# Birt-Hogg-Dubé Newsletter

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*You are receiving this email because you have expressed an interest in BHD. We hope you will enjoy this and future editions. If you do not wish to receive this newsletter, please see the end of the newsletter for instructions*.

## BHDSyndrome.org updates

"What is BHD?", our BHD literature review for researchers and clinicians, has been updated. This is the first major update since March 2011, and incorporates all the new literature since then. It is available in both html and PDF formats, and will now be updated on a monthly rolling basis to ensure it remains an up to date and useful resource for those interested in BHD. More information about this update can be found here.

A new range of introductory leaflets about BHD have been designed for new patients and can be found on our website here. To read more about why and how we developed this new range of leaflets, please read our blog post on the subject here.

## Getting to know you

This quarter, meet Doris from the USA who was diagnosed with BHD in October, and Lindsay Middelton, a Genetic Counsellor and Clinical Research Nurse in Dr W. Marston Linehan's team at the National Cancer Institute, at the NIH in Bethesda, MD. The interviews can be found here.

## BHD Research Highlights

Noteworthy papers from the last quarter include:

**BASIC:**

Petit *et al*. Recruitment of folliculin to lysosomes supports the amino acid-dependent activation of Rag GTPases. J Cell Biol. 2013; 202 (7):1107-22.

- Petit *et al*. show that under basal cell conditions FLCN was broadly expressed in the cell, but under amino acid starvation, was quickly recruited to the cytosolic surface of lysosomes in a FNIP1-dependent manner. Upon restimulation with amino acids, FNIP1 and FLCN activate RagA or RagB, which in turn activates mTORC1 signalling, and rapidly dissociates from the lysosome. Subsequently, Ser211 of the transcription factor TFEB is phosphorylated, precluding it from the nucleus and inhibiting its function. This suggests that when amino acid levels are low, FNIP1 and FLCN are recruited to the lysosome, meaning that they can activate the Rag proteins and mTOR signalling, rapidly once amino acid levels are restored.

Tsun *et al*. The Folliculin Tumor Suppressor Is a GAP for the RagC/D GTPases That Signal Amino Acid Levels to mTORC1. Mol Cell. 2013; 52 (4):495-505.

- Tsun et al. show that the GDP-bound form of RagC is required to recruit mTORC1 to lysosomes, where it is activated in response to amino acid stimulation. Furthermore, the authors show that during amino acid starvation, FNIP2 recruits Folliculin to the lysosome, where it interacts with the Rag proteins. Upon restimulation with amino acids, FLCN and FNIP2 act as a GTPase activating protein (GAP) towards RagC and RagD, facilitating the hydrolysis of GTP-bound RagC to GDP, and subsequently activating mTORC1 signalling.

Pemberton *et al*. A mutation in the canine gene encoding folliculin-interacting protein 2 (FNIP2) associated with a unique disruption in spinal cord myelination. Glia. 2014; 62 (1):39-51.

- A naturally occurring truncating FNIP2 mutation in the Weimaraner and Chow Chow breeds of dog causes a recessive tremor phenotype, which starts at 12-14 days after birth and typically abates around 3-4 months of age. Myelination of the spinal cord and throughout the brain is incomplete in affected dogs. The authors also found that Sox10 – a known determinant of oligodendrocyte differentiation – activates FNIP2 expression in rat oligodendrocytes. Together, these data suggest that FNIP2 is required for oligodendrocyte function and myelination of the central nervous system.

Zhang *et al*. Suppression of autophagy enhances preferential toxicity of paclitaxel to folliculin-deficient renal cancer cells. J Exp Clin Cancer Res. 2013;32(1):99. (Free full text)

- Zhang *et al* show that the chemotherapy drug Paclitaxel promotes apoptosis in FLCN-null, but not FLCN-expressing cells. FLCN-null cells showed increased levels of autophagy, mediated by the MEK-ERK signalling pathway, in response to Paclitaxel treatment, suggesting that increased autophagy might protect FLCN-null cells from Paclitaxel-induced apoptosis. Toxicity was further increased by combined Paclitaxel and autophagy inhibition.

**CLINICAL:**

Fabre *et al*. Distinguishing histological and radiological features between pulmonary cystic lung disease in Birt-Hogg-Dubé Syndrome and tobacco-related spontaneous pneumothorax. Histopathology. 2013 [Epub ahead of print]

- Fabre *et al*. performed a restrospective analysis of CT scans and tissue taken during lung resection from a cohort of 5 confirmed BHD patients and 5 patients with recurrent pneumothorax caused by smoking. The authors find that there is a distinct difference between the histological characteristics of BHD and spontaneous pneumothorax patients. In particular, BHD patients generally had numerous (more than 20) punch-out type cysts with no inflammation, showing a basal predominance.

**REVIEW:**

Czyzyk-Krzeska and McCormack. Birt-Hogg-Dubé syndrome. Fam Cancer. 2013 Sep;12(3):355-6.

- Czyzyk-Krzeska and McCormack briefly review the clinical symptoms and current research on FLCN and BHD, as an introduction to a special edition of Familial Cancer, which publishes the abstracts from the Fourth Birt-Hogg-Dubé Symposium held in Cincinnati in 2012.

Bhardwaj and Bhardwaj. Differentiation pulmonary lymphangioleiomyomatosis from pulmonary Langerhans cell histiocytosis and Birt-Hogg-Dubé Syndrome. Lung India. 2013; 30(4):372-3. (Free full text)

- Bhardwaj & Bhardwaj comment on a recent case study of a woman with lymphangioleiomyomatosis (LAM) and review the radiological differences between PLCH, LAM and BHD, to aid distinguishing between the three diseases.

***To participate in an interview feature, submit information or suggest a topic for the next newsletter, please contact us at contact@BHDSyndrome.org.***



BHD foundation