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Author/s:

Dow, E;Winship, I

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Renal Angiomyolipoma in Birt-Hogg-Dube Syndrome:

A Case Study Supporting Overlap with Tuberous Sclerosis Complex

Eryn Dow<sup>1</sup>, Ingrid Winship<sup>1,2</sup>

<sup>1</sup>Genetic Medicine and Family Cancer Clinic, Royal Melbourne Hospital, Melbourne, Victoria, Australia

<sup>2</sup> Department of Medicine, University of Melbourne, Parkville, Victoria, Australia

Running Heads: Dow, Winship - Angiomyolipoma in BHD Supports TSC Overlap

Corresponding Author: Eryn Dow (eryn.dow@mh.org.au), Familial Cancer Centre, Department of Genetic Medicine, Level 2 Centre, The Royal Melbourne Hospital, Grattan St, Parkville, Victoria 2050, Australia, Ph +61 3 9342 7151, Fax +61 3 9342 4267

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## ABSTRACT

Birt-Hogg-Dube Syndrome (BHD) is an autosomal dominant disease characterised by benign cutaneous lesions, pulmonary cysts and an increased risk of renal tumors. This rare condition is due to a mutation in the folliculin (*FLCN*) gene on chromosome 17q11.2, which has a role in the mechanistic/mammalian target of rapamycin (mTOR) signalling pathway of tumorigenesis. This case illustrates a patient with BHD and a renal angiomyolipoma, a neoplastic lesion not usually associated with BHD but common in Tuberous Sclerosis Complex (TSC). There is both clinical and molecular overlap between BHD and TSC which may arise from similarities in function of the TSC and FLCN proteins in the mTOR pathway; this case further demonstrates this potential correlation.

KEYWORDS: Renal Angiomyolipoma, Birt-Hogg-Dube Syndrome, Tuberous Sclerosis Complex, mTOR

## INTRODUCTION

Birt-Hogg-Dube Syndrome (BHD) is a rare autosomal dominant disease caused by a mutation in the folliculin (*FLCN*) gene on chromosome 17q11.2. The disease is characterised by benign cutaneous lesions including fibrofolliculomas, trichodiscomas and acrochordons [Byrne et al., 2012]. Systemically the disease manifests as pulmonary cysts which can rupture spontaneously or during depressurised activities, resulting in pneumothorax [Toro et al., 2008]. Birt-Hogg-Dube Syndrome results in an increased risk of developing both malignant and benign renal tumors, likely secondary to the inhibitory role the folliculin protein complex plays in the mechanistic/mammalian target of rapamycin (mTOR) signaling pathway [Misago and Narisawa, 2009]. Renal angiomyolipomas (AML) are not generally associated with BHD but are a characteristic feature of Tuberous Sclerosis Complex (TSC). Emerging evidence supports the clinical overlap between BHD and TSC; at the molecular level this overlap may be due to similarities in function of the *FLCN* and *TSC* genes and proteins in the mTOR pathway [Byrne et al., 2012].

### **CLINICAL REPORT**

A 47 year old man presented for predictive genetic testing after his sister was diagnosed with BHD; her diagnosis followed genetic testing precipitated by biopsy proven fibrofolliculomas of the face and neck at the age of 48 years. The patient also has facial, neck and torso skin papules consistent with fibrofolliculomas and a history of spontaneous pneumothorax requiring pleurodesis. Despite having been a scuba diver, his sister had no history of pneumothorax; she had no renal lesions identified on imaging at the time of diagnosis. There is no known family history of renal malignancy. Their father is the only other family member with fibrofolliculomas; he had neither pulmonary nor renal complications at the time of diagnosis. There are no clinical features of TSC in the examined family members.

Following genetic counselling, the familial heterozygous gene mutation in exon 9 (NM\_144997.5(FLCN):c.890\_893del/p.Glu297Alafs\*25) identified in his sister, was confirmed in the patient and their father. This mutation, a causative frameshift and downstream nonsense mutation [Woodward et al., 2008], has been previously reported in the literature in three families. The mutation was first identified in a patient with young onset renal cancer (25 years) and pulmonary cysts [Woodward et al., 2008], again in a families with a history of multiple cancers (stomach, colon, breast and parotid gland) [Palmirotta et al., 2008], and most recently in a family with pulmonary cysts, pneumothoracies, renal cysts, thyroid nodules as well as colonic polyps [Kluger et al., 2010]. Computerized tomography (CT) scans of the patient's chest demonstrated multiple bullae and surveillance magnetic resonance imaging (MRI) of the kidneys demonstrated a 12mm simple cyst and a 6mm renal AML. The AML was stable on serial MRI surveillance over a period of three years, was characteristically non-contrast enhancing and demonstrated subtle signal drop out on opposed phase imaging [Patel et al., 2005] (Figure 1); the lesion has therefore has not been biopsied. Ultrasound could not visualise the small lesion. The patient continues yearly renal screening with alternate ultrasound and MRI imaging, as does his sister; their father elected to be followed by his local family doctor due to age, comorbidities, and difficulty in travelling for medical appointments.

## **DISCUSSION**

The risk of both benign and malignant renal tumours is increased in BHD with a prevalence of 23-34% of renal cancers, a seven-fold increase compared to unaffected family members [Zbar et al., 2001]. Birt-Hogg-Dube Syndrome associated renal tumours include hybrid chromophobe/oncocytic tumors (67%), chromophobe renal cell tumours (23%), clear cell renal carcinoma (7%), renal oncocytoma (3%) and rarely papillary renal cell carcinoma

[Pavlovich et al., 2005]. Renal cysts have also been observed but renal angiomyolipomas are characteristic of TSC not BHD [Toro et al., 2008].

Tuberous Sclerosis Complex (TSC) is an autosomal dominant syndrome affecting one of the tumor suppressor genes *TSC1* and *TSC2* on chromosomes 9q34 and 16p13.3 respectively. TSC is characterised by cutaneous lesions (facial and unguinal angiofibromas, facial fibrous plaques, hypomelanotic macules, and shagreen patches), central nervous system tumors, which may manifest as epilepsy and/or intellectual disability, ocular hamartomas, renal cysts and angiomyolipomas, and lymphangiomyomatosis (LAM) as well as cardiac rhabdomyomas [Inoki and Guan, 2009]. While cardiac rhabdomyomas and renal AML are associated with TSC, they are not commonly observed in BHD.

There have been two reported cases of cardiac rhabdomyoma [Toro et al., 2008, Bondavalli et al., 2015] in BHD, and a report of fibrofolliculoma, characteristic of BHD, within a cluster of angiofibromas in an individual with TSC [Misago and Narisawa, 2009]. Additionally, two prior reports of renal AML in patients with BHD support the emerging evidence of phenotypic overlap between the two syndromes [Byrne et al., 2012, Tobino and Seyama, 2012]. While the renal AML in our patient may have been incidental, we propose this case as further evidence of overlap in the spectrum of these conditions.

The clinical similarities between TSC and BHD may be explained by the overlapping function within the mTOR pathway of the TSC and FLCN proteins. *TSC1* and *TSC2* produce the proteins Hamartin and Tuberin respectively; these proteins heterodimerise and inhibit the mTOR pathway via mTOR Complex 1 (mTORC1) [Inoki and Guan, 2009]. Similarly, FLCN forms a complex with folliculin interacting protein 1 and protein 2 (FNIP1 or FNIP2) which is involved in the regulation of 5' AMP-activated protein kinase (AMPK), an energy sensing mechanism in the mTOR pathway [Hasumi et al., 2016] (Figure 2). The mTORC1 pathway

is involved in regulation of metabolism and cell proliferation, and when deregulated, may result in aberrant proliferation and tumorigenesis [Hasumi et al., 2016].

Individuals with BHD and TSC are at an increased risk of development of malignant renal neoplasms and surveillance is recommended [Misago and Narisawa, 2009]. Renal AMLs are generally considered benign lesions, however some can develop into malignant lesions, particularly the epithelioid subtype [Jimenez et al., 2001]. These lesions should be monitored for growth, as analysis of growth rates can aid differentiation of benign from malignant lesions [Patel et al., 2005].

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## LEGENDS

Figure 1. Magnetic Resonance Imaging (MRI) of the renal angiomyolipoma on the lower pole of the left kidney. Clockwise from top left image MRI sequences: out of phase, in phase, T1 with contrast, and T1 without contrast.

Figure 2. Schematic drawing of the interaction between the TSC1/2 and FLCN proteins via the common mTOR pathway and subsequent effects on metabolism and cell proliferation as a potential pathway of tumourigenesis (adapted from [Hasumi et al., 2016]). AMPK - 5' AMP Activated Protein Kinase, TSC1 – Tuberous Sclerosis Complex 1, TSC2 – Tuberous Sclerosis Complex 2, FLCN – Folliculin, FNIP1 - Folliculin Interacting Protein 1, FNIP2 - Folliculin Interacting Protein 2, mTORC1 - Mechanistic/Mammalian Target of Rapamycin Complex 1, HIF1a – Hypoxia Inducible Factor 1 alpha, PGC1a –Peroxisome Proliferator-Activated Receptor gamma.

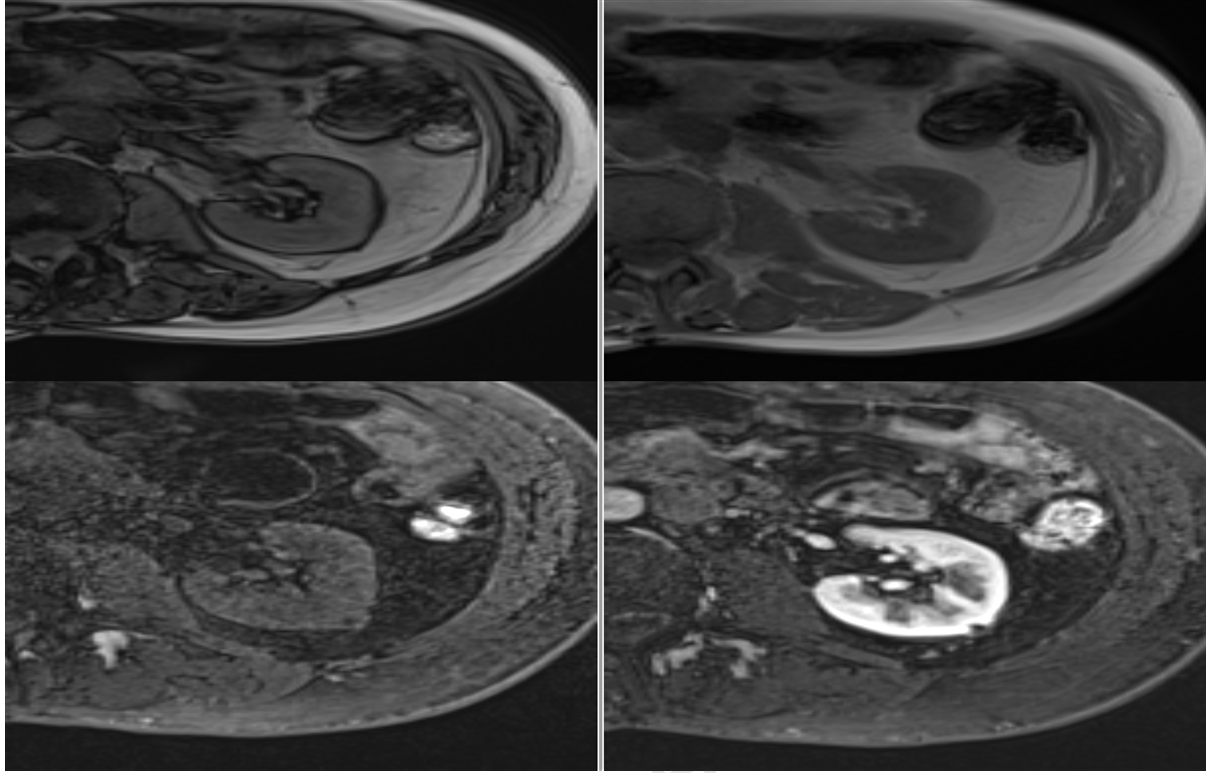


Figure 1 - Renal Angiomyolipoma in Birt Hogg Dube Syndrome .

Author Manish

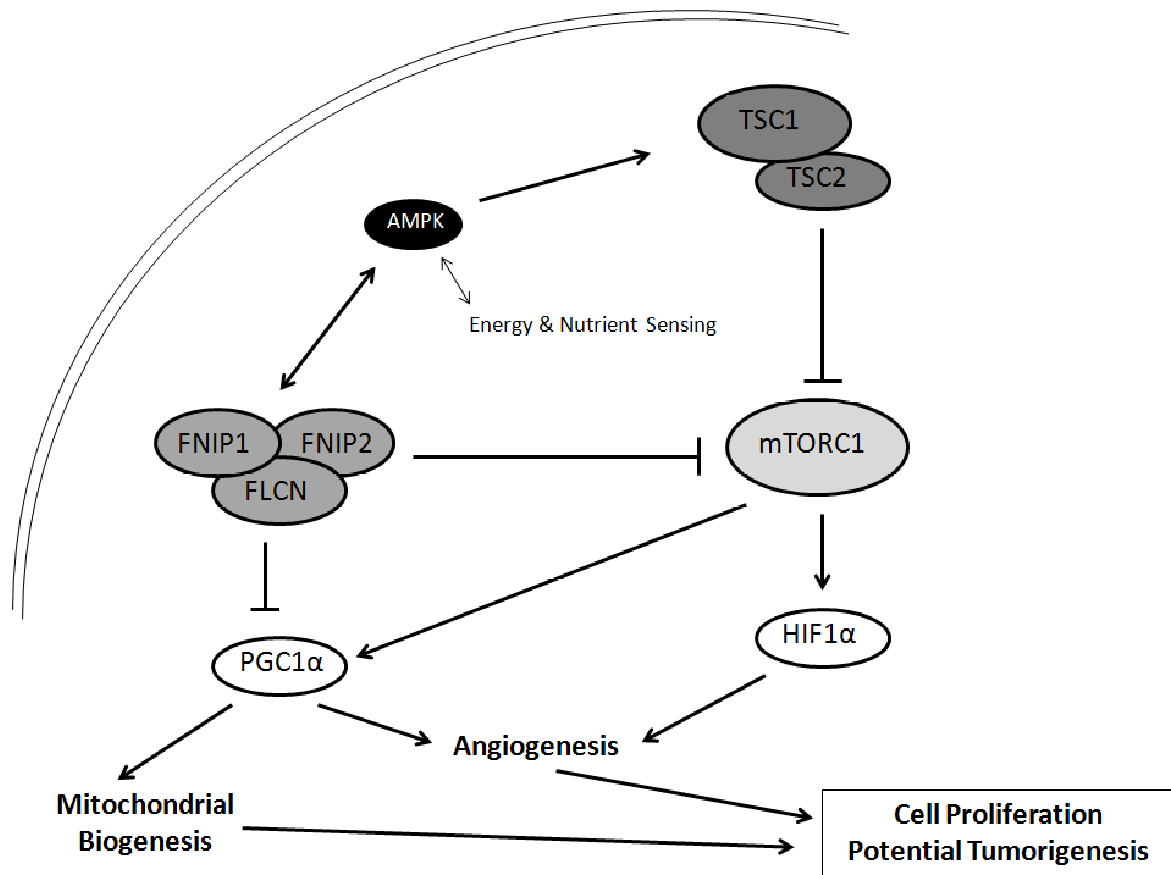


Figure 2 - Renal Angiomyolipoma in Birt Hogg Dube Syndrome .

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