Author's response to reviews

Title: Evaluation of the need for routine clinical testing of PALB2 c.1592delT mutation in BRCA negative Northern Finnish breast cancer families

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Author's response to reviews: see over
Dear Editor,

Thank you very much for your response concerning our manuscript “Evaluation of the need for routine clinical testing of PALB2 c.1592delT mutation in BRCA negative Northern Finnish breast cancer families” by Haanpää et al., and for the opportunity to submit a revised version of the manuscript for your further consideration.

We would like to thank all the reviewers for their valuable comments. We have made modifications to our manuscript according to reviewers’ requests and the changes have been highlighted in red. Here are the point-by-point descriptions of the changes made and our response to the concerns of the reviewers. We hope that the revised manuscript is now suitable for publication in *BMC Medical Genetics*.

I am looking forward to hearing from you soon.

Yours sincerely,

*Robert Winqvist*

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RESPONSE TO THE REVIEWER COMMENTS

Reviewer Sanna Pakkanen

Major Comments:

Question 1
The authors found that in the Northern Finnish 1997-2011 study cohort 4.8% of the 62 female index individuals tested negative for germline mutations in BRCA1/BRCA2 were PALB2 c.1592delT mutation carriers. The authors suggest that PALB2 c.1592delT testing should be a routine part of national counselling protocol.

However in a study by Kuusisto et al. (2011) (http://breast-cancer-research.com/content/13/1/R20) with very similar patient material from Tampere University Hospital District, 82 BRCA1/BRCA2 mutation negative index females were tested for PALB2 c.1592delT mutation and no mutation carriers were found. The authors have not discussed this contradictory finding. Could there be regional differences in the frequency of this mutation in Finland? Is it possible to confirm the finding in a nationwide breast cancer family data?

Indeed, in Kuusisto et al. they did not identify any PALB2 mutation carriers, which was a bit surprising, because the c.1592delT alteration seems to be prevalent in whole Finland. In a study by Heikkinen et al. (2009, Clin Cancer Res) utilizing a patient cohort from the Helsinki University Central Hospital they found 19 PALB2 mutation carriers among 947 familial breast cancer cases (2%), which is slightly lower than in the current study. In addition, our previous study by Erkko et al. (2007, Nature) included also an unselected breast cancer cohort from the Tampere region (n=888), in which altogether four PALB2 c.1592delT carriers were identified.

Although the previous results suggest that there might be some slight regional differences in the population frequency of this mutation potentially resulting from founder effects, so far it has been identified in breast cancer patients originating from all of the studied geographical regions in Finland (Oulu, Helsinki, Tampere (in Erkko et al.) and Kuopio]. Consequently, we recommend the same screening protocols for the entire country.

Question 2
How is the pedigree data collected? Are family histories registry based confirmed?

The pedigree data was collected in the Department of Clinical Genetics at the Oulu University Hospital by a Clinical Geneticist (MD) during the clinical consultation of the patient. All cancer cases have been confirmed through pathology reports, if they existed. For very old cancer cases there were no medical records available.
Question 3
In Abstract the authors state that given the potential benefits versus harms of this testing, this PALB2 c.1592delT should be a routine part of the genetic counselling protocol. The benefits are well discussed later in text, but the harms have not been addressed. Here the possibly found mutation carriers may have a risk to other cancers too (pancreatic cancer).

We consider the only potential harm of the PALB2 mutation testing offered to people already screened for BRCA1/2 mutations to be the slight cost of the mutation analysis, which is why this issue has not been discussed any further. If a mutation carrier is identified, appropriate follow-up can be arranged. The knowledge of a person’s PALB2 mutation carrier status would be advantageous for malignancy risk assessment as well as for the surveillance of certain other disease types besides breast cancer.

Minor comments:

Question 4
In Materials and Methods, Patient material first paragraph, when defining the Lund criteria number four criteria is “four or more relatives”. Should it be ”four or more first degree relatives”?

According to Lund criteria, if there are five or more (index + relatives) cancer cases in the whole family, the family fills the criteria. These cancer cases should be 1st or 2nd degree relatives to each others. Consequently, we would like to leave the text as it is.

Question 5
In Figure 2 FAM A on female is marked as “Cancer ?” If that cancer is not confirmed is it better left out from the pedigree?

To avoid any confusion, “Cancer ?” has now been renamed to “Cancer” to indicate cancer of an unknown type for which no pathology report was not available to verify this very old diagnosis. We think that this information is relevant and would therefore like to keep it in Figure 2. This marking has also been clarified in the figure legend.

Question 6
The information on family pedigrees on Figure 2 and in supplementary data Table 1 are different. Has the family ids been mixed? (For example FAM A in figure 2 does not have a breast cancer female whose age at diagnosis is 43).

We thank the reviewer for pointing out this mistake. Now all the family IDs have been checked and changed accordingly.
Discretionary revisions

Question 7
In Figure 2, how is the index person selected?

The index person is the one who has contacted the Clinical Genetics department, usually with a referral from the Oncology department. Genetic testing of BRCA genes is always performed for that individual in the family who has had her cancer at the youngest age, if she is alive and willing to come to the genetic counselling.

Reviewer Maria A Caligo

No required revisions.