Reviewer's report

Title: Family-specific, novel, deleterious germline variants provide a rich source to identify genetic predispositions for BRCAx familial breast cancer

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Reviewer: Aiguo Li

Reviewer's report:

The authors in this manuscript detected some new predispositions using exome-sequencing data derived from three BRCAx familial breast cancers as well as a set of probands. The sequencing data analysis is common and objective in which they eliminated common variants present in human population using dbSNP137, ESP6500 and 1000 genome database and family-specific normal variants by filtering out the common variants shared by unaffected individuals in the family. As a result, the authors found about 337 deleterious variants present in the affected members of the three families and 689 variants from probands with some of them validated. The patient samples in this study are valuable and findings represent some degree of advancement to our current understanding. However the annotation of the gene lists borne the variants are poorly annotated both at single gene level as well as at the high throughput level. Additionally, the association of these findings with the published literature is not adequately addressed in the discussion. I would recommend the acceptance of this manuscript after the following concerns are addressed properly.

Major comments

1. As shown in Fig.2, the intersection of the deleterious variants found from each family or proband is very low. The authors should have tried functional analysis of variant gene lists from each family. This analysis should help to understand the functional alterations in the BRCAx breast cancer patients. It is also likely that commonality might be revealed across family through high-level functional analysis.

2. It is not clear in the manuscript on what specific criteria the authors used to choose the genes in the table 3 and the three focused genes discussed in the manuscript. Is it based on penetrance within the family? Or purely based on the damaging score generated by Polyphen-2. Further the functions of these genes in the previous publications and their contributions to cancer are not fully explored.

3. Not all the variants are contributed equally in any case. For example, transcriptional factors are determinant of the expression for a set of downstream genes. Is there any transcription factor in the affected gene lists?

Minor comments

Pg 4 ln 9 – [ is missing.
Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests.