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.

BHD Awareness Campaign for Pulmonologists

The BHD Foundation is working to raise awareness of BHD among pulmonologists and radiologists to increase diagnosis rates in patients with a spontaneous pneumothorax. We plan to collaborate with multiple BHD clinical research groups. As part of this campaign the BHD Foundation attended the BTS Winter Conference in December to increase contact with target clinicians.

Sixth BHD Symposium and First International Upstate Kidney Cancer Symposium

Summaries from the Sixth BHD Symposium and First International Upstate Kidney Cancer Symposium are now available, separated in to coverage of the Scientific & Clinical and Patient & Family Members sessions. Thank you again to everyone involved in making the symposium such a success.

Getting to know you

This quarter meet Tracy from the USA who was diagnosed with BHD in 2012, and Dr Yu Jiang who is an associate professor at the University of Pittsburgh. Dr Jiang is interested in the role of folliculin at the primary cilium relative to mTOR signalling. The interviews can be found here.

BHD Research Highlights

Noteworthy papers from the last quarter include:

Basic:

Pacitto *et al.* Lst4, the yeast Fnip1/2 orthologue, is a DENN-family protein. Open Biol. 2015 Dec; 5(12). pii 150174

- Pacitto *et al*. used x-ray crystallography to solve the crystal structure of yeast Lst4 confirming it, and the human orthologues FNIP1 and FNIP2, as DENN-family proteins. Lst4 binds the yeast orthologue of FLCN, Lst7, as a 1:1 heterodimer and functionally recapitulates the FLCN-FNIP2 complex at the vaculoar membrane.

Péli-Gulli *et al*. Amino Acids Stimulate TORC1 through Lst4-Lst7, a GTPase-Activating Protein Complex for the Rag Family GTPase Gtr2. Cell Rep. 2015 Sep 16 [Epub ahead of print]

- Péli-Gulli *et al*. describe the roles of the yeast FLCN and FNIP orthologues - Lst7 and Lst4 - in stimulating TORC1 activity in response to increased amino acid levels. At the vaculoar membrane the Lst4-Lst7 complex act as a GAP for the GTPase Gtr2, a conserved role as FLCN-FNIP2 does the same for mammalian RagC.

Possik *et al*. FLCN and AMPK Confer Resistance to Hyperosmotic Stress via Remodeling of Glycogen Stores. PLoS Genet. 2015 Oct 6; 11(10):e1005520

- Possik *et al*. reported that a loss of FLCN increased cellular resistance to hyperosmotic stress in *C.elegans*. This resistance is due to the development of greater glycogen stores, a process mediated by AMPK, enabling a higher level of osmolites to be rapidly produced when required.

Wu *et al*. Flcn-deficient renal cells are tumorigenic and sensitive to mTOR suppression. Oncotarget 2015 Sep 21 [Epub ahead of print]

- Wu *et al*. confirmed the tumourigenic potential of kidney-specific FLCN knockout mouse renal cyst cells after *in vitro* culture and *in vivo* implantation. The resulting tumours also responded to sirolimus treatment providing more evidence that mTOR inhibitors could be a suitable treatment for BHD tumours.

Xia *et al*. Folliculin, a tumor suppressor associated with Birt-Hogg-Dubé (BHD) syndrome, is a novel modifier of TDP-43 cytoplasmic translocation and aggregation. Hum Mol Genet. Oct 29 [Epub ahead of print]

- Xia *et al*. reported a novel role for FLCN in the cytoplasmic translocation and aggregation of TDP-43. Overexpression of FLCN enhanced translocation and the formation of stress aggregates, with a loss of FLCN reducing translocation even under stress.

Clinical:

Lang *et al*. Mitochondrial DNA mutations distinguish bilateral multifocal renal oncocytomas from familial Birt–Hogg–Dubé tumors. Mod Pathol. 2015 Oct 2 [Epub ahead of print]

- Lang *et al.* determined that mitochondrial DNA mutations were only detectable in sporadic renal oncocytomas and not those associated with BHD. Additionally, sequencing mtDNA from biopsy samples is predictive of tumour mtDNA enabling reliable preoperative diagnosis.

Johannesma *et al*. Are lung cysts in renal cell cancer (RCC) patients an indication for FLCN mutation analysis? Fam Cancer. 2015 Nov 24 [Epub ahead of print]

- Johannesma *et al.* assessed whether screening for the presence of pulmonary cysts in RCC patients can be indicative of BHD. Although no additional BHD patients were identified in this small cohort, such screening could be beneficial in identifying patients who have multiple lung cysts and a positive family history of pneumothorax or RCC that could benefit from further testing for BHD.

Review:

Ferreira Francisco *et al.* Multiple cystic lung disease. Eur Respir Rev. 2015 Dec; 24 (138): 552-64

- Ferreira Francisco *et al.,* discussed the characteristic CT imaging findings of various cystic lung diseases including BHD. Greater recognition of cyst patterns could reduce the need for surgical biopsies and increase early diagnoses.

Hasumi *et al*. Birt-Hogg-Dubé syndrome: Clinical and molecular aspects of recently identified kidney cancer syndrome. Int J Urol. 2015 Nov 25 [Epub ahead of print]

- Hasumi *et al*. succinctly reviewed the clinical features of BHD and proposed management strategies. The report also covers lessons from animal models, clearly summarising known molecular pathways in BHD-RCC that could be key to the development of new treatments.

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