Reviewer’s report

Title: The BRCA2 variant c.68-7T>A is associated with breast cancer

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Reviewer: Abhishek Kumar

Reviewer's report:

This manuscript is interesting for familial breast cancer where authors describe that a splice variant of BRCA2 (c.68-7T>A) is associated with breast cancer.

However, I am not convinced with pathogenic nature of this variant. Reasons are several fold as

a) CADD score of this variant is 3.7 and conservation scores are very low (phastCons 0.514, GERP++ 0.355 and phyloP 0.456).

b) Additionally there is no evidence of impact by SNPeff.

c) Vlinvar database is also predicting it to be begin

Clinvar: phenotype not specified likely benign ClinVar
RCV000168529.2
Breast-ovarian cancer, familial 2 conflicting interpretations of pathogenicity ClinVar
RCV000077384.7
Familial cancer of breast benign ClinVar
RCV000074550.4
Hereditary breast and ovarian cancer syndrome conflicting interpretations of pathogenicity

d) It also appears to be common variant for European populations like allele frequencies are European (Finnish) - 0.006566 and European (Non-Finnish) - 0.002366. I assume a familial variant to be rare in the population like allele frequencies below 0.001. If not requires proper explanation.

As you see completely reverse results are existing databases and by bioinformatics tools for pathogenic nature of this variant. I recommend some experiments to confirm the totally opposite results.

I will like to the improvements as I am supporter of familial cancer genetics, but given facts improvements are required.
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