Reviewer's report

Title: Age-Adjusted Association of Homologous Recombination Genes with Ovarian Cancer Using Clinical Exomes as Controls

Version: 0 Date: 20 Mar 2019

Reviewer: Thomas Hansen

Reviewer's report:

In the paper by Arvai et al., the authors perform a retrospective case-control study on 6,182 women with ovarian cancer examined by multi-gene panel testing and 4,690 mothers from trio WES analysis, and present age-adjusted odds ratios to determine the association of ovarian cancer with pathogenic variants in ten homologous recombination genes. The authors confirm the association for pathogenic variants in BRCA1, BRCA2, RAD51C and RAD51D with ovarian cancer, while pathogenic variants in BARD1, NBN and PALB2 were not significantly associated with ovarian cancer. Moreover, ATM, CHEK2 and BRIP1 pathogenic variants were only significantly associated with ovarian cancer by crude odds ratio or by adjusted odds ratio. Arvai et al., conclude that their study design and analysis provide more informed estimates of association compared to recently published ovarian cancer associations by reporting both crude and adjusted odds ratio. The results are most relevant for BRIP1 pathogenic variant carriers as their findings regarding this gene is inconsistent with previous studies and current management recommendations.

Taken together, the manuscript is well-written, and the data is clearly presented.

Minor points

1) The authors should state in the method or in the beginning of the results section which HR genes were included in the analysis (genes in Table 1).

2) In line 108 (page 5), please include Supplementary Table 3 for uniformity.
3) In the last section on page 7, the authors mention that one gene, BRIP1, was significantly associated with OC by ORcrude. However, ATM was also significantly associated with OC by ORcrude. Should be rewritten.

4) The reference list should be checked. It seems that several references lack information regarding volume and page numbers.

5) In Supplementary Table 3, information regarding nucleotide change is missing for several variants. Moreover, please use either Ter or * (not X) for nonsense variants at the protein level (follow the HGVS guidelines). Moreover use * for frameshift variants (not X). Finally, regarding ATM c.7636_7644del, use HGVS guidelines for protein nomenclature.

6) I would suggest that the authors update variant classification in ClinVar for the pathogenic variants listed in Supplementary Table 3, e.g. ATM c.3848T>C, p.Leu1283Pro (classified by GeneDX in 2015 as a variant of unknown significance).

---

**Level of interest**
Please indicate how interesting you found the manuscript:

An article of importance in its field

**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