Reviewer’s report

Title: Somatic Variants of Potential Clinical Significance in the Tumors of BRCA Phenocopies

Version: 0 Date: 23 May 2019

Reviewer: Brianna Morten

Reviewer's report:

This study examined the possible genetic causes of a small cohort of BRCA phenocopies, patients who demonstrate a cancer phenotype similar to that of their BRCA-positive relatives, but do not present with the known familial germline mutation. They examined a panel of 572 cancer-associated genes and identified potential clinically significant variants.

The research question is very interesting and valid, the study is scientifically sound, but the conclusions drawn fall down slightly due to a lack of experimental data. Testing only cancer-associated genes was limiting, in that it couldn't identify novel causative somatic mutations, particularly considering it is only a small sample size. Furthermore, conclusions surrounding the methylation effect are interesting but also only speculative. This paper could have been a lot stronger by performing methylation arrays, for example, to determine the methylation patterns between patients, or between BRCA-negative phenocopies and their BRCA-positive family members, if possible, and also if there are any correlations with their identified genetic variants.

Instead of targeted sequencing, could whole exome sequencing provide a greater understanding of the genetic differences between BRCA phenocopy patients? This may provide more depth to identify additional novel causative gene mutations, or novel candidate susceptibility genes, which may explain the phenotype.

Of the patients who had somatic genetic variants, how many had multiple genetic mutations across the genes discovered? This wasn't clear from Table 1. Could you include a Table that shows which patients had a ROS1/NUP98/BRCA2 mutation or those that had some but not the others? Could there be some sort of polygenic risk attributed to patients who had multiple mutations in the same genes? This was discussed but not clearly presented in the results.

Have the genetic variations described in this paper been validated by sanger sequencing? Do you know if these genetic variants are also present in the familial BRCA-positive tumour tissues?

More discussion is needed as to the possible reasons why BRCA non-carriers develop these similar phenotypes. Could it be due to other, unknown driver germline mutations?
**Level of interest**  
Please indicate how interesting you found the manuscript:

An article whose findings are important to those with closely related research interests

**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:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests.

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal.