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

We have written a BHD Family Letter, which patients can personalise. We hope this will help newly diagnosed patients educate their families about BHD, and encourage blood relatives to get a genetic test.

We have also re-designed the BHD Medicard. This contains some brief information about BHD, and has room for patients to add their symptoms and past treatments. The card can be printed out at home and folds up into the size of a credit card.

Getting to know you

This quarter, meet Mary from the USA who was diagnosed with BHD in 2005, and Ming Yan. Ming Yan is a PhD candidate at McGill University, and holds a Doctoral Research Award from The Canadian Institutes of Health Research. His work focuses on molecular signalling of FLCN and its binding partner AMPK in BHD syndrome tumour metabolism. The interviews can be found here.

BHD Research Highlights

Noteworthy papers from the last quarter include:

BASIC:

Hasumi *et al*. Folliculin (Flcn) inactivation leads to murine cardiac hypertrophy through mTORC1 deregulation. Hum Mol Genet. 2014. [Epub ahead of print].

- Hasumi *et al*. report that biallelic *FLCN* inactivation in murine heart muscle causes cardiac hypertrophy, cardiac dysfunction and significantly reduces lifespan compared to wild type littermates. This effect was mediated by *PGC1a*, as *FLCN*/*PGC1a* double knock out animals' hearts not show this phenotype. *FLCN* deletion led to overexpression of PGC1a, leading to increased mitochondrial mass and high intracellular ATP levels. This led to a reduction in AMPK phosphorylation at T172, and subsequent mTORC1 dysregulation. In support of this model, Rapamycin rescued the heart disease phenotype of these mice.

Dunlop *et al*. FLCN, a novel autophagy component, interacts with GABARAP and is regulated by ULK1 phosphorylation. Autophagy. 2014 ; 10(10) : 1749-60.

- Dunlop *et al*. show that FLCN enhances basal autophagic flux through its interaction with the autophagy proteins GABARAP and ULK1. The authors find that FLCN binding to GABARAP is enhanced by FNIP1 and FNIP2, and inhibited by ULK1. ULK1 inhibits FLCN's interaction with GABARAP by phosphorylating three novel phosphorylation sites at S406, S537 and S542. Dunlop *et al*. also show that reduced autophagy is likely to contribute to BHD-associated renal tumorigenesis and that BHD patient *FLCN* mutations that truncate the C-terminal end of the protein show reduced binding to GABARAP.

Khabibullin *et al*. Folliculin regulates cell-cell adhesion, AMPK, and mTORC1 in a cell-type-specific manner in lung-derived cells. Physiol Rep. 2014 ; 2(8) : e12107.

- Khabibullin *et al*. show that loss of FLCN has distinct effects in human bronchial epithelital (HBE) cells and small airway epithelial (SAEC) cells. Loss of FLCN in HBE cells led to reduced AMPK signalling and increased cell-cell adhesion, but no effects on mTOR signalling. Conversely, loss of FLCN in SAEC cells led to increase mTOR signalling with no effect on AMPK signalling or cell-cell adhesion. The authors also show that although mice heterozygous for a FLCN deletion do not display spontaneous airway enlargement, their lungs do show increased elastance and interstitial edema when exposed to increased pulmonary mechanical stress.

CLINICAL:

Johannesma *et al*. Spontaneous pneumothorax as indicator for Birt-Hogg-Dubé syndrome in paediatric patients. BMC Pediatr. 14:171.

- Johannesma *et al*. report the cases of two unrelated male patients who had suffered recurrent episodes of pneumothorax from the age of 14. Subsequent genetic testing confirmed both patients had Birt-Hogg-Dubé Syndrome. The authors suggest that Birt-Hogg-Dubé Syndrome should be considered in paediatric cases of recurrent spontaneous pneumothorax.

Pritchard *et al*. Successful treatment of facial papules with electrodessication in a patient with Birt-Hogg-Dubé syndrome. Dermatol Online. 2014; 20(7).

- Pritchard *et al*. describe the case of a 51 year old Hispanic woman with a medical history of fibrofolliculomas and trichodiscomas, which were treated successfully with low setting hyfrecation. There has been no recurrence of skin lesions at two years following treatment.

Bradley *et al*. No association between Birt-Hogg-Dubé syndrome skin fibrofolliculomas and the first 10 described human polyomaviruses or human papillomaviruses. Virology. 2014. [Epub ahead of print].

- Bradley *et al*. hypothesized that the clinical variability seen in BHD may be due to infection by human polyomaviruses (HPyV) or papillomaviruses (HPV), which can affect the skin, lungs or kidneys. They analysed tissue from seven fibrofolliculomas, one renal tumour and one lung cyst biopsied from nine BHD patients for HPV and HPyV DNA. All samples were negative for viral DNA, suggesting that these viruses do not explain the clinical variability between patients.

Postmust *et al*. In-flight pneumothorax: diagnosis may be missed because of symptom delay. Am J Respir Crit Care Med. 2014; 190(6): 704-5.

- Postmus *et al*. describe the case of a BHD patient who suffered recurrent pneumothoraces within ten days of flying. A survey of 190 BHD patients and found that 12 patients (6%) suffered 13 episodes of pneumothorax within one month of flying. This time lag is thought to be due to the time taken for air to build up in the pleural cavity following cyst rupture caused by air travel.

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