Dr. Lian-Sheng Ma,
Science Editor, Company Editor-in-Chief,
Editorial Office

Dear Dr. Lian-Sheng Ma,

Thank you very much for reviewing our manuscript entitled "Neonatal cholestasis can be the first symptom of McCune–Albright syndrome: A case report and review of literature". We greatly appreciate your comments to our manuscript and your advice to resubmit the revised manuscript to the World Journal of Clinical Pediatrics. We tried to respond to the reviewer's comments and advises point-by-point as shown below and revised the manuscript accordingly. All changes in the manuscript are highlighted in bold to facilitate the re-review of the manuscript.

We sincerely hope that you will find our manuscript acceptable for publication in the World Journal of Clinical Pediatrics.

Point-by-point response to reviewers' comments.
Major points:

1. I don't know whether a diagnosis of ALGS can be excluded because of the identification of a GNAS mutation. It is theoretically possible for a patient to have both diseases. The reason I raise this issue is that the patient phenotypes suggestive of ALGS were not limited to the liver. Peripheral pulmonary stenosis is also a relatively common finding in ALGS patients. Moreover, a significant proportion of ALGS patients suffer from kidney disease as well. Furthermore, the bile duct paucity was very severe in this patient, although it could be that the biopsy was taken from the liver periphery and therefore was not representative of the status of the intrahepatic biliary system throughout the liver. I understand that the authors did not identify any mutations in JAG1 or NOTCH2. But a small percentage of patients with clinical criteria of ALGS do not have a mutation in any of these two genes. Due to these issues, the authors should consider keeping open the possibility that the patient has both diseases (or they can discuss in the manuscript how they think the pulmonary and kidney phenotypes might be explained by their mutation).

Response: Thank you for pointing out this critical point. We agree with this comment. A recent manuscript reported that combined sequencing of JAG1 and *NOTCH2* along with copy number variant analysis of *JAG1* did not identify pathogenic variants in 3.2% of patients who met the diagnostic criteria for ALGS [1]. Regarding renal tubular dysfunction and peripheral pulmonary artery stenosis in our case, we did not extract and sequence genomic DNA from renal tubular epithelial cells and pulmonary artery to detect the mutation in the tissues. Although our patient did not meet the classical diagnostic criteria of AGLS which is based on the presence of intrahepatic bile duct paucity on liver biopsy in association with at least three of the major clinical features: chronic cholestasis, cardiac disease, skeletal abnormalities, ocular abnormalities and characteristic facial features, it is still possible that some other genes than *GNAS* or mutations in *JAG1/NOTCH2* genes that cannot be detected with current methods are

involved in AGLS-like renal and pulmonary features in our case. We added the sentence accordingly in DISCUSSION section, on page 13 lines 6-19 and added the reference [1] as reference No 24 in the main text.

2. What is the basis for calling this mutation an activating mutation? Has it been identified in other patients and characterized to be activating? Without some experiments or reference to previous work, it is not clear whether this is indeed an activating mutation.

Response: Thank you very much for the comment on this point. The mutation in *GNAS* gene identified in our case has already been reported as an activating mutation in a previous study [2] and we cited the manuscript on page 10 lines 21 as reference No 4 in the main text.

3. In the Discussion, the authors wrote "however, continuous stimulation of adenylyl cyclase has been suggested to play a role in bile metabolism". Bile duct paucity at that age is more likely to be caused by a failure to generate bile ducts as opposed to degeneration or injury. It is not clear how a role in bile metabolism can affect the number of bile ducts in the liver. The authors should remove this sentence and instead speculate how stimulation of adenylyl cyclase can potentially affect bile duct development. Alternatively, this paragraph can be removed.

Response: Thank you very much for your suggestion. We removed this paragraph, according to the suggestion. (in DISCUSSION section)

Minor points:

1. Instead of "during liver biopsy", it's better to use "based on liver biopsy" or "in liver biopsy", because "during" would imply something happening while the biopsy is being performed on the patient.

Response: Thank you for your kind suggestion. We changed "during liver biopsy" to "in liver biopsy" in Abstract, Core tip, and INTRODUCTION sections, on page 4 lines 11, page 5 lines 12 and page 6 lines 21.

2. On page 4, lines 9-11, the authors wrote "Although mutation was not observed in the JAG1 gene by the fluorescence in situ hybridization analysis". This technique will presumably detect structural variations in JAG1 but not necessarily point mutations. Please clarify.

Response: Thank you for the comment on this point. We agree with this comment. We changed the sentence to "Although any large deletion and duplication were not observed in the *JAG1* gene by the fluorescence in situ hybridization analysis". (in History of past illness section, on page 8 lines 9-11)

3. Same page, line 15: Instead of "His gene was further applied for a targeted next-generation sequencing", I suggest using "His DNA was further subjected to a targeted next-generation sequencing".

Response: Thank you for your kind suggestion. We agree with your suggestion. We changed to the sentence according to your suggestion. (in History of past illness section, on page 8 lines 15-16)

4. Please specify at what age the clinical assessment described under Physical examination section was performed.

Response: We apologize for not mentioned to this point in our original manuscript. We added "At the age of 4 years and 9 months". (in Physical examination section, on page 9 lines 3)

5. In several places, the authors imply that PCR was used to identify the mutations. It's probably sequencing after the PCR. This should be clarified (unless I'm missing something).

Response: Thank you for the comment on this point. According to your suggestion, we changed "PCR" to "PCR and sequencing". (in Further diagnostic work-up section, on page 10 lines 12 and 20, on page 11 lines 8 and 9)

[1] Gilbert MA, et.al., Alagille syndrome mutation update: Comprehensive overview of JAG1 and NOTCH2 mutation frequencies and insight into missense variant classification. *Human Mutation* 2019; **40**(12): 2197-2220
[2] Weinstein LS, et.al., Activating mutations of the stimulatory G protein in the McCune-Albright syndrome. *N Engl J Med* 1991; **325**(24): 1688-1695

Sincerely,

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