RE: World Journal of Clinical Cases-70809

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Column: Case Report
Title: A Case of Autosomal Dominant Osteopetrosis Type II Mutations in the CLCN7 Gene in a Patient with Osteopetrosis and Literature Review

Dear Editors:

Thank you very much for giving us an opportunity to improve our paper. We have revised the manuscript according to the reviewers' constructive comments and suggestions. You may find our answers to the reviewers on the following pages. If any other concerns exist, please let me know at your first convenience.

Looking forward to hearing from you.

Best wishes,

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Reviewer #1:
Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Major revision
Specific Comments to Authors: This case report presented a 5-year-old boy diagnosed with autosomal dominant osteopetrosis type II (ADO II), who had a de novo heterozygous missense mutation c.746C>T (p. P249L) in the CLCN7 gene as revealed by whole-exome sequencing. However, authors stated in the text that "To date, nearly forty mutations in CLCN7 have been identified linked to ADO II (page 8)," and "mutation c.746C>T (p.P249L) of the CLCN7 gene (NM_001287.5) has been previously described in patients with ADO II (References # 5 and 7) (page 6), so identification of this missense mutation c.746C>T in the CLCN7 gene in patient with ADO II is not a novel finding. In contrast, de novo mutation is the novelty of this case report authors should emphasize, thereby highlighting the fact that this mutation c.746C>T may or may not be inherited. The take-home message of this case report appears to be that "Even without the family history of ADO II, the possibility of de novo mutation in the CLCN7 gene and subsequent ADO II cannot be ruled out. In addition to the conventional neurological, imaging, and biochemical examinations, whole-exome sequencing is critical for final diagnosis."

Answer: We appreciate your comments very much and agree with you. The novelty of our case report was the de novo mutation. We have added the statement of "Even without the family history of ADO II, the possibility of de novo mutation in the CLCN7 gene and subsequent ADO II cannot be ruled out. In addition to the conventional neurological, imaging, and biochemical examinations, whole-exome sequencing is critical for final diagnosis." on page 9-10.

In addition, please consider the following suggestions to strengthen the present case report for readers.
1. As mentioned in the Core tip: "CLCN7 mutation can be due to de novo variants or due to inherited variants." The first statement in the Discussion section, "Osteopetrosis is an inherited disorder with symptoms including failure of osteoclasts and impaired bone resorption (page 7)" will be better to be amended to emphasize the possibility of de novo mutation in the first statement.

Answer: Thanks for your suggestion. We have changed the statement on page 7.

2. The de novo CLCN7 mutation has been report, although mutation sites are different. The possibility of de novo CLCN7 mutation should be briefly discussed with the following citation. Nicoli ER, Weston MR, Hackbarth M, Becerril A, Larson A, Zein WM, Baker PR 2nd, Burke JD, Dorward H, Davids M, Huang Y, Adams DR, Zerfas PM, Chen D, Markello TC, Toro C, Wood T, Elliott G, Vu M; Undiagnosed Diseases Network, Zheng W, Garrett LJ, Tifft CJ, Gahl WA, Day-Salvatore DL, Mindell JA, Malicdan MCV. Lysosomal Storage and Albinism Due to Effects of a De Novo CLCN7 Variant on Lysosomal Acidification. Am J Hum Genet. 2019 Jun 6;104(6):1127-1138. doi: 10.1016/j.ajhg.2019.04.008. Epub 2019 May 30. PMID: 31155284; PMCID: PMC6562152.

Answer: Thanks for your suggestion. We have discussed the de novo mutation on page 8.

3. To stay focus, it is not relevant to mention "infantile malignant autosomal recessive osteopetrosis (ARO) and intermediate ARO (IARO) [1, 10] (page 7)" in this case report.
Answer: Thanks for your suggestion. We have deleted the statement on page 7.

4. (page 8) It should read as "…there have been more reports of CLCN7 mutations causing cases of ADO II in the Asian population than in Western countries over the last decades."
Answer: We sincerely apologize for our mistake and have changed the statement on page 8.

5. (page 9) "Biochemical markers have been considered for the diagnosis of osteopetroses, such as elevated creatine kinase MB isoenzyme (CK-MB), serum LDH and AST [27, 28]." So, the extent to which the serum levels of creatine kinase, LDH and AST of this boy facilitates the final diagnosis of ADO II should be illustrated in the Results section.
Answer: Thanks for your suggestion. Elevated levels of creatine kinase, LDH, and AST of this boy has been illustrated in the CASE PRESENTATION section- Laboratory examinations (page 5, Suppl. Table 1)

6. Table I summarized the findings from the literature review. However, some drawbacks were observed as follows: a) The starting time point of your literature review is unclear in the text. b) Most importantly, in-table citations do no match their references list. c) Why only case report studies were included in Table 1? If patients' demographic and clinical characteristics were clearly presented in the population-based studies, those patients should be included in Table 1 for comparison. d) Table 1 should be updated for comprehensive comparison and correct citation.
Answer: a) We added the starting time point of our literature review from January 2004. b) We sincerely apologize for our mistakes and have changed the citations in table 1. c) The novel mutations were reported as case reports, as usual, so most of the literature was case report studies. In the progression of the literature review, we deleted 17 pieces of literature, including the review. d) Thanks for your suggestion. We have updated the mistakes in table 1.

Reviewer #2:
Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Minor revision
Specific Comments to Authors: Thank you for having an opportunity to review this case report by Dr. Song, et al. They reported a rare case of autosomal-dominant osteopetrosis with Type II mutations in the CLCN7 gene. The authors emphasized the rarity of de novo missense mutation in the CLCN7 gene to further understand this rare disease with the literature review. Although their work is valuable, there are several major and minor points which should be addressed for the acceptance.
Major 1. In Table 1, if possible, the authors should summarize and provide the data about main symptoms, treatments and prognosis of the osteopetrosis patients with CLCN7 mutation in previous reports. The additional data can be beneficial for early diagnosis and management of autosomal-dominant osteopetrosis with CLCN7 mutations.

Answer: Thanks for your suggestion. We have added the symptoms of the osteopetrosis patients in Table 1. However, the treatments and prognosis were not indicated in the references listed in Table 1.

2. In Background of Abstract section, the authors should mention briefly about clinical unsolved problems related to this rare disease and the reason why they want to report this case, which will be linked to the proof of clinical value of this case report.
Answer: Thanks for your suggestion. We changed the statement in the background of abstract section.

Minor 1. In Table 1, the authors should fill in the blank in the line of reference #11.
Answer: We have filled the blank in Table 1.

2. In Table 1, "united kingdo" is typo in reference #15.
Answer: We sincerely apologize for our mistake and have changed the "United Kingdo" into "United Kingdom".

3. The authors should refer to the acquisition of informed consent from the patients and the family in the manuscript.
Answer: We added the statement of "Informed consent statement" on page 10.

4. In Discussion section, page 8, the authors should provide the percentage of gender ratio in the line where they referred to it.
Answer: We added the percentage of female patients on page 8.

5. In Discussion section, page 9, next-generation sequencing should be replaced to "NGS" after abbreviated.
Answer: We sincerely apologize for our mistakes and have changed the "next-generation sequencing" into "NGS" on page 9.

6. If possible, the imaging results at the 2-year follow-up should be presented in Figure 1.
Answer: Thanks for your suggestion. We added the imaging results at the 2-year follow-up in Figure 1.

7. In Supplementary Table 1, the legends of Hb and ALT should be provided in the footnote.
Answer: We have added the footnote of Hb and ALT in Supplementary Table 1.