Delayed diagnosis of Birt-Hogg-Dubé syndrome might be aggravated by gender bias

Ortrud K. Steinlein,[a]* Marlene Reithmair,[a] Zulfiya Syunyaeva,[b,c] and Elke C. Sattler[d]

[a]Institute of Human Genetics, University Hospital, LMU Munich, Goethestr. 29, 80336 Munich, Germany
[b]University of Munich, Department of Medicine V, University Hospital, LMU, Munich, Germany
[c]Department of Pediatric Pulmonology, Immunology and Critical Care Medicine and Cystic Fibrosis Center, Charite -Universitätsmedizin Berlin, Berlin, Germany
[d]Department of Dermatology and Allergy, University Hospital, LMU Munich, Frauenlobstraße 9-11, 80337 Munich, Germany

eClinicalMedicine 2022;51: 101572
Published online xxx
https://doi.org/10.1016/j.eclinm.2022.101572

Summary

Background Birt-Hogg-Dubé syndrome is a rare genetic tumor syndrome characterized by renal cell cancer, lung bullae, pneumothorax, and fibrofolliculoma. Patients with such orphan tumor disorders are at risk of not receiving a timely diagnosis. In the present, gender-sensitive study, we analyzed the delay between onset of symptoms and diagnosis of Birt-Hogg-Dubé syndrome.

Methods Clinical data of 158 patients from 91 unrelated families were collected. *FLCN* mutation testing was performed in index patients and family members.

Findings The occurrence of the first symptom (fibrofolliculoma, pneumothorax or renal cell cancer) was rarely followed by a timely diagnosis of Birt-Hogg-Dubé syndrome and did so significantly less often in female (1.3%) compared to male (11.4%) patients (chi-square 6.83, p-value 0.009). Only 17 out of 39 renal cell cancers (7/17 female, 10/22 male patients) were promptly recognized as a symptom of Birt-Hogg-Dubé syndrome. Patients in which renal cell cancer was initially not recognized as a symptom of Birt-Hogg-Dubé syndrome waited 9.7 years (females SD 9.2, range 1-29) and 8.8 years (males, SD 4.1, range 2-11) for their diagnosis, respectively. Four (three female, one male) patients developed renal cell cancer twice before the genetic tumor syndrome was diagnosed. The delay between fibrofolliculoma or pneumothorax as a first symptom and diagnosis of Birt-Hogg-Dubé syndrome was considerable but not significantly different between females and males (18.1/17.19 versus 16.1/18.92 years). Furthermore, 73 patients were only diagnosed due to family history (delay 15.1 years in females and 17.4 years in males).

Interpretation The delay between onset of symptoms and diagnosis of Birt-Hogg-Dubé syndrome can be substantial and gender-dependent, causing considerable health risks for patients and their families. It is therefore important to create more awareness of Birt-Hogg-Dubé syndrome and resolve gender biases in diagnostic work-up.

Funding None declared.

Keywords: Spontaneous pneumothorax lung bullae; Renal cell carcinoma; Gender

Introduction

Birt-Hogg-Dubé syndrome (BHDS, MIM: 135150) is an inherited tumor syndrome with major symptoms that affect lung, skin and kidney.[1] Nearly all patients develop lung bullae, resulting in an average risk for spontaneous pneumothorax of about 44%.[2] There are gender differences regarding pneumothorax risk; female patients tend to be affected more often before age 20 years but rarely after age 50 years. Male patients mostly develop spontaneous pneumothorax (SP) between age 20 and 40 years but their risk again increases after age 50 years.[2] Fibrofolliculoma (FF), the typical benign skin tumors, start to appear between age 20 and 40 years, mostly on face and neck. They are small grayish–white papules with a mostly smooth surface, may be subtle but tend to increase in number and size over time, and may coalesce into plaques.[3]

Abbreviations: BHDS, Birt-Hogg-Dubé syndrome; RCC, renal cell carcinoma; SD, standard deviantion

*Corresponding author at: Institute of Human Genetics, University Hospital, LMU Munich, Goethestrae 29, D-80336 Munich, Germany.
E-mail address: Ortrud.Steinlein@med.uni-muenchen.de (O.K. Steinlein).

Research in context

Evidence before this study

A trend towards delayed diagnosis of BHDS was obvious in samples reported by other groups. This trend is best demonstrated by the fact that the mean patient age is often well after the average age of symptom onset.

Added value of this study

Using one of the largest existing samples of BHDS families, we analyzed how likely RCC and other typical symptoms are to prompt diagnosis of BHDS. To the best of our knowledge this is the first time that this question has been systematically addressed.

Implications of all the available evidence

The patients' chances to be timely diagnosed with BHDS were small for all major symptoms. Female patients were significantly less often diagnosed after the occurrence of the first symptom compared to male patients. It is important to continue creating awareness of BHDS and recognize gender biases in diagnostic work-up.

Patients with BHDS are at risk of developing benign or malignant renal tumors that can be multifocal and/or bilateral. The risk for renal cell carcinoma (RCC) is about 14-35% (median age 56 years) and different histological subtypes are possible, including the rather characteristic chromophobe/oncocytoma hybrid renal tumor.[4–9] Furthermore, the possibility for an increased colorectal cancer risk is controversially discussed, a tumor type that in our sample showed a small but significant increase in frequency and a trend towards early onset.[10] Increased risks for colorectal cancer in BHDS have also been reported by Nahorski et al.[11] and Khoo et al.[12] but were not present in the samples of Zbar et al.[13] and Toro et al.[14] Associations with different other tumor types were suggested but not confirmed yet.[15,16]

BHDS is inherited as an autosomal dominant trait and caused by mutations in the *FLCN* gene that encodes the protein folliculin.[17] *FLCN* is a tumor suppressor gene for which various important roles in cell function and tumorigenesis are discussed. These include the regulation of metabolic homeostasis by coordination of the main signaling pathways mTORC1 and AMPK, a context dependent function in stem cell biology, and an involvement in lysosomal biogenesis and autophagy.[18–20] BHDS is usually described as a rare syndrome but numbers of reported patients steadily increased during the last years, strongly suggesting that the syndrome is more frequent than previously assumed and that many patients still not receive a timely diagnosis.[21] Exploring a large sample of BHDS families that has been collected over a time span of more than 15 years, we analyzed how likely RCC and other typical symptoms are to prompt diagnosis of BHDS. Our results demonstrate that the delay between the occurrence of the first symptoms and recognition of the syndromic origin is often substantial and tends to be gender-dependent, causing avoidable health risks for BHDS patients and their family members.

Methods

Patients

All patients attending the Munich BHDS outpatient clinic and family members for which the relevant clinical information was available were part of the study. Included in the study were 79 female (mean age 51·5 years, SD 14·5, range 15-86 years) and 79 male BHDS patients (mean age 55·4 years, SD 17·1, range 4-87 years), belonging to 91 unrelated families. Informed consent for DNA testing and study participation was obtained from all index patients as well as from family members visiting our BHDS outpatient clinic between 2005 and 2021. Of the 91 BHDS families, 80 were of German descent, one each from Turkey, Portugal, Switzerland, France and Greece, two from Great Britain and four of Eastern European origin with German roots (Volga Germans). Clinical data were collected when patients were first seen in the outpatient clinic and on subsequent visits as well as from regular follow-up contacts by email and phone. Diagnosis of fibrofolliculoma was either established by histopathology after biopsy, or judged by visual inspection performed independently by two specialists in dermatology in combination with confocal laser scan microscopy (VivaScope 1500/3000, VivaScope Munich, Germany). The reasons for diagnosis were mainly a family history for BHDS (43 female, 33 males), fibrofolliculoma (18 females, 22 males), pneumothorax (11 females, 10 males), RCC (seven females, 12 males), renal adenoma (0 females, one male) and somatic tumor sequencing (i.e. sequencing the tumor to determine the mutational burden for therapeutic purposes) (0 females, one male).

Genetic testing

The coding region of the *FLCN* gene including adjacent intronic sequences was amplified by PCR and analyzed by Sanger sequencing following standard protocols.[4] In summary, PCR amplification was performed with 50-100 ng DNA using HotStarTaq DNA Polymerase or Invitrogen^{TM}Taq DNA Polymerase recombinant (Qiagen, Hilden, Germany; Thermo Fisher Scientific, Dreieich, Germany). PCR products were prepared for sequencing with the Qiagen PCR purification kit (Qiagen, Hilden, Germany), and Sanger sequencing was performed using the 3500 Genetic Analyser (Thermo Fisher Scientific, Dreieich, Germany). For MLPA the

SALSA MLPA P256 *FLCN* probemix (MRC Holland, Amsterdam, The Netherlands) was used on the ABI 3100 Avant (Applied Biosystems, Darmstadt, Germany) and analyzed by Coffalyser Net software (MRC Holland, Amsterdam, The Netherlands).[22]

Statistical analyses

Statistical analyses were performed using the two-tailed Mann−Whitney U test (significance level $p \leq 0.05$) to exclude age differences between females and males regarding all patients included, time of diagnosis, age of first symptom and follow-up period. The Chi-Square test (significance level $p \leq 0.05$) was used to test the hypothesis that sex influences the likelihood that the first symptom prompted diagnosis.

Ethics approval

The study has been approved by the ethical committee/ institutional review board (IRB) of the Medical Faculty, University Hospital Munich, under the project-number 508/16UE.

Role of funding source

Non declared, OS and ES had access to all raw data.

Results

Mostly truncating *FLCN* mutations were found in all but two of the 91 BHDS families. A table summarizing the mutations has been published earlier.[10] Mutations affecting the known *FLCN* hotspot at nucleotide 1285 of the coding sequence (LRG_325t1/NM_144997.7: c.1285dup or c.1285del) were present in 18 families. There was no significant difference regarding the age of female and male patients included in the study (*u*-value 2646, z-score -1.648, *p*-value 0.10). At the time diagnosis of BHDS was established the mean age was 47.4 years (SD 13.9, range 10-82 years) for females and 51.7 years for males (SD 15.7, range 12-83 years) (*u*-value 2620, z-score -1.739, *p*-value 0.08). The first symptom from the typical BHDS clinical triad (fibrofolliculoma, pneumothorax or RCC) appeared at the mean age of 33.6 years (SD 12.9, range 15-69 years) in females and at the mean age of 38.8 years (SD 15.8, range 15-83 years) in males (u-value 1258.5, z-score 1.703, *p*-value 0.11).

The mean follow-up period after diagnosis of BHDS was 4.9 years (SD 5.8, range 0-42 years) in female and 5.0 years (SD 3.1, range 0-15 years) in male patients (u-value 3051., z-score 0.240, *p*-value 0.81). There were no significant differences regarding the reason for diagnosis between female and male patients, and the symptom that caused diagnosis was rarely the first symptom the patients developed. The occurrence of the first symptom significantly less often prompted diagnosis of BHDS in females (1.3%) compared to males (11.4%) (females 1(1xRCC)/79; males 9 (6xRCC, 2xSP, 1xFF)/79) (chi-square 6.83, p-value 0.009).

A total of 39 RCC occurred in 14 female (mean age of occurrence 53.4 years, SD 11.3, range 29-75 years) and 21 male (mean age of occurrence 55.4 years, SD 10.7, range 38-70 years) BHDS patients (metachronous tumors included). Seven RCC in females (mean age of occurrence 48.4 years, SD 11.1, range 29-60 years) and five RCC in males (mean age 61.2 years, SD 7.8, range 50-69 years) were only retrospectively recognized as a symptom of BHDS. Four (three female, one male) patients twice developed RCC before BHDS diagnosis was established (mean time between first and second RCC: 10.8 years, range 2-29 years). The mean delay between occurrence of RCC and diagnosis of BHDS was 5.8 years in females (SD 8.9, range 0-29 years) and 2.9 years in males (SD 4.8, range 0-13 years), if patients in which RCC was immediately recognized as a symptom of BHDS are included. The differences in delay between occurrence of RCC and diagnosis of BHDS were not significant between females and males (*u*-value 34.5, z-score -1.433, *p*-value 0.153). Patients in which RCC was initially not recognized as a BHDS symptom waited 9.7 years (females SD 9.2, range 1-29) and 8.8 years (males, SD 4.1, range 2-11) for their BHDS diagnosis, respectively. Two female and four male patients were found to be presently affected by RCC when surveillance started after BHDS became known in the family. Four additional patients (one female, three males) developed RCC within two years after diagnosis of BHDS (Table S1).

The delay between fibrofolliculoma as a first symptom (female *n*=19, male *n*=23) and diagnosis of BHDS did not significantly differ between female and male patients (delay in females 18.1 years (SD 13.0, range 4-52 years); delay in males 16.1 years (SD 13.8, range 0-51 years); z-score -0.705, p-value 0.48). The same was true for the delay between pneumothorax as a first symptom (female *n*=12, male *n*=2) and BHDS diagnosis (delay in females 17.19 years (SD 11.6, range 1-46 years); delay in males 18.92 years (SD 15.4, range 1-54 years); z-score -0.037, *p*-value 0.97). Furthermore, the delay between the occurrence of first symptoms and diagnosis due to family history (female *n*=41, male *n*=32) was approximately the same for female and male patients (delay in females 15.1 years (range 1-46 years, SD 11.6), delay in males 17.4 years (range 0-54 years, SD 16.8); z-score -0.056, *p*-value 0.95) (Figure 1). All patients diagnosed because of their family history were symptomatic.

Discussion

In our sample, 29 RCC occurred before BHDS was known to segregate in the respective families but only 17 of them were promptly recognized as a possible symptom of BHDS. In the remaining patients, BHDS diagnosis was on average delayed for 9.3 years and four

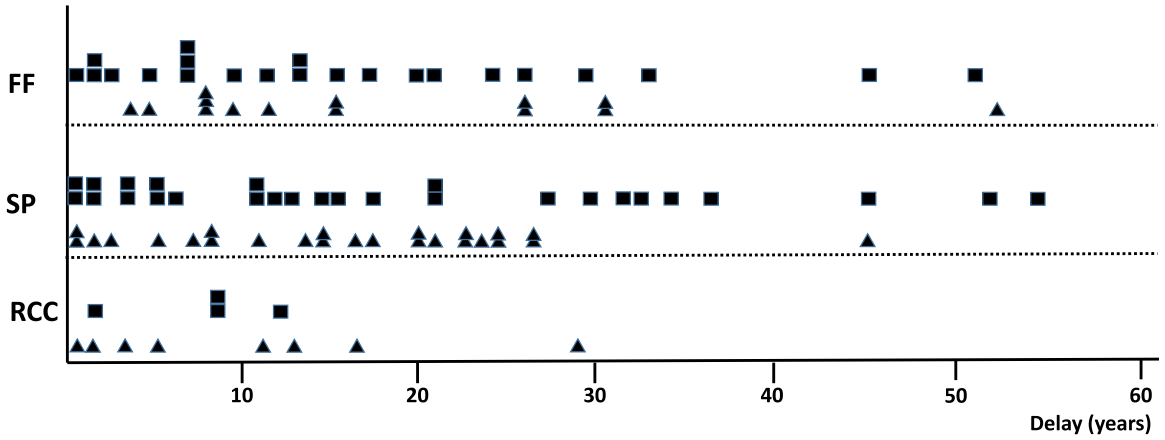

Figure 1. Time between first symptom and BHDS diagnosis.

Shown is the often considerable delay between the occurrence of the first major symptom and the diagnosis of BHDS. BHDS, Birt-Hogg-Dubé syndrome; RCC, renal cell cancer; SP, spontaneous pneumothorax; FF, fibrofolliculoma; triangle, female; square, male.

of these patients developed metachronous RCC during this delay. Such missed opportunities endanger both the index patient and the family members because years are lost in which a preventive tumor screening could have been implemented. This is especially worrisome because routine tumor staging before or after removal of RCC usually includes lung scans, which should have led to the discovery of typical lung bullae that are present in most adult BHDS patients. Interpreted correctly as a symptom of BHDS, such findings would have prompted regular surveillance which in two of our patients would have enabled earlier detection of later occurring metachronous RCC. Furthermore, the main age at which RCCs occurred in our sample was 55.1 years, therefore most of the patients were of an age at which many of them should have already developed fibrofolliculoma of face and neck. This means, diagnosis was missed in the majority of RCC patients although they were probably presenting with all three major BHDS symptoms. It is also worth to mention that three of the female patients in which RCC was initially missed as a sign of BHDS developed their tumor before age 50 years, one of them even before age 30 years. Early onset RCC has a high probability for a genetic origin and should therefore prompt an extensive search for an underlying familiar tumor syndrome. Reasons for these missed opportunities could be a low level of awareness of BHDS and a lack of knowledge of its typical manifestations. Most of our patients that were diagnosed with BHDS shortly after detection of RCC, received their diagnosis within the last five years. In this time span several publications about BHDS appeared in membership magazines of different German professional medical organizations and might have helped to increase awareness of BHDS.[23,24] This is also supported by the observation that the numbers of patients attending our outpatient clinic increased from an average of 4.4 patients/year between 2005

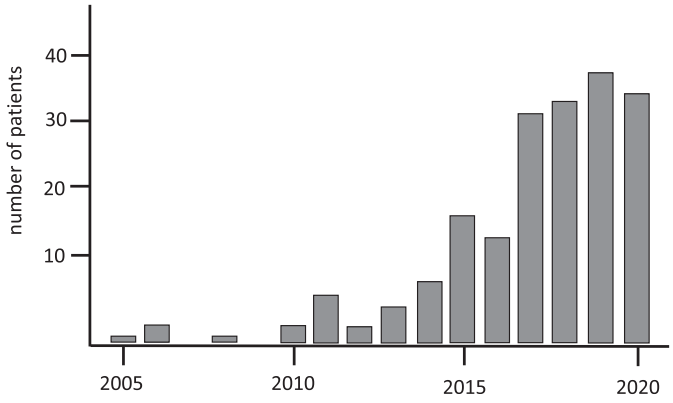

Figure 2. Recruitment of BHDS patients.

Schematic overview demonstrating the recent increase in numbers of new patients seeking treatment and genetic counselling in the Munich interdisciplinary BHDS outpatient clinic. BHDS, Birt-Hogg-Dubé syndrome.

and 2017 to 35.0 patients/year between 2018 and 2020. Without repeated lockdowns due to COVID-19 pandemic, the increase would have probably been even more pronounced (Figure 2).

The patients' chances to be timely diagnosed with BHDS were small for all major symptoms, and female patients were significantly less often diagnosed after the occurrence of the first symptom compared to male patients. The gender differences were mainly caused by RCC that as a first symptom was less likely to prompt diagnosis in females compared to males. This is especially striking, since RCC appears almost twice as often in males than in females.[25] According to the Carter rule, RCC in females is therefore more likely to be of genetic origin.[26] The observed gender differences could have different reasons. Several studies have shown that, for different reasons, women tend to be underdiagnosed with respect to many medical conditions. Men on average are examined and treated more extensively than women presenting with the same condition.[27–29] Gender bias should therefore also be considered as a possible explanation for the disparity in timely diagnosis of BHDS between female and male RCC patients.

The delay in establishing the correct diagnosis was most pronounced, without significant gender differences, when patients developed fibrofolliculoma or spontaneous pneumothorax as a first symptom (average delay 17.1 and 18.1 years, respectively). Regarding fibrofolliculoma, the considerable delay can, at least in part, probably be explained by the fact that patients might not be too worried about the skin lesions as long as they are low in number. Furthermore, correct classification of these skin tumors can be difficult to establish without biopsy. However, spontaneous pneumothorax, which occurs in about 43% of patients,[2] is a serious health complication. In our patients, it nevertheless often failed to prompt a thorough search for the underlying medical condition, despite the fact that approximately 10% of spontaneous pneumothorax are caused by BHDS.[30]

It is interesting that relatives diagnosed with BHDS rather than the patient's own symptoms were the most frequent reason for *FLCN* testing in our sample. This is most likely explained by the structure of our interdisciplinary outpatient clinic in which all attending patients are offered genetic counseling including extensive pedigree analysis. Family members at risk are identified and the patients receive recommendations how to inform these relatives about their possibilities of genetic counseling and testing. Many relatives at risk obviously decide in favor of genetic testing after learning about the inherited condition in their family. This had a positive effect on timely diagnosis of RCC that were found in nine family members within two years of establishing BHDS diagnosis in the families. Six of these patients were alerted to the need of *FLCN* testing and check-ups because BHDS had been diagnosed in a family member, who in turn informed relatives at risk. All of these RCC patients had favorite outcomes as most tumors were detected at a rather early stage, could be removed by partial nephrectomy and none of those patients needed kidney removal or had signs of metastasis.[4]

The present study has several limitations. It is practically impossible to collect a completely unbiased sample, especially if dealing with a syndrome that is likely to be still grossly underdiagnosed. We like to think that our sample is as unbiased as possible because patients attending our outpatient clinic are coming from many different sources, i.e. self-referral after 'Google diagnosis', family members of index patients, referrals from dermatologists, nephrologists, oncologists, and pulmonologists. Furthermore, the relatively small number of patients included did not allow us to analyze the sample according to ethnicity or to perform multivariate analysis because the patient numbers in the subgroups became too small to perform any meaningful statistical analysis. Given the rarity of the disorder, one probably would need to perform a metaanalysis to overcome this problem. Nevertheless, a trend towards delayed diagnosis is also obvious in BHDS samples reported by other groups, often demonstrated by a mean patient age well after the average age of symptom onset. These studies also underline the importance of *FLCN* testing for timely diagnosis in patients presenting with typical symptoms.[31–35]

Overall, it is important to continue creating awareness of orphan tumor syndromes and recognize gender biases in diagnostic work-up. This will be especially beneficial for patients with complex genetic tumor syndromes such as BHDS that can present with apparently unrelated symptoms and require interdisciplinary approaches. Timely diagnosis and continuous surveillance are crucial for BHDS patients because of their high risk for RCC.

Contributors

OS recruited patients, drafted the manuscript and performed the statistical analysis. ES and ZS recruited patients and contributed to the manuscript. MR performed the molecular analyses and contributed to the manuscript. OS and ES had access to all raw data.

Data sharing statement

All data are included in the manuscript and the supplementary files.

Declaration of interests

OS, ES, ZS and MR declare no competing interests.

Acknowledgements

We wish to thank the BHDS families for participating in this study. Furthermore, we thank Franz Jansen for excellent technical assistance.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2022.101572.

References

1 Hornstein OP, Knickenberg M. Perifollicular fibromatosis cutis with polyps of the colon - a cutaneo-intestinal syndrome sui generis. *Arch Derm Res*. 1975;253:161–175.
2 Sattler EC, Syunyaeva Z, Mansmann U, et al. Genetic risk factors for spontaneous pneumothorax in Birt-Hogg-Dubé syndrome. *Chest*. 2020;157:1199–1206.
3 Tong Y, Schneider JA, Coda AB, et al. Birt-Hogg-Dubé syndrome: a review of dermatological manifestations and other symptoms. *Am J Clin Dermatol*. 2018;19:87–101.
4 Sattler EC, Reithmair M, Steinlein OK. Kidney cancer characteristics and genotype-phenotype-correlations in Birt-Hogg-Dubé syndrome. *PLoS One*. 2018;13:e0209504.
5 Lagerstedt-Robinson K, Baranowska Körberg I, Tsiaprazis S. A retrospective two centre study of Birt-Hogg-Dubé syndrome reveals a pathogenic founder mutation in FLCN in the Swedish population. *PLoS One*. 2022;17:e0264056.
6 Hasumi H, Baba M, Hasumi Y, et al. Birt-Hogg-Dubé syndrome: clinical and molecular aspects of recently identified kidney cancer syndrome. *Int J Urol*. 2016;23:204–210.
7 Khoo SK, Giraud S, Kahnoski K, et al. Clinical and genetic studies of Birt-Hogg-Dubé syndrome. *J Med Genet*. 2002;39:906–912.
8 Schmidt LS, Linehan WM. Molecular genetics and clinical features of Birt-Hogg-Dubé syndrome. *Nat Rev Urol*. 2015;12:558–569.
9 Menko FH, van Steensel MAM, Giraud S, et al. Birt-Hogg-Dubé syndrome: diagnosis and management. *Lancet Oncol*. 2009;10:1199–1206.
10 Sattler EC, Syunyaeva Z, Reithmair M, et al. Colorectal cancer risk in families with Birt-Hogg-Dubé syndrome increased. *Eur J Cancer*. 2021;151:168–174.
11 Nahorski MS, Lim DH, Martin L, et al. Investigation of the Birt-Hogg-Dubé tumour suppressor gene (FLCN) in familial and sporadic colorectal cancer. *J Med Genet*. 2010;47:385–390.
12 Khoo SK, Giraud S, Kahnoski K, et al. Clinical and genetic studies of Birt-Hogg-Dubé syndrome. *J Med Genet*. 2002;39:906–912.
13 Zbar B, Alvord WG, Glenn G, et al. Risk of renal and colonic neoplasms and spontaneous pneumothorax in the Birt-Hogg-Dubé syndrome. *Cancer Epidemiol Biomarkers Prev*. 2002;11:393–400.
14 Toro JR, Glenn G, Duray P, et al. Birt-Hogg-Dubé syndrome: a novel marker of kidney neoplasia. *Arch Dermatol*. 1999;135:1195–1202.
15 Liu V, Kwan T, Page EH. Parotid oncocytoma in the Birt-Hogg-Dubé syndrome. *J Am Acad Dermatol*. 2000;43:1120–1122.
16 Chung JY, Ramos-Caro FA, Beers B, et al. Multiple lipomas, angiolipomas, and parathyroid adenomas in a patient with Birt-Hogg-Dubé syndrome. *Int J Dermatol*. 1996;35:365–367.
17 de Martin Garrido N, Aylett CHS. Nutrient signaling and lysosome positioning crosstalk through a multifunctional protein, folliculin. *Front Cell Dev Biol*. 2020;8:108.
18 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.
19 Napolitano G, Di Malta C, Esposito A, et al. A substrate-specific mTORC1 pathway underlies Birt-Hogg-Dube syndrome. *Nature*. 2020;585:597–602.
20 Goodwin JM, Walkup 4th WG, Hooper K, et al. GABARAP sequesters the FLCN-FNIP tumor suppressor complex to couple autophagy with lysosomal biogenesis. *Sci Adv*. 2021;7:eabj2485.
21 Liu S, Xia K, Liu X, et al. Bibliometric analysis of Birt-Hogg-Dubé syndrome from 2001 to 2021. *Front Med (Lausanne)*. 2022;9:857127.
22 Schouten JP, McElgunn CJ, Waaije Rr, et al. Relative quantification of 40 nucleic acid sequences by multiplex ligation-dependent probe amplification. *Nuc Acids Res*. 2002;30:e57.
23 Steinlein OK, Ertl-Wagner B, Ruzicka T, et al. Birt-Hogg-Dubé syndrome: an underdiagnosed genetic tumor syndrome. *J Dtsch Dermatol Ges*. 2018;16:278–283.
24 Steinlein OK, Ertl-Wagner B, Sattler EC. Pulmonary bullae as an indicator of an elevated risk of renal carcinoma. *Dtsch Arztebl Int*. 2018;115:294.
25 Capitanio U, Bensala K, Bex A, et al. Epidemiology of renal cell carcinoma. *Eu Urol*. 2019;75:74–84.
26 Carter CO. The inheritance of congenital pyloric stenosis. *Br Med Bull*. 1961;17:251–253.
27 Peired AJ, Campi R, Angelotti ML, et al. Sex and gender differences in kidney cancer: clinical and experimental evidence. *Cancers (Basel)*. 2021;13:4588.
28 Din NU, Ukoumunne OC, Rubin G, et al. Age and gender variations in cancer diagnostic intervals in 15 cancers: analysis of data from the UK clinical practice research datalink. *PLoS One*. 2015;10:e0127717.
29 Zhou Y, van Melle M, Singh H, et al. Quality of the diagnostic process in patients presenting with symptoms suggestive of bladder or kidney cancer: a systematic review. *BMJ Open*. 2019;9:e029143.
30 Muller ME, Daccord C, Taffé P, et al. Prevalence of Birt-Hogg-Dubé syndrome determined through epidemiological data on spontaneous pneumothorax and bayes theorem. *Front Med*. 2021;8:631168. https://doi.org/10.3389/fmed.2021.631168.
31 Al-Shinnag M, Marfan H, Susman R, et al. Birt-Hogg-Dubé syndrome and hereditary leiomyomatosis and renal cell carcinoma syndrome: an effective multidisciplinary approach to hereditary renal cancer predisposing syndromes. *Front Oncol*. 2021;11:738822.
32 Maffé A, Toschi B, Circo G, et al. Constitutional FLCN mutations in patients with suspected Birt-Hogg-Dubé syndrome ascertained for non-cutaneous manifestations. *Clin Genet*. 2011;79:345–354.
33 Benusiglio PR, Giraud S, Deveaux S, et al. Renal cell tumour characteristics in patients with the Birt-Hogg-Dubé cancer susceptibility syndrome: a retrospective, multicentre study. *Orphanet J Rare Dis*. 2014;9:163.
34 Toro JR, Wei MH, Glenn GM, et al. BHD mutations, clinical and molecular genetic investigations of Birt-Hogg-Dubé syndrome: a new series of 50 families and a review of published reports. *J Med Genet*. 2008;45:321–331.
35 Kunogi M, Kurihara M, Ikegami TS, et al. Clinical and genetic spectrum of Birt-Hogg-Dube syndrome patients in whom pneumothorax and/or multiple lung cysts are the presenting feature. *J Med Genet*. 2010;47:281–287.