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: elizabeth henske

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Klomp et al. present gene expression data from BHD-derived renal tumors and compare it globally to the other subtypes of renal cell carcinoma (clear cell, papillary, oncocytic, and chromophobe), and also compare it directly to the two subtypes (oncocytic and chromophobe) that develop in BHD patients. Using gene set enrichment analysis the authors identified gene sets related to oxidative phosphorylation and mitochondrial function that are upregulated in BHD-derived tumors compared to the other renal cell carcinoma subtypes. To my knowledge this is the first report connecting BHD with oxidative phosphorylation and mitochondrial function. The authors also show that TSC1 and PGC-1a (substrate of AMPK) expression levels are increased in BHD-derived tumors, both of which are very interesting findings, potentially related to previous reports that folliculin is involved in mTOR and AMPK signaling.

Overall this is a very well-written and important manuscript that provides a great deal of insight into the relationship between renal carcinomas in BHD, and points toward potential mechanisms underlying tumorigenesis in BHD. I have only minor suggestions to improve the clarity.

Discretionary revisions:

1) In Figure 1 the authors show the clustering analysis (1A-B) for all of the renal cell carcinoma subtypes, however, they only show the actual data for the 50 most upregulated genes (1E) for the BHD, CH, and ON tumors. It would be nice to see the data for these same 50 genes for clear cell and papillary tumors as well.

2) For tumor ON20 which seemed to cluster with the BHD tumors, was BHD expression decreased? How did the levels of BHD transcript compare between the BHD tumors and the other tumors? Were any of the BHD tumors analyzed for "second hit" mutations or loss of heterozygosity? Isn't it surprising that none of them had evidence of loss of chromosome 17p on the prediction in Fig 2A?

3) Figure 3A - I cannot find the lists of genes that are in these 15 functional sets or a reference to them - is this included?

4) Interestingly the levels of TSC1 and FNIP2 were elevated in the BHD tumors (Figure 4B), both of which have been previously linked to the function of folliculin. The authors might comment, however, that no links between AMPK or Akt and
the levels of TSC1 transcript have been established, to my knowledge, or between BHD and FNIP transcript.

5) Typo - Figure 3A, subyptes should be subtypes

**Level of interest:** An article of outstanding merit and interest in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests