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Final Decision made for SREP-15-21934

1 message

scientificreports@nature.com <scientificreports@nature.com> Wed, Sep 2, 2015 at 4:49 AM
Reply-To: scientificreports@nature.com
To: scguo@ucsd.edu

Dear Dr. Guo:

Thank you for your help with manuscript SREP-15-21934, "Epidemiological correlation between cancer risk and tumor genomic mutation rate confirms the predominant contribution of somatic mutation", which you recently reviewed for Scientific Reports.

For your records, the decision for this manuscript, based partly on your input, was Major revision. A full copy of the comments to authors is appended, below.

Your assistance and participation in the review process for Scientific Reports is greatly appreciated.

Best regards,

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Scientific Reports
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London N1 9XW
E-mail: scientificreports@nature.com

Referee comments to the authors:

Reviewer #1:
Remarks to the Author:
Comments to the Authors,

In the present study, Dapeng Hao and his colleagues investigated the correlation between cancer risk and tumor genomic mutation rate and provided an important evidence of the predominant contribution of somatic mutation to cancer risk. This study is a critical and prompt response to the recent paper published on the journal of Science few month ago. The authors collected huge number of genome-wide or exon-sequence data from 5,542 cancer samples throughout 41 different cancer types. The authors found the revised Armitage-Doll model can interpret the relationship between mutation counts and cancer risk with high accuracy. The study was performed rigorously and the findings are very interesting.

Maor Essential Revisions
1, What would happen if the number of the stem cell divisions was adjusted in the models?

Minor Essential Revisions
1, In the section of "Robustness Analysis", the distribution of Pearson, Spearman and corresponding P-value in the 10,000 iterations should be provided in the supplementary.
2, The influence of the variation in the estimation of lifetime risk for each cancer to the correlation be-tween mutation ratio and cancer risk should be evaluated.
3, A detailed definition and selection of consensus mutations as well as a complete list of consensus muta-tions should be provided as the supplementary and the influence of the variation of the number of the mu-tation to the

conclusion should be validated.
4, In the supplementary section, authors has provided the mutation counts per Mb and lifetime risk for each cancer, however, the explicit data which was used to establish the Figure 1 should be showed as the form of table.
5, In the analysis, the authors actually established a log-log relationship between mutation counts and life-time risk. However, in the title, the author used "mutation rate". Is there any difference between these two terms, especially when considering difference division speed for different cell type?

Discretionary Revisions
1, the role of the factorial of N in the formula of logarithm of cancer lifetime risk (Armitage-Doll model) might be need some introduction.

Reviewer #2:
Technical Comments to the Author:
This paper focused on the relationship between estimated mutation rates and lifetime cancer risks of many cancers, and presented a simplified mathematical model attributing to a 1:1 relationship between the two in log-log scale. The topic is interesting, but the mutation rates were not well demonstrated, and the interpretations of the linear regression results were not sound.

The average/"consensus" mutation rates neglect the mutational heterogeneity in each cancer, especially regional heterogeneity. Since original data about the mutation rates and their distributions are missing, the representativeness of a "consensus" mutation rate is not clear. This is the fundamental deficit of this study.

The 1:1 ratio between the mutation rate and cancer risk in log-log scale came from a simplified model. The observed regression fit did not reject that, but provided little to support it. The phrase "nearly perfect" was over interpretation.

Remarks to the Author:
1. First, the concept "consensus" mutation rate needs detailed demonstration. Reference 13 emphasizes mutational heterogeneity. It writes "In melanoma and lung cancer, the frequency ranged across 0.1-100/Mb. Despite the low median frequency in acute myeloid leukaemia (AML; 0.37/Mb), the patient-specific frequencies similarly spanned three orders of magnitude, from0.01 to 10/Mb." It would make much more sense to include only those cancers first for which a "consensus" mutation rate can be defined meaningfully, and discuss the others after.

2. The supporting mutation frequency data are needed for this paper. In the robustness analysis, the author mentioned "The std. of mutation rate was similar among cancers benchmarked against the average (avg.) of mutation, and overall was about ~5% of the avg. of mutation rate in the magnitude." But no data were included to support that. Figure 1 in reference 1 and Figure 1 in reference 13 both show distributions of somatic mutation frequencies.

3. The interpretations of the regression coefficient need rewriting. The meaning of the mathematical model is to provide a reasonable approximation rather than a prediction. Discussions of the applicable situations of the model will enhance this study.

4. Discussions on the limitations of this study are needed.

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