Reviewer’s report

Title: Circadian pathway genetic variation and cancer risk: evidence from genome wide association studies

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Reviewer: Sarah Markt

Reviewer's report:

In this article by Mocellin et al., the authors use publically available data from GWA studies to investigate the association between circadian rhythm related genes and risk of three cancers, breast, prostate and lung. The authors utilize a pathway analysis approach to evaluate the association and found variation in 15 genes were associated with risk of cancer, and four were associated with all three cancers. The paper is well-written and described, but I do have some comments.

Introduction:

1. The first paragraph is repetitive with the information included in the methods describing the pathway approach. Would suggest focusing and starting the introduction more on why the circadian rhythm genes in particular are interesting for risk of these three cancers. The justification for choosing these cancers was in my opinion lacking.

2. Figure 1 was confusing in the sentence it was ascribed to. Would suggest explaining the figure a bit more in the text. Perhaps mention the negative and positive feedback loops. You describe it in more detail in the methods - either move to introduction, or wait to introduce the figure until methods.

Methods:

1. Was there a reason data had to be from case-control studies? Could you have utilized cohort study data?

2. On page 8, it says the method adjusts the p-value for multiple testing. This was in parentheses and I missed it the first time. Would suggest taking out of parentheses and describing how it adjusts.

3. The first paragraph on page 9 is confusing and I don't know what it adds to describing the method.
4. It is stated that there are 3 values reported: the pathway p-value, the gene p-value and the top gene and SNP. Is the pathway p-value all of the genes you evaluated, or restricted to the top genes?

5. The first part of the results describing the study populations belongs in the methods section under study population.

Results:

1. The results are presented somewhat confusingly. I read through the results multiple times before figuring out where the pathway p-value was and what the top SNP was. I would suggest re-arranging the tables to include this information. Also, would be helpful to put all the results in supplementary information so that one can compare the results for each gene across all the cancer types.

Discussion:

In general, I thought the discussion re-hashed the results rather than including a full discussion of the 'why'. For example, a more detailed discussion of the four genes that came up in all three cancers would add to the paper. Breast and prostate are hormonally driven cancers, lung different, why would they have similar genes and/or why not.

General minor comments:

1. The manuscript is well-written, but there are some instances where the meaning is a bit confusing. For example, on page 9: "this gene-based pathway analysis implies to obtain …."
   Do you mean, the gene-based pathway analysis obtains?

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

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

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