Reviewer’s report

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

Version: 0 Date: 22 May 2019

Reviewer: Florentia Fostira

Reviewer's report:

The work submitted by Arvai et al performs a case-control study in an effort to provide estimates on ovarian cancer risk associated with pathogenic variants in a number of genes sequenced.

I think that these type of data are extremely important since valuable results can emerge in respects to patient clinical management, as well as therapeutic choices. Most works published so far use data from public databases, such as ExAC, to perform statistical associations. Therefore, the backbone of this study is relatively novel and can be valuable.

Although I don't have a major in Statistics, I am a little concerned about the "control" group. The total number of controls used was 4690, while the number of patients used was significantly larger (6182). But, the major issue is the relatively young age of the controls. Considering that even in BRCA1/2 carriers, the mean age at ovarian cancer diagnosis is ~51 years, the authors state the mean age in their control group was 41.9 years. This means that we cannot actually rule out that some of these women will ultimately be diagnosed with ovarian cancer. FLOSSIES, on the contrary has such data, since all the women included in the study were all over 70 years. Since the number of ovarian cases genotyped herein is relatively large, I feel that the best way out is to compare these data with data from FLOSSIES and/or ExAC.
Minor Comments

-There are some inconsistencies throughout the manuscript, but foremost the Results presented in Table 1 are rather misleading; it seems that RAD51C PVs confer higher risk than BRCA2 PVs, while the authors comment that their results are comparable to previous studies.

-CNVs are excluded from analysis and this should be highlighted and mentioned in the Discussion.

-The mutation rate, i.e. 9.2%, is quite lower that those already reported and there should be a comment on that.

-Exome seq Vs panel seq has differences in the sensitivity of variant detection; again this should be mentioned in the Discussion.

-The two ORs is rather confusing and difficult to follow.

Level of interest
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Quality of written English
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