Reviewer's report

Title: Prevalance of BRCA1 and BRCA2 mutations in familial breast cancer patients in Lebanon.

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Reviewer: Irene Konstantopoulou

Reviewer's report:

This work presents the first attempt to identify the prevalence and spectrum of BRCA1 & BRCA2 mutations in the Lebanese population.

Overall, the paper is in most parts well written and the data presented are novel and decent. However, they are not described in clarity and therefore a major revision of the Results section is recommended before publication.

In more detail:

Major compulsory revisions:

1. In Results, throughout the whole section and including Tables, there is confusion about the clearly deleterious mutations reported and the suspected deleterious variants. In detail, it is stated in paragraph 2 that “Five confirmed disease-associated BRCA1 mutations and two confirmed disease-associated BRCA2 mutations were found in this cohort”, however in Table 1 only the nonsense mutation W1815X (found x2) is reported as clearly deleterious, and the two missense mutations C44F (found x2) & P142A (found x1) are designated by asterisks as “considered deleterious”, which in my mind is not the same as “confirmed deleterious”. Moreover, there is no justification in the following paragraph (Results, paragraph 3) for this classification (references proving pathogenicity) other than the vague family information. In fact, there is an abundance of evidence in the bibliography towards the pathogenicity of the first mutation (p.C44F, a RING-finger domain mutation), both functional and in silico, but very little evidence exists for p.P142A. These references should be retrieved and mentioned. Also, it is advised that pedigrees should be included for these 3 families and, if possible, segregation analysis of the variants should be performed to show co-occurrence with the disease.

2. In concordance to the above, it should be clear in Tables 1 and 2 which are the definitely deleterious and which are the suspected deleterious mutations. Maybe a separation of all genetic variation found in three categories (deleterious, unclassified variants, known polymorphisms) should help make the Table data more clear.

3. Reference also needed for BRCA2 mutation causing exon skipping (Results paragraphs 4 and 5).

Minor essential revisions:
1. In Introduction, end of paragraph 3, there is a much more recent reference that I believe should be used instead (or together with) ref. 8: Lakkis NA, Adib SM, Osman MH, Musharafieh UM, Hamadeh GN, ‘Breast cancer in Lebanon: incidence and comparison to regional and Western countries’, Cancer Epidemiol 2010, 34(3):221-5. According to this, median age for breast cancer onset in Lebanon is 52.5 years.

2. In Discussion paragraph 1 ‘deleterious or pathogenic’ should be either ‘deleterious’ or ‘pathogenic’.

Discretionary revisions:

1. The first inclusion criterion for participation in the screening cohort (‘A’ in Materials & Methods, under ‘Participants’) is two or more relatives with breast cancer at any age. This is not generally used in similar studies and I believe is the main reason for the reported low penetrance (12%) of BRCA1 and BRCA2 mutations in the 72 families screened. In Discussion (2nd paragraph) this is very briefly addressed, maybe it could be explained in more detail.

2. Discussion is in general well justified. One additional comment may be on the possible existence of founder mutations in the Lebanese population. Testing a larger cohort for the two mutations found to recur in your population (BRCA1 p.C44F & p.W1815X) could be a good start.

Concluding, I believe that when the above issues have been successfully addressed, this is a work worth publishing, as all population-specific studies of BRCA1-2 mutations have a wide scientific as well as clinical impact.

**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