

# Epidemiology and Clinical Features of Birt-Hogg-Dubé Syndrome: A Nationwide Population-Based Study in South Korea

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## Research

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# Abstract

## Background

Birt–Hogg–Dubé (BHD) syndrome is an ultrarare lung disease with unclear prevalence and incidence. Our study aimed to identify the epidemiological and clinical features of BHD syndrome by using nationwide claims data from the Korean Health Insurance Review and Assessment service.

## Results

We found 26 patients with BHD syndrome from 2017 to 2019. The prevalence of BHD syndrome was 5.67 per 10<sup>7</sup> population, with no peak age. Among incidence cases, the median age of diagnosis was 51 years, with slightly more females than males (n = 15, 57.7%). Over half of the patients (n = 14, 53.8%) experienced pneumothorax, and 10 (38.5%) developed malignant neoplasm within the clinical course.

## Conclusions

The prevalence of BHD syndrome in Korea is extremely low. However, affected patients manifest several comorbidities, including malignant neoplasm and repetitive pneumothorax.

## Background

Birt–Hogg–Dubé (BHD) syndrome is a rare inherited autosomal dominant disorder [1]. It is believed to be caused by the germline mutation of folliculin (FLCN) gene [2, 3]. However, the exact pathogenesis and function of FLCN remains unknown. Although FLCN mutations are often found in affected family members [4, 5], de novo development of BHD syndrome with no prior family history can also occur [6].

Typically, BHD syndrome is characterized by skin lesion, renal cancer, cystic lung disease, and spontaneous pneumothorax [7]. However, the spectrum, onset time, and frequency of these clinical manifestations are diverse, making the diagnosis difficult [8, 9]. In addition, the genetic, epidemiologic, and clinical characteristics of BHD syndrome might differ between Asian and Western populations [10, 11]. Currently, the nationwide data about its incidence, prevalence, and accompanying comorbidities are unavailable. In South Korea, the National Health Insurance Service is a universal insurance system that provides both inpatient and outpatient healthcare services for nearly all citizens. Thus, this study aimed to investigate the epidemiologic data and clinical characteristics of BHD syndrome by using the nationwide claims data of Korea.

## Results

### Prevalence of BHD syndrome

Although the FLCN gene test was introduced in 2014 in South Korea, this test was first claimed in January 2016. In the database, 26 patients had BHD syndrome (5.67 per 10 million). Among them, the number and prevalence by sex were 11 and 5.67 (95% CI: 3.71–8.32) in males and 15 and 6.60 (95% CI: 3.7–10.9) in females, respectively. BHD syndrome tended to develop more in females than in males. The median (interquartile range) age was 51 (34–58) years, with 46 (30–57) years in males and 53.5 (31–59) years in females specifically. Moreover, 11 of 26 patients (42.3%) with BHD syndrome underwent FLCN gene test around 50–59 years of age and 8 of 26 (30.8%) patients were tested around 30–49 years of age. The distribution of diagnosis age according to sex is described in Table 1.

Table 1. The number of BHD patients according to age group and sex

Age group	Total			Male			Female		
	N	Prevalence	95% CI	N	Prevalence	95% CI	N	Prevalence	95% CI
10-19	1	2.01	(0.05 - 11.2)	0	0	NA	1	4.18	(0.11 - 23.3)
20-29	3	4.40	(0.91 - 12.8)	2	5.58	(0.68 - 20.1)	1	3.09	(0.08 - 17.2)
30-39	4	5.65	(1.54 - 14.4)	2	5.50	(0.67 - 19.9)	2	5.81	(0.7 - 21)
40-49	4	4.77	(1.3 - 12.22)	2	4.69	(0.57 - 16.9)	2	4.85	(0.59 - 17.5)
50-59	11	12.69	(6.34 - 22.7)	4	9.16	(2.5 - 23.4)	7	16.27	(6.54 - 33.5)
60-69	2	3.16	(0.38 - 11.4)	1	3.24	(0.08 - 18.0)	1	3.10	(0.08 - 17.2)
70-79	1	2.78	(0.07 - 15.4)	0	0	NA	1	5.02	(0.13 - 28.0)
total	26	5.67	(3.71 - 8.32)	11	4.76	(2.38 - 8.52)	15	6.60	(3.7 - 10.9)

NA: Not applicable; N: Number of BHD patients; Prevalence: calculated per 10 million

### Comorbidities

Among the 26 BHD patients, 10 patients had malignancy in this cohort observational period. Among the patients, nine (34.6%) had malignancy before the FLCN gene test and one was diagnosed with cancer after this test (Table 2). In terms of cancer subtypes, digestive cancer (15.4%) and urologic cancer (11.5%) showed the first and second highest incidence before and after BHD syndrome diagnosis, respectively. Lip and oropharynx, thoracic, genital, and hematologic cancers were also identified. Table 3 summarizes the associated diseases identified within 1 year before and after the FLCN gene test. The common comorbidities other than respiratory disease according to organ were gingivitis and periodontal disease (84%) and gastritis and duodenitis (88%). We also found gastroesophageal reflux disease (65.4%), ophthalmic disease (53.8%), dyslipidemia (53.8%), allergic contact dermatitis (42.3%), and hypertension (38.5%) (Table 3). Meanwhile, four patients (16%) had folliculoma identified within 1 year of the FLCN gene test.

Table 2. Associated malignancy in patients with BHD syndrome before and after folliculin gene test

ICD-10 code	Cancer type	Before (N = 26)	After (N = 26)	Total (N = 26)
C00–C97	All kinds of malignancy	9 (34.6%)	1 (3.8%)	10 (38.5%)
C15–C26	Digestive	3 (11.5%)	1 (3.8%)	4 (15.4%)
C64–C68	Ureter and bladder	3 (11.5%)	0 (0%)	3 (11.5%)
C00– C14	Lip and oropharynx	2 (7.7%)	0 (0%)	2 (7.7%)
C30–C39	Respiratory and intrathoracic	1 (3.8%)	0 (0%)	1 (3.8%)
C51–C63	Genital	1 (3.8%)	0 (0%)	1 (3.8%)
C81–C96	Hematologic	1 (3.8%)	0 (0%)	1 (3.8%)

The date of malignancy contains all periods of the patients before and after the folliculin gene mutation test.

Table 3. Associated diseases before and after the diagnosis of BHD syndrome

ICD-10 code	Associated disease	Total (N = 26) (Number, %)	
K29	Gastritis and duodenitis	23	(88.5%)
J00-98	Upper respiratory disease	23	(88.5%)
K02-05	Gingivitis and periodontal disease	22	(84.6%)
J20	Acute bronchitis	18	(69.2%)
K21	Gastroesophageal reflux disease	17	(65.4%)
J93	Pneumothorax	14	(53.8%)
H04, H10, H52	Ophthalmic disease	14	(53.8%)
E78	Dyslipidemia	14	(53.8%)
L03, L23, L50, M79	Skin disease	11	(42.3%)
J84	Other interstitial lung diseases	10	(38.5%)
I10	Hypertension	10	(38.5%)

The date of the associated disease contains only within 1 year before and after the folliculin gene test. Upper respiratory disease includes following codes: J00, J01, J02, J03, J04, J06, J20, J30, J40, J44, and J98.

## Pneumothorax

During the study period, 17 (65.4%) patients suffered at least one pneumothorax, 10 of whom (58.8%) had recurrent pneumothorax (Table 4). Pneumothorax was more common in females than in males (11, 64.7% vs. 6, 35.2%). The median age of patients at pneumothorax diagnosis was 43 (31–57) years (25%–75%), with 40 (28–57) years in males and 43 (34–55) years in females specifically. Pneumothorax occurring more than once was found in 5 of 6 male patients (83%) and in 5 of 11 female patients (45%). In those with at least one pneumothorax event, the mean (standard deviation) length of hospital stay was 9.9 (6.1) days in the first event and 12.6 (6.8) days in the second event. The median length of hospital stay by sex was 8 (6.5–13) in males and 9.5 (5.75–15.25) in females. Pneumothorax that occurred within 3 months of BHD syndrome diagnosis was found in 13 of all 26 patients (Figure 1). The median (interquartile range) time from pneumothorax to BHD syndrome diagnosis was 39 (5.4–98) months.

Table 4. Number of pneumothoraxes among BHD patients

Number of pneumothoraxes	Number of patients	%
0	9	
1	7	26.9%
2	9	34.6%
>3	1	3.8%
Total	26	

## Discussion

The current study is the first population-based research performed on the prevalence of BHD syndrome in Korea by using a nationwide claims database. Although the prevalence of BHD syndrome was extremely rare in South Korea (5.67 per 10 million), various comorbidities, including malignancy and repetitive pneumothorax, were found.

Given that the BHD syndrome is a rare inherited disorder [12], its incidence and prevalence remain unknown. Several previous reports focused on the prevalence of BHD syndrome in patients with spontaneous pneumothorax [13, 14] or family history [5, 15, 16]. Recently, Hu et al. conducted a literature review of a large BHD syndrome cohort (120 families with 221 cases) in China [15]. However, they collected information using only published data; hence, the research was not representative of the nationwide data. In South Korea, Lee et al. reported only 12 patients (10 patients confirmed by FLCN gene test) who had BHD syndrome in a single largest tertiary hospital [17], suggesting the rarity of this condition. Our current data showed that BHD syndrome is ultrarare in South Korea, with a prevalence rate of only 5.67 per 10 million. As mentioned earlier, defining BHD syndrome cases using the ICD code alone seemed inadequate because it might omit other patients with BHD syndrome, leading to bias in

evaluating epidemiologic data. In addition, patients with BHD syndrome who did not undergo the FLCN gene test were excluded in our analysis; this exclusion might have led to the underestimation of actual epidemiology. However, our data might serve as a reference for understanding this rare disease in South Korea.

Clinical manifestations of patients with BHD syndrome may also differ in terms of ethnicity [15, 18]. Kunogi et al. evaluated 30 Japanese patients with BHD syndrome and reported that while nearly all patients (96.7%) experienced pneumothorax, only 7 (23.3%) had skin lesion, and 2 (6.7%) had renal tumor [18]. Hu et al. investigated 221 Chinese patients with BHD syndrome and showed prevalence of pneumothorax (71.0%), skin lesion (18.1%), and renal cancer (3.6%) [15]. Thus, Asian patients might have a higher prevalence of pneumothorax and a lower incidence of cutaneous and renal manifestations than Western patients [4, 19–21]. Similarly, our current study found that pneumothorax occurred in over half of the patients (58.8%), but skin lesion (fibrofolliculoma, trichodiscoma, or accrocardon) and ureter and bladder cancer only accounted for 9 (34.6%) and 3 patients (11.5%), respectively. Recently, Liu et al. analyzed 51 Chinese patients with BHD syndrome and showed that Chinese patients had FLCN gene mutant loci that were different from those of Western patients [11]. This observation might possibly explain the ethnic difference. Notably, our current study showed several comorbidities, especially malignant neoplasm, in patients with BHD syndrome. Various tumors other than renal cancer might also occur in these patients [5, 20, 22, 23]. However, the gold standard or guidelines on how to optimally screening and manage these patients are still unavailable. Hence, further studies are needed.

Patients with BHD syndrome are predisposed to pneumothorax [1, 7]. Zbar et al. reported that the odds ratio for spontaneous pneumothorax in patients with BHD syndrome was 32 when compared with that in the general population [24]. In the current study, 65.4% of the patients experienced pneumothorax, comparable to other previous studies (approximately 24–76%) [4, 10, 19, 25]. In addition, the median age of pneumothorax development was 43 years, which is also comparable to other previous studies with a relatively large number of patients [12, 19, 21]. Repetitive pneumothorax might also occur [19, 25]. Toro et al. showed that 101 episodes of pneumothorax (1 to 5 times in each patient) occurred in 48 patients with BHD syndrome [25]. In addition, Gupta et al. reported that the average number of pneumothorax was 3.6 in patients with BHD syndrome [19]. Our study population showed a similar recurrence rate of pneumothorax (58.8%). Notably, the hospital stay was longer in the second episode than in the first episode, suggesting that treatment might be difficult in patients with repetitive pneumothorax. Moreover, pneumothorax within 3 months of BHD syndrome diagnosis occurred in 13 patients (50% of study population), consistent with the previous study of Gupta et al. [19], which showed that pneumothorax was the presenting manifestation of BHD in 65% of their patients.

This study has some limitations. Considering that it used a nationwide medical claims database, BHD syndrome without FLCN gene mutation is not included in our dataset, thereby possibly omitting approximately 10% of patients with BHD syndrome [26]. Our study also did not include those with a family history of BHD syndrome and FLCN gene mutation, thereby reducing the representation of genetic features. Furthermore, if the clinician did not perform FLCN gene test for patients with suspected BHD

syndrome, our criteria would underestimate the real prevalence. However, this study collected all FLCN gene tests performed in South Korea from 2016 to 2019, but only 26 patients were found. Moreover, we collected a maximum of 12.8-year follow-up data of patients suspected with BHD syndrome, including their clinical phenotypes combined with comorbidities and pneumothorax history, thereby showing the characteristics and clinical course of BHD syndrome.

## Conclusions

In conclusion, the prevalence of BHD syndrome in South Korea is extremely low. However, these patients are characterized by several comorbidities, including malignant neoplasm and repetitive pneumothorax.

## Methods

### Study design and data collection

This nationwide retrospective cohort study enrolled patients diagnosed with BHD who also had an ICD-10 code and an insurance payment code. Considering its extreme rarity, the BHD syndrome does not have its own ICD-10 code; rather, it belongs to the ICD code Q878, which includes Alport syndrome, arterial tortuosity syndrome, and other congenital malformation diseases. Moreover, the confirmation test, that is, the FLCN gene test, is not common; thus, it was included in the code C5808. Supplement Table 1 lists the tests included in C5808. Patients with BHD syndrome in Korea are under the insurance policy for incurable rare diseases, which have distinct codes. However, given that BHD syndrome is rare, it is included in the rare incurable disease code V900, which consists of 127 diseases (Supplementary Table 2). Considering this limitation, the BHD syndrome was also defined using the insurance payment code for FLCN gene (C5808) and the comorbidities according to the corresponding ICD codes.

From the Health Insurance and Review Agency database between January 2007 and October 2019, we extracted patients undergoing FLCN gene tests using national health insurance payment code (C5808) after 2016 and subclass of gene test (C5808446) after 2017. As the presentation can differ among patients due to different disease onsets per organ, we defined BHD patients as those tested for FLCN gene mutation (C5808446) and having at least one of: other specified malformation syndromes (Q87.8), fibrofolliculoma (D23), acrochordon (L918), lung cyst (Q330), renal cancer (C64, C65, and cancer registration code (V027, V193, and V194)), and pneumothorax (J93) based on International Classification of Disease-10 (ICD-10). For distinction from other cystic lung diseases, the following diseases were excluded: Langerhans cell histiocytosis (J848) and lymphangioliomyomatosis (D181). In BHD patients, demographic characteristics and associated diseases including malignancy were described. To identify the diseases associated with BHD syndrome, we extracted diagnoses within 1 year before and after the FLCN gene mutation test. To protect individual privacy, anonymized and de-identified information was analyzed. To quantify pneumothorax in BHD syndrome, patient-wise pattern of hospitalization was depicted throughout the entire studied period.

### Statistical methods

The patients' age was described using median and 25% and 75% quantiles. To understand the natural course of cancer risks, we showed the cumulative incidence using number and percentage. The temporal relationship between the date of FLCN gene claim and pneumothorax, which is a clue for diagnosing BHD, is shown in Figure 1.

## **Declarations**

### **Ethics approval and consent to participate**

Not required, because this study only use publicly available Health Insurance and Review Agency database.

### **Consent for publication**

Not applicable

### **Availability of data and materials**

The datasets generated and/or analysed during the current study are available in the HIRA database of South Korea repository. (<https://hcdl.mohw.go.kr>)

### **Competing interests**

The authors declare that they have no competing interest.

### **Funding**

None

### **Authors' contribution**

Conception, design: Hyung Jun Park, Ho Cheol Kim

Data acquisition: Hyung Jun Park, Ho Cheol Kim

Analysis and interpretation of the data: Hyung Jun Park, Ye-Jee Kim, Min-Ju Kim, Ho Cheol Kim

Drafting of the work: Ho Cheol Kim

Critical revision of the paper and final approval for submission: Hyung Jun Park, Ye-Jee Kim, Min-Ju Kim, Ho Cheol Kim

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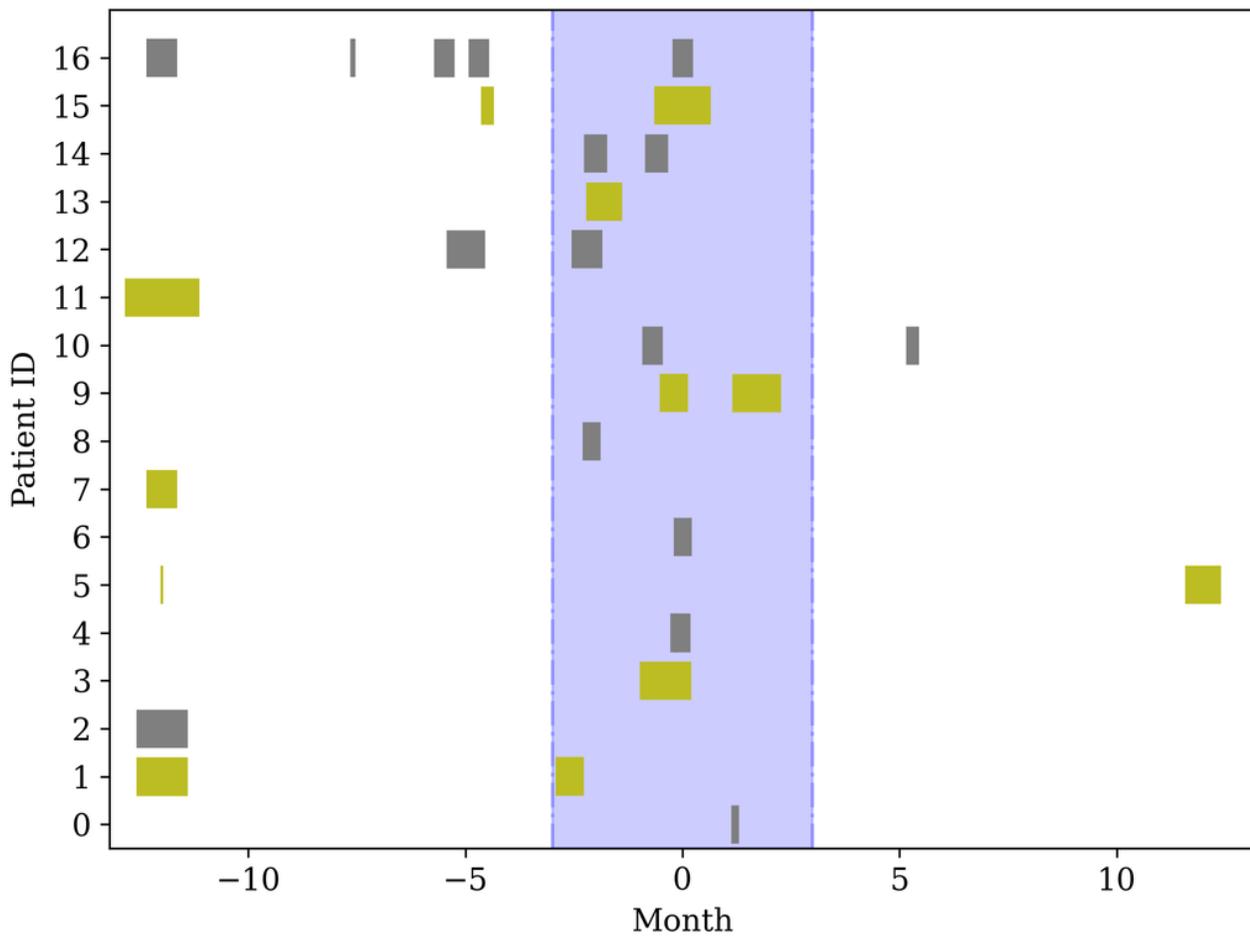
Not applicable

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## Figures



**Figure 1**

Hospitalization for pneumothorax compared with date of BHD diagnosis The figure shows the onset and in-hospital period for pneumothorax per patient. The month zero is defined by the day of BHD diagnosis, and the shaded area is the previous 3 months of the diagnosis. The hospital admission period is depicted as the length of each bar.

## Supplementary Files

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