Author's response to reviews

Title: The frequency of BRCA1 founder mutation c.5266dupC (5382insC) in breast cancer patients from Ukraine

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Date: 2 September 2015

Author's response to reviews: see over
Author's response to reviews

Title: The frequency of BRCA1 founder mutation c.5266dupC (5382insC) in breast cancer patients from Ukraine

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Version: 2 Date: 19 August 2015

Author's response to reviews: see over
Reviewer's report

Title: The frequency of BRCA1 mutation in breast cancer patients from Ukraine

Version: 2 Date: 15 July 2015

Reviewer: Frans Hogervorst

Reviewer's report:

major compulsory revisions:

1: In the last paragraph of the findings section the authors mention specifically: that in contrast to other reports our results suggest no difference in ... mutation frequencies ......between patients with and without family history of the disease. This is an important message however the authors don't provide any data other than : We documented family history of disease. Can the authors describe in more detail the family history data which support their findings e.g by providing a table.  
*We described in more details the family history data, which support our findings.*

2: I miss a recommendation /conclusion whether or not to screen for the mutation in all Ukrainian breast cancer patients

*We added a recommendation about importance to screen for the mutation in all Ukrainian breast cancer patients.*

minor essential revisions

3:abstract: carriers instead of bearers.

*We changed “bearers” by “carriers”*

4:5382insC , please mention once the HGVS nomenclature: c.5266dupC p.Gln1756fs

*We mentioned the HGVS nomenclature*

5:detection frequency: 4.66%, use 4.7% (same holds for other percentages). the overall numbers are small and do not justify such detailed percentages.

*We rounded the percentages*

6:last paragraph findings: replace 'in our result' by 'our results'

*We replaced 'in our results' by 'our results'*

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

Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I have no competing interest
Reviewer's report
Title: The frequency of BRCA1 mutation in breast cancer patients from Ukraine
Version: 2
Date: 17 June 2015
Reviewer: Rob B van der Luijt

Reviewer's report:

General comment on the manuscript:
In the manuscript submitted by Gorodetska et al, the results of a study on the frequency of the BRCA1 founder mutation 5382insC (i.e. mutation nomenclature according to HGVS guidelines: c.5266dupC) in breast cancer patients from Ukraine are presented. This BRCA1 sequence change is a well-known founder mutation that most likely arose from a single ancestor about 1800 years ago in Northern Europe and since then has spread to several populations, including the Ukrainian. The authors used a mutation-specific assay to determine the frequency of this particular mutation in a series of 193 breast cancer patients from Ukraine. Although their report does not provide new insights into the characteristics and demographics of this mutation, the paper could still be interesting to the BRCA-genes associated breast cancer community. It re-emphasizes the important role of this mutation in the etiology of breast cancer in this particular population, where (if I understand correctly) genetic testing has not yet reached the mainstream in breast cancer diagnosis and management. However, before the paper is suitable for publication, several major and minor issues have to be addressed, as can be found below.

Major Compulsory Revisions:
(1) although the founder mutation discussed in the paper is well-known under its legacy or traditional name 5382insC, the authors should also describe the mutation according to the most recent HGVS guidelines for mutation nomenclature. A way to achieve this is, to describe this mutation at least once as c.5266dupC while referring also to the traditional name 5382insC.

We described this mutation as c.5266dupC while referring also to the traditional name 5382insC.

(2) the title should be more specific. Suggestion: The frequency of the BRCA1 founder mutation c.5266dupC (5382insC) in breast cancer patients from Ukraine.

We changed the title by “The frequency of the BRCA1 founder mutation c.5266dupC (5382insC) in breast cancer patients from Ukraine

(3) the authors state that the patients were 'haphazardly selected'. It may be better to state that the patients were unselected cases of breast cancer (if indeed the case).

We changed “haphazardly selected” by unselected cases of breast cancer”

(4) The reference by Chan et al (1999) is numbered as [19] in the body of the text. However, in the references list it is numbered as [20].

We changed the number of this reference.

(5) The authors conclude that the frequency of the BRCA1 mutation 5382insC is similar in patients with and without a family history (FH) of breast cancer. However, they detected the mutation in 5 / 90 patients with a FH of (breast) cancer and in 1 / 45 patients without a FH of breast cancer.

- why do the authors reach their conclusion?
We concluded that the frequency of the BRCA1 mutation 5382insC is similar in patients with and without a family history (FH) of breast cancer using such statistical method as Fisher's exact test. We have noted F–test values in the article.

- what about the remaining 3 mutation carriers (total is 9, of which 5 have positive FH and 1 has negative FH).

Not all patients had data about family history. We have noted this in the article. We don’t have information about the remaining 3 mutation carriers with regards to FH

- 193 patients were tested for the BRCA1 mutation: how many had a positive or a negative FH of breast cancer? This is only reported for (90 + 45 =) 135 patients.

We documented family history (FH) of disease in 135 patients, but totally screened 193 person. We have noted this in the article.

(6) However plausible, the statistical significance of the difference in ages of onset between mutation-positive and mutation-negative patients may have to be stated.

**Minor Essential Revisions:**

(1) The name of the mutation is inconsistent throughout the manuscript: 5382insC as well as the incorrect 5328insC occur at several places.

*We corrected the name of the mutation*

(2) BRCA1 mutation 'bearers' could be replaced by mutation 'carriers'

*We replaced 'bearers' by mutation 'carriers'*

(3) The article should state that BRCA1 (and BRCA2) mutations are not only associated with an increased risk of breast cancer, but also of ovarian cancer.

*We noted that that BRCA1 (and BRCA2) mutations are not only associated with an increased risk of breast cancer, but also of ovarian cancer and some other types of cancer.*

(4) The authors could include a statement that identification of the BRCA1 mutation may lead to appropriate management not only in symptomatic patients, but also allows presymptomatic (or predictive) testing in at-risk family member of patients, contributing to early detection and prevention of breast cancer.

*We included a statement that identification of the BRCA1 mutation may lead to appropriate management not only in symptomatic patients, but also allows presymptomatic (or predictive) testing in at-risk family member of patients, contributing to early detection and prevention of breast cancer.*

**Discretionary Revisions:**

(1) As this journal primarily deals with genetics, there is no strict need to explain the meaning of DNA in the List of abbreviations.

*We removed the meaning of DNA out of the List of abbreviations*

**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:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests.