

CORRESPONDENCE

Open Access



Comment on Balsamo et al.: Birt-Hogg-Dubé syndrome with simultaneous hyperplastic polyposis of the gastrointestinal tract: case report and review of the literature

Irma van de Beek^{1*} , Maurice A. M. van Steensel² and Arjan C. Houweling¹

Abstract

The publication by Balsamo and colleagues describes a patient with Birt-Hogg-Dubé syndrome and hyperplastic polyposis throughout the gastro-intestinal tract. We question whether the diagnosis of BHD in this patient was justified. Using the previously proposed diagnostic criteria for establishing the diagnosis of BHD as a guideline, we systematically describe our concerns. In our opinion, the patient described by Balsamo and colleagues does not meet any of the proposed major and minor criteria for the diagnosis of Birt-Hogg-Dubé syndrome. Therefore, we believe that it is not justified to suggest a possible association between hyperplastic polyposis and Birt-Hogg-Dubé syndrome based on this patient, even though a higher risk for colorectal polyposis in Birt-Hogg-Dubé syndrome has not been excluded so far.

Keywords: Birt-Hogg-Dubé syndrome, Hyperplastic polyposis

Background

Birt-Hogg-Dubé syndrome (BHD, MIM# 135,150) is a rare disorder with autosomal dominant inheritance. It is caused by mutations in the *FLCN* gene [1, 2]. The skin phenotype, consisting of multiple fibrofolliculomas, was first described in the 1970s [3, 4]. Fibrofolliculomas consist of proliferation of specialized connective tissue surrounding an abnormal hair follicle, in which epithelial strands extend out into the connective tissue mantle [5–7]. Subsequently, many case reports described several other features that could be associated with BHD. However, it was not until 2002 that the association of BHD with pneumothorax, lung cysts and renal tumours was confirmed [8]. Specifically in rare genetic diseases, case

reports on associated features are of high importance and might lead to the discovery of additional phenotypic characteristics of the disease which may allow preventive measures or surveillance. It was therefore with considerable interest that we read the publication by Balsamo and colleagues, in which a patient with BHD and hyperplastic polyposis throughout the gastro-intestinal tract was described [9]. We question whether the diagnosis of BHD in this patient was correct given the absence of specific clinical features of BHD and no (likely) pathogenic *FLCN* mutation. Therefore the suggested association between BHD and hyperplastic polyposis might not be justified. Using the previously proposed diagnostic criteria for establishing the diagnosis of BHD as a guideline, we will further elaborate on this subject [10].

*Correspondence: i.beek@amsterdamumc.nl

¹ Department of Human Genetics, Amsterdam UMC, Vrije Universiteit Amsterdam, De Boelelaan 1117, Amsterdam, The Netherlands
Full list of author information is available at the end of the article



© The Author(s) 2022. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

FLCN pathogenic variants

The identification of a pathogenic variant in the *FLCN* gene is sufficient to establish the diagnosis of BHD. *FLCN* sequencing was performed in the patient described by Balsamo and colleagues but revealed no (likely) pathogenic mutation. As far as we can discern, no analysis for large intragenic deletions or duplications (such as MLPA) was performed, even though these have been reported in BHD patients [11, 12]. An intronic variant was detected (c.1538+14 T>G), but this variant was classified as likely benign by the authors and therefore cannot be of use in the diagnosis of BHD in this patient. The variant is present in 2.4% of African healthy control alleles and can therefore likely be classified as non-pathogenic [13]. However, the lack of a mutation in *FLCN* does not completely exclude BHD. Pathogenic variants in *FLCN* are detected in up to 95% of patients with a clinical diagnosis of BHD based on the literature and our own experience [12, 14, 15]. The remaining patients might represent cases of BHD due to a currently unidentifiable variant in *FLCN*, for example a deep intronic one or a variant in a regulatory sequence of *FLCN*. In some families previously described as having BHD, another diagnosis can now be established, for example familial multiple discoid fibromas [16].

Fibrofolliculomas

The presence of fibrofolliculomas is considered pathognomonic for BHD. One of the proposed criteria for diagnosing BHD is the presence of at least five fibrofolliculomas or trichodiscomas, of which at least one is histologically confirmed [10]. Of note, fibrofolliculomas and trichodiscomas in BHD are considered to be different histologic aspects of the same lesion as seen at different section levels, while trichodiscomas without the typical histological features of fibrofolliculomas have been described in individuals with familial multiple discoid fibromas [6, 16]. Balsamo and colleagues describe that their patient had skin lesions which were considered trichodiscomas at anatomopathological examination. However, the histological image in Fig. 1 in the paper is showing a fibroepithelial polyp without the typical characteristics of a trichodiscoma or fibrofolliculoma. Fibroepithelial polyps (also called skin tags or acrochordons) are very common in the general population [17]. If this image is representative for all the skin lesions of the patient, his skin lesions are, in our opinion, not consistent with the diagnosis of BHD. If the patient did actually have multiple trichodiscomas which are not shown in the original paper, the diagnosis of BHD should be considered, as well as the alternative diagnosis of familial multiple discoid fibromas.

Minor criteria

The proposed diagnostic criteria describe minor criteria of which two are required for the clinical BHD diagnosis: (1) multiple lung cysts, (2) renal cancer with early onset, multifocal, bilateral or specific histology and (3) a first-degree relative with BHD [10]. The patient described by Balsamo and colleagues has no family history of BHD and no lung cysts. He has two renal masses showing features suggestive of angiomyolipoma (AML) on MRI. Renal AMLs are not uncommon in the general population and most occur sporadically. For example, they have been detected in 0.13% of healthy adults and 2.2% of potential kidney donors [18, 19]. Renal AMLs are much more common in patients with tuberous sclerosis complex, which is caused by germline mutations in *TSC1* and *TSC2* [20, 21]. Several case reports have described AMLs in patients with BHD [22–25]. The involvement of both *TSC1/2* and *FLCN* in the mTOR pathway, might be a reason to suspect a causal connection between BHD and AMLs. This has, however, not been recognized in larger studies on renal tumours in BHD patients [26–29]. Furthermore, while there is a clear activation of mTOR upon loss of *TSC1* or *TSC2*, the effects of loss of *FLCN* on mTOR are dependent on the context and cell-type [30, 31]. In one of the case reports of a BHD patient with an AML, the authors show that the AML is likely sporadic, as a result of somatic loss of the *TSC* genes [25]. Altogether, the case reports more likely represent a coincidental co-occurrence of AML and BHD.

Hyperplastic polyposis

Hyperplastic polyposis (more recently referred to as serrated polyposis syndrome (SPS)) presents with multiple and/or large serrated polyps throughout the colon. Although *RNF43* germline mutations have been shown in a small proportion of (familial) cases of SPS [32–36], most cases of SPS occur sporadically and seem to have a multifactorial cause since both environmental and genetic risk factors have been shown to play a role [37, 38]. The association between BHD and colorectal polyps and/or carcinoma has been unclear for a long time. In a recent study, we did not find evidence for an increased risk for colorectal carcinoma in BHD. Furthermore, the ratio between adenomatous and hyperplastic polyps in BHD patients was comparable to that in individuals without BHD [39]. Other cohort studies also did not recognize hyperplastic polyposis as an important feature of BHD [8, 12, 27]. Therefore, an association between hyperplastic polyposis and BHD seems unlikely, but cannot be excluded.

Other medical history

Although some of the other conditions in the patient described by Balsamo et al. have been reported in BHD, an association between these features and BHD has not been confirmed in larger groups and they are not useful in establishing BHD.

Conclusion

In our opinion, Balsamo and colleagues have not provided information that is enough for establishing the diagnosis of BHD in their patient. In fact, none of the proposed clinical major and minor criteria are met. Therefore, we believe that it is not justified to suggest a possible association between hyperplastic polyposis and BHD based on the provided information about this patient. If the patient would meet the diagnostic criteria for BHD based on data not yet provided, the co-occurrence of BHD and hyperplastic polyposis might still be co-incidental but could give rise to further studies.

Abbreviations

AML: Angiomyolipoma; BHD: Birt-Hogg-Dubé syndrome; SPS: Serrated polyposis syndrome.

Acknowledgements

Not applicable.

Author contributions

Drafting the manuscript: IvdB, ACH. Critical revision and interpretation of histology data: MAMS. All authors read and approved the manuscript.

Funding

Not applicable.

Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no conflict of interest.

Author details

¹Department of Human Genetics, Amsterdam UMC, Vrije Universiteit Amsterdam, De Boelelaan 1117, Amsterdam, The Netherlands. ²Lee Kong Chian School of Medicine, Nanyang Technological University, 50 Nanyang Avenue/ Singapore Skin Research Institute of Singapore, Agency for Science, Technology and Research, 11 Mandalay Road, Singapore, Singapore.

Received: 2 November 2020 Accepted: 1 April 2022

Published online: 15 April 2022

References

- Nickerson ML, Warren MB, Toro JR, Matrosova V, Glenn G, Turner ML, 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-Dube syndrome. *Cancer Cell*. 2002;2(2):157–64.
- Khoo SK, Bradley M, Wong FK, Hedblad MA, Nordenskjold M, Teh BT. Birt-Hogg-Dube syndrome: mapping of a novel hereditary neoplasia gene to chromosome 17p12-q11.2. *Oncogene*. 2001;20(37):5239–42.
- Birt AR, Hogg GR, Dube WJ. Hereditary multiple fibrofolliculomas with trichodiscomas and acrochordons. *Arch Dermatol*. 1977;113(12):1674–7.
- Hornstein OP, Knickenberg M. Perifollicular fibromatosis cutis with polyps of the colon—a cutaneo-intestinal syndrome sui generis. *Arch Dermatol Res*. 1975;253(2):161–75.
- Vincent A, Farley M, Chan E, James WD. Birt-Hogg-Dube syndrome: a review of the literature and the differential diagnosis of firm facial papules. *J Am Acad Dermatol*. 2003;49(4):698–705.
- Schulz T, Hartschuh W. Birt-Hogg-Dube syndrome and Hornstein-Knickenberg syndrome are the same. Different sectioning technique as the cause of different histology. *J Cutan Pathol*. 1999;26(1):55–61.
- Collins GL, Somach S, Morgan MB. Histomorphologic and immunophenotypic analysis of fibrofolliculomas and trichodiscomas in Birt-Hogg-Dube syndrome and sporadic disease. *J Cutan Pathol*. 2002;29(9):529–33.
- Zbar B, Alvord WG, Glenn G, Turner M, Pavlovich CP, Schmidt L, et al. Risk of renal and colonic neoplasms and spontaneous pneumothorax in the Birt-Hogg-Dube syndrome. *Cancer Epidemiol Biomarkers Prev*. 2002;11(4):393–400.
- Balsamo F, Cardoso PAS, do Amaral J unior SA, Theodoro TR, de Sousa Gehrke F, da Silva Pinhal MA et al. Birt-Hogg-Dube syndrome with simultaneous hyperplastic polyposis of the gastrointestinal tract: case report and review of the literature. *BMC Med Genet*. 2020; 21(1):52.
- Menko FH, van Steensel MA, Giraud S, Friis-Hansen L, Richard S, Ungari S, et al. Birt-Hogg-Dube syndrome: diagnosis and management. *Lancet Oncol*. 2009;10(12):1199–206.
- Benhammou JN, Vocke CD, Santani A, Schmidt LS, Baba M, Seyama K, et al. Identification of intragenic deletions and duplication in the FLCN gene in Birt-Hogg-Dube syndrome. *Genes Chromosomes Cancer*. 2011;50(6):466–77.
- Houweling AC, Gijzen LM, Jonker MA, van Doorn MB, Oldenburg RA, van Spaendonck-Zwarts KY, et al. Renal cancer and pneumothorax risk in Birt-Hogg-Dube syndrome; an analysis of 115 FLCN mutation carriers from 35 BHD families. *Br J Cancer*. 2011;105(12):1912–9.
- Karczewski KJ, Francioli LC, Tiao G, Cummings BB, Alfoldi J, Wang Q et al. The mutational constraint spectrum quantified from variation in 141,456 humans. *bioRxiv*. 2020:531210.
- Toro JR, Wei MH, Glenn GM, Weinreich M, Toure O, Vocke C, et al. BHD mutations, clinical and molecular genetic investigations of Birt-Hogg-Dube syndrome: a new series of 50 families and a review of published reports. *J Med Genet*. 2008;45(6):321–31.
- Schmidt LS, Nickerson ML, Warren MB, Glenn GM, Toro JR, Merino MJ, et al. Germline BHD-mutation spectrum and phenotype analysis of a large cohort of families with Birt-Hogg-Dube syndrome. *Am J Hum Genet*. 2005;76(6):1023–33.
- Starink TM, Houweling AC, van Doorn MB, Leter EM, Jaspars EH, van Moorselaar RJ, et al. Familial multiple discoid fibromas: a look-alike of Birt-Hogg-Dube syndrome not linked to the FLCN locus. *J Am Acad Dermatol*. 2012;66(2):259.
- Banik R, Lubach D. Skin tags: localization and frequencies according to sex and age. *Dermatologica*. 1987;174(4):180–3.
- Rule AD, Sasiwimonphan K, Lieske JC, Keddiss MT, Torres VE, Vrtiska TJ. Characteristics of renal cystic and solid lesions based on contrast-enhanced computed tomography of potential kidney donors. *Am J Kidney Dis*. 2012;59(5):611–8.
- Fujii Y, Ajima J, Oka K, Tosaka A, Takehara Y. Benign renal tumors detected among healthy adults by abdominal ultrasonography. *Eur Urol*. 1995;27(2):124–7.
- Au KS, Williams AT, Roach ES, Batchelor L, Sparagana SP, Delgado MR, et al. Genotype/phenotype correlation in 325 individuals referred for a diagnosis of tuberous sclerosis complex in the United States. *Genet Med*. 2007;9(2):88–100.
- Sancak O, Nellist M, Goedbloed M, Elfferich P, Wouters C, Maat-Kievit A, et al. Mutational analysis of the TSC1 and TSC2 genes in a diagnostic

- setting: genotype–phenotype correlations and comparison of diagnostic DNA techniques in Tuberous Sclerosis Complex. *Eur J Hum Genet.* 2005;13(6):731–41.
22. Dow E, Winship I. Renal angiomyolipoma in Birt-Hogg-Dube syndrome: A case study supporting overlap with tuberous sclerosis complex. *Am J Med Genet A.* 2016;170(12):3323–6.
 23. Tobino K, Seyama K. Birt-Hogg-Dube syndrome with renal angiomyolipoma. *Intern Med.* 2012;51(10):1279–80.
 24. Byrne M, Mallipeddi R, Pichert G, Whittaker S. Birt-Hogg-Dube syndrome with a renal angiomyolipoma: further evidence of a relationship between Birt-Hogg-Dube syndrome and tuberous sclerosis complex. *Australas J Dermatol.* 2012;53(2):151–4.
 25. Sager RA, Woodford MR, Shapiro O, Mollapour M, Bratslavsky G. Sporadic renal angiomyolipoma in a patient with Birt-Hogg-Dube: chaperones in pathogenesis. *Oncotarget.* 2018;9(31):22220–9.
 26. Sattler EC, Reithmair M, Steinlein OK. Kidney cancer characteristics and genotype-phenotype-correlations in Birt-Hogg-Dube syndrome. *PLoS One.* 2018; 13(12):e0209504.
 27. Furuya M, Yao M, Tanaka R, Nagashima Y, Kuroda N, Hasumi H, et al. Genetic, epidemiologic and clinicopathologic studies of Japanese Asian patients with Birt-Hogg-Dube syndrome. *Clin Genet.* 2016;90(5):403–12.
 28. Benusiglio PR, Giraud S, Deveaux S, Mejean A, Correas JM, Joly D, et al. Renal cell tumour characteristics in patients with the Birt-Hogg-Dube cancer susceptibility syndrome: a retrospective, multicentre study. *Orphanet J Rare Dis.* 2014;9:163.
 29. Johannesma PC, van de Beek I, van der Wel T, Reinhard R, Rozendaal L, Starink TM et al. Renal imaging in 199 Dutch patients with Birt-Hogg-Dube syndrome: Screening compliance and outcome. *PLoS One.* 2019; 14(3):e0212952.
 30. Khabibullin D, Medvetz DA, Pinilla M, Hariharan V, Li C, Hergueter A et al. Folliculin regulates cell-cell adhesion, AMPK, and mTORC1 in a cell-type-specific manner in lung-derived cells. *Physiol Rep.* 2014; 2(8).
 31. Inoki K, Li Y, Zhu T, Wu J, Guan KL. TSC2 is phosphorylated and inhibited by Akt and suppresses mTOR signalling. *Nat Cell Biol.* 2002;4(9):648–57.
 32. Buchanan DD, Clendenning M, Zhuoer L, Stewart JR, Joseland S, Woodall S, et al. Lack of evidence for germline RNF43 mutations in patients with serrated polyposis syndrome from a large multinational study. *Gut.* 2017;66(6):1170–2.
 33. Gala MK, Mizukami Y, Le LP, Moriichi K, Austin T, Yamamoto M, et al. Germline mutations in oncogene-induced senescence pathways are associated with multiple sessile serrated adenomas. *Gastroenterology.* 2014;146(2):520–9.
 34. Quintana I, Mejias-Luque R, Terradas M, Navarro M, Pinol V, Mur P, et al. Evidence suggests that germline RNF43 mutations are a rare cause of serrated polyposis. *Gut.* 2018;67(12):2230–2.
 35. Taupin D, Lam W, Rangiah D, McCallum L, Whittle B, Zhang Y, et al. A deleterious RNF43 germline mutation in a severely affected serrated polyposis kindred. *Hum Genome Var.* 2015;2:15013.
 36. Yan HHN, Lai JCW, Ho SL, Leung WK, Law WL, Lee JFY, et al. RNF43 germline and somatic mutation in serrated neoplasia pathway and its association with BRAF mutation. *Gut.* 2017;66(9):1645–56.
 37. JE IJ, Bossuyt PM, Kuipers EJ, Stegeman I, de Wijkerslooth TR, Stoop EM et al. Smoking status informs about the risk of advanced serrated polyps in a screening population. *Endosc Int Open.* 2016; 4(1):E73–78.
 38. Arnau-Collell C, Soares de Lima Y, Diaz-Gay M, Munoz J, Carballal S, Bonjoch L et al. Colorectal cancer genetic variants are also associated with serrated polyposis syndrome susceptibility. *J Med Genet.* 2020.
 39. van de Beek I, Glykofridis IE, Wolthuis RMF, Gille H, Johannesma PC, Meijers-Heijboer HEJ, et al. No evidence for increased prevalence of colorectal carcinoma in 399 Dutch patients with Birt-Hogg-Dube syndrome. *Br J Cancer.* 2020;122(4):590–4.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

