Reviewer’s report

Title: A putative role for the aryl hydrocarbon receptor (AHR) gene in a patient with cyclical Cushing’s disease

Version: 1 Date: 12 Nov 2019

Reviewer: Ashley Grossman

Reviewer's report:

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The authors have analyzed the DNA from tumor and germline in a patient with a large corticotropinoma and periodicity. They claim this is due to a germline mutation of AHR plus a somatic copy number increase.

While this is novel and interesting observation, it actually raises as many questions as it answers. It is odd to find a major germline 'mutation', with no family history, and the involvement of this gene in circadian rhythms remains pretty speculative. I think the authors should be much more circumspect about their findings, and simply introduce this as a novel largely unexplained observation. The extensive discussion is unnecessary, especially as none of the classic clock genes seem to be involved.

Specific points:

1. What do they mean when they say that all rare pituitary-circadian variants were present in the germline DNA?

2. I assume the germline AHR mutation was heterozygous: was this present in the tumor?

3. As this was from a patients with a very large tumor, perhaps as clinical endocrinologists we could have some follow-up of the patient's subsequent progress.
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript

Quality of written English
Please indicate the quality of language in the manuscript:

Acceptable

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