The clinical characteristics of East Asian patients with Birt-Hogg-Dubé syndrome

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Background: Birt-Hogg-Dube (BHD) syndrome is an autosomal dominant disease that has been characterized by skin lesions, multiple pulmonary cysts, spontaneous pneumothorax, and renal tumors, but the patients in Asian countries may show fewer symptoms. We aimed to explore and summarize the clinical features of BHD patients in East Asia to facilitate early diagnosis and timely interventions.

Methods: We collected and analyzed the clinical data of patients diagnosed with BHD in our hospital by reviewing medical records. We performed a systematic literature search regarding the presenting clinical features in BHD patients from China, Japan, and Korea and then reviewed the publications that were identified.

Results: In our hospital, 10 patients were diagnosed with BHD from April 2015 to September 2019. After reviewing the literature, we recruited 38 articles, including 12, 20, and 6 reports from China, Japan, and Korea, respectively. A total of 166 patients were included in this study, and 100 of them (60.2%) were females. Multiple pulmonary cysts were present in 145 patients (87.3%), and 124 patients (74.7%) had a history of pneumothorax on at least one occasion. Skin biopsy confirmed fibrofolliculomas (FFs) alone in 22 patients (13.3%), trichodiscomas (TDs) alone in 3 patients (1.8%), and both FFs and TDs in 7 patients (4.2%). Renal carcinoma only occurred in 12 (7.2%) patients. The most frequent genetic mutations in East Asian patients were c.1285delC on exon 11 (18.4%), c.1285dupC on exon 11 (18.4%), and c.1347_1353dupCCACCCT on exon 12 (8.2%).

Conclusions: Our findings suggested that pulmonary cysts are the most frequent radiological findings, and pneumothorax is the most common symptom in East Asian patients with BHD, and that skin lesions and kidney involvement are less frequent. To make an early diagnosis and minimize the severity of complications, careful observation, and timely genetic examination of the *FLCN* gene is essential.

Keywords: Birt-Hogg-Dube syndrome (BHD syndrome); East Asia; pulmonary cysts; pneumothorax

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Introduction

Birt-Hogg-Dube (BHD) syndrome is an autosomal dominant disorder characterized by skin fibrofolliculomas (FFs), renal cancer, and multiple lung cysts with spontaneous pneumothorax (1,2). This syndrome is caused by germline mutations in the *FLCN* gene located on the short arm of chromosome 17 (17p11.2). Folliculin, the highly conserved tumor suppressor protein, is encoded by *FLCN* and is widely expressed in skin, kidney, and alveolar epithelial cells (3). Those affected may present with a single organ lesion or with multiple cutaneous lesions, multiple lung cysts, and bilateral renal tumors.

In previous studies, typical skin lesions and renal tumors have been more frequently observed in BHD patients diagnosed in Europe and the United States, where typical skin FFs were reported in 82–90% of BHD patients, and renal tumors ranged from 13.4–45% (2,4-6). In other areas, the clinical presentations have also shown some differences. A Japanese study (7) investigated 156 *FLCN* mutation carriers, and 76 of them had skin papules; however, only six (3.8%) were confirmed as typical FFs. Lee *et al.* (8) conducted a retrospective study, including 12 Korean BHD patients, and only two of those patients' skin lesions were verified as FFs. In China, Liu *et al.* (9) identified 27 patients with *FLCN* mutations, and the minority of them showed skin lesions or renal tumors. These studies suggest that clinical characteristics may show discrepancies among different populations. However, the information about BHD patients in East Asian countries is limited, and a comprehensive study is needed.

In this study, we provided the clinical information of 10 BHD patients in our hospital, and we performed a systematic literature review to analyze and summarize the clinical features of BHD patients in the East Asian population. Due to a lack of awareness, there is commonly a delay in achieving a diagnosis of BHD syndrome, and patients are frequently misdiagnosed as having chronic obstructive lung disease (COPD), emphysema, common bullae/blebs, or other diseases (4,10,11). The present study aimed to highlight the prevalent characteristics of BHD in the East Asian population in order to assist the correct diagnosis and treatment of BHD syndrome in its early stage.

We present the following article in accordance with the MDAR reporting checklist (available at http://dx.doi.org/10.21037/atm-20-1129).

Methods

Study population

A total of 10 patients who had been receiving medical care at the Second Xiangya Hospital of Central-South University and were diagnosed with BHD syndrome from April 2015 to September 2019 were enrolled in this study. The diagnosis of BHD syndrome was based on the criteria proposed by the European BHD consortium published in *The Lancet Oncol*, 2009 (10). The diagnosis was made when patients fulfilled at least one major or two minor criteria. The major criteria were as follows: (I) at least five fibrofolliculomas or trichodiscomas (at least one histologically confirmed, of adult-onset); (II) pathogenic *FLCN* germline mutation. The minor criteria were as follows: (I) multiple lung cysts (bilateral basally located lung cysts with no other apparent cause, with or without spontaneous primary pneumothorax); (II) renal cancer (early-onset before age 50, or multifocal or bilateral, or mixed chromophobe and oncocytic histology); (III) a first-degree relative with BHD.

The trial was conducted in accordance with the Declaration of Helsinki. The study was approved by the institutional review board of the Second Xiangya Hospital of Central-South University (NO. 2014S009) and informed consent was taken from all the patients.

Review of the literature

Three PubMed searches with the term "Birt-Hogg-Dubé syndrome" and "China", "Korea", "Japan", respectively, were performed in September 2019. Articles were restricted to those published and available as full texts in the English language; conference abstracts were excluded. Articles were not included if they were case-control studies, review articles, including systematic analysis and meta-analysis, non-clinical studies, and original studies without sufficient clinical data.

Statistical analysis

The continuous variables were summarized as means and standard deviations. For categorical variables, the percentages of patients in each category were calculated. All analyses were done with SPSS software,

Table 1 Baseline characteristics of the study population (n=10)

Characteristics	Value
Age, year	54.4±7.5
Female	8 (80.0)
Smoking	2 (20.0)
Initial presentation	
Pneumothorax	9 (90.0)
Asymptomatic screening	1 (10.0)
Age of the first pneumothorax	44.3±13.9
Pulmonary cysts	10 (100.0)
Kidney lesions	2 (20.0)
Skin lesions	1 (10.0)
Family history	5 (50.0)

Values are presented as mean ± SD or number (%).

version 24.0

Results

Study population

Our study involved 10 independent individuals from different families, who were diagnosed with BHD in our hospital. Among them, only two patients were males. The mean diagnostic age was 54.4 years, and 20% were current smokers. All patients had CT-detectable pulmonary cysts. Pneumothorax was the most common initial manifestation in 9 of the participants. The mean age of first pneumothorax was 44.3 years. Only 2 of the patients had renal lesions at the time of diagnosis, 1 had renal cysts, and the other 1 had renal clear-cell carcinoma. Skin involvement was present in 1 patient. The clinical characteristics are summarized in *Tables 1,2*.

Table 2 Clinical features of the study population (n=10)

Patient No.	Age/Sex	Smoking history	PTX Age[†]	Kidney	Skin	Site of *FLCN* mutation	Nucleotide changes	Other presentations	Family history (NO.)
1	62/M	Current	26	Simple cysts (bilateral, multiple, up to 1.7 cm)	–	Exon 11	c.1285delC	–	Pulmonary cyst (3; younger sister, younger brother, son)
2	48/F	Never	41	–	–	Exon 11	c.1285delC	Cervical cyst	BHD (4; mother, younger sister, older sister, son)
3	58/M	Current	–	–	–	Exon 11	c.1285dupC	–	–
4	61/F	Never	61	–	–	N/A	N/A	–	BHD (1; son)
5	53/F	Never	25	–	–	Exon 11	c.1285dupC	–	–
6	46/M	Never	46	Clear cell RCC (Rt, single, 2.6cm); Simple cyst (Lt, single, 1.7 cm)	–	Exon 7	c.668delA	Liver cyst	BHD (2; mother, older brother)
7	64/F	Never	62	–	+ (not biopsied)	Exon 13	c.1533_1536delGATG	Liver cyst	–
8	51/F	Never	38	–	-	Exon 6	c.924_926del	Thyroid nodule	BHD (3; mother, younger sister, son)
9	42/F	Never	42	–	–	Exon 14	c.1579_1580insA	–	–
10	59/F	Never	58	–	–	Exon 11	c.1285delC	–	–

[†]Age of the first pneumothorax; PTX, pneumothorax; *FLCN*, folliculin gene; BHD, Birt-Hogg-Dubé syndrome; RCC, renal cell carcinoma; Rt, right-sided; Lt, left-sided.
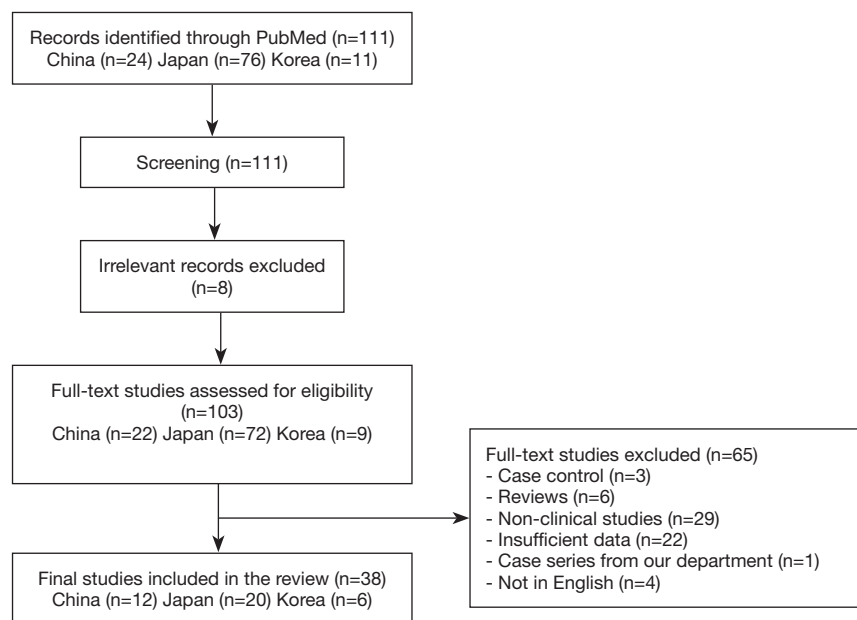
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Figure 1 Flow chart summarizing studies that are included in the systematic review based on the predefined inclusion and exclusion criteria.

Review of the literature

There were 111 articles relating to reports of Birt-Hogg-Dubé syndrome in China, Korea, or Japan retrieved from the PubMed database. We excluded 73 studies due to their failure to meet our eligibility criteria. A flow chart summarizing the inclusion and exclusion criteria of the searched studies is presented in *Figure 1*. Ultimately, a total of 38 reports were included in this study; there were 12, 20, and 6 reports from China, Japan, and Korea, respectively. Detailed characteristics of all of the studies included are provided in *Tables 3-5*.

A total of 166 East Asian patients were enrolled in this study from 38 articles; this number included the 10 patients that we recruited. Among these 166 patients, 100 (60.2%) were females. Multiple pulmonary cysts were presented in 145 patients (87.3%), and 124 patients (74.7%) had a history of at least one pneumothorax. Skin lesions were detected in 61 patients (36.7%), of whom 23 did not undergo a pathological biopsy. Skin biopsy confirmed fibrofolliculomas (FFs) alone, trichodiscomas (TDs) alone, and FFs and TDs in 22 patients (13.3%), 3 patients (1.8%), and 7 patients (4.2%) respectively. Other skin lesions detected included sarcoma cutis (1, 0.6%), milia (1, 0.6%), mucinosis (1, 0.6%), angiofibroma (1, 0.6%), syringoma (1, 0.6%), and perifollicular fibromas (1, 0.6%). Renal involvement had developed in 38 patients (22.9%) at the time of diagnosis,

and the renal lesions included renal cysts (22, 13.3%), renal cell carcinoma (RCC) (12, 7.2%), hamartoma (2, 1.2%), oncocytoma (1, 0.6%), and angiomyolipoma (1, 0.6%). The information above is provided in *Table 6*.

The mutations of BHD in enrolled patients are listed in *Table 7*. The details of genetic mutations were not clear in 19 patients. Among 147 BHD patients with definite information about mutation site, c.1285delC on exon 11 (18.4%), c.1285dupC on exon 11 (18.4%), and c.1347_1353dupCCACCCT on exon 12 (8.2%) were the most frequent BHD mutations. The identified mutation sites included introns 4, 5, 7, 9, 10, 11, and exons 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14. Exon 11 was the most common site of mutation (37.4%), followed by exon 14 (10.2%), exon 12 (10.2%), and exon 6 (9.5%).

Discussion

BHD syndrome was initially described in 1977 (1) as an association of 3 characteristic cutaneous lesions: FFs, TDs, and acrochordon. The first description of pneumothorax in association with these lesions was reported in 1986 (48). In 1993, a case of renal cancer associated with FFs was reported (49). More recent studies have shown that the *FLCN* gene plays a role in inhibiting RCC and skin FFs that are associated with BHD. However, the role of *FLCN* in the development of pulmonary cysts (PCs) remains unclear.

Table 3 Clinical findings of the BHD cases diagnosed in Chinese population

First author, year (no. patients)	Country	Males	Females	Family history	Pulmonary cysts	PTX	Skin histology	Renal lesions	FLCN mutation
Huajie Xing et al. (12) 2017 (n=18)	China	10	8	PTX	8/18	6/18	–	–	17/18
Yaping Liu et al. (9) 2017 (n=27)	China	3	24	Pulmonary bulla; PTX	25/27	20/27	3/27 (2 FFs; 1 sarcoma cutis)	6/27 (4 renal cysts; 2 hamartoma)	27/27
Shengyu Hao et al. (13) 2017 (n=1)	China	-	1	RCC; PTX	+	+	+ (not biopsied)	–	+
Teng Li et al. (14) 2017 (n=2)	China	2	-	PTX	N/A	2/2	–	2/2 (2 RCC)	2/2
Li Dong et al. (15) 2016 (n=2)	China	2	–	N/A	–	–	2/2 (not biopsied)	2/2 (2 RCC)	2/2
Shun-Yang So et al. (16) 2009 (n=1)	China	–	1	PTX	+	+	+ (FFs)	–	+
Xiaocan Hou et al. (17) 2018 (n=8)	China	4	4	PTX	6/8	7/8	1/8 (not biopsied)	1/8 (1 renal cysts)	8/8
JF Zhu et al. (18) 2017 (n=1)	China	–	1	PTX	+	+	–	–	+
Gee Gwo Yang et al. (19) 2013 (n=1)	China	–	1	PTX	+	+	–	–	+
Zhibo Liu et al. (20) 2014 (n=4)	China	2	2	PTX	4/4	1/4	–	–	4/4
Zhichun Lin et al. (21) 2014 (n=2)	China	1	1	N/A	2/2	1/2	1/2 (not biopsied)	1/2 (RCC)	2/2
HZ Ren et al. (22) 2008 (n=10)	China	8	2	PTX	10/10	10/10	–	–	10/10
Total (n=77)		32	45		59	51	9	12	76

N/A, data not available; PTX, pneumothorax; FLCN, folliculin gene; BHD, Birt-Hogg-Dubé syndrome; RCC, renal cell carcinoma; FFs, fibrofolliculomas; TDs, trichodiscomas; PFs, perifollicular fibromas.

Researchers have concluded that PCs associated with BHD are a distinct entity and can be considered to be hamartoma-like lesions associated with the dysfunctional mammalian target of rapamycin (mTOR) signaling (50,51). The protein kinase mTOR regulates cell growth, proliferation, movement, and protein synthesis and transport.

Multiple PCs with repeated pneumothorax, renal tumors, and FFs are currently the three main manifestations of BHD. Toro et al. (4) reported that FFs are present in 90% of the families with BHD in Europe and the United States. Renal tumors and FFs are also present in more than 27% and 80% of these BHD patients, respectively (10,52). In Europe and the United States, BHD is well known, and treatment approaches are established. In contrast,

BHD is not yet well known in Asia, and this may be due to differences in the major presenting symptoms of BHD. In China, BHD syndrome is not commonly reported, and few patients show all the typical signs, including PCs, renal tumors, and skin lesions. Liu et al. (9) studied 27 Chinese patients with FLCN mutation, and among them, 25 patients (92.6%) had multiple PCs, while only two patients had FFs (7.4%), and no patients had developed renal tumors at the time of diagnosis. In our case series, all 10 BHD patients (100.0%) had multiple PCs, and only one patient showed skin lesions. Kidney lesions were also relatively rare, RCC was detected in 1 patient, and 1 patient had renal cysts. In combination with the other 12 reports relating to Chinese patients, we deduced that PCs and pneumothorax were the

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Table 4 Clinical findings of the BHD cases diagnosed in Korean population

First author, year (no. patients)	Country	Males	Females	Family history	Pulmonary cysts	PTX	Skin histology	Renal lesions	FLCN mutation
Joo Hee Lee et al. (8) 2018 (n=12)	Korea	4	8	PTX; Skin lesion; RCC	12/12	8/12	6/12 (2 FFs; 1 milia; 1 mucinosis; 1 angiofibroma; 1 not biopsied)	5/12 (2 renal cysts; 2 RCC; 1 oncocytoma)	10/12
Kyung Soo Kim et al. (23) 2017 (n=1)	Korea	–	1	PTX	+	+	–	–	+
Juwon Kim et al. (24) 2012 (n=1)	Korea	–	1	PTX; RCC	+	+	+ (syringoma)	–	+
Won Woong Shin et al. (25) 2011 (n=1)	Korea	1	–	–	+	+	+ (FFs)	Renal cysts	+
Geon Park et al. (26) 2011 (n=1)	Korea	1	–	PTX; Skin lesions	–	–	+ (FFs and TDs)	–	+
En Hyung Kim et al. (27) 2008 (n=1)	Korea	–	1	–	+	+	+ (FFs and TDs)	–	+
Total (n=17)		6	11		16	12	10	6	15

N/A, Data not available; PTX, pneumothorax; FLCN, folliculin gene; BHD, Birt-Hogg-Dubé syndrome; RCC, renal cell carcinoma; FFs, fibrofolliculomas; TDs, trichodiscomas; PFs, perifollicular fibromas.

main manifestations of BHD patients in China, with skin and kidney lesions being not as common as in patients in Europe or the United States.

Limited articles were referring to BHD patients in Korea in our search, and most of them were case reports. A Korean retrospective study (8) involving 12 BHD patients showed only 2 patients with FFs and 2 patients with RCC. Skin lesions and kidney lesions seemed more frequent in Korean BHD patients, but typical FFs or TDs were found only in 5 patients, and RCCs were reported in 2 patients. In Japan, Furuya et al. (7) found that 139 individuals had radiologically determinable cysts out of 142 FLCN mutation carriers, 31 of 120 BHD probands indicated RCC, and 76 of 156 FLCN mutation carriers had skin lesions detected by physicians; however, most of them did not receive a histological examination. Their research suggested PCs are also main manifestations in Japanese BHD patients, and that RCC and skin lesions are less common. The results of our literature review confirmed those of previous studies. We excluded the study from Furuya et al. in our literature review due to difficulties in statistical analysis. All the above considered, compared to BHD patients in Europe or the United States, PCs and pneumothorax are the most frequent manifestations in East Asian patients, while skin lesions and kidney involvements are less common. A probable explanation for this discrepancy may be the ethnic

backgrounds of the patients. No obvious differences in major genetic mutations between East Asian patients and patients from other areas were found, as the most frequent mutations in our study were c.1285delC on exon 11, c.1285dupC on exon 11, and c.1347_1353dupCCACCCT on exon 12, which were similar to those in Europe and the USA (4,10). Whether the clinical difference was determined by other, less frequent genetic mutations is still unknown; a comparative study is needed in the future to explore the underlying gene discrepancy.

This report confirms that cutaneous manifestations are less identifiable in East Asian BHD patients, but FFs and TDs are still the predominant lesions in those patients with skin manifestations. Angiofibroma and perifollicular fibromas might also be considered as BHD-associated skin lesions (53). Other skin lesions, including sarcoma cutis, milia, mucinosis, and syringoma, have been seldom reported, and whether they are part of the clinical spectrum of BHD remains to be investigated. Skin neoplasms including malignant melanoma, cutaneous leiomyoma, dermatofibrosarcoma protuberans, basal cell carcinoma, and squamous cell carcinoma have been reported in Caucasian BHD patients (11,54), but there is no similar patient report in the East Asian population. Renal cancer is the most threatening complication of BHD in Caucasians; Pavlovich et al. (55) indicated that 27% of BHD individuals

Table 5 Clinical findings of the BHD cases diagnosed in Japanese population

First author, year (no. patients)	Country	Males	Females	Family history	Pulmonary cysts	PTX	Skin histology	Renal lesions	*FLCN* mutation
Masahide Inoue *et al.* (28) 2018 (n=1)	Japan	–	1	PTX	+	+	+ (not biopsied)	Renal cysts	+
Kazuki Yoshida *et al.* (29) 2018 (n=1)	Japan	1	–	PTX	+	+	–	–	+
Mitsuko Furuya *et al.* (30) 2018 (n=1)	Japan	1	–	PTX	+	+	–	–	+
Chikako Iwabuchi *et al.* (31) 2018 (n=31)	Japan	16	15	PTX; skin lesions; RCC	31/31	30/31	26/31 (10 FFs alone, 2 TDs alone, 4 FFs and TDs, 10 not biopsied)	12/31 (renal cysts)	30/31
Kyoshiro Takegahara *et al.* (32) 2017 (n=1)	Japan	1	–	PTX	+	+	–	–	+
Tomohiko Tanegashima *et al.* (33) 2017 (n=1)	Japan	1	–	RCC	+	–	+ (FFs)	+ (RCC)	+
Yoko Gunji-Niitsu *et al.* (34) 2016 (n=1)	Japan	–	1	PTX; skin lesions; RCC	+	+	+ (FFs)	–	+
Noriyuki Matsutani *et al.* (35) 2016 (n=1)	Japan	1	–	PTX	+	–	+ (not biopsied)	–	+
Kentaro Miura *et al.* (36) 2015 (n=1)	Japan	–	1	PTX	+	–	-	–	+
Takahiro Kamada *et al.* (37) 2015 (n=1)	Japan	–	1	PTX	+	+	+ (PFs)	–	+
Chinatsu Nishida *et al.* (38) 2015 (n=1)	Japan	–	1	PTX	+	–	+ (not biopsied)	–	+
Yasutaka Yamada *et al.* (39) 2015 (n=1)	Japan	–	1	–	+	+	–	+ (RCC)	+
Yukako Murakami *et al.* (40) 2014 (n=2)	Japan	1	1	PTX	2/2	–	2/2 (1 FFs; 1 not biopsied)	2/2 (2 RCC)	2/2
Makiko Kunogi Okura *et al.* (41) 2013 (n=1)	Japan	–	1	PTX	+	+	+ (TDs)	–	+
Teppei Nishii *et al.* (42) 2013 (n=1)	Japan	–	1	PTX	+	+	+ (not biopsied)	–	+
Takeru Kashiwada *et al.* (43) 2012 (n=1)	Japan	–	1	PTX	+	+	+ (not biopsied)	–	+
Kazunori Tobino *et al.* (44) 2012 (n=1)	Japan	–	1	PTX	+	+	–	+ (renal angiomyolipoma)	+
Kazunori Tobino *et al.* (45) 2011 (n=12)	Japan	3	9	PTX; skin lesions; RCC	12/12	11/12	2/12 (FFs)	0/12	12/12
Noriyuki Misago *et al.* (46) 2008 (n=1)	Japan	–	1	Skin lesions	–	–	+ (FFs and TDs)	–	+
Sei-ichiro Motegi *et al.* (47) 2018 (n=1)	Japan	1	–	Skin lesions	+	–	+ (FFs)	–	+
Total (n=62)		26	36		60	52	41	18	61

N/A, Data not available; PTX, pneumothorax; *FLCN*, folliculin gene; BHD, Birt-Hogg-Dubé syndrome; RCC, renal cell carcinoma; FFs, fibrofolliculomas; TDs, trichodiscomas; PFs, perifollicular fibromas.

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Table 6 Comparation of clinical features among three counties

Country	Patients	Males	Females	Pulmonary cysts	Pneumothorax	Skin lesions	Kidney lesions	FLCN mutation
China	87	34 (39.1)	53 (60.9)	69 (79.3)	60 (69.0)	10 (11.5)	14 (16.1)	85 (97.7)
Korea	17	6 (35.3)	11 (64.7)	16 (94.1)	12 (70.6)	10 (58.8)	6 (35.3)	15 (88.2)
Japan	62	26 (41.9)	36 (58.1)	60 (96.8)	52 (83.9)	41 (66.1)	18 (29.0)	61 (98.4)
Total	166	66 (39.8)	100 (60.2)	145 (87.3)	124 (74.7)	61 (36.7)	38 (22.9)	161 (97.0)

Data are presented as number (%).

Table 7 FLCN gene mutations of patients among three countries

Mutation sites	Nucleotide changes	The number of patients
Intron 4	c.249+1G>T	1
Intron 5	c.397-1G>C	2
Intron 7	c.780-1G>T	1
Intron 7	c.780-2A>G	1
Intron 9	c.1062+1G>A	1
Intron 10	c.1179-10_1179-8delTCC	1
Intron 10	c.1177-5_1177-3delCTC	1
Intron 11	c.1300+1G>A	1
Exon 4	c.31T>C	1
Exon 4	c.145G>T	1
Exon 4	c.157C>T	1
Exon 4	c.185delG	1
Exon 4	c.214delA	1
Exon 5	c.332_349delACCCCAGCCACCCCCAGC	1
Exon 6	c.397-7_399delCCTCCAGGTC	1
Exon 6	c.469_471delTTC	8
Exon 6	c.510C>G	1
Exon 6	c.543C>G	4
Exon 7	c.649C>T	2
Exon 7	c.658C>T	1
Exon 7	c.668delA	1
Exon 7	c.747_756insGTGATGACAA	1
Exon 7	c.769_771delTCC	1
Exon 7	c.770-772delCCT	1
Exon 8	Break points were not determined?	1
Exon 9	c.933delT	1
Exon 9	c.946_947delAG	2

Table 7 (continued)

Table 7 (*continued*)

Mutation sites	Nucleotide changes	The number of patients
Exon 9	c.1015C>T	1
Exon 10	c.1067T>C	1
Exon 10	c.1135A>T	1
Exon 10	c.1153C>T	2
Exon 10	c.1156_1175del	4
Exon 10	c.1165G>T	1
Exon 10	Genomic deletion of exon 10	1
Exon 11	c.1285C>T	1
Exon 11	c.1285dupC	27
Exon 11	c.1285delC	27
Exon 12	c.1347_1353dupCCACCCT	12
Exon 12	c.1379_1380delTC	1
Exon 12	c.1429C>T	2
Exon 13	c.1481A>G	1
Exon 13	c.1522_1524delAAG	2
Exon 13	c.1533_1536delGATG	6
Exon 13	c.1533G>A	1
Exon 14	c.1557delT	3
Exon 14	c.1579_1580insA	7
Exon 14	c.1645C>G	1
Exon 14	c.1658G>A	1
Exon 14	c.2297T>C	1
Exon 14	Genomic deletion of exon 14	1
Exon 14	Unclear	1
Unclear	Unclear	19
Negative	–	1
Total		166

had renal tumors, and Zbar *et al.* (56) found a 7-fold increase in the risk of renal tumors for BHD-affected patients. According to our review, though 38 (22.9%) BHD individuals had kidney lesions, only 12 (7.2%) had RCC in this East Asian patient group. Some of the patients had benign renal cysts, but the exact frequency of these cysts in comparison with the prevalence in the general population is currently unknown. Renal hamartoma, oncocytoma, and angiomyolipoma were reported in China, Korea, and Japan, respectively. Byrne *et al.* (57) had never reported an Australian BHD patient with renal angiomyolipoma before their research. This phenomenon suggests that *FLCN* and tuberous sclerosis complex (TSC) proteins may function on a common pathway involving mTOR, as angiomyolipoma occurs in 69% of patients with TSC. Renal oncocytoma is regarded as a BHD-associated renal manifestation and comprises a 3% proportion of BHD renal lesions in an American study (52).

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Although the majority of patients in our study were female, BHD syndrome is usually regarded as an autosomal dominant disease without gender discrimination, and some studies have supported this aspect. For example, a large Canadian family involving 36 members with *FLCN* mutations did not show a discrepancy in genders (58), and the study from Zbar *et al.* (56) also showed similar rates in males and females. Meanwhile, some other articles show a higher frequency of these mutations in females. Toro *et al.* (4) studied the clinical information of 89 individuals with *FLCN* mutations, and among them, 52 (58%) were women. In their studies from East Asia, Lee *et al.* (8) and Liu *et al.* (9) showed that there was a higher frequency in females. This phenomenon may be associated with the bias of symptoms. In East Asian patients, according to our literature review, skin lesions and renal tumors are not common, and PCs, as well as pneumothorax, are the main manifestations, which may be misdiagnosed as other diseases. In China, particularly, COPD mainly occurs in males with a history of smoking (59). So we speculate that some males with BHD have not been properly diagnosed, and have been misdiagnosed with COPD. More epidemiological data are needed to confirm whether there is a gender dominance for BHD syndrome in East Asia.

There were several limitations to our study. Although it revealed that fewer typical skin lesions and renal tumors were present in East Asian patients with BHD and that pulmonary cysts with pneumothorax were the most common manifestations, we could not find the fundamental causes of these different clinical characteristics. The main genetic mutations of East Asian patients were similar to those in other areas, and it is still unknown whether other, less frequent genetic mutations determined the clinical differences. Medical habits or diagnostic processes may be different in these regions. Patients presenting with only skin lesions may potentially be overlooked, and those who had pulmonary cysts with pneumothorax may be misdiagnosed. All of these reasons can lead to clinical discrepancies between East Asia and Europe/USA. A large comparative study is necessary and needed in the future, concurrently in East Asia and Europe/USA, to explore these discrepancies.

Conclusions

Overall, the findings of the case series we presented, combined with the symptoms of other East Asian people diagnosed with BHD, have enhanced our understanding of BHD syndrome. It has also been highlighted that patients with multiple pulmonary cysts and spontaneous pneumothorax should be considered for BHD syndrome, independent of whether a skin rash or renal tumors are presented, particularly among individuals of the East Asian population.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The trial was conducted in accordance with the Declaration of Helsinki. The study was approved by the institutional review board of the Second Xiangya Hospital of Central-South University (NO. 2014S009) and informed consent was taken from all the patients.

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