Author's response to reviews

Title: Ten modifiers of BRCA1 penetrance validated in a Norwegian series

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Author's response to reviews:

Comments to referees

Reviewer:
Michelle Wong-Brown

Reviewer's report:
Minor essential revisions:

Intro:
Paragraph 3, 2nd sentence - Sentence structure needs to be changed, do not understand what the reasons are
Corrected
Paragraph 3, last sentence - Sentence structure needs to be changed
Corrected

Discussion:
Paragraph 1 - Is there a different statistical test for small sample size to test for complex interaction? According to the methods, power calculation had been performed to determine sample number, so why is the sample size now too small to detect this interaction?
No, power calculations and upon which premises they were made, were as described. One such premise is prevalences of the SNPs examined. When considering results like this, variations by chance (which may both increase and deflate results of testing for significance) is to us but an obligatory discussion when considering to which degree the results are conclusive.

Paragraph 2 - "Most of the mutation carriers...." A percentage value may be more
How does having 2 mutations/SNPs affect RR and OR?
Testing for combinations would lead to a large number (10!) of strata and testing outside the format of the report which is a prospective validation of 10 separate associations reported in literature, and the question of random variations in limited numbers would be difficult to handle.

Conclusion:
"Do not know which of the associations are valid". Does this mean that the study has not confirm validity as claimed in the title? The title may have to be changed if this is the case.
Re-writen in text to avoid misunderstandings. The title means to us that we have validated the claimed associations, not that our validation did confirm all of them.

Quality of written English:
Needs some language corrections before being Published
Language corrected.

Reviewer:
Evgeny Imyanitov
Reviewer's report:
This is a very elegant paper. The authors have decided to compare small groups of BRCA1 carriers with “extreme” genotypes, i.e. young-onset breast cancer patients vs. (more or less) elderly healthy women.
Minor comments:
There are multiple inaccuracies and inconsistencies in punctuation, e.g. sometimes dots are typed in duplicate (.. instead of .), title is ended by a dot, etc.
Please check the submitted manuscript for the formatting.
Corrected
First paragraph of the introduction is unnecessary for HCCP readers.
We respectfully disagree, but we will follow editor’s advice.
Instead I
would suggest to provide clear-cut justification for the comparison of SMALL groups with EXTREME phenotypes – I think, this original approach is a main advantage of the study.
This now stated in methods, where we think it fits best.

Methods can be presented as a single paragraph, there is no need in subsections.
We have partly followed the advice, but found one single section to be too compact.

Please consider the correction for multiple comparisons. How many p < 0.05 are expected to be obtained in case of random distribution?

We did 10 free-standing tests to validate 10 reported associations, in contrast to CIMBA publishing 10 separate papers to these ends. We do not find that our 10 results should be corrected for multiple testing. This should be done if looking for associations without any assumptions of what to find (cfr comments on why we did not test for combinations of SNPs, for which we had no established hypothesis of what to find). Considering random variation in the test results, the results were expected to be distributed around expected outcome – cfr comments above on why we may have failed to demonstrate a true association despite power tests indicating that we should find it. When testing for many (>>10) associations this way, one may look at the distribution of the test results to consider deviation from random distribution, but 10 results were considered insufficient for such an approach, also when bearing in mind that the 10 SNPs had different expected outcomes.

Table 2 does not add to the paper, can be omitted.

The table lists the temperatures necessary for reproducing the experiments, and should thus be declared. The table can be listed as supplementary information, at editor’s decision.