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Receipt of reviewer's report for SREP-16-24635-T

scientificreports@nature.com <scientificreports@nature.com>

Mon, Aug 15, 2016 at 1:16 PM

Reply-To: scientificreports@nature.com

To: scguo@ucsd.edu

Dear Dr Guo,

Many thanks for submitting your referee report on "Blood-based omic profiling supports female susceptibility to tobacco smoke-induced cardiovascular diseases" by Dr Kyrtopoulos. We appreciate the time you have taken to review this manuscript for Scientific Reports. A copy of this report is attached below for your reference.

Best regards,

Manuscript Administration

Scientific Reports

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Is the manuscript technically sound?: Yes

Could the manuscript become technically sound with revision?: Yes

Are the conclusions supported by the evidence presented?: Yes

Are additional experiments or data required to support the conclusions?: Yes

Does the manuscript only duplicate previous work?: No

Appropriate use of statistics and treatment of uncertainties?: No

References: appropriate credit given to previous work?: Yes

Is the manuscript written clearly using Standard English?: No

Images (including electrophoretic gels and blots) are free from apparent manipulation?: N/A

Technical Comments to the Author:

Recommendation: Major Revision

Remarks to the Editor:

Remarks to the Author:

Dr. Kyrtopoulos and colleagues provided epidemiological analysis to the gender effect on the susceptibility to tobacco smoke-induced cardiovascular diseases. It is an extension research based on his previous study which published on Sci Rep on Feb, 2016 (doi: 10.1038). The study was performed rigorously and the findings sound quite interesting. However, I only have some small concerns on the analysis method.

Major Compulsory Revisions

- 1, Line 400-403 checked for the bias from the sample size of male and female, however, the false-positive can be avoid by this single control. I recommend the author to conduct the permutation test to avoid the false positive conclusion.
- 2, The current result was only derived from beadchip (microarray), as we known, the accuracy of the microarray data is limited and the result should be validated. Is there any possibility to have a validation for the current conclusion? or could the author to collect another independent dataset from GEO to find some supportive evidence to the current manuscript?

Minor Revisions

- 1, Line 80, it is not clear the definition of differentially methylated genes and differentially expressed genes, smoking vs non-smoking or male vs female?
- 2, Reference should be provided for line 68-70.
- 3, Detail information for DMR and DGE should be provided as the supplementary Tables between line 80-82.
- 4, it is a high level analysis/manuscript since all the basic analysis were based on the reference #10, however, this dataset is not public. I recommend the author to upload it to GEO so that all the process could be repeated.
- 5, Line 95-105 should be re-organized. It is not quite clear since it is the most important content to interpret the statistical method, meanwhile, it is not
- 6, the subtitle for the result section should be provided.
- 7, For the methylation part, DMS is quite not stable compared with DMR and majority such kind of different were caused by stochastic noise. I am strongly suspecting whether the result could be repeated by others. DMR based analysis should be conducted to increase the credibility of the conclusion.
- 8, How did the p-value difference was calculated in Table 2 and Table 3?

Discretionary Revisions

- 1, For line 107-109, Is there any significant probes were identified both in smoking and non-smoking group?
- 2, Certain effective footnote to the Tables would be helpful.

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