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CLCN7-Related Osteopetrosis

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Summary

Clinical characteristics

The spectrum of *CLCN7*-related osteopetrosis includes infantile malignant *CLCN7*-related autosomal recessive osteopetrosis (ARO), intermediate autosomal osteopetrosis (IAO), and autosomal dominant osteopetrosis type II (ADOII; Albers-Schönberg disease).

- **ARO.** Onset is at birth. Findings may include: fractures; reduced growth; sclerosis of the skull base (with or without choanal stenosis or hydrocephalus) resulting in optic nerve compression, facial palsy, and hearing loss; absence of the bone marrow cavity resulting in severe anemia and thrombocytopenia; dental abnormalities, odontomas, and risk for mandibular osteomyelitis; and hypocalcemia with tetanic seizures and secondary hyperparathyroidism. Without treatment maximal life span in ARO is ten years.
- **IAO.** Onset is in childhood. Findings may include: fractures after minor trauma, characteristic skeletal radiographic changes found incidentally, mild anemia, and occasional visual impairment secondary to optic nerve compression. Life expectancy in IAO is usually normal.
- **ADOII.** Onset is usually late childhood or adolescence. Findings may include: fractures (in any long bone and/or the posterior arch of a vertebra), scoliosis, hip osteoarthritis, and osteomyelitis of the mandible or septic osteitis or osteoarthritis elsewhere. Cranial nerve compression is rare.

Diagnosis/testing

The diagnosis of a *CLCN7*-related osteopetrosis is established in a proband with suggestive findings and biallelic pathogenic variants or a heterozygous pathogenic variant in *CLCN7* identified by molecular genetic testing.

Management

Treatment of manifestations:

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- **ARO.** Calcium supplementation for hypocalcemic convulsions; management of calcium homeostasis per individual needs; erythrocyte or platelet transfusions as needed; antibiotics for leukocytopenia; immunoglobulins for hypogammaglobulinemia. Newly diagnosed individuals should be transferred as soon as possible to a pediatric center experienced in allogeneic stem cell transplantation in this disease. The collaboration of pediatricians, pediatric neurologists, ophthalmologists, and psychologists is required to determine best treatment of neurologic and ophthalmic issues, which may include surgical decompression of the optic nerve and hearing aids. Treatment of fractures by an experienced orthopedist and dental care with attention to tooth eruption, ankylosis, abscesses, cysts, and fistulas.
- **ADOII.** Orthopedic treatment for fractures and arthritis with attention to potential post-surgical complications (delayed union or non-union of fractures, infection); fractures near joints may require total joint arthroplasty. Medical treatment for arthritis with anti-inflammatory agents; transfusions for anemia and thrombocytopenia; surgical optic nerve decompression, hearing aids, and regular dental care and good oral hygiene.

Prevention of primary manifestations: In ARO, hematopoietic stem cell transplantation (HSCT) can be curative; however, cranial nerve dysfunction is usually irreversible, and progressive neurologic sequelae occur in children with the neuronopathic form even after successful HSCT.

Surveillance: Complete blood count, ophthalmologic examination, and audiologic evaluation at least once a year; dental evaluation every 6-12 months or as directed. For ARO, follow up as directed by the transplantation center following HSCT.

Agents/circumstances to avoid: In ADOII, activities with high fracture risk. Orthopedic surgery should only be performed when absolutely necessary.

Genetic counseling

CLCN7-related osteopetrosis is inherited in an autosomal recessive or autosomal dominant manner: ARO is inherited in an autosomal recessive manner; about 40% of IAO is inherited in an autosomal recessive manner and about 60% in an autosomal dominant manner; and ADOII is inherited in an autosomal dominant manner.

- **Autosomal recessive inheritance.** If both parents are known to be heterozygous for a *CLCN7* pathogenic variant associated with autosomal recessive osteopetrosis, each sib of an affected individual has at conception a 25% chance of inheriting biallelic pathogenic variants and being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of inheriting neither of the familial *CLCN7* pathogenic variants. Carrier testing for at-risk relatives requires prior identification of the *CLCN7* pathogenic variants in the family.
- **Autosomal dominant inheritance.** Most individuals diagnosed with autosomal dominant *CLCN7*-related osteopetrosis have an affected parent. Each child of an individual with autosomal dominant osteopetrosis has a 50% chance of inheriting the pathogenic variant.

Once the *CLCN7* pathogenic variant(s) have been identified in an affected family member, prenatal testing and preimplantation genetic testing for *CLCN7*-related osteopetrosis are possible.

GeneReview Scope

CLCN7-Related Osteopetrosis: Included Phenotypes

Phenotype [1]	Synonym
Autosomal recessive osteopetrosis (ARO)	Infantile malignant *CLCN7*-related autosomal recessive osteopetrosis
Intermediate autosomal osteopetrosis (IAO)	

Table continued from previous page.

Phenotype [1]	Synonym
Autosomal dominant osteopetrosis type II (ADOII)	Albers-Schönberg disease

1. For other genetic causes of these phenotypes see Differential Diagnosis.

Diagnosis

The spectrum of *CLCN7*-related osteopetrosis includes the following:

- Autosomal recessive osteopetrosis (ARO; infantile malignant *CLCN7*-related autosomal recessive osteopetrosis)
- Intermediate autosomal osteopetrosis (IAO)
- Autosomal dominant osteopetrosis type II (ADOII; Albers-Schönberg disease)

Suggestive Findings

A *CLCN7*-related osteopetrosis **should be suspected** in individuals with osteosclerosis noted on radiographs, which may be accompanied by hypocalcemia and resulting convulsions, anemia, thrombocytopenia, visual impairment, and/or central nervous system involvement (Table 1).

Table 1. Diagnostic Features of the Subtypes of *CLCN7*-Related Osteopetrosis

Finding	Subtype of *CLCN7*-Related Osteopetrosis		
	ARO	IAO	ADOII
Radiographic changes	Pathognomonic [1]	Characteristic [2]	Characteristic [3]
Hypocalcemia	Severe to absent	Absent	Absent
Anemia	Severe to moderate	Mild to absent	Absent
Thrombocytopenia	Severe to absent	Absent	Absent
Visual impairment	Frequent	Rare	Very rare
CNS involvement	Severe to absent [4]	Absent	Absent
Age of onset of symptoms	Birth	First 2 years	First 10 yrs
Inheritance	AR	AR or AD	AD

ADOII = autosomal dominant osteopetrosis type II; ARO = infantile malignant *CLCN7*-related autosomal recessive osteopetrosis; CNS = central nervous system; IAO = intermediate autosomal osteopetrosis

1. Generalized osteosclerosis, club-shaped long bones, sclerosis of the skull base, bone-within-bone appearance; these signs are observed in all types of ARO.

2. Findings similar to ARO, already present in early childhood, but less severe

3. Findings:

• Osteosclerosis of the spine ("sandwich vertebrae")
• Bone-within-bone appearance, mainly in iliac wings
• Erlenmeyer-shaped femoral metaphysis
• Mild osteosclerosis of the skull base
• Transverse bands of osteosclerosis in long bones

4. Typical signs of CNS involvement:

• Delayed psychomotor development
• Loss of abilities
• Seizures (can be also due to hypocalcemia)
• On MRI: global brain atrophy, cortical abnormalities, and in rare individuals, heterotopias

Establishing the Diagnosis

The diagnosis of a *CLCN7*-related osteopetrosis **is established** in a proband with suggestive findings and biallelic pathogenic variants or a heterozygous pathogenic variant in *CLCN7* identified by molecular genetic testing (see Table 2).

Note: Identification of biallelic *CLCN7* variants of uncertain significance, of one known *CLCN7* pathogenic variant and one *CLCN7* variant of uncertain significance, or of a heterozygous *CLCN7* variant of uncertain significance does not establish or rule out a diagnosis of this disorder.

Because the phenotype of a *CLCN7*-related osteopetrosis may be indistinguishable from other inherited sclerosing bone dysplasias resulting from impaired osteoclast function, recommended molecular genetic testing approaches include use of a **multigene panel** or **comprehensive genomic testing**.

Note: Single-gene testing (sequence analysis of *CLCN7*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

An osteopetrosis multigene panel that includes *CLCN7* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Comprehensive genomic testing does not require the clinician to determine which genes is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 2. Molecular Genetic Testing Used in *CLCN7*-Related Osteopetrosis

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
CLCN7	Sequence analysis [3]	~99% [4, 5]
	Gene-targeted deletion/duplication analysis [6]	Rare [7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. A noncoding deep intronic variant in *CLCN7* causing autosomal recessive osteopetrosis was reported to have been missed on genome sequencing [Chorin et al 2020].
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
7. A homozygous 101-kb contiguous gene deletion including exons 7-25 of *CLCN7* has been reported [Pangrazio et al 2012].

Clinical Characteristics

Clinical Description

To date, approximately 300 individuals have been identified with a pathogenic variant in *CLCN7* [Stenson et al 2020]. The three different associated phenotypes are described in this section.

Infantile Malignant *CLCN7*-Related Autosomal Recessive Osteopetrosis (ARO)

ARO is a systemic, life-threatening disorder. Onset of symptoms is at birth. Without treatment, life span is approximately ten years (although rare exceptions of far longer survival have occurred). Note: Many of the most complete clinical descriptions of ARO were published prior to the discovery of the causative gene.

Possible clinical manifestations of ARO include the following.

Skeletal findings

- **Fractures.** The near-complete absence of osteoclastic bone resorption leads to osteosclerosis of the whole skeleton within the first few months after birth (Figure 1). Because of defective microarchitecture, the bones become brittle, resulting in recurrent fractures (usually of the long bones).
- **Reduced growth.** Resorption of cartilage and bone at the growth plate is a prerequisite for longitudinal growth; its absence results in variable growth retardation. In severely affected children, body length at age 12 months is as much as 5 cm below the third centile.
- **Skull.** In some severely affected children, macrocephaly and frontal bossing develop within the first year. This is not necessarily paralleled by sclerosis of the cranial vault. The sclerosis of the skull base often leads to choanal stenosis.

Calcium and blood cell findings

- **Hypocalcemia.** Hypocalcemia may result in tetanic seizures and secondary hyperparathyroidism.
- **Anemia and thrombocytopenia.** The absence of the bone marrow cavity leads to extramedullary hematopoiesis, hepatosplenomegaly, anemia, and thrombocytopenia. The bleeding associated with thrombocytopenia can be severe and life threatening, especially in the central nervous system (CNS).

- **Immune function.** Immune function may be impaired. Leukocytosis, present in the early stage of the disease, can become leukocytopenia. In conjunction with the frequently observed choanal stenosis, impaired immune function may lead to chronic rhinitis. Defective superoxide generation by granulocytes and monocytes has been reported in ARO [Wilson & Vellodi 2000].

CNS involvement

- **Neurologic complications**
  - Visual impairment beginning shortly after birth is common. In most individuals it is caused by optic nerve compression within the osteosclerotic skull base.
  - Skull changes may also cause hydrocephalus.
  - A prominent and large anterior fontanelle is common and sometimes associated with hydrocephalus, possibly caused by obstruction of cerebral blood flow and cerebrospinal fluid circulation as a result of hyperostosis.
  - Facial palsy caused by facial nerve entrapment is an uncommon manifestation.
  - Seizures can result from hypocalcemia.
- **Neuronopathic form.** If seizures appear together with normal serum calcium concentration and developmental delay, a neuronopathic form must be considered. In these individuals the neuronal phenotype resembles neuronal ceroid-lipofuscinosis [Steward 2003]. In this subset of very severely affected children, primary degeneration of the retina and CNS occurs. If the onset is very early brain development can be disturbed, resulting in structural brain anomalies and heterotopias [Rössler et al 2021]. It is important to differentiate these rare primary neurologic manifestations of the neuronopathic form of ARO (which has a poor prognosis) from more common secondary lesions resulting from hyperostosis of the skull base. It is noteworthy that pathologic EEG changes with a characteristic pattern of very frequent multifocal spikes and sharp waves usually precede the clinical symptoms and brain MRI findings of neurodegeneration [A Schulz, unpublished results].

Other

- **Otologic manifestations.** According to Dozier et al [2005], 78% of individuals with ARO showed variable hearing loss. Poor pneumatization of the mastoid bone and narrowing of the external auditory canal, eustachian tube, and internal auditory canal frequently lead to otitis media, conductive and sensorineural hearing loss, and facial nerve paralysis [Dozier et al 2005].
- **Dental.** Oral problems in ARO are delayed tooth eruption, hypodontia, malformed teeth, enamel hypoplasia, hypomineralization of enamel and dentin, the presence of odontomas, and severe mandibular osteomyelitis. Even if the primary dentition is impaired, the secondary dentition can be normal after successful stem cell transplantation [Kantaputra et al 2012, Wang et al 2016, Zhang et al 2019].

Intermediate Autosomal Osteopetrosis (IAO)

IAO is characterized by childhood onset with a milder course than ARO. Life expectancy is normal in most individuals. Children may present with fractures after minor trauma or characteristic changes on x-rays obtained for other clinical indications. Hematologic signs are milder than those in ARO and are usually restricted to anemia. Although CNS involvement is usually absent, visual impairment secondary to optic nerve encroachment can occur [Campos-Xavier et al 2003, Frattini et al 2003].

Autosomal Dominant Osteopetrosis Type II (ADOII)

Although ADOII is sometimes called "benign osteopetrosis," as many as 60%-80% of individuals with radiologic signs of ADOII experience clinical problems (Figure 2).

Onset of radiologic and clinical manifestations of ADOII is usually in late childhood or adolescence, although earlier occurrence has been reported. Osteosclerosis of the spine predominates, with a "sandwich vertebra"

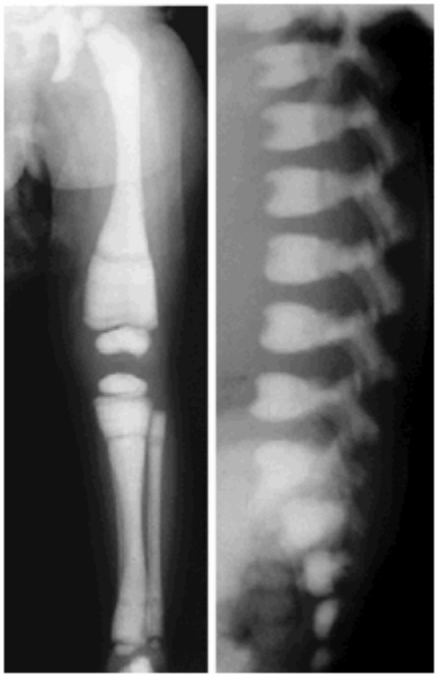

Figure 1. Autosomal recessive osteopetrosis radiographs

appearance, a diagnostic criterion for ADOII. Most affected individuals have a "bone-within-bone" appearance primarily in the iliac wings, but also in other bones. Transverse bands of sclerosis, perpendicular to the main axis, are often observed in long bones. Increase in the skull base density can be seen [Bénichou et al 2000, Cleiren et al 2001].

Clinical findings vary even within the same family [Waguespack et al 2007]. In three families in which most affected individuals had mild ADOII, early-onset disease, anemia, and blindness caused by optic nerve compression were observed in some affected family members; this phenotype has been called "intermediate osteopetrosis" because of its overlap with mild ARO.

The main complications affect the skeleton:

- **Fractures** occur in 60%-80% of affected individuals, with a mean of three fractures per person [Bénichou et al 2000, Waguespack et al 2007]. Some individuals had more than ten fractures. The most frequently affected bone is the femur, but fractures occur in any long bone and in the posterior arch of the vertebrae, thereby inducing spondylolisthesis.
- **Scoliosis** is seen in a number of individuals.
- **Hip osteoarthritis** is common (up to 27%) and could be caused by the excessive toughness of the subchondral bone.
- **Osteomyelitis** of the mandible is often associated with dental abscess or caries [Bénichou et al 2000, Waguespack et al 2007]. Septic osteitis or osteoarthritis at other localizations can also occur.

Cranial nerve compression caused by osteosclerosis of the skull base is rare. Hearing loss and visual loss occurs in up to 19% of affected individuals.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

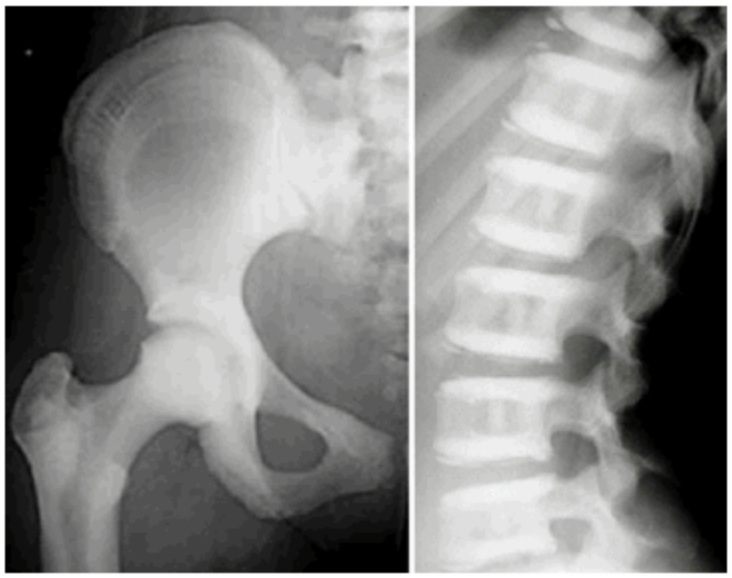

Figure 2. Autosomal dominant osteopetrosis type II radiographs

Reprinted from Bénichou et al [2000] with permission from Elsevier

Penetrance

Penetrance ranges from 60% to 90% in families with ADOII [Waguespack et al 2007].

Prevalence

The prevalence of ADOII has been estimated at up to 1:20,000 [Bénichou et al 2000]. The disease is probably underdiagnosed in those with milder phenotypes.

ARO is less common, with an estimated prevalence of 1:250,000.

Genetically Related (Allelic) Disorders

Heterozygous germline pathogenic variants in *CLCN7* have been reported in children with hypopigmentation, organomegaly, and delayed myelination and development (OMIM 618541). Osteopetrosis was not observed in the two affected children reported to date [Nicoli et al 2019].

Differential Diagnosis

Pathogenic variants in *CLCN7* account for 13% of the infantile autosomal recessive osteopetrosis (ARO), 40% of the recessive intermediate autosomal osteopetrosis (IAO), 60% of the dominant IAO, and 99% of the autosomal dominant osteopetrosis type II (ADOII) [Authors, personal observation].

ARO

Table 3. Other Types of Autosomal Recessive Osteopetrosis

Gene	Disorder	Clinical Characteristics	Features Distinguishing this Disorder from *CLCN7*-Related ARO
CA2	ARO w/renal tubular acidosis (RTA) (OMIM 259730)	Generalized osteosclerosis. Cerebral calcifications are typical & may be assoc w/ID. [1]	Onset of ARO w/RTA is usually later than in infantile malignant form of ARO & disease course is milder.

Table 3. continued from previous page.

Gene	Disorder	Clinical Characteristics	Features Distinguishing this Disorder from *CLCN7*-Related ARO
OSTM1	*OSTM1*-related ARO (OMIM 259720)	~4% of ARO is caused by pathogenic variants in *OSTM1*. Extremely severe form of ARO w/CNS involvement [2] that is indistinguishable from most severe forms of *CLCN7*-related ARO.	*OSTM1*-related ARO is frequently assoc w/structural brain anomalies.
PLEKHM1	*PLEKHM1*-related ARO (OMIM 611497)	Very rare, can look like ADOII	*PLEKHM1*-related ARO appears to be very mild & can regress w/↑ age. [3] One person w/*PLEKHM1*-related ARO caused by a heterozygous pathogenic variant has been described. [4]
SNX10	*SNX10*-related ARO (OMIM 615085)	~4% of ARO is caused by pathogenic variants in *SNX10*; in particular, "Västerbottenian osteopetrosis" is caused by *SNX10* pathogenic variants. Loss of vision, anemia, & bone fragility are frequently observed, warranting use of HSCT. [5]	*SNX10*-related ARO appears to be slightly less severe than *CLCN7*-related ARO.
TCIRG1	*TCIRG1*-related ARO (OMIM 259700)	>50% of ARO is caused by pathogenic variants in *TCIRG1*.	Higher frequency of neurodevelopmental delay & seizures in *CLCN7*-related ARO than in *TCIRG1*-related ARO. [6] Noncoding *TCIRG1* variants can cause milder phenotype that resembles ADOII.
TNFRSF11A	Osteoclast-poor ARO (OMIM 612301)	Characterized by onset w/in 1st yr of life & typical ARO manifestations. Investigation of bone biopsy is prerequisite for reliable diagnosis.	*TNFSF11* pathogenic variants cause a slight T-cell defect & *TNFRSF11A* pathogenic variants can lead to hypogammaglobulinemia similar to a common variable immune deficiency. [7] It is crucial to rule out *TNFSF11*- & *TNFRSF11A*-related ARO, as HSCT is not successful in these persons.
TNFSF11	Osteoclast-poor ARO (OMIM 259710)		

ADOII = autosomal dominant osteopetrosis type II; ARO = autosomal recessive osteopetrosis; CNS = central nervous system; ID = intellectual disability; HSCT = hematopoietic stem cell transplantation

1. Jacquemin et al [1998]
2. Pangrazio et al [2006]
3. Van Wesenbeeck et al [2007]
4. Bo et al [2016]
5. Aker et al [2012], Pangrazio et al [2013]
6. Frattini et al [2000], Kornak et al [2000]
7. Sobacchi et al [2007], Guerrini et al [2008]

A mild form of ARO can be caused by deep intronic or splice site variants in *TCIRG1* (OMIM 259700) [Sobacchi et al 2014, Palagano et al 2015]. This form can be very similar to *CLCN7*-related IAO or ADOII.

Autosomal Dominant Osteopetrosis (ADO)

Heterozygous pathogenic variants in *LRP5* are associated with ADO type I (ADOI) (OMIM 607634). In ADOI, osteosclerosis is most pronounced in the skull vault and does not lead to sandwich vertebrae. ADOI is not associated with an increased fracture rate. (Note: It is debated whether this disease entity should be called "endosteal hyperostosis" or "high bone mass disorder," as "osteopetrosis" should be reserved for osteoclast-related disorders.)

Other

Table 4. Other Disorders to Consider in the Differential Diagnosis of *CLCN7*-Related Osteopetrosis

Gene	Disorder/Phenotype	MOI	Comment
ANKH	AD craniometaphyseal dysplasia	AD	• Clinical hallmark is skull hyperostosis → deep-set eyes & paranasal bossing. Facial nerve palsy is common & more frequent than optic nerve compression. • The femur shows a modeling defect, but no osteosclerosis. Susceptibility to fractures is not ↑.
CSF1R	Brain anomalies, neurodegeneration, & dysosteosclerosis (BANDDOS) (OMIM 618476)	AR	Characterized by structural brain anomalies & a primary neurodegenerative phenotype. Like other forms of dysosteosclerosis, affected persons have platyspondyly.
CTSK	Pycnodysostosis	AR	• Short-limbed short stature, typical facial appearance (convex nasal ridge & small jaw w/obtuse mandibular angle), osteosclerosis w/↑ bone fragility, acroosteolysis of distal phalanges, delayed closure of cranial sutures, & dysplasia of clavicle • In some affected persons clinical presentation can resemble IAO. [1]
FERMT3	Leukocyte adhesion deficiency type III (OMIM 612840)	AR	Affected persons present w/recurrent infections & bleeding diathesis regardless of platelet or leukocyte count. In some, high bone density can be found, since fermitin family homolog 3 signaling is required for osteoclast-mediated bone resorption. [2]
GJA1	AR craniometaphyseal dysplasia (OMIM 218400)	AR	• Typical features of craniometaphyseal dysplasia (macrocephaly, hearing loss, skull hyperostosis w/paranasal bossing, metaphyseal widening) but less pronounced calvarial thickening [3] • Due to diaphyseal osteosclerosis; can occasionally resemble mild forms of osteopetrosis
LRP6	High bone mass phenotype [4]	AD	Endosteal hyperostosis similar to ADOI but w/hypodontia
LRRK1	Osteosclerotic metaphyseal dysplasia (OSMD) [5]	AR	• While the disorder name differs, *LRRK1*-related OSMD is a typical recessive osteopetrosis w/dysfunctional osteoclasts. No neurologic complications. • *LRRK1*-related OSMD is milder than *CLCN7*-related ARO & can be best compared to IAO.
SLC29A3	Dysosteosclerosis [6]	AR	• Assoc w/platyspondyly (a distinguishing feature). Disorder appears to be osteoclast-poor. No neurologic complications. • *SLC39A3*-related dysosteosclerosis is milder than *CLCN7*-related ARO & is best compared to IAO.
SOST	*SOST*-related sclerosing bone dysplasias, incl van Buchem disease & sclerosteosis	AR	Moderate-to-gross skull hyperostosis → cranial nerve dysfunction, mandibular enlargement, & generalized osteosclerosis. Sclerosteosis also comprises syndactyly & tall stature & can be lethal as a result of ↑ intracranial pressure.

AD = autosomal dominant; ADO = autosomal dominant osteopetrosis; AR = autosomal recessive; ARO = autosomal recessive osteopetrosis; IAO = intermediate autosomal osteopetrosis; MOI = mode of inheritance

1. Pangrazio et al [2014]
2. Crazzolara et al [2015]
3. Hu et al [2013]
4. Brance et al [2020]
5. Howaldt et al [2020]
6. Howaldt et al [2019]

Management

General guidelines for diagnosis, therapy, and follow up are available for all forms of osteopetrosis; see Author Information.

Due to the difference in severity, the evaluation, treatment, and surveillance recommendations for infantile malignant *CLCN7*-related autosomal recessive osteopetrosis (ARO) and *CLCN7*-related autosomal dominant osteopetrosis type II (ADOII) differ. The *CLCN7*-related intermediate autosomal osteopetrosis (IAO) phenotype lies between these two forms and has variable manifestations and prognosis. Therefore, management options for *CLCN7*-related IAO must be evaluated on an individual basis.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with **ARO**, the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 5. Recommended Evaluations Following Initial Diagnosis in Individuals with Infantile Malignant *CLCN7*-Related Autosomal Recessive Osteopetrosis (ARO)

System/Concern	Evaluation	Comment
Osteosclerosis	Baseline radiographic skeletal survey	
Choanal stenosis	Otorhinolaryngologic exam to evaluate for choanal stenosis assoc w/sclerosis of skull base	
Hypocalcemia & secondary hyper-parathyroidism	Calcium concentrations in blood & urine	
Anemia & thrombocytopenia	CBC w/reticulocyte count	
	Abdominal ultrasound	Evaluate for hepatosplenomegaly assoc w/ extramedullry hematopoeisis.
Neurologic complications	MRI &/or CT of neurocranium to evaluate for narrowed neuroforamina, hydrocephalus, & brain abnormalities in neuronopathic form of osteopetrosis	
	EEG	Evaluate for evidence of neurodegeneration.
	Baseline neurodevelopmental assessment	
Visual impairment	Ophthalmologic exam incl VEPs to evaluate for optic nerve atrophy assoc w/optic nerve compression w/in skull base	
Hearing loss	Baseline audiologic assessment	
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *CLCN7*-related ARO to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

ARO = autosomal recessive osteopetrosis; MOI = mode of inheritance; VEP = visual evoked potential
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

To establish the extent of disease and needs in an individual diagnosed with **ADOII**, the evaluations summarized in Table 6 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 6. Recommended Evaluations Following Initial Diagnosis in Individuals with *CLCN7*-Related Autosomal Dominant Osteopetrosis Type II

System/Concern	Evaluation	Comment
Osteosclerosis	Baseline radiographic skeletal survey	
Anemia & thrombocytopenia	CBC w/reticulocyte count	
Neurologic complications	MRI &/or CT of neurocranium to evaluate for narrowed neuroforamina	
Visual impairment	Ophthalmologic exam incl VEPs to evaluate for optic nerve atrophy assoc w/optic nerve compression w/in skull base	
Hearing loss	Baseline audiologic assessment	
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *CLCN7*-related ADOII to facilitate medical & personal decision making

ADOII = autosomal dominant osteopetrosis type II; MOI = mode of inheritance; VEP = visual evoked potential
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Due to the difference in severity, treatment strategies for ARO and ADOII differ. IAO lies between these two forms and has a variable prognosis. Therefore, treatment options must be evaluated on an individual basis.

Table 7. Treatment of Manifestations in Individuals with Infantile Malignant *CLCN7*-Related Autosomal Recessive Osteopetrosis (ARO)

Manifestation/ Concern	Treatment	Considerations/Other
Hypocalcemic convulsions	Calcium supplementation [1]	
Bone marrow failure	Erythrocyte or platelet transfusions (irradiated products) as needed	In case of leukocytopenia &/or hypogammaglobulinemia, which may develop in a subset of persons, antibiotics & immunoglobulins may be given in a prophylactic or therapeutic manner.
	Newly diagnosed persons should be transferred as soon as possible to pediatric center experienced in allogeneic HSCT in this disease.	See Prevention of Primary Manifestations.
Neurologic issues	The collaboration of pediatricians, pediatric neurologists, ophthalmologists, & psychologists is required to determine best treatment.	
Visual impairment	Surgical decompression of optic nerve, a difficult procedure, has been performed w/some success to prevent vision loss in those w/ARO in general [Hwang et al 2000].	
Hearing loss	Hearing aids	

Table 7. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Fractures	Treatment by orthopedist w/experience w/ARO in collaboration w/treating pediatrician	
Dental issues	Treatment as needed by dentist	Oral surgery may be needed for defective tooth eruption, ankylosis, abscesses, & formation of cysts & fistulas.

ARO = autosomal recessive osteopetrosis; HSCT = hematopoietic stem cell transplantation
1. The management of calcium homeostasis may be difficult and recommendations are conflicting: whereas physiologic doses of calcium and vitamin D have been used to treat children with osteopetrosis who have rickets, restriction of calcium and vitamin D has been used to prevent progression of disease and hypercalcemic crisis following HSCT. Treatment needs to take into account the particular situation of the affected individual.

Table 8. Treatment of Manifestations in Individuals with *CLCN7*-Related Autosomal Dominant Osteopetrosis Type II (ADOII)

Manifestation/Concern	Treatment	Considerations/Other
Fractures	Treatment by orthopedist w/experience w/ADOII	Fractures near joints may require total joint arthroplasty [Strickland & Berry 2005].
Arthritis	Medical treatment w/anti-inflammatory agents	
Anemia & thrombocytopenia	Transfusions	
Visual impairment	Surgical optic nerve decompression	
Hearing loss	Hearing aids	
Dental issues	Regular dental care & good oral hygiene	

ADOII = autosomal dominant osteopetrosis type II

Prevention of Primary Manifestations

Infantile Malignant *CLCN7*-Related ARO

Hematopoietic stem cell transplantation (HSCT). Since the defective osteoclasts in osteopetrosis are of hematopoietic origin, allogeneic HSCT can be curative. Most manifestations (bone sclerosis, bone marrow failure, and extramedullary hematopoiesis) can be prevented or reversed by HSCT.

- Restricted intake of calcium and vitamin D just before, during, and following HSCT to prevent hypercalcemia is recommended.
- Secondary neurosensory impairments caused by nerve compression may be prevented by early transplantation, but not reversed when they are already present.

  Cranial nerve dysfunction (visual impairment caused by optic nerve atrophy) is irreversible in most individuals. In the authors' series including about 30 individuals, about two thirds of affected individuals were visually impaired after successful transplantation [A Schulz, unpublished results]. Even-Or et al [2022] report blindness in 26% of a group with ARO associated with mutation of different genes.
- Primary neurologic problems and retinal degeneration developing in the neuronopathic form of ARO, however, are independent of the bone disease and therefore cannot be improved or prevented by HSCT. Persons with ARO resulting from *CLCN7* pathogenic variants who do not develop neurologic complications have been reported [Pangrazio et al 2010; Gaytán-Morales et al 2021; A Schulz & U Kornak, unpublished results].

It is highly important but difficult to exclude individuals with the neuronopathic form from this invasive treatment [Rössler et al 2021]. On the other hand, HSCT should be performed as soon as possible in the majority of those without primary neurologic sequelae to prevent irreversible secondary complications, including visual impairment. The evaluation of affected individuals and treatment by HSCT should therefore be performed in experienced pediatric centers after multidisciplinary evaluation to assess the severity of the disease and individual prognostic factors.

- Progressive neurologic sequelae, developmental delay, and repeated seizures occur in a subset of individuals after successful HSCT [Steward 2003]. Severe neurologic manifestations other than visual impairment following transplant have been seen in about 10% of individuals in the authors' series [A Schulz, unpublished results]. However, it must be stressed that individuals with ARO who do not have primary CNS involvement can be cured by HSCT [Gaytán-Morales et al 2021].
- **Reported outcomes of HSCT**
  - The incidence of severe complications post-HSCT is high, particularly when alternative stem cell sources are used. Complications include rejection, delayed hematopoietic reconstitution, venous occlusive disease, pulmonary hypertension, and hypercalcemic crisis [Steward et al 2004, Corbacioglu et al 2006, Shroff et al 2012].
  - The outcome of HSCT in ARO has been analyzed in a retrospective survey of the European Society of Immunodeficiencies (ESID) and the European Group of Bone Marrow Transplantation (EBMT) [Sobacchi et al 2013]. The five-year disease-free survival was estimated at 88% for HLA-identical donor transplants, 80% for HLA-matched unrelated donor transplants, and 66% for HLA-haplotype-mismatched related donor transplants [Sobacchi et al 2013].
  - In a published report of 193 individuals transplanted in various centers by a cyclophosphamide-based regimen, the five-year probabilities of survival were 62% after HLA-matched sib transplantation and 42% after alternative donor transplantation [Orchard et al 2015].
  - A further improved outcome was reported from three large transplant centers using a fludarabine-based conditioning regimen [Natsheh et al 2016; Schulz & Moshous, personal communication].
  - In HLA-haploidentical HSCT, the implementation of post-transplant cyclophosphamide according to a modified Baltimore protocol achieved promising results. Therefore, this protocol was included in the recently updated treatment guidelines of the EBMT/ESID inborn errors working party [Lankester et al 2021].

Note: Because *TCIRG1* pathogenic variants are more often the cause of ARO than are *CLCN7* pathogenic variants, the majority of HSCTs have been performed in infants with *TCIRG1* rather than *CLCN7* pathogenic variants. However, there appears to be no significant difference in treatment outcome between individuals with *TCIRG1* and *CLCN7* pathogenic variants [A Schulz et al, unpublished results].

Surveillance

Table 9. Recommended Surveillance for Individuals with Infantile Malignant *CLCN7*-Related Autosomal Recessive Osteopetrosis (ARO)

System/Concern	Evaluation	Frequency
Bone marrow failure	CBC	Annually at a minimum
Visual loss	Ophthalmic exam	
Hearing loss	Audiologic eval	
Dental issues	Dental eval	Every 6-12 mos or as directed
Potential for graft failure after HSCT	Transplant center surveillance	As directed by specialists

CBC = complete blood count; HSCT = hematopoietic stem cell transplantation

Table 10. Recommended Surveillance for Individuals with *CLCN7*-Related Autosomal Dominant Osteopetrosis Type II (ADOII)

System/Concern	Evaluation	Frequency
Anemia & thrombocytopenia	CBC	At least annually
Visual loss	Ophthalmic exam	
Hearing loss	Audiologic eval	
Dental issues	Dental eval	Every 6-12 mos or as directed

Agents/Circumstances to Avoid

ADOII

- Activities with high fracture risk should be avoided.
- Orthopedic surgery should only be performed when absolutely necessary and the surgeon should be aware of potential complications and difficulties in handling osteopetrotic bone.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic older and younger sibs of an affected individual by molecular genetic testing of the *CLCN7* pathogenic variant(s) in the family in order to identify as early as possible those who would benefit from prompt initiation of treatment and preventive measures.

For hematopoietic stem cell donation (relatives of a proband with *CLCN7*-related ARO). Any relative considering stem cell donation should undergo molecular genetic testing to clarify their genetic status. Whenever possible, related donors who do not have a familial *CLCN7* pathogenic variant are preferred.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

CLCN7-related osteopetrosis is inherited in an autosomal recessive or autosomal dominant manner:

- Infantile malignant *CLCN7*-related autosomal recessive osteopetrosis (ARO) is inherited in an autosomal recessive manner.
- About 40% of *CLCN7*-related intermediate autosomal osteopetrosis (IAO) is inherited in an autosomal recessive manner and about 60% in an autosomal dominant manner.
- *CLCN7*-related autosomal dominant osteopetrosis type II (ADOII) is inherited in an autosomal dominant manner.

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for a *CLCN7* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *CLCN7* pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - One of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017].
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband.
- Individuals who are heterozygous for a *CLCN7* pathogenic variant associated with ARO are asymptomatic; however, no systematic studies have been performed to evaluate for subtle changes in bone mass.

Sibs of a proband

- If both parents are known to be heterozygous for a *CLCN7* pathogenic variant associated with autosomal recessive osteopetrosis, each sib of an affected individual has at conception a 25% chance of inheriting biallelic *CLCN7* pathogenic variants and being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of inheriting neither of the familial *CLCN7* pathogenic variants.
- The limited data available suggest that in the presence of ARO, a similar presentation of the disorder is expected in individuals with biallelic *CLCN7* pathogenic variants in the same family; in particular, if the neuronopathic form of the disorder is present in the proband, a primary central nervous system involvement is likely to be present in other affected sibs [Sobacchi, unpublished observation].
- Individuals who are heterozygous for a *CLCN7* pathogenic variant associated with autosomal recessive osteopetrosis are asymptomatic; however, no systematic studies have been performed to evaluate for subtle changes in bone mass.

Offspring of a proband

- The offspring of an individual with autosomal recessive *CLCN7*-related osteopetrosis are obligate heterozygotes (carriers) for a pathogenic variant in *CLCN7*.
- In general, individuals with ARO reproduce only if successfully treated by hematopoietic stem cell transplantation.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *CLCN7* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *CLCN7* pathogenic variants in the family.

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- Most individuals diagnosed with autosomal dominant *CLCN7*-related osteopetrosis have an affected parent.

- A proband with autosomal dominant *CLCN7*-related osteopetrosis may have the disorder as the result of a *de novo* pathogenic variant. The proportion of individuals with *CLCN7*-related osteopetrosis caused by a *de novo* pathogenic variant is unknown.
- If the proband appears to be the only affected family member (i.e., a simplex case), recommendations for the evaluation of parents include x-ray investigation of the skeleton and molecular genetic testing for the pathogenic variant identified in the proband. Evaluation of the parents is used to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.
- Evaluation of parents may determine that one is affected but has escaped previous diagnosis because of reduced penetrance, failure by health care professionals to recognize the syndrome, and/or a milder phenotypic presentation. Therefore, an apparently negative family history cannot be confirmed without appropriate clinical evaluation of the parents and/or molecular genetic testing (to establish that neither parent is heterozygous for the pathogenic variant identified in the proband).

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the *CLCN7* pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%. Because ADOII is associated with both intrafamilial clinical variability and reduced penetrance (see Penetrance), a sib who inherits a *CLCN7* pathogenic variant associated with autosomal dominant *CLCN7*-related osteopetrosis may be more or less severely affected than the proband.
- If the proband has a known *CLCN7* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *CLCN7* pathogenic variant but are clinically unaffected, the risk to the sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for *CLCN7*-related osteopetrosis because of the possibility of reduced penetrance in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with autosomal dominant *CLCN7*-related osteopetrosis has a 50% chance of inheriting the pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents. If a parent has the *CLCN7* pathogenic variant, his or her family members may be at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Testing

Once the *CLCN7* pathogenic variant(s) have been identified in an affected family member, prenatal testing and preimplantation genetic testing for *CLCN7*-related osteopetrosis are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **The OsteoPETrosis Society (OPETS)**
  Email: osteopetrosispatient@gmail.com; janecastello.opets@gmail.com
  osteopetrosis.org
- **MedlinePlus**
  Osteopetrosis
- **National Institute of Arthritis and Musculoskeletal and Skin Diseases**
  Phone: 877-226-4267
  Email: niamsinfo@mail.nih.gov
  niams.nih.gov
- **Network for Rare Osteopathies (NetsOs)**
  CeSER
  Alexandrinenstraße 5
  Germany
  Phone: 49 (0)234 509-2601
  Fax: 49 (0)234 509-2688
  Email: ceser@klinikum-bochum.de
  Netzwerks für Seltene Osteopathien
- **European Society for Immunodeficiencies (ESID) Registry**
  Email: esid-registry@uniklinik-freiburg.de
  ESID Registry
- **UCLA International Skeletal Dysplasia Registry (ISDR)**
  Phone: 310-825-8998
  International Skeletal Dysplasia Registry

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. CLCN7-Related Osteopetrosis: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar

Table A. continued from previous page.

CLCN7	16p13.3	H(+)/Cl(-) exchange transporter 7	CLCN7 database	CLCN7	CLCN7

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for CLCN7-Related Osteopetrosis (View All in OMIM)

166600	OSTEOPETROSIS, AUTOSOMAL DOMINANT 2; OPTA2
602727	CHLORIDE CHANNEL 7; CLCN7
611490	OSTEOPETROSIS, AUTOSOMAL RECESSIVE 4; OPTB4

Molecular Pathogenesis

CLCN7-related osteopetrosis is caused by osteoclast dysfunction. The osteoclast is a highly specialized cell with the unique ability to resorb large amounts of mineralized bone tissue. After attaching to the bone surface, a sealing zone that isolates the resorption lacuna from the extracellular environment is formed. Large quantities of acidic vesicles then fuse with the plasma membrane juxtaposed to the bone surface to create the ruffled membrane. This structure is exclusively found in osteoclasts and secretes large amounts of acid into the resorption lacuna, which therefore is also referred to as an "extracellular lysosome" [Sobacchi et al 2013]. The low pH is required to dissolve the bone mineral and for the optimal activity of acid hydrolases that degrade the bone matrix.

CLCN7 encodes the ClC-7 chloride channel, which resides in lysosomal vesicles and in the ruffled membrane and acts as a $2Cl^-/1H^+$ exchanger transporting negative charges into the resorption lacuna in parallel to the protons pumped in this extracellular space by the ruffled membrane v-type H^+-ATPase [Kornak et al 2001, Leisle et al 2011].

Mechanism of disease causation. Pathogenic variants in *CLCN7* lead to a loss of chloride channel function of varying degree. In the most severe autosomal recessive osteopetrosis phenotype, the ClC-7 chloride channel is absent, while the autosomal dominant osteopetrosis type II phenotype-causing pathogenic variants do not necessarily impair chloride currents, but do result in abnormal gating behavior of the channel [Leisle et al 2011].

Table 11. Notable *CLCN7* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_001287.6 NP_001278.1	c.643G>A	p.Gly215Arg	Recurrent pathogenic variants assoc w/ADOII [Cleiren et al 2001]
	c.856C>T	p.Arg286Trp	

ADOII = autosomal dominant osteopetrosis type II
Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

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Guidelines for diagnosis, therapy, and follow up for this disorder are available online (pdf) and from author Ansgar Schulz, MD, at ansgar.schulz@uniklinik-ulm.de.

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