Reviewer's report

Title: Birt-Hogg-Dube renal tumors are genetically distinct from other renal neoplasias and are associated with up-regulation of mitochondrial gene expression

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Reviewer: Chia-Huey Ooi

Reviewer's report:

General comment: This manuscript shows that loss of FLCN is related to dysregulation of mitochondrial function not just in renal cell carcinoma, but also other types of cancer. It is certainly an article of relevance in the field of cancer genomics and well-written. However, there are a few points that need to be clarified before it is acceptable for publication.

Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)

While the authors did investigate the activation status of PI3K-Akt in BHDS-derived tumors, it appears that they did not do the same for mTOR. It is possible that PI3K-Akt is far too upstream in the cascade (Figure 4A) to show discernible activation in BHDS-derived tumors, compared to the more downstream mTOR. Is there any mTOR signature among the 1892 gene sets analyzed using PGSEA? (The public database MSigDB does contain some mTOR signatures.) If yes, it’d be interesting to see where the mTOR signature ranks in terms of differential activation in BHDS-derived tumors vs. other RCC subtypes (Figure 3A).

Figure 1D: Why were PCR validations of PVALB, CDH19, and RGS20 expression not shown for CH samples?

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Figure 4A: Shouldn’t the mode of interaction between FLCN (or FLCN-AMPK-FNIP1/2 complex) and PGC-1a be repressive (---|) instead of activating (--->) since the authors showed that FLCN expression inversely correlates with PGC-1# activation?

Figure 4D: An R-value (correlation) and associated p-value should be shown on the graph to quantify the extent of correlation between the scores derived from the two PGC signatures.

Figure 5B: r^2=-0.64 should either be r^2 = 0.64 or r = -0.64; either way, r should be a real number.
Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)

Figure 1E shows genes that are most upregulated in BHDS tumors compared to CH and ON subtypes. What about genes that are most downregulated?

Moreover, considering that 1) FLCN mutation is associated with BHDS, 2) FLCN expression inversely correlates with PGC-1a activation, and 3) PGC-1a itself is overexpressed in BHDS tumors compared to other RCC subtypes, should not FLCN be downregulated in BHDS-derived tumors compared to other RCC subtypes or compared to normals? However, there is apparently no mention of the differential expression of FLCN in BHDS tumors in the manuscript.

Figure 4B: How do the authors relate the high expression of TSC1 in BHDS tumors to the implied activation of mTOR pathway in BHDS tumors (or tumors where there is loss of FLCN)? The presence of both traits at the same time (high TSC1 and activated mTOR) seem to contradict what is shown on Figure 4A, where TSC1 inhibits mTOR (and also previously published reports on TSC1 and mTOR, for example this paper: Zhang et al. Loss of Tsc1/Tsc2 activates mTOR and disrupts PI3K-Akt signaling through downregulation of PDGFR. J Clin Invest. 2003 Oct;112(8):1223-33.) Furthermore, if FLCN loss is a characteristic in BHDS tumors and FLCN activates TCS1 (Figure 4A), why is it that TCS1 is overexpressed in BHDS tumors? It would be good to have a sentence or two considering/explaining the cause(s) of these seemingly contrasting phenomena in the Discussion.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests.