Author’s response to reviews

Title: Molecular Epidemiology and Hematologic Characterization of δβ-thalassemia and Hereditary Persistence of Fetal Hemoglobin in 125661 Families of Greater Guangzhou Area, the metropolis of Southern China

Authors:

FAN JIANG (496779026@qq.com)

Can Liao (canliao7981@21cn.com)

Version: 1 Date: 03 Jan 2020

Author's response to reviews:

Reviewer #1: This manuscript reports significant observations about the prevalence and molecular epidemiology of HPFH/δβ-thalassemia in Southern China that will, ultimately, help to improve thalassemia screening programs and genetic counseling in China. Nevertheless, in my opinion, a suitably revised version of this manuscript might be appropriate for publication in BMC Medical Genetics.

Major points:

1. The Background section is too short and needs to gradually describe in more detail about HPFH and δβ-thalassemia molecular characteristics, phenotype, prevalence and epidemiology in general and in Southern China specifically. Thus, providing the reader the general background of these diseases, why is important to study (i.e. in terms of the disease-specific burdens) and how epidemiology and prevalence studies help to construct guidelines for prenatal screening tests. Furthermore, in my opinion, the first paragraph of the Discussion section should be moved to the Background section. A table listing the most commonly known mutations and their associated phenotypes (please include standardized vocabulary, e.g. HPO codes, if available) of HPFH/δβ-thalassemia in Southern China will greatly enhance the Background section.

Answer: We have revised the background section according to the reviewer’s comment. Please see line 6-30 of background in the revised manuscript. We have also listed the most commonly known mutations and their associated phenotypes in Table 1.
2. In Results section a summary table listing all the mutations identified in this study along with the number and percentages of people/couples having theses mutations and their main clinical symptoms will provide the reader a quick summary of the results, serve as a reference point for prenatal screening tests and provide more information about the genotype-phenotypes associations.

Answer: We have revised the manuscript according to the reviewer’s comment. The hematological data of individuals with the main genotypes have been presented in Table 2 in the revised manuscript.

3. In line 29-30 of the Results section it says that none of the subjects were from the same family creating confusion on how it is a (line 39-40 of the same paragraph) of Chinese. Please clarify or choose a more suitable word.

Answer: We have looked it up by many ways, but no suitable word was found. We, therefore, have clarified the word “familial prevalence” in the revised manuscript. Please see line 14-17 in the result section. If the reviewers or editors suggest more suitable word, we’d like to replace “familial prevalence” with it immediately.

4. Results section line 44-45: please provide more information on your observation about the significant differences in the prevalence of deletional HPFH/δβ-thalassemia between Guangzhou districts. What is the composition of the population? How the population diversity affects the carrier rate of these disorders?

Answer: We have provided some information about the composition of the population in Guangzhou in the revised manuscript. Please see line 24-27 in the result section. As the information of the population diversity is hard to be collected, we have discussed how the population diversity affected the carrier rate of these disorders in line 1-27 in the discussion section.

5. I would expect a small discussion (2-3 lines) about the significance of your observation of the homozygous carrier of the Aγ-196 C-T mutation (line 53-54 of the Results section). This is an important finding which you should emphasize its significance.

Answer: We have revised the manuscript according to the reviewer’s comment. Please see line 103-122 in the discussion section.
6. Please review the Discussion section and add the respective references when comparing your findings to other studies. As an example, in line 10 of the second paragraph: "Compared to the three types […] than 6% of our study" in comparison to which study?

Answer: We revised the manuscript according to the reviewer’s suggestion. Please see reference 9, 10 and 20.

7. Line 32-33 of third paragraph of Discussion: please provide an explanation of why capillary electrophoresis is better than HPLC.

Answer: we have provided an explanation of why capillary electrophoresis is better than HPLC according to the reviewer’ comment. Please see line 64-68 in the discussion section.

8. Line 53 of the fifth paragraph of Discussion: could you suggest possible ways or experiments for exploring the mechanism of γ-thalassemia caused by HBG2-HBG1 gene fusion?

Answer: We have revised the manuscript according to the reviewer’s suggestion. Please see line 87-89 in the discussion section.

Minor points

1. Extra spaces, minor grammatical and spelling errors need to be corrected throughout the paper.

Answer: We have tried our best to remove these errors. And the company named American Journal Experts (AJE) has helped us to revise the manuscript to eliminate the minor mistakes.

2. In Fig.2 legend please add a more detailed caption to the figure.

Answer: We have added a more detailed caption to the figure 2 in the revised manuscript.
Reviewer #2: Comments to the authors

This is an interesting paper that presents a survey of haemoglobinopathy mutations in a region of southern China. The work is of high quality. The results are interesting and are likely to be clinically helpful, in terms of enhancing diagnosis and genetic counselling. In particular the observation that the Italian ndHPFH is common in this region is new. In addition the analysis of novel deletions and characterisation of mutations that involve the foetal globin genes, including deletion of one of the genes, or triplication, is also very interesting.

I have only a few minor comments.

1. The paper would be enhanced by an illustration of the b-globin locus showing Chinese, Taiwanese, Hb Lepore and the SEA deletions. These are the main ones found, as shown in the pie chart, but many readers may benefit from seeing how they affect the locus.

2. Would it be possible to present a table with the main genotypes shown in the pie chart and the levels of HbF and HbA2?

Answer: We have revised the manuscript according to the reviewer’s comment. Please see Fig. 2 and Table 2.

3. In the final page of the manuscript it is stated that "Using K562 cells and HUDEP-2 cells, Gabriella E revealed that mutations at -200 of the γ-globin promoter disrupt ZBTB7A for HbF repressor binding" but not reference is given. I think this refers to work by Gabriella E Martyn et al.?

Answer: We have revised the manuscript according to the reviewer’s comment. Please see reference 27.

Note: In the revised manuscript the corrections and/or supplementations have to be highlighted in red font!