GENEReviews

Funded by the NIH · Developed at GeneTests (www.genetests.org), University of Washington, Seattle

Birt-Hogg-Dubé Syndrome

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Initial Posting: February 27, 2006.
Last Update: September 9, 2008.

Summary

Disease characteristics. The clinical characteristics of Birt-Hogg-Dubé syndrome (BHDS) include cutaneous manifestations (fibrofolliculomas, trichodiscomas/angiofibromas, perifollicular fibromas, and acrochordons), 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 during the third and fourth decades of life and typically increase in size and number with age. Lung cysts are mostly bilateral and multifocal; most individuals are asymptomatic but have a high risk for spontaneous pneumothorax. Individuals with BHDS have an increased risk of renal tumors that are typically bilateral and multifocal and usually slow growing; median age of tumor diagnosis is 48 years. The most common renal tumors are renal hybrids of oncocytoma and chromophobe histologic cell types. Some families have renal tumor and/or autosomal dominant spontaneous pneumothorax without cutaneous manifestations.

Diagnosis/testing. BHDS is diagnosed by clinical findings and by molecular genetic testing. *FLCN* (also known as *BHD*) is the only gene known to be associated with BHDS. Sequence analysis, available on a clinical basis, detects mutations in *FLCN* in 88% of affected individuals; therefore, some affected individuals who fulfill clinical diagnostic criteria do not have an identifiable mutation.

Management. *Treatment of manifestations:* Laser ablation of folliculoma/trichodiscoma results in substantial improvement for a period of time, but relapse usually occurs. 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. Total nephrectomy may be necessary in some cases. *Surveillance:* periodic abdominal/pelvic CT scan with contrast or MRI. *Agents/circumstances to avoid:* cigarette smoking and high ambient pressures. *Testing of relatives at risk:* Molecular genetic testing for the family-specific mutation 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 disease-causing mutation.

Genetic counseling. BHDS is inherited in an autosomal dominant manner. The offspring of an individual with BHDS have a 50% chance of inheriting the mutation. Prenatal diagnosis for pregnancies at increased risk is possible if the disease-causing allele of an affected family member has been identified.

Diagnosis

Clinical Diagnosis

The three major features of Birt-Hogg-Dubé syndrome (BHDS) are the presence of the following:

- **Cutaneous manifestations.** Individuals with BHDS usually present with multiple, small, skin-colored, dome-shaped papules distributed over the face, neck, and upper trunk. The original characteristic dermatologic triad was fibrofolliculomas, trichodiscomas, and acrochordons [Toro et al 1999]; however, only fibrofolliculomas are specific for BHDS. Perifollicular fibromas and angiofibromas have been also described associated with BHDS. Trichodiscomas are essentially histologically and clinically indistinguishable from angiofibromas; the term trichodiscoma has been used to describe angiofibromas when they occur in the setting of BHDS.

  The dermatologic diagnosis of BHDS is made in individuals who have five or more facial or truncal papules with at least one histologically confirmed fibrofolliculoma [Toro et al 1999]:

  - **Fibrofolliculomas** are defined as multiple anastomosing strands of two to four epithelial cells extending from a central follicle. Sometimes a well-demarcated, mucin-rich, or thick connective tissue stroma encapsulates the epithelial component. Biopsy is required to make the diagnosis.

    Note: Shave biopsy is usually not adequate. More than one skin-punch biopsy is sometimes needed to make the diagnosis of fibrofolliculomas.

  - **Trichodiscomas** are hamartomatous lesions comprising a round to elliptically shaped well-demarcated proliferation of thick fibrous and vascular stroma in the reticular dermis with a hair follicle at the periphery. Because of the high density of hair follicles in the face, hair follicles are commonly found at the periphery of these lesions. **Angiofibromas** are clinically and histologically essentially the same as trichodiscomas.

    Note: Trichodiscomas/angiofibromas are suspicious for the diagnosis of BHDS, but are not diagnostic. Angiofibromas are commonly also found in tuberous sclerosis complex (TSC) and multiple endocrine neoplasia type 1 (MEN1).

  - **Acrochordons,** or skin tags, are soft pedunculated papules that histologically are characterized by acanthotic and mild papillomatous epidermis with loose connective tissue stroma and blood vessels.

  - **Perifollicular fibromas are** well-demarcated proliferations of fibrous and vascular stroma in the reticular dermis surrounding a hair follicle.

- **Lung cysts and spontaneous pneumothorax.** Most individuals (89%) with BHDS have multiple, bilateral lung cysts, identified by chest CT. The total number of lung cysts per individual ranges from 0 to 166 (mean 16). Twenty-four percent (48/198) of individuals with BHDS had a history of one or more pneumothoraces [Toro et al 2007]. All individuals with a history of pneumothorax had multiple lung cysts identified by chest CT imaging.

- **Renal tumors.** The renal tumors are usually bilateral and multifocal. Tumor types include renal oncocytoma, chromophobe renal cell carcinoma, oncocytic hybrid tumor, and a minority of clear cell renal cell carcinoma.

Note: The original description and diagnosis of BHDS is based on skin pathology. However, recent investigations have shown that some individuals with BHDS could present with pulmonary involvement and/or renal tumors without skin lesions.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Gene. *FLCN* is the only gene known to be associated with BHDS.

Clinical testing

- **Sequence analysis of select exons.** Fifty-three percent (27 of 51) 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 2).
- **Sequence analysis of the entire coding region**, including coding exons 4 through 14, increases the mutation detection in probands to 88%.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Birt-Hogg-Dubé Syndrome

Gene Symbol	Test Method	Mutations Detected	Mutation Detection Frequency by Test Method [1]	Test Availability
FLCN	Sequence analysis of exon 11	Polycytosine tract deletion (c. 1285delC) /duplication (c. 1285dupC)	~53%	Clinical Testing
	Sequence analysis of entire coding region	Sequence alterations	~88%	

1. Schmidt et al [2005], Toro et al [2008]

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

To confirm the diagnosis in a proband

Molecular genetic testing is indicated in all individuals known to have or suspected of having BHDS, including individuals with one of the following:

- Five or more facial or truncal papules with at least one histologically confirmed fibrofolliculoma [Toro et al 1999], with or without a family history of BHDS
- Facial papules histologically confirmed to be angiofibroma in an individual who does not fit the clinical criteria of tuberous sclerosis complex (TSC) or multiple endocrine neoplasia type 1 (MEN1)
- Multiple and bilateral chromophobe, oncocytic, and/or hybrid renal tumors
- A single oncocytic, chromophobe, or oncocytic hybrid renal tumor and a family history of renal cancer with any of the above renal cell tumor types

- A family history of autosomal dominant primary spontaneous pneumothorax without a history of smoking or COPD

Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the disease-causing mutation in the family.

Genetically Related (Allelic) Disorders

Autosomal dominant primary spontaneous pneumothorax. Germline mutations in *FLCN* were found in families with dominantly inherited spontaneous pneumothorax. Pulmonary involvement appears to be the only manifestation; penetrance is 100% [Graham et al 2005, Painter et al 2005].

Somatic mutation. Acquired mutations in *FLCN* have been identified in sporadic clear cell renal cell carcinoma [da Silva et al 2003, Khoo et al 2003] and colon cancer [Kahnoski et al 2003, Shin et al 2003], without other associated tumors characteristic of the heritable disease.

Clinical Description

Natural History

The clinical characteristics of Birt-Hogg-Dubé syndrome (BHDS) include fibrofolliculomas (specific cutaneous lesions), pulmonary cysts/history of pneumothorax, and various types of renal tumors. Disease severity can vary significantly among family members and between families.

Cutaneous lesions. BHDS is associated with a spectrum of cutaneous hamartomas ranging from angiofibroma to perifollicular fibromas to fibrofolliculomas [Toro et al 2008]. Families with germline mutations in *FLCN* can have angiofibromas (i.e., trichodiscomas), perifollicular fibroma, or both angiofibroma and perifollicular fibromas as their only BHDS cutaneous phenotype [Toro et al 2008]. In addition, some individuals with BHDS develop oral papules and cutaneous collagenomas [Nadershahi et al 1997, Toro et al 1999].

The onset of skin lesions is typically during the third or fourth decade of life. Skin lesions tend to increase in size and number with age. Later onset of cutaneous lesions tends to correlate with a milder skin phenotype. In addition, women tend to have smaller and fewer lesions than men.

Recently, three individuals with germline *FLCN* mutations who also had a history of malignant melanoma were reported [Khoo et al 2002, Toro et al 2008].

A family with BHDS in which one sib developed a dermatofibrosarcoma protuberans (DFSP) and another sib had a cutaneous leiomyosarcoma was also recently described [Toro et al 2008].

Pulmonary cysts and spontaneous pneumothorax. Lung cysts are mostly bilateral and multifocal. Most individuals with BHDS and lung cysts are asymptomatic, but they have a high risk of developing spontaneous, often recurrent, pneumothorax. Clinical presentation of a pneumothorax ranges from asymptomatic to dyspnea and chest pain. Clinical findings include tachypnea or decreased or absent breath sounds. Radiographic investigation may require a high-resolution CT of the chest to confirm the diagnosis of pneumothorax because chest x-ray may not be sensitive enough to detect a loculated pneumothorax.

In the recent study of Toro et al [2008], 89% of individuals with a *FLCN* germline mutation were found to have pulmonary cysts on chest CT, a rate that is higher than the 77% observed in all earlier reports combined.

In the same study of Toro et al [2008], 38% of individuals with a *FLCN* germline mutation were found to have a history of spontaneous pneumothorax, a rate similar to the 33% in all earlier reports combined.

Individuals with BHDS and a family history of pneumothorax have a statistically significant increased risk of pneumothorax compared to individuals with BHDS without a family history of spontaneous pneumothorax.

Individuals with BHDS have a 50-fold increased risk for spontaneous pneumothorax compared to family members who do not have BHDS [Zbar et al 2002].

Renal tumors. Approximately 70 individuals with *FLCN* germline mutation and kidney tumors have been reported [Toro et al 2008]. The most common tumors are a hybrid of oncocytoma and chromophobe histologic cell types, so-called oncocytic hybrid tumor (67%), chromophobe renal cell carcinoma (23%), and renal oncocytoma (3%). Only renal oncocytoma is considered a benign tumor [Pavlovich et al 2005]. Other types of renal tumors reported in lower frequency include clear cell renal cell carcinoma and papillary renal carcinoma.

Most renal tumors associated with BHDS are bilateral, multifocal, and slow growing. Median age of diagnosis is 48 years, with a range from 31 to 71 years [Schmidt et al 2005].

Individuals with BHDS had a sevenfold increased risk of renal tumors compared with their unaffected sibs [Zbar et al 2002]. Using combined ascertainment in dermatologic and urologic oncology clinics at the National Cancer Institute (NCI) at the National Institutes of Health (NIH), the overall prevalence of kidney tumors among individuals with germline *FLCN* mutations was 29%-34% [Toro et al 2008]. This high frequency compared to the 6.5% frequency of kidney tumors in BHDS cases determined from a combination of other investigators may reflect ascertainment bias.

The renal tumors associated with BHDS may affect morbidity more than mortality in persons with BHDS. Nephron-sparing surgery may decrease the morbidity associated with renal tumors by preserving functioning renal tissue because affected individuals usually develop multifocal and bilateral kidney tumors.

Renal oncocytosis observed at surgery or at postmortem examination is evidence of the potential of persons with BHDS to develop kidney tumors [Toro et al 2008].

Other manifestations

Oral papules [Nadershahi et al 1997, Toro et al 1999] and **parotid oncocytoma** [Liu et al 2000, Schmidt et al 2005, Toro et al 2008] have been seen in increased frequency in BHD syndrome.

Non-renal tumors recently reported in BHDS include [Toro et al 2008]:

- Two cases of thyroid cancer
- Two cases of Colon cancer

  The evidence associating colonic neoplasm and BHDS is conflicting [Khoo et al 2002, Zbar et al 2002].
- Single cases of the following:
  - Squamous cell carcinoma of the head and neck
  - Hodgkin's disease

- Uterine cancer
- Prostate cancer
- Breast cancer
- Squamous cell carcinoma of the cervix
- Rhabdomyoma
- An adrenal mass

Single cases of the following have also been reported:

- Lipoma, angiolipoma, and collagenoma [Toro et al 1999]
- Cutaneous neurothekeoma (benign myxoma of cutaneous nerve sheath origin) and meningioma [Vincent et al 2003]
- Multinodular goiter [Drummond et al 2002, Welsch et al 2005];
- Ovarian cyst [Godbolt et al 2003]
- Parathyroid adenoma;
- Chorioretinal lesions [Walter et al 1997, Godbolt et al 2003]

Genotype-Phenotype Correlations

Genotype-phenotype correlations have been reported; however, whether these manifestations are truly associated with BHDS remains to be determined through larger studies.

No correlation is observed between the type of *FLCN* mutation and pulmonary and cutaneous manifestations.

A previous study suggested that individuals who have a c.1285delC mutation may have a lower risk of developing renal cancers than individuals with other *FLCN* mutations, but this needs to be evaluated in large studies.

Penetrance

Based on the three major clinical manifestations, penetrance of BHDS is considered to be very high.

Anticipation

Anticipation is not known to occur in BHDS.

Nomenclature

Hornstein-Knickenberg syndrome (HK), which describes familial multiple perifollicular fibromas, is considered to fall within the spectrum of BHDS [Schulz & Hartschuh 1999].

Prevalence

More than 60 affected families from various populations have been described.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Cutaneous lesions. Fibrofolliculomas are rare and specific for Birt-Hogg-Dubé syndrome (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.

BHDS-associated hamartomas should be distinguished from other genodermatoses with an increased risk for internal malignancy, including tuberous sclerosis complex (TSC), familial trichoepitheliomas, MEN1, and Cowden syndrome (see *PTEN* hamartoma tumor syndrome).

Pulmonary manifestation. Several inherited and noninherited conditions can present with lung cysts and/or pneumothorax. A thorough history and physical examination help to differentiate these conditions from BHDS. These conditions include the following:

- Marfan syndrome
- Ehlers-Danlos syndrome, vascular type
- TSC
- Alpha1-antitrypsin deficiency [Daniel & Teba 2000]
- Cystic fibrosis [Flume et al 2005]
- Langerhan cell histiocytosis [Mendez et al 2004]
- Pulmonary lymphangioleiomyomatosis (LAM), which can occur as an isolated finding or as part of TSC

Renal tumor. Unlike BHDS, most familial renal cancer syndromes are associated with different types of renal pathology [Linehan et al 2005]. Familial renal cancer syndromes and their renal pathology include the following:

- von Hippel-Lindau syndrome (VHL syndrome). Bilateral and multifocal clear cell renal cell carcinomas. Individuals with VHL syndrome are also at risk for central nervous system hemangioblastoma, retinal angioma, pheochromocytoma, and endolymphatic sac tumors.
- Hereditary papillary renal cancer (HPRC). Bilateral and multifocal type 1 papillary renal cell carcinomas
- Hereditary leiomyomatosis and renal cell cancer (HLRCC). Usually solitary renal tumors with a histologic spectrum ranging from tubo-papillary renal cell cancer to type 2 papillary renal cancer to collecting duct renal cell cancer. Individuals with HLRCC can present with cutaneous leiomyoma and/or with early-onset and aggressive uterine fibroids.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with Birt-Hogg-Dubé syndrome (BHDS), the following evaluations are recommended:

- Detailed dermatologic examination and punch biopsy of suspected cutaneous lesion
- High-resolution computed tomography (HRCT) or CT of the chest highly recommended for visualization of pulmonary cysts. Individuals who have symptoms/signs of pneumothorax should immediately undergo chest x-ray and CT of the chest and appropriate treatment.

- Baseline abdominal/pelvic CT scan with contrast or MRI to screen for renal tumor. Renal ultrasound examination may distinguish cystic from solid renal lesions.

Treatment of Manifestations

Treatment of fibrofolliculomas and trichodiscomas is difficult. Laser ablation shows substantial improvement, but relapse can occur [Gambichler et al 2000].

Treatment of pneumothorax is the same as in the general population.

Nephron-sparing surgery is the treatment of choice for renal tumors whenever possible, depending on the size and location of the tumors [Pavlovich et al 2005]. Renal tumors greater than 3.0 cm and/or rapidly growing tumors usually require partial nephrectomy. Total nephrectomy may be necessary in some cases. The main objective is to preserve as much of the kidney as possible to help preserve long-term kidney function because affected individuals usually develop multifocal and bilateral kidney tumors.

Prevention of Primary Manifestations

No preventive or curative treatment is available for BHDS. However, development of renal cell carcinoma has the strongest positive association with cigarette smoking [Moore et al 2005].

Surveillance

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

Individuals with known BHDS, individuals known to have a disease-causing mutation in *FLCN* without clinical manifestations, and at-risk family members who have not undergone genetic testing should have regular monitoring by physicians familiar with the spectrum of BHDS. In particular, surveillance for and monitoring of renal tumors include the following:

- If normal at baseline, abdominal/pelvic CT scan with contrast or MRI (if CT is not possible) every two to three years are the optimal studies for complete assessment of kidney lesions. However, as a result of the low aggressiveness of kidney tumors and the 3.0-cm rule used by surgeons in treating renal tumors [Pavlovich et al 2005], the use of renal ultrasound examination for screening individuals with BHDS and/or a *FLCN* germline mutation may be adequate in some patients, while avoiding long-term cumulative radiation exposure.

  Note: The use of renal ultrasound examination is especially applicable to individuals who have had two normal CT examinations or MRI examinations and individuals without a family history of kidney cancer.

- If any suspicious lesion (<1.0 cm in diameter, indeterminate lesion, or complex cysts) is noted on a previous examination, annual abdominal/pelvic CT scan with contrast alternating every other year with renal MRI or abdominal ultrasound examination to reduce lifetime exposure to radiation is recommended.
- Evaluation of renal tumors by a urologic surgeon is appropriate
- Monitor tumors less than 3.0 cm in diameter by periodic imaging; they may not require surgical intervention while this small.
- Rapidly growing lesions and/or symptoms including pain, blood in the urine, or atypical presentations require a more individualized approach.

Agents/Circumstances to Avoid

The following should be avoided:

- Cigarette smoking
- High ambient pressures, which may precipitate spontaneous pneumothorax

Testing of Relatives at Risk

When the family-specific mutation 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 disease-causing mutations.

Early recognition of clinical manifestations may allow timely intervention and improve outcome. Therefore, clinical surveillance of asymptomatic at-risk relatives for early detection is appropriate.

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

Therapies Under Investigation

Search ClinicalTrials.gov 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.

Other

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

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. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

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

Risk to Family Members

Parents of a proband

- Some individuals with BHDS have an affected parent, and some have BHDS as a result of a *de novo* gene mutation.
- The proportion of cases caused by *de novo* mutations is unknown because a sufficient number of parents has not been evaluated for subtle manifestation, nor are there

sufficient data on clinically unaffected parents who have been evaluated by molecular genetic testing.

- Recommendations for the evaluation of parents of a proband with a suspected *de novo* mutation include molecular genetic testing if the disease-causing mutation in *FLCN* in the proband is identified.

Note: Although some individuals diagnosed with BHDS have an affected parent, the family history 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 proband's parents.
- If a parent of a proband is clinically affected or has a disease-causing mutation, the sibs of the proband are at a 50% risk of inheriting the mutation.
- If neither parent has the disease-causing mutation identified in the proband, the risk to sibs is low but greater than that of the general population because of the possibility of germline mosaicism.

Offspring of a proband. Each child of an individual with BHDS is at a 50% risk of inheriting the mutation. The degree of clinical severity is not predictable.

Other family members of a proband

- The risk to other family members depends on the status of the proband's parents.
- If a parent is found to be affected, his or her family members are at risk.

Related Genetic Counseling Issues

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

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

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 a disease-causing mutation has been identified in an affected family member. Those who have a disease-causing mutation require lifelong, regular surveillance. Meanwhile, family members who have not inherited the mutation 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].

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, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant when the sensitivity of currently available testing is less than 100%. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

Prenatal diagnosis for pregnancies at 50% risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15-18 weeks' gestation or chorionic villous sampling (CVS) at approximately ten to 12 weeks' gestation. The disease-causing allele of an affected family member must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Preimplantation genetic diagnosis (PGD). Preimplantation genetic diagnosis may be available for families in which the disease-causing mutation has been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Birt-Hogg-Dubé Syndrome

Gene Symbol	Chromosomal Locus	Protein Name
FLCN	17p11.2	Folliculin

Data are compiled from the following standard references: gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Birt-Hogg-Dubé Syndrome

135150	BIRT-HOGG-DUBE SYNDROME; BHD
607273	FOLLICULIN; FLCN

Table C. Genomic Databases for Birt-Hogg-Dubé Syndrome

Gene Symbol	Entrez Gene	HGMD
FLCN	201163 (MIM No. 607273)	FLCN

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Normal allelic variants. The *FLCN (BHD)* gene was identified by positional cloning by Nickerson et al [2002]. The gene is highly conserved across species. The human *FLCN* gene consists of 14 exons.

Pathologic allelic variants. See Table 2. Various mutations have been identified in families with Birt-Hogg-Dubé syndrome (BHDS). All mutations predict protein truncation. The most common mutations are c.1285dupC and c.1285delC, which duplicate or delete a single C nucleotide in a polycytosine tract in exon 11, suggesting the presence of a hypermutable site [Schmidt et al 2005].

Table 2. *FLCN* Pathologic Allelic Variants Discussed in This *GeneReview*

DNA Nucleotide Change (Alias [1])	Protein Amino Acid Change	Reference Sequence
c.1285dupC (1733ins C)	p.His429ProfsX26	NM_144997.4 NP_659434.2
c.1285delC (1733delC)	p.His429ThrfsX38	

See Quick Reference for an explanation of nomenclature. *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (http://www.hgvs.org).

1. Variant designation that does not conform to current naming conventions

For more information, see Genomic Databases table.

Normal gene product. Folliculin, the product of *FLCN*, has 579 amino acid residues. It has no known function, but is highly expressed in a variety of tissues including skin and skin appendages, type 1 pneumocytes, and distal nephrons of the kidney [Warren et al 2004].

Abnormal gene product. Germline mutations in *FLCN*, plus somatic mutations and loss of heterozygosity in tumor tissue, suggest that loss of function of the folliculin protein is the basis of tumor formation in BHDS [Vocke et al 2005]. Reduced expression of folliculin in renal tumors from individuals with BHDS supports its role in tumor suppression [Warren et al 2004].

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

National Library of Medicine Genetics Home Reference
Birt-Hogg-Dubé syndrome

American Lung Association
1740 Broadway
New York NY 10019
Phone: 212-315-8700
Email: infor@lungusa.org
Spontaneous Pneumothorax Fact Sheet

Kidney Cancer Association
1234 Sherman Avenue Suite 203
Evanston IL 60202-1375
Phone: 800-516-8051; 312-436-1455
Fax: 847-332-2978

Email: office@kidneycancerassociation.org
CureKidneyCancer.org

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

American Society of Clinical Oncology (2003) Statement on genetic testing for cancer susceptibility

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Chapter Notes

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Revision History

- 9 September 2008 (me) Comprehensive update posted live
- 27 February 2006 (me) Review posted to live Web site
- 30 November 2005 (jt) Original submission