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: Wei Tang

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Minor Essential Revisions

Wen et al., reported a study on exome-seq of germline mutation of BRCA-negative familial breast cancer. They sequenced 62MB genomic region of three families and 22 probands using Hiseq2000 with paired-end reads at 100x coverage per sample. They identified family-specific, novel, deleterious germline variants but they only share within the families not between the families. The variants they found enriched in cancer related pathway and provide as a good resource to genetic predispositions for BRCA negative breast cancer.

I do not have major concern but several suggestions to improve the quality of this report.

1/ Authors should provide a better description of Exome-seq samples, which should include all the statistical data about reads number, alignment, coverage for each sample.

2/ Authors mentioned GATK and Varscan, which one did authors use for variants calling needs to be clarified.

3/ Since authors claimed 100x coverage for each sample, but why used read depth at 10 as the parameter of SamTools.

4/ Annotation of ANNOVAR usually reported several predictions of deleterious effects; please explain why only PolyPhen-2 was kept in the manuscript.

5/ Please make a better summary of the validation section, how many variants have been validation and the concordance rate with sequencing data.

6/ When removing the common variants in human population, what is the cut-off of the frequencies.

7/ Please provide power calculation of detecting germline variants of current study design, and mutation rate.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:

I declare that I have no competing interests.