

Dear editor,

Thanks for your professional work on our article. As you are concerned, there are several problems that need to be addressed. According to your nice suggestions, we have made corrections to our previous draft. The amendments are highlighted in red in the revised manuscript.

The following is a point-to-point response to reviewers's kind comments.

Reviewer 1

1. The following to be reviewed 1. p3 line 61 hematopathy p77 unsaturated iron.

Answer: We agree with this suggestion and have modified the terminology and spelling individually in p4 line 86 and p6.

2. Please review terminology and spelling More details on the instrumentation used for NGS

Answer: We have reviewed terminology and spelling, and More details on the instrumentation used for NGS have been described in p4-5, line86-100 in the revised version.

Reviewer 2

1. Please mention OMIM number with each malformation and gene reported in the text.

Answer: we have mentioned OMIM number in the article (p2 line 37).

2. Please mention the prevalence estimate of Hereditary spherocytosis in the global populations and the study populations.

Answer: The prevalence estimate of Hereditary spherocytosis was mentioned in the article (p2 lin 39-43).

3. Unclear statement, "a suspicious positive family history, and then finally confirmed by genetic sequencing.". Please elaborate the statement. What is the phenotypic presentation in the father of the index person.

Answer: We apologize for the unclear statement generated by the previous version of the manuscript and sincerely hope that we have elaborated the statement clearly in this new version (p7 line 131-133). And the phenotypic presentation in the father was described in p3 line 66-67, p6 line 128-129.

4. The protocol of next-generation sequencing is not described. Please give detail of library preparation, controls, cut-off values, assembly used, etc.

Answer: We thank the reviewer for pointing out this issue. We have added the protocol of next-generation sequencing in the revised manuscript (line 86-97).

5. The variant filtration strategy has not been given.

Answer: We will give the variant filtration strategy in the revised manuscript (line 97-100).

6. It is not clear who many rare variants were left in the final filtration scheme.

Answer: Frequencies of identified variants had to be equal to zero or below 1% in the Asian populations in all used databases, such as HGMD, ExAC, gnomAD and 1000 genomes databases.

7. Please give the allele frequency of the variant as reported in public databases like 1000G and ExAC.

Answer: It indeed hasn't been reported in any public databases so far.

8. Discussion part is weak and redundant. Second paragraph of Discussion may be shifted to Introduction.

Answer: We agree. We have appropriately removed part of the discussion. And the second paragraph of Discussion is shifted to Introduction in the new version based on your suggestions.

9. Strengths and limitations of the study are not given.

Answer: Thanks again. We indeed did not give the limitations of the study. We will give the advantages and limitations of the study in the new manuscript (p8 line 176-179; p9 line 189-193).

Reviewer 3

The manuscript is well written and may be accepted for publication. The authors may include in the discussion a section on the mutation-nonsense mutation (exon23:c.G2467T;p.E823X) of ANK1. This would help the general readers about the location, impact and consequences of the mutation. Unsaturated iron on page 77.

Answer: Thanks for your constructive comments. We agree with your suggestions and include in the discussion a section on the mutation-nonsense mutation of ANK1 in the new manuscript (p6 line 121-129). And we have modified the terminology in the article (p6).

Science editor:

Next-generation sequencing identified a new nonsense mutation in ank1 in patients with hereditary spherocytosis. The manuscript is well written and can be helpful for the readers to

ameliorate the diagnostic and therapeutic approach for this scenario. Nevertheless, there are a number of points that may deserve some revisions.

1. The format of the abstract does not conform to the format of case report, and the author needs to adjust the format.

Answer: We have adjusted the format of the abstract and sincerely hope it will conform to the format of case report.

2. In the introduction, the incidence rate of epidemiology should be supplemented.

Answer: We agree with this suggestion and the incidence rate of epidemiology is supplemented in the revised manuscript.(p2 line 39-43)

3. figure 1 is not a figure.

Answer: We apologize for the mistake and it has been corrected (p6).

Company editor-in-chief:

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Clinical Cases, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1 Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". The title of the manuscript is too long and must be shortened to meet the requirement of the journal (Title: The title should be no more than 18 words). Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor. Authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.

Answer: Thanks for your practical suggestions. We have shortened title of the manuscript to meet the requirements(p1). The article is modified according to the format requirements.

As soon as receiving your E-mail, all the authors discussed the comments one by one carefully. And we will correct all the mistakes based on your nice comments to meet the journal's requirement. We will be happy to edit the text further, based on helpful comments from the reviewers and we really appreciate your help.

Sincerely yours,

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