Dear Editors and Reviewers:

On behalf of my co-authors, we thank you very much for giving us an opportunity to revise our manuscript, we appreciate editors and reviewers very much for their positive and constructive comments and suggestions on our manuscript ID 73709 entitled "Novel SLC12A3 gene compound heterozygous mutation in Gitelman syndrome co-existent with hyperthyroidism: A case report and literature review". We have studied comments carefully and have made correction which we hope meet approval. Revised portion are marked in red in the paper (please refer to the 73709-Supplementary-Material-revision). The main corrections in the paper and the responds to the reviewers' comments are as flowing:

Responds to the reviewers' comments:

Reviewer 1

1. Response to comment (**Reviewer 1**): I have few comments about the treatment and treatment outcome. The authors should add the result of thyroid function test after treatment in the outcome and follow-up. Moreover, GS is one of genetic disease that could present in early life, why clinical hypokalemia was detected at adult period ? Does the patient have other clinical manifestations of GS in the past (vomiting, diarrhea, cramp, thirst)? If possible, please discuss this point in the discussion part and add more data including the age of onset and serum potassium before and after treatment for all case reports in table 2.

Response: *We sincerely appreciate the reviewer's comment and thank for the reviewer pointing this out. After more than one year of follow-up, the patient's hyperthyroidism was relieved. The follow-up results for the thyroid functions are shown in Table 3. In table 2, we have added the sex, the age of onset and serum electrolyte levels including potassium and magnesium on admission. Considering that most of the case reports did not fully describe the electrolyte changes after treatment, this parts of the data were not added. Furthermore, we have added recent follow-up results for electrolytes (shown in figure 4). Because of the newly added data and for a more perfect presentation, we have remade the figure 4.*

GS is usually detected during adulthood but can also be found in children, as early as in the infancy, either fortuitously or in association with mild or nonspecific symptoms or both (Am J Med.2002;112:183–190; Pediatr Nephrol. 2010;25:2179–2182). As shown in Table 2, the vast majority of cases described were adolescents and adults. GS was observed with a diversity of clinical manifestations ranging from asymptomatic, fatigue, numbness, paresthesia, and neuromuscular weakness to

paralysis or fatal arrhythmia (J Am Soc Nephrol 2019; 30: 1345-1348; Clin Endocrinol (Oxf) 2015; 83: 985-993; Kidney Int 2001; 59: 710-717). Moreover, phenotypic variability has also been documented in genetically confirmed GS patients, including in patients with identical SLC12A3 mutations(Am J Kidney Dis.2004;43:304–312). A combination of sex, genetic heterogeneity, modifying genes, compensatory mechanisms, environmental factors and dietary habits might be involved in such variability (Pediatr Nephrol. 2007;22:326–332). All of these increase the difficulty of diagnosing GS. Thank you very much for your understanding.

We double-checked the patient's medical history. The patient presented with bilateral lower limb weakness, without vomiting, diarrhea, cramp and thirst.

2. Response to comment (**Reviewer 2**): Page 5 line 19: the phrase "the results are presented in Table 1", should be deleted since it is indicated in the first line of the paragraph that they are presented in Table 1, so it is redundant. - The authors indicate in the description of the case that the hyperthyroidism is refractory to the initial treatment, but they do not indicate if they consider any additional treatment. Since the control of the electrolyte disturbances is not complete and, as they indicate, hyperthyroidism could worsen these disturbances, it should be commented whether any definitive treatment of the patient's Graves' Disease was performed. Or at least discuss why it was not done and the possible influence in the patient's condition. Therefore, I recommend that you consider publishing the case after clarifying these issues.

Response: *Thanks for the reviewer's in-depth comment. We have removed redundant parts ("the results are presented in Table 1") of the manuscript. We are very sorry to make the reviewer confused for not showing the treatment of hyperthyroidism. We have added this part. The follow-up results for the thyroid functions are shown in Table 3. In the past year, the patient's thyroid function has been basically maintained within the normal range.*

In August 2020, the patient was diagnosed with hyperthyroidism and thyrotoxic hypokalemic periodic paralysis(THPP) and treated at a local county hospital. Within the next four months, she had been followed up in the outpatient department of the local hospital, and treated as hyperthyroidism and THPP. The patient was initially prescribed methimazole (15 mg/day) and potassium chloride (3 g/day). After four months of treatment, the patient's symptoms did not improve. The patient also tried traditional Chinese medicine, but fatigue symptoms persist. So she presented to our hospital for evaluation in December 2020.

THPP mainly affects young males more often than individuals of other ethnicities. It is rare in young women. In addition, the patient had hypomagnesemia, hypocalciuria, metabolic alkalosis, and hyperreninemic hyperaldosteronism. Based on the above findings, we suspected that the patient did not have THPP. She was subsequently re-diagnosed as GS concomitant with hyperthyroidism, following genetic testing. The symptoms of her lower limb weakness were relieved after sufficient potassium, magnesium supplementation and improvement of thyroid function. At present (date: 15/12/2021), the patient's thyroid function is normal (methimazole, 2.5 mg/day).Thank you very much for your understanding.

Once again, thank you for your consideration. We look forward to hearing from you.

Sincerely,

Li-Xia Xiao
Associate Chief Physician
Department of Endocrinology
First Affiliated Hospital of Gannan Medical University
No. 128 Jinling Road, Ganzhou 341000, Jiangxi Province
China
Email: xlx981107@163.com