Reviewer’s report

Title: Targeted next generation sequencing with an extended gene panel does not impact variant detection in mitochondrial diseases

Version: 1 Date: 27 Nov 2017

Reviewer: Elizabeth Chao

Reviewer's report:

Dear Authors,

Overall, the manuscript address an important question that we are all struggling with as NGS has invaded clinical diagnosis when to select a panel as compared with WES. This is true not just in mitochondrial disorders but across a number of other areas of genetic disease. The data presented is quite striking and makes an interesting argument for the clinical utility of NGS in the diagnosis of mitochondrial disease as well as supporting the paradigm of increased mtDNA mutations in adults as compared with children.

However, I do not feel that the study design adequately address the question they are asking, which is the comparison of NGS panels with WES. Specifically, they do not apply WES to any of the patient sin the cohort and so this comparison is not available based on the data presented. There is some argument for comparison of the data presented to published data, but authors themselves appropriately recognize the challenges and in adequateness of comparing across different cohorts and published data sets.

If authors wish to conclude on the utility of WES compared with panel testing then there needs to data presented from both these methodologies. I would strongly suggest the need for additional experiments including WES on the cohort in order to provide data to support the conclusion of increased diagnostic yield of WES. Alternatively, the data authors di present has intrinsic value and the conclusion could be modified to more appropriately be drawn from the data presented. The discussion could then include the possibility that WES would have greater utility than the panel data presented with historical comparisons to the historic literature, but this can NOT be concluded based on the data presented in this manuscript.
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.

No

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

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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

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I previously held a small amount of stock in Ambry Genetics, a commercial genetic diagnostic laboratory.

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