Birt-Hogg-Dubé Syndrome

Clinicopathologic Findings and Genetic Alterations

Brian P. Adley, MD; Norm D. Smith, MD; Ritu Nayar, MD; Ximing J. Yang, MD, PhD

• ***Context.*—Birt-Hogg-Dubé (BHD) syndrome is a rare clinicopathologic condition transmitted in an autosomal dominant fashion. This complex entity is characterized by cutaneous fibrofolliculomas, kidney tumors, pulmonary cysts, and spontaneous pneumothorax. Recently, the gene possibly responsible for the clinical manifestations of BHD syndrome has been cloned and characterized. The few reviews of BHD syndrome found in the English literature mostly focus on the skin lesions or genetics, with limited information on other pathologic changes, particularly the kidney lesions.**

***Objective.*—To review the literature on this subject with a special emphasis on BHD syndrome-associated renal pathology as well as recent advances in molecular genetic discovery of the BHD syndrome.**

***Data Sources.*—We used all data available after performing a literature search using MEDLINE and searching under the headings "Birt-Hogg-Dubé," "hybrid oncocytic tumors," and "folliculin."**

***Conclusions.*—The presence of BHD syndrome should be investigated in any patient with multiple bilateral kidney tumors, especially if the predominant histologic type is chromophobe renal cell carcinoma or the so-called hybrid oncocytic tumor. The genetic alteration for BHD syndrome has been mapped to chromosome 17p12q11, and the gene in this region has been cloned and believed to be responsible for the BHD syndrome. The function of the BHD product, called folliculin, is still unknown, although it is speculated to be a tumor suppressor gene. Numerous mutations have been described in the *BHD* gene. Studies are ongoing to determine the relationship between the *BHD* gene and development of sporadic renal cell carcinoma and other lesions.**

(*Arch Pathol Lab Med.* 2006;130:1865–1870)

Although the majority of kidney neoplasms occur sporadically, approximately 4% are associated with heritable syndromes such as Beckwith-Wiedemann syndrome associated with Wilms tumor, von Hippel-Lindau syndrome associated with renal cell carcinoma (RCC), tuberous sclerosis associated with angiomyolipoma, hereditary papillary RCC, and familial renal oncocytoma. Birt-Hogg-Dubé (BHD) syndrome is another rare clinicopathologic complex associated with renal neoplasms.

In 1975, Hornstein and Knickenberg[1] described an inherited syndrome in 2 siblings that was characterized by multiple perifollicular fibromas on the face, neck, and trunk that were associated with multiple intestinal polyps. Numerous soft pedunculated fibromas resembling skin tags were also noted in both patients. The patients' father reportedly had similar skin lesions and a history of kidney cysts and lung cysts. The authors discussed the possibility of a peculiar cutaneointestinal syndrome not previously described in the literature.

In 1977, Birt, Hogg, and Dubé[2] reported on a Canadian kinship in which 15 of 70 members were reported to have multiple 2-mm to 4-mm yellow-white, dome-shaped papules on the forehead, scalp, face, and neck that were inherited in an autosomal dominant fashion. Multiple small skin tags were intermingled with the facial tumors and also appeared on the upper eyelids and axillary folds. Histologic findings of biopsied papules revealed circumscribed proliferations of specialized connective tissue around the variably dilated hair follicles. The authors designated the term *fibrofolliculoma* to describe these lesions. In addition, previously described trichodiscomas were present in 3 of the 5 patients who underwent skin biopsies. Skin tumors appeared only after the age of 25 years. The authors proposed the possibility of an autosomally inherited cutaneous syndrome but made no mention of any additional gastrointestinal, pulmonary, or kidney findings in these patients.

The aforementioned syndromes described by Hornstein and Knickenberg[1] and Birt et al[2], respectively, are now considered to represent the same syndrome designated as the Birt-Hogg-Dubé syndrome,[3,4] although it was also referred to as the Hornstein-Knickenberg syndrome in literature in the past. Since the sentinel studies, more than 30 families have been identified with BHD syndrome, and it has been shown that patients with this syndrome also have an increased incidence of renal tumors, lung cysts, and spontaneous pneumothorax.[5] In this article we review the literature on BHD syndrome, with special emphasis on associated renal and pulmonary pathology and recent molecular discoveries concerning this interesting entity.

Accepted for publication May 15, 2006.

From the Departments of Pathology (Drs Adley, Nayar, and Yang) and Urology (Dr Smith), Northwestern University, Feinberg School of Medicine, Chicago, Ill.

The authors have no relevant financial interest in the products or companies described in this article.

Reprints: Ximing J. Yang, MD, PhD, Department of Pathology, Feinberg 7–334, Northwestern Memorial Hospital, Northwestern University, Feinberg School of Medicine, 251 E Huron St, Chicago, IL 60611 (e-mail: xyang@northwestern.edu).

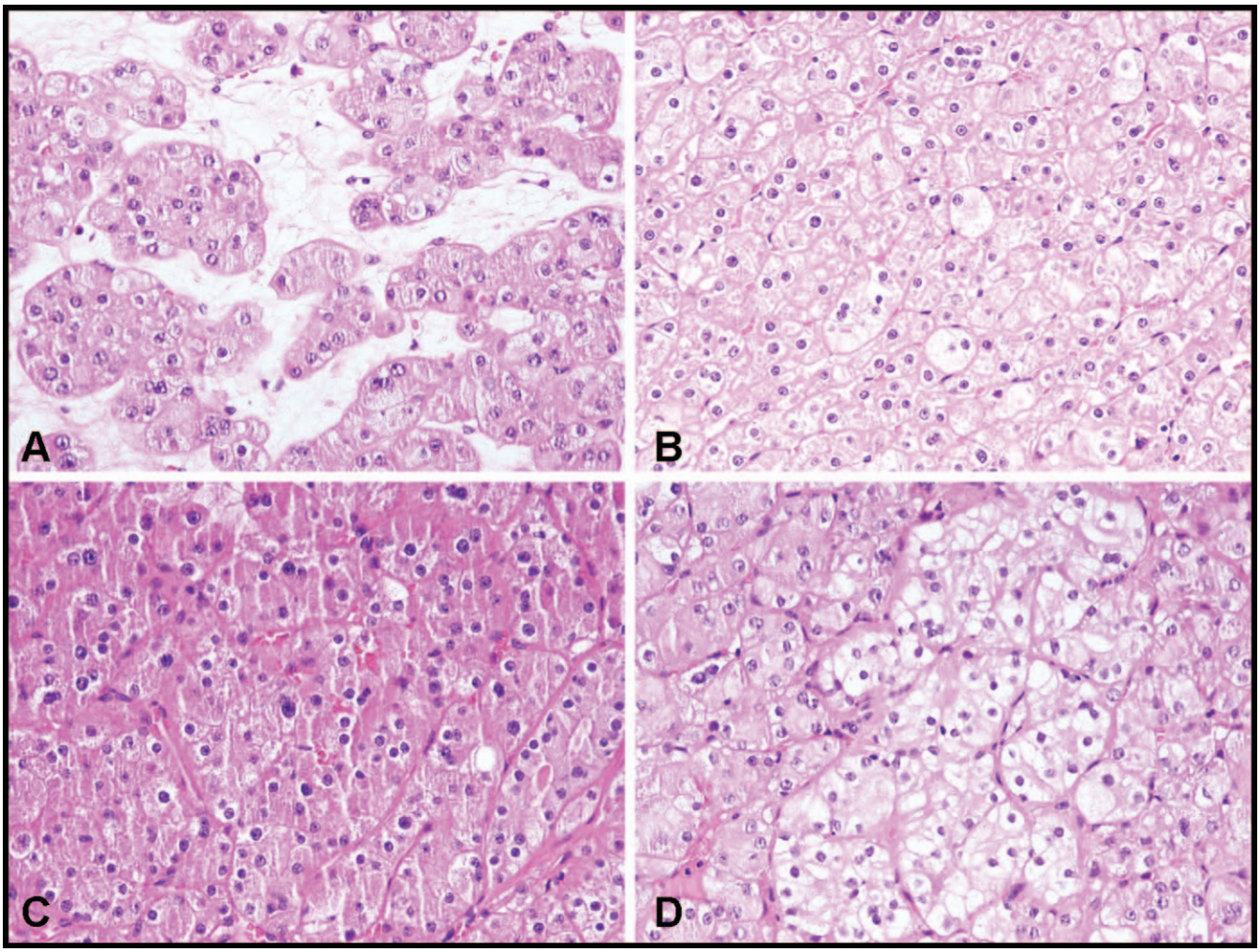

Figure 1. *Different types of kidney tumors that occurred in a single patient with Birt-Hogg-Dubé (BHD) syndrome: renal oncocytoma (A), chromophobe renal cell carcinoma (B), and hybrid oncocytic tumor, which typically has an admixture of eosinophilic cells with round nuclei resembling oncocytes (C), as well as clear cells with prominent nuclear membranes that are more reminiscent of chromophobe renal cell carcinoma (D)(hematoxylin-eosin, original magnifications ×400 [A through D]).*

RENAL PATHOLOGY

In the initial reports by Hornstein and Knickenberg[1] and Birt et al,[2] kidney lesions were not recognized as a part of the BHD syndrome. Only since 1993, 18 years after the first description of BHD syndrome, has the association between BHD syndrome and renal neoplasms become clearer. Birt-Hogg-Dubé syndrome has been reported in association with renal tumors of a variety of histologic types including clear cell, papillary, and chromophobe types of RCC as well as oncocytomas.[6–9]

In 1993 Roth et al[7] described the first documented association of the BHD syndrome with renal pathology in a man with bilateral kidney tumors. Histopathologic examination revealed 1 clear cell RCC and 1 chromophobe RCC with a mixed population of clear and eosinophilic cells in the same tumor. In a study of 13 patients with BHD syndrome, Toro et al[9] later reported that 7 of these patients had renal neoplasms, including renal oncocytomas and papillary RCCs. In the largest single study of 98 patients with BHD syndrome, Zbar et al[6] determined that the odds ratio for developing renal tumors in BHD syndrome-affected family members adjusted for age was 6.9, with renal tumors found in 15 (15%) of the patients.

Two unique features of renal tumors in patients with BHD syndrome are the diversity of histologic types of tumors seen even in a single kidney (or patient) (Figure 1) and distinct cell populations within individual tumors. Prior analyses have noted the presence of clear cell RCCs, papillary RCCs, chromophobe RCCs, and oncocytomas, as well as so-called hybrid oncocytic tumors (not previously described in other syndromes) in patients with BHD syndrome.[10,11] Moreover, chromophobe RCC is the most predominant type of renal tumor.[6,10,11] Kidney tumors in BHD syndrome seem to occur earlier than sporadic tumors, and are usually multiple and bilateral.[10,11]

CHROMOPHOBE RCC, ONCOCYTOMA, AND HYBRID TUMORS

Oncocytoma and chromophobe RCC are thought to originate from the intercalated cells of renal collecting tubules and share overlapping histologic features.[12] In fact, these 2 tumors share strong similarities in gene expression profiles in addition to their overlapping morphologies.[13] Numerous case reports have described both oncocytoma (Figure 1, A) and chromophobe RCC (Figure 1, B) occurring in patients with BHD syndrome.[7,9–11,14,15] In the pre-

viously mentioned study of 98 patients with BHD syndrome by Zbar et al,[6] chromophobe RCC was the predominant type of renal cancer found in these patients, seen in 7 of 14 histologically examined tumors.[6]

In addition to diverse histologic subtypes of renal tumors, a single tumor may be composed of multiple distinct cell populations. So-called hybrid oncocytic tumors are frequently observed in patients with BHD syndrome. Hybrid oncocytic tumors are characterized by histologic features similar to both chromophobe RCC and oncocytoma. Furthermore, a mixture of several distinct populations of tumor cells can be seen in hybrid tumors (Figure 1, C and D). Curiously, the case report of the first documented renal tumors in a patient with BHD syndrome gave a peculiar description of ''chromophobe adenocarcinoma with a mixed population of clear and eosinophilic cells,''[7] which raises the possibility that this tumor was actually a hybrid tumor. Typically, hybrid tumors contain an admixture of areas histologically resembling oncocytoma (Figure 1, C) and areas more reminiscent of chromophobe RCC (Figure 1, D).[10] Hybrid oncocytic tumors have been reported to be frequent in patients with BHD syndrome.[10,16] In 2002, Pavlovich et al[16] reviewed 130 renal tumors from 30 patients with BHD syndrome in 19 affected families. Mean patient age was 51 years; there were 25 men, and 5 women, and most patients had multiple and bilateral tumors associated with oncocytosis. The authors designated 50% of tumors as hybrid oncocytic neoplasms, 34% as chromophobe RCCs, 9% as clear cell RCCs, 7% as oncocytomas, and 2% as papillary RCCs. The hybrid tumors contained oncocytes and chromophobe cells but rarely contained cells with perinuclear halos, and they were usually arranged in a plantlike pattern reminiscent of oncocytoma.

The biological behavior of hybrid oncocytic tumors is still not entirely certain. The initial studies by Tickoo et al[10] and Pavlovich et al[16] did not mention any worrisome features such as tumor necrosis, vascular invasion, or distant metastasis in any of the tumors studied. Recently, Mai et al[17] examined 5 hybrid tumors, although none were associated with BHD syndrome, ranging in size from 1.8 to 5 cm and with no tumoral necrosis seen. Vascular invasion into medium-sized veins was identified in only one tumor. None of the patients had distant metastasis. From these observations, the authors concluded that sporadic hybrid oncocytic tumors may have a favorable prognosis.[17] To our knowledge, there has not been a report of a hybrid oncocytic tumor, either sporadic or associated with BHD syndrome, behaving in an aggressive or malignant fashion. It may be reasonable to assume that these renal hybrid oncocytic tumors have biological behavior somewhere between oncocytoma and low-grade chromophobe RCC.

CLEAR CELL AND PAPILLARY RCC

There also appears to be an association between BHD syndrome and clear cell RCC and, to a lesser extent, papillary RCC. The initial case report of renal tumors in a patient with BHD syndrome by Roth et al[7] describes one of the 2 lesions as a clear cell RCC. The previously mentioned epidemiologic study by Zbar et al[6] reported 4 of 14 renal tumors as clear cell RCCs in patients with BHD syndrome. Similarly, papillary RCC has also been reported in patients with BHD syndrome, although less commonly than clear cell RCC.[8,9,16] In the study by Pavlovich et al,[16] the patients with clear cell RCC often had multiple bilateral hybrid tumors and/or chromophobe RCCs as well as oncocytosis. The clear cell RCCs tended to be much larger than the other renal tumors. Molecular analysis performed on some of the clear cell RCCs showed 3p loss and von-Hippel Lindau *(VHL)* gene mutations, raising the question as to whether hybrid tumors and chromophobe RCCs progress to more aggressive clear cell RCCs through additional genetic mutations. Further investigation is required to answer this question definitively.

The clinical behavior of clear cell and papillary RCC in patients with BHD syndrome is not entirely clear because of the relatively small number of cases reported. In 9 patients with BHD syndrome with clear cell RCC studied by Pavlovich et al,[16] 3 had T3 lesions, with one showing sarcomatoid change and another showing lymph node metastasis. In addition, 3 of 9 patients had tumors with grade 3 nuclei; the remainder had grade 2 nuclei. Therefore, it appears that these tumors show behavior similar to that of sporadic clear cell RCC.

PULMONARY PATHOLOGY

Another important and well-recognized component of BHD syndrome is pulmonary cysts and spontaneous pneumothorax. Toro et al,[9] in 1999, originally described the association between pulmonary cysts and BHD syndrome when they observed lung cysts in 4 of 28 patients studied. Since then, numerous patients with BHD syndrome have been reported to have pulmonary cysts and/or spontaneous pneumothorax. Zbar et al[6] determined the odds ratio for pneumothorax in BHD syndrome-affected individuals, adjusted for age, was 50.3, and approximately 32 times higher when adjusted for the other risk variables.

Histologically, pulmonary cysts are characterized by cystic dilatation of alveolar spaces ranging from microscopic foci to a few millimeters in diameter. The thin-walled cysts are lined by cuboidal epithelium (Figure 2) with no obvious fibrous or smooth muscle tissue in the wall. Sometimes cysts may bulge into the pleural surface. When the cysts rupture under pressure of inhalation, pneumothorax may develop. By a strict definition, pneumothorax in BHD syndrome is not spontaneous but rather is secondary to the ruptured pulmonary cysts.

CUTANEOUS PATHOLOGY

The initial article by Birt et al[2] described only skin tumors as part of BHD syndrome. They also coined the term for the most commonly seen lesion in these patients as *fibrofolliculoma.* This tumor is a circumscribed proliferation of collagen and fibroblasts that surrounds distorted hair follicles from which basaloid cells protrude into the surrounding fibromucinous stroma (Figure 3).[2] Trichodiscomas, sharply defined fibrovascular tumors in the superficial dermis, and acrochordons were also described in these patients. Birt et al[2] also noted that these lesions may be subtle and may increase with age. Most consider the skin findings as the defining pathology of BHD syndrome, and the 3 aforementioned lesions have been extensively reported in BHD syndrome in the literature. In fact, before genetic testing became available, 1 publication defined an individual as having BHD syndrome if he or she had more than 10 lesions clinically consistent with fibrofolliculomas and a minimum of one lesion confirmed as a fibrofolliculoma by examination of a biopsy specimen.[6] However, whether these lesions are neoplastic in nature or a result of hair follicle malformation is still unknown. We will dis-

cuss the lack of *BHD* gene mutation in these skin lesions later in this article, but the relationship between skin lesions and *BHD* gene function is far from clear.

Some experts question whether fibrofolliculoma and trichodiscoma represent the same lesion. Ackerman et al[18] contend that fibrofolliculoma and trichodiscoma are different names for a single pathologic process at different stages of development. In addition, immunophenotypic studies with perifollicular vimentin and CD34 support a similar histogenic precursor of fibrofolliculoma and trichodiscoma.[18] Other authors have challenged the notion that acrochordons are a part of BHD syndrome. De la Torre et al[19] reported that 2 patients with BHD syndrome had lesions that were clinically acrochordon-like and proved to correspond to the same histopathologic spectrum as fibrofolliculoma and trichodiscoma on biopsy. They concluded that fibrofolliculoma, trichodiscoma, and the acrochordon-like lesions are histologic variations of a single entity.

OTHER LESIONS WITH UNCERTAIN ASSOCIATION WITH BHD SYNDROME

In the initial study by Hornstein and Knickenberg,[1] the authors described intestinal polyps in their 2 sibling patients in addition to cutaneous lesions. Almost 15 years later, Rongioletti et al[20] described a patient with multiple fibrofolliculomas, trichodiscomas, and acrochordons associated with intestinal polyps. One of the polyps showed severe epithelial dysplasia. The authors proposed that patients with BHD syndrome should be examined periodically for intestinal polyps. However, in the large epidemiologic study by Zbar et al,[6] no association was found between BHD syndrome and colon cancer and colon polyps. The general consensus now is that patients with BHD syndrome are not at increased risk for colon polyps or colonic adenocarcinoma.

Some patients with BHD syndrome also have been reported to have neurothekeomas,[21] meningiomas,[21] multiple lipomas,[22] parathyroid adenomas,[22] intraoral papules,[23] flecked chorioretinopathy,[24] and a parotid oncocytoma,[25] although a real association of these lesions with BHD syndrome has not been proven. Other cutaneous tumors described in patients with BHD syndrome include lipomas,[9] collagenomas,[9] perivascular fibromas,[26] angiofibromas,[27] and melanomas,[9,28] although their correlations to BHD syndrome are not as striking or definitive as fibrofolliculoma, trichodiscoma, and acrochordon lesions.

MOLECULAR GENETICS

In 2001, Khoo et al[29] first reported their finding of the *BHD* gene location. They used polymorphic microsatellite markers on a large Swedish family with BHD syndrome, and mapped the *BHD* gene locus to chromosome 17p12q11.2 a genomic region that, because of the presence of low copy number-repeat elements, is unstable and associated with a number of diseases. Two months later, Schmidt et al[30] reported their localization of the gene locus to the same pericentromeric region of chromosome 17p by performing a genomewide linkage analysis in one large kindred with BHD syndrome. The *BHD* locus was found within the same chromosomal band, 17p12q11.2.

The next year, by positional cloning, Nickerson et al[31] cloned the *BHD* gene. They named the 579-amino acid BHD gene product *folliculin* after the skin lesion fibrofolliculoma. By northern blot analysis, expression of the 3.8-kb transcript was found in a wide spectrum of normal tissues, including kidney, lung, and skin.

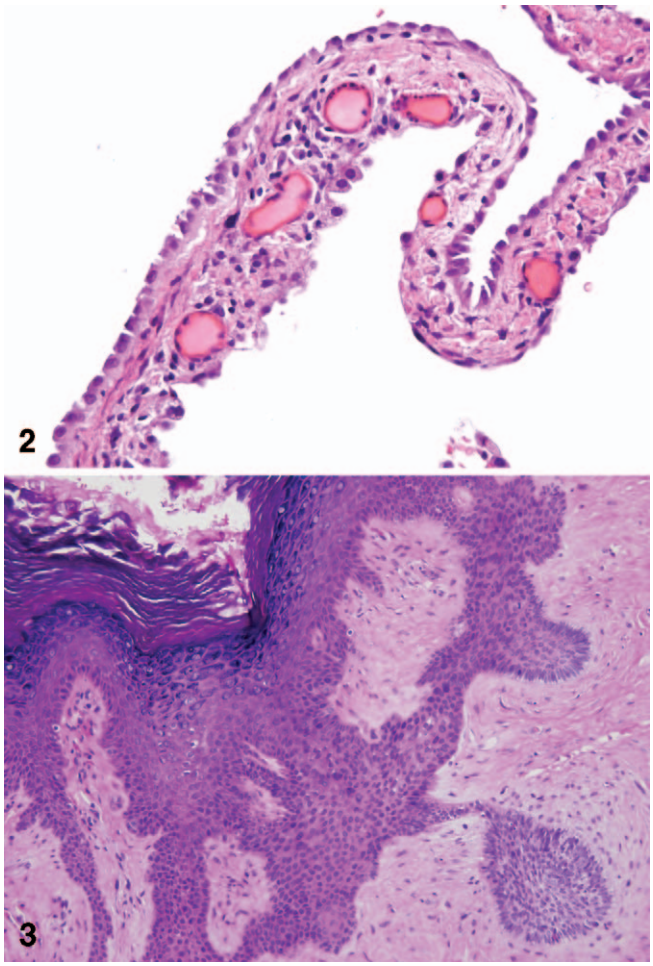

Figure 2. *Pulmonary cyst excised from a patient with Birt-Hogg-Dubé syndrome who initially presented with pneumothorax. The cyst is lined by cuboidal cells, which express cytokeratins (H&E, original magnification ×400).*

Figure 3. *Fibrofolliculoma in a patient with Birt-Hogg-Dubé syndrome, the lesion that defines the syndrome (H&E, original magnification ×200).*

BHD GENE MUTATIONS

To confirm the identity of the *BHD* gene, Nickerson et al[31] found protein-truncating mutations in a panel of families with BHD syndrome, with a 44% frequency of insertion/deletion mutations within a hypermutable 8 cytosine tract. In 2004, Warren et al[32] measured the expression of folliculin mRNA in healthy and neoplastic human tissues by fluorescent in situ hybridization. They also further defined that folliculin mRNA was expressed in a variety of tissues, including the skin and its appendages, the distal nephron of the kidney, and stromal cells and type 1 pneumocytes of the lung. Tissues with reduced expression of folliculin mRNA included heart, muscle, and liver. In addition, folliculin mRNA was expressed strongly in fibrofolliculomas but not in renal tumors from patients with BHD syndrome. Because of loss of folliculin expression in chromophobe RCCs and hybrid tumors, the authors postulated a tumor suppressor role for the protein.[32] However, this finding ironically does not explain the role of follic-

ulin in the development of fibrofolliculomas, one of the major defining characteristics of BHD syndrome.

Since its identification, various specific mutations have been identified in the folliculin gene in patients with BHD syndrome, and molecular testing has been developed to identify these mutations. In 2002, Khoo et al[33] identified 2 distinct germline mutations on exon 11 of the folliculin gene (c.1733insC and c.1733delC) in 3 of 4 families with BHD syndrome. In addition, a novel somatic mutation, c.1732delTCinsAC, was detected in a BHD syndrome-related chromophobe renal carcinoma, supposedly providing a ''second hit'' toward tumor development. Their results confirmed the $(C)_8$ tract in exon 11 as a mutational hot spot in the *BHD* gene.

In 2005, Schmidt et al[34] identified mutations along the entire length of the coding region of the folliculin gene, including 16 insertion/deletion, 3 nonsense, and 3 splice-site mutations in 51 of 61 families with BHD syndrome. The majority of BHD mutations were predicted to truncate the BHD protein, folliculin. Interestingly, among patients with a mutation in the exon 11 hot spot, significantly fewer renal tumors were observed in patients with the C-deletion than those with the C-insertion mutation.[34] The same group also studied 77 renal tumors from 12 patients with BHD syndrome. Using DNA sequencing, alterations were detected in the majority of renal tumors (41/77 [53%]), with loss of heterozygosity at the BHD locus in a minority of additional tumors (14/77 [18%]). The somatic mutations were distributed across the entire gene, and the majority resulted in frameshifts predicted to lead to truncated BHD proteins.[35]

In addition, mutations truncating folliculin have been described in patients with familial lung cysts and/or spontaneous pneumothorax[36,37] without skin lesions or kidney tumors. Currently, these patients are not considered to have BHD syndrome because of the lack of defining skin lesions. Perhaps the spectrum of clinical criteria for BHD syndrome should be reexamined using existing genetic data.

Genetic analyses in sporadic renal tumors have shown that folliculin inactivation occurs in a subset of tumors of various histologic types.[38,39] Another study also suggests that folliculin inactivation may play a role in colorectal carcinogenesis in a subset of tumors, further supporting the role of folliculin as a tumor suppressor gene.[40]

FUNCTION OF FOLLICULIN

The full-length BHD cDNA sequence predicted a novel 64 kd protein, folliculin, which was highly conserved across species. As predicated from RNA analysis, there is widespread tissue expression of folliculin, including expression in kidney, lung, and skin.[31]

The studies of folliculin at protein levels are limited by the availability of antibodies specific for folliculin. By immunohistochemical evaluation, Wang et al[41] reported folliculin immunoreactivity occurred in the nucleolus of normal cells and was associated with mitosis. Furthermore, loss of folliculin expression was seen in oncocytoma (1/30 [3.3%]), chromophobe RCC (17/28 [60.7%]), papillary RCC (4/11 [36.4%]), and clear cell RCC (20/95 [21.1%]). Abnormal accumulation in the cytoplasm was also observed in oncocytoma (23/30 [76.7%]), chromophobe RCC (1/28 [3.6%]), and clear cell RCC (14/95 [14.7%]). The authors concluded that loss of *BHD* tumor suppressor gene expression was a common event in tumorigenesis of different types of sporadic renal cell neoplasms.

In summary, the Birt-Hogg-Dubé syndrome is an autosomal dominantly inherited syndrome consisting of skin lesions, lung cysts/spontaneous pneumothorax, and kidney lesions. The presence of BHD syndrome should be investigated in any patient with multiple bilateral kidney tumors, especially if the predominant histologic type is chromophobe RCC or the so-called hybrid oncocytic tumor. The genetic alteration for BHD syndrome has been mapped to chromosome 17p12q11.2, and the gene in this region has been cloned and believed to be responsible for the BHD syndrome. The function of the BHD product, identified as folliculin, is still unknown, although it is speculated to be a tumor suppressor gene. Numerous mutations have been described in the *BHD* gene, and most have been located within a hypermutable 8 cytosine tract, resulting in a truncated folliculin. Studies are ongoing to determine the relationship between the *BHD* gene and the development of sporadic RCC and other lesions.

References

1. Hornstein OP, Knickenberg M. Perifollicular fibromatosis cutis with polyps of the colon: a cutaneo-intestinal syndrome sui generis. *Arch Dermatol Res.* 1975; 253:161–175.
2. Birt AR, Hogg GR, Dubé WJ. Hereditary multiple fibrofolliculomas with trichodiscomas and acrochordons. *Arch Dermatol.* 1977;113:1674–1677.
3. Frantzen B, Rose C, Schulz T, Brocker EB, Hamm H. Hornstein-Knickenberg and Birt-Hogg-Dube syndrome: report of a case with spontaneous pneumothorax and aplasia of the left internal carotid artery [in German]. *Hautarzt.* 2001;52: 1016–1020.
4. Schulz T, Hartschuh W. Birt-Hogg-Dube syndrome and Hornstein-Knickenberg syndrome are the same: different sectioning technique as the cause of different histology. *J Cutan Pathol.* 1999;26:55–61.
5. Ubogy-Rainey Z, James WD, Lupton GP, Rodman OG. Fibrofolliculomas, trichodiscomas, and acrochordons: the Birt-Hogg-Dube syndrome. *J Am Acad Dermatol.* 1987;16:452–457.
6. Zbar B, Alvord WG, Glenn G, et al. Risk of renal and colonic neoplasms and spontaneous pneumothorax in the Birt-Hogg-Dube syndrome. *Cancer Epidemiol Biomarkers Prev.* 2002;11:393–400.
7. Roth JS, Rabinowitz AD, Benson M, Grossman ME. Bilateral renal cell carcinoma in the Birt-Hogg-Dube syndrome. *J Am Acad Dermatol.* 1993;29:1055–1056.
8. Takahashi A, Hayashi T, Yoshida O, Uede K, Furukawa F, Shuin T. Renal cell carcinoma in the Birt-Hogg-Dube syndrome: report of a case [in Japanese]. *Hinyokika Kiyo.* 2001;47:719–721.
9. Toro JR, Glenn G, Duray P, et al. Birt-Hogg-Dube syndrome: a novel marker of kidney neoplasia. *Arch Dermatol.* 1999;135:1195–1202.
10. Tickoo SK, Reuter VE, Amin MB, et al. Renal oncocytosis: a morphologic study of fourteen cases. *Am J Surg Pathol.* 1999;23:1094–1101.
11. Weirich G, Junker K, Salles PGO, et al. Comparative genomic hybridization analysis of renal oncocytomas, chromophobe renal cell carcinomas, and tumors with hybrid histology: hybrid oncocytic tumors [abstract]. *Mod Pathol.* 2002;15:186.
12. Storkel S, Eble JN, Adlakha K, et al. Classification of renal cell carcinoma: Workgroup No. 1, Union Internationale Contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC). *Cancer.* 1997;80:987–989.
13. Takahashi M, Yang XJ, Sugimura J, et al. Molecular subclassification of kidney tumors and the discovery of new diagnostic markers. *Oncogene.* 2003; 22:6810–6818.
14. Durrani OH, Ng L, Bihrle W III. Chromophobe renal cell carcinoma in a patient with the Birt-Hogg-Dube syndrome. *J Urol.* 2002;168:1484–1485.
15. Welsch MJ, Krunic A, Medenica MM. Birt-Hogg-Dube Syndrome. *Int J Dermatol.* 2005;44:668–673.
16. Pavlovich CP, Walther MM, Eyler RA, et al. Renal tumors in the Birt-Hogg-Dube syndrome. *Am J Surg Pathol.* 2002;26:1542–1552.
17. Mai KT, Dhamanaskar P, Belanger E, Stinson WA. Hybrid chromophobe renal cell neoplasm. *Pathol Res Pract.* 2005;201:385–389.
18. Ackerman AB, Reddy VB, Soyer HP. Fibrofolliculoma/Trichodiscoma. In: Ackerman AB, Reddy VB, Soyer HP, eds. *Neoplasms With Follicular Differentiation.* Philadelphia, Pa: Ardor Scribendi; 2001:221–244.
19. De la Torre C, Ocampo C, Doval IG, Losada A, Cruces MJ. Acrochordons are not a component of the Birt-Hogg-Dube syndrome: does this syndrome exist? Case reports and review of the literature. *Am J Dermatopathol.* 1999;21:369–374.
20. Rongioletti F, Hazini R, Gianotti G, Rebora A. Fibrofolliculomas, tricodiscomas and acrochordons (Birt-Hogg-Dube) associated with intestinal polyposis. *Clin Exp Dermatol.* 1989;14:72–74.

21. Vincent A, Farley M, Chan E, James WD. Birt-Hogg-Dube syndrome: two patients with neural tissue tumors. *J Am Acad Dermatol.* 2003;49:717–719.
22. Chung JY, Ramos-Caro FA, Beers B, Ford MJ, Flowers F. Multiple lipomas, angiolipomas, and parathyroid adenomas in a patient with Birt-Hogg-Dube syndrome. *Int J Dermatol.* 1996;35:365–367.
23. Nadershahi NA, Wescott WB, Egbert B. Birt-Hogg-Dube syndrome: a review and presentation of the first case with oral lesions. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 1997;83:496–500.
24. Walter P, Kirchhof B, Korge B, Heimann K. Flecked chorioretinopathy associated with Birt-Hogg-Dube syndrome. *Graefes Arch Clin Exp Ophthalmol.* 1997;235:359–361.
25. Liu V, Kwan T, Page EH. Parotid oncocytoma in the Birt-Hogg-Dube syndrome. *J Am Acad Dermatol.* 2000;43:1120–1122.
26. Schulz T, Ebschner U, Hartschuh W. Localized Birt-Hogg-Dube syndrome with prominent perivascular fibromas. *Am J Dermatopathol.* 2001;23:149–153.
27. Schaffer JV, Gohara MA, McNiff JM, Aasi SZ, Dvoretzky I. Multiple facial angiofibromas: a cutaneous manifestation of Birt-Hogg-Dube syndrome. *J Am Acad Dermatol.* 2005;53:S108–111.
28. Lindor NM, Hand J, Burch PA, Gibson LE. Birt-Hogg-Dube syndrome: an autosomal dominant disorder with predisposition to cancers of the kidney, fibrofolliculomas, and focal cutaneous mucinosis. *Int J Dermatol.* 2001;40:653–656.
29. Khoo SK, Bradley M, Wong FK, Hedblad MA, Nordenskjold M, Teh BT. Birt-Hogg-Dube syndrome: mapping of a novel hereditary neoplasia gene to chromosome 17p12q11.2. *Oncogene.* 2001;20:5239–5242.
30. Schmidt LS, Warren MB, Nickerson ML, et al. Birt-Hogg-Dube syndrome, a genodermatosis associated with spontaneous pneumothorax and kidney neoplasia, maps to chromosome 17p11.2. *Am J Hum Genet.* 2001;69:876–882.
31. 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-Dube syndrome. *Cancer Cell.* 2002;2:157–164.
32. Warren MB, Torres-Cabala CA, Turner ML, et al. Expression of Birt-Hogg-Dube gene mRNA in normal and neoplastic human tissues. *Mod Pathol.* 2004; 17:998–1011.
33. Khoo SK, Giraud S, Kahnoski K, et al. Clinical and genetic studies of Birt-Hogg-Dube syndrome. *J Med Genet.* 2002;39:906–912.
34. Schmidt LS, Nickerson ML, Warren MB, et al. Germline BHD-mutation spectrum and phenotype analysis of a large cohort of families with Birt-Hogg-Dube syndrome. *Am J Hum Genet.* 2005;76:1023–1033.
35. Vocke CD, Yang Y, Pavlovich CP, et al. High frequency of somatic frameshift BHD gene mutations in Birt-Hogg-Dube-associated renal tumors. *J Natl Cancer Inst.* 2005;97:931–935.
36. Painter JN, Tapanainen H, Somer M, Tukiainen P, Aittomaki K. A 4-bp deletion in the Birt-Hogg-Dube gene (FLCN) causes dominantly inherited spontaneous pneumothorax. *Am J Hum Genet.* 2005;76:522–527.
37. Graham RB, Nolasco M, Peterlin B, Garcia CK. Nonsense mutations in folliculin presenting as isolated familial spontaneous pneumothorax in adults. *Am J Respir Crit Care Med.* 2005;172:39–44.
38. Khoo SK, Kahnoski K, Sugimura J, et al. Inactivation of BHD in sporadic renal tumors. *Cancer Res.* 2003;63:4583–4587.
39. da Silva NF, Gentle D, Hesson LB, Morton DG, Latif F, Maher ER. Analysis of the Birt-Hogg-Dube (BHD) tumour suppressor gene in sporadic renal cell carcinoma and colorectal cancer. *J Med Genet.* 2003;40:820–824.
40. Kahnoski K, Khoo SK, Nassif NT, et al. Alterations of the Birt-Hogg-Dube gene (BHD) in sporadic colorectal tumours. *J Med Genet.* 2003;40:511–515.
41. Wang D, Yao YL, Messing EM, et al. Birt-Hogg-Dube tumor suppressor expression in sporadic renal cell carcinomas [abstract]. *J Urol.* 2005;173:A625.