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NLM Citation: Skefos CM, Waguespack SG, Perrier ND, et al. *CDC73*-Related Disorders. 2008 Dec 31 [Updated 2023 Sep 21]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

CDC73-Related Disorders

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Created: December 31, 2008; Updated: September 21, 2023.

Summary

Clinical characteristics

The spectrum of *CDC73*-related disorders includes the following phenotypes:

- *Hyperparathyroidism-jaw tumor (HPT-JT) syndrome.* Primary hyperparathyroidism occurs in a vast majority of affected individuals, with onset typically in late adolescence or early adulthood. HPT-JT syndrome-associated primary hyperparathyroidism is usually caused by a single parathyroid adenoma. In at least 10%-15% of individuals, primary hyperparathyroidism is caused by parathyroid carcinoma. Ossifying fibromas of the mandible or maxilla, also known as cementifying fibromas and cemento-ossifying fibromas, occur in 30%-40% of individuals with HPT-JT syndrome. Although benign, these tumors can be locally aggressive and may continue to enlarge if not treated. Up to 20% of individuals with HPT-JT syndrome have kidney lesions, most commonly cysts; renal hamartomas and (more rarely) Wilms tumor have also been reported. Benign uterine tumors appear to be common in women with HPT-JT syndrome; uterine malignancies have also been reported.
- *Parathyroid carcinoma.* Most parathyroid carcinomas are functional, resulting in primary hyperparathyroidism and a high serum calcium level; however, nonfunctioning parathyroid carcinomas are also rarely described in individuals with a *CDC73*-related disorder. A germline *CDC73* pathogenic variant has been identified in 20%-29% of individuals with parathyroid carcinoma without a known family history of *CDC73*-related conditions.
- *Familial isolated hyperparathyroidism (FIHP).* Characterized by primary hyperparathyroidism without other associated syndromic features. Individuals with *CDC73*-related FIHP tend to have a more severe clinical presentation and younger age of onset than individuals with FIHP in whom a *CDC73* pathogenic variant has not been identified.

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Diagnosis/testing

The diagnosis is established in a proband with a germline heterozygous *CDC73* pathogenic variant identified by molecular genetic testing.

Management

Treatment of manifestations: Parathyroidectomy is the preferred treatment for primary hyperparathyroidism, especially in individuals with HPT-JT syndrome. If parathyroid carcinoma is clinically suspected, an en bloc resection of the parathyroid gland with surrounding adherent tissue and the ipsilateral thyroid lobe should be considered. Intravenous fluids and a bisphosphonate infusion for severe or symptomatic hypercalcemia. Cinacalcet hydrochloride may be used for hypercalcemia in those with inoperable parathyroid adenoma or carcinoma. Calcium and vitamin D as needed for postoperative hypoparathyroidism. Jaw tumors should be treated surgically as indicated by size, location, and symptoms; the treatment of choice is complete resection, which may not be possible in all individuals. Treatment of kidney and uterine manifestations should be managed per nephrologist and gynecologist recommendations, respectively.

Surveillance: Serum calcium, intact parathyroid hormone (iPTH), and 25-hydroxyvitamin D levels annually starting by age ten years. Periodic neck ultrasound as indicated based on serum calcium and iPTH levels. Dental examinations every six months; panoramic jaw x-ray with neck shielding at least every five years. Renal ultrasound at least every five years. Annual serum creatinine in those with kidney cysts. For women of reproductive age, annual gynecologic examination for uterine tumors with pelvic ultrasound every five years.

Agents/circumstances to avoid: Dehydration; radiation exposure to the neck; biopsy of extrathyroidal tissue in the neck, which increases the risk of seeding of parathyroid tissue.

Evaluation of relatives at risk: Molecular genetic testing for the *CDC73* germline pathogenic variant identified in the proband should be offered to at-risk relatives by age ten years in order to identify those who would benefit from initiation of surveillance and treatment.

Pregnancy management: Observation for mild asymptomatic hypercalcemia; minimally invasive resection of the parathyroid tumor (preferably in the second trimester) is required for symptomatic primary hyperparathyroidism or evidence of adverse effects on the fetus; management in conjunction with a maternal-fetal medicine specialist.

Genetic counseling

CDC73-related disorders are inherited in an autosomal dominant manner. An individual with a *CDC73*-related disorder may have inherited a *CDC73* pathogenic variant from an affected parent or have the disorder as the result of a *de novo* pathogenic variant. The proportion of individuals with a *de novo* pathogenic variant is unknown. Each child of an individual with a *CDC73*-related disorder has a 50% chance of inheriting the pathogenic variant. Once the *CDC73* pathogenic variant has been identified in an affected family member, predictive testing for at-risk relatives and prenatal and preimplantation genetic testing are possible.

GeneReview Scope

CDC73-Related Disorders: Included Phenotypes [1]
• Hyperparathyroidism-jaw tumor syndrome • Parathyroid carcinoma • Familial isolated hyperparathyroidism

For synonyms and outdated names see Nomenclature.

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

Diagnosis

Suggestive Findings

CDC73-related disorders **should be suspected** in individuals with any of the following clinical, family history, laboratory, radiographic, and/or histopathology features.

Clinical features

- Primary hyperparathyroidism and ossifying fibroma(s) of the jaw
- Primary hyperparathyroidism with age of onset <45 years and cystic, atypical, and/or malignant parathyroid histology
- Childhood- or adolescent-onset primary hyperparathyroidism
- Childhood-onset ossifying fibroma(s) of the maxilla or mandible. Note: The frequency of *CDC73* pathogenic variants in individuals with apparently sporadic ossifying fibromas of the jaw appears low [Chen et al 2016]; however, this has not been extensively studied (see Clinical Characteristics).

Family history of primary hyperparathyroidism or other hyperparathyroidism-jaw tumor (HPT-JT)-associated manifestations (such as renal cysts, uterine fibromas, or Wilms tumor) is consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations). Absence of a known family history does not preclude the diagnosis.

Laboratory features

- Elevated total calcium corrected for albumin (preferred) or ionized calcium
- Elevated or inappropriately normal intact parathyroid hormone (iPTH)
- Somatic *CDC73* pathogenic variant identified in a parathyroid carcinoma, benign parathyroid tumor, or renal tumor

Radiographic features of ossifying fibromas. Panoramic and/or mandibular x-ray series reveals mandibular or maxillary well-circumscribed lesions that are often, but not always, radiolucent and expand the underlying bone. Note: (1) Sporadic mandibular ossifying fibromas tend to appear as mixed radiolucent/radiopaque lesions [Aldred et al 2006]. (2) The panoramic x-ray interpretation must be correlated with clinical and, in some individuals, tissue examination. X-rays of this type should be interpreted by someone familiar with the variables of anatomy and nuances of the panoramic x-ray.

Histopathologic features of resected parathyroid lesions

- Parathyroid carcinoma
- Atypical parathyroid adenoma
- Parathyroid adenoma with or without cystic features
- Absence of nuclear parafibromin staining as demonstrated by immunohistochemistry

Establishing the Diagnosis

The diagnosis of a *CDC73*-related disorder is established in a proband with a heterozygous germline *CDC73* pathogenic (or likely pathogenic) variant identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include likely pathogenic variants. (2) Identification of a heterozygous *CDC73* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include **single-gene testing** and use of a **multigene panel**.

- **Single-gene testing.** Concurrent *CDC73* sequence analysis and deletion/duplication analysis may be considered using next-generation sequencing or a tiered testing approach with sequence analysis of *CDC73* first, followed by gene-targeted deletion/duplication analysis if no pathogenic variant is found by sequence analysis.

  Note: Targeted analysis for *CDC73* pathogenic variant c.766_767delGT (p.Val256LysfsTer10) can be performed first in individuals of Roma ancestry from Portugal, if available (see Table 6).

- **A multigene panel** that includes *CDC73* and other genes of interest (see Differential Diagnosis) should be considered 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) See De Sousa et al [2022] for a discussion of multigene panel testing for hereditary hyperparathyroidism. (2) 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. (3) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (4) 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. (5) 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.

Table 1. Molecular Genetic Testing Used in *CDC73*-Related Disorders

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
CDC73	Sequence analysis [3]	>70% [4]
	Gene-targeted deletion/duplication analysis [5]	≤30% [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. Iacobone et al [2009], Newey et al [2010], Panicker et al [2010], Rekik et al [2010], Wang et al [2010], Cavaco et al [2011], Frank-Raue et al [2011], Pichardo-Lowden et al [2011], Siu et al [2011], Starker et al [2012], Bricaire et al [2013], Kutcher et al [2013], Tora et al [2023]
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. Bricaire et al [2013], Tora et al [2023], and data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]

Clinical Characteristics

Clinical Description

The spectrum of *CDC73*-related disorders includes the following overlapping phenotypes:

- Hyperparathyroidism-jaw tumor (HPT-JT) syndrome
- Parathyroid carcinoma
- Familial isolated hyperparathyroidism (FIHP)

HPT-JT Syndrome

Primary hyperparathyroidism. Individuals with primary hyperparathyroidism may be asymptomatic or may present with nephrolithiasis, reduced bone mass, fracture, fatigue, muscle weakness, bone or joint pain, and/or constipation.

Primary hyperparathyroidism occurs in up to 95% of individuals with HPT-JT syndrome. The onset is typically in late adolescence or early adulthood and is often the first feature of HPT-JT syndrome [Figueiredo et al 2023, Tora et al 2023]. The youngest reported individual with hypercalcemia was age seven years [Pichardo-Lowden et al 2011]. The median age of diagnosis reported in more recent studies has ranged from 23 years to 38 years [Bricaire et al 2013, van der Tuin et al 2017, Iacobone et al 2020, Tora et al 2023].

Penetrance increases with age: in a Dutch population the penetrance of primary hyperparathyroidism in individuals with HPT-JT syndrome at ages 25, 50, and 70 years was reported to be 8%, 53%, and 75%, respectively [van der Tuin et al 2017], while an Italian study of five kindreds showed 68% penetrance in those older than age 30 years [Iacobone et al 2020].

In most individuals with HPT-JT syndrome, hyperparathyroidism is caused by a single benign parathyroid adenoma, which is often cystic or has atypical histologic features. Pathology of parafibromin-deficient parathyroid tumors may show distinct morphology, including microcystic features, sheet-like morphology, eosinophilic cytoplasm, nuclear enlargement with coarse chromatin, prominent vascularity, and a thickened capsule [Gill et al 2019, Erickson et al 2022].

Many families segregating a *CDC73* pathogenic variant have at least one affected member with a cystic, malignant, and/or atypical parathyroid tumor. A second parathyroid tumor may occur synchronously or metachronously months to decades after appearance of the first tumor. Analysis of 20 individuals showed single-gland disease in 95%, with 23.5% of these individuals experiencing metachronous recurrence in a second gland; the disease-free interval ranged from five to 27 years [Iacobone et al 2020]. Similarly, a series of 20 individuals showed 25% rate of recurrence of primary hyperparathyroidism [Figueiredo et al 2023].

In at least 10%-15% of individuals with HPT-JT syndrome, primary hyperparathyroidism is caused by parathyroid carcinoma. Two recent studies of individuals with HPT-JT syndrome and primary hyperparathyroidism identified that 31% (17/55) and 23.5% (4/17) had parathyroid carcinoma [Figueiredo et al 2023, Tora et al 2023]. The earliest reported diagnosis of parathyroid carcinoma was age eight years in a girl with pulmonary metastases [Davidson et al 2016]. However, onset may be delayed until the sixth decade [van der Tuin et al 2017, Iacobone et al 2020]. Nonfunctioning parathyroid carcinomas have also been reported [Guarnieri et al 2006].

Jaw tumors. Ossifying fibromas of the mandible or maxilla, also known as cementifying fibromas and cemento-ossifying fibromas, occur in 11%-40% of individuals with HPT-JT syndrome [Bricaire et al 2013, Torresan & Iacobone 2019, Tora et al 2023]. Some ossifying fibromas present as an enlarging visible or palpable mass, whereas others are only detected on dental x-ray. Although benign, these tumors can disrupt normal dentition, impair breathing, and be of significant cosmetic concern. Tumors may occasionally be bilateral/multifocal and may recur. The tumors are considered aggressive and continue to enlarge if not treated.

The frequency of *CDC73* pathogenic variants in individuals with ossifying fibromas of the jaw has not been extensively studied. Pimenta et al [2006] found a heterozygous germline pathogenic variant in one of three individuals with an ossifying fibroma of the mandible and no family history, but not in an individual with a juvenile ossifying fibroma of the mandible without a family history. Haag et al [2008] and Kutcher et al [2013] reported individuals with heterozygous germline *CDC73* pathogenic variants who had an ossifying fibroma and later developed primary hyperparathyroidism. Chen et al [2016] reported 19 children and 21 adults with sporadic ossifying fibromas, none of whom had a germline *CDC73* pathogenic variant identified by sequence

analysis (deletion/duplication analysis was not performed); two individuals had somatic *CDC73* pathogenic variants confined to the ossifying fibroma.

The specific features of jaw tumors associated with HPT-JT syndrome have not been well defined; in fact, pathologists disagree on the nomenclature used to classify benign fibro-osseous lesions. Most jaw tumors in HPT-JT syndrome are reported as ossifying fibromas or cementifying fibromas that occur in molar or premolar areas [Chen et al 2003], most often appear to be radiographically radiolucent, and usually develop prior to the third decade of life. Sporadic cemento-ossifiyng fibromas may appear as radiolucent or mixed radiolucent/radiopaque lesions, have a female preponderance, and typically develop after the third decade of life [Szabó et al 1995, Aldred et al 2006, Soluk-Tekkesin & Wright 2022].

Juvenile fibromas are histologic variants of ossifying fibromas that, when they occur sporadically, tend to occur at a younger mean age than ossifying fibromas. It is not clear if juvenile fibromas are part of HPT-JT syndrome. Of nine sporadic-appearing ossifying fibromas, parafibromin staining was negative in four of seven ossifying and cemento-ossifying fibromas and positive in three juvenile ossifying fibromas, indicating that loss of CDC73 expression may contribute to the development of ossifying fibromas but not juvenile fibromas [Costa-Guda et al 2021].

Of note, the jaw tumors of HPT-JT syndrome are distinct from the "brown" tumors/osteoclastomas associated with severe hyperparathyroidism (osteitis fibrosa cystica) and do not resolve following curative parathyroidectomy.

Kidney manifestations. Approximately 15%-20% of individuals with HPT-JT syndrome have kidney lesions, most commonly cysts; renal hamartomas and (more rarely) Wilms tumor, including adult-onset Wilms tumor, have also been reported [Torresan & Iacobone 2019].

Kidney cystic disease is variable and ranges from a few minor cysts to bilateral polycystic disease presenting with end-stage kidney disease [Tan & Teh 2004]. Cysts have also been observed in association with rare solid tumors, which were histologically similar to mixed epithelial-stromal tumors or adult mesoblastic nephroma (described in one family), or hamartomatous-type tumors [Teh et al 1996, Tan & Teh 2004]. Three individuals with a *CDC73* pathogenic variant from one family had mixed epithelial and stromal tumors [Vocke et al 2019].

Renal malignancy is rare in individuals with HPT-JT syndrome. One individual with HPT-JT syndrome had both papillary renal carcinoma and multiple renal cell adenomas [Haven et al 2000]. Wilms tumor has been reported in at least three unrelated families with HPT-JT syndrome, including an individual who developed bilateral Wilms tumor at age 53 years, and a child, age six years, who developed metastatic Wilms tumor with biallelic loss of *CDC73* on tumor tissue testing [Kakinuma et al 1994, Szabó et al 1995, Tora et al 2023].

Individuals with HPT-JT syndrome may be at risk for multiple bilateral kidney lesions, and nephron-sparing surgery rather than radical kidney resection should be considered [Vocke et al 2019].

Uterine manifestations. Benign uterine tumors appear to be common and can be the presenting manifestation in women with HPT-JT syndrome [Tora et al 2023]. Rare uterine malignancies have also been documented. In one study of HPT-JT syndrome kindreds, uterine pathology was described in women who underwent hysterectomy for menorrhagia [Bradley et al 2005]. The following were identified at time of surgery (average age: 35 years; range: 23-55 years): adenomyosis (8), adenofibroma (5), endometrial hyperplasia (4), leiomyoma (4), and adenosarcoma (2). A similar array of uterine findings and age of diagnosis were described in a more recent series of 32 females, in which 38% developed uterine tumors. In addition to the above pathologies, this series also described cervical polyps in four women, adenomyoma in five women, and adenocarcinoma in one woman [Tora et al 2023]. A 2019 review [Torresan & Iacobone 2019] suggested that 45.1% of women with HPT-JT syndrome reported in the literature were diagnosed with uterine lesions. Women with HPT-JT syndrome may present with menorrhagia and require hysterectomy at a younger than average age. In addition, the observation

that women with HPT-JT syndrome have a higher rate of miscarriage than unaffected controls and a lower rate of fertility than both unaffected controls and affected males suggests that uterine tumors may contribute to decreased reproductive fitness of women with HPT-JT syndrome [Bradley et al 2005].

Other tumors. Pancreatic adenocarcinoma, testicular mixed germ cell tumor, and Hürthle cell (oncocytic) thyroid adenoma were reported in individuals from a large kindred with HPT-JT syndrome; colon adenocarcinoma, leukemia, papillary thyroid carcinoma, neurofibroma, and chronic lymphatic leukemia have been reported in other kindreds [Mallette et al 1987, Inoue et al 1995, Haven et al 2000, Iacobone et al 2009]. However, it is not clear that these tumors are present at a higher frequency in individuals with HPT-JT syndrome than in the general population, nor that these tumors were caused by a *CDC73* pathogenic variant. A woman with HPT-JT syndrome had an ovarian granulosa cell tumor diagnosed at age 31; however, parafibromin staining was intact on analysis of tumor tissue [Sirbiladze et al 2019].

Parathyroid Carcinoma

Clinical manifestations of parathyroid carcinoma can include palpable neck mass, renal calculi, hoarseness, difficulty speaking or swallowing, muscle weakness, nausea/vomiting, altered mental status, bone pain, and/or pathologic fractures. Parathyroid carcinomas are most often associated with extremely high serum calcium concentration (>12 mg/dL) and extremely high iPTH levels (>3x the upper limit of normal). However, nonfunctioning parathyroid carcinoma can rarely occur [Guarnieri et al 2006]. A germline *CDC73* pathogenic variant has been identified in 18%-29% of individuals with parathyroid carcinoma and no family history of syndromic features or primary hyperparathyroidism [Carpten et al 2002, Shattuck et al 2003, Cetani et al 2004, Cetani et al 2007, Haven et al 2007, Cetani et al 2013, van der Tuin et al 2017, Erickson et al 2022].

Familial Isolated Hyperparathyroidism

Familial isolated hyperparathyroidism (FIHP) is characterized by primary hyperparathyroidism without other associated syndromic features. Individuals with *CDC73*-related FIHP tend to have a more severe clinical presentation and younger age of onset than individuals with FIHP in whom a *CDC73* pathogenic variant has not been identified. Individuals with *CDC73*-related FIHP are also at risk of developing parathyroid carcinoma. The overall prevalence of heterozygous germline *CDC73* pathogenic variants in families with FIHP has been estimated to be between 7% and 26% [Cetani et al 2004, Simonds et al 2004, Villablanca et al 2004, Warner et al 2004, Bradley et al 2006, Cetani et al 2006, Mizusawa et al 2006, van der Tuin et al 2017]. A *CDC73* pathogenic variant has been identified in approximately 1%-2% of individuals with early-onset (age <45 years) primary hyperparathyroidism without a family history [Starker et al 2012, van der Tuin et al 2017].

The vast majority of individuals with *CDC73*-related FIHP have had (1) at least one family member with a histopathologic diagnosis of parathyroid carcinoma; and/or (2) a parathyroid adenoma with atypical or cystic features [Cetani et al 2004, Simonds et al 2004, Villablanca et al 2004, Mizusawa et al 2006].

Genotype-Phenotype Correlations

Although no genotype-phenotype correlations for *CDC73* pathogenic variants have been formally established to date, it has been suggested that pathogenic missense variants are more likely to be associated with the FIHP phenotype; pathogenic variants that cause gross disruption of the protein product are more likely to be associated with the HPT-JT phenotype. However, some variants (e.g., c.679_680insAG, c.131+1G>A) have been reported in association with more than one *CDC73*-associated phenotype [Cardoso et al 2017]. Families with FIHP appear to have a higher ratio of missense to frameshift/nonsense variants than families with HPT-JT syndrome (4/7 vs 3/38, respectively) [Iacobone et al 2009, Newey et al 2010, Panicker et al 2010, Rekik et al 2010, Cavaco et al 2011, Frank-Raue et al 2011, Pichardo-Lowden et al 2011, Siu et al 2011, Starker et al 2012, Kutcher et al 2013].

A study of 419 individuals with a *CDC73* germline pathogenic variant suggested several genotype-phenotype correlations [Li et al 2020]. Pathogenic variants categorized as "high impact" (defined as gross indels, splice site, frameshift, and nonsense variants) were more common in individuals with parathyroid carcinoma, whereas only one individual with a "low impact" pathogenic variant (e.g., missense variants, in-frame insertion/deletion) developed parathyroid carcinoma. Likewise, individuals with high-impact pathogenic variants were more likely to develop jaw tumors. In contrast to low-impact pathogenic variants that impacted the N-terminal domain of parafibromin, high-impact pathogenic variants were all expected to affect the C-terminal domain. No association was found between type of pathogenic variant and development of primary hyperparathyroidism, kidney lesions, or uterine manifestations.

Despite emerging information regarding genotype-phenotype correlations, the phenotype (including age of onset and disease manifestations) may vary widely within the same family [Tora et al 2023].

Penetrance

While the penetrance in HPT-JT syndrome is estimated at 80%-90%, lower penetrance in females has been reported in two families [Teh et al 1996] and was closer to 70% in two different studies [Bradley et al 2005, Iacobone et al 2009]. The overall age-related penetrance in a Dutch population was estimated to be 11% at age 25 years, 65% at age 50 years, and 83% at age 70 years [van der Tuin et al 2017]. In a series of 61 individuals, 93% showed some manifestation of HPT-JT syndrome by age 40 years [Tora et al 2023].

Nomenclature

Hyperparathyroidism-jaw tumor (HPT-JT) syndrome is also known as familial primary hyperparathyroidism with multiple ossifying jaw fibromas and familial cystic parathyroid adenomatosis.

The gene *CDC73* was formerly known as *HRPT2*.

Prevalence

The prevalence of HPT-JT syndrome is not well established.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *CDC73*.

Cancer and Benign Tumors

Sporadic tumors (including parathyroid carcinoma, benign parathyroid tumors, and renal tumors [clear cell, papillary, chromophobe renal cell carcinomas, oncocytomas, and Wilms tumors]) occurring as single tumors in the absence of any other findings of *CDC73*-related disorders may contain a somatic pathogenic variant in *CDC73* that is **not** present in the germline. More than 75% of sporadic parathyroid carcinomas show biallelic somatic loss of *CDC73* [Cardoso et al 2017, Marini et al 2022]. Heterozygous somatic *CDC73* pathogenic variants were identified in two of 40 tumors studied from individuals with a sporadic ossifying jaw fibroma [Chen et al 2016]. In these circumstances, predisposition to these tumors is not heritable.

Differential Diagnosis

The following disorders should be considered in the differential diagnosis of *CDC73*-related disorders.

Primary Hyperparathyroidism / Familial Isolated Hyperparathyroidism

Sporadic primary hyperparathyroidism. Primary hyperparathyroidism has a prevalence of one to three in 1,000 in the general population, with a female-to-male ratio of approximately 2.5:1 [Yeh et al 2013]. Sporadic primary hyperparathyroidism is typically caused by a single parathyroid adenoma, with peak age of onset in the sixth decade of life. Sporadic atypical parathyroid adenomas do not tend to show loss of CDC73 staining [Saponaro et al 2021].

Hereditary primary hyperparathyroidism / familial isolated hyperparathyroidism. See Table 2.

Table 2. Genes of Interest in the Differential Diagnosis of Primary Hyperparathyroidism / Familial Isolated Hyperparathyroidism

Gene	Disorder	MOI	Clinical Characteristics
AP2S1 *CASR* *GNA11*	Familial hypocalciuric hypercalcemia (FHH) (OMIM PS145980)	AD	• *CASR*-related FHH is a benign condition characterized by hypercalcemia, low urinary calcium excretion (assessed via a calcium-to-creatinine clearance ratio), normal to minimally ↑ PTH, & frequent hypermagnesemia. Biochemical findings in FHH can overlap w/those of primary hyperparathyroidism. However, FHH is not a pathologic process & represents a higher, yet normal, baseline serum calcium concentration. • In a small proportion of persons w/FHH, germline pathogenic variants in *GNA11* or *AP2S1* have been identified. It is not known whether pathogenic variants in these genes account for any proportion of FIHP.
CASR	Familial isolated hyperparathyroidism (FIHP) [1]	AD	Heterozygous *CASR* pathogenic variants have been reported in 14%-18% of persons w/FIHP. [1]
	Neonatal severe primary hyperparathyroidism (OMIM 239200)	AR (AD)	Rare condition assoc w/severe neonatal or infantile hypercalcemia & hyperparathyroidism that may lead to death if untreated. Diagnosis is typically w/in 1st mo of life but may range from birth to ~3 mos. [2]
CDKN1B	Multiple endocrine neoplasia type 4 (MEN4)	AD	• Phenotype overlaps w/MEN1; however, less is known about penetrance of MEN4 & assoc lifetime risk for endocrine tumors. • Primary hyperparathyroidism tends to occur at a later age in MEN4 than in MEN1. • The proportion of simplex or familial primary hyperparathyroidism explained by MEN4 remains unknown. • Additional endocrine tumors seen in persons w/MEN4 incl pituitary adenomas & foregut neuroendocrine tumors, which also appear to exhibit a less aggressive course than those seen in MEN1.
GCM2	FIHP type 4 (OMIM 617343)	AD	• Early data suggest that persons w/*GCM2*-related primary hyperparathyroidism are more likely to have aggressive disease, incl lower rate of biochemical cure & ↑ incidence of parathyroid carcinoma. • Persons in these kindreds do not appear to be at ↑ risk for other endocrine tumors.
MAX	Multiple endocrine neoplasia type 5 (MEN5) [3]	AD	Primarily hereditary pheochromocytoma & paraganglioma syndrome that may be assoc w/other endocrine neoplasms incl primary hyperparathyroidism & pituitary adenomas [3]

Table 2. continued from previous page.

Gene	Disorder	MOI	Clinical Characteristics
MEN1	FIHP [4]	AD	*MEN1* germline pathogenic variants have been reported in ~20% of persons w/ FIHP.
	Multiple endocrine neoplasia type 1 (MEN1)	AD	• Most common hereditary cause of primary hyperparathyroidism, accounting for 2%-4% of primary hyperparathyroidism • *MEN1*-related primary hyperparathyroidism is characterized by onset in late adolescence to early adulthood (w/nearly all persons affected by age 50 yrs), multiglandular disease, & histology usually demonstrating parathyroid hyperplasia. • MEN1 is also assoc w/pituitary adenomas & foregut neuroendocrine tumors, primarily gastrinomas & insulinomas.
RET	Multiple endocrine neoplasia type 2A (MEN2A)	AD	• Primary hyperparathyroidism occurs in up to 20%-30% of persons w/ MEN2A but is rarely the presenting feature. • Additional manifestations of MEN2A incl medullary thyroid carcinoma & pheochromocytoma.

AD = autosomal dominant; AR = autosomal recessive; FHH = familial hypocalciuric hypercalcemia; FIHP = familial isolated hyperparathyroidism; MOI = mode of inheritance; PTH = parathyroid hormone

1. Simonds et al [2002], Warner et al [2004]

2. Sadacharan et al [2020]

3. Seabrook et al [2021]

4. Warner et al [2004], Cetani et al [2006], Mizusawa et al [2006]

An as-yet unknown gene. In many individuals with familial primary hyperparathyroidism, an underlying genetic cause cannot be identified.

Jaw Tumors

The differential diagnosis for ossifying fibromas of the jaw seen as part of hyperparathyroidism-jaw tumor (HPT-JT) syndrome is dependent on the radiologic characteristics of the lesions, specifically whether they are radiolucent, have mixed radiographic features, or are completely radiopaque [Chang et al 2008, Vered & Wright 2022]. Cemento-ossifying fibromas tend to be radiolucent and occur in a tooth-bearing region of the jaw, particularly in the premolar and molar region of the mandible [Soluk-Tekkesin & Wright 2022]. One of the most important diagnoses to consider is fibrous dysplasia, which is a reactive lesion rather than a true neoplasm. In addition, osseous dysplasia, including focal osseous dysplasia, should be considered [de Andrade et al 2013]. Familial florid cemento-osseous dysplasia, which can be caused by pathogenic variants in *ANO5* (OMIM 166260), may be considered when familial jaw growths are the main phenotype. Histologic features of these growths may resemble lesions found in HPT-JT syndrome [Nel et al 2021].

Benign lesions that can be confused with HPT-JT on panoramic x-rays include but are not limited to periapical cementoplasia, giant cell lesions of the jaw (including central and peripheral giant cell granulomas), and idiopathic bone cyst. Benign anatomic variations such as exostosis, mandibular tori, maxillary torus palatinus, and the lingual concavity of the body of the mandible can also be misinterpreted as jaw tumors. See Chang et al [2008] and de Andrade et al [2013] for clinicopathologic case series of individuals with ossifying fibromas of the jaw, including discussion and review of pertinent differential diagnoses to consider. The 5th Edition of the World Health Organization Classification of Head and Neck Tumours contains an extensive discussion of the differences between the lesions listed above (see WHO Classification of Tumors Online).

Kidney Cysts

Sporadic kidney cysts. The prevalence of at least one kidney cyst detected by MRI examination in the general population [Mensel et al 2018] is as follows:

- Age 20-29 years: 14% of men and 7% of women
- Age 30-39 years: 20% of men and 11% of women
- Age 40-49 years: 26% of men and 15% of women
- Age 50-59 years: 36% of men and 19% of women
- Age 60-69 years: 49% of men and 34% of women
- Age 70+ years: 55% of men and 43% of women

  Note: Of individuals with kidney cysts, 31.7% of men and 19.7% of women had bilateral cysts.

Syndromic renal cysts. Syndromic conditions associated with kidney cystic disease are usually diagnosed by the presence of additional manifestations (see Table 3).

Table 3. Genes of Interest in the Differential Diagnosis of Renal Cysts

Gene	Disorder	MOI	Clinical Characteristics
PKD1 *PDK2* [1]	Autosomal dominant polycystic kidney disease	AD	• Multiple bilateral kidney cysts; cysts in other organs (primarily liver, seminal vesicles, pancreas, & arachnoid membrane); vascular abnormalities; & abdominal wall hernias • Onset typically in adulthood
TSC1 *TSC2*	Tuberous sclerosis complex	AD	Abnormalities of skin (hypomelanotic macules, facial angiofibromas, shagreen patches, fibrous facial plaques, ungual fibromas); brain (cortical tubers, subependymal nodules); kidney (angiomyolipomas, cysts, renal cell carcinomas); & heart (rhabdomyomas, arrhythmias); as well as seizures & intellectual disability / developmental delay
VHL	von Hippel-Lindau syndrome	AD	Retinal &/or CNS hemangioblastomas; kidney cysts & clear cell renal carcinoma; pheochromocytoma; cysts & neuroendocrine tumors of the pancreas; & epididymal & broad ligament cysts

1. PKD1 and *PKD2* are the most commonly involved genes; less commonly involved genes include *ALG5*, *ALG9*, *DNAJB11*, *GANAB*, and *IFT140*.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual identified to have a pathogenic variant in *CDC73*, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. *CDC73*-Related Disorders: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Primary hyperparathyroidism	• Measurement of concomitant serum calcium & iPTH • Serum 25-hydroxyvitamin D to evaluate for coexisting vitamin D deficiency as a cause of ↑ iPTH or unexpectedly "normal" calcium concentrations	Beginning by age 10 yrs
	24-hour urine calcium-to-creatinine clearance ratio	In persons w/hypercalcemia
	DXA scan to assess bone density of lumbar spine, hips, & distal radius	As indicated

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Jaw tumors	Panoramic jaw x-ray w/neck shielding	Beginning at diagnosis
Renal lesions	Renal US is preferred; CT &/or MRI as clinically indicated	
Uterine tumors	• Pelvic exam as part of routine gynecologic care • Pelvic US is preferred; CT &/or MRI as clinically indicated	Beginning in women at reproductive age
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *CDC73*-related disorders to facilitate medical & personal decision making

DXA = dual-energy x-ray absorptiometry; iPTH = intact parathyroid hormone; MOI = mode of inheritance; US = ultrasound
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Primary hyperparathyroidism. Preoperative assessment including labs and imaging (preoperative serum calcium and parathyroid hormone [PTH] levels, large or irregular gland size, or cystic features) can assist in distinguishing parathyroid adenoma involving a single gland and suspected parathyroid carcinoma. Preoperative biopsy via fine-needle aspiration should not be performed, as this can cause seeding of tumor tissue. The optimal surgical approach includes preparation to perform complete gland removal and en bloc resection of surrounding structures if there are intraoperative findings suggestive of parathyroid carcinoma. Experienced surgeons can usually distinguish normal parathyroid tissue from parathyroid adenomas and carcinomas intraoperatively. **Normal parathyroid tissue** is peanut butter colored, soft, small, and nonadherent to surrounding structures. **Parathyroid adenomas** are usually oval, round, or kidney shaped in appearance. **Parathyroid carcinoma** is usually hard/firm, white-gray, large, and intimately attached to surrounding structures [Authors, personal experience].

Parathyroid adenoma involving a single gland can be resected. Multigland resection increases the risk for hypoparathyroidism with no true benefit of reducing disease recurrence. Therefore, subtotal parathyroidectomy is not recommended. Iacobone et al [2020] evaluated 20 individuals from three large families with hyperparathyroidism-jaw tumor (HPT-JT) syndrome; 95% had single-gland disease. These findings supported unilateral parathyroid adenoma resection when preoperative imaging identified the abnormal gland, although bilateral intraoperative exploration may be preferred in individuals with inconclusive or discordant preoperative imaging. Perrier et al [2020] recommended imaging to identify the abnormal gland followed by an open operation with inspection of both glands on the ipsilateral side. Contralateral exploration was not recommended if the findings were congruent with preoperative imaging and the second ipsilateral gland was normal in appearance.

Parathyroid carcinoma. Preoperative findings suggestive of parathyroid carcinoma include extremely elevated serum calcium and intact PTH (iPTH), more profound symptoms, palpable cervical disease, and radiographic evidence of parathyroid carcinoma (e.g., irregular-shaped gland, attachment to other tissues, cystic aspects). Intraoperative findings of parathyroid carcinoma include tissue that is firm, irregular, attached to other tissues, or cystic. In those with suspected parathyroid carcinoma, an en bloc resection including the ipsilateral thyroid lobe is indicated. Care to prevent fracture of the tumor, which could seed the local area and cause parathyromatosis, is critical.

Hypercalcemia. Intravenous fluids and a bisphosphonate infusion can be used to treat severe or symptomatic hypercalcemia. Cinacalcet hydrochloride (Sensipar®), a calcimimetic that binds to the calcium-sensing receptor,

can be used for long-term control of hypercalcemia that occurs in individuals who are unable to undergo parathyroidectomy and for the treatment of parathyroid carcinoma-related hypercalcemia [Messa et al 2011]. Cinacalcet has proven effective in individuals with inoperable parathyroid carcinoma [Silverberg et al 2007] and has been used in an individual with *CDC73*-associated primary hyperparathyroidism for whom parathyroidectomy was considered high risk [Sato et al 2016]. Other medications that prevent calcium resorption (e.g., denosumab) can be used for bisphosphonate-refractory hypercalcemia.

Postoperative hypoparathyroidism. The risk of postoperative hypoparathyroidism can be minimized by ensuring normal preoperative 25-hydroxyvitamin D concentrations; recognizing risk factors for hungry bone syndrome preoperatively (e.g., elevated serum alkaline phosphatase concentration and radiologic evidence of osteitis fibrosa cystica); and implementing close postoperative monitoring that includes prompt replacement of calcium and vitamin D as indicated. Minimization of postoperative nausea and vomiting can help prevent an increase in venous pressure, which could lead to oozing and devascularization of the remaining in situ parathyroid glands.

Jaw tumors should be treated surgically as indicated based on the size, location, and symptoms of the lesion. Treatment of choice is complete resection, which may not be possible in all individuals. There are no well-defined medical approaches to unresectable jaw tumors. Individuals with a history of jaw tumors should be followed closely because of the possibility of recurrence.

Kidney manifestations. No treatment guidelines for kidney manifestations associated with HPT-JT syndrome have been proposed to date. Management guidelines are available for other polycystic kidney diseases, such as autosomal dominant polycystic kidney disease; however, the natural history and likelihood of end-stage kidney disease is likely to be different in HPT-JT syndrome-associated kidney disease. Individuals with evidence of cystic kidney disease should be managed by nephrology. Individuals with solid kidney lesions should be referred to nephrology and/or oncology.

Uterine tumors. No treatment guidelines for uterine manifestations associated with HPT-JT syndrome have been proposed to date. Individuals with evidence of a uterine tumor should be managed by a gynecologist.

Surveillance

There are currently no well-established, evidence-based surveillance guidelines for individuals with a *CDC73*-related disorder. Based on an extensive literature review and to monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 5 are recommended.

Table 5. *CDC73*-Related Disorders: Recommended Surveillance

System/Concern	Evaluation	Frequency
Primary hyperparathyroidism / Parathyroid tumors	• Measurement of concomitant serum calcium & iPTH • Serum 25-hydroxyvitamin D to evaluate for coexisting vitamin D deficiency as a cause of ↑ iPTH or unexpectedly "normal" calcium concentrations	Annually beginning by age 10 yrs
	Consider neck US exam for detection of nonfunctioning parathyroid carcinoma.	Periodically as indicated based on serum calcium & iPTH levels
	Evaluate via localization studies [1] for new primary parathyroid tumor or recurrence/progression of malignant disease.	In those w/history of parathyroid carcinoma, who develop a rise in calcium levels

Table 5. continued from previous page.

System/Concern	Evaluation	Frequency
Jaw tumors	• Regular dental visits • Note: Dental providers should be notified of presence of a *CDC73*-related disorder & need for monitoring for osseous fibromas of maxilla & mandible.	Every 6 mos
	Panoramic jaw x-ray w/neck shielding	At least every 5 yrs beginning at diagnosis
Renal lesions	• Renal US exam to assess for kidney lesions • CT or MRI as clinically indicated	
	Serum creatinine concentrations in those w/kidney cysts	Annually
Uterine tumors	• Gynecologic eval (incl pelvic exam) • Note: Gynecologist should be notified of risk of uterine tumors.	Annually in women starting at reproductive age
	• Pelvic US • Further imaging studies (CT/MRI) as clinically indicated	Pelvic US every 5 yrs even in absence of signs/symptoms of uterine tumors

iPTH = intact parathyroid hormone; US = ultrasound
1. Localization studies may include thyroid/parathyroid ultrasound, sestamibi, and 4D neck CT with contrast.

Agents/Circumstances to Avoid

The following should be avoided:

- Dehydration
- Radiation exposure to the neck
- Biopsy of extrathyroidal tissue in the neck, which increases the risk of seeding of parathyroid tissue

Evaluation of Relatives at Risk

Molecular genetic testing for the *CDC73* germline pathogenic variant identified in the proband should be offered to at-risk relatives by age ten years in order to identify those who would benefit from initiation of surveillance and treatment.

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

Pregnancy Management

Primary hyperparathyroidism during pregnancy may pose increased risks to the mother (symptomatic hypercalcemia) and to the fetus (intrauterine growth deficiency, preterm delivery, intrauterine fetal demise, and/or postpartum neonatal hypocalcemia) [Strebeck et al 2022]. Conservative observation may be appropriate for mild asymptomatic hypercalcemia, but for symptomatic primary hyperparathyroidism or evidence of adverse effects on the fetus, surgery (preferably in the second trimester) is required for definitive treatment. These individuals should be managed in conjunction with a maternal-fetal medicine specialist.

See MotherToBaby for more information on medication use during pregnancy.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for 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

CDC73-related disorders are inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Some individuals with a *CDC73*-related disorder inherited a *CDC73* pathogenic variant from an affected parent.
- Some individuals diagnosed with a *CDC73*-related disorder have the disorder as the result of a *de novo* pathogenic variant; however, the proportion of probands who have a *de novo* pathogenic variant is unknown.
- If the proband appears to be the only affected family member (i.e., a simplex case), molecular genetic testing is recommended for the parents of the proband to confirm their genetic status, determine their need for appropriate clinical surveillance (see Management), and allow reliable recurrence risk counseling.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
    - The proband has a *de novo* pathogenic variant.
    - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism.* Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.

      * A parent with somatic and germline mosaicism for a *CDC73* pathogenic variant may be mildly/minimally affected [Villablanca et al 2004].
- The family history of some individuals diagnosed with a *CDC73*-related disorder may appear to be negative because of failure to recognize the disorder in family members, reduced penetrance, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for the pathogenic variant identified in the proband.

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

- If a parent of the proband is affected and/or is known to be heterozygous for the *CDC73* pathogenic variant, the risk to the sibs of inheriting the pathogenic variant is 50%.
- Age of onset, severity, type of symptoms, and rate of progression cannot be predicted in sibs who inherit a *CDC73* pathogenic variant. Some *CDC73* pathogenic variants have been reported in association with more than one *CDC73*-related phenotype, and the phenotype may vary widely within the same family [Tora et al 2023]. (See Penetrance and Genotype-Phenotype Correlations).

- If the *CDC73* pathogenic variant detected in the proband cannot be detected in the leukocyte DNA of either parent, the risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism [Villablanca et al 2004].
- The absence of clinical symptoms in parents whose genetic status is unknown cannot be used to predict risk to sibs of a proband because of the possibility of reduced penetrance in a heterozygous parent or parental germline mosaicism.

Offspring of a proband. Each child of an individual with a *CDC73*-related disorder has a 50% chance of inheriting the pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *CDC73* pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

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

Testing of at-risk asymptomatic individuals. Molecular genetic testing of at-risk asymptomatic family members is strongly recommended for all first-degree relatives of an affected person with an identified *CDC73* pathogenic variant. Molecular genetic testing should be offered to at-risk asymptomatic individuals by age 10 years so that individuals with a *CDC73* pathogenic variant can receive the appropriate clinical surveillance (see Management). Education and genetic counseling of all at-risk individuals and their families prior to genetic testing is appropriate.

Genetic cancer risk assessment and counseling. For a comprehensive description of the medical, psychosocial, and ethical ramifications of identifying at-risk individuals through cancer risk assessment with or without molecular genetic testing, see Cancer Genetics Risk Assessment and Counseling – for health professionals (part of PDQ®, National Cancer Institute).

Family planning

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

Prenatal Testing and Preimplantation Genetic Testing

Once the *CDC73* pathogenic variant has 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.

- **MedlinePlus**
  Familial isolated hyperparathyroidism

- **MedlinePlus**
  Hyperparathyroidism-jaw tumor syndrome
- **MedlinePlus**
  Parathyroid Cancer
- **National Cancer Institute**
  National Institutes of Health
  Phone: 800-4-CANCER
  Email: NCIinfo@nih.gov
  Parathyroid Cancer Treatment (PDQ®)–Patient Version
- **National Institute of Diabetes and Digestive and Kidney Diseases**
  National Institutes of Health
  Phone: 800-860-8747
  Email: healthinfo@niddk.nih.gov
  Primary hyperparathyroidism

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. CDC73-Related Disorders: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
CDC73	1q31.2	Parafibromin	CDC73 database	CDC73	CDC73

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 CDC73-Related Disorders (View All in OMIM)

145000	HYPERPARATHYROIDISM 1; HRPT1
145001	HYPERPARATHYROIDISM 2 WITH JAW TUMORS; HRPT2
607393	CELL DIVISION CYCLE 73; CDC73
608266	PARATHYROID CARCINOMA

Molecular Pathogenesis

CDC73 encodes parafibromin, a subunit of the PAF1 protein complex that likely functions as a transcription factor [Rozenblatt-Rosen et al 2005]. Three putative nuclear localization signals are thought to be located between codons 76 and 92, codons 192 and 194, and codons 393 and 409 [Bradley et al 2005, Hahn & Marsh 2007]. The finding of loss of heterozygosity of the wild type *CDC73* allele in parathyroid tumors from individuals with hyperparathyroidism-jaw tumor (HPT-JT) syndrome strongly supports a tumor suppressor role for *CDC73* [Bradley et al 2006]. Parafibromin has also been shown to inhibit cell proliferation by repression of the c-myc proto-oncogene and mediate cyclin D1 repression through histone methylation, further supporting the role of *CDC73* as a tumor suppressor [Woodard et al 2005, Lin et al 2008, Yang et al 2010].

Mechanism of disease causation. Loss of function

Table 6. *CDC73* Pathogenic Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Comment [Reference]
NM_024529.4	c.131+1G>A	--	See Genotype-Phenotype Correlations.
NM_024529.4 NP_078805.3	c.679_680insAG	p.Arg227LysfsTer31	
	c.766_767delGT (255/256delTG)	p.Val256LysfsTer10	Founder variant in Roma families from Portugal [Cavaco et al 2004]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions

Chapter Notes

Author Notes

All four authors are actively working with individuals with *CDC73*-related disorders. They would be happy to communicate with health care professionals who have questions regarding diagnosis and management of a *CDC73*-related disorder (Steven Waguespack and Mimi Hu), review of *CDC73* variants (Catherine Skefos), or surgical considerations (Nancy Perrier).

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Revision History

- 21 September 2023 (sw) Comprehensive update posted live
- 26 April 2018 (sw) Comprehensive update posted live
- 15 January 2015 (me) Comprehensive update posted live
- 24 May 2012 (me) Comprehensive update posted live
- 31 December 2008 (me) Review posted live
- 12 August 2008 (tar) Original submission

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