

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 Patient Registry launched

[The Cancer in our Genes International Patient Databank](#) (CGIP) was launched on 20th March 2014. This is a patient registry for BHD, VHL, HLRCC and SDHB patients. The registry is an initiative of Ilene Sussman, Joyce Graff and the team at the [VHL Alliance](#), and is part-funded by the Myrovlytis Trust. To read more about the registry, or to find out how to take part, please click [here](#).

Information Standard

The Myrovlytis Trust has passed its annual audit for the [Information Standard](#) under the new version of the scheme. This means that we remain a provider of high quality, safe and reliable health information. The Information Standard is an independent certification scheme for health and social care information, commissioned by [NHS England](#).

Getting to know you

This quarter, meet Janet from the USA who was diagnosed with BHD in 2013, and Shawn Ferguson, Assistant Professor of Cell Biology at the Yale School of Medicine, whose team discovered the role of FLCN in activating mTORC1 signalling at the lysosome. The interviews can be found [here](#).

BHD Research Highlights

Noteworthy papers from the last quarter include:

BASIC:

Zhang *et al.* [Folliculin deficient renal cancer cells show higher radiosensitivity through autophagic cell death](#). J Urol 2014 [Epub ahead of print]

- Zhang *et al.* show that FLCN-null renal cell carcinoma cell lines show decreased survival following irradiation, due to an increase in autophagic cell death caused by dysregulated MEK-ERK signalling. Treatment of cells with autophagy inhibitors abrogated the effects of irradiation, whilst Rapamycin increased cells' sensitivity to irradiation.

Martina *et al.* [The nutrient-responsive transcription factor TFE3 promotes autophagy, lysosomal biogenesis, and clearance of cellular debris](#). Sci Signal 2014; 7 (309): ra9

- Martina *et al.* show that under amino acid sufficiency, active GTP-bound Rag proteins recruit TFE3 to the lysosome, where it is phosphorylated at S311 by mTORC1. During amino acid depletion, the Rag proteins become inactive, mTORC1 is released from the lysosome, TFE3 is not phosphorylated and can translocate to the nucleus where it activates the transcription of lysosome and autophagy genes. Knock down of FLCN led to hypo-phosphorylation of TFE3 by mTORC1. Thus, FLCN inhibits autophagy by facilitating the phosphorylation of TFE3.

CLINICAL:

Johannesma *et al.* [How reliable are clinical criteria in distinguishing between Birt-Hogg-Dubé syndrome and smoking as a cause for pneumothorax?](#) Histopathology 2014. [Epub ahead of print]

- Johannesma *et al.* comment on the recent study by Fabre *et al.* 2013, that showed radiological and histopathological differences between cystic lung changes caused by smoking and BHD. Johannesma *et al.* point out that in this study the control cohort were not tested for a *FLCN* mutation, that the pattern of TTF1 staining in the control cohort is not clearly described, and that there is no evidence that female BHD patients are at increased risk of spontaneous pneumothorax than male patients. Johannesma *et al.* agree with the assertion that pathologists should be aware of alternative causes of spontaneous pneumothorax, particularly in non-smokers, but state that the findings of the original Fabre *et al.* study need to be extended before clinicians change their diagnostic approach.

Kumasaka *et al.* [Characterization of pulmonary cysts in Birt-Hogg-Dubé syndrome: histopathological and morphometric analysis of 229 pulmonary cysts from 50 unrelated patients.](#) Histopathology 2014. [Epub ahead of print]

- Kumasaka *et al.* analysed 229 lung cysts in resections from 50 BHD patients and compared them with 117 lung cysts from 34 PSP patients, comparing samples for number, size, location and presence of inflammation. They found that BHD lung cysts were found in both subpleural and intrapulmonary areas; often found at interlobular septa and 40% had venules; and only showed signs of inflammation if located in the subpleura. The authors suggest that loss of *FLCN* causes alveoli walls to become weak and vulnerable to disruption by mechanical stress during breathing, which causes cysts to form. Furthermore, based on the observation that inflamed cysts tended to be larger and located in the subpleura, they suggest that pneumothorax inflames existing cysts, causing them to grow and subsume neighbouring cysts.

REVIEW:

Trotman-Dickenson. [Cystic lung disease: achieving a radiologic diagnosis.](#) Eur J Radiol, 2014; 83 (1): 39-6

- Trotman-Dickenson reviews the epidemiology, clinical symptoms and radiological hallmarks that differentiate Birt-Hogg-Dubé syndrome, lymphangioliomyomatosis, pulmonary Langerhans cell histiocytosis and lymphocytic interstitial pneumonia.

Haas and Nathanson. [Hereditary kidney cancer syndromes.](#) Adv Chronic Kidney Dis, 2014; 21 (1): 81-90

- Haas and Nathanson review the characteristics of hereditary kidney cancer, including BHD, VHL, TSC and HLRCC.

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