

## Skin Findings Reveal Deeper Issues: A Case of Birt Hogg Dubé Syndrome

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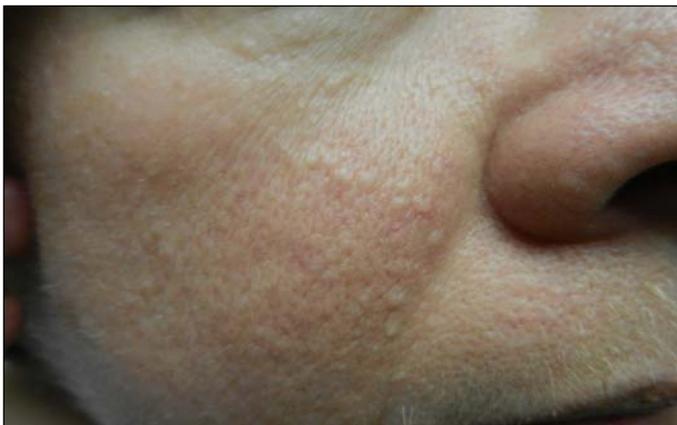
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### ABSTRACT

Birt-Hogg-Dubé syndrome is a rare, multi-system genetic disorder. The diagnosis consists of a triad of findings; dermatologic, pulmonary, and renal. This article aims to increase awareness of this rare syndrome and the need to consider Birt-Hogg-Dubé syndrome in patients with fibrofolliculomas or trichodiscomas, pneumothorax or lung cysts, and renal tumors. Early diagnosis allows for management and screening of the associated lung and renal findings, which benefits patients with this autosomal dominant condition as well as their families.

### CASE:

A 59 year old woman presented to her dermatologist (B.S.) with a history of multiple flesh colored papules of the face (**Figure 1**). The papules were clinically felt to be angiofibromas and a shave biopsy was performed. The dermatologic diagnosis was confirmed on a superficial biopsy. As angiofibromas can be associated with several genetic syndromes, including multiple endocrine neoplasia, type I (MEN1) and tuberous sclerosis, genetic consultation was recommended.



**Figure 1.** Flesh Colored Facial Papules

The patient was noted to have a medical history significant for a retinal tear with “thin retinas”, hypertension, arthritis, 20 to 30 facial lesions that she noticed over the previous 10 years, as well as 24 skin tags located under the inner thighs, arms and breasts (**Figure 2**). Genetic consultation (J.H., N.V.) revealed a family history significant for a paternal cousin diagnosed with renal cell carcinoma at 52 years of age. The patient had 3 children, aged 35, 33, and 29 years. The 35 year-old

daughter had a history of 2 episodes of pneumothorax of unknown cause in college. The brother, sister, and father of the patient were all reported to have similar facial growths to those of the patient.



**Figure 2a.** Skin Tags (Acrochordons)

a

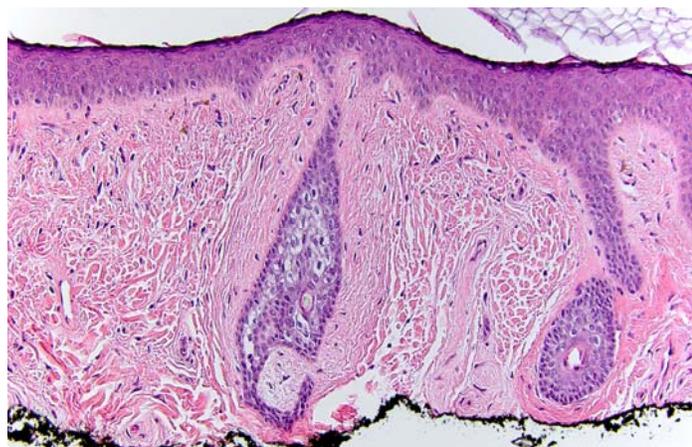


**Figure 2b.** Skin Tags (Acrochordons)

b

Physical examination was significant for multiple, small, flesh colored papules in the infraorbital regions extending over the cheeks and neck as well as multiple skin tags on the neck and under the breasts. A renal ultrasound revealed a single simple cyst (G.S).

Due to the family history of flesh colored papules, pneumothorax, and renal carcinoma, Birt-Hogg-Dubé syndrome (BHDS) was considered. A second evaluation of the skin histopathology (A.S.) showed a dome shaped lesion with small vellus hair follicles and columns of epithelial cells—resembling the mantle of normal follicles—that extended from preexisting follicles (**Figure 3**). Sebocytes were present within the follicles. A myxoid stroma at the peripheral aspects of these follicles contained thin, oval, spindle-shaped fibrocytes. The findings were consistent with fibrofolliculoma (**Figure 4**) and not angiofibroma, as originally diagnosed. Complete sequencing of the *FLCN* gene was performed revealing a heterozygous mutation in exon 11, c.1252delC (at the time—a previously unreported mutation), predicted to cause frameshift and a premature stop codon.

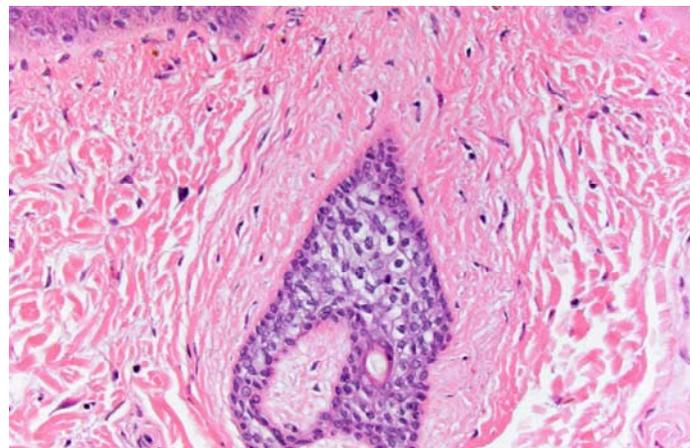


**Figure 3.** Fibrofolliculoma. A column of epithelial cells that resembles mantle of a normal follicle extends from a pre-existing vellus follicle. (hematoxylin and eosin x200).

#### Further Details About the Proband’s Family:

The family of our patient was asked to complete a survey regarding their past medical history and BHDS testing status after Tufts University Institutional Review Board approved informed consent.

The proband’s son aged (33 years) reported 3 to 5 skin tags of the face and underarm. He reported no facial papules but was noted to have many on physical examination. He tested positive for the BHDS mutation detected in his mother. The older daughter aged (35 years) reported 10 to 12 skin tags around the neck and 1 on the stomach. She reported no papules but was also



**Figure 4.** Fibrofolliculoma. The peripheral stroma contains thin and oval spindle-shaped fibrocytes. Focal sebaceous differentiation is noted within the follicle (hematoxylin and eosin x400).

noted to have many on physical examination. This daughter reported 2 episodes of pneumothorax, 3 episodes of lung collapse and required surgery for pleurodesis. She was found to have lung cysts on computed tomography (CT). A renal MRI was normal. She also tested positive for BHDS. The younger daughter aged (29 years) was examined and found to have no skin lesions. She tested negative for BHDS.

The proband’s sister reported 50 to 100 facial papules and ~ 75 skin tags of the face, neck, stomach, and below the breasts. She tested positive for BHD. She was found to have vaginal, uterine, and colon polyps. The proband’s father reported hyperpigmented spots and dozens of papules, and required removal of malignant lesions of the nose and cheek. An X-ray for pneumonia did not reveal lung cysts, but more recent chest CTs showed blebs. The proband’s brother reported 2 skin tags of the neck.

A paternal uncle reported cataracts, chest skin lesions, several papules on the face and nose, and a history of bladder cancer at 80 years of age. Another paternal uncle reported cataracts and a history of colon cancer in his late 60s.

A female paternal first cousin reported having  $\geq 400$  facial papules, appearing in her late 30s and 2 skin tags (neck and shoulder). Her 3 daughters did not report signs of BHDS. Another female paternal first cousin reported pressure in the right upper abdomen and a “ptotic” right kidney was found; she also had hypothyroidism. Yet

another paternal cousin had a benign thyroid nodule. He was diagnosed with 2 renal cell carcinomas of the left kidney at 52 years of age and also had a basal cell carcinoma as well as melanoma of the face at age 58. Testing of the relatives for the familial BHDS mutation is on-going.

#### **INTRODUCTION:**

Birt Hogg Dubé syndrome is an autosomal dominant genetic syndrome that has been reported in ~100 families to date. The cardinal signs of BHDS include (1) skin findings such as fibrofolliculomas, (2) pulmonary cysts and susceptibility to pneumothorax, and (3) increased risk for renal tumors. This syndrome was first described in 1977.<sup>1</sup>

#### **Skin Findings:**

Greater than 90% of all people with BHDS develop fibrofolliculomas, which are 1 to 5mm white or skin-colored papules. At the microscopic level, fibrofolliculomas appear as hair follicles surrounded, at the level of infundibulum, by a stroma composed of loose connective tissue containing fine collagen, excess hyaluronic acid and no elastic fibers. Fine epithelial cords, usually with a thickness of 2 to 4 cells, originate from the infundibulum.<sup>2,3</sup>

As fibrofolliculomas are not seen solely in BHDS, diagnosis usually includes >5 lesions, 1 of which is histologically confirmed. As a shave biopsy may be too superficial to allow for histologic diagnosis, a punch is the preferred method of sampling.<sup>4</sup>

Other lesions occurring with BHDS include trichodiscomas, which are benign hamartomatous proliferations of the mesodermal component of the hair disk (*haarscheibe*). Trichodiscomas usually contain a collarette, and the tumor is predominantly composed of connective tissue including collagen and myxoid contents. Thin cords of undifferentiated epithelial cells extend from the infundibulum into the stroma. Trichodiscomas can closely mimic angiofibromas, a finding commonly observed in tuberous sclerosis complex 1 and 2. Perifollicular fibromas, proliferations surrounding a hair follicle, can also be seen.<sup>3,5</sup> Although fibrofolliculoma and trichodiscoma may significantly vary in their histomorphologic features, currently they are considered as a single tumor in its different evolutionary

stages that can be collectively referred to as fibrofolliculoma trichodiscoma.

Acrochordons (skin tags), are often seen on the neck and intertriginous region of people with BHDS. It is important to note these are fibrofolliculoma/trichodiscomas that clinically appear as achrochordons and are not considered conventional skin tags.<sup>6,7</sup>

Skin lesions usually appear in the third to fourth decades of life. They increase in size and number with age. A later onset usually indicates a milder skin phenotype.

*“Birt Hogg Dubé syndrome (BHDS) is an autosomal dominant genetic syndrome that has been reported in ~ 100 families to date.”*

#### **Pulmonary Findings:**

On CT, bilateral, multifocal lung cysts are observed in 77% to 89% of people with BHDS<sup>8,9</sup>. The lesions predispose to pneumothoraces, which occur in ~32% to 38% of patients with BHDS and are more likely to occur in individuals with a positive family history of this complication.<sup>8,9</sup>

Lung cysts and pneumothorax may be asymptomatic or cause dyspnea. Cysts are often discovered as an incidental finding on chest CT. The risk of pneumothorax in BHDS is 50 fold that of the general population.<sup>10</sup>

#### **Renal Findings:**

Bilateral, unilateral and/or multifocal renal tumors are seen at increased frequency in BHDS. A National Institutes of Health study found a 23% to 34% risk, while previous studies showed a 6.5% to 7% risk.<sup>8,9</sup> The mean age of onset of these tumors is 48 years (range 20-71 years), with a 7 to 9 fold risk over the general population.<sup>10</sup> These tumors tend to be slow growing, with a low risk of metastasis. Renal tumors are more likely in individuals with a positive family history. Tumor types include oncocytic hybrid tumor (67%), chromophobe renal cell carcinoma (23%), and benign renal oncocytoma (3%).<sup>11</sup> Clear cell renal cell carcinoma and papillary renal carcinoma have been rarely reported; however both have caused early demise.

#### **Other Findings:**

Although no statistical increase for other tumors or cancers has been established, cancers reported in patients with BHDS include colon, thyroid, breast,

uterine, prostate, Hodgkin's lymphoma, chondrosarcoma (personal report J.H.), and squamous cell carcinoma of the head, neck, and cervix.<sup>9</sup>

Other growths reported include collagenoma, cutaneous neurothekeoma (benign myxoma of cutaneous nerve sheath origin), meningioma, oral papules, parotid oncocyoma, lipoma/angiolioma, multinodular goiter, parathyroid adenoma, ovarian cyst, rhabdomyoma, and adrenal mass.

#### **Genetics:**

BHDS is due to mutations in the *FLCN* gene,<sup>12</sup> located at 17p11.2, that encodes the folliculin protein.<sup>13,14</sup> This gene is highly expressed in skin and skin appendages, type 1 pneumocytes, stromal cells, and distal nephrons of the kidney.<sup>15</sup> Folliculin likely has a role in tumor suppression, as loss of heterozygosity is observed in sporadic cases of renal cell carcinoma. Folliculin is known to participate in the AMP-activated protein kinase (AMPK) and mammalian target of rapamycin (mTOR) signaling pathways.<sup>16</sup>

Approximately half of the *FLCN* mutations detected to date are deletions or duplications located at c.1285 nucleotide C in a polycytosine tract in exon 11.<sup>8</sup> Other mutations have been frameshift and nonsense in nature. Complete sequencing of the *FLCN* gene is positive for a mutation in 88% of clinically diagnosed cases.<sup>9</sup> At this time there is no other known molecular etiology. Variable expression has been noted within families with the same mutation. The sporadic mutation rate of this gene is also currently unknown.

#### **Differential Diagnosis:**

Because of the diverse medical issues associated with BHDS, the differential diagnosis encompasses conditions that may include an individual feature of BHDS, but none of the conditions to follow include the whole triad of skin findings, lung disease, and renal growths seen in BHDS.

#### *Skin findings*

As mentioned previously, angiofibromas are seen in tuberous sclerosis and MEN1. Superficial biopsy of fibrofolliculomas may lead the clinician to consider these syndromes initially. Although due to *FLCN* mutations, Hornstein-Knickenberg syndrome, characterized by familial multiple perifollicular fibromas, is a condition that does not seem to encompass the lung and renal findings of BHDS. It is not yet clear why some mutations result in the complete syndrome, while others do not.

#### *Lung cysts/pneumothorax*

Connective tissue disorders such as Marfan syndrome and vascular Ehlers Danlos syndrome can cause familial and recurrent pneumothorax. Pneumothorax and lung cysts can also be seen in tuberous sclerosis complex, cystic fibrosis, and  $\alpha$ -1-antitrypsin deficiency. Inherited spontaneous pneumothorax has been attributed to mutations in *FLCN* without the accompanying findings of BHDS.<sup>17,18</sup>

#### *Renal neoplasia*

Renal tumors have been noted in Von Hippel–Lindau syndrome, hereditary papillorenal cancer syndrome, and hereditary leiomyomatosis and renal cell carcinoma syndrome. Mutations in *FLCN* have been found in pathology samples of renal tumors, likely due to somatic damage to DNA.<sup>19</sup>

#### **Management:**

As the skin findings of BHDS are generally not believed to be problematic from a medical perspective, no treatment is needed. For those patients with aesthetic concerns, temporary improvement with laser ablation has been reported for fibrofolliculomas, but can reoccur. Acrochordons can be easily removed. New skin lesions tend to occur over time.

*“Due to the increased risk for renal tumors, most patients with BHDS are followed carefully by an oncologist.”*

For those who are aware of their diagnosis of BHDS, avoidance of cigarette smoke and sudden changes in air pressure may be warranted. Screening for lung cysts is not necessary, as no intervention is required for the cysts themselves and standard treatment is recommended for acute pneumothorax.

Because of the increased risk for renal tumors, most patients with BHDS are followed carefully by an oncologist. There is currently no evidence-based screening protocol for renal tumors. Some specialists recommend an initial CT or MRI at the time of diagnosis with screening for renal tumors at least every 1 to 3 years (ultrasound is used by some, CT by others). Some specialists recommend yearly screening, especially in families with a history of renal tumors. Repeated CT may result in too much radiation over time,<sup>20</sup> but ultrasound may not be sensitive enough,<sup>21</sup> while MRI is prohibitively

expensive, leaving no definitive best practice for screening at this time. If a tumor is identified, nephron-sparing surgery may be considered for the more common renal tumors of BHDS, as metastasis is rare.

**CONCLUSIONS:**

Birt-Hogg-Dubé syndrome is an easily identifiable syndrome due to the distinctive triad of skin findings, lung cysts and pneumothorax along with renal tumors. Screening for renal tumors may expedite diagnosis and treatment of this serious aspect of BHDS. Early identification of people with BHDS can shorten the diagnostic odyssey for the individual as well as family members, eliminating the need for unnecessary studies and incorrect diagnoses.

**REFERENCES:**

1. Birt AR, Hogg GR, Dubé WJ. Hereditary multiple folliculomas with trichodiscomas and acrochordons. *Arch Dermatol.* 1977;113;1674-1677.
2. Fibrofolliculoma/Trichodiscoma. In: Weedon D, ed. *Weedon's Skin Pathology.* 3rd ed. London: Churchill Livingstone Elsevier; 2010:771-772.
3. Ackerman AB, Reddy VB, Soyer HP. Fibrofolliculoma/Trichodiscoma. *Neoplasms With Follicular Differentiation.* New York, NY: Ardor Scribendi; 2001:221-244.
4. Toro JR. Birt-Hogg-Dubé syndrome. In: Pagon RA, Bird TD, Dolan CR, Stephens K, eds. GeneReviews [Internet]. Seattle, Wash: University of Washington, Seattle; 1993-2006 Feb 27 [updated 2008 Sep 9].
5. Collins GL, Somach S, Morgan MB. Histomorphologic and immunophenotypic analysis of fibrofolliculomas and trichodiscomas in Birt-Hogg-Dubé syndrome and sporadic disease. *J Cutan Pathol.* 2002;29:529-533.
6. Lookingbill DP, Spangler N, Sexton FM. Skin involvement as the presenting sign of internal carcinoma. A retrospective study of 7316 cancer patients. *J Am Acad Dermatol.* 1990;21:19-26.
7. De la Torre C, Ocampo C, Doval IG, Losada A, Cruces MJ . Acrochordons are not a component of the Birt-Hogg-Dubé syndrome: does this syndrome exist? Case reports and review of the literature. *Am J Dermatopathol.* 1999;21(4):369-374.
8. Schmidt LS, Nickerson ML, Warren MB, et al. Germline BHD-mutation spectrum and phenotype analysis of a large cohort of families with Birt-Hogg-Dubé syndrome. *Am J Hum Genet.* 2005;76:1023-1033.

9. Toro JR, Wei M-H, Glenn GM, et al. BHD mutations, clinical and molecular genetic investigations of Birt-Hogg-Dubé syndrome: a new series of 50 families and review of published reports. *J Med Genet.* 2008;45:321-331.
10. Zbar B, Alvord WG, Turner M, et al. Risk of renal and colonic neoplasms and spontaneous pneumothorax in the Birt-Hogg-Dubé syndrome. *Cancer Epidemiol Biomarkers Prev.* 2002; 11:393-400.
11. Pavlovich CP, Grubb RL 3rd, Hurley K, et al. Evaluation and management of renal tumors in the Birt-Hogg-Dubé syndrome [published correction appears in *J Urol.* 2005;174(2):796]. *J Urol.* 2005;173:1482-1486.
12. Nickerson ML, Warren MB, Toro JR, et al. Mutations in a novel gene lead to kidney tumors, lung wall defects, and benign tumors of the hair follicle in patients with the Birt-Hogg-Dubé syndrome. *Cancer Cell.* 2002;2:157-164.
13. Khoo SK, Bradley M, Wong FK, et al. Birt-Hogg-Dubé syndrome: mapping of a novel hereditary neoplasia gene to chromosome 17p12-q11.2. *Oncogene.* 2001;20:5239-5242.
14. Schmidt LS, Warren MB, Nickerson ML, et al. Birt-Hogg-Dubé syndrome, a genodermatosis associated with spontaneous pneumothorax and kidney neoplasia, maps to chromosome 17p11.2. *Am J Hum Genet.* 2001;69:876-882.
15. Warren MB, Torres-Cabala CA, Turner ML, et al. Expression of Birt-Hogg-Dubé gene mRNA in normal and neoplastic human tissues. *Mod Pathol.* 2004;17:998-1011.
16. Baba M, Hong SB, Saharma N, et al. Folliculin encoded by the BHD gene interacts with a binding protein, FNIP1, and AMPK, and is involved in AMPK and mTOR signaling. *Proc Natl Acad Sci U S A.* 2006;103;15552-15557.
17. Graham RB, Nolasco M, Peterlin B, Garcia CK. Nonsense mutations in folliculin presenting as isolated familial spontaneous pneumothorax in adults. *Am J Resp Crit Care Med.* 2005;172:39-44.
18. Painter JN, Tapanainen H, Somer M, et al. A 4bp deletion in the Birt-Hogg-Dubé gene (FLCN) causes dominantly inherited spontaneous pneumothorax. *Am J Hum Genet.* 2005; 76:522-527.
19. Khoo SK, Kahnoski K, Sugimura J, et al. Inactivation of BHD in sporadic renal tumors. *Cancer Res.* 2003;63:4583-4587.
20. Morrison PJ, Donnelly DE, Atkinson AB, Maxwell AP. Advances in the genetics of familial renal cancer. *The Oncologist.* 2010;15:532-538.
21. Choyke PL, Glenn GM, Walther MM, et al. Hereditary renal cancers. *Radiology.* 2003;226:33-46.

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