Reviewer’s report

Title: Molecular diagnosis in recessive pediatric neurogenetic disease can help reduce disease recurrence in families

Version: 0 Date: 02 Jul 2019

Reviewer: Research Square Reviewer 1

Reviewer's report:

PEER REVIEWER ASSESSMENTS:

OBJECTIVE - Full research articles: is there a clear objective that addresses a testable research question(s) (brief or other article types: is there a clear objective)?
Yes - there is a clear objective

DESIGN - Is the current approach (including controls and analysis protocols) appropriate for the objective?
No - there are major issues

EXECUTION - Are the experiments and analyses performed with technical rigor to allow confidence in the results?
No - there are major issues

STATISTICS - Is the use of statistics in the manuscript appropriate?
No - there are issues with the statistics in the study

INTERPRETATION - Is the current interpretation/discussion of the results reasonable and not overstated?
No - there are major issues

OVERALL MANUSCRIPT POTENTIAL - Is the current version of this work technically sound? If not, can revisions be made to make the work technically sound?
Maybe - with major revisions

PEER REVIEWER COMMENTS:

GENERAL COMMENTS: My main concern remains and concerns the numbers used for analysis. The authors find that NGS diagnosis leads to a significant reduction in recurrence, but this is by selecting the analysis to &lt;10% of the original cohort, who a) had a diagnosis and b) returned for prenatal counselling with a subsequent pregnancy. This is equivalent to performing a clinical trial and analysing only those patients who have responded to the intervention. To then make a statement about the success of the intervention is meaningless! For this reason, in a clinical trial, analysis is performed on an intention-to-treat basis. In this case it would mean using all 1172 families that were initially enrolled as denominator. I understand that this is difficult to do, as the authors do not know about the pregnancy rate in those that did not return. This needs to be discussed. Supposedly, estimations can be made about average fertility rates about the number of expected pregnancies. For instance, if one assumes that the 91 families who were used for analysis are representative of the entire
cohort, then there would have been a total of $1172 \times 101/91 = 1287$ pregnancies in the observation period, of which $25\% = 322$ would have been likely affected. The termination of 16 of these thus reduces the number of affected siblings by $<5\%$. Is that statistically significant?

REQUESTED REVISIONS:
I do not accept the answer the authors have provided to my previous comment in that regard that "the recurrence rate even in families in whom no genetic diagnosis could be made might be less than the predicted 25\%. " That's precisely the point! Parents may make decisions on either not becoming pregnant again or using alternative diagnostic methods and that's exactly why using a "historic 25\%" as comparison is meaningless and biasing the results in favor of the authors' hypothesis.

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

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

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Please indicate the quality of language in the manuscript:

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