Author’s response to reviews

Title: Compound heterozygous LPIN2 pathogenic variants in a patient with Majeed syndrome with recurrent fever and severe neutropenia: case report

Authors:

jun liu (ljun2005@163.com)
Xu-Yun Hu (hu_xuyun@126.com)
Zhi-Peng Zhao (bchpeng@foxmail.com)
Ruo-Lan Guo (guoruolan_bch@163.com)
Jun Guo (guojunbjmu@163.com)
Wei Li (liwei@bch.com.cn)
Chan-Juan Hao (hchjhchj@163.com)
Bao-Ping Xu (xubaopingbch@163.com)

Version: 1 Date: 21 Oct 2019

Author’s response to reviews:

Dear Editors and Reviewers:

Thank you for your letter and for the reviewers’ comments concerning our manuscript entitled "Compound heterozygous LPIN2 pathogenic variants in a patient with Majeed syndrome with recurrent fever and severe neutropenia: case report" (MGTC-D-19-00253). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. Revised portion are marked in red in the paper. The main corrections in the paper and the responds to the reviewer's comments are as flowing:

1. Majeed syndrome is rare and so reports should be encouraged to build a better picture the natural history of this disease. In addition to its value as a case report this work contains two novel contributions: i. identification of a novel mutation and ii. the severity of the neutropenia. Regarding the first point, the novel mutation identified is a 4bp deletion leading to a frameshift and premature termination codon so this clearly pathogenic. The very severe neutropenia is potentially interesting but neutropenia has been reported previously in Majeed Syndrome, as the authors themselves point out. Perhaps the it should be highlighted in the abstract and introduction that neutropenia is a known feature of Majeed Syndrome and is worse in this particular patient.
Response: The picture has been changed. Neutropenia has been mentioned in the abstract.

2. This work needs extensive editing to correct the English as currently some of the meaning is obscured.

Response: Manuscript has been modified.

3. Some of the terminology should be rewritten to improve readability, for example it could be pointed out that erythrocyte sedimentation rate and C-protein reactivity are markers of inflammation.

Response: We revised the sentence in page 3(lines 77-79).

4. The patient and mutation reported in Roy 2019 (PMID: 31377798 DOI: 10.1093/rheumatology/kez317) should be included in Table 1 and Figure 2 and in the discussion in reference to the phenotypic variability seen in Majeed Syndrome.

Response: We revised Table 1 and Figure 2.

5. The values for neutrophil count should be given per mm3 rather than per L to allow easy comparison with existing literature.

Response: We revised the values for neutrophil count.

6. It should be stated whether IL-1 blockade was tried in this case.

Response: The patient did not use IL-1 blockade. Page 7(lines 160 and 161)

7. MRI scans of the patient's limbs should be included if available.

Response: Because he had no limbs pain, the patient did not do MRI scan. Page 4(line 85)

8. One page 3 (line 100) it is stated that the splice variant was previously reported in reference 2, when in fact it is in reference 3.

Response: We changed the reference order.

9. On page 4 line 130-131 the further information regarding the lipin domains should be given.

Response: We provided more information of the lipin domains. We searched published literature but the function of lipin domains was still unclear.
10. Is it possible this patient has no functional Lipin2 protein? We would have to know the consequence of the aberrant splicing, perhaps the patients LPIN2 cDNA should be sequenced to better define this?

Response: We are sorry that no RNA or cDNA samples of this patient are preserved. According to previous report, this splice site mutation is predicted to produce an R776S change followed by 65 amino acids prior to encountering a stop codon in intron 17 (Arg776SerfsX66 unless another splice site is encountered).

11. Table 1 is very unclear and the references should be more clearly given and the the column headings need to be improved (G should be changed to Gender?).

Response: We revised table 1.

12. In Figure 1 normal chromatograms should be shown and the 4 deleted base pairs should be annotated in case of the deletion, in the case of the point mutation the chromatograms should be annotated with the intron/exon boundary.

Response: We revised Figure 1. We did not perform Sanger sequencing for normal control and therefore we did not have normal chromatograms.

13. In Figure 2 the c.2327+1G>C change should be shown below the line (perhaps still in red) to highlight that this is a previously discovered variant. Also previous literature and gene browsers show 20 exons in LPIN2, whereas Figure 2 shows only 19. This should be checked and clarified.

Response: We revised Figure 2.

14. This is a new paper describing compound heterozygosity for LPIN2 gene in Majeed syndrome showing heterogeneity in clinical symptoms. Two further points may increase the interest of the readers; authors should emphasize the parental segregation of the alleles- in the text - that the patient is compound and second point is that the functional consequences of the variations should be discussed.

Response: We provided more information of the functional consequences. However, no RNA or protein samples of this patient are preserved, so we do not know the actual result. Page 4(line 85)

15. If improvements to the English language within your manuscript have been requested, you should have your manuscript reviewed by someone who is fluent in English. If you would like professional help in revising this manuscript, you can use any reputable English language editing service. We can recommend our affiliates Nature Research Editing Service (http://bit.ly/NRES_BS) and American Journal Experts (http://bit.ly/AJE_BS) for help with English usage. Please note that use of an editing service is neither a requirement nor a guarantee of publication. Free assistance is available from our English language tutorial
Response: My manuscript has been reviewed by someone who is fluent in English.