Author’s response to reviews

Title: A family pedigree of malignancies associated with BRCA1 pathogenic variants: A reflection of the state of art in China

Authors:

Wenhui Li (liwenhui1025@163.com)
Lei Li (lileigh@163.com)
Ming Wu (wuming@pumch.cn)

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Author’s response to reviews:

Reviewer #1: The authors improved the manuscript significantly. However, there are some minor corrections required.

1) Page 4, line 94 - please provide the BRCA1 variant.

The same referees to supplementary materials - it is not clear what was the nature of the variant. I assume it might be a deletion of entire exon 8?? That needs to be corrected.

Response: Thank you! As you have pointed out, it is indeed a deletion of the entire exon 8, which was validated by qPCR. According to your instructions, we have added relevant text (page 4, line 83).

2) Pedigree: for alive individuals do not use "Death: N/A", just insert the diagnosis and the age of onset.

Regarding the way of presentation for other cancers - please check the https://www.ncbi.nlm.nih.gov/pubmed/18792771 for recommendations.

Response: Thank you! We have made the modifications according to your instructions (Figure 1 and its legend; and page 4, lines 67-68).
Reviewer #3: This is a report of a relatively large family of Chinese ancestry, members of which carry a deleterious BRCA1 variant. Simultaneously, the authors highlight lack of specialized hereditary cancer centers in China.

Firstly, the Discussion section should be shortened. Focus on the main points raised in your study, i.e. multiple cancer diagnoses in the family reported and the lack of experts in China.

Response: Thank you! We have made the modifications according to your instructions and have deleted irrelevant contents from the Discussion. The total words of the Discussion section were reduced from 1201 to 721 words.

-1st paragraph should be polished and rephrased.
Response: Thank you! We have rewritten the first paragraph.

-2nd paragraph (lines 113-121) is irrelevant, at least where it is, and it doesn't flow with the rest of the text.
Response: Thank you! We have deleted the text according to your instructions.

-I am really worried about the genetic testing in a minor. Although the authors tried to explain the reasons why they pursued the test, it still is against all Bioethics rules. What is the relevant law in China?
Response: Thank you! Your concern and attention made a profound impression on us. As you have pointed out, testing of a juvenile is against bioethics. However, there is no relevant law in China for appropriate ages in genetic counseling. In an expert consensus about the testing of BRCA1/2 in epithelial ovarian cancer published in Chinese Journal of Obstetrics and Gynecology (in Chinese language, 2017, 52(1):8-10), the age issue is not discussed. In the Law on the Protection of Minors published in 1991, last modified in 2016, there is no mandatory regulation for genetic testing. As this is an extremely important problem, we have addressed your concern in the Discussion section (page 7, lines 138-139, lines 144-145). We are very sorry for this problem, and we state that genetic testing for asymptomatic children in this report is beyond the authors’ consensus and general practice and that the flaw and limitation in the current professional and administrative regulations should be addressed soon.

- The authors report QPCR as a method, but this is not described anywhere in detail.
Response: Thank you! We have supplemented the description (page 5, lines 84-88).

Other Minor Comments:

1. What is the exact nomenclature of the mutation?
Response: Thank you! We have added the standards of nomenclature (page 6, lines 86-88).

2. All abbreviations used should be refereed before using them.
Response: Thank you! We have checked the text and made modifications (page 3, line 42; page 5-6, lines 105-106).

3. There are multiple grammatical errors, eg. line 72 (pg5), throughout.
Response: Thank you! We apologize for such errors. We have checked the texted carefully and sent the manuscript for language editing for a third time. The certification is attached as a supplement.

4. After the age (number) the word years should be added.
Response: Thank you! We have made modifications (page 4, line 69, line 71).

5. Reference 1 is not relevant to the sentence.
Response: Thank you! We have changed the reference.

6. Reference 3 is not appropriate - please proceed to a careful read-through of all references.
Response: Thank you! We apologize for such problem, and have checked all the references and made proper changes (References 1, 3 were replaced, and 15 references with their text were deleted)

7. Figures and tables are not numbered correctly.
Response: Thank you! We have made the modification.