Reviewer's report

**Title:** Clinical Utility of Exome Sequencing in Individuals with Large Homozygous Regions Detected by Chromosomal Microarray Analysis

**Version:** 1  **Date:** 20 Dec 2017

**Reviewer:** Raiyan Khan

**Reviewer's report:**

The manuscript by Prasad et al. makes a case for the use of whole-exome sequencing (WES) analysis as a means to unearth pathogenic variants in individuals with large runs of homozygosity (ROH). While the authors present examples from a wide-variety of patients, there need to be additional changes to evaluate the significance for these mutations.

The manuscript would benefit from the addition of a figure to supplement the "Analysis of sequence data" section under Methods. This figure should present a detailed step-by-step of the WES quality control and variant discovery pipeline that was followed in the paper.

The report is missing certain details regarding the participants and variants discovered:

1. Please provide the ancestral background of each of the subjects reported on in the manuscript.
2. The list of discovered variants (Additional File 3) would benefit from additional information. Please provide scores from Variant Effect Predictor (from SIFT, Polyphen, and MutationTaster) for each variant.
3. It would be beneficial to cross-check the variants found in the 53 subjects with relevant, publicly available genomic databases specific to each disease. For example, for subjects with ASD related variants, the authors should check the autism database of genomic variants (AutDB, autism.mindspec.org), and make a note of any variants in Additional File 3 that are reported in the database.
4. Please report the thresholds used for evaluating read quality in the WES pipeline.
In the discussion section, please discuss the subjects in which no obviously pathogenic variants were found.

**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.

Unable to assess

**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.

Not relevant to this manuscript

**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:

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