# Birt-Hogg-Dubé Syndrome with Mixed Renal Oncocytic/Chromophobe Tumor: A Family Genetic Investigation and Literature Analysis Postprint

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## Abstract

Objective To investigate the familial inheritance pattern, clinical manifestations, diagnostic and therapeutic basis, and pathological characteristics of Birt-Hogg-Dubé (BHD) syndrome complicated with renal cell tumors. Methods A retrospective analysis was performed on the clinical data of a patient with BHD syndrome complicated by hybrid oncocytic/chromophobe tumor admitted in April 2018, and relevant literature was reviewed. The patient was a 65-year-old female. Physical examination ultrasound revealed a right renal mass. CT urography indicated a right renal mass measuring approximately 33 mm × 26 mm, with contrast-enhanced scan showing rapid wash-in and wash-out enhancement pattern. Chest CT demonstrated multiple pulmonary bullae in both lungs. A presumptive diagnosis of renal tumor was made, and BHD syndrome could not be excluded; retroperitoneal laparoscopic partial nephrectomy of the right kidney was performed on April 8, 2018. Concurrent peripheral blood DNA sequencing analysis and pedigree investigation were conducted. Results Postoperative pathology revealed a yellowish nodule measuring 3.6 cm × 3.1 cm × 3 cm, with a grayish-yellow cut surface, medium consistency, and well-circumscribed margins; microscopic examination revealed hybrid oncocytic/chromophobe tumor (HOCT) involving the renal capsule, with surgical margins free of tumor. Follow-up at 3 months showed no abnormalities. DNA sequencing analysis identified a frameshift mutation c.823_824delGA in the FLCN (folliculin) gene located on chromosome 17 (17p11.2). Pedigree investigation revealed that the patient's mother had renal cancer and pulmonary bullae during her lifetime, and two younger brothers, one son, and one daughter were found to have pulmonary bullae. Literature review indicated that only a few families with BHD syndrome have been reported in China, with pulmonary cysts and pneumothorax being common clinical manifestations, while skin lesions and renal tumors are rela-

tively rare. Conclusion BHD syndrome is a clinically rare autosomal dominant inherited disease, characterized by FLCN gene mutation. Clinically, hybrid oncocytic/chromophobe tumors constitute the majority among renal involvement cases, and the management principle should emphasize early detection and nephron-sparing renal tumor resection.

## Full Text

# Familial Genetic Investigation and Literature Analysis of a Birt-Hogg-Dubé Syndrome Case with Renal Hybrid Oncocytic/Chromophobe Tumor

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## Abstract

**Objective:** To investigate the familial inheritance patterns, clinical manifestations, diagnostic basis, and pathological characteristics of Birt-Hogg-Dubé (BHD) syndrome with renal cell tumors.

**Methods:** We retrospectively analyzed the clinical data of a patient with BHD syndrome and renal hybrid oncocytic/chromophobe tumor who was admitted in April 2018, and conducted a comprehensive literature review. The patient was a 65-year-old woman whose physical examination revealed a right renal mass on B-ultrasound. CT urography (CTU) demonstrated a right renal lesion measuring approximately 33 mm × 26 mm with rapid wash-in and wash-out enhancement. Chest CT showed multiple pulmonary bullae in both lungs. Preoperative diagnosis was renal tumor with suspected BHD syndrome. On April 8, 2018, the patient underwent retroperitoneal laparoscopic partial nephrectomy. Venous blood DNA sequencing analysis and familial investigation were subsequently performed.

**Results:** Pathological examination revealed a grayish-yellow nodule measuring 3.6 cm × 3.1 cm × 3 cm with a clear boundary and medium consistency. Microscopic examination confirmed renal hybrid oncocytic/chromophobe tumor (HOCT) involving the renal capsule, with negative surgical margins. No abnormalities were observed during 3 months of follow-up. DNA sequencing identified a frameshift mutation c.823_824delGA in the FLCN (folliculin) gene located on chromosome 17 (17p11.2). Familial investigation revealed that the patient' s mother had renal cancer and pulmonary bullae during her lifetime, while two brothers, one son, and one daughter were found to have pulmonary bullae. Literature review showed that only a few BHD syndrome families have been

reported in China. Pulmonary cysts and pneumothorax are common clinical manifestations, whereas skin lesions and renal tumors are relatively rare.

**Conclusions:** BHD syndrome is a rare autosomal dominant hereditary disease characterized by FLCN gene mutation. Renal involvement predominantly manifests as hybrid oncocytic/chromophobe tumors. The management principle should emphasize early detection and nephron-sparing renal tumor resection.

**Keywords:** BHD syndrome; renal tumor; FLCN; renal hybrid oncocytic/chromophobe tumor

## Introduction

Birt-Hogg-Dubé syndrome, first reported in 1977, is an autosomal dominant hereditary disease caused by mutation of the folliculin (FLCN) gene on chromosome 17 [1]. It is characterized by benign hamartomas of the skin on the head and neck, pulmonary cysts with spontaneous pneumothorax, and associated renal tumors. Literature searches indicate that approximately 16-34% of BHD syndrome patients develop renal tumors by age 50. These tumors are often bilateral and multifocal with complex histological types, comprising about 50% hybrid oncocytic/chromophobe tumors (HOCT), 34% chromophobe renal cell carcinoma, 9% clear cell renal cell carcinoma, and a small proportion of oncocytomas and papillary renal cell carcinomas. Since renal tumors in this disease commonly involve both kidneys and more than half are benign, coupled with the insidious nature of the condition, early diagnosis and nephron-sparing renal tumor resection are crucial in clinical management.

## Case Report

The patient, a 65-year-old female, underwent physical examination in March 2018, during which urinary system ultrasound revealed a 35 mm × 31 mm hypoechoic nodule with clear boundaries at the upper pole of the right kidney. Further CTU examination showed an occupying lesion measuring approximately 33 mm × 26 mm with rapid wash-in and wash-out enhancement, where central enhancement was slightly lower than peripheral enhancement. Plain chest CT scan demonstrated multiple pulmonary bullae in both lungs. The patient' s past medical history revealed that pulmonary bullae were detected during a physical examination in November 2017, without symptoms of cough, chest pain, or dyspnea, and no history of spontaneous pneumothorax. Family history was significant for renal cancer in her mother, and pulmonary bullae in two brothers, one son, and one daughter, among whom one brother and one son had experienced spontaneous pneumothorax.

Physical examination showed no flank prominence or tenderness, no tenderness along the ureteral courses, and no bladder distension. Lung percussion revealed hyperresonant sounds, while no characteristic papules were observed on the

head and neck skin. Based on the patient' s condition and family disease characteristics, preoperative diagnosis was highly suspicious for BHD syndrome with right renal tumor (T1aNxMx) and bilateral pulmonary bullae. After excluding surgical contraindications, the patient underwent retroperitoneal laparoscopic partial nephrectomy on April 8, 2018.

Postoperative pathology showed a grayish-yellow nodule measuring 3.6 cm × 3.1 cm × 3 cm, solid with medium consistency and relatively clear boundaries. The distance from the resection margin to the renal capsule was 0.2 cm. Microscopic examination revealed renal hybrid oncocytic/chromophobe tumor involving the renal capsule. Immunohistochemistry results were positive for PAX-8, CD117, AE1/AE3, EMA, and partially positive for CK7 and P504, while negative for CA9, CD10, RCC, TFE3, and Vimentin. The patient recovered uneventfully, and follow-up at 3 months showed no abnormalities in both kidneys.

DNA sequencing analysis of peripheral venous blood revealed a frameshift mutation c.823_824delGA (p.Glu275ArgfsX16) in the FLCN gene on chromosome 17 (17p11.2). This mutation involves deletion of GA bases at positions 823 and 824, leading to premature termination of the encoded protein at position 290 and truncation of the polypeptide chain. No previous literature reports of this specific mutation have been identified.

[Figure 1: see original paper] Pedigree chart. The patient' s mother had renal cancer and pulmonary bullae during her lifetime; two brothers, one son, and one daughter were found to have pulmonary bullae.

[Figure 2: see original paper] A: Plain chest CT scan showing multiple pulmonary bullae in both lungs; B: CTU enhancement (arterial phase) showing an occupying lesion at the upper pole of the right kidney measuring approximately 33 mm × 26 mm with rapid wash-in and wash-out enhancement at the lesion margin and slightly lower central enhancement; C: CT reconstruction; D: Postoperative pathology showing renal hybrid oncocytic/chromophobe tumor (HOCT).

[Figure 3: see original paper] DNA sequencing analysis revealing the frameshift mutation c.823_824delGA in the patient' s FLCN gene.

## Diagnostic Criteria

BHD syndrome is an autosomal dominant hereditary disease first reported in 1977, characterized by benign hamartomas of the skin on the head and neck, pulmonary cysts, spontaneous pneumothorax, and significantly increased risk of renal cancer. The disease is caused by mutation of the folliculin (FLCN) gene on chromosome 17 [2]. This tumor suppressor gene' s expression product may participate in energy metabolism through the mammalian target of rapamycin (mTOR) pathway, inhibiting cell growth and proliferation [3]. Menko et al. [4] proposed diagnostic criteria for BHD syndrome in 2009, while Schmidt et al. [2] established criteria for suspected and definitive diagnosis in 2015, as shown in

Table 1 and Table 2 :

**Table 1. 2009 Diagnostic Criteria for BHD Syndrome**

*Major Criteria:* 1. At least five fibrofolliculomas and/or trichodiscomas appearing in adulthood, with at least one confirmed by pathology; 2. Identification of a germline FLCN gene mutation by DNA sequence analysis;

*Minor Criteria:* 1. Multiple pulmonary cysts: bilateral multiple pulmonary cysts predominantly located at the lung bases, excluding other clear causes, with or without a history of spontaneous pneumothorax; 2. Renal cancer: early-onset (before age 50)/multiple/bilateral renal cancer, or pathology showing chromophobe and oncocytic hybrid tumors; 3. First-degree relatives of BHD patients;

*Diagnostic Standard:* Diagnosis of BHD syndrome is established by meeting one major criterion or two minor criteria.

**Table 2. 2015 Diagnostic Criteria for BHD Syndrome**

*Suspected Diagnosis Criteria:* 1. Presence of 2 skin lesions consistent with fibrofolliculomas and/or trichodiscomas, with 1 skin lesion histologically confirmed as fibrofolliculoma; 2. Bilateral multiple pulmonary cysts predominantly located at the lung bases, with or without a history of spontaneous pneumothorax before age 40, especially when there is a family history of similar pulmonary manifestations; 3. Bilateral multiple renal chromophobe carcinomas, or hybrid chromophobe and oncocytic tumors, especially in patients with a family history of renal tumors occurring before age 50; 4. Combined presence of these skin, pulmonary, or renal manifestations in the patient or family members;

*Definitive Diagnosis Criterion:* Identification of a germline FLCN gene mutation by DNA sequence analysis.

In this patient, chest CT showed bilateral multiple pulmonary bullae, which were considered bilateral multiple pulmonary cysts given no history of pulmonary disease. The renal tumor was HOCT, and DNA sequence analysis identified a frameshift mutation in the FLCN gene. According to both the 2009 and 2015 diagnostic criteria, a definitive diagnosis of BHD syndrome can be established.

## Discussion

The penetrance of various clinical symptoms in BHD syndrome differs significantly. Literature reports [2][5] indicate that the median age of onset for Western BHD syndrome patients is 48-52 years, with >90% developing skin lesions, 70-84% showing bilateral pulmonary cysts, 5-10% experiencing spontaneous pneumothorax, and 12-34% developing renal tumors. Among renal tumors, approximately 50% are hybrid chromophobe and oncocytic tumors, 35% are chromophobe renal cell carcinoma, 9% are clear cell renal cell carcinoma, and 5% are renal oncocytomas.

Zhan Yongzhong [6] summarized 50 Chinese BHD syndrome patients and found

that 94% had a family history of pneumothorax or pulmonary bullae, 96% presented with pulmonary cystic lesions, 62% had a history of pneumothorax, and only 10% developed skin lesions (with one case pathologically confirmed as fibrofolliculoma and another as cutaneous soft tissue sarcoma). Eight percent were found to have renal tumors, including one confirmed case of clear cell renal cell carcinoma and three cases of renal cysts. Lv Liu et al. [7] studied two Chinese BHD syndrome families and found that among eight BHD patients, seven had pulmonary cysts, seven had renal tumors, and two had skin lesions. Huajie Xing et al. [7] reported a Chinese BHD syndrome family where, among 17 patients with confirmed FLCN gene mutations, five had pulmonary cysts with concurrent pneumothorax history, but none had renal tumors. These studies suggest that Chinese BHD syndrome patients predominantly present with pulmonary cysts and pneumothorax, while skin lesions and renal tumors are relatively rare, differing from the main clinical manifestations in Western patients. Furthermore, a DNA sequencing study of 51 highly suspected Chinese BHD patients [8] identified FLCN gene mutations in 27 individuals, with 20 mutation types, 14 of which were novel. Among these 27 patients, only three had skin lesions, five (with incomplete data for another five) had renal tumors, but 25 had pulmonary bullae, suggesting that unique FLCN gene mutation characteristics in Chinese patients may be associated with their distinct clinical features. In this case, the patient presented with bilateral pulmonary cysts and renal cancer without clear skin lesions. Although HOCT is a common pathological type of renal cancer in Western BHD syndrome patients, it is rare in China. Besides racial and genetic factors, under-recognition leading to missed diagnosis may also contribute.

For clinical diagnosis and management, DNA sequence analysis to identify germline FLCN gene mutations is highly valuable for definitive diagnosis. Literature reports [2] indicate that high-precision DNA sequencing can detect FLCN gene mutations in nearly 90% of cases, with over 100 mutation types identified to date, including DNA fragment insertions or deletions, nucleotide insertions or deletions, and gene silencing. However, detection methods for FLCN-related proteins, such as immunohistochemistry, are currently difficult to implement, not only due to complex expression of mutant genes but also because FLCN gene expression levels in other tissues and organs can affect test results, making definitive conclusions challenging. Nevertheless, DNA sequence analysis remains relatively expensive and difficult to widely implement clinically. Therefore, patient history collection, routine examinations, and family investigation still play important roles in diagnosis and management.

There is currently no etiology-specific treatment for BHD syndrome; management focuses on symptomatic treatment. The only treatment for renal tumors is surgical intervention. Schmidt et al. [2] recommend active surveillance for primary renal tumors <3 cm in diameter, and nephron-sparing surgery for tumors  3 cm, considering the risks of postoperative tumor recurrence and repeat surgery. BHD syndrome patients require lifelong renal tumor surveillance: when no renal tumors are detected, abdominal imaging should be performed at least every 36 months; after renal tumor detection, the interval depends on tumor

size and growth rate. Ultrasound may miss small renal tumors; therefore, CT or MRI should be used when feasible. In this case, the patient and her relatives should undergo regular lifelong follow-up and imaging examinations to monitor for renal tumor development. Regarding skin lesions, fibrofolliculomas and trichodiscomas are benign and typically require no treatment. Pneumothorax management focuses on prevention, with symptomatic treatment during episodes. Patients should be educated to quit smoking and avoid high-pressure environments (air travel, diving), and excessive positive-pressure ventilation should be avoided during surgery.

The prognosis of BHD syndrome primarily depends on renal tumor development and histological type [2]. Renal tumor-related death is uncommon in BHD syndrome because renal tumors are generally more indolent, with metastatic disease-related deaths mostly seen in clear cell renal cell carcinoma. To date, there have been no reports of metastasis or death from HOCT, the most common renal tumor type in these patients.

## References

[1] Birt A R, Hogg G R, Dubé W J. Hereditary multiple fibrofolliculomas with trichodiscomas and acrochordons[J]. Archives of dermatology, 1977, 113(12): 1674-1677.
[2] Schmidt L S, Linehan W M. Molecular genetics and clinical features of Birt-Hogg-Dube syndrome[J]. Nature Reviews Urology, 2015, 12(10): 558.
[3] 陈健, 纪志刚. 肾细胞癌相关遗传性综合征 [J]. 协和医学杂志, 2016, 7(2): 136-140.
[4] Menko F H, Van Steensel M A M, Giraud S, et al. Birt-Hogg-Dubé syndrome: diagnosis and management[J]. The lancet oncology, 2009, 10(12): 1199-1206.
[5] Steinlein O K, Ertl-Wagner B, Ruzicka T, et al. Birt-Hogg-Dubé syndrome: an underdiagnosed genetic tumor syndrome[J]. JDDG: Journal der Deutschen Dermatologischen Gesellschaft, 2018, 16(3): 278-283.
[6] 詹永忠. 淋巴管肌瘤病 (LAM) 诊疗新技术应用评估和 Birt-Hogg-Dubé (BHD) 综合征临床特征分析 [D]. 北京协和医学院, 2015.
[7] Liu L, Yang K, Wang X, et al. Detection of Folliculin gene mutations in two Chinese families with Birt-Hogg-Dubé syndrome[J]. BioMed research international, 2017, 2017.
[8] Xing H, Liu Y, Jiang G, et al. Clinical and genetic study of a large Chinese family presented with familial spontaneous pneumothorax[J]. Journal of thoracic disease, 2017, 9(7): 1967.
[9] Liu Y, Xu Z, Feng R, et al. Clinical and genetic characteristics of chinese patients with Birt-Hogg-Dubé syndrome[J]. Orphanet journal of rare diseases, 2017, 12(1): 104.

*Note: Figure translations are in progress. See original paper for figures.*