Reviewer’s report

Title: Lessons learned from Whole Exome Sequencing reanalysis: Our experience on 200 Lebanese exomes

Version: 0 Date: 07 Sep 2018

Reviewer: Prashant Suravajhala

Reviewer's report:

Please include all comments for the authors in this box rather than uploading your report as an attachment. Please only upload as attachments annotated versions of manuscripts, graphs, supporting materials or other aspects of your report which cannot be included in a text format.

Please overwrite this text when adding your comments to the authors.

The authors come up with a gist of their WES analyses based on 200 samples. The work was aimed to improve the diagnostic yield from the re-analyzed WES samples.

The article weighs substantial strengths but the authors could have improved the manuscript with better reasoning.

1. The patients’ diagnoses success rate for the diseases they studied lacked a statistical interpretation based on the population sub-strata. Is there such interpretation? Am I missing something?

2. Whilst reanalyzing the exomes, what were the underlying outliers from previous analysis?

3. The point on technical limitation in page 7 needs to be revisited. It is expected with tools such as CGH but isn't it more nice to go for integrated (exome+transcriptome) instead?

4. On the point where there must be communication between the geneticists and clinicians, it would be nice the authors mentioned about the precision medicine.

5. The sfari.org URL cited in page 8 could have an accurate URL. If this is rendered, then please add "last accessed date"

6. The authors in conclusion make a note that the WGS could perhaps be performed to detect ncRNAs. I don't think the depth would be that efficient to get the ncRNAs and even if they do, they might end up with mere identifying them, not characterize them for bona fidelty. Instead, it would have been nice to extend the targets from WES to intergenic regions or go for transcriptome analyses to leverage better understanding of ncRNAs. This must be
elaborated. I would like to suggest authors to get articles in PubMed on "Identifying ncRNAs from exomes"

It is still in infancy, though. A point on it would be nice.

7. In Page 10, while the authors focused on intron-exon boundaries, a careful assessment (BLAST etc.) would entail identifying ncRNAs. Did the authors find any

8. On a hindsight, the subheads mentioned in italics could be in small sentences.

9. A pictographic flowchart of methods would be nice. The tables are made more descriptive though.

On a scale of 0-5, the following are the scores rendered, with 5 being the best:

Novelty: 4
Language: 4
Scope and Relevance: 3
Brevity: 3

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.

No
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.

I am able to assess the statistics

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

Acceptable

**Declaration of competing interests**
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests whatsoever!

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal