GENEReviews

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CLCN7-Related Osteopetrosis

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Summary

Disease characteristics. The spectrum of *CLCN7*-related osteopetrosis includes infantile malignant *CLCN7*-related recessive osteopetrosis (ARO), intermediate autosomal osteopetrosis (IAO), and autosomal dominant osteopetrosis type II (ADOII, Albers-Schoenberg disease). Onset of ARO is in infancy; findings may include fractures; poor growth; sclerosis of the skull base (with or without choanal stenosis or hydrocephalus) resulting in optic nerve compression, facial palsy, hearing loss; absence of the bone marrow cavity resulting in severe anemia and thrombocytopenia; dental abnormalities, odontomas, risk for mandibular osteomyelitis; and hypocalcemia with tetanic seizures and secondary hyperparathyroidism. Without treatment maximal life span in ARO is ten years. Onset of IAO is in childhood; findings may include fractures after minor trauma; characteristic skeletal radiographic changes found incidentally; mild anemia; occasional visual impairment secondary to optic nerve compression. Life expectancy in IAO is usually normal. Onset of ADOII 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; osteomyelitis of the mandible or septic osteitis or osteoarthritis elsewhere. Cranial nerve compression is rare.

Diagnosis/testing. Diagnosis of *CLCN7*-related osteopetrosis usually relies on radiographic changes that are pathognomoic in ARO (generalized osteosclerosis, club-shape of the long bones, osteosclerosis of the skull base, bone-within-bone appearance) and characteristic in ADOII (osteosclerosis of the spine ("sandwich vertebra" appearance), bone within bone appearance (mainly iliac wings), Erlenmeyer-shaped femoral metaphysis, mild osteosclerosis of the skull base, transverse bands of osteosclerosis in long bones). *CLCN7* is the only gene associated with *CLCN7*-related osteopetrosis. Sequencing of all exons and adjacent splice sites is available on a clinical basis.

Management. *Treatment of manifestations:* ARO: calcium supplementation for hypocalcemic convulsions; management of calcium homeostasis per each patient's needs; erythrocyte or platelet transfusions as needed; antibiotics and immunoglobulins for leukocytopenia and/or

hypogammaglobulinemia; surgical decompression of the optic nerve; treatment of fractures by an orthopedist; dental care with attention to tooth eruption, ankylosis, abscesses, cysts, 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. *Prevention of primary manifestations:* ARO: Hematopoietic stem cell transplantation (HSCT) can be curative; however, cranial nerve dysfunction is usually irreversible, and progressive neurologic sequelae occur in some children even after successful HSCT. *Prevention of secondary complications:* ARO: restricted intake of calcium and vitamin D just before, during, and following HSCT to prevent hypercalcemia. ADOII: good routine dental care and oral hygiene to help prevent osteomyelitis of the mandible. *Surveillance:* ARO: complete blood count and ophthalmologic examination at least once a year; follow-up per the transplantation center following HSCT. *Agents/circumstances to avoid:* ADOII: Activities with high fracture risk.

Genetic counseling. ARO is inherited in an autosomal recessive manner; ADOII is inherited in an autosomal dominant manner; about 40% of IAO is inherited in an autosomal recessive manner and about 60% in an autosomal dominant manner. Autosomal recessive inheritance: at conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Individuals with ARO in general only reproduce if successfully treated by HSCT. Autosomal dominant inheritance: most individuals diagnosed with autosomal dominant *CLCN7*-related osteopetrosis have an affected parent. The proportion of cases caused by *de novo* mutations is unknown. Each child of an individual with autosomal dominant *CLCN7*-related osteopetrosis has a 50% chance of inheriting the mutation. Prenatal diagnosis for pregnancies at risk for *CLCN7*-related osteopetrosis is possible if the disease-causing allele(s) have/has been identified in the family.

Diagnosis

Clinical Diagnosis

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-Schoenberg disease).

The diagnostic features of each of the subtypes of *CLCN7*-related osteopetrosis are listed in Table 1.

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

Finding	ARO [1]	IAO [2]	ADOII [3]
Radiographic changes	Pathognomonic [4]	Characteristic [5]	Characteristic [6]
Hypocalcemia	Severe to absent	Absent	Absent
Anemia	Severe to absent	Mild to absent	Absent
Thrombocytopenia	Severe to absent	Absent	Absent
Visual impairment	Frequent	Rare	Very rare
CNS involvement	Severe to absent	Absent	Absent

1. ARO = infantile malignant autosomal *CLCN7*-related recessive osteopetrosis
2. IAO = intermediate autosomal *CLCN7*-related osteopetrosis
3. ADOII = autosomal dominant osteopetrosis type II
4. Generalized osteosclerosis, club-shape of the long bones, sclerosis of the skull base, bone-within-bone appearance

5. Findings similar to ARO, already present in early childhood, but less severe
6. Findings include:

   a) Osteosclerosis of the spine ("sandwich vertebrae")

   b) Bone within bone appearance, mainly in iliac wings

   c) Erlenmeyer-shaped femoral metaphysis

   d) Mild osteosclerosis of the skull base

   e) Transverse bands of osteosclerosis in long bones

Testing

Serum concentrations of the BB-isoenzyme of creatine kinase (CK) and tartrate resistant acid phosphatase (TRAP). Increases in the serum concentrations of these two enzymes have been reported as biological markers of ADOII. They could reflect increased osteoclast numbers and could help identify affected individuals who do not have diagnostic radiographic findings [Waguespack et al 2002, Alatalo et al 2004, Del Fattore et al 2006].

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene. *CLCN7* is the only gene associated with *CLCN7*-related osteopetrosis.

Clinical uses

- Confirmatory diagnostic testing
- Prenatal testing
- Preimplantation genetic diagnosis

Clinical testing

- **Sequencing of all exons and adjacent splice sites**

Table 2 summarizes molecular genetic testing for this disorder.

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

Test Method	Proportion of Osteopetrosis Phenotype Caused by Mutation of *CLCN7*				Mutations Detected	Mutation Detection Rate by Method	Test Availability
	ARO [1]	IAO [2]		ADOII [3]			
	Two Mutations	Two Mutations [4]	One Mutation [4]	One Mutation			
Sequence analysis	15%	40%	60%	75% [5]	*CLCN7* sequence variants	~80%	Clinical Testing

1. ARO = infantile malignant *CLCN7*-related autosomal recessive osteopetrosis
2. IAO = intermediate autosomal *CLCN7*-related osteopetrosis
3. ADOII = autosomal dominant osteopetrosis type II
4. Campos-Xavier et al 2003, Frattini et al 2003

5. Del Fattore et al (2006) found *CLCN7* mutations in 78% of ADOII cases; Frattini et al (2003) found *CLCN7* mutations in 72% of ADOII cases. In other cohorts, rates may be higher [unpublished observations]. It remains possible that mutations in another gene cause the ADOII phenotype in a subset of cases.

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

To establish the diagnosis in a proband

- If symptoms begin in early childhood, x-rays show general osteosclerosis, and hypocalcemia and hematologic abnormalities are present, an autosomal recessive form should be considered. Testing should begin with *TCIRG1*, followed by *CLCN7* and *OSTM1* (see Differential Diagnosis).
- If symptoms begin after age six years (usually because of fractures) and x-rays show less pronounced osteosclerosis (i.e., typical sandwich appearance of the vertebrae), the autosomal dominant form is more likely and testing should begin with *CLCN7*.

Genetically Related (Allelic) Disorders

No other phenotype is associated with alterations in *CLCN7*.

Clinical Description

Natural History

Infantile Malignant *CLCN7*-Related Autosomal Recessive Osteopetrosis (ARO)—ARO is a systemic, life-threatening disorder. Without treatment, maximal life span is ten years. Possible clinical manifestations of ARO:

- **Fractures.** The nearly complete absence of osteoclastic bone resorption caused by the loss of chloride channel protein 7 (also known as ClC-7) 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.** Growth is retarded to a variable degree because resorption of cartilage and bone at the growth plate is a prerequisite for longitudinal growth. 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. Additionally, the skull changes can cause hydrocephalus.
- **Neurologic complications.** Visual impairment beginning shortly after birth is common. In most cases it is caused by optic nerve compression within the osteosclerotic skull base.

  A prominent and large anterior fontanel is common and sometimes associated with hydrocephalus, possibly caused by obstruction of cerebral blood flow and cerebrospinal fluid (CSF) 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 has to be considered. In these cases the neuronal phenotype resembles neuronal ceroid-lipofuscinosis, a lysosomal storage disorder [Steward 2003]. In this subset of very severely affected children, primary degeneration of the retina and CNS occurs. It is important to differentiate these rare primary neurologic manifestations of the neuronopatic form of ARO, which has a poor prognosis, from more common secondary lesions resulting from hyperostosis of the skull base.

  The basis of the neuronopathic form of ARO is incompletely understood so far, but neurologic complications seem to be more common and more severe in persons with *CLCN7* mutations than in those with *TCIRG1* mutations [A Villa, personal communication; A Schulz, unpublished results]. This is mirrored by neurodegeneration in *CLCN7*-null mice [Kasper et al 2005].

- **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 [Jalevik et al 2002, Helfrich 2005, Luzzi et al 2006].

- **Hypocalcemia.** Hypocalcemia may result in tetanic seizures and secondary hyperparathyroidism.

- **Anemia and thrombocytopenia.** The absence of the bone marrow cavity leads to extramedullary hematopoesis, hepatosplenomegaly, anemia, and thrombocytopenia. The bleeding associated with thrombocytopenia can be severe and life threatening, especially in the 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].

Intermediate Autosomal Osteopetrosis (IAO) —IAO is characterized by childhood onset, but a milder course than ARO. Life expectancy is normal in most cases. 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 (see Figure 2).

Onset of clinical and radiologic manifestations of ADOII is usually late childhood or adolescence, although earlier occurrence has been reported. Osteosclerosis of the spine predominates, with a "sandwich vertebra" 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 [Benichou et al 2000, Cleiren et al 2001].

Clinical findings vary even within the same family [Chu et al 2006]. In three families in which most affected individuals had mild ADOII, early-onset disease, anemia, and blindness caused by optic nerve compression was 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 about 80% of affected individuals in the largest study, with a mean of three fractures/patient. 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** can be seen in a number of cases.
- **Hip osteoarthritis** is common (27%) and could be caused by the excessive toughness of the sub-chondral bone.
- **Osteomyelitis** of the mandible is often associated with dental abscess or caries [Benichou et al 2000]. 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 occur in fewer than 5% of affected individuals.

Genotype-Phenotype Correlations

Except for the following, no clear genotype-phenotype correlation exists, including analysis of the polymorphisms.

- Nonsense mutations in *CLCN7* are more likely to cause ARO.
- The proportion of mutations in the C-terminal CBS-domains of the chloride channel type 7 is higher in ADOII than in ARO.

Penetrance

Depending on the population studied, penetrance ranges from 60% to 90% in families with ADOII [Bollerslev 1989, Benichou et al 2000, Waguespack et al 2003].

Anticipation

Anticipation is not observed.

Prevalence

The prevalence of ADOII has been estimated to be approximately 1:100,000.

ARO is probably even less common.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

CLCN7 mutations underlie approximately 15% of all autosomal recessive osteopetrosis (ARO) and 100% of all intermediate autosomal osteopetrosis (IAO) described so far. In autosomal

dominant osteopetrosis type II (ADOII), *CLCN7* mutations are identified in approximately 75% of cases [Cleiren et al 2001, Frattini et al 2003, Del Fattore et al 2006].

ARO secondary to *TCIRG1* mutations. Approximately 50% of ARO is caused by mutations in *TCIRG1*. ARO caused by *TCIRG1* mutations is difficult to distinguish from *CLCN7*-related disease [Frattini et al 2000, Kornak et al 2000]. The frequency of developmental delay and seizures is higher in osteopetrosis caused by mutations in *CLCN7*.

ARO secondary to *OSTM1* mutations. Approximately 2% of ARO is caused by mutations in *OSTM1*. *OSTM1* mutations seem to cause an extremely severe form of ARO with frequent CNS involvement [Pangrazio et al 2006].

ARO with renal tubular acidosis (RTA). The onset of ARO with RTA is usually later than in the malignant infantile form of ARO and the disease course is milder. In addition to the generalized osteosclerosis, cerebral calcifications are typical and may be associated with mental retardation [Jacquemin et al 1998]. Mutations are found in *CAII*, the gene encoding carbonic anhydrase type II [Bolt et al 2005].

X-linked osteopetrosis, lymphedema, anhidrotic ectodermal dysplasia, and immunodeficiency (OL-EDA-ID). Mutations in *NEMO* cause an extremely rare combination of ectodermal dysplasia and osteopetrosis. Osteopetrosis is not clinically relevant in these cases as the immunodeficiency is very severe [Doffinger et al 2001].

Autosomal dominant osteopetrosis type I (ADOI). Osteosclerosis in ADOI is most pronounced in the skull vault and does not lead to sandwich vertebrae. ADOI is not associated with an increased fracture rate. Mutations in *LRP5* are causative [Van Wesenbeeck et al 2003].

Pyknodysostosis. Affected individuals usually have small stature (adult height less than 150 cm), frontal bossing, a persistent (open) anterior fontanel, and acroosteolysis of the terminal phalanges [Vanhoenacker et al 2000]. The bones are generally sclerotic and prone to fractures. Pyknodysostosis is caused by mutations in *CTSK*, the gene encoding cathepsin K [Gelb et al 1996].

***SOST*-related sclerosteosis,** including Van Buchem disease and sclerosteosis, is characterized by moderate to gross skull hyperostosis leading to cranial nerve dysfunction, mandibular enlargement, and a generalized osteosclerosis. Sclerosteosis also comprises syndactyly and tall stature and can be lethal as a result of increased intracranial pressure [Hamersma et al 2003].

Craniometaphyseal dysplasia (CMD). The clinical hallmark of CMD is skull hyperostosis leading to deep-set eyes and paranasal bossing. Facial nerve palsy is common and occurs more frequently than optic nerve compression [Braun et al 2001]. The femur shows a modeling defect, but no osteosclerosis. Susceptibility to fractures is not increased. Mutations in *ANKH* are causative [Nurnberg et al 2001].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with *CLCN7*-related osteopetrosis:

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

- Full blood cell count to evaluate for leukocytosis or leukocytopenia, thrombocytopenia,f anemia with low reticulocyte count

- Investigation of calcium metabolism in blood and urine to evaluate for hypocalcemia and secondary hyperparathyroidism
- Bone marrow aspirates and bone biopsy histology to confirm and classify the disease. Osteopetrosis is generally characterized by high levels of osteoclasts and persistence of cartilage in bone trabeculae. If osteoclast-poor disease is seen, genes other than *CLCN7*, *TCIRG1*, and *OSTM1* should be considered. More information about such genes will soon become available.
- Ultrasonography of abdomen to evaluate for hepatosplenomegaly
- MRT and/or CT of the neurocranium to evaluate for narrowed neuroforamina, hydrocephalus, brain abnormalities in neuronopathic form of OP
- Ophthalmologic examination including VEPs to evaluate for optic nerve atrophy
- Otorhinolaryngologic examination including AEPs to evaluate for choanal stenosis
- Neurologic examination to evaluate developmental delay, including EEG to evaluate for seizures

Autosomal Dominant Osteopetrosis type II (ADOII)—Given the broad range of possible manifestations, the diagnostic measures should be in accordance with the individual clinical signs. A blood cell count, abdominal ultrasonography and ophthalmologic examination can be generally recommended. In severely affected cases of early onset, the diagnostic work-up is the same as for ARO.

Treatment of Manifestations

ARO—Hypocalcemic convulsions, occurring in a substantial number of neonates as the first disease manifestation, should be treated by calcium supplementation. The management of calcium homeostasis may be difficult and recommendations are conflicting: physiologic doses of calcium and vitamin D have been used to treat children with osteopetrosis who have rickets. On the other hand, restriction of calcium and vitamin D were used to prevent progression of disease and hypercalcemic crisis following hematopoetic stem cell transplantation (HSCT). Treatment needs to take into account the particular situation of the affected individual.

Bone marrow failure may require erythrocyte or platelet transfusions (irradiated products). In the case of leukocytopenia and/or hypogammaglobulinemia, which may develop in a subset of individuals, antibiotics and immunoglobulins may be given in a prophylactic or therapeutic manner.

Newly diagnosed individuals should be transferred as soon as possible to a pediatric center experienced in allogeneic stem cell transplantation in this disease.

Sensory and neurologic manifestations require the collaboration of pediatricians, pediatric neurologists, ophthalmologists, and psychologists. Surgical decompression of the optic nerve, a difficult procedure, has been performed with some success to prevent vision loss [Hwang et al 2000].

Fractures require treatment and surveillance by an experienced bone surgeon or orthopedist in collaboration with the treating pediatrician.

Dental. Without HSCT, most children do not reach the age at which secondary dentition erupts. Children undergoing early HSCT may have normal secondary dentition despite defective primary dentition [Jalevik et al 2002].

In some cases, defective tooth eruption, ankylosis, abscesses, and the formation of cysts and fistulas may require surgical intervention. Special attention is required to prevent mandibular osteomyelitis and extreme brittleness of the alveolar bone [Luzzi et al 2006].

ADOII—Orthopedic treatment is often required for fractures and arthritis. Post-surgical complications such as delayed union or non-union of fractures and infections are common (50%) because of the brittleness of the bones. Fractures near joints may require total joint arthroplasty [Strickland & Berry 2005].

Prevention of Primary Manifestations

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

Secondary sensorineurologic impairments caused by nerve compression may be prevented by early transplantation, but not reversed when they are already present.

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. However, persons with ARO resulting from *CLCN7* mutations who do not develop neurologic complications after HSCT have been reported [A Schulz and U Kornak, unpublished results].

It is highly important but difficult to exclude individuals with the neuronopatic form from this invasive treatment. 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, such as 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.

HSCT using HLA-identical donors has an acceptable outcome (73% five-year disease-free survival) [Driessen et al 2003]. The success rate of HSCT from experienced centers using alternative sources as T-cell depleted hematopoietic stem cells from HLA-haploidentical family donors or cord blood from unrelated donors has improved markedly in recent years [Martin et al 2000; Schulz et al 2002; Marc Bierings, personal communication].

Note: Because of the higher frequency of *TCIRG1* mutations as a cause of ARO compared to *CLCN7* mutations, the majority of HSCTs have been performed in infants with *TCIRG1* rather than *CLCN7* mutations.

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].

Cranial nerve dysfunction (visual impairment caused by optic nerve atrophy) is irreversible in most cases. In the authors' series including about 30 individuals, about two-tirds of affected individuals were visually impaired after successful transplantation [A Schulz, unpublished results].

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 have been seen in about 10% of individuals in the authors' series [A Schulz, unpublished results].

Other. Conservative treatment strategies include stimulation of host osteoclasts with calcium restriction, calcitrol, steroids, parathyroid hormone, and interferon [Kocher & Kasser 2003]. Since evidence for a favorable outcome in severe osteopetrosis is limited and because side effects are severe particularly in infants, these drugs may be administered in special situations only.

Prevention of Secondary Complications

ADOII—Good routine dental care and oral hygiene may help prevent osteomyelitis of the mandible.

Surveillance

ARO—The possible manifestations and complications of osteopetrosis require repeat investigations; however, no general recommendations are available for the extent and frequency of investigations. A blood cell count and an ophthalmologic examination should be performed once a year at a minimum in all individuals with ARO.

In individuals who have undergone HSCT, surveillance should be coordinated by the transplantation center; chimerism analysis should be performed repeatedly, as secondary graft failures have been reported. However, such individuals may be free of disease manifestation even in the case of stable mixed chimerism, if a substantial part of blood cells are donor derived (coexistence of hematopoietic cells of donor and recipient origin).

ADOII—In ADOII, skeletal manifestations do not progress and therefore no special surveillance is necessary.

Agents/Circumstances to Avoid

ARO—Avoidance of calcium and vitamin D is not generally recommended. However, just before, during, and following HSCT, calcium intake is restricted and vitamin D prophylaxis is discontinued to prevent hypercalcemia following stem cell engraftment.

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.

Testing of Relatives at Risk

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

Therapies Under Investigation

Search ClinicalTrials.gov 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.

Other

Studies have been initiated to investigate the relation of genotype and clinical outcome after stem cell transplantation (for current information, see the European Society of Immunodeficiencies (ESID) and European Group of Bone Marrow Transplantation (EBMT) Web sites).

Parents and patients should be informed about possible complications of the disease and recommendations for prevention should be given accordingly (e.g., severe CNS bleeding in patients with thrombocytopenia, pathologic fractures). Because of the heterogeneity of the disease, recommendations should be given on an individual basis.

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

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

Risk to Family Members — Autosomal Recessive Osteopetrosis

Parents of a proband

- The parents of an affected child are obligate heterozygotes and therefore carry one mutant allele.
- Heterozygotes (carriers) are asymptomatic; however, no systematic studies have been performed to evaluate for subtle changes in bone mass.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband

- Individuals with ARO in general only reproduce if successfully treated by bone marrow transplantation.
- The offspring of an individual with autosomal recessive *CLCN7*-related osteopetrosis are obligate heterozygotes (carriers) for a disease-causing mutation in the *CLCN7* gene.

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

Carrier Detection

Carrier testing for at-risk family members is available on a clinical basis once the mutations have been identified in the proband.

Risk to Family Members — Autosomal Dominant Osteopetrosis

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 new mutation of the *CLCN7* gene. The proportion of cases caused by *de novo* mutations is unknown.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation include x-ray investigation of the skeleton. Evaluation of parents may determine that one is affected but has escaped previous diagnosis because of failure by health care professionals to recognize the syndrome and/or a milder phenotypic presentation. Therefore, an apparently negative family history cannot be confirmed until appropriate evaluations have been performed.

Note: Although most individuals diagnosed with autosomal dominant *CLCN7*-related osteopetrosis have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members, or late onset of the disease in the affected parent.

Sibs of a proband

- The risk to the sibs of the proband depends upon the genetic status of the proband's parents.
- If a parent of the proband is affected, the risk to the sibs is 50%.
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low.
- If the disease causing mutation found in the proband cannot be detected in the DNA of the parents, the risk to sibs is low, but greater than that of the general population, because, although not reported, the possibility of germline mosaicism exists.

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

Other family members of a proband. The risk to other family members depends upon the status of the proband's parents. If a parent is found to be affected, his or her family members are at risk.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has the disease-causing mutation or clinical evidence of the disorder, it is likely that the proband has a *de novo* mutation. However, possible non-medical explanations including alternate paternity or undisclosed adoption could also be explored.

Family planning. The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Prenatal diagnosis for pregnancies at *CLCN7*-related osteopetrosis risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation. The disease-causing allele(s) of an affected family member must be identified or linkage established in the family before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified in an affected family member. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of CLCN7-Related Osteopetrosis

Gene Symbol	Chromosomal Locus	Protein Name
CLCN7	16p13	Chloride channel protein 7

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for CLCN7-Related Osteopetrosis

166600	OSTEOPETROSIS, AUTOSOMAL DOMINANT, TYPE II
602727	CHLORIDE CHANNEL 7; CLCN7

Table C. Genomic Databases for CLCN7-Related Osteopetrosis

Gene Symbol	Locus Specific	Entrez Gene	HGMD
CLCN7	CLCN7	1186 (MIM No. 602727)	CLCN7

For a description of the genomic databases listed, click here.

Molecular Genetic Pathogenesis

ARO, IAO, and ADOII are caused by osteoclast dysfunction. The osteoclast is a highly specialized cell with the unique ability to resorb large amounts of mineralized bone tissue. Like macrophages, osteoclasts are giant multinuclear cells formed by fusion of mononuclear hematopoietic precursors that subsequently differentiate under the influence of M-CSF and RANKL.

After attaching to the bone surface, a sealing zone that isolates the resorption lacuna from the extracellular environment is formed. Large amounts 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" [Teitelbaum & Ross 2003]. The low pH is required to dissolve the bone mineral and for the optimal activity of acid hydrolases that degrade the bone matrix, particularly cathepsin K.

Most forms of human osteopetrosis for which the genetic causes have been identified so far are the result of defects in the acid secretion mechanism. The ClC-7 chloride channel resides in lysosomal vesicles and in the ruffled membrane and is thought to transport negative charges in parallel to the protons pumped into the resorption lacuna by the ruffled membrane v-type H^+-ATPase [Kornak et al 2001].

The *TCIRG1* gene encodes an important subunit of this H^+-ATPase and carbonic anhydrase type II (CAII) generates the necessary protons in the osteoclast cytoplasm; thus, defects in these genes also cause osteopetrosis.

Mutations in *CLCN7* lead to a loss of chloride channel function of varying degree. In the most severe ARO cases, chloride channel protein 7 (ClC-7) is absent. As illustrated by a knockout mouse model, which shows degeneration of the CNS and the retina, a complete loss of the protein entails a strong risk for the neuronopathic form of ARO [Kornak et al 2001, Steward 2003, Kasper et al 2005].

The less severe forms of osteopetrosis are thought to be caused by mutations that incompletely inactivate the protein. Mutations found in ADOII apparently have dominant negative effects. It can be speculated that many of these mutations selectively affect chloride channel function, as has been described for the Thomsen type of myotonia congenita, caused by dominant mutations in *CLCN1* [Jentsch, Poet et al 2005]. This is underlined by preliminary data suggesting that many *CLCN7* mutations do not alter expression and subcellular localization of the protein. The strictly intracellular localization of chloride channel protein 7 has so far precluded direct electrophysiologic measurements of these mutants.

Normal allelic variants: The *CLCN7* gene contains a coding region of 2409 bp subdivided into 25 exons. The most common coding single-nucleotide polymorphism (SNP) is rs12926089, which leads to the amino acid exchange V418M. Although clearly not pathogenic, this polymorphism has been found to be associated with bone mineral density in postmenopausal women [Pettersson et al 2005]. A prominent intronic polymorphism is a 50-bp variable number tandem repeat (VNTR) in intron 8, which ranges from 100 bp to 450 bp in length. This polymorphism is also associated with bone mineral density in postmenopausal women as well as with resorption markers and with the penetrance of dominant *CLCN7* mutations [Kornak et al 2006].

Pathologic allelic variants: Fifteen percent of the mutations found in ARO are nonsense and 85% are missense mutations. Approximately 25% of these mutations reside in the C-terminal CBS domains of the protein. In ADOII, nonsense mutations are found in 6%; 72% are missense mutations. Twelve percent are deletions, 6% are insertions, and 6% are frameshift mutations. Almost 50% of these mutations are found in the C-terminal CBS domains (CLCN7 Mutation Database).

Normal gene product: The *CLCN7* gene encodes the 803 aa chloride channel protein 7 (also known as ClC-7), which resides in late endosomes and lysosomes of most cell types. In osteoclasts, the protein is translocated to the ruffled membrane. Like the other CLC-channels, ClC-7 contains two C-terminal CBS domains, supposed to be involved in protein-protein interaction. This interaction might facilitate the formation of the functional channel dimers. It

has been shown recently that CLC-channels are not pure chloride channels but rather function as chloride/proton antiporters [Jentsch, Maritzen et al 2005].

Abnormal gene product: Some mutations associated with ARO lead to a complete loss of the ClC-7 protein, which has been demonstrated to completely abolish osteoclast resorptive activity [Kornak et al 2001]. Some mutations associated with ARO and most likely all mutations associated with ADOII lead to only minor changes in ClC-7 protein levels. No abnormal subcellular distribution has yet been described as a consequence of *CLCN7* mutations. It can be assumed that the majority of mutations associated with ADOII alter the electrophysiologic properties of the channel, thereby reducing the chloride conductance under physiologic conditions. This is thought to lead to an attenuation of osteoclast activity of varying degrees, giving rise to the variability of the clinical course [Chu et al 2006, Del Fattore et al 2006].

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

The Paget Foundation
120 Wall Street Ste. 1602
New York NY 10005-4001
Phone: 800-23-PAGET (800-237-2438); 212-509-5335
Fax: 212-509-8492
Email: Pagetfdn@aol.com
www.paget.org

National Institute of Arthritis & Musculoskeletal & Skin Diseases
www.niams.nih.gov

International Skeletal Dysplasia Registry
Medical Genetics Institute
8635 West Third St. Suite 665
Los Angeles CA 90048
Phone: 800-CEDARS-1 (800-233-2771)
Fax: 310-423-0462
www.csmc.edu

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Chapter Notes

Revision History

- 12 February 2007 (me) Review posted to live Web site
- 8 September 2006 (uk) Original submission

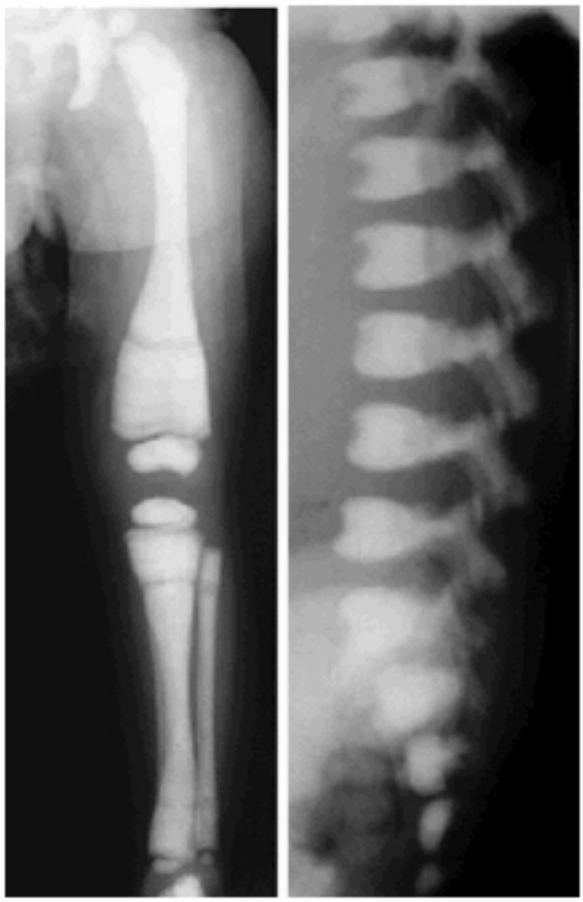

Figure 1. ARO x-rays

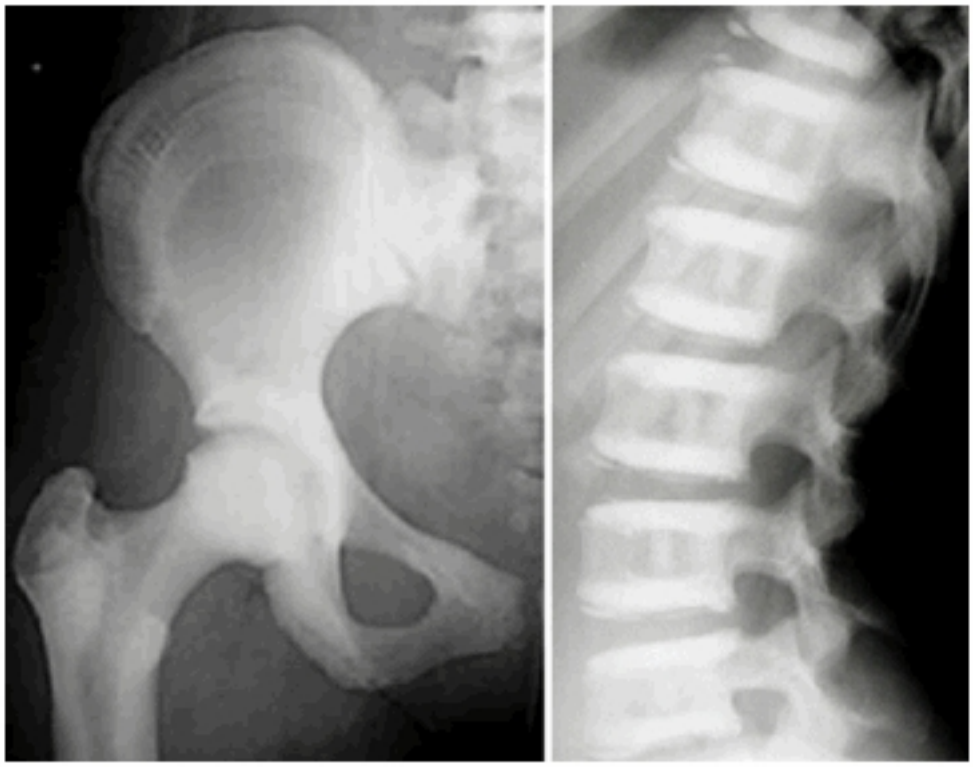

Figure 2. ADOII x-rays (reprinted from Benichou et al 2000 with permission from Elsevier)