Reviewer's report

Title: Efficient strategy for the molecular diagnosis of intractable early-onset epilepsy using targeted gene sequencing

Version: 0 Date: 16 Aug 2017

Reviewer: Mark Corbett

Reviewer's report:

Dear Dr Rim and colleagues,

I have reviewed you paper and have the following comments to make. Overall the work is fine as is. It represents an incremental increase in knowledge however I found your thorough analysis approach of interest and others in a clinical genomics setting may benefit from this work.

Given large number of individuals with West Syndrome in this cohort how well was the ARX gene covered in this panel? Is it possible that variants in that gene especially polyalanine tract expansions were missed in some males?

For statistical analyses in table 3, were multiple testing corrections done? This is not mentioned in the materials and methods.

How many of the unsolved West Syndrome had variants with lower pathogenicity / ACMG scores in the the most frequently mutated genes? Might it be possible that milder cases have milder mutations (by current classification standards) that caused you to miss them?

What is the total personnel time taken for steps 2 and 3 per variant or per individual. Others have reported this and deciding if to take up your method or not may come down to what resources are available.

For supp Table 3 it would be good to provide the the mean or median depth of coverage of targets in addition to these other metrics. It would be good to know if with your chosen design if these data are suitable for seeking somatic variants. As you mention in your discussion this may be a source of missing variants.
Minor corrections.

Page 8:

For the customized NGS panel, we selected 172 candidate causative genes known to cause...

Genes don't cause disease, mutations do. Suggest:

For the customized NGS panel, we selected 172 candidate genes implicated in...

Sup Table 4

SYNCAP1 should be SYNGAP1

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.

Yes

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:

Needs some language corrections before being published
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