Commentary

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The Birt-Hogg-Dubé cancer predisposition syndrome: Current challenges

Patrick R. Benusiglio[1,2,*]

[1] *Centre Expert National Cancers Rares PREDIR INCa, Hôpital Bicêtre AP-HP, Le Kremlin Bicêtre, France;*
[2] *Département de Médecine Oncologique, Consultation d'Oncogénétique, Gustave Roussy Cancer Campus, Villejuif, France.*

Summary **Birt-Hogg-Dubé is a rare syndrome in which carriers of germline mutations in the *FLCN* tumor suppressor gene are at risk of renal cell carcinoma of all histologies, most often of the chromophobe or hybrid chromophobe-oncocytoma type. Non-oncological manifestations such as lung cysts, pneumothoraces and skin fibrofolliculomas are also common. How germline mutations in a single gene can cause such different clinical features is intriguing and not fully explained, but involvement of the mTOR (renal cell carcinomas, lung cysts) and WNT (fibrofolliculomas) pathways has been described. Given the rarity of the condition, frequent exchanges of ideas between expert teams from around the world, multicentre international collaborations, and interactions between patients and researchers are essential. These needs are fulfilled through dedicated international symposia held every one to two years and through online resources aimed at patients and relatives.**

Keywords: Birt-Hogg-Dubé, fibrofolliculoma, hereditary neoplastic syndromes, pneumothorax, renal cell carcinoma

Birt-Hogg-Dubé (BHD) is a rare syndrome in which carriers of germline mutations in the *FLCN* gene are at risk of renal cell carcinoma (RCC) of all histologies, but most often of the chromophobe or hybrid chromophobe-oncocytoma type (*1,2*). Transmission is dominant. What is particularly interesting about this cancer predisposition syndrome is its association with non-oncological manifestations, more specifically lung cysts that often spare the apexes, spontaneous pneumothoraces and dome-shaped whitish skin lesions of the face and upper torso called fibrofolliculomas.

How germline mutations in a single gene can cause such different clinical features is intriguing and not fully explained. *FLCN* is a tumour suppressor gene, and gene inactivation follows the classic "two hit" model. BHD patients already have a germline mutation, and therefore a second somatic event is enough to initiate tumorigenesis (*e.g.* loss of heterozygozity, mutation, methylation). In the kidney, *FLCN* exerts its anti-tumour activity mainly by modulating the mTOR pathway (*3*). There are however conflicting data regarding the precise consequences of an inactivated FLCN protein, as both mTOR up- and down-regulation have been reported. Epithelial cells lining pulmonary cysts have no neoplastic or atypical characteristics but, like in kidney cancer cells, mTOR involvement is likely (*4*). Indeed, immunostaining studies suggest activation of the pathway and of its downstream effectors. As for cutaneous manifestations, fibrofolliculomas can be described as benign epithelial tumours of the hair follicles that could be caused by WNT pathway activation in neighbouring fibroblasts (*5*).

BHD illustrates the difficulties encountered with other rare diseases as awareness of the syndrome is limited, even among specialists involved in the management of associated clinical manifestations (*e.g.* urologists, oncologists, pulmonologists). As a result, the syndrome is often overlooked, patients are not referred to genetics clinics as often as they should and *FLCN* analysis is not performed. Underdiagnosing BHD in an index case and subsequently in his at-risk relatives can

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**Address correspondence to:*
Dr. Patrick R. Benusiglio, Centre Expert National Cancers Rares PREDIR INCa, Hôpital Bicêtre AP-HP, 94275 Le Kremlin Bicêtre, France; Département de Médecine Oncologique, Consultation d'Oncogénétique, Gustave Roussy Cancer Campus, 94805 Villejuif, France.
E-mail: pbenusiglio.wk@gmail.com or patrick.benusiglio@gustaveroussy.fr

have damaging medical consequences, in particular with respect to RCC risk. Up to 34% of patients with BHD develop RCC (*6*), and regular screening with abdominal imaging is therefore essential (*1*).

Given the rarity of the condition, frequent exchanges of ideas between expert teams from around the world and multicentre international collaborations are essential. Every one to two years, scientists and clinicians working on BHD convene for an international symposium where they present and discuss the latest developements on the topic, start national and international collaborations, and review the available data in order to establish international guidelines or write state-of-the-art review articles. For example, a special issue on BHD adressing all the molecular and clinical aspects of the syndrome was published in Familial Cancer after the fourth BHD Symposium that took place in 2012 in Cincinatti, Ohio (*7*). The last symposium was held in Paris in June 2013, and from a French perspective it proved to be the springboard for a large national study on RCC characteristics associated with BHD (*8*). The next one will take place in Syracusae, New York State in September 2015, and will put an emphasis on drug development and therapeutics, and on the intra-operative management of patients with multi-focal RCC (*http://www.upstate.edu/urology/conference/index.php*). Sessions dedicated to patients are an essential component of these symposia, and a welcome opportunity to interact with physicians, surgeons, bench scientists and other affected individuals in an informal way. However, only a minority of patients have the chance to travel to these meetings, and alternative means of accessing reliable and up to date information are fundamental. Some online resources fulfil this need remarkably, and I would encourage all those interested in BHD, professionals and patients alike, to visit the BHD foundation website (*http://www.bhdsyndrome.org*).

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