J Cancer Immunol. 2024;6(4):169-171.

Journal of Cancer Immunology Commentary

Beyond the Mutation: A Closer Look at Birt-Hogg-Dubé Syndrome

Alamin Alkundi[1,*], **Basma Bakhiet**[1,*]

[1]Department of Diabetes and Endocrinology, East Kent Hospitals University NHS Foundation Trust, UK

[*]Correspondence should be addressed to Alamin Alkundi, dr.alkundi@gmail.com

Received date: September 15, 2024, **Accepted date:** October 28, 2024

Citation: Alkundi A, Bakhiet B. Beyond the Mutation: A Closer Look at Birt-Hogg-Dubé Syndrome. J Cancer Immunol. 2024;6(4):169-171.

Introduction

This commentary aims to delve into the diagnostic challenges associated with Birt-Hogg-Dubé (BHD) syndrome, as outlined in the BMJ case report titled "A Case of Phaeochromocytoma in a Female Patient with Phenotypical Expressions for the Rare Birt-Hogg-Dubé (BHD) Syndrome" (doi:10.1136/bcr-2022-252362) [1]. BHD syndrome is a rare genetic disorder that is inherited in an autosomal dominant manner and is caused by mutations in the *FLCN* gene on chromosome 17. Affected individuals show a range of clinical signs and symptoms that can vary by the age of presentation [12].

According to Menko *et al.* diagnosis of Birt-Hogg-Dubé syndrome (BHDS) is confirmed in an individual who meets either one major criterion—such as having five or more facial or truncal papules, with at least one histologically confirmed fibrofolliculoma, or identification of a heterozygous pathogenic variant in the *FLCN* gene—or two minor criteria. Importantly, negative *FLCN* gene testing does not rule out the diagnosis, as up to 40% of patients with negative results still fulfill the diagnostic criteria. Minor criteria include early-onset renal cell cancer (before age 50), multifocal or bilateral renal cell cancer, renal cell cancer with mixed chromophobe and oncocytic histology, multiple lung cysts (with or without spontaneous pneumothorax), and/or a first-degree relative with BHDS [9].

Additionally, patients with BHD syndrome may exhibit a range of cutaneous manifestations, including connective tissue nevi, lipomas, angiolipomas, acrochordons, and facial angiofibromas. Systemic features such as medullary thyroid cancer, thyroid adenomas, parathyroid adenomas, and parotid oncocytomas have also been reported in individuals with BHD. A recent systematic review by Peraza Labrador *et al.* [13] analyzed 16 BHD cases from publications between 1977 and 2023, focusing on the prevalence of oral lesions. The study found that 47.8% of patients had oral lesions, including soft papules on the lips, gingiva, and buccal mucosa [14].

The genetic basis of BHD syndrome lies in mutations in the *FLCN* gene, which encodes the tumor suppressor protein folliculin. This protein plays a crucial role in various cellular processes, including cell growth, metabolism, and stress response pathways [2].

Despite the known association between *FLCN* mutations and BHD syndrome, as the BMJ case report highlights, diagnosis can be challenging when genetic testing fails to identify pathogenic mutations. This emphasizes the need for a comprehensive diagnostic approach that combines clinical, radiological, and biochemical markers to reach a diagnosis, even in the absence of definitive genetic evidence.

The Case Report

The BMJ case report in question focuses on a female patient in her 50s who presented with recurrent bilateral flank pain, notable skin lesions, recurrent episodic high blood pressure, anxiety, diaphoresis, and headaches. These symptoms initially led the healthcare team to consider a wide range of potential differential diagnoses. Radiological studies revealed that the patient had bilateral renal cysts and a right adrenal cyst. Both renal and adrenal cysts are relatively common findings in individuals with BHD syndrome, further raising the suspicion of this rare genetic disorder in this patient.

To clarify the diagnosis, genetic testing was conducted to investigate a potential link to BHD syndrome. Although no pathological mutations were found in the *FLCN* gene, a provisional diagnosis of BHD syndrome was made based on the patient's clinical features.

Notably, the discovery of a pheochromocytoma in the biopsy of the right adrenal cyst complicated the case, as this condition is not typically associated with BHD syndrome. With limited evidence linking these two conditions in medical literature, this raises important questions about the broader clinical spectrum of BHD syndrome and whether it might include manifestations beyond those traditionally recognized.

The Challenges of Diagnosing BHD Syndrome

Birt-Hogg-Dubé (BHD) syndrome, presents a significant diagnostic challenge due to its diverse clinical manifestations and potential for overlap with other conditions. The primary difficulties in diagnosing BHD stem from the variable penetrance of the *FLCN* gene [3], the subtle or asymptomatic nature of early-stage manifestations, and the potential for misdiagnosis.

While bilateral renal cysts and skin lesions (such as fibrofolliculomas) are hallmark features of BHD syndrome, the disorder can also involve pulmonary cysts and an increased risk of spontaneous pneumothorax.

However, there are a few published cases that describe additional organ pathologies potentially linked to BHD syndrome, which fall outside the standard diagnostic criteria used to identify the disease.

For instance, Renfree and Lawless [4] reported a young woman with BHD syndrome who developed multiple neurilemmomas. Similarly, Lindor *et al.* [5] documented a case involving bilateral parotid gland tumors in a patient with skin changes and bilateral basal lung cysts. A more recent report by Lin *et al.* [6] described a rare case of BHD and Sjogren Syndrome in a Chinese man in his 50s, who presented with symptoms of dry mouth, dry eyes, multiple tooth caries, increased thirst, and suspected fibrofolliculoma lesions. A chest CT revealed bilateral cystic lung lesions, and genetic testing confirmed the diagnosis of both disorders.

This brings us to another key challenge in diagnosing BHD syndrome: the reliance on the presence of *FLCN* mutations, which are not always detectable. The absence of these mutations, despite a clinical presentation consistent with BHD syndrome, poses a significant diagnostic challenge and hinders the development of standardized screening tests for these individuals.

The *FLCN* gene, located on chromosome 17p11.2, encodes the folliculin protein, which is involved in regulating cell growth, metabolism, and stress responses. Mutations in *FLCN* disrupt these processes, leading to the formation of cysts, tumors, and skin lesions characteristic of BHD syndrome [3].

Researchers have identified a variety of mutations associated with BHD syndrome, including nonsense mutations, missense mutations, and small deletions. These mutations impair folliculin's ability to function normally, contributing to the clinical features of the disease.

In recent years, researchers have been investigating *FLCN*'s role in BHD syndrome, though the exact mechanisms by which *FLCN* dysregulation leads to the syndrome's diverse manifestations remain unclear.

Ongoing studies are illuminating the cellular pathways that FLCN interacts with, and it is anticipated that further discoveries of related pathways will be made. These insights may lead to a deeper understanding of BHD syndrome's pathophysiology and possibly pave the way for the development of targeted therapies in the future.

The Role of *FLCN*-Negative BHD Syndrome

Since the publication of this case report, additional research has emerged recently on *FLCN*-negative BHD syndrome. The case by Dwikat *et al*. [7] described a patient with clinical features of BHD syndrome but no detectable *FLCN* mutation. It also referenced earlier work by Enomoto *et al.* [8] which described a man with clinical features suggestive of BHD syndrome, but genetic testing of the patient and his family revealed a large genomic deletion in the *FLCN* gene, undetectable by standard sequencing methods. Further analysis confirmed the absence of *FLCN* expression, suggesting that quantitative loss of the gene product, rather than a mutation detectable by sequencing, may be responsible for the syndrome.

This case serves as a reminder that clinicians may need to rely more heavily on clinical and radiological criteria to make a diagnosis. It highlights several diagnostic criteria have been established for diagnosing *FLCN*-negative BHD syndrome, including those developed by Schmidt *et al.*, Menko *et al.*, and Gupta *et al.* [9,10,3], which emphasize the importance of integrating clinical and radiological findings with genetic data.

Extra-Renal Manifestations and the Expanding Clinical Spectrum of BHD

While the renal and pulmonary manifestations of BHD syndrome are well-documented, there is increasing evidence to suggest that the clinical spectrum of the disease may be broader than initially thought. There is growing recognition that BHD syndrome may be associated with extra-renal tumors and lesions. However, these manifestations are still poorly represented in the medical literature, and there is limited understanding of their frequency and clinical significance. Most reports of extra-renal manifestations in BHD syndrome focus on pulmonary cysts and cutaneous fibrofolliculomas, which are the most common systemic features seen in affected individuals [1].

A more recent report published in 2024 describes a case of a primary extra-renal oncocytic epithelial neoplasm associated with BHD syndrome [11]. This tumor developed between

the duodenum and the head of the pancreas, an unusual location for a BHD-associated lesion. Immunohistochemical and molecular analysis revealed that the tumor was driven by *FLCN* loss.

Could there be a broader association between *FLCN* loss and other diverse manifestations of BHD syndrome, or is this merely a coincidence? Understanding whether *FLCN* loss plays a more widespread role in the syndrome's varied presentations could have significant implications for both diagnosis and treatment. It may be that some manifestations of BHD syndrome are currently under-recognized or misattributed to other conditions.

Conclusion: Integrating Genetic and Clinical Data for Better Outcomes

The BMJ case report serves as a valuable contribution to the literature on BHD syndrome, providing insight into the challenges of diagnosing this rare and complex disorder. Despite advances in genetic testing and our growing understanding of the molecular basis of BHD syndrome, there remain significant diagnostic challenges, particularly in cases where genetic testing does not reveal the expected *FLCN* mutations.

A comprehensive approach that incorporates clinical, radiological, and biochemical markers is essential for accurate diagnosis. As research continues to unravel the molecular mechanisms underlying BHD syndrome, new diagnostic tools and therapies may emerge to improve outcomes for affected individuals.

Beyond the well-documented renal and pulmonary manifestations, BHD syndrome has been associated with a broader range of organ involvement. Further investigation is needed to better understand the clinical significance of these associations and to identify potential targets for treatment.

References

1. Alkundi A, Momoh R. Phaeochromocytoma in a patient with a Birt-Hogg-Dubé syndrome phenotype. BMJ Case Rep. 2023 Mar 30;16(3):e252362.
2. Reese E, Sluzevich J, Kluijt I, Teertstra HJ, De Jong D, Horenblas S, et al. Birt-Hogg-Dubé Syndrome. In: Riegert-Johnson DL, Boardman LA, Hefferon T, Roberts M, editors. Cancer Syndromes. Bethesda (MD): National Center for Biotechnology Information (US); 2009.
3. Schmidt LS, Linehan WM. FLCN: The causative gene for Birt-Hogg-Dubé syndrome. Gene. 2018 Jan 15;640:28-42.
4. Renfree KJ, Lawless KL. Multiple neurilemmomas in Birt-Hogg-Dubé syndrome: case report. J Hand Surg Am. 2012 Apr;37(4):792-4.
5. Lindor NM, Kasperbauer J, Lewis JE, Pittelkow M. Birt-Hogg-Dube syndrome presenting as multiple oncocytic parotid tumors. Hered Cancer Clin Pract. 2012 Oct 10;10(1):13.
6. Lin Y, Guo T, Lei C, Yang B, Yang D, Luo H, et al. Coexistent Sjogren's syndrome and Birt-Hogg-Dube´ syndrome: a case report. BMC Pulm Med. 2023 Nov 22;23(1):460.
7. Dwikat MF, Azar J, Rabayah R, Salameh R, Abdeljaleel F, Almadhoun W, et al. Folliculin gene-negative Birt-Hogg-Dube syndrome: a case report. Ann Med Surg (Lond). 2024 Jan 3;86(2):1055-60.
8. Enomoto Y, Namba Y, Hoshika Y, Komemushi Y, Mitani K, Kume H, et al. A case of Birt-Hogg-Dubé syndrome implying reduced or no wild-type folliculin without mutated protein is pathogenic. Eur J Med Genet. 2020 Apr;63(4):103820.
9. Menko FH, van Steensel MA, Giraud S, Friis-Hansen L, Richard S, Ungari S, et al. European BHD Consortium. Birt-Hogg-Dubé syndrome: diagnosis and management. Lancet Oncol. 2009 Dec;10(12):1199-206.
10. Gupta N, Seyama K, McCormack FX. Pulmonary manifestations of Birt-Hogg-Dubé syndrome. Fam Cancer. 2013 Sep;12(3):387-96.
11. Baraban E, Fishman EK, Lafaro K, Lin MT, Ged Y, Hruban RH, et al. A Confirmed Extrarenal Birt-Hogg-Dubé-Associated Oncocytic Neoplasm. Am J Surg Pathol. 2024 Sep 2.
12. Steinlein OK, Ertl-Wagner B, Ruzicka T, Sattler EC. Birt-Hogg-Dubé syndrome: an underdiagnosed genetic tumor syndrome. J Dtsch Dermatol Ges. 2018 Mar;16(3):278-83.
13. Peraza Labrador A, Umorin M, Shrestha M, Abad Villacrez C, Wright J. A Possible Association of Salivary Gland Tumors and Oral Lesions with Birt-Hogg-Dube Syndrome: A Systematic Review. Head Neck Pathol. 2024 Jun 19;18(1):52.
14. Crane JS, Rutt V, Oakley AM. Birt-Hogg-Dube Syndrome. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan.