Reviewer's report

Title: Molecular Genetics Analysis of Hereditary Breast and Ovarian Cancer Patients in India

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Reviewer: Irene Konstantopoulou

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Population-based studies of BRCA1/BRCA2 mutations can have a wide publication impact for scientific (differences in mutation spectra) as well as clinical reasons (migration of people). In this paper the authors have screened 91 families from the Chennai (Madras) region of India with characteristics of hereditary breast and/or ovarian cancer for germline mutations in the complete coding region of BRCA1 and BRCA2, as well as for the most common CHEK2 predisposing mutation 1100delC. They have discovered 15 pathogenic mutations (12 in BRCA1 and 3 in BRCA2) of which 6 are novel BRCA1 mutations reported for the first time here. The authors also attempt to associate 5-year survival and other clinico-pathological features with mutation status.

Overall, the data presented are decent and complementary to those previously reported by other Indian groups. The study includes the largest cohort so far of Indian familial breast/ovarian cancer cases. The percentage of carriers found (16%) is in accordance to most international studies performed in groups of similar characteristics.

In more detail:

Major compulsory revisions:

None

Minor essential revisions:

1. (In Materials & Methods:) A clearer description of the 91 cases included in the study should be given. Were they enrolled in a single hospital or several hospitals from the Chennai region? How many have family history? What are the exact criteria for classification as ‘family history’? How many were early-onset and what is the age limit for that classification? This section should include all the above information.

2. (In Results:) Table 1 should have an indication of the mutations that were previously reported by the authors (with a reference), since the current data is summed with that already published.

3. (In Results:) It should be noted here or in the discussion section that mutation c.68_69delAG (187delAG in BIC nomenclature) of BRCA1, a founder in various populations worldwide, is the only recurrent in their patients' sample. It is
reported here 5 times, as c.66_67delAG (187delAG in BIC nomenclature) in sample no. 13 is the same mutation; the confusion appears often in literature as nucleotides c.66-69 are AGAG. Mutation naming should be consistent in all 5 cases of this variant’s carriers.

4. (In Results:) It is not mentioned whether the two CHEK2 variants reported here are novel or previously described. Actually, R406H was reported once previously (Novak et al. 2008, BMC Cancer 8:239) with results that support its neutral effect, consistent to the authors’ findings. This should be discussed somewhere in the manuscript, stressing that (novel?) variant A392V is likely to be pathogenic. Personal and family history of the carrier should be given.

Discretionary revisions:

5. (In Introduction:) More recent references could be mentioned where estimated risks are given (refs 6 & 7). Also, it is recommended that other genes recently implicated in breast cancer risk should be mentioned.

6. (In Results:) In the 1st paragraph, page 6, Gene Bank should be changed to GenBank (a url link is recommended).

7. (In Results:) As the paper is focused on BRCA1/2 mutational analysis, my feeling is that in the statistical analysis results presentation (results section, page 7), the mutation status association with clinico-pathological features should be at least mentioned, if not stressed, even if no correlation was found. This is mentioned in discussion, but it is also useful to include it as a result here.

8. (In Discussion:) First paragraph, page 8: The authors’ finding is not only similar to the work by Wagner et al in an Austrian population, but to numerous other studies worldwide that give a frequency of BRCA1 and BRCA2 mutations around 20% when studying high-risk families in heterogeneous populations. This discussion should be made in a broader context, as it concerns the major finding of this work: BRCA1/2 mutation prevalence in the population studied.

9. (In Discussion:) The second paragraph (page 8) discusses two different aspects of the authors’ results: (a) that breast-ovarian cancer families tend to show a greater prevalence of BRCA1 rather than BRCA2 mutations, and (b) present results compared to results from other Indian groups. These separate subjects should be better handled in separate paragraphs, where the point should be made clearer. Table 4 is helpful in that direction.

10. (In Discussion:) Concerning the missense variants, it would be helpful if Table 2 included the number of cases reported in the BIC database, as an indication of their overall frequency.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being
published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests