a,b], M. Carola Zillikens [c], Gavin Clunie [d], Heide Siggelkow [e,f], Natasha M. Appelman-Dijkstra [g], Martine Cohen-Solal [a,b,*]

[a] Reference Center for Rare Bone Diseases and Department of Rheumatology, Hôpital Lariboisière, APHP, Université Paris Cité, Paris, France
[b] INSERM UMR1132 BIOSCAR, Paris, France
[c] Bone Center, Department of Internal Medicine. Erasmus MC, University Medical Center Rotterdam, the Netherlands
[d] Metabolic Bone Physician, Cambridge University Hospitals, Box 204, Hills Rd, Cambridge, CB2 0QQ, UK
[e] MVZ Endokrinologikum, Göttingen, Germany
[f] Clinic of Gastroenterology, Gastrointestinal Oncology and Endocrinology, University Medical Center, 37075, Göttingen, Germany
[g] Center for Bone Quality, Department of Internal Medicine, Division of Endocrinology, Leiden University Medical Center, Leiden, the Netherlands

ARTICLE INFO

Handling editor: A. Verloes

Keywords:
Osteopetrosis
Osteoclast
Fractures
High bone mass

ABSTRACT

Osteopetrosis refers to a group of related rare bone diseases characterized by a high bone mass due to impaired bone resorption by osteoclasts. Despite the high bone mass, skeletal strength is compromised and the risk of fracture is high, particularly in the long bones. Osteopetrosis was classically categorized by inheritance pattern into autosomal recessive forms (ARO), which are severe and diagnosed within the first years of life, an intermediate form and an autosomal dominant (ADO) form; the latter with variable clinical severity and typically diagnosed during adolescence or in young adulthood. Subsequently, the AD form was shown to be a result of mutations in the gene *CLCN7* encoding for the ClC-7 chloride channel). Traditionally, the diagnosis of osteopetrosis was made on radiograph appearance alone, but recent molecular and genetic advances have enabled a greater fidelity in classification of osteopetrosis subtypes. In the more severe ARO forms (e.g., malignant infantile osteopetrosis MIOP) typical clinical features have severe consequences and often result in death in early childhood. Major complications of ADO are atypical fractures with delay or failure of repair and challenge in orthopedic management. Bone marrow failure, dental abscess, deafness and visual loss are often underestimated and neglected in relation with lack of awareness and expertise. Accordingly, the care of adult patients with osteopetrosis requires a multidisciplinary approach ideally in specialized centers. Apart from hematopoietic stem cell transplantation in certain infantile forms, the treatment of patients with osteopetrosis, has not been standardized and remains supportive. Further clinical studies are needed to improve our knowledge of the natural history, optimum management and impact of osteopetrosis on the lives of patients living with the disorder.

1. Introduction

Osteopetrosis was first described by Albers-Schönberg in 1904 (Albers-Schönberg, 1904). Following the original disease description, osteopetrosis was defined on the age at diagnosis and heritability. Over time several forms of osteopetrosis were distinguished: the autosomal recessive types (AROs) that include the neonatal or infantile forms, the intermediate form, the X-linked and the autosomal dominant form (ADO). It became evident that the term "osteopetrosis" was adopted to describe several rare hereditary bone diseases characterized by a generalized or focal increase in bone mass, related to a failure of bone resorption by osteoclasts (Vernejoul and Kornak, 2010). The most recent classification of osteopetrosis – the 2023 nosology (Unger et al., 2023) distinguishes subtypes according to genotype and from other high bone mass disorders (the rare hereditary bone sclerosing diseases), where an increase in bone formation, rather than reduced bone resorption, results in the high bone mass. For example, the high bone mass caused by gain of function from a pathogenic variant in the LRP5 gene, was previously

* Corresponding author. Reference Center for Rare Bone Disease, Hopitl Lariboisiere, Paris, France.
E-mail addresses: thomas.funck-brentano@aphp.fr (T. Funck-Brentano), martine.cohen-solal@inserm.fr (M. Cohen-Solal).

https://doi.org/10.1016/j.ejmg.2024.104936
Received 30 August 2023; Received in revised form 13 December 2023; Accepted 1 April 2024
Available online 7 April 2024

classified as AD osteopetrosis type 1 (OPTA1), but is now classified within 'osteosclerotic disorders' (Unger et al., 2023). In this review, we describe the main clinical features of osteopetrosis in adults, present and discuss the evidence for optimal care of patients with osteopetrosis, and offer insights into where clinical research efforts may be focused in future.

2. Recessive forms of osteopetrosis

Recessive forms of osteopetrosis have been reviewed recently (Penna et al., 2021; Sobacchi and Abinun, 2022) and will not been detailed here. In the most recent genetic classification of disorders, 13 separate autosomal recessive (AR) osteopetrosis (ARO) entities are listed, arising from pathogenic variation in 11 different genes. The most severe form of ARO is termed malignant infantile osteopetrosis (MIOP), is diagnosed soon after birth, is fatal if left untreated. The ultra-rare autosomal intermediate osteopetrosis (AIO) occurs in AR or AD forms, is characterized by onset in infancy, anemia and fractures, but without life-threatening myelosuppression. The X-linked form is also extremely rare, involving NEMO, the regulatory subunit of the IKK complex, essential for activation of the NFκB pathway. These 3 recessive forms are lethal during the first years of life (Sobacchi et al., 2013) and should not be seen as adults. In MIOP and AR AIO, bones become diffusely dense with extremely narrow intramedullary cavities and a 'bone-in-bone' appearance on radiographs. The lack of space within the bone marrow cavity results in bone marrow failure and increased susceptibility to infections.

It has been proposed to distinguish 2 forms of ARO according to the number of osteoclasts: maintained or increased in osteoclast-rich osteopetrosis; but reduced number or absent in osteoclast-poor osteopetrosis (Penna et al., 2021). Such sub-classification may serve to link understanding in gene defects and associated clinical features. Fig. 1 and Table 1 show the genes identified and their relation to osteoclast function.

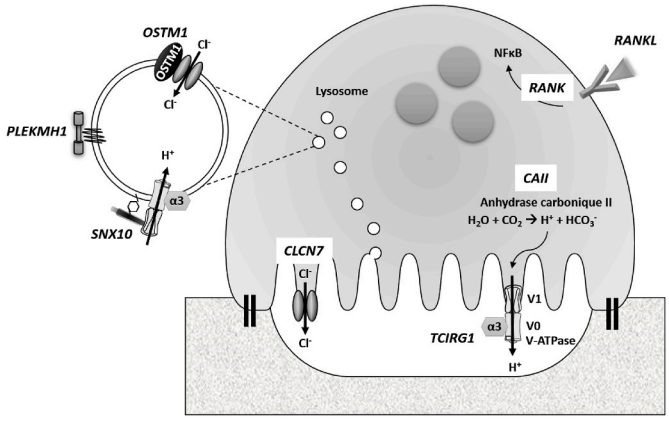

Fig. 1. Major gene mutations known to be responsible for osteopetroses.
CAII encodes type II carbonic anhydrase and allows cytoplasmic H+ production. TCIRG1 encodes for the α3 subunit of the V-ATPase proton pump allowing proton secretion into the resorption chamber. CLCN7 encodes for the chlorine channel 7 allows Cl-excretion into the resorption chamber via the ruffled border. The left panel represents a detail of the abnormalities leading to a failure in the lysosomal system. OSTM1 encodes for the β-subunit of chloride channel 7 allowing its transport to the ruffled border by lysosomes. PLEKMH1 encodes a cytosolic Rab7-binding protein, which is associated with a defect in endosome and lysosome formation. SNX10 encodes sorting nexin 10 and binds to the V1 subunit of the proton pump, suggesting its involvement in the transport of this pump to the ruffle border. These mutations result in a failure of osteoclast function, reducing formation of the ruffled border or its acidification. These forms of osteopetrosis are called osteoclast-rich. In addition, abnormalities in RANK or RANKL prevent the differentiation of osteoclasts, thereby called osteoclast-poor osteopetrosis.

3. Autosomal dominant osteopetrosis (ADO)

3.1. Clinical presentation

Autosomal dominant osteopetrosis (formerly ADO type 2), also known as Albers-Schönberg disease, is the most frequent form primarily seen in adults with an estimated incidence of 1 in 20,000 births. The majority of ADO have been reported with mutations in CLCN7 encoding the chloride channel 7, an antiporter exchanging 2 Cl-for 1 H + in the vesicular membrane and the ruffled border (Fig. 1). So far, more than 34 CLCN7 mutations have been reported. The Ostm1 subunit binds to the dimerized chloride channel in the vesicular membrane and is essential for its cellular transport to the ruffled border. Bone symptoms appear in adolescents or in young adults. The penetrance of Albers-Schönberg disease is incomplete since only about 66% of patients carrying the mutation have clinical manifestations and even a considerable variability of expression even among siblings of the same family (Campos-Xavier et al., 2005). ADO shows a wide spectrum of symptoms ranging from simple radiological abnormalities to severe disability due to complications such as multiple fractures, osteomyelitis or even, exceptionally, hematological complications due to bone marrow failure.

The diagnosis of ADO is based on radiological features with a diffuse dense aspect affecting long bones, pelvis, toes and fingers. More specifically, X-Rays reveal bands of parallel condensed bone separated by a less dense area of bone, giving the appearance of "bone in the bone" which is characteristic for the disease (Fig. 2). At the spine, the appearance of a "sandwich vertebra" is also pathognomonic. Densification of the base of the skull and a lack of ventilation of the sinuses can be seen. Long bones reveal an enlargement of the metaphyses with thinning of the cortices, giving the appearance of "Erlenmeyer bottle". Finally, atypical fractures located at the diaphysis have been reported (Fig. 2E) (Zhou et al., 2021). These radiological elements are highly characteristic and sufficient to confirm the diagnosis of ADO. Beside the skeletal features, nerve damage may occur due to bone compression. Impingements of cranial nerves may lead to blindness and deafness. Attention should be paid to the optic foramen, particularly during growth in children. They are best monitored by MRI or tomodensitometry since they may reveal hydrocephalus or vascular anomalies. These manifestations are rare in adult patients, although they should be investigated to detect mild forms with minimal clinical signs.

Because of the osteoclast failure, bone mass increases thereby reducing the space of the marrow cavity, thus generating anemia and hepatosplenomegaly. The latter is compensation for lack of space in the bone marrow cavities, but bone marrow failure is rare in adults. Fractures are the main issue as they occur in 46% of the patients (Wang et al., 2022). They affect typical sites (vertebrae, long bones), but are often atypical, located at the metaphysis or diaphysis. Pedicle fractures may be seen after a minor trauma sometimes leading to spondylolysis and can be a source of chronic pain (Mohapatra et al., 2010). For all these fractures, there is an unusual delay of consolidation in adults. Fracture repair may take several months to even several years, causing severe morbidity and impaired quality of life.

3.2. Bone phenotype

Bone mineral density (BMD) quantified by DXA consistently shows a high bone density, the Z-score being above +2 standard deviations at the spine and hip sites. However, the magnitude of the high BMD does not correlate with the risk of fracture although there was a tendency of a higher number of fractures with higher Z-score in 31 Chinese patients (Wang et al., 2022). The kinetics of changes of BMD is poorly known. The follow-up of 15 patients for a mean of 6 years revealed no change in BMD at any site assessed (Wang et al., 2022). However, 5 of 15 patients experienced a new fracture independently of the BMD level. For this reason, it was not recommended to re-evaluate the BMD for monitoring the fracture risk. However, the effect of age and menopause is unknown

Table 1
Transmission and genes involved in osteopetrosis
The mode of transmission, the genes and their function and the clinical phenotype are shown according to the 2023 update (Unger et al., 2023).

	Gene	Form		Protein	OMIM	Function	Clinical phenotype
Autosomic recessive	*TCIRG1*	Osteopetrosis	Neonatal or infantile form/Intermediate form	α3 subunit of V-ATPase proton pomp	259800	H+ secretion/ vesicular trafficking	Severe
	CLCN7	Osteopetrosis	Neonatal or infantile form/Intermediate form	Chloride channel 7	611490/ 259710	H+ secretion	From mild to severe form, scarcely lethal
	SNX10	Osteopetrosis	Neonatal or infantile form	Sorting nexin 10	615085	Lysosome trafficking/ fusion	Severe
	OSTM1	Osteopetrosis	Infantile form	Osteopetrosis associated transmembrane protein	259720	Lysosome trafficking/ acidification	Severe, neurodegenerative involvement
	TNFSF11A	Osteopetrosis	Infantile form, osteoclast-poor, immunoglobulin deficiency	RANK (receptor activator of NF-KB)	612301	Osteoclast differentiation	Severe
	TNFSF11	Osteopetrosis	Intermediate form	RANKL (ligand of the receptor of NF-KB)	259710	Osteoclast differentiation	Mild to severe form
	PLEKHM1	Osteopetrosis	Intermediate form	Pleckstrin homology domain containing family M, member 1	611497	Lysosome trafficking/ fusion	Mild to severe form
	CAII	Osteopetrosis	Infantile form	Anhydrase carbonique type II	259730	Acidification	Tubular kidney acidosis, vascular brain calcifications
	CTSK	Pycnodysostosis	Early to late-onset	Cathepsin K	265800	Osteoclast function - Failure to degrade bone matrix	Mild to severe form
	TNFSF11A	Dysosteosclerosis	Infantile form	RANK (receptor activator of NF-KB)	224300	Osteoclast differentiation	Severe
	Slc29a3	Dysosteosclerosis	Infantile form	Nucleoside transporter (Solute carrier family 29 number 3)	224300	Osteoclast differentiation	Mild to severe form
	CSF1R	Dysosteosclerosis	Infantile form	Colony-stimulating factor 1 receptor	618476	Osteoclast differentiation	Severe, brain abnormalities and neurodegeneration
Autosomic dominant	CLCN7	Osteopetrosis	Late-onset, dominant form	Chloride channel 7	166600	H+ secretion	Mild to severe form

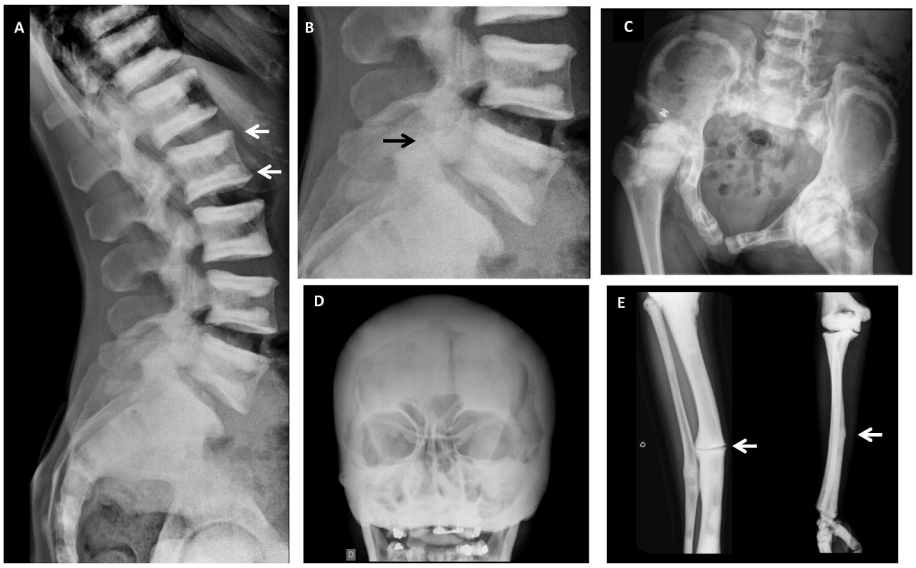

Fig. 2. X-Rays of osteopetrotic patients
A-B: Spinal X-Ray of an adult with osteopetrosis showing a condensation of vertebral endplates (white arrows). B: pseudarthrosis of the transversal apophysis (black arrow). C- X-Ray of the pelvis reveals a « bone in the bone » aspect of the iliac crests. D: X-Ray of the skull shows a high bone density and the lack of air in the sinuses. E: X-Ray reveals a fracture of the metaphysis of the tibia and radius (white arrows).

since most of the studies were performed in patients aged below 50 years; these missing data deserve further research in the future. Bone microarchitecture is also severely altered when measured by HRpQCT (Butscheidt et al., 2018). Eight patients with ADO were compared to 16 patients with high bone mass without genetic mutations. ADO patients show a higher trabecular number while patients with benign high bone mass rather showed a higher cortical BMD. Further, bone islets were seen only in ADO patients who experienced fractures. Consistently, bone islets were also found in bone biopsies, suggesting that they may be the accumulation of micro callus in the trabecular bone or related to impaired endochondral ossification with remaining mineralized cartilage. A larger study is required to ascertain whether this typical aspect

correlates with the BMD and the history of fractures. Indeed, in the single report describing histological pattern of osteopetrosis, persistence of unresorbed calcified cartilage has been described as remnants of growth plates in the mature bone and was suggested to be a hallmark of osteoclast failure (Marks, 1987). Serum markers of bone and mineral metabolism markers should be included for the diagnosis and monitoring of ADO patients, including serum PTH and blood count for hematological abnormalities. Monitoring of serum TRAP5b (tartrate resistant acid phosphatases 5 b) level is recommended as a marker of osteoclast number. The TRAP5b levels are always above the normal range in ADO, but not in other sclerosing osteopathies. However, the magnitude of the serum levels does not correlate with the severity of the disease (Coudert et al., 2014). Further analysis in a large number of patients is recommended to evaluate the prognostic value in terms of e.g., the severity of bone mineral density elevation with other complications such as the fracture rate and hematological disorders. Importantly, there is no cognitive impairment described in patients with ADO although sometimes mentioned in the clinical practice.

Musculoskeletal pain is a frequent concern, but is not well investigated through questionnaires. Joint pain and stiffness are often reported as "osteoarthritis". In 36 adult patients (age 32–75 years), hip or knee osteoarthritis based on X-Rays was found in only 5/36 (13%) (Wang et al., 2022). Indeed, cartilage damage may develop earlier when located in a subchondral bone which is stiffer by nature. Recently, we have found that chronic bone pain was reported by 86% of the patients (Cohen-Solal et al., 2023). Several causes might be involved such as trabecular microfractures related to the poor quality of the bone matrix, impaired bone vascularization or a dysregulation of the peripheral neurological system. These issues deserve to be addressed in the future and raise the hypothesis of shared mechanism between the failure of bone resorption and bone pain.

3.3. Treatment of ADO

As there is no specific genetic or pharmacological treatment available in ADO, medical management aims to prevent or provide care of disease complications. Because of the diversity of complications affecting several organs, the management must be multidisciplinary, involving clinical bone experts, hematologists and dentists with experience in rare bone diseases. Because of the scarcity of studies and reports and the great variability of clinical presentation, guidelines have been proposed based on consensus (Wu et al., 2017). Transfusion requirement are restricted to patients with bone marrow failure in an attempt to alleviate the anemia or thrombocytopenia (Wu et al., 2017). Interferon gamma-1b, assessed in 3 children and 8 adults for 18 weeks in a phase 2 trial, failed to show any improvement on serum CTX levels or quality of life (Imel et al., 2019; Nguyen et al., 2022). Calcium and ergocalciferol or cholecalciferol may correct secondary hypocalcemia or hyperparathyroidism with a target of 25 (OH) D $\geq$ 30 ng/mL [5]. To our knowledge, bone marrow or stem cell transplantation have not been performed in adult patients with ADO.

Orthopedic surgery is one of the main challenges of ADO. Technical skills and surgical expertise are required for repairing the fractures of dense bones as there are difficulties to implant the materials. Conservative orthopedic treatment may expose to delayed union, pseudarthrosis and deformities, especially at the femur. When surgery is required, use of nail device is not recommended because of the low space volume in the marrow cavity. Surgical screws and long plates are preferred to ensure proper mechanical strength. Iatrogenic risk of fracture is high in the vicinity of the materials due to the properties of the bone. Pseudofractures or fractures may occur in early postoperative period and in long term which may be responsible for an implantation failure (Burke et al., 2023; Palagano et al., 2018). Risk of osteomyelitis is also reported that may alter bone repair. The correction of limb deformities may be a patient request, but should be limited considering the delay of consolidation and complication of implants in dense bone (Siljander et al., 2021; Tu et al., 2022).

Dental abnormalities may sometimes reveal the disease, due to dental agenesis or delayed eruption. Following dental infections, osteomyelitis of the mandible is a particularly difficult complication that may require long-term antibiotic therapy and surgical debridement. The risk of neurological complications, in particular of the impingement of the optic, auditory and facial nerves, requires specialized ophthalmological and ENT monitoring to early detection of disorders and to plan possible decompression surgery. Basal skull involvement can also lead to cerebrovascular stenosis or occlusion, Arnold-Chiari malformation, and craniosynostosis which may require neurosurgical interventions. Involvement of the ear with infections and chronic sinusitis are also the concern of ENT and infectious disease specialists.

In order to be specific for the underlying defect, innovative treatment should aim to design a new tool to induce the capacity of osteoclasts to resorb bone. Original approaches using gene therapy have been developed to silence the CNCL7 gene (Maurizi, 2022). RNA interference approaches are suitable since most of the ADO patients carry a haploinsufficient mutation of this gene. Systemic administration of siRNA was able to restore bone resorption in mouse and human primary cells and to improve bone mass and bone resorption in animal models (Capulli et al., 2015; Maurizi et al., 2018). More recently, nanoparticles complexed with a small interfering RNA designed against the human $CLCN7^{G215R}$ mRNA were tested in mice carrying the heterozygous mutation (Maurizi et al., 2023). Intraperitoneal injection induced the downregulation of the $Clcn7^{G213R}$ mRNA levels in bone and rescued the bone phenotype without toxicity after 4 weeks. Therefore, the RNA-based therapy represents an opportunity to cure ADO and should be transferred to the clinic in the near future.

3.4. Knowledge gap

Despite great improvement in the clinical and genetic characterization, the diagnosis of ADO remains underestimated. The large variability of clinical and imaging phenotype might dampers the possibility to evoke the diagnosis in mild cases. Suspected in the presence of familial history, genetic testing should be proposed as this will promote investigations of the complications and participate to their prevention. In case of de novo mutation, the delay to reach the diagnosis might be high since the radiological signs are scarce before the patient becomes adult and because ADO is discovered when atypical fractures occur or in conventional imaging requested for other reasons. The time to reach the diagnosis by a bone expert, also called odyssee, is a recurrent concern reported by the patients (Cohen-Solal et al., 2023). Reducing the delay in diagnosis appears therefore crucial by better delineating the different steps of clinical and imaging features. Such a natural history appears now mandatory and should concern the different aspects of the disease. Hence, the kinetics of radiographic patterns of all bones, characterization of bone and hematological biomarkers and their changes, should be investigated as well as early eye, ear and teeth complications (Fig. 4). These parameters should be collected and linked to the genotype in order to better define several profiles. There is also an urgent need to develop orthopedic guidelines for the management of fractures and the replacement of joint damage. Indeed, despite neurological alterations described in osteopetrotic mice, such observations are missing in humans in terms of cognitive functions or imaging abnormalities. A clinical effort in research needs therefore to be supported, establishing evidence for management and compiling registry data is required. As rare diseases, the in-depth data collection of several centers remains an essential step to increase the number of cases and facilitate the interpretation. The structuration of bone networks based on scientific societies and organizations have made significant improvement by developing tools to feed the database. Collaborative projects have been implemented by ECTS or ERN Bond with the ambition to provide database to scientists, enhance observational studies and reduces the morbidity and the burden of the disease.

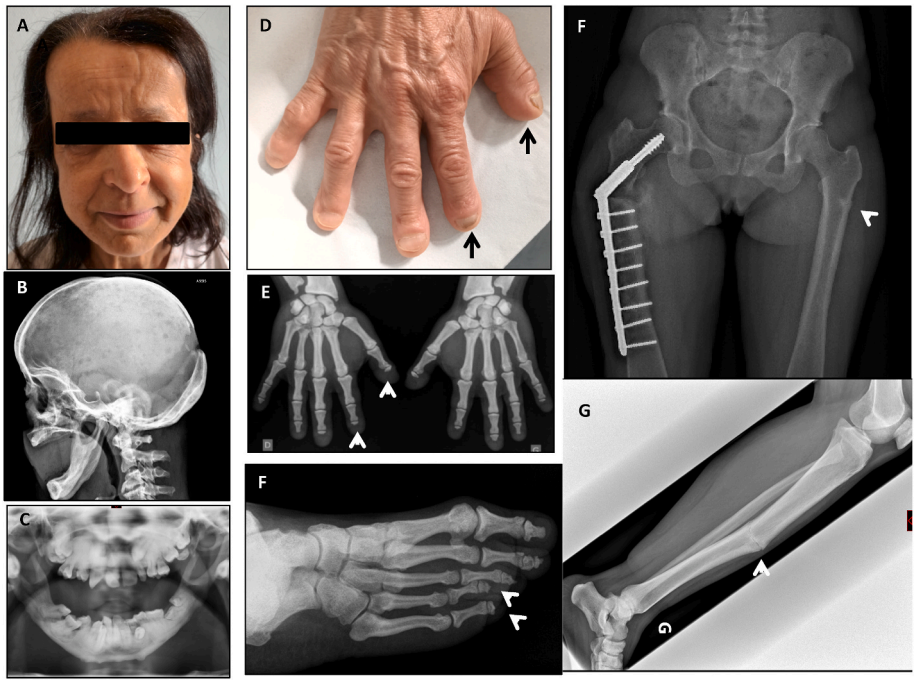

Fig. 3. Clinical and imaging features of patients with pycnodysostosis.
A: Frontal bossing, hypoplastic and obtuse mandible, hypotelorism and a convex nasal ridge. B: open fontanelle seen at the skull X-Ray, C: crowded and misalignment of the teeth, D: Brachydactyly and acroosteolysis of the 2 first fingers (black arrows). E: Acro-osteolysis of the 3 last phalanx of the hand (white arrows). F: acro-osteolysis of the last phalanx of the foot (white arrows). F: atypical fracture of the right femur and pseudo-fracture of the left femur (white arrow). G: diaphysal fracture of the tibia (white arrow).

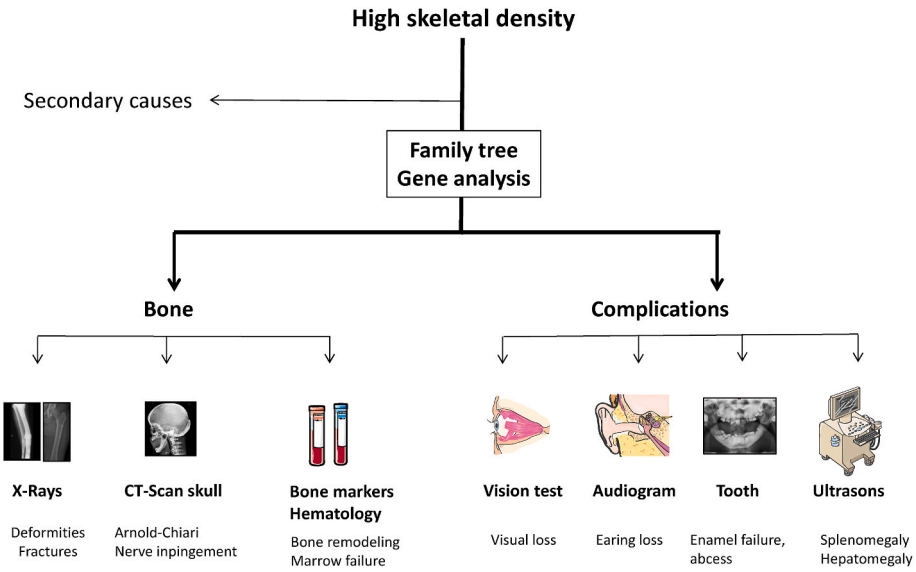

Fig. 4. Check-list for diagnosis and management of osteopetroses
In the presence of high bone mineral density, elimination of secondary cause is the first step. Then, genetic evaluation should be conducted in the family. In any case, the strategy involves bone tests for the assessment of the severity and investigation of complications of other organs.

Several questions remain to be addressed by basic or translational approach (Table 2). Among them, the major issue is the bone pain resistant to conventional pain killers while the mechanism of bone pain is unknown. It is also unresolved if a dysregulation of the peripheral neurological system exists in osteopetrosis and if bone vascular dysfunction contributes to the severity of the disease. The question of the variability of the phenotype in relation with osteoclast failure has not been analyzed yet.

4. Pycnodysostosis

Pycnodysostosis is an autosomal recessive disorder with a prevalence of 1–3/100000 caused by a mutation in CTSK gene encoding for cathepsin K. This lysosomal cysteine protease is matured intracellularly by osteoclasts and secreted into the sealing zone allowing degradation of collagens and other components of bone matrix such as osteopontin and osteonectin (Dodds et al., 2001). Therefore, mutations of cathepsin K inhibit the resorption of bone matrix, but do not affect osteoclast

Table 2
Unmet research knowledge for osteopetrosis in adults
This table summarizes the main concerns and orientation of research to improve the knowledge of natural history and the management.

Clinical research	Outcomes
Epidemiology	Fracture prevalence Characteristics of fractures (long, vertebrae, others) Type: typical or atypical fracture
History of fracture	Time of fracture repair Pseudoarthrosis
Natural history	Changes in bone mineral density Serum bone biomarkers
Effect of aging	Changes in fracture rate Changes in bone parameters
Guidelines for orthopedic management	Techniques for fracture repair Indications and techniques for joint replacement
Neurological assessment	Imaging anomalies Cognitive function
Preclinical/translational research	
Characterization of pain	Mechanism of pain in bones or in joints Identification of pain mediators
Phenotype variability in relation with osteoclast failure (human and preclinical models)	Bone parameters during development and growth Bone parameters during aging
Vascularization of bone	Vessel density in axial and appendicular bone Vessel density according to the magnitude of bone density
Systemic effects of osteopetrosis	Description of non-bone tissue abnormalities
Effects of bone marrow transplantation	Fracture and bone mineral density Hematology parameters

differentiation. First described by Maroteaux and Lamy (1962), pycnodysostosis is characterized by a triad that associates short stature, cranial dysmorphia and acro-osteolysis. The clinical bone presentation has been extensively described in adults and children (Doherty et al., 2021; Hald et al., 2023). Facial features are typical, including a hypoplastic and obtuse mandible, a hypotelorism and a convex nasal ridge (Fig. 3). Brachycephaly and frontal bossing are predominant and anterior cranial sutures remain opened throughout life. Platybasia and Arnold-Chiari malformation are observed in ~20% of the patients (Bizaoui et al., 2019). Brachydactylia is consistently seen in addition to the acro-osteolysis which is associated with a softening of the nails. Fractures occur in childhood, but are scare in adults (Bizaoui et al., 2019; Doherty et al., 2021). Bone fragility is suspected when fractures occur in atypical sites such as metaphysis of the femur or of the tibia that may resemble to atypical femoral fractures (Bizaoui et al., 2019; Taka et al., 2022). Bone mineral density shows a Z-score above +2 SD (Bizaoui et al., 2019; Doherty et al., 2021). High resolution computed tomography revealed a high cortical thickness and area as well as trabecular bone volume and density (Doherty et al., 2021). Serum bone markers P1NP and CTX are within the normal range. Because of the mandibular hypoplasia, dental features are common, illustrated by crowded and misalignment of teeth, giving the impression of a double row in relation to persistent of decidual teeth (Alves and Cantín, 2014). Moreover, dentine failure is also reported. Osteomyelitis is a complication that occurs in a context of teeth extraction or mandibular fracture (de França et al., 2021). Obstruction sleep apnea occurs in 50% of the patients as a result of a narrow pharyngeal space and ogival palate in addition to scoliosis and chest deformations (Bizaoui et al., 2019; Ferlias et al., 2022). Mild failure in cognitive functions has been reported inconstantly, this needs to be documented. As for osteopetrosis, pycnodysostosis is orphaned of any causal treatment and therefore, the care is focused on the prevention and treatment of the complications. There are no studies about the effect of native vitamin D on the disease progression or bone mass. In a 37 year-old woman, Teriparatide given for 6 months induced no change in bone microarchitecture, histology pattern or serum biomarkers and does not modify the capacity of bone resorption of osteoclast precursors (Chavassieux et al., 2008). In these conditions, the use of bisphosphonate may be contra-indicated in particular because they may induce atypical fractures.

5. Dysosteosclerosis

Dysosteosclerosis is a skeletal disease which was initially classified as osteosclerosis, part of sclerosis disorders. The clinical presentation is heterogenous, but common features emerged such as a triad of diffuse high density of the skull and the jaw, platyspondyly and osteosclerotic and widened metaphyses of long bones (Sule et al., 2013). Thereafter, genetic characterization resulted in better delineation of this skeletal disease. Several genes have been identified in particular TNFRSF11A, SLCA29A3, TCIRG1, CSF1R and LRRK1. Because these genes impair osteoclast differentiation and function, the 2023 nomenclature includes dysosteosclerosis in the osteopetrosis-related diseases. Then, the recent classification of dysosteosclerosis covers 3 different entities: TNFRSF11-related due to osteoclast-poor osteopetrosis which was addressed above, CSF1R1-related that is associated with degenerative encephalopathy and brain malformation and finally SlC29A3-related dysosteosclerosis (Table 1).

As in children (Turan, 2023), short stature with short trunk is a constant feature in adult age (Turan et al., 2022). Severity of platyspondyly is variable. The cortices of long bones, which are sclerostic in children, become thinner with age (Uludağ Alkaya et al., 2021; Xue et al., 2019). Fractures occur in all the children harboring Slc29A3 mutations (Campos-Xavier et al., 2005; Turan et al., 2022), but only in 25% of children with CSF1R variants (Guo et al., 2019). They have not been reported in adults (Turan, 2023). Fracture sequelae or large metaphysis promote deformities that require surgery optimally performed in expert centers. Brain encephalopathy is constant in adults carrying CSF1R-biallelic mutations characterized with leukoencephalopathy associated with seizures, early impairment of cognitive function and Parkinson symptoms (Guo et al., 2019). Since cranial osteosclerosis is constant in dysosteosclerosis, cranial nerve palsy and optic atrophy are frequent in children as a result of bony compression, but are observed in adults with CSF1R variants (Guo et al., 2019; Lemire and Wiebe, 2008). One case of Arnold-Chiari complication was reported. Dental impairment is common in childhood as shown by oligodontia, delayed tooth eruption and caries, which remain in adults (Lemire and Wiebe, 2008). Propensity of infections could be complicated by osteomyelitis and osteonecrosis (John et al., 1996).

6. Future directions for research

Despite the clarification of the new nomenclature that combine the genes involved with the bone phenotype, several clinical questions remain unanswered. A better understanding of the natural history and research key points are needed to be improved the management of the patients. Table 2 summarize some clinical and preclinical issues that are missing. The epidemiology and the natural history of fracture in adults with bone sclerosing disorders are not well described. Hence, the fracture prevalence according to the age and gender is unknown. The type of fracture of long bones (metaphysis or diaphysis), the delay of consolidation and the proportion of pseudoarthrosis are not described. Moreover, the natural history should provide information about the changes in bone mineral density and bone biomarkers with time in relation with the genotype in order to explain the variability of the phenotype. Because ADO is a rare disease, the sharing data collection in an international consortium would allow to draw a more complete picture of the diseases. Since the orthopedic management of fracture is crucial, shared experiences of orthopedic surgeons with expertise in sclerosing bone diseases and the development of guidelines are mandatory for fracture repair and joint replacement. Because animal models suggest neurological involvement in ADO, brain assessment is recommended in terms

of imaging and cognitive functions. This knowledge is required for patient monitoring and will identify the criteria to for identifying the patients at risk of complication and to select the patients for future treatment.

Unanswered questions could benefit of research strategies through the use of preclinical models or human bone samples. Among those, the characterization of the mechanism of pain, the description of the vascular profile and the systemic effect of the variant in other tissues are awaited.

7. Conclusions

Osteopetrosis and diseases related to osteoclast failure are illustrated by a great variability in clinical presentation. Recent advances in genetic investigation have led to a better understanding and classification of these pathologies but there is still a large gap in knowledge on the natural history of the disease and patient reported outcomes and treatment options are currently limited. The monitoring and treatment of patients must be multidisciplinary and carried out in reference centers for skeletal diseases. Systematic assessment of complications and long-term follow-up are necessary to improve the knowledge of the natural history. The use of novel global registries will help in this respect. A better delineation of complications and severity stage will be required to identify the patients that will benefit of pharmacological or genetic treatment in the future.

Funding sources

None.

Disclosure of conflict of interest

Authors declare no conflict of interest in relation to the work.

CRediT authorship contribution statement

Thomas Funck-Brentano: Conceptualization, Methodology, Validation, Writing – original draft, Writing – review & editing. **M. Carola Zillikens:** Formal analysis, Writing – original draft, Writing – review & editing. **Gavin Clunie:** Writing – original draft, Writing – review & editing. **Heide Siggelkow:** Writing – original draft, Writing – review & editing. **Natasha M. Appelman-Dijkstra:** Writing – original draft, Writing – review & editing. **Martine Cohen-Solal:** Conceptualization, Validation, Writing – original draft, Writing – review & editing.

Data availability

No data was used for the research described in the article.

Acknowledgements

the authors thank European Calcified Tissue Society (ECTS) and ERN Bond for their support.

References

Albers-Schönberg, 1904. Rontgenbilder einer seltenen Knockenerkrankung. Munch Med. Wochenschr. 5, 365–368.

Alves, N., Cantín, M., 2014. Clinical and radiographic maxillofacial features of pycnodysostosis. Int. J. Clin. Exp. Med. 7, 492–496.

Bizaoui, V., Michot, C., Baujat, G., Amouroux, C., Baron, S., Capri, Y., Cohen-Solal, M., Collet, C., Dieux, A., Geneviève, D., Isidor, B., Monnot, S., Rossi, M., Rothenbuhler, A., Schaefer, E., Cormier-Daire, V., 2019. Pycnodysostosis: natural history and management guidelines from 27 French cases and a literature review. Clin. Genet. 96, 309–316. https://doi.org/10.1111/cge.13591.

Burke, J.F., Quinlan, N.D., Werner, B.C., Barnes, C.L., Browne, J.A., 2023. Osteopetrosis is associated with an increased risk for Intraoperative periprosthetic fracture in total hip arthroplasty but not in total knee arthroplasty. J. Arthroplasty 38, 24–29. https://doi.org/10.1016/j.arth.2022.08.016.

Butscheidt, S., Rolvien, T., Kornak, U., Schmidt, F.N., Schinke, T., Amling, M., Oheim, R., 2018. Clinical significance of DXA and HR-pQCT in autosomal dominant osteopetrosis (ADO II). Calcif. Tissue Int. 102, 41–52. https://doi.org/10.1007/s00223-017-0332-x.

Campos-Xavier, A.B., Casanova, J.-L., Doumaz, Y., Feingold, J., Munnich, A., Cormier-Daire, V., 2005. Intrafamilial phenotypic variability of osteopetrosis due to chloride channel 7 (CLCN7) mutations. Am. J. Med. Genet. A. 133A, 216–218. https://doi.org/10.1002/ajmg.a.30490.

Capulli, M., Maurizi, A., Ventura, L., Rucci, N., Teti, A., 2015. Effective small interfering RNA therapy to treat CLCN7-dependent autosomal dominant osteopetrosis type 2. Mol. Ther. Nucleic Acids 4, e248. https://doi.org/10.1038/mtna.2015.21.

Chavassieux, P., Karsdal, M.A., Segovia-Silvestre, T., Neutzsky-Wulff, A.V., Chapurlat, R., Boivin, G., Delmas, P.D., 2008. Mechanisms of the anabolic effects of Teriparatide on bone: insight from the treatment of a patient with pycnodysostosis. J. Bone Miner. Res. 23, 1076–1083. https://doi.org/10.1359/jbmr.080231.

Cohen-Solal, M., Collet, C., Bizot, P., Pavis, C., Funck-Brentano, T., 2023. Osteopetrosis: the patient point of view and medical challenges. Bone 167, 116635. https://doi.org/10.1016/j.bone.2022.116635.

Coudert, A.E., Fattore, A.D., Baulard, C., Olaso, R., Schiltz, C., Collet, C., Teti, A., Vernejoul, M.-C. de, 2014. Differentially expressed genes in autosomal dominant osteopetrosis type II osteoclasts reveal known and novel pathways for osteoclast biology. Lab. Invest. 94, 275–285. https://doi.org/10.1038/labinvest.2013.140.

de França, G.M., Felix, F.A., de Morais, E.F., Medeiros, M.R. de S., Andrade, A.C. de M., Galvão, H.C., 2021. Osteomyelitis of the jaws in patients with pycnodysostosis: a systematic review. Braz. J. Otorhinolaryngol. 87, 620–628. https://doi.org/10.1016/j.bjorl.2020.12.009.

Dodds, R.A., James, I.E., Rieman, D., Ahern, R., Hwang, S.M., Connor, J.R., Thompson, S. D., Veber, D.F., Drake, F.H., Holmes, S., Lark, M.W., Gowen, M., 2001. Human osteoclast cathepsin K is processed intracellularly prior to attachment and bone resorption. J. Bone Miner. Res. Off. J. Am. Soc. Bone Miner. Res. 16, 478–486. https://doi.org/10.1359/jbmr.2001.16.3.478.

Doherty, M.A., Langdahl, B.L., Vogel, I., Haagerup, A., 2021. Clinical and genetic evaluation of Danish patients with pycnodysostosis. Eur. J. Med. Genet. 64, 104135 https://doi.org/10.1016/j.ejmg.2021.104135.

Ferlias, N., Gjørup, H., Doherty, M.A., Haagerup, A., Pedersen, T.K., 2022. Obstructive sleep apnoea in pycnodysostosis: a three-dimensional upper airway analysis. Orthod. Craniofac. Res. 25, 494–501. https://doi.org/10.1111/ocr.12561.

Guo, L., Bertola, D.R., Takanohashi, A., Saito, A., Segawa, Y., Yokota, T., Ishibashi, S., Nishida, Y., Yamamoto, G.L., Franco, J.F. da S., Honjo, R.S., Kim, C.A., Musso, C.M., Timmons, M., Pizzino, A., Taft, R.J., Lajoie, B., Knight, M.A., Fischbeck, K.H., Singleton, A.B., Ferreira, C.R., Wang, Z., Yan, L., Garbern, J.Y., Simsek-Kiper, P.O., Ohashi, H., Robey, P.G., Boyde, A., Matsumoto, N., Miyake, N., Spranger, J., Schiffmann, R., Vanderver, A., Nishimura, G., Passos-Bueno, M.R.D.S., Simons, C., Ishikawa, K., Ikegawa, S., 2019. Bi-Allelic CSF1R mutations cause skeletal dysplasia of dysosteosclerosis-pyle disease spectrum and degenerative encephalopathy with brain malformation. Am. J. Hum. Genet. 104, 925–935. https://doi.org/10.1016/j.ajhg.2019.03.004.

Hald, J.D., Beck-Nielsen, S., Gregersen, P.A., Gjørup, H., Langdahl, B., 2023. Pycnodysostosis in children and adults. Bone 169, 116674. https://doi.org/10.1016/j.bone.2023.116674.

Imel, E.A., Biggin, A., Schindeler, A., Munns, C.F., 2019. FGF23, hypophosphatemia, and emerging treatments. JBMR Plus 3, e10190. https://doi.org/10.1002/jbm4.10190.

John, E., Kozlowski, K., Masel, J., Muralinath, S., Vijayalakshmi, G., 1996. Dysosteosclerosis. Australas. Radiol. 40, 345–347. https://doi.org/10.1111/j.1440-1673.1996.tb00417.x.

Lemire, E.G., Wiebe, S., 2008. Clinical and radiologic findings in an adult male with dysosteosclerosis. Am. J. Med. Genet. A. 146A, 474–478. https://doi.org/10.1002/ajmg.a.32182.

Marks, S.C., 1987. Osteopetrosis–multiple pathways for the interception of osteoclast function. Appl. Pathol. 5, 172–183.

Maroteaux, P., Lamy, M., 1962. [2 cases of a condensing osseous disease: pynodysostosis]. Arch. Fr. Pediatr. 19, 267–274.

Maurizi, A., 2022. Experimental therapies for osteopetrosis. Bone 165, 116567. https://doi.org/10.1016/j.bone.2022.116567.

Maurizi, A., Capulli, M., Patel, R., Curle, A., Rucci, N., Teti, A., 2018. RNA interference therapy for autosomal dominant osteopetrosis type 2. Towards the preclinical development. Bone 110, 343–354. https://doi.org/10.1016/j.bone.2018.02.031.

Maurizi, A., Patrizii, P., Teti, A., Sutera, F.M., Baran-Rachwalska, P., Burns, C., Nandi, U., Welsh, M., Torabi-Pour, N., Dehsorkhi, A., Saffie-Siebert, S., 2023. Novel hybrid silicon-lipid nanoparticles deliver a siRNA to cure autosomal dominant osteopetrosis in mice. Implications for gene therapy in humans. Mol. Ther. Nucleic Acids 33, 925–937. https://doi.org/10.1016/j.omtn.2023.08.020.

Mohapatra, B., Kishen, T., Diwan, A.D., 2010. Multiple lumbar pedicle fractures in osteopetrosis: a case report. Spine 35, E311–E315. https://doi.org/10.1097/BRS.0b013e3181c39082.

Nguyen, A., Miller, W.P., Gupta, A., Lund, T.C., Schiferl, D., Lam, L.S.K., Arzumanyan, Z., Orchard, P.J., Polgreen, L.E., 2022. Open-label pilot study of interferon gamma-1b in patients with non-infantile osteopetrosis. JBMR Plus 6, e10597. https://doi.org/10.1002/jbm4.10597.

Palagano, E., Menale, C., Sobacchi, C., Villa, A., 2018. Genetics of osteopetrosis. Curr. Osteoporos. Rep. 16, 13–25. https://doi.org/10.1007/s11914-018-0415-2.

Penna, S., Villa, A., Capo, V., 2021. Autosomal recessive osteopetrosis: mechanisms and treatments. Dis. Model. Mech. 14, dmm048940 https://doi.org/10.1242/dmm.048940.

Siljander, M.P., Trousdale, R.T., Perry, K.I., Mabry, T.M., Berry, D.J., Abdel, M.P., 2021. Total hip arthroplasty in patients with osteopetrosis. J. Arthroplasty 36, 1367–1372. https://doi.org/10.1016/j.arth.2020.10.018.

Sobacchi, C., Abinun, M., 2022. Osteoclast-poor osteopetrosis. Bone 164, 116541. https://doi.org/10.1016/j.bone.2022.116541.

Sobacchi, C., Schulz, A., Coxon, F.P., Villa, A., Helfrich, M.H., 2013. Osteopetrosis: genetics, treatment and new insights into osteoclast function. Nat. Rev. Endocrinol. 9, 522–536. https://doi.org/10.1038/nrendo.2013.137.

Sule, G., Campeau, P.M., Zhang, V.W., Nagamani, S.C.S., Dawson, B.C., Grover, M., Bacino, C.A., Sutton, V.R., Brunetti-Pierri, N., Lu, J.T., Lemire, E., Gibbs, R.A., Cohn, D.H., Cui, H., Wong, L.-J., Lee, B.H., 2013. Next-generation sequencing for disorders of low and high bone mineral density. Osteoporos. Int. J. Establ. Result Coop. Eur. Found. Osteoporos. Natl. Osteoporos. Found. USA 24, 2253–2259. https://doi.org/10.1007/s00198-013-2290-0.

Taka, T.M., Lung, B., Stepanyan, H., So, D., Yang, S., 2022. Orthopedic treatment of pycnodysostosis: a systematic review. Cureus. https://doi.org/10.7759/cureus.24275.

Tu, Y., Liu, F.-X., Jia, H.-L., Yang, J.-J., Lv, X.-L., Li, C., Wu, J.-W., Wang, F., Yang, Y.-L., Wang, B.-M., 2022. The treatment of subtrochanteric fracture with reversed contralateral distal femoral locking compression plate (DF-LCP) using a progressive and intermittent drilling procedure in three osteopetrosis patients. Orthop. Surg. 14, 254–263. https://doi.org/10.1111/os.13112.

Turan, S., 2023. Osteopetrosis: gene-based nosology and significance dysosteosclerosis. Bone 167, 116615. https://doi.org/10.1016/j.bone.2022.116615.

Turan, S., Mumm, S., Alavanda, C., Kaygusuz, B.S., Gurpinar Tosun, B., Arman, A., Huskey, M., Guran, T., Duan, S., Bereket, A., Whyte, M.P., 2022. Dysosteosclerosis: clinical and radiological evolution reflecting genetic heterogeneity. JBMR Plus 6, e10663. https://doi.org/10.1002/jbm4.10663.

Uludağ Alkaya, D., Akpınar, E., Bilguvar, K., Tüysüz, B., 2021. Resolution of sclerotic lesions of dysosteosclerosis due to biallelic SLC29A3 variant in a Turkish girl. Am. J. Med. Genet. A. 185, 2271–2277. https://doi.org/10.1002/ajmg.a.62198.

Unger, S., Ferreira, C.R., Mortier, G.R., Ali, H., Bertola, D.R., Calder, A., Cohn, D.H., Cormier-Daire, V., Girisha, K.M., Hall, C., Krakow, D., Makitie, O., Mundlos, S., Nishimura, G., Robertson, S.P., Savarirayan, R., Sillence, D., Simon, M., Sutton, V.R., Warman, M.L., Superti-Furga, A., 2023. Nosology of genetic skeletal disorders: 2023 revision. Am. J. Med. Genet. A. 191, 1164–1209. https://doi.org/10.1002/ajmg.a.63132.

Vernejoul, M.-C. de, Kornak, U., 2010. Heritable sclerosing bone disorders. Ann. N. Y. Acad. Sci. 1192, 269–277. https://doi.org/10.1111/j.1749-6632.2009.05244.x.

Wang, Z., Li, X., Wang, Y., Fu, W., Liu, Y., Zhang, Z., Wang, C., 2022. Natural history of type II autosomal dominant osteopetrosis: a single center retrospective study. Front. Endocrinol. 13, 819641 https://doi.org/10.3389/fendo.2022.819641.

Wu, C.C., Econs, M.J., DiMeglio, L.A., Insogna, K.L., Levine, M.A., Orchard, P.J., Miller, W.P., Petryk, A., Rush, E.T., Shoback, D.M., Ward, L.M., Polgreen, L.E., 2017. Diagnosis and management of osteopetrosis: consensus guidelines from the osteopetrosis working group. J. Clin. Endocrinol. Metab. 102, 3111–3123. https://doi.org/10.1210/jc.2017-01127.

Xue, J.-Y., Wang, Z., Shinagawa, S., Ohashi, H., Otomo, N., Elcioglu, N.H., Nakashima, T., Nishimura, G., Ikegawa, S., Guo, L., 2019. TNFRSF11A-Associated dysosteosclerosis: a report of the second case and characterization of the phenotypic spectrum. J. Bone Miner. Res. Off. J. Am. Soc. Bone Miner. Res. 34, 1873–1879. https://doi.org/10.1002/jbmr.3805.

Zhou, W., van Rooij, J.G.J., Ebeling, P.R., Verkerk, A.J.M.H., Zillikens, M.C., 2021. The genetics of atypical femur fractures—a systematic review. Curr. Osteoporos. Rep. 19, 123–130. https://doi.org/10.1007/s11914-021-00658-y.