Author’s response to reviews

Title: Identification of a novel splicing mutation in the SLC25A13 gene from a patient with NICCD: a case report

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Author’s response to reviews:

Dear Editor:

Thanks again for providing us another opportunity to revise our manuscript. As requested, we revised our manuscript in response to the reviewer’s comments. Our point-by-point response can be found below.

We wish that you will now find our revised manuscript suitable for publication in BMC Pediatrics. Thank you in advance for your kind consideration of this paper.

Sincerely yours

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Reviewer reports:
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Dear the Editor of BMC Pediatrics

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While I appreciate the changes that the authors have made, this manuscript can be improved further by adding more information into the differential diagnosis and discussion sections.

The authors have responded to my comments by 1) adding a paragraph describing differential diagnoses based on clinical data, basic laboratory findings and radiologic investigation; and 2) detailing the result of splice site change in Supplementary Table 2.

Here are my comments
- Line 33-46 or line 1-7 of the new paragraph is useful.
- The authors should beware of saying 'the only possible pathogenesis is inherited metabolic diseases' is not absolutely correct. There are still other possibilities. The authors may tone down the statement, such as 'likely possible…'
Reply: Sorry for this inexact statement, we revised this part as required.

- Elevated AFP is not specific finding, it can be found in several metabolic liver diseases including tryosinemia, galactosemia, fatty acid oxidation and cartitine cycle defects, and of course NICCD. I hope the to see authors make use other laboratory data for differential diagnoses, for examples, the elevated lactate level, uric acid level, procaltitonic, ammonia, and glucose. How this values help the authors in supporting and/or excluding which disorder.
Reply: We appreciate the meaningful advice, and we would like to practice in cases in the future. However, according to our knowledge, there is no diagnostic criteria for NICCD in China at present. As described in this manuscript, we first diagnosed this patient with neonatal hepatitis based on typical clinical symptoms, then we excluded infection and congenital biliary atresia. Considering the high frequency in Southern China, NICCD could be the most likely cause. Both result of genetic test and the therapy support this speculate.

- There was nothing wrong with the HSF data and information provided in Supplemental Table 2. To be more specific, I request that the authors add the statement of the predicted protein change as a result of splice site error of the novel mutation they identified c.1841+3_1841+4delAA. How the authors predict about the mutant mRNA for example, the mutant mRNA resulting in exon 17 skipping, aberrant mRNA contacting part of IVS17, and/or an activation of a nearby cryptic splice site and its location, etc. With this/these predictions what is the predicted mutant protein, such as the where the frameshift starts and where the new stop codon take place (if applicable).
Reply: We try to describe the influence of this splice-site mutation more specifically, so we used the NNSPLICE online provided by BDGP (Berkeley Drosophila Genome Project). The result was provided in our revised manuscript and Figure 1c. We wish this could meet the requirement.