Published in final edited form as:

Fam Cancer. 2013 September ; 12(3): 355–356. doi:10.1007/s10689-013-9679-y.

Birt–Hogg–Dubé syndrome

Maria F. Czyzyk-Krzeska and

Department of Cancer Biology, The Vontz Center for Molecular Studies, University of Cincinnati College of Medicine, 3125 Eden Avenue, Cincinnati, OH 45267-0521, USA

Francis X. McCormack

Division of Pulmonary, Critical Care and Sleep Medicine, Department of Internal Medicine, University of Cincinnati College of Medicine, MSB 6165, 231 Albert Sabin Way, Cincinnati, OH 45267-0564, USA frank.McCormack@uc.edu

Birt–Hogg–Dubé (BHD) syndrome is a rare autosomal dominant disorder associated with renal cysts and cancer, lung cysts, pneumothorax and skin fibrofolliculomas. The disease is caused by germline mutations in the *FLCN* gene located on chromosome 17p11.2 that result in loss of function of the tumor suppressor, folliculin. While the genetic basis of BHD has been well established, the biochemical and signaling functions of FLCN remain incompletely understood. To address this knowledge deficit, the Myrovlytis Trust and BHD Foundation have conducted annual meetings over the past 5 years to promote scientific interaction between scientists and clinicians interested in BHD. The Fourth Annual BHD meeting took place in March 2012 in Cincinnati, Ohio. This special issue of *Familial Cancer* summarizes the new data presented and the status of knowledge discussed at the meeting, from both the basic and clinical perspective. The authors provide an overview of the currently understood functions of FLCN, as well as recommendations for detection and treatment of BHD.

Dr. Laura Schmidt, one of the co-discoverers of the role of *FLCN* mutations in the pathogenesis of BHD from the NCI Urologic Oncology Branch [1, 2], reviewed the history and chronology of discovery in BHD. Seminal findings from their group and others include the identification of loss of heterozygosity indicative of somatic ‘second hits’ in the majority of renal cancers in BHD [3], recapitulation of the BHD phenotype including renal tumors in mouse models of FLCN deficiency, and identification of first protein binding partners of FLCN, FNIP1 and FNIP2. Further on, articles by Dr. L. Schmidt and Drs. A.R. Tee and A. Pause discuss a conundrum in our understanding of the relationship between FLCN and mTOR; that FLCN has been shown to either reduce or activate signal transduction through mTORC1 signaling, depending on the model system used. Understanding this controversy is of major clinical importance, since trials of inhibition of mTORC1 activity by sirolimus and other ‘rapalogs’ is under consideration in patients with BHD syndrome. Other established functions of FLCN include regulation of TGF- β , HIF- and TFE3-signaling, as well as a role in cilia formation. Solution of the crystal structure of the C-terminal region of FLCN

revealed a DENN-like domain similar to that found in GEF proteins, which in vitro experiments indicate may act on RAB35 [4]. This is the first evidence that FLCN has enzymatic activity that may contribute to its tumor suppressing activity. Plakophilin-4 (PKP4, p0071) was identified as a novel FLCN-interacting protein [5, 6], suggesting a possible role for FLCN in regulation of the Rho complex. Interestingly Dr. F. Menko and collaborators report identification of a BHD de novo mutation leading to premature termination of FLCN protein in a patient with clinical symptoms of BHD. Such de novo mutations in BHD syndrome are thought to be rare, but could become more widely recognized as awareness of the disorder grows.

The clinical manifestations of BHD are primarily limited to the kidneys, skin and lungs. The most threatening complication of BHD is renal cell cancer, which develops in approximately 15 % of patients by age 70. The earliest reported case of renal cancer in a patient with BHD occurred at age 20 years. There is no consensus regarding an optimal screening program, but periodic imaging every 12–36 months beginning at an age of 20 years of age has been suggested. The optimal method for surveillance is MRI, because of the high degree of resolution and absence of radiation, but this approach may be impractical for some patients given considerations of expense and availability. Ultrasound can miss some forms of BHD-associated cancer that have echogenicities similar to normal kidney tissue. Chromophobe renal cancer and mixed patterns of oncocytic and chromophobe histologies are most common, but clear cell renal cell carcinomas and papillary cancers also occur. Once kidney masses are detected, the surveillance program outlined by Dr. Stamatakis and collaborators that includes annual renal imaging and nephron sparing resection for tumors of >3 cm has been associated with excellent outcomes. There is interest in exploring a role for mTOR inhibitors in the management of metastatic renal tumors in BHD.

The major pulmonary manifestations of BHD are basilar and peripheral bullous changes and parenchymal cysts which are associated with increased susceptibility to pneumothorax. Skin and renal findings are less common in cohorts of patients ascertained through presentation with pneumothorax than they are in populations that are ascertained through renal presentations. Although the risk of pneumothorax is 50 times higher in BHD than in the general population, lung function is usually normal, and progressive disease is thought to be unusual. The cysts are lined by hyperplastic type II cells, and stain with antibodies to phosphor-mTOR and phosphor-S6, consistent with activation of the mTOR pathway. Lung biopsy is not typically helpful in patients with BHD, however, since histological changes are highly similar to or indistinguishable from those that occur in emphysema. Management of pneumothorax in patients with BHD is similar to that for other cystic lung diseases; Dr. Gupta and collaborators recommend early pleurodesis because the risk of recurrence is high.

The skin lesions in patients with BHD typically appear after the age of 20 years. They are usually found as whitish, dome shaped papules on the face, but can also be found on the neck, trunk and ears, in distributions that are enriched for sebaceous glands. Benign hair follicle tumors called fibrofolliculomas are most common. Multiple biopsies and careful sectioning are often required for correct diagnosis; shave biopsies may lead to confusion between angiofibromas and fibrofolliculomas. There is evidence that the hair follicle tumors may arise within the mantle layer, and that Hif1 signaling and the WNT pathway are

dysregulated; conflicting results have been reported for the role of mTOR signaling however. Conventional therapies including laser, shave, cautery, and curettage can result in improvement but are generally not curative. Dr. Vernooij and collaborators report that their favored treatment includes hyfrecation (electrocoagulation), followed by curettage (if necessary). A preliminary report of a randomized trial of topical sirolimus for BHD skin lesions presented at the meeting was disappointing. There is interest in retinoic acid derivatives for primary prevention of lesions, but they do not appear to be active against existing lesions. There was much enthusiasm for using the accessibility of skin lesions to advantage for discovery science in BHD.

It is essential that patients who are diagnosed with BHD be offered genetic and psychological counseling. Once the causative mutation has been discovered in the index patient, presymptomatic testing may be offered to unaffected at-risk relatives. Genetic testing is often delayed until after age 18–20 years, to allow for informed consent. Middleton [7] emphasizes that the psychological consequences of living with disfiguring skin lesions and the threat of renal cancer should not be underestimated. Counseling regarding pregnancy and childbirth is important for all couples considering starting a family.

References

1. 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. [PubMed: 15852235]
2. 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. [PubMed: 12204536]
3. Vocke CD, Yang Y, Pavlovich CP, et al. High frequency of somatic frameshift BHD gene mutations in Birt-Hogg-Dubé-associated renal tumors. *J Natl Cancer Inst.* 2005; 97:931–9315. [PubMed: 15956655]
4. Nookala RK, Langemeyer L, Pacitto A, et al. Crystal structure of folliculin reveals a hidDENN function in genetically inherited renal cancer. *Open Biol.* 2012; 2:120071. doi:10.1098/rsob.120071. [PubMed: 22977732]
5. Nahorski MS, Seabra L, Straatman-Iwanowska A, et al. Folliculin interacts with p0071 (plakophilin-4) and deficiency is associated with disordered RhoA signalling, epithelial polarization and cytokinesis. *Hum Mol Genet.* 2012; 21:5268–5279. [PubMed: 22965878]
6. Medvetz DA, Khabibullin D, Hariharan V, et al. Folliculin, the product of the Birt-Hogg-Dubé tumor suppressor gene, interacts with the adherens junction protein p0071 to regulate cell–cell adhesion. *PLoS One.* 2012; 7:e47842. [PubMed: 23139756]
7. Middleton LA. Birt-Hogg-Dubé: beyond the clinical manifestations. *Fam Cancer.* 2013; 12:97–99. [PubMed: 23179794]