Reviewer's report

Title: Identification of candidate breast cancer predisposing variants by performing whole exome sequencing on index patients from BRCA1 and BRCA2-negative breast cancer families

Version: 1 Date: 09 Nov 2018

Reviewer: Michel – Longy

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The paper by Shahi et al. entitled "Identification of candidate breast cancer predisposing variants in a virtual panel of 492 cancer-associated genes by performing WES on breast cancer cases from BRCA1/2 negative families with elevated breast cancer risk" reports the exome sequencing of a series of 54 breast cancer patients belonging to BRCA1/2 negative breast cancer families and of 120 control cases recruited for cardiac arrhythmias.

A huge number of genetics variants were detected in both, the cases and the controls without obvious difference between the two groups.

The selection of a 492 cancer associated genes panel allow to objective an excess of nonsense mutation in these genes for the breast cancer group with respect to the controls suggesting the implication of some of them in breast cancer risk but this result is not observed with the frameshift truncating mutations.

My main concern about the WES analysis is that the variant filtration does not take into account the genes involved in the detected mutations. Because of the construction of the study as a case control study, the objective should be the search for an enrichment of genetic variants in specific genes in the breast cancer group with respect to the controls. I suggest selecting the variants that affect the same gene in at least 2 or three cases of breast cancer and compare with the controls. May be the small size of the studied group will not allow to reach significance, but such results should be provided.

In the same way, the table 2 list the genes observed with high impact mutations (named "Protein Damaging Allelic Variants") in the breast cancer group. Five of them are found mutated in two separate cases but no information is provided about the mutational status of these genes in the control group arguing or not for their specificity. Moreover, information about the frequency in the general population of high impact mutations in these genes can be obtained from public mutational databases.
More generally, the genes showing "PDAV" in the control group should be provided at least in supplementary data.

Minor points:

The title is too long and needs to be more concise

Page 7, line 38: "a variant allele ratio" rather "a variant allele frequency"

Page 15, line 24, the sentence "some of these genes were found… different types of cancer" is too vague and needs to be change with precise data.

**Ae 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.

No

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
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