Reviewer's report

Title: FANCM and RECQL genetic variants and breast cancer susceptibility: relevance to South Poland and West Ukraine

Version: 0 Date: 03 Nov 2017

Reviewer: Elizabeth Chao

Reviewer's report:

Overall this study is well designed and performed in an appropriate population given the prior genetic results which have been published related to breast cancer risk and FANCM/RECQL. It is important to continue to try to understand the relative contribution of various genes to breast cancer risk in different world populations. Currently only BRCA1/2 are mentioned in the paper, some attention showed be paid to other "bona fide" moderate risk genes on panels and their clinical utility as preliminary suggests that FACM/RECQL would be more moderate risk. Data that support the inclusion of moderate risk breast cancer genes in genetic testing algorithms are available (including NCCN).

Specific comments:

Background

Line 64- Consider "candidate genes in breast cancer susceptibility" or similar rather than "potential" breast cancer genes

Consider include some discussion of accepted practices of panels which include both high and moderate risk breast cancer genes.

Methods:

Please clarify that patients in the case cohorts had BRCA1/2 comprehensive analysis as compared with just testing for the Founder mutations in this Polish population- and whether the Ukrainian cohort had been previously screened for BRCA1/2 at all.

Discussion:

193: Since the proposed mechanism is loss of function and some missense can certainly cause loss of function, this sentence is not well structured. Recommend something more similar to "no
published reports of missense changes leading to loss of FACM protein function" as connecting missense to breast cancer risk directly removes this logical step.

Conclusion:

The final conclusion could be clarified in the wording. If I understand correctly authors are suggesting that these SHOULD be included on panel because data will accumulate and then help to better their role in breast cancer risk. Authors could also comment on risk for ovarian cancer since these patients were included in the cohorts as well- the lack of findings in this patients may suggest that the study for underpowered in this condition rather than substantiate no ovarian cancer risk.

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:

Acceptable
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I was a previous employee (2011-2016) of Ambry Genetics, a US commercial laboratory which performs NGS panel testing for hereditary breast cancer.

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