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PTEN Hamartoma Tumor Syndrome

Synonym: PHTS

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Summary

Clinical characteristics

The *PTEN* hamartoma tumor syndrome (PHTS) includes Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), *PTEN*-related Proteus syndrome (PS), and Proteus-like syndrome.

- CS is a multiple hamartoma syndrome with a high risk for benign and malignant tumors of the thyroid, breast, and endometrium. Affected individuals usually have macrocephaly, trichilemmomas, and papillomatous papules, and present by the late 20s. The lifetime risk of developing breast cancer is 85%, with an average age of diagnosis between 38 and 46 years. The lifetime risk for thyroid cancer (usually follicular, rarely papillary, but never medullary thyroid cancer) is approximately 35%. The risk for endometrial cancer may approach 28%.
- BRRS is a congenital disorder characterized by macrocephaly, intestinal hamartomatous polyposis, lipomas, and pigmented macules of the glans penis.
- PS is a complex, highly variable disorder involving congenital malformations and hamartomatous overgrowth of multiple tissues, as well as connective tissue nevi, epidermal nevi, and hyperostoses.
- Proteus-like syndrome is undefined but refers to individuals with significant clinical features of PS who do not meet the diagnostic criteria for PS.

Diagnosis/testing

The diagnosis of PHTS is established in a proband by identification of a heterozygous germline *PTEN* pathogenic variant on molecular genetic testing.

Management

Treatment of manifestations: Treatment for the benign and malignant manifestations of PHTS is the same as for their sporadic counterparts. Topical agents (e.g., 5-fluorouracil), curettage, cryosurgery, or laser ablation may alleviate the mucocutaneous manifestations of CS but are rarely utilized; cutaneous lesions should be excised only if malignancy is suspected or symptoms (e.g., pain, deformity, increased scarring) are significant.

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Surveillance: To detect tumors at the earliest, most treatable stages:

- Children (age <18 years). Yearly thyroid ultrasound from the time of diagnosis and skin check with physical examination.
- Adults. Yearly thyroid ultrasound and dermatologic evaluation.
- Women beginning at age 30 years. Monthly breast self-examination; annual breast screening (at minimum mammogram; MRI may also be incorporated) and transvaginal ultrasound or endometrial biopsy.
- Men and women. Colonoscopy beginning at age 35 years with frequency dependent on degree of polyposis identified; biennial (every 2 years) renal imaging (CT or MRI preferred) beginning at age 40 years.
- Those with a family history of a particular cancer type at an early age. Consider initiating screening 5-10 years prior to the youngest age of diagnosis in the family.

Evaluation of relatives at risk: When a *PTEN* pathogenic variant has been identified in a proband, molecular genetic testing of asymptomatic at-risk relatives can identify those who have the family-specific pathogenic variant and warrant ongoing surveillance.

Genetic counseling

PHTS is inherited in an autosomal dominant manner. Because CS is likely underdiagnosed, the actual proportion of simplex cases (defined as individuals with no obvious family history) and familial cases (defined as ≥2 related affected individuals) cannot be determined. The majority of CS cases are simplex. Perhaps 10%-50% of individuals with CS have an affected parent. Each child of an affected individual has a 50% chance of inheriting the pathogenic variant and developing PHTS. Once a *PTEN* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk is possible.

GeneReview Scope

PTEN Hamartoma Tumor Syndrome: Included Phenotypes [1]
• Cowden syndrome (CS) • Bannayan-Riley-Ruvalcaba syndrome (BRRS) • *PTEN*-related Proteus syndrome • Proteus-like syndrome

For synonyms and outdated names see Nomenclature.
1. For other genetic causes of these phenotypes see Differential Diagnosis.

Diagnosis

Suggestive Findings

The *PTEN* hamartoma tumor syndrome (PHTS) includes Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), *PTEN*-related Proteus syndrome (PS), and Proteus-like syndrome.

A *PTEN* hamartoma tumor syndrome (PHTS) **should be suspected** in individuals with the following clinical features.

Cowden Syndrome (CS)

Based on more than 3,000 prospectively accrued individuals with CS or a Cowden-like syndrome (CSL) from the community, a scoring system (which can be found online) that takes into account phenotype and age at diagnosis has been developed. The scoring system allows input of clinical information on an individual

suspected of having CS/CSL and subsequently generates the prior probability of finding a *PTEN* pathogenic variant.

- In adults, a clinical threshold score of ≥10 leads to a recommendation for referral to a genetics professional to consider PHTS.
- In children, macrocephaly and ≥1 of the following leads to the consideration of PHTS:
  - Autism or developmental delay
  - Dermatologic features, including lipomas, trichilemmomas, oral papillomas, or penile freckling
  - Vascular features, such as arteriovenous malformations or hemangiomas
  - Gastrointestinal polyps

Additionally, consensus diagnostic criteria for CS have been developed [Eng 2000] and are updated each year by the National Comprehensive Cancer Network [NCCN 2015]. However, the CS scoring system discussed in this section has been shown to be more accurate than the NCCN diagnostic criteria [Tan et al 2011].

The NCCN consensus clinical diagnostic criteria have been divided into three categories: pathognomonic, major, and minor.

Pathognomonic criteria

- Adult Lhermitte-Duclos disease (LDD), defined as the presence of a cerebellar dysplastic gangliocytoma [Zhou et al 2003a]
- Mucocutaneous lesions:
  - Trichilemmomas (facial) (see Figure 1)
  - Acral keratoses
  - Papillomatous lesions (see Figure 2)
  - Mucosal lesions

Major criteria

- Breast cancer
- Epithelial thyroid cancer (non-medullary), especially follicular thyroid cancer
- Macrocephaly (occipital frontal circumference ≥97th percentile)
- Endometrial carcinoma

Minor criteria

- Other thyroid lesions (e.g., adenoma, multinodular goiter)
- Intellectual disability (IQ ≤75)
- Hamartomatous intestinal polyps
- Fibrocystic disease of the breast
- Lipomas
- Fibromas
- Genitourinary tumors (especially renal cell carcinoma)
- Genitourinary malformation
- Uterine fibroids

An operational diagnosis of CS is made if an individual meets **any one** of the following criteria:

- Pathognomonic mucocutaneous lesions combined with one of the following:
  - Six or more facial papules, of which three or more must be trichilemmoma
  - Cutaneous facial papules and oral mucosal papillomatosis
  - Oral mucosal papillomatosis and acral keratoses
  - Six or more palmoplantar keratoses

- Two or more major criteria
- One major and three or more minor criteria
- Four or more minor criteria

In a family in which one individual meets the diagnostic criteria for CS listed above, other relatives are considered to have a diagnosis of CS if they meet **any one** of the following criteria:

- The pathognomonic criteria
- Any one major criterion with or without minor criteria
- Two minor criteria
- History of Bannayan-Riley-Ruvalcaba syndrome

Bannayan-Riley-Ruvalcaba Syndrome (BRRS)

Diagnostic criteria for BRRS have not been set but are based heavily on the presence of the cardinal features of macrocephaly, hamartomatous intestinal polyposis, lipomas, and pigmented macules of the glans penis [Gorlin et al 1992].

Proteus Syndrome

Proteus syndrome (PS) is highly variable and appears to affect individuals in a mosaic distribution (i.e., only some organs/tissues are affected). Thus, it is frequently misdiagnosed despite the development of consensus diagnostic criteria [Biesecker et al 1999] (see Proteus Syndrome).

Proteus-Like Syndrome

Proteus-like syndrome is undefined but describes individuals with significant clinical features of PS but who do not meet the diagnostic criteria.

Establishing the Diagnosis

The diagnosis of PHTS **is established** in a proband by identification of a heterozygous germline pathogenic variant in *PTEN* on molecular genetic testing (see Table 1).

Molecular genetic testing approaches can include **single-gene testing**, use of a **multigene panel**, and **more comprehensive genomic testing**:

- **Single-gene testing.** Sequence analysis of *PTEN* is performed first and followed by gene-targeted deletion/duplication analysis if no pathogenic variant is found. If a pathogenic variant is not identified with deletion/duplication analysis, perform sequence analysis of the *PTEN* promoter region for variants that decrease gene expression.

  Note: In individuals with Cowden syndrome (CS) and Cowden-like syndrome also consider *KLLN* promoter methylation analysis (see Differential Diagnosis, Germline *KLLN* Epimutation), *SDHB-D* analysis (see Differential Diagnosis, New Susceptibility Genes in Individuals with Non-PHTS CS and a CS-Like Disorder) including *PIK3CA, AKT1* [Orloff et al 2013], and *SEC23B* [Yehia et al 2015].

- **A multigene panel** that includes *PTEN* and other genes of interest (see Differential Diagnosis) may also be considered. 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*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a

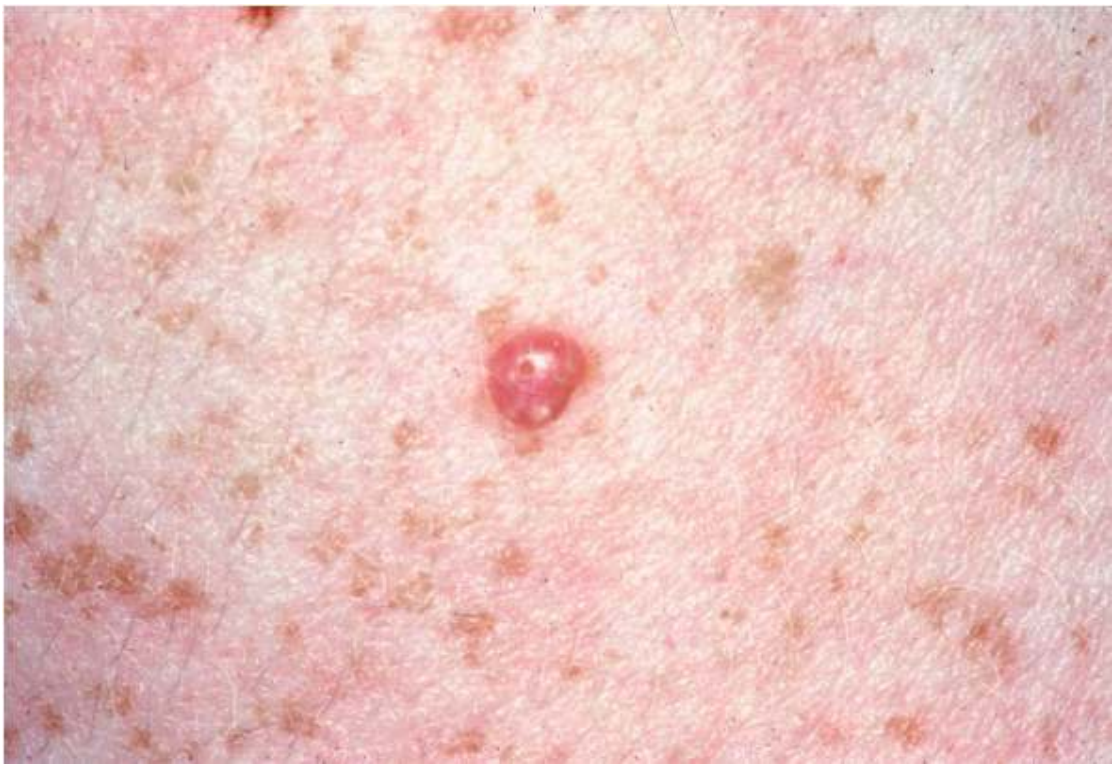

Figure 1. Trichilemmoma

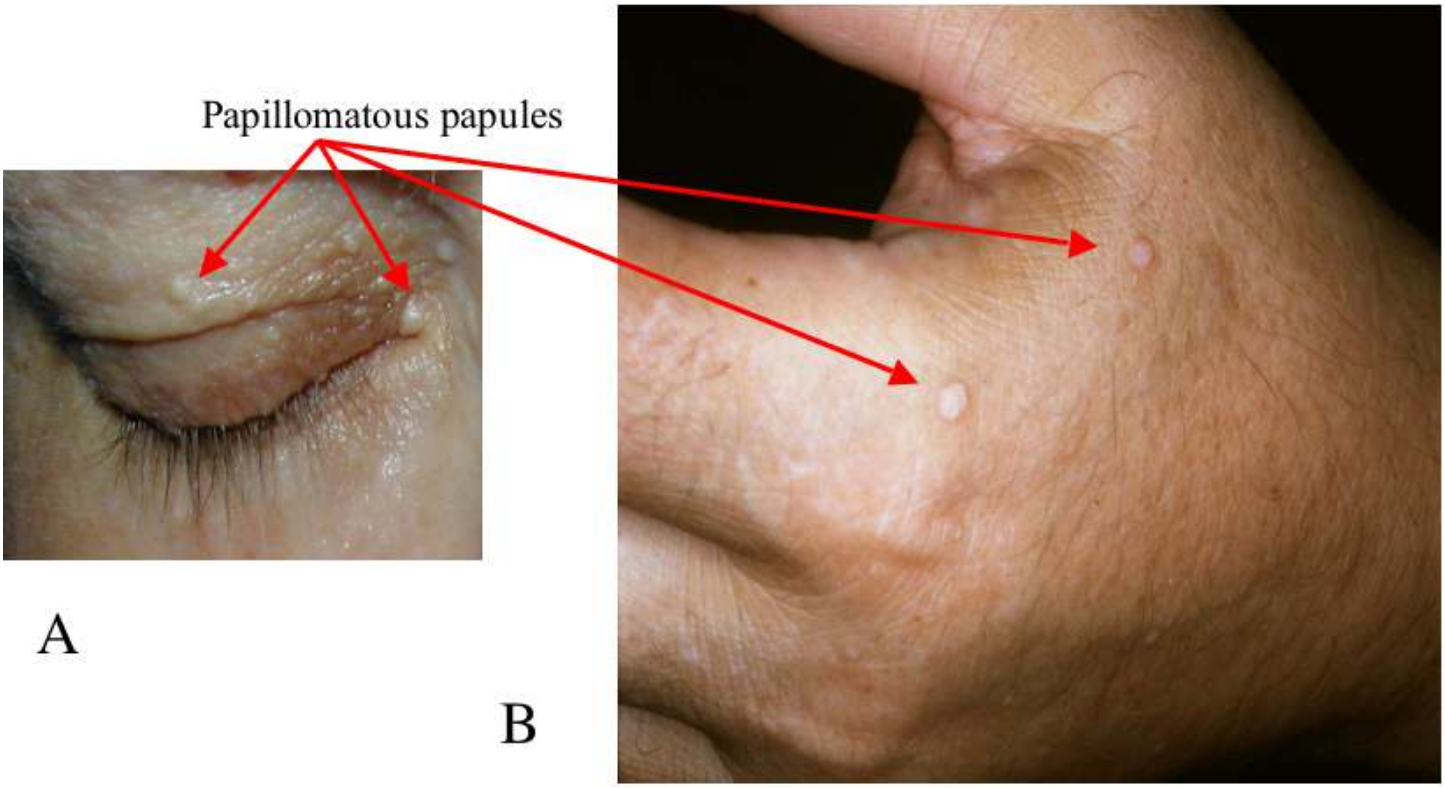

Figure 2. Papillomatous papules in the periocular region (A) and on the dorsum of the hand (B)

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.

- **More comprehensive genomic testing** (when available) including exome sequencing or genome sequencing may be considered if single-gene testing (and/or use of a multigene panel that includes *PTEN*) fails to confirm a diagnosis in an individual with features of PHTS. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene or genes that results in a similar clinical presentation).

  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 *PTEN* Hamartoma Tumor Syndrome

Gene [1]	Test Method	Proportion of Probands by Phenotype with a Pathogenic Variant Detectable by This Method			
		CS	BRRS	PLS	PS
PTEN	Sequence analysis of coding region [2]	25%-80%	60%	50% [3]	20%
	Deletion/duplication analysis [4]	See footnote 5	11% [6]	Unknown	Unknown
	Sequence analysis of promoter region [2]	10% [7]	See footnote 5	Unknown	Unknown

CS = Cowden syndrome
BRRS = Bannayan-Riley-Ruvalcaba syndrome
PLS = Proteus-like syndrome
PS = *PTEN*-related Proteus syndrome

1. See Table A. Genes and Databases for chromosome locus and protein. See Molecular Genetics for information on allelic variants.

2. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. 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.

3. Data suggest that up to 50% of individuals with a Proteus-like syndrome and 20% of individuals who meet the clinical diagnostic criteria of Proteus syndrome have *PTEN* pathogenic variants [Zhou et al 2001, Smith et al 2002, Eng 2003, Loffeld et al 2006, Orloff & Eng 2008].

4. Testing that identifies exon or whole-gene deletions/duplications not readily detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA; included in the variety of methods that may be used are: quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) that includes this gene/chromosome segment.

5. Finite but unknown; individuals with CS who have large deletions have been reported [Zbuk & Eng 2007, Orloff & Eng 2008, Tan et al 2011].

6. Approximately 10% of individuals with BRRS who do not have a pathogenic variant detected in the *PTEN* coding sequence have large deletions within or encompassing *PTEN* [Zhou et al 2003b].

7. 10% of individuals with CS phenotype do not have an identifiable *PTEN* sequence variant in the coding/flanking intronic regions [Zhou et al 2003b].

Clinical Characteristics

Clinical Description

The *PTEN* hamartoma tumor syndrome (PHTS) is characterized by hamartomatous tumors and germline *PTEN* pathogenic variants. Clinically, PHTS includes Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), *PTEN*-related Proteus syndrome (PS), and Proteus-like syndrome.

- CS is a multiple hamartoma syndrome with a high risk for benign and malignant tumors of the thyroid, breast, and endometrium. Renal cell carcinoma and colorectal carcinoma have recently been shown to be in the PHTS spectrum.
- BRRS is a congenital disorder characterized by macrocephaly, intestinal polyposis, lipomas, and pigmented macules of the glans penis.
- PS is a complex, highly variable disorder involving congenital malformations and overgrowth of multiple tissues.
- Proteus-like syndrome is undefined but refers to individuals with significant clinical features of PS who do not meet the diagnostic criteria for PS.

Cowden Syndrome (CS)

More than 90% of individuals with CS have some clinical manifestation of the disorder by the late 20s [Nelen et al 1996, Eng 2000]. By the third decade, 99% of affected individuals develop the mucocutaneous stigmata (primarily trichilemmomas and papillomatous papules) as well as acral and plantar keratoses. In addition, individuals with Cowden syndrome usually have macrocephaly and dolicocephaly.

Hamartomatous and mixed gastrointestinal polyps, seen frequently in the majority of people with PHTS, do confer an increased risk for colorectal cancers [Heald et al 2010].

Based on anecdotal observations, glycogenic acanthosis in the presence of features of CS appears to be associated with a high likelihood of finding a *PTEN* pathogenic variant [Eng 2003, McGarrity et al 2003].

Tumor risk. Individuals with CS are at high risk for breast, thyroid, and endometrial cancers. As with other hereditary cancer syndromes, the risk for multifocal and bilateral (in paired organs such as the breasts) cancer is increased:

- **Breast disease**
  - Women with Cowden syndrome are at as high as a 67% risk for benign breast disease.
  - An analysis of prospectively accrued and followed probands and family members with a *PTEN* pathogenic variant revealed an 85% lifetime risk for female breast cancer, with 50% penetrance by age 50 years [Tan et al 2012].
  - Although breast cancer has been described in males with a *PTEN* pathogenic variant [Fackenthal et al 2001], it was not observed in a study of more than 3,000 probands [Tan et al 2011].
- **Thyroid disease**
  - Benign multinodular goiter of the thyroid as well as adenomatous nodules and follicular adenomas are common, occurring in up to 75% of individuals with CS [Harach et al 1999].
  - The lifetime risk for epithelial thyroid cancer is approximately 35% [Tan et al 2012]. Median age of onset was 37 years; seven years was the youngest age at diagnosis [Ngeow et al 2011].

Note: (1) Follicular histology is overrepresented in adults compared to the general population in which papillary histology is overrepresented. (2) No medullary thyroid carcinoma was observed in the cohort with molecularly confirmed CS.

- **Endometrial disease**
  - Benign uterine fibroids are common.
  - Lifetime risk for endometrial cancer is estimated at 28%, with the starting age at risk in the late 30s to early 40s [Tan et al 2012].
- **Gastrointestinal neoplasias**
  - More than 90% of individuals with a *PTEN* pathogenic variant who underwent at least one upper or lower endoscopy were found to have polyps [Heald et al 2010]. Histologic findings varied, ranging from ganglioneuromatous polyps, hamartomatous polyps, and juvenile polyps to adenomatous polyps.
  - Lifetime risk for colorectal cancer is estimated at 9%, with the starting age at risk in the late 30s [Tan et al 2012].
- **Renal cell carcinoma.** Lifetime risk for renal cell carcinoma is estimated at 35%, with the starting age at risk in the 40s [Tan et al 2012]. The predominant histology is papillary renal cell carcinoma [Mester et al 2012].
- **Other**
  - Lifetime risk for cutaneous melanoma is estimated at more than 5%.
  - Brain tumors as well as vascular malformations affecting any organ are occasionally seen in individuals with CS.

    Note: Because meningioma is so common in the general population, it is not yet clear if meningioma is a true manifestation of CS.
  - A rare central nervous system tumor, cerebellar dysplastic gangliocytoma (Lhermitte-Duclos disease), is also found in CS and may be pathognomonic.

Bannayan-Riley-Ruvalcaba Syndrome (BRRS)

Common features of BRRS, in addition to those mentioned above, include high birth weight, developmental delay, and intellectual disability (50% of affected individuals), a myopathic process in proximal muscles (60%), joint hyperextensibility, pectus excavatum, and scoliosis (50%) [Zbuk & Eng 2007].

Individuals with BRRS and a *PTEN* pathogenic variant are thought to have the same cancer risks as individuals with CS. Note: It is not clear whether these risks apply to individuals with BRRS who do not have a *PTEN* pathogenic variant.

The gastrointestinal hamartomatous polyps in BRRS (seen in 45% of affected individuals) may occasionally be associated with intussusception, but rectal bleeding and oozing of "serum" is more common. These polyps are not believed to increase the risk for colorectal cancer. PHTS hamartomatous polyps are different in histomorphology from the polyps seen in Peutz-Jeghers syndrome.

PTEN-Related Proteus Syndrome (PS)

PS is characterized by progressive segmental or patchy overgrowth of diverse tissues of all germ layers, most commonly affecting the skeleton, skin, and adipose and central nervous systems. In most individuals Proteus syndrome has minimal or no manifestations at birth, develops and progresses rapidly beginning in the toddler period, and relentlessly progresses through childhood, causing severe overgrowth and disfigurement. It is

associated with a range of tumors, pulmonary complications, and a striking predisposition to deep vein thrombosis and pulmonary embolism. See Proteus Syndrome.

Proteus-Like Syndrome

Proteus-like syndrome is undefined but describes individuals with significant clinical features of PS who do not meet the diagnostic criteria.

Genotype-Phenotype Correlations

For purposes of *PTEN* genotype-phenotype analyses, a series of 37 unrelated probands with CS were ascertained by the operational diagnostic criteria of the International Cowden Consortium, 1995 version [Nelen et al 1996, Eng 2000]. Association analyses revealed that families with CS and a germline *PTEN* pathogenic variant are more likely to develop malignant breast disease than are families who do not have a *PTEN* pathogenic variant [Marsh et al 1998]. In addition, pathogenic missense variants and others 5' to or within the phosphatase core motif appeared to be associated with involvement of five or more organs, a surrogate phenotype for severity of disease [Marsh et al 1998].

More than 90% of families with CS-BRRS overlap were found to have a germline *PTEN* pathogenic variant. The mutational spectra of BRRS and CS have been shown to overlap, thus lending formal proof that CS and BRRS are allelic [Marsh et al 1999]. No difference in mutation frequencies was observed between BRRS occurring in a single individual in a family and BRRS occurring in multiple family members.

An individual presenting as a simplex case (i.e., one with no known family history) of Proteus-like syndrome comprising hemihypertrophy, macrocephaly, lipomas, connective tissue nevi, and multiple arteriovenous malformations was found to have a germline p.Arg335Ter *PTEN* pathogenic variant and the same somatic pathogenic variant (p.Arg130Ter) in three separate tissues, possibly representing germline mosaicism [Zhou et al 2000]. Both pathogenic variants have been previously described in classic CS and BRRS.

Two of nine individuals who met the clinical diagnostic criteria of Proteus syndrome and three of six with Proteus-like syndrome were found to have germline *PTEN* pathogenic variants [Zhou et al 2001]. Since then multiple single cases of germline *PTEN* pathogenic variants in individuals who met the clinical diagnostic criteria of Proteus and Proteus-like syndrome have been reported [Smith et al 2002, Loffeld et al 2006].

Penetrance

More than 90% of individuals with CS have some clinical manifestation of the disorder by the late 20s [Nelen et al 1996, Eng 2000, Zbuk & Eng 2007]. By the third decade, 99% of affected individuals develop the mucocutaneous stigmata, primarily trichilemmomas and papillomatous papules, as well as acral and plantar keratoses. (See also Clinical Description for age at which specific manifestations are likely to become evident.)

Nomenclature

Cowden syndrome, Cowden disease, and multiple hamartoma syndrome have been used interchangeably.

Bannayan-Riley-Ruvalcaba syndrome, Bannayan-Ruvalcaba-Riley syndrome, Bannayan-Zonana syndrome, and Myhre-Riley-Smith syndrome refer to a similar constellation of signs that comprise what the authors refer to as BRRS. When a *PTEN* pathogenic variant is found, the gene-related name, PHTS, should be used.

One form of Proteus-like syndrome, with a clinical presentation similar to that first described by Zhou et al [2000] and with a germline *PTEN* pathogenic variant, was termed SOLAMEN (*s*egmental *o*vergrowth, *l*ipomatosis, *a*rteriovenous *m*alformation and *e*pidermal *n*evus) syndrome [Caux et al 2007]. This is not useful, especially in the molecular era, as any phenotype associated with a *PTEN* pathogenic variant should be termed PHTS with all its implications for clinical management [Zbuk & Eng 2007, Orloff & Eng 2008].

Prevalence

Because the diagnosis of CS is difficult to establish, the true prevalence is unknown. The prevalence has been estimated at one in 200,000 [Nelen et al 1999], likely an underestimate. Because of the variable and often subtle external manifestations of CS/BRRS, many individuals remain undiagnosed [Zbuk & Eng 2007; Eng, unpublished].

Genetically Related (Allelic) Disorders

No phenotypes other than Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, *PTEN*-related Proteus syndrome, and Proteus-like syndrome are known to be **consistently** caused by pathogenic variants in *PTEN*.

Phenotypes that can be associated with *PTEN* germline pathogenic variants:

- **Lhermitte-Duclos disease (LDD).** Most, if not all, adult-onset Lhermitte-Duclos disease (dysplastic gangliocytoma of the cerebellum, a hamartomatous overgrowth known to be a feature of CS) can be attributed to pathogenic variants in *PTEN*, even in the absence of other clinical signs of CS/BRRS. However, germline *PTEN* pathogenic variants appear to be rare in individuals with childhood-onset LDD [Zhou et al 2003a].
- **Autism/pervasive developmental disorder and macrocephaly.** Germline *PTEN* pathogenic variants were identified in individuals with these findings, especially in the presence of other personal or family history consistent with CS/BRRS [Dasouki et al 2001, Goffin et al 2001]. Butler et al [2005] found that approximately 20% of individuals with autism spectrum disorders and macrocephaly have germline *PTEN* pathogenic variants. The 10%-20% prevalence of germline *PTEN* pathogenic variants in autism spectrum disorders with macrocephaly has now been confirmed by several independent groups [Herman et al 2007a, Herman et al 2007b, Orrico et al 2009, Varga et al 2009].
- **Juvenile polyposis of infancy (JPI).** In this rare condition, caused by germline deletion of *BMPR1A* and *PTEN*, juvenile polyposis is diagnosed before age six years [Delnatte et al 2006]. Often the gastrointestinal manifestations of bleeding, diarrhea, and protein-losing enteropathy are severe. External stigmata may mimic BRRS.

Differential Diagnosis

Table 2. Disorders to Consider in the Differential Diagnosis of *PTEN* Hamartoma Tumor Syndrome

Disorder	Gene(s)	MOI	Clinical Features of the Differential Diagnosis Disorder	
			Overlapping w/PHTS	General
Primary differential diagnoses to consider: other hamartoma syndromes incl JPS & PJS				
JPS	*BMPR1A* *SMAD4*	AD	Hamartomatous gastrointestinal polyps [1]	Characterized by predisposition to hamartomatous polyps in GI tract Most individuals have some polyps by age 20 yrs; some may have only 4-5 polyps over a lifetime; others in same family may have >100. Left untreated, polyps may cause bleeding & anemia. Most juvenile polyps are benign, but malignant transformation can occur.

Table 2. continued from previous page.

Disorder	Gene(s)	MOI	Clinical Features of the Differential Diagnosis Disorder	
			Overlapping w/PHTS	General
PJS	*STK11*	AD	Hamartomatous gastrointestinal polyps [2]	Characterized by GI polyposis, mucocutaneous pigmentation, & cancer predisposition The pigmentation of perioral region is pathognomonic, particularly if it crosses the vermilion border. Hyperpigmented macules on the fingers are also common.
Less likely differential diagnoses to consider				
BHD	FLCN	AD	Cutaneous manifestations incl skin tags, fibromas, & trichiepitheliomas (can be mistaken for trichilemmomas)	Characterized by cutaneous findings [3], pulmonary cysts/history of pneumothorax, & various types of renal tumors [4] Lung cysts are mostly bilateral & multifocal; most individuals are asymptomatic but at high risk for spontaneous pneumothorax.
NF1	*NF1*	AD	Café au lait macules & fibromatous tumors of the skin [5]	May be mistakenly diagnosed in persons w/CS/BRRS due to presence of ganglioneuromas in GI tract.
Nevoid basal cell carcinoma (Gorlin) syndrome	*PTCH1* *SUFU*	AD	Hamartomatous gastric polyps	Characterized by development of multiple jaw keratocysts &/or basal cell carcinomas Affected individuals can also develop other tumors & cancers incl fibromas, hamartomatous gastric polyps, & medulloblastomas. Dermatologic findings & developmental features in CS & Gorlin syndrome are quite different.

Table 2. continued from previous page.

Disorder	Gene(s)	MOI	Clinical Features of the Differential Diagnosis Disorder	
			Overlapping w/PHTS	General
AKT1-related Proteus syndrome	*AKT1*	See footnote 6	Proteus syndrome is a "PTEN-pathway-opathy" [7]. Macrocephaly, overgrowth	Characterized by progressive segmental or patchy overgrowth of diverse tissues of all germ layers In most individuals: minimal or no manifestations at birth; progresses rapidly beginning in toddler period & relentlessly through childhood, causing severe overgrowth & disfigurement Associated w/a range of tumors, pulmonary complications, & striking predisposition to deep vein thrombosis & pulmonary embolism

AD = autosomal dominant; AR = autosomal recessive; BHD = Birt-Hogg-Dubé syndrome; GI = gastrointestinal; JPS = juvenile polyposis syndrome; the term "juvenile" refers to the type of polyp rather than to the age of onset of polyps; MOI = mode of inheritance; NF1 = neurofibromatosis type 1; PJS = Peutz-Jeghers syndrome; XL = X-linked

1. Juvenile polyps are hamartomas that show a normal epithelium with a dense stroma, an inflammatory infiltrate, and a smooth surface with dilated, mucus-filled cystic glands in the lamina propria. (See Juvenile Polyposis Syndrome.)

2. The Peutz-Jeghers polyp has a diagnostic appearance and is quite different from the hamartomatous polyps seen in CS or JPS. Clinically, Peutz-Jeghers polyps are often symptomatic (intussusception, rectal bleeding), whereas CS polyps are rarely so. (See Peutz-Jeghers Syndrome.)

3. Cutaneous findings characteristic of BHD: fibrofolliculomas, trichodiscomas/angiofibromas, perifollicular fibromas, and acrochordons. Skin lesions typically appear during the third or fourth decade of life and usually increase in size and number with age. (See Birt-Hogg-Dubé syndrome.)

4. Individuals with BHDS are at increased risk for renal tumors that are typically bilateral and multifocal, and usually slow growing.

5. The only two features seen in both NF1 and CS/BRRS are café au lait macules and fibromatous tumors of the skin. (See Neurofibromatosis type 1.)

6. All individuals with clinically confirmed Proteus syndrome (known to authors of the Proteus Syndrome *GeneReview*) have been simplex cases caused by somatic mosaicism for the specific *de novo AKT1* pathogenic variant c.49G>A (p.Glu17Lys).

7. Since *PTEN* downregulates *AKT1* by decreasing phosphorylation, the finding of an activating *AKT1* pathogenic variant in Proteus syndrome confirms that Proteus syndrome is a 'PTEN-pathway-opathy.'

Germline *KLLN* Epimutation

Bennett et al [2010] determined that approximately 30% of individuals with Cowden syndrome (CS) (OMIM 615107) and Cowden-like syndrome who do not have a *PTEN* germline pathogenic variant have a germline *KLLN* methylation epimutation, which resulted in downregulation of expression of *KLLN*, but not of *PTEN*. Of note, *KLLN* shares a bidirectional promoter with *PTEN*. Pilot data suggest that individuals with CS and Cowden-like syndrome with a germline *KLLN* epimutation have a greater prevalence of breast and renal cell carcinomas than do those with a germline *PTEN* pathogenic variant. Thus, individuals with Cowden-like syndrome (especially those with breast and/or renal carcinomas or a family history of such tumors) should be offered *KLLN* methylation analysis first because it accounts for 30% of such individuals, whereas *PTEN* germline pathogenic variants account for 5%-10%.

New Susceptibility Genes in Individuals with Non-PHTS CS and a CS-Like Disorder

A pilot study found that individuals with Cowden syndrome (CS) and a CS-like (CSL) disorder without germline *PTEN* pathogenic variants (but with increased levels of manganese superoxide dismutase) harbored germline variants in *SDHB* (OMIM 612359) and *SDHD* (OMIM 615106) [Ni et al 2008]. That germline variants in *SDHB*, *SDHC*, and *SDHD* occur in approximately 10% of persons with CS or CSL who do not have a *PTEN* pathogenic

variant has been validated in an independent series of 608 research participants [Ni et al 2012]. These variants were associated with stabilization of HIF1a, destabilization of p53 secondary to decreased NQ01 interaction, and increased reactive oxygen species with consequent apoptosis resistance. Approximately 10% of individuals with CS/CSL disorder without germline *PTEN* or *SDHx* pathogenic variants have been found to harbor germline *PIK3CA* (see *PIK3CA*-Related Segmental Overgrowth) or *AKT1* pathogenic variants [Orloff et al 2013]. Another 3%-6% of CS and CS-like individuals without pathogenic variants in the above known genes have germline heterozygous *SEC23B* pathogenic variants, which are particularly associated with thyroid carcinoma [Yehia et al 2015].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with *PTEN* hamartoma tumor syndrome (PHTS), the following evaluations are recommended:

- Complete medical history and family history
- Physical examination with particular attention to skin, mucous membranes, thyroid, breasts
- In children: consideration of neurodevelopmental evaluation
- Urinalysis with cytospin
- Baseline thyroid ultrasound examination* (on identification of a PTEN pathogenic variant)
- For women age ≥30 years at diagnosis*:
  - Breast screening (at minimum mammogram; MRI may also be incorporated)
  - Transvaginal ultrasound or endometrial biopsy
- For men and women age ≥35 years at diagnosis*: colonoscopy
- For men and women age ≥40 years at diagnosis*: renal imaging (CT or MRI preferred)
- Consultation with a clinical geneticist and/or genetic counselor

* For individuals with a family history of a particular cancer type at an early age, screening may be considered five to ten years prior to the youngest diagnosis in the family.

Treatment of Manifestations

The mucocutaneous manifestations of Cowden syndrome are rarely life threatening:

- If asymptomatic, observation alone is prudent.
- Cutaneous lesions should be excised only if malignancy is suspected or symptoms (e.g., pain, deformity, increased scarring) are significant.

  When symptomatic, topical agents (e.g., 5-fluorouracil), curettage, cryosurgery, or laser ablation may provide only temporary relief [Hildenbrand et al 2001]. Surgical excision is sometimes complicated by cheloid formation and recurrence (often rapid) of the lesions [Eng, unpublished data].

Treatment for the benign and malignant manifestations of PHTS is the same as for their sporadic counterparts.

Prevention of Primary Manifestations

Some women at increased risk for breast cancer consider prophylactic mastectomy, especially if breast tissue is dense or if repeated breast biopsies have been necessary. Prophylactic mastectomy reduces the risk of breast cancer by 90% in women at high risk [Hartmann et al 1999]. Note: The recommendation of prophylactic mastectomy is a generalization for women at increased risk for breast cancer from a variety of causes, not just from PHTS.

No **direct** evidence supports the routine use of agents such as tamoxifen or raloxifene in individuals with PHTS to reduce the risk of developing breast cancer. Physicians should discuss the limitations of the evidence and the risks and benefits of chemoprophylaxis with each individual. In addition, the clinician must discuss the increased risk of endometrial cancer associated with tamoxifen use in a population already at increased risk for endometrial cancer.

Surveillance

The most serious consequences of PHTS relate to the increased risk of cancers including breast, thyroid, endometrial, and to a lesser extent, renal. In this regard, the most important aspect of management of **any** individual with a *PTEN* pathogenic variant is increased cancer surveillance to detect any tumors at the earliest, most treatable stages. Current suggested screening by age follows:

Cowden Syndrome

Pediatric (age <18 years)

- Yearly thyroid ultrasound examination** (on identification of a *PTEN* pathogenic variant)
- Yearly skin check with physical examination

Adult

- Yearly thyroid ultrasound** and dermatologic evaluation
- Women beginning at age 30 years:
  - Monthly breast self-examination**
  - Yearly breast screening (at minimum mammogram); MRI may also be incorporated.**
  - Yearly transvaginal ultrasound or endometrial biopsy**
- For men and women:
  - Colonoscopy beginning at age 35 years**; frequency dependent on degree of polyposis identified
  - Biennial renal imaging (CT or MRI preferred) beginning at age 40 years**

** For those with a family history of a particular cancer type at an early age screening may be initiated five to ten years prior to the youngest diagnosis in the family. For example, in a woman whose mother developed breast cancer at age 30 years breast surveillance may begin at age 25-30 years.

Note: Although the NCCN Guidelines removed endometrial surveillance after 2007 (without expert PHTS input), it is prudent to ensure the minimal surveillance for endometrial cancer as detailed if family history is positive for endometrial cancer.

Bannayan-Riley-Ruvalcaba Syndrome

Screening recommendations have not been established for BRRS. Given recent molecular epidemiologic studies, however, individuals with BRRS and a germline *PTEN* pathogenic variant should undergo the same surveillance as individuals with CS.

Individuals with BRRS should also be monitored for complications related to gastrointestinal hamartomatous polyposis, which can be more severe than in CS.

Proteus Syndrome/Proteus-Like Syndrome

Although the observation of germline *PTEN* pathogenic variants in a minority of individuals who meet the clinical diagnostic criteria for Proteus syndrome and Proteus-like syndrome is relatively new, clinicians should consider instituting the CS surveillance recommendations for individuals with these disorders who have germline *PTEN* pathogenic variants.

Agents/Circumstances to Avoid

Because of the propensity for rapid tissue regrowth and the propensity to form keloid tissue, it is recommended that cutaneous lesions be excised only if malignancy is suspected or symptoms (e.g., pain, deformity) are significant.

Evaluation of Relatives at Risk

When a *PTEN* pathogenic variant has been identified in a proband, testing of asymptomatic at-risk relatives can identify those who have the family-specific pathogenic variant and, therefore, have PHTS. These individuals are in need of initial evaluation and ongoing surveillance.

Molecular testing is appropriate for at-risk individuals younger than age 18 years, given the possible early disease presentation in individuals with BRRS and Proteus syndrome. In individuals with PHTS, the earliest documented breast cancer and thyroid cancer are at age 17 years and before age nine years, respectively.

Relatives who have not inherited the *PTEN* pathogenic variant found in an affected relative do not have PHTS or its associated cancer risks.

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

Therapies Under Investigation

Although mTOR inhibitors show promise for treatment of malignancies in individuals who have a germline *PTEN* pathogenic variant, use should be limited to clinical trials. A clinical trial specifically directed at PHTS recently concluded; results have not been published at the time of this *GeneReview* update.

An mTOR inhibitor trial will open shortly for pediatric, adolescent, and young adult patients with germline *PTEN* pathogenic variants and autism spectrum disorder.

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.

Genetic Counseling

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

Mode of Inheritance

PTEN hamartoma tumor syndrome (PHTS) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- **Cowden syndrome (CS).** Because CS is likely underdiagnosed, the actual proportion of simplex cases (defined as individuals with no obvious family history) and familial cases (defined as ≥2 related affected individuals) cannot be determined. As a broad estimate, 55%-90% of individuals with CS have an affected parent [Marsh et al 1999, Mester et al 2012]. However, a family history estimate based on practical experience is likely nearer to 50%.

- **Bannayan-Riley-Ruvalcaba syndrome (BRRS).** The majority of evidence suggests that *PTEN* pathogenic variants occur in both simplex and familial occurrences of BRRS [Eng 2003, Zbuk & Eng 2007].
- ***PTEN*-related Proteus syndrome and Proteus-like syndrome.** Virtually all individuals are simplex cases.
- If a *PTEN* pathogenic variant is identified in the proband, the parents should be offered molecular genetic testing to determine if one of them has previously unidentified PHTS.
- The family history of many individuals diagnosed with PHTS may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent.

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

- If a parent of the proband has the *PTEN* pathogenic variant, the risk to the sibs of inheriting the variant is 50%.
- If it has been shown that neither parent has the *PTEN* pathogenic variant found in the proband, the risk to sibs is probably negligible, as germline mosaicism has rarely been reported in PHTS [Pritchard et al 2013].
- If the genetic status of the parents is unknown but they have no clinical signs of CS/BRRS and are in their thirties, it is unlikely either parent is heterozygous for a *PTEN* pathogenic variant and the risk to sibs is therefore minimal (penetrance of PHTS is close to 99% by the thirties in individuals with a *PTEN* pathogenic variant).

Offspring of a proband. Each child of an individual with PHTS has a 50% chance of inheriting the *PTEN* pathogenic variant and developing PHTS.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *PTEN* pathogenic variant, his or her family members are 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 relatives. When a pathogenic variant has been identified in a proband, testing of asymptomatic at-risk relatives can identify those who also have the pathogenic variant and have PHTS. These individuals are in need of initial evaluation and ongoing surveillance. Molecular testing is appropriate for at-risk individuals younger than age 18 years, given the possible early disease presentation in individuals with BRRS and Proteus syndrome, and of thyroid cancer in PHTS.

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

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 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.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Diagnosis

Once the *PTEN* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis for PHTS are possible.

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.

- **My46 Trait Profile**
  PTEN Hamartoma Tumor Syndrome
- **National Library of Medicine Genetics Home Reference**
  Cowden syndrome
- **PTEN Hamartoma Tumor Syndrome Foundation**
  The PTEN Hamartoma Tumor Syndrome Foundation was founded with a mission to educate about PTEN syndromes, provide financial support to patients, support research, and to promote awareness.
  Email: ptensyndromefoundation@gmail.com
  www.ptenfoundation.org
- **American Cancer Society (ACS)**
  250 Williams Street Northwest
  Atlanta GA 30303
  Phone: 800-227-2345 (toll-free 24/7); 866-228-4327 (toll-free 24/7 TTY)
  www.cancer.org
- **CancerCare**
  275 Seventh Avenue
  22nd Floor
  New York NY 10001
  Phone: 800-813-4673 (toll-free); 212-712-8400 (administrative)
  Fax: 212-712-8495
  Email: info@cancercare.org
  www.cancercare.org
- **National Breast Cancer Coalition (NBCC)**
  An advocacy group seeking public policy change to benefit breast cancer patients and survivors
  1101 17th Street Northwest
  Suite 1300

Washington DC 20036

Phone: 800-622-2838 (toll-free); 202-296-7477

Fax: 202-265-6854

Email: info@stopbreastcancer.org

www.stopbreastcancer.org

- **National Coalition for Cancer Survivorship (NCCS)**

  A consumer organization that advocates on behalf of all people with cancer

  8455 Colesville Road

  Suite 930

  Silver Spring MD 20910

  Phone: 877-622-7937 (toll-free); 301-650-9127

  Fax: 301-565-9670

  Email: info@canceradvocacy.org

  www.canceradvocacy.org

- **Susan G. Komen Breast Cancer Foundation**

  Information, referrals to treatment centers. Answers questions from recently diagnosed women and provides emotional support. Funds research programs for women who do not have adequate medical service and support.

  5005 LBJ Freeway

  Suite 250

  Dallas TX 75244

  Phone: 877-465-6636 (Toll-free Helpline)

  Fax: 972-855-1605

  Email: helpline@komen.org

  ww5.komen.org

- **Prospective Registry of MultiPlex Testing (PROMPT)**

  PROMPT is an online research registry for patients and their families that helps researchers answer the question: "How do genetic variants affect your cancer risk?"

  PROMPT

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. PTEN Hamartoma Tumor Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar

Table A. continued from previous page.

PTEN	10q23.31	Phosphatidylinositol 3,4,5-trisphosphate 3-phosphatase and dual-specificity protein phosphatase PTEN	PTEN database	PTEN	PTEN

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 PTEN Hamartoma Tumor Syndrome (View All in OMIM)

153480	none found
158350	COWDEN SYNDROME 1; CWS1
601728	PHOSPHATASE AND TENSIN HOMOLOG; PTEN

Molecular Pathogenesis

While much functional research has been accomplished, complete function of PTEN is not yet fully understood. PTEN belongs to a sub-class of phosphatases called dual-specificity phosphatases that remove phosphate groups from tyrosine as well as serine and threonine. In addition, PTEN is the major phosphatase for phosphoinositide-3,4,5-triphosphate, and thus downregulates the PI3K/AKT pathway.

In vitro and human immunohistochemical data suggest that PTEN traffics in and out of the nucleus [Ginn-Pease & Eng 2003, Chung et al 2005, Minaguchi et al 2006]. When PTEN is in the nucleus, it predominantly signals down the protein phosphatase and MAPK pathway to elicit cell cycle arrest [Chung & Eng 2005]. One of the nuclear functions of PTEN is to stabilize the genome [Shen et al 2007]. When in the cytoplasm, its lipid phosphatase predominantly signals down the AKT pathway to elicit apoptosis.

Somatic *PTEN* variants and loss of gene expression are frequently found in both endometrioid endometrial adenocarcinoma and precancerous endometrial lesions (intraepithelial neoplasia), confirming the critical role that *PTEN* must play in endometrial tissues [Mutter et al 2000].

Gene structure. *PTEN* comprises nine exons and likely spans a genomic distance of more than 120 kb. The 1209-bp coding sequence is predicted to encode a 403-amino acid protein. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Germline pathogenic variants have been found throughout *PTEN* (with the exception of exon 9) and include missense, nonsense, and splice-site variants, small deletions, insertions, and large deletions. More than 150 unique pathogenic variants are currently listed in the Human Gene Mutation Database (see Table A). Nearly 40% of pathogenic variants are found in exon 5, which encodes the phosphate core motif [Eng 2003]. Most pathogenic variants are unique, although a number of recurrent pathogenic variants have been reported, particularly those in Table 3.

Table 3. Selected *PTEN* Recurrent Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.388C>T [1]	p.Arg130Ter	NM_000314.4 NP_000305.3
c.697C>T [1]	p.Arg233Ter	
c.1003C>T [1]	p.Arg335Ter	

Note on variant classification: Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.
Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Recurrent pathogenic variants [Bonneau & Longy 2000, Zbuk & Eng 2007, Orloff & Eng 2008]

Approximately 10% of individuals with CS who do not have a pathogenic variant detected in the *PTEN* coding sequence have heterozygous germline pathogenic variants in the *PTEN* promoter [Zhou et al 2003b]. In contrast, 10% of individuals with BRRS who do not have an identifiable *PTEN* pathogenic variant on sequence analysis have large deletions within or encompassing *PTEN* [Zhou et al 2003b].

Normal gene product. *PTEN* encodes an almost ubiquitously expressed dual-specificity phosphatase. The PTEN protein localizes to specific nuclear and cytoplasmic components. The wild-type protein is a major lipid phosphatase that downregulates the PI3K/Akt pathway to cause G1 cell cycle arrest and apoptosis. In addition, the protein phosphatase appears to play an important role in inhibition of cell migration and spreading, as well as downregulating several cell cyclins [Eng 2003]. It appears that nuclear PTEN mediates cell cycle arrest, while cytoplasmic PTEN is required for apoptosis [Chung & Eng 2005].

Abnormal gene product. The majority (76%) of germline pathogenic variants in *PTEN* predict either truncated PTEN protein, lack of protein (haploinsufficiency), or dysfunctional protein. Many missense variants are functionally null and several act as dominant negatives [Weng et al 2001a, Weng et al 2001b]. When PTEN is absent, decreased, or dysfunctional, phosphorylation of AKT1 is uninhibited, leading to the inability to activate cell cycle arrest and/or to undergo apoptosis. In addition, through lack of protein phosphatase activity, the mitogen-activated protein kinase (MAPK) pathway is dysregulated, leading to abnormal cell survival [Eng 2003].

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Chapter Notes

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Dr Eng is the chair and coordinator of the International Cowden Syndrome Consortium, founding Chairwoman of the Cleveland Clinic Genomic Medicine Institute and a primary researcher in the field of PTEN-related disorders. The Cleveland Clinic Genomic Medicine Institute program features the only multidisciplinary Cowden Syndrome center in the US, with ongoing clinical and molecular research protocols in PHTS.

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Revision History

- 2 June 2016 (sw) Comprehensive update posted live
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