Dear Lian-Sheng Ma and reviewers:

Thank you very much for considering our revised manuscript entitled “Gitelman syndrome caused by a rare homozygous mutation in the SLC12A3 gene: a new case report and review of literature” (NO. 54879).

We appreciate the careful review and constructive comments provided by the reviewers of our manuscript. We have studied the comments carefully and provided answers in a point-by-point manner to each of the reviewers’ questions. We had made corrections which we hope are suitable for publication in World Journal of Clinical Cases. Below are our answers for questions raised by the reviewers.

Comments: *Introduction -Start with Gitelman syndrome not hypokalemia. Describe all associated symptoms to clarify the whole picture to the reader Suggest "Gitelman's syndrome (GS), an autosomal recessive disorder caused by a defect of the thiazide-sensitive Na-Cl cotransporter (TSC) at the distal tubule, is characterized by hyperreninemic hyperaldosteronism with normal or low blood pressure, hypokalemia, metabolic alkalosis, hypomagnesemia and hypocalciuria. It is usually diagnosed in late childhood or adulthood. Symptoms of hypokalemia include fatigue, leg cramps and constipation, but, most critically, the slowing of the heart rhythm and even cardiac arrest. Affected individuals may experience episodes of fatigue, dizziness, fainting due to hypotension, muscle weakness, muscle aches, cramps and spasms or even tetany. Symptomatic episodes may also be accompanied by abdominal pain, vomiting, diarrhea or constipation, and fever. Seizures may also occur and in some people may be the initial reason they seek medical assistance. Facial paresthesia characterized by numbness or tingling is common. Less often, tingling or numbness may affect the hands. Affected individuals may or may not experience polydipsia, polyuria including nocturia. When these symptoms do occur they are usually mild. Affected individuals often crave salt or high-salt foods. Some affected adults develop chondrocalcinosis which is thought to be related to hypomagnesemia. Affected joints may be swollen, tender, reddened, and warm to the touch."*

Response: Thank you for your suggestion. As suggested by the reviewer, we have changed the text and described all associated symptoms (please see page 3, line 59-72).

Comments: *Suggest adding the reference: Blanchard et al. Gitelman syndrome: consensus and guidance from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney International 2017; 91: 24–33. Case*
Response: Thank you for providing this pertinent paper which is helpful to improve our research. As suggested by the reviewer, we have changed and added the reference (please see page 7, line 188-191).

Comments: *In the discussion, seizures were mentioned, though not in the case presentation*
Response: We have add the symptom of seizures in the part of case presentation (please see page 3, line 82).

Comments: *The choice of a case with hepatitis B is actually confusing the message. Suggest attempting to divide the studies relating to hep B from those related to GS. Start with GS findings (Mention low K, mag to stress the findings in text) and mention "In addition, etc. Alternatively just mention GS findings in text and divide table into GS and Hep B studies with the available normograms to help in the interpretation of increased, deccreased, or normal.*
Response: As suggested, we have changed the case presentation, starting with the characteristics of GS and described the hepatitis B information after “In addition” (please see page 4, line 88-90).

Comments: *a missense mutation affecting gene function, and one novel SLC12A3 pathogenic mutation was reported in a cohort of Chinese patients with GS previously-need to put reference.*
Response: Sorry for our mistake. We have added the reference (please see page 7, line 199-201).

Comments: *Treatment Dosage should be mentioned clearly: "He was maintained on potassium 1 g/d and spironolactone 20 mg twice daily"*
Response: We have changed the word as suggested (please see page 4, line 106-107).

Comments: *Discussion -A better description of Bartter syndrome is warranted: "Some researchers believe it is better to consider the Bartter syndrome and Gitelman syndrome as a spectrum of disease rather than distinct disorders. The defect in GS involves the distal convoluted tubule while in Bartter it is in the thick ascending limb. Renal salt wasting is more severe and begins earlier in life in Bartter syndrome than in Gitelman syndrome with manifestations occurring rarely in the newborn (neonatal) period".*
Response: Thanks for advising. We have added these suggesting sentences (please see page 5, line 120-124).

Comments: *Cl- superaturization ---clarify??*
Response: We apologize for our wrong expression. We have re-described this mechanism (please see page 5, line 137).

Comments: *aldosterone receptor antagonists, ACEI/ARB and other drugs. Add precautions against the use of these drugs from Blanchard et al*
Response: We have added precautions against the use of these drugs from Blanchard et al (please see page 6, line 156-160).

Comments: *Add a few sentences on the pathogenesis of proteinuria. Suggest " Proteinuria might develop due to abnormalities of the glomerular basement membrane. Chronic kidney disease might develop in GS patients due to either chronic hypokalemia, which is associated with tubulointerstitial nephritis, tubule vacuolization, and cystic changes, or volume depletion and increased reninangiotensin-aldosterone, which may contribute to renal damage and fibrosis"*
Response: We have added these sentences on the pathogenesis of proteinuria as suggested (please see page 6-7, line 172-176).

Editorial comments:

Comment 1: *The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s).*

Response: We have uploaded the approved grant application form. Please see the revision files.

Comment 2: *The authors did not provide original pictures. 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;*

Response: We have arranged original figures and legends using PowerPoint detailed in the revision files.

Comment 3: *PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout;*

Response: Thanks for your correction. We have added the PMID and DOI numbers in revised manuscript and listed all authors of the references (please see page 7-9, line 188-241).

Comment 4: *The "Case Presentation" section was not written according to the Guidelines for Manuscript Preparation. Please re-write the "Case Presentation" section, and add the "FINAL DIAGNOSIS", "TREATMENT", and "OUTCOME AND FOLLOW-UP" sections to the main text, according to the Guidelines and Requirements for Manuscript Revision.*

Response: We have re- re-written the "Case Presentation" section and added the suggested sections to the main text.

Once again, thank you very much for your constructive comments and suggestions which would help us both in English and in depth to improve the quality of the paper.

Kind regards,

Maosheng Chen M.D.
Zhejiang Provincial People's Hospital
People's Hospital of Hangzhou Medical College
No. 158 Shangtang Rd,
Hangzhou, Zhejiang, China
Zip code: 310014
E-mail: maoshengc@126.com