ISSN: 2754-4931

Journal of Gastroenterology & Hepatology Reports

SCIENTIFIC Research and Community

Review Article

Open Access

The Role of CTSK Gene Mutation in Pycnodysostosis Syndrome

Shahin Asadi

Medical Genetics Director of the Division of Medical Genetics and Molecular Pathology Research. Division of Medical Genetics and Molecular Pathology Research, Center of Complex Disease, USA

ABSTRACT

Pycnodysostosis is a rare genetic disorder characterized by distinctive facial features and skeletal abnormalities. Affected individuals may have osteosclerosis, a condition characterized by abnormal hardening and increased bone density. The abnormalities in affected individuals' bones cause them to become brittle and weak. Affected individuals are prone to frequent fractures. Affected individuals may fail to grow and be shorter than expected (short stature). Intelligence is not affected, and the disorder is not thought to be life-threatening. The severity of the disorder, including frequency of fractures, final adult height, and specific symptoms, can vary greatly among affected individuals. Although researchers have been able to establish a clear syndrome with characteristic or "core" symptoms, much about the disorder is not fully understood. Several factors, including the small number of cases identified, the lack of large clinical studies, and the possibility that other genes may influence the disorder, prevent doctors from developing a complete picture of the symptoms and associated prognosis. Pycnodysostosis is caused by a change (mutation) in the cathepsin K (CTSK) gene, which is located on the long arm of chromosome 1 at 1q21.3.

***Corresponding author**

Shahin Asadi, Medical Genetics Director of the Division of Medical Genetics and Molecular Pathology Research. Division of Medical Genetics and Molecular Pathology Research, Center of Complex Disease, USA.

Received: October 23, 2026; **Accepted:** October 27, 2026; **Published:** November 04, 2026

Keywords: Pycnodysostosis, CTSK Gene, Genetic Mutation, Cathepsin K

Pycnodysostosis Syndrome Overview

Pycnodysostosis is a rare genetic disorder characterized by distinctive facial features and skeletal abnormalities. Affected individuals may have osteosclerosis, a condition characterized by abnormal hardening and increased bone density. The abnormalities in affected individuals' bones cause them to become brittle and weak. Affected individuals are prone to frequent fractures. Affected individuals may fail to grow and be shorter than expected (short stature). Intelligence is not affected, and the disorder is not thought to be life-threatening. The severity of the disorder, including frequency of fractures, final adult height, and specific symptoms, can vary greatly among affected individuals. Pycnodysostosis is caused by changes (mutations) in the cathepsin K (CTSK) gene and is inherited in an autosomal recessive manner. Pycnodysostosis belongs to a larger group of diseases known as lysosomal storage disorders [1]. Lysosomes are membrane-bound compartments inside cells. They contain enzymes that break down large molecules such as proteins, carbohydrates, and fats into their constituent components. Low levels or lack of activity of an enzyme called cathepsin K leads to the abnormal accumulation (storage) of toxic substances in lysosomes. Pycnodysostosis is similar to osteopetrosis and is sometimes discussed together in medical literature. Osteopetrosis is a disorder characterized by abnormally dense bones that are brittle and prone to fracture. Osteopetrosis is sometimes associated with skeletal abnormalities.

Clinical Signs and Symptoms of Pycnodysostosis Syndrome

Although researchers have been able to establish a clear syndrome with characteristic or "core" symptoms, much about the disorder is not fully understood. Several factors, including the small number of cases identified, the lack of large clinical studies, and the possibility that other genes may influence the disorder, prevent doctors from developing a complete picture of the symptoms and associated prognosis. Therefore, it is important to note that affected individuals may not have all of the symptoms listed below. Parents should talk to their child's doctor and medical team about their specific case, associated symptoms, and overall prognosis. Infants with pycnodysostosis may experience delayed closure of the cranial sutures. A baby's skull has seven bones and several joints called sutures. The sutures are made of strong, elastic fibrous tissue that separates the bones from each other.The sutures meet (cross) at two points on the skull called fontanelles, which are more commonly known as the baby's "soft spots." The seven bones of a baby's skull usually fuse together by about age two or later. In babies with pycnodysostosis, the sutures take longer to fuse together, which can affect proper skull development. The skull is often larger than normal [1,2].

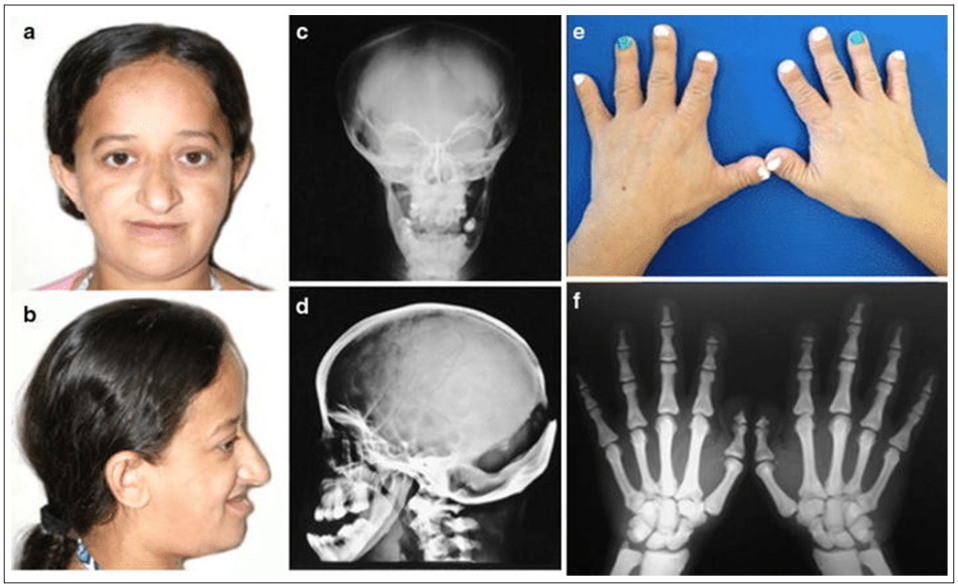

Figure 1: Images of Disorders Associated with Pycnodysostosis Syndrome

Distinctive facial features are common and include an unusually prominent forehead (buzzing forehead), a pointed nose, a high-arched roof of the mouth (palate), prominent eyes with a blue discoloration of the whites of the eyes (bluish sclera), and a small jaw due to underdevelopment of the jaw bones (maxillary and mandibular hypoplasia). Affected individuals may have a variety of dental problems, including delayed eruption of primary teeth and subsequent retention of these teeth after they have erupted. Some individuals may lose teeth because the teeth do not grow (hypodontia) [3].



Figure 2: Images of Patients with Pycnodysostosis Syndrome with Distinctive Facial Features

People with pycnodysostosis may have an abnormality of the collarbone (clavicular dysplasia) and bone breakdown (osteolysis), especially of the outermost bones of the fingers and toes (acroosteolysis). The fingers may be small and dry, and the nails may be absent or abnormally small. People with pycnodysostosis experience abnormal hardening and thickening of the bone (osteosclerosis). Osteosclerosis causes the bone to become brittle, and affected people are prone to repeated fractures with minimal or no impact (spontaneous). The legs are commonly affected by fractures. Some people may have an abnormal curvature of the spine, such as having an S-shaped spine (scoliosis). Back pain from stress fractures in the lower bones of the spine (vertebrae) can occur.There

may be abnormalities in the development of the chest that can cause breathing problems. Some people may snore, while others may have sleep apnea. Sleep apnea is a condition in which a person momentarily stops breathing while sleeping. Sometimes, sleep apnea can be severe [4].



Figure 3: Radiological Images of Various Disorders Associated with Pycnodysostosis Syndrome

Some people with pycnodysostosis have a deficiency of growth hormone and a deficiency of another hormone called insulin-like growth factor 1 (IGF-1), which is also present in childhood. Affected people are shorter than expected as adults (short stature). Affected people's arms and legs are usually abnormally short. In rare cases, pycnodysostosis may occur with other symptoms such as loose joints, underdeveloped (hypoplastic) sinuses, enlarged liver and spleen (hepatosplenomegaly), and underdeveloped pituitary gland [5].

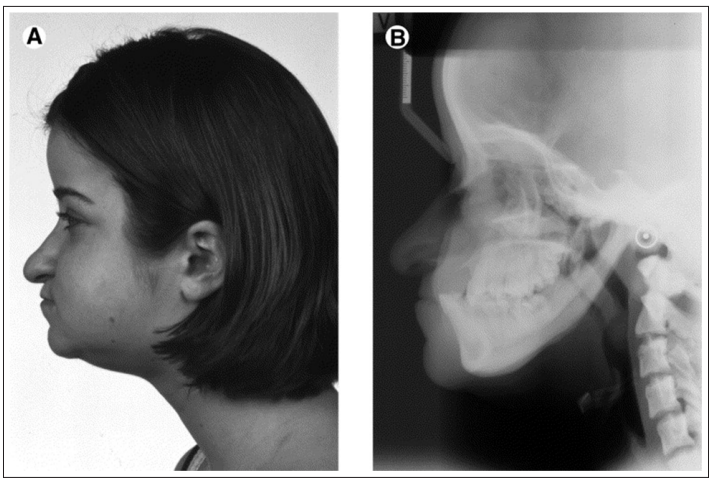

Figure 4: Image of a female child with pycnodysostosis syndrome with prominent facial features

Etiology of Pycnodysostosis Syndrome

Pycnodysostosis is caused by a change (mutation) in the cathepsin K (CTSK) gene, which is located on the long arm of chromosome 1 at 1q21.3. Genes provide instructions for making proteins that play an important role in many body functions. When a mutation occurs in a gene, the protein product may be defective, ineffective, or absent. Depending on the function of the specific protein, this can affect many organs in the body [6].

Pycnodysostosis is inherited in an autosomal recessive manner. Most genetic diseases are determined by the status of two copies of a gene, one from the father and one from the mother. Recessive genetic disorders occur when a person inherits two copies of an abnormal gene for a trait, one from each parent. If a person inherits one normal gene and one disease gene, the person will be a carrier of the disease but will usually not show symptoms. The risk of both carrier parents passing on both altered genes and having an affected child is 25 percent in each pregnancy. The risk of having a child who is a carrier like the parent is 50 percent in each pregnancy. The chance of a child receiving normal genes from both parents is 25 percent. This risk is the same for men and women.

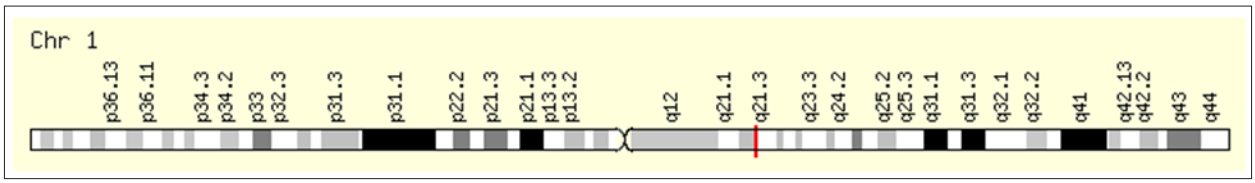

Figure 5: Schematic of the physical map of chromosome number 1, where the CTSK gene is located on the long arm of this chromosome as 1q21.3

In certain populations, pycnodysostosis has been found in families where parents are closely related. Parents who are closely related (familial) are more likely than parents who are not related to each other to both have the same abnormal gene, which increases the risk of having a child with a recessive genetic disorder. The CTSK gene produces an enzyme called cathepsin K. This enzyme is a lysosomal enzyme that breaks down certain substances in the body, including bone matrix proteins, certain types of collagen, and other substances. This enzyme is found primarily in osteoclasts, which are bone cells that resorb bone tissue during growth and repair. Osteoclasts essentially break down bone, a natural process called resorption. Bone is a dynamic system that is constantly undergoing remodeling, resorption, and formation. Osteolysis refers to the breakdown of bone followed by the formation of new bone. In pycnodysostosis, some of these substances are not completely broken down and accumulate in the lysosomes of the cell. When enough of these substances accumulate, they become toxic to the damaged cells and tissues of the body [7].

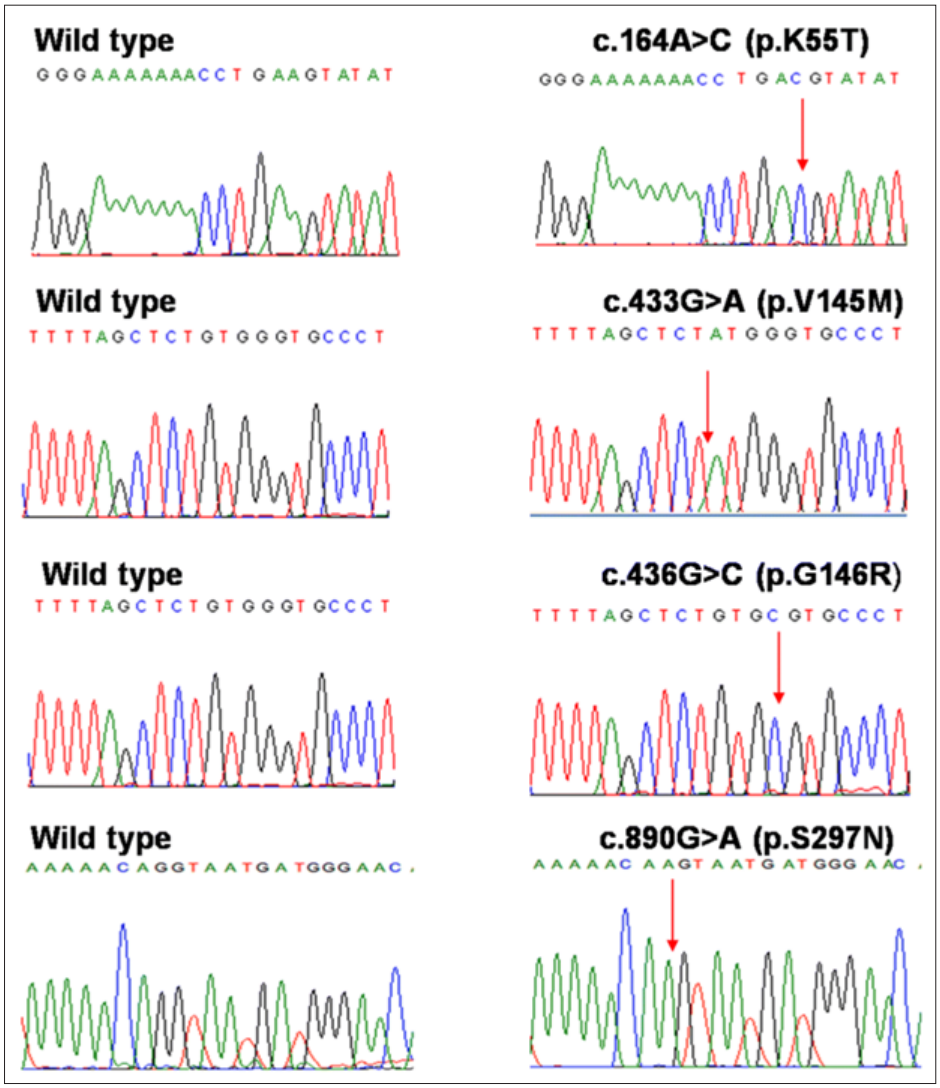

Figure 6: Schematic of a Nucleotide Mutation Example in the CTSK Gene

Frequency of Pycnodysostosis Syndrome

Pycnodysostosis is a very rare disorder that affects both men and women. About 200 people have been reported in the medical literature with the disorder. It is estimated to affect about 1 in 1.7 million people in the general population. Pycnodysostosis may be undiagnosed or misdiagnosed, making it difficult to determine the true frequency in the general population [8].

Disorders Associated with Pycnodysostosis Syndrome

The symptoms of the following disorders can be similar to those of pycnodysostosis. Comparisons may be useful for differential diagnosis: Osteopetrosis may be inherited as a dominant or recessive trait and is characterized by increased bone density, brittle bones, and, in some individuals, skeletal abnormalities. Although symptoms may not be apparent at first in people with mild forms of the disorder, minor trauma may cause a bone to break due to the bone abnormalities. There are three main types of osteopetrosis: the malignant neonatal form, the intermediate form, and the adult form. The adult form is milder than the other forms and may not be diagnosed until adolescence or adulthood when symptoms first appear.The mild form, found in children under ten years of age, is more severe than the adult form but less severe than the neonatal malignant form. The neonatal malignant form is present at birth and often shortens life expectancy. Specific forms of osteopetrosis are caused by mutations in specific genes.

Cleidocranial dysplasia is a rare skeletal dysplasia characterized by short stature, distinctive facial features, and narrow, sloping shoulders caused by a defect or absence of the collarbone (clavicle). The main symptoms may include premature closure of the soft spot on the head (coronal), delayed closure of the space between the skull bones (fontanel), abnormally narrow pelvic and pubic bones, and deformity of the thorax (chest region). Delayed teething, short stature, high arched palate, wide hip joint, nonunion of the mandibular joints, and fingers that are of irregular length may also be present. Cleidocranial dysplasia is inherited as an autosomal dominant genetic trait.

Osteogenesis imperfecta (OI) is a group of rare disorders affecting connective tissue, characterized by extremely fragile bones that break easily—often without an apparent cause. The specific symptoms and physical findings associated with OI vary widely from case to case. The severity of the condition also varies significantly, even among members of the same family; OI can range from a mild disorder to one resulting in severe complications. Four main types of OI have been identified. Type I is the most common and mildest form, while Type II is the most severe. In most cases, the various forms of osteogenesis imperfecta are inherited as autosomal dominant traits.

Hajdu-Cheney syndrome (HCS) is a rare genetic connective tissue disorder. Only about 50 cases have been reported in the medical literature. Bone resorption (osteolysis)-specifically of the outermost bones of the fingers and toes (acro-osteolysis)-is a hallmark feature of HCS. Additionally, affected individuals often exhibit craniofacial abnormalities, short stature, abnormal joint laxity, reduced bone mass (osteoporosis), and other signs or symptoms. Most affected individuals have normal intellectual development, though a small proportion exhibit mild intellectual disability. Hajdu-Cheney syndrome is caused by mutations in the *NOTCH2* Gene; these mutations are inherited in an autosomal dominant pattern.

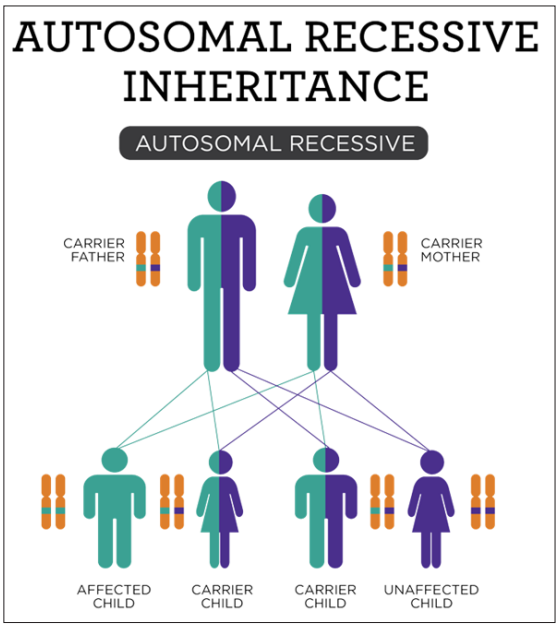

Figure 7: Schematic of the Autosomal Recessive Inheritance Pattern Followed by Pycnodysostosis Syndrome

Diagnosis of Pycnodysostosis

The diagnosis of pycnodysostosis is based on the identification of characteristic symptoms, a detailed patient and family history, a comprehensive clinical evaluation, and X-ray studies. X-ray imaging can reveal many of the characteristic skeletal abnormalities associated with this disorder. Molecular genetic testing can confirm the diagnosis of pycnodysostosis; it can identify mutations in the *CTSK* gene responsible for the disorder, though it is available only as a diagnostic service through specialized laboratories [9].

Treatment Pathways for Pycnodysostosis Syndrome

Treatment for pycnodysostosis is directed at the specific symptoms that are evident in an individual. Treatment may require the coordinated efforts of a team of specialists. Pediatricians, specialists who diagnose and treat bone disorders (orthopedists), orthopedic surgeons, specialists who diagnose and treat hormone disorders (endocrinologists), dental specialists, and other health care professionals may need to plan a systematic and comprehensive treatment plan for the affected child. Genetic counseling may be helpful for affected individuals and their families. Psychosocial support for the entire family is also essential. There is no standard treatment protocol or guideline for affected individuals. Because of the rarity of the condition, there are no treatment trials that have been tested on large groups of patients.Various treatments have been reported in the medical literature as part of single case reports or small patient series [10].

Therapeutic trials to determine the long-term safety and efficacy of specific medications and treatments for individuals with pycnodysostosis would be highly beneficial. Individuals with pycnodysostosis require orthopedic care in the event of a fracture; however, there are no standard guidelines regarding the optimal surgical approach or intervention for treating fractures associated with this condition. Specialized dental care is necessary, and craniofacial surgery may be indicated.

Pycnodysostosis can potentially complicate the administration of anesthesia in some individuals due to abnormalities affecting the jaw and the roof of the mouth (palate). Affected individuals should undergo an evaluation prior to any procedure requiring anesthesia.

Investigational Therapies

Some children with pycnodysostosis have been treated with growth hormone, as short stature is a common feature of this disorder. Preliminary results have shown positive outcomes regarding the final adult height of affected individuals. Researchers are studying specific drugs known as enzyme inhibitors to treat pycnodysostosis and similar bone disorders. These drugs work by inhibiting the activity of a specific enzyme in the body, thereby preventing the negative or harmful effects that such enzymes might cause due to an underlying genetic abnormality [11].

Discussion

People with pycnodysostosis may have an abnormality of the collarbone (clavicular dysplasia) and bone breakdown (osteolysis), especially of the outermost bones of the fingers and toes (acroosteolysis). The fingers may be small and dry, and the nails may be absent or abnormally small. People with pycnodysostosis experience abnormal hardening and thickening of the bone (osteosclerosis). Osteosclerosis causes the bone to become brittle, and affected people are prone to repeated fractures with minimal or no impact (spontaneous). The legs are commonly affected by fractures. Some people may have an abnormal curvature of the spine, such as having an S-shaped spine (scoliosis). In certain populations, pycnodysostosis has been found in families where parents are closely related. Parents who are closely related (familial) are more likely than parents who are not related to each other to both have the same abnormal gene, which increases the risk of having a child with a recessive genetic disorder. The CTSK gene produces an enzyme called cathepsin K. This enzyme is a lysosomal enzyme that breaks down certain substances in the body, including bone matrix proteins, certain types of collagen, and other substances. This enzyme is found primarily in osteoclasts, which are bone cells that resorb bone tissue during growth and repair. Osteoclasts essentially break down bone, a natural process called resorption. Treatment for pycnodysostosis is directed at the specific symptoms that are evident in an individual. Treatment may require the coordinated efforts of a team of specialists. Pediatricians, specialists who diagnose and treat bone disorders (orthopedists), orthopedic surgeons, specialists who diagnose and treat hormone disorders (endocrinologists), dental specialists, and other health care professionals may need to plan a systematic and comprehensive treatment plan for the affected child. Genetic counseling may be helpful for affected individuals and their families.

References

1. Asadi S (2017-2026) Medical Genetic Pathology Books. Amidi Publications 26.
2. Whyte MP, Jameson JL, De Groot LJ (2016) Hereditary Disorders of the Skeleton. In: Endocrinology: Adult and Pediatric. 7th Eds. Elsevier Saunders, Philadelphia 2:1173-1183.
3. Mankin HJ, Mankin KP (2013) A Rare Genetic Hyperostotic Diseases. In: Rare Genetic Disorders That Affect the Skeleton. Eds Pycnodysostosis Author House LLC, Bloomington, 78-83.
4. Appelman-Dijkstra NM, Papapoulos SE (2016) From disease to treatment: from rare skeletal disorders to treatments for osteoporosis. Endocrine 52: 414-426.
5. Ketterer S, Gomez-Auli A, Hillebrand LE, Agnese Petrera, Anett Ketscher, et al. (2016) Inherited diseases caused by mutations in cathepsin protease genes. FEBS J 284 https://www.researchgate.net/publication/311505589_Inherited_diseases_caused_by_mutations_in_cathepsin_protease_genes.
6. Valdes-Flores M, Hidalgo-Bravo A, Casas-Avila L, Carmen Chima-Galan, Eric J Hazan-Lasri, et al. (2014) Molecular and clinical analysis in a series of patients with pyknodystosis reveals some uncommon phenotypic findings. Int J Clin Exp Med 7: 3915-3923.
7. Arman A, Bereket A, Coker A, Pelin Özlem Simşek Kiper, Tülay Güran, et al. (2014) Cathepsin K analysis in a pycnodysostosis cohort: demographic, genotypic and phenotypic features. Orphanet J Rare Dis 9: 60.
8. Turan S (2014) Current research on pycnodysostosis. Intractable Rare Dis Res 3: 91-93.
9. Le Merrer M (2016) Pycnodysostosis. Orphanet Encyclopedia, September 2003. Available at: http://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=763.
10. McKusick VA (2016) ed. Online Mendelian Inheritance in Man (OMIM). Baltimore MD: The Johns Hopkins University; Available at: http://www.omim.org/entry/265800.
11. Girbal I, Nunes T, Medeira A, Bandeira T (2013) Pycnodysostosis with novel gene mutation and severe obstructive sleep apnoea: management of a complex case. BMJ Case Rep 2013: bcr2013200590.

Copyright: ©2026 Shahin Asadi. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.