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.

Fifth BHD and Second HLRCC Symposium

The Fifth BHD and Second HLRCC Symposium was held at the École de Louvre in Paris on 28th – 29th June, 2013. The meeting was hosted by Professor Stéphane Richard, and included sessions for researchers on both BHD and HLRCC and a session for patients. Abstracts and conference reports will be available on BHDSyndrome.org in due course.

BHDSyndrome.org updates

The signalling diagram illustrating the protein and signalling interactions of Folliculin has been updated to incorporate recent research. The diagram is interactive and fully referenced with peer-reviewed publications. To read more about the new diagram, click here.

A new page providing patient information about Clinical Trials has been added to the "For Families" area of the website. This page provides basic information about how trials are conducted, what trials are currently open to BHD patients and where to find more information.

Getting to know you

This quarter, meet Paula from the USA who was diagnosed with BHD in 2008, and Dr Paul Johannesma, a Medical Resident and PhD student and his supervisor Professor Pieter Postmus, who talk about their work characterising the pulmonary symptoms of BHD Syndrome. The interviews can be found here.

BHD Research Highlights

Noteworthy papers from the last quarter include:

BASIC:

Zhang *et al*. Discovery of Novel DENN Proteins: Implications for the Evolution of Eukaryotic Intracellular Membrane Structures and Human Disease. *Front Genet. 2012;3:283.* (Free full text)

- Zhang *et al.* used the divergent DENN domain of FLCN to screen for similar divergent DENN proteins and found six proteins: SMCR8, Npr2, Npr3, C9orf72, FNIP1 and FNIP2. Like FLCN, the newly identified DENN domain proteins carry a Longin domain, suggesting that they may interact with Rab GTPases and may have GEF function.

Gharbi *et al*. Loss of the Birt-Hogg-Dubé gene product folliculin induces longevity in a hypoxia-inducible factor-dependent manner. *Aging Cell*. 2013 [Epub ahead of print]

- Gharbi *et al.* report that worms lacking the C. elegans homologue of FLCN, F22D3.2, lived significantly longer than wild type worms and that this effect was mediated by HIF-1 signalling, but not insulin signalling.

Betschinger et al. Exit from pluripotency is gated by intracellular redistribution of the bHLH transcription factor Tfe3. *Cell. 2013 Apr 11;153(2):335-47*. (Free full text)

- Betschinger *et al.* identified that FLCN, together with FNIP1 and FNIP2, causes stem cells to exit pluripotency by excluding TFE3 from the nucleus and consequently reducing Esrrb expression. FLCN appears to act either downstream or independently of mTOR signalling, and independently of other known pluripotency pathways, such as the GSK3 and MAPK/Nanog pathways.

Liu *et al*. Genetic Characterization of the *Drosophila* Birt-Hogg-Dubé Syndrome Gene. *PLoS ONE 8(6): e65869.*

- Liu *et al*. generated and characterized a *Drosophila* model of BHD Syndrome. They find that the DBHD-null larvae showed delayed growth and development, and died before pupation. This phenotype was due to dysregulated dTOR signalling and could be partially rescued by dietary yeast, dietary leucine or rescue with the human *FLCN* gene.

Luijten et al. Birt-Hogg-Dubé syndrome is a novel ciliopathy. *Hum Mol Genet*. 2013. [Epub ahead of print]

- Luijten *et al*. find that aberrant FLCN expression leads to a disruption of canonical Wnt signalling and consequently causes abnormal ciliogenesis. The authors suggest that BHD is therefore a novel ciliopathy.

CLINICAL:

Stamatakis *et al*. Diagnosis and management of BHD-associated kidney cancer. *Fam Cancer. 2013* [Epub ahead of print]

- Stamatakis *et al*. suggest diagnosis and management guidelines for BHD-associated kidney cancer. The authors recommend abdominal screening every 36 months upon diagnosis, and more regularly once lesions are identified. Once the largest tumour reaches 3 cm in size, nephron sparing surgery should be performed.

Gupta *et al*. Pulmonary manifestations of Birt-Hogg-Dubé syndrome. *Fam Cancer. 2013*. [Epub ahead of print]

- Gupta *et al*. review the pathology of the pulmonary symptoms of BHD and suggest diagnostic criteria of pulmonary BHD and management guidelines for pulmonary symptoms. The authors recommend that patients should meet with a pulmonologist and have lung function tests periodically; that patients should be equipped with an action plan for pneumothorax; and advice regarding air travel and scuba diving.

BOOKS:

Sireau *et al*. Rare Diseases: Challenges and Opportunities for Social Entrepreneurs.

- Galina Shyndriayeva and Dr John Solly of the Myrovlytis Trust have contributed a chapter to “Rare Diseases”, discussing the successes and challenges in setting up the Myrovlytis Trust, and future directions.

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