Atlas of Genetics and Cytogenetics
in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section
Review

FLCN (folliculin gene)

Laura S Schmidt

Laboratory of Immunobiology, National Cancer Institute Frederick, Bldg 560, Rm 12-69, Frederick, MD 21702, USA

Published in Atlas Database: February 2007

Online updated version: http://AtlasGeneticsOncology.org/Genes/FLCNID789ch17p11.html
DOI: 10.4267/2042/38436

Identity

Hugo: FLCN
Other names: BHD; FLCL; Folliculin
Location: 17p11.2
Note: Putative tumor suppressor gene.

DNA/RNA

Description

The FLCN/BHD gene consists of a 3717 nt mRNA (using NM_144997 derived from BQ423946 and AF517523, the coding sequence extends from nt499 to nt2238) and contains 14 coding exons. The initiation codon is located within exon 4.

Transcription

Northern blot analysis revealed a 3.8 kb FLCN/BHD mRNA transcript expressed in most tissues
Alternate splicing of FLCN/BHD results in two transcript variants encoding two different isoforms. Transcript 1 is the full-length isoform. Transcript 2 has a shorter and distinct C-terminus from Transcript 1.

Protein

Description

The BHD protein, folliculin (FLCN), consists of 579 amino acids with a central glutamic acid-rich coiled-coil domain, one N-glycosylation site and three myristoylation sites, and an estimated molecular weight of 64.5 kDa.

Expression

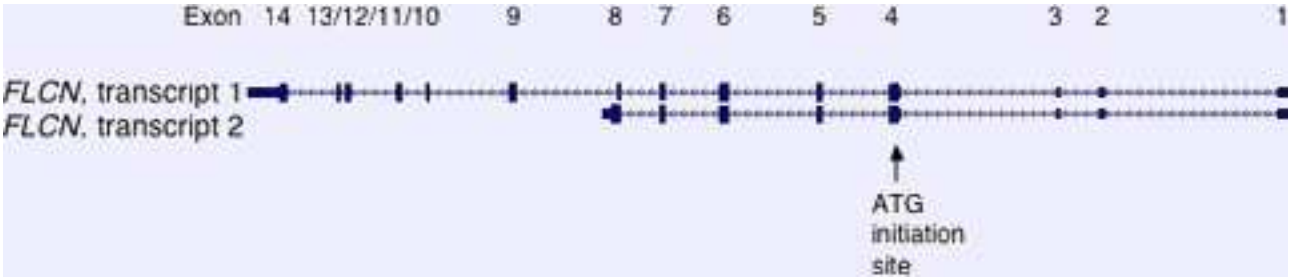
Expressed in most major adult tissues, including kidney, lung and skin, which are involved in the BHD phenotype.

Localisation

Epitope-tagged FLCN expressed in HEK293 cells localized in both the nucleus and cytoplasm by fluorescence in situ hybridization.

Function

FLCN is a novel protein, with no characteristic domains to suggest function. Coimmunoprecipitation studies have identified a novel folliculin-binding partner, FNIP1, which also interacts with 5'AMP-



activated protein kinase (AMPK), a key molecule for energy sensing and a negative regulator of mTOR (mammalian target of rapamycin). FLCN exists in signaling including rapamycin and amino acid starvation, and by an AMPK inhibitor, Compound C. These data suggest that FLCN and its interacting partner, FNIP1, may be involved in energy and nutrient-sensing through the AMPK and mTOR signaling pathways.
Using a genetic approach in Drosophila, RNA interference studies to decrease expression of the fly BHD homolog, DBHD, have established a requirement for DBHD in male germline stem cell maintenance in the fly testis. Further genetic studies to examine the interaction between DBHD and the JAK/STAT pathway, which is necessary for germline stem cell self-renewal, suggested that DBHD may regulate maintenance of germline stem cells downstream of or in parallel with the JAK/STAT and Dpp (a TGFbeta family member) signaling pathways. Thus the work with the Drosophila homolog of FLCN/BHD supports a potential role for DBHD in stem cell maintenance and raises the possibility that dysregulation of FLCN in human tumors may result from aberrant modulation of stem cells.

Homology

Folliculin shows no strong homology to any known proteins but is evolutionarily conserved, and orthologs have been identified in chimpanzee, dog, cow, rat, mouse, red jungle fowl, frog, fly, and worm.

Mutations

Germinal

All FLCN/BHD germline mutations identified in Birt-Hogg-Dubé (BHD) patients are predicted to truncate the mutant protein, including frameshift (insertions/deletions), nonsense and splice-site mutations. To date, no missense germline mutations have been identified. The mutation detection rate in BHD families is about 84%. Mutations are located along the entire length of the coding region, with no genotype-phenotype correlations noted between type of mutation, location within the gene and phenotypic disease manifestations (BHD skin lesions, lung cysts/spontaneous pneumothorax and renal tumors). The most frequent mutation found in the germline of BHD patients is the insertion or deletion of a cytosine in a C8 tract located in exon 11, predicted to cause a frameshift and prematurely truncate the mutant protein. This hot spot mutation occurs in about half of all BHD patients. Among BHD patients with the exon 11 mutation, significantly fewer renal tumors developed in patients with the C-deletion than those with the C-insertion mutation.
Germline FLCN/BHD mutations have been reported in primary spontaneous pneumothorax (PSP) families with nearly 100% penetrance in family members in which lung blebs or bullae indicated affected status. The PSP-associated mutations, including 2 nonsense and one 4-bp deletion, are predicted to prematurely truncate the protein and are located in exons 9, 12 and 4, respectively.

Somatic

FLCN/BHD somatic mutations have been found at only a very low frequency (0-10%) in sporadic renal tumors and therefore, may not represent a major mechanism for the development of sporadic renal carcinoma. Loss of 17p DNA including p53 (36%) or partial methylation (28%) of the FLCN/BHD promoter were reported in sporadic renal carcinomas with various histologies.
Mutations have been identified in the mutational hot spot in exon 11 of the FLCN/BHD gene in other tumor types exhibiting microsatellite instability, including colorectal carcinoma (20%), endometrial carcinoma (12%) and gastric carcinoma (16%).

Implicated in

Birt-Hogg-Dubé (BHD) syndrome

Disease

Birt-Hogg-Dubé (BHD) syndrome is an inherited autosomal dominant genodermatosis characterized by benign tumors of the hair follicle (fibrofolliculoma), lung cysts, spontaneous pneumothorax and renal neoplasia. Colon polyps or colon cancer may be part of the disease manifestations in some BHD cohorts although no statistically significant association was found. BHD syndrome is caused by germline mutations in the FLCN/BHD gene. Any or all of these phenotypic features may develop in a BHD patient; the phenotype is variable within and among BHD families inheriting the identical FLCN/BHD mutation (i.e., C-insertion/deletion in exon 11).

Prognosis

BHD is a rare disorder occurring in about 1/200,000 individuals. The BHD skin lesions, which develop after puberty (above 25 years of age) are highly penetrant (above 85%) and may be disfiguring, but they are benign and have no health consequences. Lung cysts detected by thoracic CT scan are very frequent (above 85%) in BHD patients. Episodes of spontaneous pneumothorax in BHD patients occur with a higher frequency before the age of 40, and repeat episodes cease after surgical intervention. The risk for developing renal neoplasia is about 7-fold higher for BHD mutation carriers than for their unaffected siblings. Most commonly, chromophobe renal carcinoma (34%) and oncocytic hybrid tumors (50%), develop in about half of BHD families with an average age at diagnosis of 48-50 and a male/female ratio of 2:1. Tumors may develop bilaterally with multiple foci

or unilaterally with a single focus, and variable tumor histology may be seen in a single patient's kidney and among BHD family members carrying the same FLCN/BHD mutation.

Oncogenesis

Patients with BHD syndrome are at a higher risk for the development of chromophobe renal carcinoma, oncocytic hybrid renal tumors and clear cell renal carcinoma, which may be aggressive and metastatic. Renal oncocytosis, which are small clusters of cells resembling those found in the larger hybrid tumors, have been found scattered throughout the kidney of a majority of BHD patients, suggesting that the entire renal parenchyma may be at risk for tumor development. Second hit somatic mutations in the remaining wild type copy of the FLCN/BHD gene have been identified in renal tumors from BHD patients with germline mutations and may contribute to the progression of renal oncocytosis to renal neoplasia (see below).

Primary Spontaneous Pneumothorax (PSP)

Disease

Primary spontaneous pneumothorax is a condition in which air is present in the pleural space without a precipitating event that results in the secondary partial or complete collapse of the lung. FLCN/BHD mutations have been found associated with inherited autosomal dominant primary spontaneous pneumothorax (PSP) in some PSP families. In these families PSP was the only phenotypic feature and the mutation was 100% penetrant with lung bullae.

To be noted

Note: Animal models of BHD: A germline single nucleotide insertion in the first coding exon of the rat Bhd ortholog was found in the Nihon rat, an established animal model of renal carcinoma, which develops renal tumors by 8 weeks of age. A germline mutation in the canine Bhd ortholog, which changes a conserved histidine to arginine (H255R), gives rise to RCND (renal cystadenoma nodular dermatofibroma) in the German Shepherd dog with a renal tumor and skin nodule phenotype.

Tumor suppressor role for FLCN/BHD: Somatic mutations in the wild type copy of the FLCN/BHD gene or loss of heterozygosity at 17p11.2 have been identified in a majority of renal tumors from BHD patients who inherit germline mutations, suggesting that FLCN/BHD may act as a tumor suppressor gene. Tumors from a single BHD patient have different second mutations or LOH, but within the same tumor, even within regions with different histologies, the same second mutation was observed, suggesting that multiple tumors arise from independent, clonal events initiated by the second hit.

Haploinsufficiency, however, may be sufficient for the development of the benign hair follicle tumors (fibrofolliculomas), because the wild type copy of the FLCN/BHD gene is retained in microdissected tissue from these skin lesions.

References

Khoo SK, Bradley M, Wong FK, Hedblad MA, Nordenskjöld M, Teh BT. Birt-Hogg-Dubé syndrome: mapping of a novel hereditary neoplasia gene to chromosome 17p12-q11.2. Oncogene 2001;20:5239-5242.

Schmidt LS, Warren MB, Nickerson ML, Weirich G, Matrosova V, Toro JR, Turner ML, Duray P, Merino M, Hewitt S, Pavlovich CP, Glenn G, Greenberg CR, Linehan WM, Zbar B. 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.

Khoo SK, Giraud S, Kahnoski K, Chen J, Motorna O, Nickolov R, Binet O, Lambert D, Friedel J, Lévy R, Ferlicot S, Wolkenstein P, Hammel P. Bergerheim U, Hedblad MA, Bradley M, Teh BT, Nordenskjöld M, Richard S. Clinical and genetic studies of Birt-Hogg-Dubé syndrome. J Med Genet 2002;39:906-912.

Nickerson ML, Warren MB, Toro JR, Matrosova V, Glenn G, Turner ML, Duray P, Merino M, Choyke P, Pavlovich CP, Sharma N, Walther M, Munroe D, Hill R, Maher E, Greenberg C, Lerman MI, Linehan WM, Zbar B, Schmidt LS. 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.

Pavlovich CP, Walther MW, Eyler RA, Hewitt SM, Zbar B, Linehan WM, Merino MJ. Renal tumors in the Birt-Hogg-Dubé syndrome. Am J Surg Path 2002;26:1542-1552.

Zbar B, Alvord WG, Glenn G, Turner M, Pavlovich CP, Schmidt L, Walther M, Choyke P, Weirich G, Hewitt SM, Duray P, Gabril F, Greenberg C, Merino MJ, Toro J, Linehan WM. Risk of renal and colonic neoplasms and spontaneous pneumothorax in the Birt-Hogg-Dubé syndrome. Cancer Epidemiol. Biomarkers Prev 2002;11:393-400.

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.

Kahnoski K, Khoo SK, Nassif NT, Chen J, Lobo GP, Segelov E, Teh BT. Alterations of the Birt-Hogg-Dube gene (BHD) in sporadic colorectal tumours. J Med Genet 2003;40:511-515.

Khoo SK, Kahnoski K, Sugimura J, Petillo D, Chen J, Shockley K, Ludlow J, Knapp R, Giraud S, Richard S, Nordenskjöld M, Teh BT. Inactivation of BHD in sporadic renal tumors. Cancer Res 2003;63:4583-4587.

Lingaas F, Comstock KE, Kirkness EF, Sørensen A, Aarskaug T, Hitte C, Nickerson ML, Moe L, Schmidt LS, Thomas R, Breen M, Galibert F, Zbar B, Ostrander EA. A mutation in the canine BHD gene is associated with hereditary multifocal renal cystadenocarcinoma and nodular dermatofibrosis in the German Shepherd dog. Hum Mol Genet 2003;12:3043-3053.

Shin JH, Shin YK, Ku JL, Jeong SY, Hong SH, Park SY, Kim WH, Park JG. Mutations of the Birt-Hogg-Dube (BHD) gene in sporadic colorectal carcinomas and colorectal carcinoma cell lines with microsatellite instability. J Med Genet 2003;40:364-367.

Nagy A, Zoubakov D, Stupar Z, Kovacs G. Lack of mutation of the folliculin gene in sporadic chromophobe renal cell carcinoma and renal oncocytoma. Int J Cancer 2004;109:472-475.

Okimoto K, Sakurai J, Kobayashi T, Mitani H, Hirayama Y, Nickerson ML, Warren MB, Zbar B, Schmidt LS, Hino O. A germ-line insertion in the Birt-Hogg-Dube (BHD) gene gives rise to the Nihon rat model of inherited renal cancer. Proc Natl Acad Sci USA 2004;101:2023-2027.

Schmidt LS. Birt-Hogg-Dube syndrome, a genodermatosis that increases risk for renal carcinoma. Curr Mol Med 2004;4:877-885. (Review).).

Warren MB, Torres-Cabala CA, Turner ML, Merino MJ, Matrosova VY, Nickerson ML, Ma W, Linehan WM, Zbar B, Schmidt LS. Expression of Birt-Hogg-Dubé gene mRNA in normal and neoplastic human tissues. Mod Pathol 2004;17:998-1011.

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.

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.

Pavlovich CP, Grubb RL 3rd, Hurley K, Glenn GM, Toro J, Schmidt LS, Torres-Cabala C, Merino MJ, Zbar B, Choyke P, Walther MM, Linehan WM. Evaluation and management of renal tumors in the Birt-Hogg-Dubé syndrome. J Urol 2005;173:1482-1486.

Schmidt LS, Nickerson ML, Warren MB, Glenn GM, Toro JR, Merino MJ, Turner ML, Choyke PL, Sharma N, Peterson J, Morrison P, Maher ER, Walther MM, Zbar B, Linehan WM. 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.

Vocke CD, Yang Y, Pavlovich CP, Schmidt LS, Nickerson ML, Torres-Cabala CA, Merino MJ, Walther MM, Zbar B, Linehan WM. High frequency of somatic frameshift BHD gene mutations in Birt-Hogg-Dube-associated renal tumors. J Natl Cancer Inst 2005;97:931-935.

Adley BP, Smith ND, Nayar R, Yang XJ. Birt-Hogg-Dube syndrome: clinicopathologic findings and genetic alterations. Arch Pathol Lab Med 2006;130:1865-1870. (Review).

Baba M, Hong SB, Sharma N, Warren MB, Nickerson ML, Iwamatsu A, Esposito D, Gillette WK, Hopkins RF 3rd, Hartley JL, Furihata M, Oishi S, Zhen W, Burke TR Jr, Linehan WM, Schmidt LS, Zbar B. 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 USA 2006;103:15552-15557.

Bessis D, Giraud S, Richard S. A novel familial germline mutation in the initiator codon of the BHD gene in a patient with Birt-Hogg-Dube syndrome. Br J Dermatol 2006;155:1067-1069.

Fujii H, Jiang W, Matsumoto T, Miyai K, Sashara K, Ohtsuji N, Hino O. Birt-Hogg-Dube gene mutations in human endometrial carcinomas with microsatellite instability. J Pathol 2006;209:328-335.

Jiang W, Fujii H, Matsumoto T, Ohtsuji N, Tsurumaru M, Hino O. Birt-Hogg-Dube (BHD) gene mutations in human gastric cancer with high frequency microsatellite instability. Cancer Lett 2006;[Epub ahead of print].

Singh SR, Zhen W, Zheng Z, Wang H, Oh SW, Liu W, Zbar B, Schmidt LS, Hou SX. The Drosophila homolog of the human tumor suppressor gene BHD interacts with the JAK-STAT and Dpp signaling pathways in regulating male germline stem cell maintenance. Oncogene 2006;25:5933-5941.

Gad S, Lefèvre SH, Khoo SK, Giraud S, Vieillefond A, Vasiliu V, Ferlicot S, Molinié V, Denoux Y, Thiounn N, Chrétien Y, Méjean A, Zerbib M, Benoit G, Hervé JM, Allègre G, Bressac-de Paillerets B, Teh BT, Richard S. Mutations in BHD and TP53 genes, but not in HNF1beta gene, in a large series of sporadic chromophobe renal cell carcinoma. Br J Cancer 2007;96:336-340.

van Steensel MA, Verstraeten VL, Frank J, Kelleners-Smeets NW, Poblete-Gutiérrez P, Marcus-Soekarman D, Bladergroen RS, Steijlen PM, van Geel M. Novel mutations in the BHD gene and absence of loss of heterozygosity in fibrofolliculomas of Birt-Hogg-Dube patients. J Invest Dermatol 2007;127:588-593.

This article should be referenced as such:
Schmidt LS. FLCN (folliculin gene). Atlas Genet Cytogenet Oncol Haematol.2007;11(3):188-191.