Author’s response to reviews

Title: PALB2: research reaching to clinical outcomes for women with breast cancer

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Author’s response to reviews:

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Dear Rodney,

RE: HCCP-D-16-00002

Thank you for the helpful feedback on our invited review article. We address each of the comments from the reviewers below.

Reviewer #1:
This is a state-of-art review on PALB2 gene.

Just a few minor comments:

1. Was the PALB2 ever defined as a really "moderate risk gene"? If yes, could the references be provided? I am not really sure that a change in the perception of its BC-predisposing role has occurred, because many investigators always considered PALB2 as a true hereditary BC gene.
The authors of this review are not suggesting that there has been any new data that questions PALB2 as a bona fide breast cancer predisposition gene. What we are addressing is the increase in evidence related to the magnitude of the breast cancer risk associated with mutations in this gene. We detail the new evidence that estimates the risk of breast cancer associated with loss-of-function mutations to be comparable to mutations in BRCA2, which is contrary to the report of Rahman et al., (Nature Genetics 2007) who reported “the increase in breast cancer risk associated with PALB2 monoallelic mutations is clearly more modest than that conferred by BRCA2 monoallelic mutations, which result in approximately a tenfold increase in risk”. Until very recently the literature has, almost without exception, categorised PALB2 as a moderate risk breast cancer susceptibility gene. We have cited Rahman et al 2007 to clarify this aspect as follows.

Page 4: “It is now well established that women who carry mutations in the PALB2 gene are at similar breast cancer risks as those who carry mutations in BRCA2 [6, 7]) making many rethink the appropriateness of the initial “moderate or intermediate risk gene” label [Rahman et al., 2007]

2. Introduction repeats the Summary in many instances, please double-check to avoid redundancy.

This is a helpful comment and we have edited the abstract to reduce the redundancy. Please refer to the marked up document for details.

3. If we consider a breast cancer patient with a certain number of clinical features of hereditary BC, she would have, say, about 5-20% probability to be diagnosed with either BRCA1 or BRCA2 mutation. If we do not find BRCA1/2 mutation, what would be the probability to find PALB2 truncating mutation? Approximately a quarter of probability of detecting BRCA1 or BRCA2? I think, it is highly desirable to have a very rough estimate of this, although, I understand, this quantitation is indeed challenging.

This is an important question but there is insufficient data to address this question with precision, and there are considerable population-specific issues and considerations. The range of probability proposed by the reviewer (5-20% probably of carrying of BRCA1 or BRCA2
mutation) makes the question even more challenging as the majority of clinical practices would not test for BRCA1 or BRCA2 mutation unless the probability was greater than 10% (as determined in a variety of ways over a number of decades). There is some data for some populations in the context of women who have met criteria for clinical BRCA1 and BRCA2 mutation testing and found not to carry a mutation in these genes. However, there is much variation in the inclusion criteria and or definition of family history in these reports that makes direct comparison and combination inappropriate.

In Australia the estimate is that approximately 1-1.5% of women who meet clinical criteria for BRCA1 and BRCA2 testing in the last two decades carry a PALB2 loss-of-function mutation (Teo et al., Familial Cancer 2013 and Thompson et al., J Clin Oncol 2016) and similar estimates have been published for the Spanish population (Garcia et al., Breast Cancer Res Treat 2009). Other populations have reported a higher frequency (eg Peterlongo et al., report a frequency of 5.3% in the province of Bergamo in Northern Italy, in Genetic Medicine, 2014) and other populations may have lower frequency (eg 0.5% in China; Cao et al., Breast Cancer Res Treat, 2009) or even no contribution from PALB2 mutations (Iceland; Gunnarsson et al., J Negat Results Biomed 2008). A series of reports detailing the outcome of PALB2 mutation screening in a number of studies of women at high risk of breast cancer from a number of populations have been published and reviewed elsewhere – there has not been any significant change in this information since our last review (Southey et al., Appl Clin Genet 2013) and therefore we did not include this detail in the current review.

4. Were the large rearrangements of PALB2 ever investigated systematically, by MLPA or equivalent techniques?

Systematic and or extensive assessment of the role of large rearrangements in PALB2 has not been reported. A small number of single study reports indicate that the frequency (proportion of all PALB2 mutations) of this type of mutation is extremely small. A survey of mutation frequency and type was not the subject of this review.

Reviewer #2:

This is a concise and well written review of the current knowledge of PALB2 germline mutations and their clinical consequences. As the focus of this review is on the relation between PALB2 en hereditary breast cancer, it zou goed zijn to have the words hereditary breast cancer in the title. As PALB2 is (at least) also involved in Fanconi anemia and pancreatic cancer.
In this review the authors describe why it is now justifiable to include mutation scanning of PALB2 in the search for germline mutations in cases of familial breast cancer. As many laboratories are in the process of setting up (breast)cancer gene testing panels this is much needed information.

Some comments:

1. As the focus of this review is on the role of PALB2 in hereditary breast cancer and not or less on other diseases in which PALB2 is involved like pancreatic cancer or Fanconi anemia, breast cancer should be mentioned in the title of this review.

This is an excellent suggestion. We have changed the title to the following;

PALB2: research reaching to clinical outcomes for women with breast cancer.

2. In the abstract it is stated that ‘women who carry mutations in the PALB2 gene are at similarly elevated breast cancer risks to those who carry mutations in BRCA2’. This should be loss-of-function mutations as the authors discuss at the end of this abstract that 'classification of the vast array of non-loss-of-function genetic variants identified in PALB2 is in its infancy'.

This is an excellent point and we have incorporated this detail into the abstract.

3. In the introduction, the authors write that 20% of women who undergo testing are found to carry a mutation in BRCA1 or BRCA2, and that the remainder of the tests are uninformative. This is an unclear statement. In half of the cases in which a mutation is found in BRCA1 or BRCA2 the outcome of the test is still uninformative because the mutation found is a 'variant of unknown clinical significance'. It is better to mention the percentage of pathogenic or causative mutations. How high this percentage is, is dependent on the inclusion criteria for women in the testing program, and is nowadays often much lower than 20%.

The reviewer brings up important detail that sits behind our scene setting text. To keep the text concise and to address the above points from the reviewer we have edited the text as follows;
Page 3: “Indeed clinical criteria used to determine eligibility for BRCA1 and BRCA2 testing in many settings have been founded on the number of affected relatives and their age at diagnosis and then developed over time with increased evidence and local practice issues. Of those women who undergo testing, up to 20% are found to carry a clinically actionable mutation in BRCA1 or BRCA2. Until very recently additional genetic testing was not possible unless other clinical indicators were present (such as Li-Fraumeni syndrome that might indicate genetic testing of TP53). Women and their families who received uninformative genetic test results for BRCA1 and BRCA2 were clinically managed solely on the basis of their personal and family history. This limited the use of invasive strategies such as risk reduction surgery.

4. On page 6 the 'PALB2 interest group' is mentioned for the first time, reference to the list of references [36] is missing here.

We have added this reference as suggested.

5. There is no reference in the main body of the review to figure 1. The majority of the text of the legend can be incorporated in the body of the review.

We have corrected the error and acted on the suggestion. The figure legend text is now incorporated in a new section titled “Evidence-based translation into breast cancer clinical genetics practice” that also references Figure 1 (page 7).

Thank you for the constructive comments.
Regards,

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