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Receipt of reviewer's report for SREP-16-10787-T

1 message

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

Sat, May 14, 2016 at 3:51 PM

Reply-To: scientificreports@nature.com

To: scguo@ucsd.edu

Dear Dr Guo,

Many thanks for submitting your referee report on "Tertiary Epimutations - A Novel Aspect of Epigenetic Transgenerational Inheritance Promoting Genome Instability" by Dr McCarrey. 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,

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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?: Yes

References: appropriate credit given to previous work?: Yes

Is the manuscript written clearly using Standard English?: Yes

Electrophoretic gels and blots are presented clearly and are free from apparent manipulation?: Yes

Technical Comments to the Author:

Recommendation: Major Revision

Remarks to the Editor:

Remarks to the Author:
Comments to the Authors,

Dr. McCarrey in his manuscript "Tertiary Epimutations-A Novel Aspect of Epigenetic Transgenerational Inheritance Promoting Genome Instability" proposed a very interesting concept of tertiary epimutations, which is the extension of

primary and secondary epimutation. The authors observed the mutation frequency were higher in F3 generation progeny rather than F1 and F2. The idea and the strategy were excellent and it would give a great help to understand the relationship between environment exposure and human heredity. I only have several tiny considerations on the study.

1, In the Figure 1, Is there any explanation for 'Panel A have smaller mean, larger error bars (SE) compared with Panel B'? Did you check the visualization of Panel A and Panel B with SD as the error bar? What I am worrying is that only few samples in F3 have large mutation frequency (MF) while majority of them have similar MF, should we check the conclusion more cautiously? Could another exposure treatment or validation study could be assigned?

2, Can you make some interpretation on the ratio of TS/TV in F1 control-lineage is about 2-3 while this ratio become 1-2 in F3 control-lineage? It should not be caused by batch effect? Would there be some reason from biology or technique?

3, In the title, the authors want to claim "Genome Instability" would be the consequence of tertiary epimutations. However, I don't know whether it is suitable to take it as the "Genome Instability" or just consider "Genomic Mutation"? Since the I/D and DBS were not quite significantly different between V and C-lineage, right?

4, The authors mentioned 'Vinclozolin is not directly mutagenic'. Would you mind explaining which drugs could be considered to be directly mutagenic? Is there any necessary to set a such positive control in present study?

5, I just want to confirm is there any previous study have been discovered such F3 higher mutation before? Do you think there would be higher mutation frequency in F4 or more? Another question is why sperm and kidney were selected in the present study?

6, Significant different among the numbers of column Total number of plaque-forming units in Table 1 and Table 2, any explicitly and non-affect reason to caused such difference?

7, Vinclozolin is associated with cancer onset, and the high mutation frequency (Genome-instability) might be the consequence for pre-cancer event. For other disease, such as diabetes, rheumatology disease, how to demonstrate the tertiary permutations in such scenarios?

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