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Pycnodysostosis

Synonyms: Pyknodysostosis, Toulouse-Lautrec Syndrome, *CTSK*-Related Pyknodysostosis

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Summary

Clinical characteristics

Pycnodysostosis is characterized by short-limbed short stature, typical facial appearance (convex nasal ridge and small jaw with obtuse mandibular angle), osteosclerosis with increased bone fragility, acroosteolysis of the distal phalanges, delayed closure of the cranial sutures, and dysplasia of the clavicle. In affected individuals, the facial features become more prominent with age, likely due to progressive acroosteolysis of the facial bones, but can usually be appreciated from early childhood, particularly the small jaw and convex nasal ridge. Additional features include dental and nail anomalies. Intelligence is typically normal with mild psychomotor difficulties reported in some individuals.

Diagnosis/testing

The diagnosis of pycnodysostosis can be established in a proband with characteristic clinical and radiographic features and/or biallelic pathogenic variants in *CTSK* identified by molecular genetic testing.

Management

Treatment of manifestations: Growth hormone therapy; environmental or occupational modifications as needed; orthopedic management of fractures and scoliosis; craniofacial and neurosurgical management as required for cleft palate, craniosynostosis, maxillary and mandibular hypoplasia; pulmonology and sleep medicine specialist management of obstruction sleep apnea; consultation with expert anesthetist prior to any planned surgery; dental and orthodontic care for dental anomalies; standard management per ophthalmologist for vision concerns.

Surveillance: Annual physical examination including assessment for scoliosis, asymmetry, frequency of fractures, weight and nutrition, and psychological assessment; polysomnography every two years; annual evaluation with specialist dentist and ophthalmologist.

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Agents/circumstances to avoid: If general anesthesia is needed, consider the possibility of difficult intubation prior to scheduling anesthesia.

Pregnancy management: In individuals with a small pelvis, delivery by cæsarean section should be considered. However, each individual should be assessed by an obstetrician and anesthetist familiar with skeletal dysplasia.

Genetic counseling

Pycnodysostosis is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *CTSK* pathogenic variant, each sib of an affected individual has at conception 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 the *CTSK* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible.

Diagnosis

Formal diagnostic criteria for pycnodysostosis have not been established, however the radiographic features of acroosteolysis, osteosclerosis, and loss of the normal angle of the jaw are almost pathognomonic.

Suggestive Findings

Pycnodysostosis **should be suspected** in probands with the following clinical, radiographic, and laboratory findings.

Clinical findings

- Short-limbed short stature in all individuals (prenatal onset in ~30%)
- Brachydactyly
  - Craniofacial findings
  - Frontal bossing
  - Persistently open anterior fontanelle
  - Prominent nose with convex nasal ridge
  - Midface retrusion and small jaw due to hypoplasia of the maxilla and mandible
  - Stridor, laryngomalacia, and obstructive sleep apnea
  - Prominent eyes with blueish sclera
  - High arched palate / grooved palate
- Dental anomalies (e.g., delayed eruption of deciduous and permanent teeth, persistence of deciduous teeth resulting in a double row of teeth, hypodontia)
- Nail anomalies (e.g., dysplastic, grooved, flattened)

Radiographic findings (See Figure 1.)

- Generalized progressive osteosclerosis, particularly of the long bones
- Acroosteolysis of the terminal phalanges
- Non-pneumatized mastoids
- Delayed fusion of the cranial sutures
- Obtuse mandibular angle due to loss of the normal mandibular (gonial) angle
- Increased incidence of fractures
- Clavicular dysplasia, congenital pseudarthrosis of the clavicle

Laboratory findings

- Normal serum calcium, phosphate, vitamin D, and alkaline phosphatase

- Growth hormone deficiency
- Low IGF-1
- No abnormalities of other pituitary hormones

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of pycnodysostosis **can be established** in a proband with characteristic clinical and radiographic features and/or biallelic pathogenic (or likely pathogenic) variants in *CTSK* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of biallelic *CTSK* variants of uncertain significance (or of one known *CTSK* pathogenic variant and one *CTSK* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with osteosclerosis and/or short stature are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and radiographic findings suggest the diagnosis of pycnodysostosis, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *CTSK* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected.
- **A multigene panel** that includes *CTSK* 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.

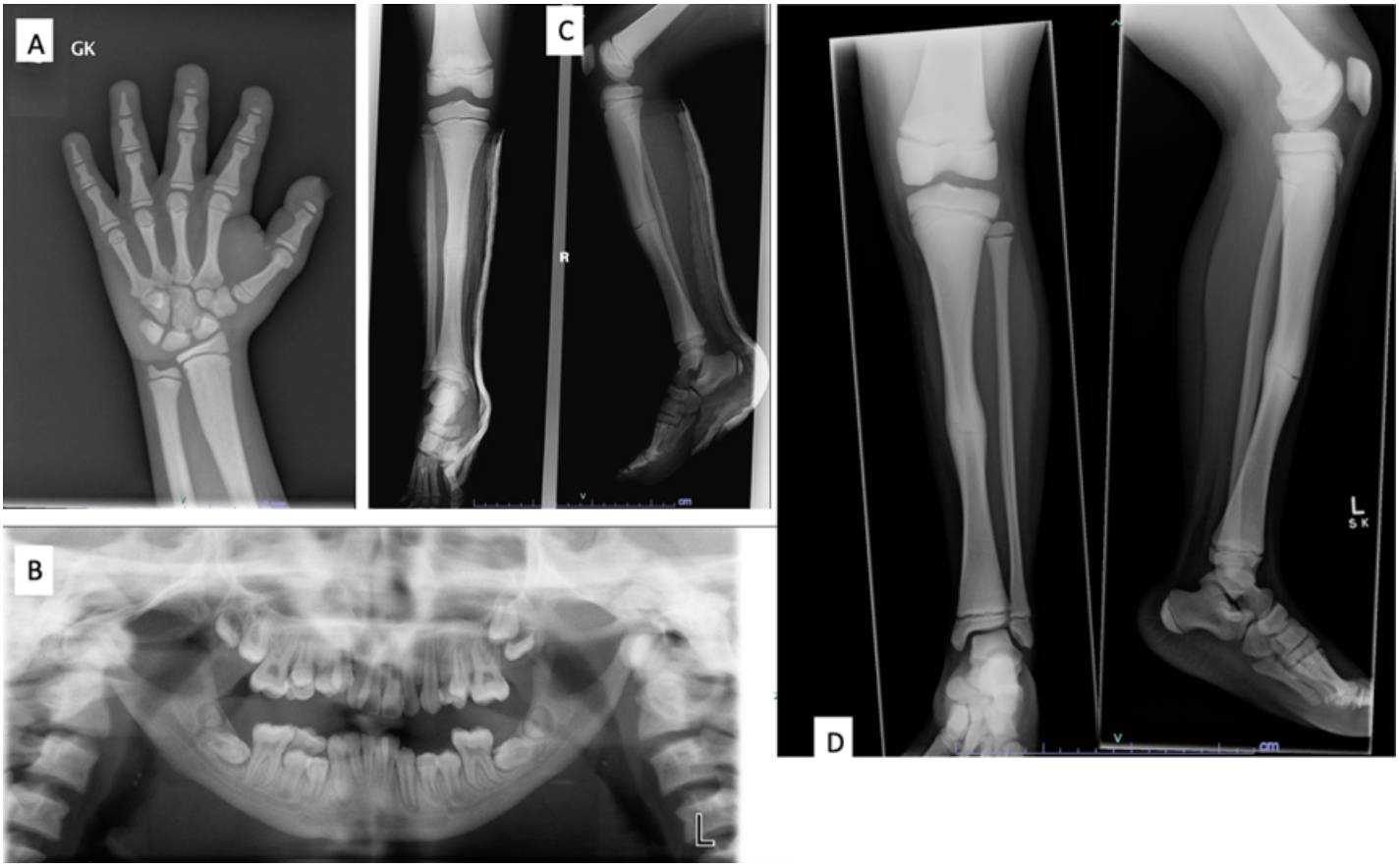

Figure 1. Radiographic features of pycnodysostosis

A. Hand and wrist radiograph in a female age 12 years, showing marked acroosteolysis of the terminal phalanges and generalized increase in bone density.

B. Orthopantomogram in the same individual with mixed dentition present. The mandible is hypoplastic and sclerotic with loss of the gonial angle.

C. Radiographs of the tibia and fibula demonstrating diffuse sclerosis and a transverse midshaft tibial fracture at age ten years.

D. The fracture remains clearly visible three months later with periosteal new bone formation.

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by osteosclerosis and short stature, **comprehensive genomic testing** (which does not require the clinician to determine which gene is likely involved) is an option. **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 1. Molecular Genetic Testing Used in Pycnodysostosis

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
CTSK	Sequence analysis [3]	~100% [4]
	Gene-targeted deletion/duplication analysis [5]	One reported [6]

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. Review of approximately 35 pathogenic variants in all available published case literature, ClinVar [Landrum et al 2014], and data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. A 301-bp Alu sequence insertion in intron 7 that creates a new potential splice acceptor site [Arman et al 2014]

Clinical Characteristics

Clinical Description

Pycnodysostosis is characterized by short stature, typical facial appearance (small jaw with obtuse mandibular angle and convex nasal ridge), osteosclerosis with increased bone fragility, acroosteolysis of the distal phalanges, delayed closure of the cranial sutures, and dysplasia of the clavicle. In affected individuals, the facial features become more prominent with age, likely due to progressive acroosteolysis of the facial bones, but can usually be appreciated from early childhood, particularly the small jaw and convex nasal ridge [Turan 2014].

A comprehensive review of previously published reports [Xue et al 2011] identified 159 individuals including 59 unrelated families with confirmed homozygous or compound heterozygous pathogenic variants in *CTSK*. A further 27 affected individuals from 17 unrelated families were recently described, with molecular data available for 14 families [Bizaoui et al 2019]. The following description of the phenotypic features associated with pycnodysostosis is based on these reports.

Table 2. Pycnodysostosis: Frequency of Select Features

Feature		% of Persons w/Feature
Clinical	Short limb, short stature	~100%
	Intrauterine growth restriction	~30%
	Brachydactyly	>90%
	Frontal bossing	>80%
	Persistently open anterior fontanelle	80%
	Convex nasal ridge	~70%
	Small jaw	>70%
	Midface retrusion	60%
	Proptosis	60%
	Blueish sclerae	30%-40%
	Obstructive sleep apnea	>65%

Table 2. continued from previous page.

Feature		% of Persons w/Feature
	Increased incidence of fractures	~70%
	Nail anomalies	>50%
	Dental anomalies	30%-40%
Radiographic	Osteosclerosis	~100%
	Acroosteolysis of the terminal phalanges	>90%
	Non-pneumatized mastoids	80%
	Delayed fusion of cranial sutures	67%
	Obtuse mandibular angle	65%
	Clavicular dysplasia	25%

Growth deficiency / short stature. Short stature is reported in almost 100% of individuals with pycnodysostosis. Individuals typically develop short stature by early childhood with decreased growth velocity, although 30% are reported to have intrauterine growth deficiency. Limbs are often disproportionately short compared to the trunk, with rhizo-, meso-, and acromelia. Documented adult heights are typically <150 cm for males (average 2.9 SD below the mean) and 130-134 cm for females (average 4.1 SD below the mean) [Bizaoui et al 2019].

About 50% have growth hormone deficiency but almost all have low IGF-1 levels. Administration of growth hormone has been shown to result in a satisfactory elevation in IGF-1 levels and near-normalization of adult height and skeletal proportions [Rothenbühler et al 2010].

Individuals with a growth hormone deficiency often also have pituitary hypoplasia identified on head imaging; no other abnormalities in pituitary hormones or pubertal development have been detected [Turan 2014].

Three individuals (2 diagnosed clinically and 1 with a molecular diagnosis) have been reported with taller-than-expected stature including an adult Mexican male of 153 cm (-1.9 SD), an adult Mexican female of 150 cm (-0.6 SD), and a Chinese boy age eleven years with normal height (137cm; -0.9 SD) [Zheng et al 2013, Valdes-Flores et al 2014].

Craniofacial appearance. The characteristic facial features (midface retrusion due to hypoplastic maxilla and small jaw with an obtuse mandibular angle) can become more apparent with age but are often detectable in infants, along with large anterior and posterior fontanelles and open cranial sutures with frontal and parietal bossing [Appelman-Dijkstra & Papapoulos 2016]. Additional common facial features include a convex nasal ridge. Less common features include proptosis with blueish sclera, and cleft palate or high palate with a midline groove [Bizaoui et al 2019]. The apparent palatal midline groove is due to narrow palate with shallow vault and fallen palatal wings with prominent median palatal raphe in eight individuals studied by Otaify et al [2018].

Skeletal. The second most common feature (after short stature) is increased bone density (osteosclerosis), which occurs throughout the skeleton and is progressive. The medullary canals, while often narrowed, remain present with evidence of hematopoiesis.

More than 90% of reported individuals have short hands and feet with short digits and progressive acroosteolysis of the terminal phalanges of the fingers and toes. Short metatarsals and metacarpals have not been described.

Other common imaging features include non-pneumatized mastoids (80%) and delayed fusion of the skull sutures (67%). The clavicles may be dysplastic (25%) with acroosteolysis of the acromial end. Less common features include wormian bones (18%), mild scoliosis (12%), leg length discrepancy (8%), spondylolysis, spondylolisthesis, and narrow ilia. Coronal craniosynostosis has been reported in four individuals [Bertola et al

2010, Caracas et al 2012, Bizaoui et al 2019]. Chronic pain is reported in up to 60% of adults with pycnodysostosis, with onset usually in the third decade [Bizaoui et al 2019].

Bone fragility. Individuals with pycnodysostosis have an increased fracture rate with an average 0.2 fractures per year and an average age of first fracture around age ten years [Bizaoui et al 2019]. The youngest reported individual with a fracture was age ten months; This individual had two sibs who died, reportedly from the same disorder, suggesting a more severe phenotype or genotype; however, molecular studies were not performed [Caracas et al 2012].

Fracture healing is often delayed with incomplete remodeling. Surgical fixation is often complicated by narrow medullary canals, and sclerotic bone poses an increased risk of intraoperative iatrogenic fracture [Grewal et al 2019]. To date, no effective pharmaceutical treatments have been established for the bone fragility. Bisphosphonate therapy is contraindicated due to underlying osteoclast dysfunction in pycnodysostosis.

ENT. Stridor and laryngomalacia (20%) are not uncommon manifestations, and can lead to an early suspicion of pycnodysostosis. Obstructive sleep apnea (OSA) is frequently reported (>60%), and can be particularly severe in children with pycnodysostosis. Of those with OSA, 48% required noninvasive ventilation between ages five and ten years [Testani et al 2014, Bizaoui et al 2019]. Mild conductive hearing loss occurs in up to 50% of individuals [Bizaoui et al 2019].

Dental abnormalities include delayed eruption of the deciduous and permanent teeth, persistence of deciduous teeth (resulting in a double row of teeth), hypodontia, malocclusion, enamel hypoplasia, and increased caries [Turan 2014, Khoja et al 2015, Otaify et al 2018].

Nails are often flat, grooved, and dysplastic. The skin may be wrinkled over the dorsa of the fingers, secondary to shortened digits and acroosteolysis.

Neurologic. Intelligence is typically normal in affected individuals unless a brain malformation is present. Mild psychomotor difficulties have been reported in up to 30% of individuals [Bizaoui et al 2019]. Rarely reported neurologic abnormalities include Chiari malformation (1 individual), cerebral demyelination (3 individuals), and pyramidal syndrome (1 individual) [Soliman et al 2001, Stark & Savarirayan 2009, Bizaoui et al 2019].

Ocular abnormalities have been reported, including refractive disorders and strabismus. One individual was reported to have severe vision loss as a result of intracranial hypertension and papilledema [Bizaoui et al 2019].

Obesity has not been reported as a typical feature of pycnodysostosis; however, in a cohort of 27 individuals, 26% were found to be overweight [Bizaoui et al 2019].

Prognosis. Individuals with pycnodysostosis usually have normal life expectancy.

Other. Less commonly reported features include joint laxity, deformities of the chest shape (narrow chest, kyphosis, and lordosis), and hepatosplenomegaly. An ectopic pelvic kidney and unexplained pancytopenia have each been reported in one individual.

Genotype-Phenotype Correlations

No genotype-phenotype correlations for *CTSK* have been identified.

Nomenclature

The clinical features of pycnodysostosis (Greek: *pycnos* = dense; *dys* = defective; *osteon* = bone) were first described by Maroteaux and Lamy in 1962; hence, it is variably known as Maroteaux-Lamy syndrome [Xue et al 2011, Bizaoui et al 2019] (a term primarily used to refer to the unrelated condition, mucopolysaccharidosis type VI, caused by pathogenic variants in *ARSB*).

Pycnodysostosis is also sometimes referred to as "Toulouse-Lautrec syndrome," after the French artist Henri de Toulouse-Lautrec (1864-1901), who was retrospectively thought to have this condition based on several phenotypic features of the disorder including short stature, parental consanguinity, facial dysmorphism, frequent fractures, and large fontanels [Turan 2014] (see Figure 2).

In the 2023 revision of the Nosology of Genetic Skeletal Disorders [Unger et al 2023], pycnodysostosis is referred to as *CTSK*-related pyknodysostosis and is included in the osteopetrosis and related osteoclast disorders group.

Prevalence

Approximately 200 affected individuals have been reported in the medical literature. Pycnodysostosis is estimated to affect about 1-1.7 individuals per million.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *CTSK*.

Differential Diagnosis

It is critical to distinguish pycnodysostosis from other primary sclerosing conditions of bone (see Table 3) characterized by osteopetrosis, since early hematopoietic stem cell transplantation may be a therapeutic option in some forms of osteopetrosis, whereas it would be of no benefit in individuals with pycnodysostosis, which rarely presents with bone marrow insufficiency [Bizaoui et al 2019].

Figure 2. Portrait of the painter Henri de Toulouse-Lautrec, considered to have had pycnodysostosis 1898, by Edouard Vuillard (1868-1940)

Table 3. Disorders Characterized by Osteopetrosis in the Differential Diagnosis of Pycnodysostosis

Features of Differential Disorder Overlapping w/Pycnodysostosis	Gene(s)	Differential Disorder	MOI	Features of DIfferential Disorder Not Observed in Pycnodysostosis
Osteosclerosis, diffuse & focal sclerosis of varying severity, modeling defects at metaphysis, osteomyelitis, pathologic fractures, tooth eruption defects	*CA2*	Osteopetrosis w/renal tubular acidosis (OMIM 259730)	AR	Bone marrow impairment is rare; cranial nerve compression, DD, intracranial calcification, renal tubular acidosis
	CLCN7 *SNX10* *TCIRG1*	Osteopetrosis, severe neonatal or infantile forms (See *CLCN7*-Related Osteopetrosis.)	AR	Cranial nerve compression (II, VII, VIII), extramedullary hematopoiesis, hydrocephalus, hypocalcemia, pancytopenia
	CLCN7 *PLEKHM1* *TNFSF11*	Osteopetrosis, intermediate form [1] (See *CLCN7*-Related Osteopetrosis.)	AR	Anemia, extramedullary hematopoiesis, occasional optic nerve compression
	CLCN7	Osteopetrosis, late-onset form type 2	AD	Moderate hematologic failure, cranial nerve compression
	FERMT3	Osteopetrosis, moderate form w/defective leukocyte adhesion (OMIM 612840)	AR	Defective neutrophil adhesion to endothelial cells, hepatosplenomegaly, leukocytosis, mucosal bleeding

Table 3. continued from previous page.

Features of Differential Disorder Overlapping w/Pycnodysostosis	Gene(s)	Differential Disorder	MOI	Features of DIfferential Disorder Not Observed in Pycnodysostosis
	IKBKG	Osteopetrosis w/ectodermal dysplasia & immune defect (OMIM 300291)	XL	Anhidrotic ectodermal dysplasia, immunodeficiency (→ overwhelming infection), lymphedema
	OSTM1	Osteopetrosis, infantile form, w/nervous system involvement (OMIM 259720)	AR	Cranial nerve compression (II, VII, VIII), extramedullary hematopoiesis, hydrocephalus, hypocalcemia, pancytopenia, primary neurodegeneration incl retinal atrophy
	TNFRSF11A	Osteopetrosis, infantile form, osteoclast-poor w/ immunoglobulin deficiency (OMIM 612301)	AR	Anemia, hepatosplenomegaly, hypogammaglobulinemia, thrombocytopenia
Osteosclerosis, short stature, pathologic fractures	*CSF1R* *TNFRSF11A* *SLC29A3*	Dysosteosclerosis (OMIM 618476) [2]	AR	Brain abnormalities, progressive neurologic deterioration (specific to *CSF1R)*, patches of hyperpigmented skin, platyspondyly, radiolucency of widened submetaphyseal portions of tubular bones
Osteosclerosis localized mainly to metaphyses & epiphyseal margins of appendicular bones & metaphyseal equivalents of axial bones	*LRRK1*	Osteosclerotic metaphyseal dysplasia [3]	AR	DD; ↑ urinary pyridinoline & deoxypyridinoline excretion; ↑ serum alkaline phosphatase, aspartate aminotransferase & creatine kinase; seizures
Acroosteolysis, joint laxity, short stature, skull deformities	*NOTCH2*	Hajdu-Cheney syndrome (OMIM 102500)	AD	Mild ID (in a small proportion), osteoporosis
Clavicular dysplasia, delayed anterior fontanelle closure, delayed eruption of teeth, high arched palate, short stature	*RUNX2*	Cleidocranial dysplasia spectrum disorder	AD	Abnormally shaped pelvic & pubic bones, absent clavicles, thoracic deformations

AD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; ID = intellectual disability; MOI = mode of inheritance; XL = X-linked

1. Li et al [2019]

2. Campeau et al [2012], Xue et al [2019]

3. Iida et al [2016]

Secondary causes of bone sclerosis. Pycnodysostosis and other primary sclerosing conditions of bone caused by osteoclast dysfunction should be distinguished from the large number of secondary causes of bone sclerosis. Some alternative diagnoses to consider include fluorosis; beryllium, lead, and bismuth poisoning; myelofibrosis; Paget disease, sclerosing form (OMIM PS167250); and malignancies (lymphoma, osteoblastic cancer metastases) [Stark & Savarirayan 2009].

Management

There are no published treatment or surveillance guidelines for pycnodysostosis or standard guidelines on the best method or surgical intervention for fracture treatment in this condition. Management should emphasize multidisciplinary care and a considered approach to surgical intervention when appropriate.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with pycnodysostosis, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Pycnodysostosis

System/Concern	Evaluation	Comment
Constitutional	• Growth assessment • Eval for growth hormone & IGF-1 deficiency as early as practicable	Consider referral to nutritionist if needed for weight mgmt.
Musculoskeletal	Complete radiographic skeletal survey incl lateral spine radiographs	
	Consider skull CT.	If clinical concern re craniosynostosis
	Orthopedic consultation	Eval by specialist experienced in skeletal dysplasia if possible
ENT	• Eval for cleft palate or narrow nasal passages • Baseline audiology eval	
Respiratory	Polysomnography	For all affected persons as early as practicable
Dental	Baseline dental eval	
Neurologic	Consider MRI.	If neurologic symptoms or concern re Chiari malformation
Eyes	Baseline ophthalmologic exam	
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of pycnodysostosis 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.	

MOI = mode of inheritance
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 5. Treatment of Manifestations in Individuals with Pycnodysostosis

Manifestation/ Concern	Treatment	Considerations/Other
Growth hormone deficiency / Short stature	• Referral to endocrinologist • Consideration of growth hormone therapy	• Environmental or occupational modifications may be needed (e.g., step stools, lower desks). • Consultation w/OT may be beneficial.
Fractures	• Specialist orthopedic mgmt • Intervention may incl osteosynthesis or immobilization.	• At least 35% of persons require orthopedic intervention. • Complications incl non-union have been described following orthopedic surgery.
Scoliosis	Mgmt per orthopedist	

Table 5. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Craniofacial	Craniofacial/neurosurgical mgmt as required for cleft palate, craniosynostosis, maxillary & mandibular hypoplasia	May incl distraction osteogenesis of mandible &/or maxilla
Obstructive sleep apnea	• Referral to pulmonologist & sleep physician • Noninvasive ventilation	Be aware of nasal obstruction due to small/narrowed airways.
Requirement for anesthesia	Consultation w/expert anesthetist prior to any planned surgery	May be at risk for difficult intubation
Dental	• Maintenance of oral hygiene • Regular dental care to prevent oral complications • May benefit from orthodontic input	At ↑ risk for post-extraction osteomyelitis due to ↑ bone density
Vision concerns	Standard mgmt per ophthalmologist	

OT = occupational therapist

Surveillance

Table 6. Recommended Surveillance for Individuals with Pycnodysostosis

System/Concern	Evaluation	Frequency
General health	Physical exam	Annually or as indicated
Musculoskeletal	• Examine for scoliosis & asymmetry. • Assess frequency of fractures.	Annually
Respiratory	Polysomnography	Every 2 yrs
Dental	Eval w/specialist dentist	Annually
Vision	Ophthalmology exam	
Obesity	Weight assessment ± dietitian review	Annually or as indicated
Psychological	Specific attention to any issues when taking history & during physical exam	

Bizaoui et al [2019]

Agents/Circumstances to Avoid

In the case of general anesthesia, consideration should be given to the possibility of difficult intubation prior to scheduling anesthesia.

Bisphosphonate therapy is contraindicated due to underlying osteoclast dysfunction in pycnodysostosis.

Evaluation of Relatives at Risk

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

Pregnancy Management

In individuals with a small pelvis, delivery by cæsarean section should be considered. However, each individual should be assessed by an obstetrician and anesthetist familiar with skeletal dysplasia [Savarirayan et al 2018].

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

Pycnodysostosis is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., presumed to be carriers of one *CTSK* pathogenic variant based on family history).
- If a molecular diagnosis has been established in the proband, molecular genetic testing of the parents is recommended to confirm that both parents are heterozygous for a *CTSK* pathogenic variant and to allow reliable recurrence risk assessment. (*De novo* variants are known to occur at a low but appreciable rate in autosomal recessive disorders [Jónsson et al 2017].)
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for a *CTSK* pathogenic variant, each sib of an affected individual has at conception 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.
- Intrafamilial clinical variability may be observed in sibs who inherit biallelic *CTSK* pathogenic variants.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with pycnodysostosis are obligate heterozygotes (carriers) for a pathogenic variant in *CTSK*.

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

Carrier Detection

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

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, 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 are at risk of being carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the *CTSK* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing 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.

- **Human Growth Foundation**
  www.hgfound.org
- **MAGIC Foundation**
  Phone: 800-362-4423
  Email: contactus@magicfoundation.org
  www.magicfoundation.org

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. Pycnodysostosis: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
CTSK	1q21.3	Cathepsin K	CTSK database	CTSK	CTSK

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 Pycnodysostosis (View All in OMIM)

265800	PYCNODYSOSTOSIS
601105	CATHEPSIN K; CTSK

Molecular Pathogenesis

CTSK encodes cathepskin K, a lysosomal cysteine protease that is involved in bone remodeling and highly expressed in osteoclasts; it has also been detected in macrophages and bone barrow-derived dendritic cells, but rarely in splenic T cells. In pycnodysostosis, osteoclast numbers are normal as are their ruffled borders and clear zones, but the region of demineralized bone surrounding individual osteoclasts is increased. The collagen bone matrix is dissolved by two groups of enzymes, the matrix metalloproteinases and lysosomal cathepsins. Cathepsin K in particular has been identified as a key enzyme. Cathepsin K is synthesized as a pro-enzyme before being transported to lysosomes, where it is cleaved to produce the active enzyme. Cathepsin K is involved in the degradation of bone matrix proteins, type I and type II collagen, osteopontin, and osteonectin at a low pH [Stark & Savarirayan 2009, Turan 2014, Appelman-Dijkstra & Papapoulos 2016]; in pycnodysostosis, this degradation is decreased, leading to increased bone density.

Mechanism of disease causation. Loss of function

***CTSK*-specific laboratory technical considerations**

- Mutational hot spots are residues Arg241 and Ala277 [Xue et al 2011, Turan 2014, Bizaoui et al 2019].
- Approximately 60 *CTSK* pathogenic variants – encoding the mature domain (69%), the proregion (24%), and the preregion (signal sequence) (6%) – have been reported.
- Judicious primer selection will facilitate detection of the intron 7 insertion (see Table 1).

Chapter Notes

Revision History

- 6 April 2023 (sw) Revision: "*CTSK*-Related Pyknodysostosis" added as a synonym; Nosology of Genetic Skeletal Disorders: 2023 Revision [Unger et al 2023] added to Nomenclature
- 5 November 2020 (sw) Review posted live
- 17 August 2020 (rs) Original submission

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