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Birt-Hogg-Dubé Syndrome

Synonym: Hornstein-Knickenberg Syndrome

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Summary

Clinical characteristics

The clinical characteristics of Birt-Hogg-Dubé syndrome (BHDS) include cutaneous manifestations (fibrofolliculomas, acrochordons, angiofibromas, oral papules, cutaneous collagenomas, and epidermal cysts), pulmonary cysts/history of pneumothorax, and various types of renal tumors. Disease severity can vary significantly even within the same family. Skin lesions typically appear between the second and fourth decades of life and typically increase in size and number with age. Lung cysts are often bilateral and multifocal; most individuals are asymptomatic but at high risk for spontaneous pneumothorax. Individuals with BHDS are at a sevenfold increased risk for renal tumors that can be bilateral and multifocal; median age of renal tumor diagnosis is 48 years. The most common renal tumors are a hybrid of oncocytoma and chromophobe histologic cell types (oncocytic hybrid tumor) and chromophobe histologic cell types. Some families have renal tumor(s) and/or spontaneous pneumothorax without cutaneous manifestations.

Diagnosis/testing

The diagnosis of BHDS is established in a proband with either one major criteria (five or more facial or truncal papules with at least one histologically confirmed fibrofolliculoma or identification of a heterozygous pathogenic variant in *FLCN*) or two minor criteria (early-onset [age <50 years] renal cell cancer, multifocal/bilateral renal cell cancer, renal cell cancer with mixed chromophobe/oncocytic histology, multiple lung cysts with or without spontaneous pneumothorax, and/or first degree relative with BHDS).

Management

Treatment of manifestations: Surgical and laser treatment can lead to temporary improvement of folliculomas, but lesions often recur. Pneumothoraces are treated as in the general population. When possible, nephron-sparing surgery is the treatment of choice for renal tumors, depending on their size and location.

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Surveillance: Full-body skin examination every six to 12 months for possible risk of melanoma. Annual abdominal/pelvic MRI to assess for renal lesions; abdominal/pelvic CT with contrast is an alternative when MRI is not an option, but the long term-effects of cumulative radiation exposure are unknown. Consider annual review of signs/symptoms of parotid tumors and annual thyroid ultrasound. Begin screening colonoscopies at age 40 years, or earlier in those with a family history of colorectal cancer diagnosed prior to age 40 years.

Agents/circumstances to avoid: Cigarette smoking, high ambient pressures, and radiation exposure.

Evaluation of relatives at risk: Molecular genetic testing for the family-specific pathogenic variant for early identification of at-risk family members improves diagnostic certainty and reduces costly screening procedures in at-risk relatives who have not inherited the family-specific pathogenic variant.

Genetic counseling

BHDS is inherited in an autosomal dominant manner. The offspring of an individual with BHDS have a 50% chance of inheriting the pathogenic variant. Prenatal diagnosis for a pregnancy at increased risk and preimplantation genetic testing are possible if the *FLCN* pathogenic variant has been identified in an affected family member.

Diagnosis

According to guidelines for the diagnosis of Birt-Hogg-Dubé syndrome (BHDS) published by the European Birt-Hogg-Dubé consortium [Menko et al 2009], one major or two minor criteria are necessary for the diagnosis. Note: Revised diagnostic criteria, in which the identification of a pathogenic variant in *FLCN* is needed to establish the diagnosis of BHDS, have been proposed [Schmidt & Linehan 2015].

Suggestive Findings

BHDS **should be suspected** in individuals with any of the following major or minor criteria.

Major criteria

- Five or more fibrofolliculomas/trichodiscomas with at least one confirmed histologically
- Note: Identification of a heterozygous pathogenic variant in *FLCN* was included as a major criterion by Menko et al [2009].

Minor criteria

- Multiple lung cysts. Bilateral basally located lung cysts with no other apparent cause, with or without spontaneous primary pneumothorax
- Early-onset renal cancer (age <50 years)
- Multifocal or bilateral renal cancer
- Renal cancer of mixed chromophobe and oncocytic histology
- First-degree relative with BHDS

Establishing the Diagnosis

The diagnosis of BHDS **is established** in a proband with:

- One major criteria (Note: Identification of a heterozygous pathogenic variant in *FLCN* is one of the major criteria); OR
- Two minor criteria as described in Suggestive Findings.

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

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of BHDS is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with facial papules and/or renal tumors are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

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

- **Single-gene testing.** Sequence analysis of *FLCN* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.
- **A multigene panel** that includes *FLCN* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by facial papules and renal tumors, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

If exome sequencing is not diagnostic – and particularly when evidence supports autosomal dominant inheritance – **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

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 Birt-Hogg-Dubé Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
FLCN	Sequence analysis [3]	~88%-96% [4, 5]
	Gene-targeted deletion/duplication analysis [6]	<8% [4]
Unknown	NA	~4% [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic 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. Schmidt et al [2005], Toro et al [2008], Sattler et al [2018b]
5. 20%-24% of families with BHDS were found to have deletion (c.1285delC) or duplication (c.1285dupC) of a C nucleotide in the polycytosine tract in exon 11, which is a mutational hot spot (see Table 6) [Sattler et al 2018b].
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

Clinical Characteristics

Clinical Description

The clinical characteristics of Birt-Hogg-Dubé syndrome (BHDS) include fibrofolliculomas (specific cutaneous lesions), pulmonary cysts/history of pneumothorax, and various types of of renal tumors. Intra- as well as interfamilial variation in disease severity can be significant.

Table 2. Select Features of Birt-Hogg-Dubé Syndrome

Feature	% of Persons w/Feature	Comment
Cutaneous manifestations (e.g., fibrofolliculoma, acrochordons)	84% [1]	Cutaneous manifestations are unusual in individuals age <20 yrs
Pulmonary cysts	70%-85% [2]	The age when cysts start to appear is unknown; childhood onset is likely
Spontaneous recurrent pneumothorax	~25% [3]	
Renal cell carcinoma	19%-35% [4]	Frequency of specific tumor types: chromophobe (19/49 individuals); clear cell (15/49); hybrid oncocytic (5/49); papillary (4/49) [5]

1. Toro et al [2008], Schmidt & Linehan [2015]
2. Kunogi et al [2010]
3. Houweling et al [2011]
4. Zbar et al [2002], Houweling et al [2011], Sattler et al [2018b], Johannesma et al [2019]
5. Frequency of chromophobe or hybrid renal cell carcinoma was higher in studies that focused on renal symptoms.

Cutaneous Manifestations

Individuals with BHDS usually present with multiple small skin-colored opaque whitish or yellowish dome-shaped papules, known as fibrofolliculomas. These noncancerous skin lesions start to appear between the second and fourth decade of life. They are the most common cutaneous manifestation and are present in more than 80% of individuals with BHDS older than age 40 years. In early stages they are typically found centrofacially (nasal and paranasal) and in retroauricular location. They often increase in size, number, and distribution with age eventually involving the face, neck, and upper trunk. Later onset of cutaneous lesions tends to correlate with a

milder skin phenotype. Women tend to have smaller and fewer lesions than men. The large variability in age of onset and expression often limits their usefulness for clinical diagnosis, especially in younger individuals. If present, however, they are a helpful indicator of BHDS. Histopathologically circumscribed fibrosis is seen, which depending on the location is described as: perifollicular fibroma, often replacing the entire hair follicle in the corium; as fibrofolliculoma, with elongated fingerlike extensions; or as trichodiscoma, located subepidermally, mostly parallel to the skin surface.

Note: Trichodiscomas formerly described as tumors of the hair disc are now considered to be scarred remnants of fibrofolliculomas [Tellechea et al 2015].

Additional benign adnexal tumors have been described as achrocordons (skin tags) [Toro et al 2008]. Achrocordons are also common skin lesions found in 25% of the general population and are more common in individuals with obesity and/or advanced age. Achrocordons are typically located on the neck, axillae, and larger skin folds. Angiofibromas have also been reported in individuals with BHDS, but are more common in individuals with tuberous sclerosis. Individuals with BHDS may also develop oral papules (located on the buccal mucosa, tongue, gums, or lips) and cutaneous collagenomas [Nadershahi et al 1997, Toro et al 1999]. Multiple epidermal cysts have been found in approximately 14% of individuals with BHDS [Kluger et al 2010].

BHDS has been reported to be associated with cutaneous melanoma, including multiple desmoplastic melanomas [Lindor et al 2001, Khoo et al 2002, Welsch et al 2005, Toro et al 2008, Cocciolone et al 2010, Sempau et al 2010, Mota-Burgos et al 2013, Sattler et al 2018a] and choroidal melanoma [Fontcuberta et al 2011]. In one study an overall rate of 6% for melanoma was observed, which would be significantly higher than the average lifetime risk of 1.8%-2.4%. Whether individuals with BHDS are indeed at increased risk of developing melanoma compared to the general population requires further investigation.

Pulmonary Cysts and Spontaneous Pneumothorax

Lung cysts, located mainly in the basal lung regions (subpleural and intrapulmonary areas), are present in more than 80% of adults with BHDS. The total number of lung cysts per individual ranges from zero to 166 (mean 16). They are of irregular shape and variable size (1.0-30 mm). The cysts are usually embedded in normal parenchyma that does not exhibit signs of proliferation (as seen in tuberous sclerosis), inflammation (as seen in cystic fibrosis) or matrix deposition (as occurs in amyloidosis). With an average age of onset of 30.2 years (females) and 38.4 years (males), spontaneous pneumothorax is often the first symptom in individuals with BHDS (onset range 13-69 years). The overall prevalence of single or recurrent spontaneous pneumothorax associated with BHDS is estimated at 22.5%-38%. In most individuals the risk of pneumothorax decreases in later adulthood. This could indicate that the formation of lung cysts is a process mainly restricted to younger individuals. Chest CT examination to screen for lung cysts is obviously not possible in healthy children from families with BHDS; thus, the age at which the lung cysts start to develop is unknown.

Renal Cysts and Tumors

Renal tumors associated with BHDS tend to be bilateral and multifocal, but isolated tumors are also common. The reported overall prevalence of renal tumors among individuals with a germline *FLCN* pathogenic variant varies between 19% and 35%. These differences may reflect ascertainment bias as well as the inclusion or exclusion of benign renal tumors. No sex differences are observed in the median age of diagnosis (females: 54.5 years, range 37-79 years; males: 57.0 years, range 30-80 years). The median age of onset is well below that of sporadic renal cell carcinoma (61.8 years) [Furuya et al 2016, Sattler et al 2018b]. Adolescent onset of renal cell carcinoma in individuals with BHDS has been reported [Schneider et al 2018].

The most typical renal tumor in BHDS is a hybrid of oncocytoma and chromophobe histologic cell types, the so-called oncocytic hybrid tumor or hybrid oncocytoma/chromophobe tumor. It has been previously described as the most common tumor type in BHDS, but this could be an ascertainment artifact. Other common renal tumor

types are clear cell carcinoma and oncocytoma; papillary carcinoma is less common. Discordance of histologic subtypes in bilateral and multifocal tumors is common.

Multifocal renal oncocytosis, a rare pathologic condition characterized by numerous oncocytic nodules, is found in the renal parenchyma surrounding tumors in 50%-58% of individuals with BHDS [Kuroda et al 2014]. It is still unclear if renal oncocytosis represents a precursor lesion of renal cell carcinoma or a benign condition.

Other Findings

Parotid tumors. Parotid oncocytoma has been reported in several individuals with BHDS [Toro et al 2008, Yoshida et al 2018]. Additionally, pleomorphic adenoma [Palmirotta et al 2008] and Warthin parotid tumor [Maffé et al 2011] have been described. Bilateral parotid tumors have been reported in two individuals [Maffé et al 2011, Lindor et al 2012]. The frequency and the sometimes bilateral, multifocal nature of these tumors in individuals with BHDS who have not undergone specific screening for parotid tumors suggest that parotid tumors are a manifestation of BHDS.

Thyroid pathology. Several instances of thyroid cancer in individuals with BHDS have been reported [Toro et al 2008, Kunogi et al 2010, Benusiglio et al 2014, Dong et al 2016, Pérez García et al 2017, Panagiotidis et al 2018]. Multinodular goiter [Drummond et al 2002, Welsch et al 2005], thyroid nodules, and/or cysts have also been reported. In a French series, thyroid nodules and/or cysts were detected by ultrasonography in 13/20 individuals (65%) with BHDS; no medullary carcinoma or other thyroid carcinomas were detected. None of the affected individuals with thyroid nodules and/or cysts had a familial history of thyroid cancer. Overall, individuals with thyroid nodules were found in nine of ten families (90%) with *FLCN* germline pathogenic variants [Kluger et al 2010].

Colon cancer. Hornstein & Knickenberg [1975] described a family with fibrofolliculoma and colorectal polyps. The Hornstein-Knickenberg syndrome is now believed to be identical to BHDS. Several instances of colon cancer or colon polyps have been described in affected individuals and family members [Kayhan et al 2017, Motegi et al 2018], but the evidence associating colonic neoplasm and BHDS is conflicting. It has been suggested that only certain pathogenic variants are associated with an increased risk for colon cancer, but other studies were not able to confirm this [Khoo et al 2002, Zbar et al 2002, Nahorski et al 2010] (see Genotype-Phenotype Correlations and Molecular Genetics).

Other tumor types have been reported rarely in individuals with BHDS [modified from Tong et al 2018]:

- **Skin.** Basal cell carcinoma, dermatofibrosarcoma protuberans, Koenen's tumor, squamous cell carcinoma, trichoblastoma
- **Soft tissue.** Angiolipoma, leiomyoma, leiomyosarcoma, lipoma
- **Musculoskeletal.** Cardiac rhabdomyoma, fibrosarcoma, osteoma, rhabdomyoma, sarcoma
- **Gastrointestinal.** Gastric cancer, hepatic cysts, hepatic angioma, peritoneal mesothelioma
- **Head and neck.** Parathyroid adenoma, squamous cell carcinoma, throat cancer
- **Endocrine.** Adrenal adenoma, oncocytic adrenal tumor, pheochromocytoma
- **Hematologic/lymphatic.** Hodgkin's lymphoma, leukemia, and non-Hodgkin's lymphoma
- **Nervous system.** Astrocytoma, cerebral hemangioma, choroidal melanoma, meningioma, neurothekeoma, oncocytic pituitary adenoma, schwannoma
- **Lung.** Adenocarcinoma, bronchoalveolar carcinoma, clear cell sugar tumor, histiocytoma
- **Renal/urinary tract.** Neuroendocrine tumor, prostate cancer, renal angiomyolipoma
- **Reproductive system.** Breast cancer including sarcoma, endometrial carcinoma, fibroadenomatosis, uterine cancer

Genotype-Phenotype Correlations

No genotype-phenotype correlations for *FLCN* have been confirmed. The following correlations are preliminary:

- **c.1285delC** or **c.1285dupC.** A lower renal tumor frequency was observed in individuals with either of the two most common *FLCN* pathogenic variants in a study including 50 families [Sattler et al 2018b].
- **c.1285dupC.** Analysis of a subset of 51 families with BHDS demonstrated a significantly higher risk of colorectal neoplasia in those with the common *FLCN* pathogenic variant c.1285dupC compared to those with the c.610delGCinsTA pathogenic variant [Nahorski et al 2010].

Penetrance

Based on the three major clinical manifestations, penetrance of BHDS is considered to be very high. Approximately 90%-95% of individuals with a heterozygous germline *FLCN* pathogenic variant develop at least one feature of BHDS.

Nomenclature

Hornstein-Knickenberg syndrome, which describes familial multiple perifollicular fibromas and fibromata pendulantia, is considered to fall within the spectrum of BHDS [Schulz & Hartschuh 1999]. One of the individuals from the original family described by Hornstein & Knickenberg [1975] also had colon polyps.

Prevalence

More than 400 affected families from various populations have been described.

Genetically Related (Allelic) Disorders

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

Sporadic tumors (including renal cancer and colorectal cancer) occurring as single tumors in the absence of any other findings of Birt-Hogg-Dubé syndrome can harbor somatic variants in *FLCN* that are **not** present in the germline. Two missense variants (p.Ala444Ser, p.Ala238Val) have been detected in a sample of 30 renal cancer cell lines. **Somatic** frameshift variants in the *FLCN* exon 11 C(8) mononucleotide tract were detected in 23% of sporadic colorectal cancers with microsatellite instability, suggesting that *FLCN* inactivation could contribute to colorectal tumorigenesis. A non-frameshift deletion and *FLCN* loss-of-heterozygosity were found in a pancreatic neuroendocrine tumor [da Silva et al 2003, Khoo et al 2003, Nahorski et al 2010, Lawrence et al 2018]. In these circumstances predisposition to these tumors is not hereditary.

Differential Diagnosis

Table 3. Genes of Interest in the Differential Diagnosis of Birt-Hogg-Dubé Syndrome (BHDS)

Phenotype	Gene(s)	Disorder	MOI	Key Clinical Characteristics of Differential Diagnosis Disorder
Cutaneous manifestations [1]	*CYLD* [2]	Multiple familial trichoepithelioma (see *CYLD* Cutaneous Syndrome)	AD	Trichoepitheliomas
Lung cysts &/or pneumothorax	*MEN1*	Multiple endocrine neoplasia type 1	AD	Facial angiofibromas, collagenomas, lipomas
	PTEN	Cowden syndrome (see *PTEN* Hamartoma Tumor Syndrome)	AD	Trichilemmomas, acral keratoses, papillomatous lesions, mucosal lesions
	TSC1 *TSC2*	Tuberous sclerosis complex	AD	• Hypomelanotic macules, confetti skin lesions, facial angiofibromas, shagreen patches, fibrous cephalic plaques, ungual fibromas • Pulmonary lymphangioleiomyomatosis (may occur as isolated finding or as part of TSC)
	FBN1	Marfan syndrome	AD	Lung bullae may develop, especially of the upper lobes; can predispose to spontaneous pneumothorax
	COL3A1	Vascular Ehlers-Danlos syndrome	AD (AR)	Spontaneous pneumothoraces may be the 1st significant presenting feature; hemothorax, hemopneumothorax, pulmonary blebs, cystic lesions, & hemorrhagic or fibrous nodules
	SERPINA1	Alpha1-antitrypsin deficiency	AR	Chronic obstructive pulmonary disease; emphysema, sometimes w/bronchiectasis
	CFTR	Cystic fibrosis	AR	Progressive obstructive lung disease w/bronchiectasis
Renal cancer [3]	*VHL*	von Hippel-Lindau syndrome	AD	Bilateral & multifocal clear cell renal cell carcinomas; ↑ risk for CNS hemangioblastoma, retinal angioma, pheochromocytoma, & endolymphatic sac tumors
	MET	Hereditary papillary renal cancer (OMIM 605074)	AD	Bilateral & multifocal type 1 papillary renal cell carcinomas
	FH	Hereditary leiomyomatosis and renal cell cancer	AD	Usually solitary renal tumors w/histologic spectrum ranging from tubo-papillary renal cell cancer to type 2 papillary renal cancer to collecting duct renal cell cancer; may present w/cutaneous leiomyoma &/or early-onset & aggressive uterine fibroids.
	MAX *SDHA* *SDHAF2* *SDHB* *SDHC* *SDHD* *TMEM127*	Hereditary paraganglioma-pheochromocytoma syndromes	AD	↑ risk for paragangliomas, pheochromocytomas, gastrointestinal stromal tumors, & RCCs incl oncocytic renal tumors

Table 3. continued from previous page.

Phenotype	Gene(s)	Disorder	MOI	Key Clinical Characteristics of Differential Diagnosis Disorder
	BAP1	*BAP1* tumor predisposition syndrome	AD	Mesothelioma, uveal melanoma, cutaneous melanoma, & different types of renal cell cancer have been described.
	PTEN	Cowden syndrome (see *PTEN* Hamartoma Tumor Syndrome)	AD	• Benign hamartomas & ↑ risks of breast, thyroid, uterine, renal & other cancers • Dermatologic features (e.g., lipomas, trichilemmomas, oral papillomas, penile freckling)

AD = autosomal dominant; AR = autosomal recessive; CNS = central nervous system; MOI = mode of inheritance; RCC = renal cell carcinoma; TSC = tuberous sclerosis complex

1. Fibrofolliculomas are rare and specific for BHDS. Because fibrofolliculomas are clinically similar to various cutaneous lesions, histologic diagnosis is required. Acrochordons, or skin tags, are nonspecific and are found in the general population.

2. Multiple familial trichoepithelioma 1 is caused by pathogenic variants in *CYLD*; the genetic basis of multiple familial trichoepithelioma 2 is unknown (OMIM 612099).

3. Most syndromes with an increased risk of renal cancer are associated with renal pathology that is distinct from that seen in individuals with BHDS-related renal tumors [Linehan et al 2005].

Other conditions to consider in the differential diagnosis of BHDS

- **Pulmonary Langerhans cell histiocytosis** is a rare acquired smoking-related interstitial lung condition characterized by abnormal proliferation of histiocytes that predisposes for pneumothorax. Lung x-rays often show micronodular and interstitial infiltrates and individuals may develop pulmonary fibrosis and pulmonary hypertension. These symptoms are not typical for BHDS [Mendez et al 2004].
- **Sporadic pulmonary lymphangioleiomyomatosis (LAM)** is a condition characterized by multiple lung cysts and pneumothorax. The sporadic form (85% of all individuals with LAM) is more common than LAM associated with tuberous sclerosis (15%). Somatic *TSC1*/*TSC2* pathogenic variants have been identified in some individuals, but the disorder is often of unknown etiology. It affects mainly woman of childbearing age. Spontaneous pneumothorax is often the first manifestation. Features atypical for BHDS are an even distribution of cysts throughout the lung, dyspnea on exertion, hemoptysis, and chylothorax.

Management

Evaluations Following Initial Diagnosis

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

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Birt-Hogg-Dubé Syndrome

System/Concern	Evaluation	Comment
Integument	Detailed dermatologic examination	
Pulmonary	HRCT or CT of the chest for visualization of pulmonary cysts	Individuals w/symptoms/signs of pneumothorax should immediately undergo chest x-ray & CT of the chest
Renal	Abdominal/pelvic MRI to screen for renal tumor(s)	
Other	Consultation w/clinical geneticist &/or genetic counselor	

HRCT = high-resolution computed tomography

Treatment of Manifestations

Fibrofolliculomas. In general, fibrofolliculomas are benign lesions for which no treatment is required; however, affected individuals may seek treatment for such lesions for cosmetic purposes, particularly when multiple cutaneous lesions are located on the face. Surgical and laser treatment can lead to temporary improvement, but lesions often recur over time. [Gambichler et al 2000, Jacob & Dover 2001, Kahle et al 2001]. Topical treatment of fibrofolliculomas with the mTOR inhibitor rapamycin in individuals with BHDS in a double-blinded placebo-controlled randomized split-face study showed no effect [Gijezen et al 2014].

Pneumothorax. Treatment of pneumothorax is the same as in the general population. Lung cysts are usually not treated and most individuals show normal lung function. Some individuals develop mild signs of airway obstruction, which are treated conservatively.

Renal tumors. Individuals with BHDS are at risk of developing more than one renal tumor. It is therefore crucial to detect renal tumors before they exceed 3.0 cm in diameter because nephron-sparing surgery is the treatment of choice whenever possible, depending on the size and location of the tumors [Johannesma et al 2019]. It has been previously reported that renal tumors in BHDS tend to be slow growing and metastasize late. This is most likely not accurate for all tumor subtypes and several individuals with metastatic disease have been reported [Houweling et al 2011]. Renal tumors <3.0 cm in diameter are monitored by periodic imaging. When the largest renal tumor reaches 3.0 cm in diameter, evaluation by a urologic surgeon is appropriate with consideration of nephron-sparing surgery [Stamatakis et al 2013]. Rapidly growing lesions and/or symptoms including pain, blood in the urine, or atypical presentations require a more individualized approach. PET-CT scan is an option for evaluation of these lesions.

Surveillance

There is no consensus on clinical surveillance; the recommendations given are provisional until a consensus conference is conducted.

Table 5. Recommended Surveillance for Individuals with Birt-Hogg-Dubé Syndrome

System/Concern	Evaluation	Frequency
Integument	Dermatologic exam	• No routine screening for fibrofolliculoma • Full skin exam every 6-12 mos for possible risk of melanoma
Lung cysts / Pneumothoraces	Lung CT	• No routine screening in those w/out signs/symptoms to avoid cumulative radiation exposure • Lung CT: (1) for those w/suspected or treated pneumothorax; OR (2) prior to scheduled anesthesia or long-distance flights
Renal tumors	• Abdominal/pelvic MRI is optimal [1] • Abdominal/pelvic CT w/ contrast (if MRI not an option) [2]	• MRI annually starting at age 20 yrs [3] • Continue annually in those w/suspicious lesion(s) (<1.0 cm in diameter, indeterminate lesion, or complex cysts) • In those w/no family history of renal tumors, after 2-3 consecutive normal MRIs, continue screening every 2 yrs [4]
Parotid tumors	Review signs/symptoms of parotid tumors (swelling or pain of the parotid gland)	Annually
Thyroid cancer	Thyroid ultrasound	Consider annually because of the uncertain assoc w/ thyroid cancer

Table 5. continued from previous page.

System/Concern	Evaluation	Frequency
Colon cancer	Colonoscopy	• If family history of CRC, start colonoscopies 10 yrs before onset of CRC in affected relative [5] • If no family history of CRC, consider starting colonoscopies at age 40 yrs

CRC = colorectal cancer

1. The use of renal ultrasound examination is helpful in further characterization of kidney lesions but should not be used as a primary screening modality due to its unreliability in tumors <3 cm in diameter [Johannesma et al 2019]. Renal ultrasound can be considered in the 12-month interval between MRI screenings.

2. The long-term effect of cumulative radiation exposure in individuals with BHDS is unknown and has not been studied.

3. Surveillance can start earlier in those with family history of renal tumor before age 30 years.

4. According to the 3.0-cm rule used by surgeons in treating renal tumors [Pavlovich et al 2005], affected individuals without a family history of kidney tumors who have had two to three consecutive annual MRI examinations without the detection of kidney lesions may be screened every two years until a suspicious lesion is identified.

5. Families fulfilling the Amsterdam II criteria or revised Bethesda criteria should be screened according to guidelines for Lynch syndrome [Umar et al 2004].

Agents/Circumstances to Avoid

Avoid the following:

- Cigarette smoking
- High ambient pressures, which may precipitate spontaneous pneumothorax. Air travel was found to increase pneumothorax risk [Johannesma et al 2016, Gupta et al 2017].
- Radiation exposure

Evaluation of Relatives at Risk

If the familial *FLCN* pathogenic variant is known, use of molecular genetic testing for early identification of at-risk family members improves diagnostic certainty and reduces costly screening procedures in at-risk members who have not inherited the pathogenic variant.

Consensus regarding a recommended age for asymptomatic testing for a familial *FLCN* pathogenic variant has not been established. Most BHDS centers offer predictive testing after age 16 to 18 years to allow genetic counselling of at-risk individuals and facilitate informed consent [Menko et al 2009]. However, in families with a history of juvenile or adolescent onset of symptoms and/or hobbies or career plans involving potentially increased risks for pneumothorax, testing may be recommended at an earlier age.

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

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic

status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Birt-Hogg-Dubé syndrome (BHDS) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with BHDS have an affected parent.
- Some individuals diagnosed with BHDS have the disorder as a result of a *de novo* pathogenic variant. The percentage of individuals with BHDS caused by a *de novo* pathogenic variant is unknown but is most likely in the lower single-digit range.
- Parental molecular genetic testing is recommended if an apparent *de novo FLCN* pathogenic variant has been identified in the proband.
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent.* Though theoretically possible, no instances of germline mosaicism have been reported.

  * Misattributed parentage can also be explored as an alternative explanation for an apparent *de novo* pathogenic variant.
- The family history of some individuals diagnosed with BHDS 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. Therefore, an apparently negative family history cannot be confirmed unless appropriate molecular genetic testing has been performed on the parents of the proband.

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

- If a parent of a proband is clinically affected and/or is known to have the *FLCN* pathogenic variant identified in the proband, the risk to sibs of inheriting the pathogenic variant is 50%. The degree of clinical severity in sibs who inherit an *FLCN* pathogenic variant cannot be predicted; intrafamilial clinical variability has been observed.
- If the proband has a known *FLCN* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *FLCN* pathogenic variant but are clinically unaffected, sibs are still presumed to be at increased risk for BHDS because of the possibility of reduced penetrance in a parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with BHDS is at a 50% risk of inheriting the *FLCN* pathogenic variant. The degree of clinical severity in offspring who inherit the *FLCN* pathogenic variant is not predictable.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *FLCN* pathogenic variant, his or her 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 at-risk asymptomatic family members. Molecular genetic testing of at-risk family members is appropriate in order to identify the need for continued lifelong clinical surveillance. Interpretation of the result is most accurate when an *FLCN* pathogenic variant has been identified in an affected family member. Those who have the pathogenic variant require lifelong, regular surveillance. Family members who have not inherited the pathogenic variant and their offspring have risks similar to the general population.

Early detection of at-risk individuals affects medical management. However, in the absence of an increased risk of developing childhood malignancy, the American Society of Clinical Oncology (ASCO) recommends delaying genetic testing in at-risk individuals until they reach age 18 years and are able to make informed decisions regarding genetic testing [American Society of Clinical Oncology 2003]. (For a more detailed discussion, see Evaluation of Relatives at Risk.)

In a family with an established diagnosis of BHDS, it is appropriate to consider testing of symptomatic individuals regardless of age.

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.

DNA banking. 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 from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative genetic alteration/s are unknown).

Prenatal Testing and Preimplantation Genetic Testing

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

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. 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.

- **BHD Foundation**
  London
  United Kingdom
  Phone: 44(0)20 7193 8921
  Email: contact@bhdsyndrome.org
  www.bhdsyndrome.org

- **National Library of Medicine Genetics Home Reference**
  Birt-Hogg-Dubé syndrome
- **Kidney Cancer Association**
  Phone: 800-850-9132
  Email: office@kidneycancer.org
  www.kidneycancer.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Birt-Hogg-Dube Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
FLCN	17p11.2	Folliculin	Folliculin (FLCN) @ LOVD	FLCN	FLCN

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 Birt-Hogg-Dube Syndrome (View All in OMIM)

135150	BIRT-HOGG-DUBE SYNDROME 1; BHD1
607273	FOLLICULIN; FLCN

Molecular Pathogenesis

The tumor suppressor gene responsible for BHDS, *FLCN*, encodes the protein folliculin (FLCN). FLCN is ubiquitously expressed, evolutionarily highly conserved, and believed to control several important pathways of cell physiology. It was shown to act as a cytoplasmic guanine exchange factor and has been linked to different signaling pathways that are crucial for both tumorigenesis and normal cellular metabolism, including mTOR, AMPK, EGFR signaling, and HIF1α [Yan et al 2014, Laviolette et al 2017, Haley et al 2018, Zhao et al 2018, Collodet et al 2019, Martínez-Carreres et al 2019]. FLCN appears to have various roles, participating in (among others) ciliogenesis, autophagy, and lysosomal biogenesis. Several interacting proteins have been identified, including FLCN interacting proteins 1 and 2 (FNIP1/FNIP2), TOR signaling pathway regulator (TIPRL), SIN1, and Rag GTPase. In amino acid-starved cells the FLCN–FNIP complex was found to be recruited to lysosomes, a nutrient-dependent mechanism controlled by GATOR1 and RagA/B GAP [Meng & Ferguson 2018]. This enables FLCN to control the amino acid-dependent activation of mTOR, a key process both in a physiological cell state and in tumorigenesis. FLCN also appears to have a context-dependent role in the exit of cells from pluripotency, another mechanism that can become important in tumor development [Mathieu et al 2019].

Mechanism of disease causation. Loss of function

Table 6. Notable *FLCN* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_144997.5 NP_659434.2	c.1285delC	p.His429ThrfsTer39	Most common pathogenic variants, reported in 20%-24% of families [Sattler et al 2018b]
	c.1285dupC	p.His429GlnfsTer27	
	c.1347_1353dupCCACCCT	p.Val452ProfsTer6	Frequency 16%-32% in individuals of Japanese ancestry [Furuya et al 2016, Iwabuchi et al 2018]
	c.1062+2T>G	--	Danish founder variant (7.7%) [Rossing et al 2017]

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.

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