Reviewer’s report

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

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Reviewer: Paul James

Reviewer's report:

This paper examines the potential pathogenicity of a specific intronic BRCA2 variant previously identified in HBOC families and more recently at a frequency in population controls that raises concerns over the previous classification as pathogenic. The authors report a high frequency of the variant in their clinic based series of HBOC families and go on to examine the segregation of the variant with phenotype in 3 families as well as noting the incidence of 2 further breast cancers in prospective follow up of 24 carriers. Overall the data presented are supportive of a causative role - particularly the very high frequency of the variant compared to relevant population controls - but the limited numbers of carriers included in the analyses as well as the relatively simplified approach to the analysis significantly limits the strength of the conclusions. I agree that the overall conclusion, that the data provides evidence of an association with breast cancer, of unknown strength at this time, is correct but have questions about the analyses presented:

Segregation analysis - why are only 3 of 18 pedigrees included in the analysis? Acknowledging that it is the author's own described method, why use a significantly simplified segregation method that requires pruning of most of the pedigree data when other robust options such as the full likelihood method, or the co-segregation likelihood method are capable of managing this and are now openly available and widely supported by the literature?

Prospective follow-up / annual incidence: again this is a very simplified analysis on small numbers. At least a standardised incidence ratio is needed to account for the age distribution of the carriers in follow-up. Even so the width of the confidence interval around the annual incidence figure means that the strictly correct interpretation of this figure is that it provides no significant additional support for pathogenicity at this stage.

Other queries: what was the overall prevalence of pathogenic BRCA1 and BRCA2 mutations in the 714 families included in this analysis? At 2.5% was the c.68-7 variant the most frequent variant detected?

With only 18 index cases/families found to be carriers it would be useful to include a table summarising their clinical features, particularly in comparison to the cohort as a whole i.e. age of cancer dx, history of ovarian cancer, bilateral breast cancer etc.
It should be noted in the text that the population frequency figures provided come from 1000Genomes and the ExAC database respectively as the properties of these datasets are well known. Did the ExAC figures quoted have the data from TCGA removed?

Please review for language and sentence structure e.g. para 4: electronical (is not a real word)

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