Author’s response to reviews

Title: UMOD gene mutations in Chinese patients with autosomal dominant tubulointerstitial kidney disease: a pediatric case report and literature review

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Author’s response to reviews:

Dear Dr. Diana L. Cousminer,

Thank you for your letter and the reviewers’ comments concerning our manuscript entitled “UMOD gene mutation in Chinese patients with autosomal dominant tubulointerstitial kidney disease: a pediatric case report and literature review” (BPED-D-19-00010). Those comments are all valuable and very helpful for revision of our paper. We have studied comments carefully and have made corrections which have been highlighted in red in the paper. In addition, we believe that all concerns of the reviewer have been addressed point-by-point on a separate page. According to your suggestion, we have carefully read the manuscript and have it checked by a native English-speaking doctor to revise English language errors. We cordially hope the revised paper can meet the journal’s requirement for publication.

Thank you again for your consideration. We are looking forward to hear from you.

Yours sincerely

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Response to the reviewer’s comments:

Concerns of Toru Watanabe, M.D., Ph.D. (Reviewer 1)

1. page 2, line 1 and 3: “a 3-year chinese boy” should be changed to “a 3-year-old chinese boy”

Response: We truly thank Dr. Toru Watanabe for his careful reading of our manuscript and pointing out those language errors. Yes, page 1, line 19 and 21: “a 3-year chinese boy” was changed to as “a 3-year-old chinese boy”.

2. page 2, line 3-6: These sentences had grammatical errors.

Response: Agree, page 1, line 21-page 2, line 3: these sentences were rewritten as follow “A 3-year-old boy was admitted to our hospital because of persistent hematuria. Urinalysis showed BLD 2+ without proteinuria. The serum levels of uric acid, creatinine and electrolytes were normal. No renal cyst or calculus was found by ultrasonography. Renal biopsy was performed and segmental glomerulosclerosis was found in 4 glomeruli among 35 glomeruli examined.”

3. page 2, line 7: “at 29 years old” should be changed to “at the age of 29”.

Response: Yes, page 2, line 3-4: “at 29 years old” was changed to “at the age of 29”.

4. page 3, line 7-8: These sentences are confused.

Response: We are sorry for the poor expression. Page 3, line 3-7: these sentences were rewritten as follow “ADTKD-UMOD is a rare disease, almost all patients present the typical manifestation during adulthood, thus very few pediatric cases could be diagnosed in the early years of their life. Up till now, no more than 2000 families have been reported worldwide”.

5. page 3, line 22-page 4, line 2: These sentences should be change to “Here, we report a ADTKD family with UMOD gene mutation and summerized the clinical features and types of Chinese patients with UMOD gene mutation by literature review.”

Response: We agree and revised these sentences accordingly to “Here, we report a ADTKD family with UMOD gene mutation and summerized the clinical features and types of Chinese patients with UMOD gene mutation by literature review” in page 3, line 20-22.

6. page 4, line 7-10: These sentences should be changed to” His serum creatinine level was 27 umol/L, and uric acid level was 175 umol/L. Serum IgG, IgA, IgM, C3, C4 level were normal, and ANA, dsDNA and ANCA were negative”.
Response: Yes, these sentences were changed to “His serum creatinine level was 27 umol/L, and uric acid level was 175 umol/L. Serum IgG, IgA, IgM, C3, C4 level were normal, and ANA, dsDNA and ANCA were negative” in page 4, line 5-8.

7. page 4, line 13: “and” should be put between “fibrosis” and “renal tubular atrophy”.
Response: Yes, we put “and” to the place. Now it is “fibrosis and renal tubular atrophy” in page 4, line 11.

8. page 4, line 15: “and” should be put between “proteinuria” and “edema”.
Response: Yes, “and” was added in the sentence in page 4, line 13.

9. page 5, line 20-23: These sentences should be changed to “Among the 12 mutations of UMOD gene, 8 mutations were found in exon 3, 2 in exon 4, 1 in exon 5, and 1 in exon 9”.
Response: Yes, many thanks to Dr. Toru Watanabe! These sentences were changed to “Among the 12 mutations of UMOD gene, 8 mutations were found in exon 3, 2 in exon 4, 1 in exon 5, and 1 in exon 9” in page 5, line 20-21.

Concerns of John A. Sayer (Reviewer 2)

1. Would benefit from a pedigree diagram and description of phenotypes in other affected family members eg presence of gout/ckd/esrd
Response: Thank Dr. John A. Sayer for his good suggestion. It’s very important to display affected family in a pedigree diagram. Due to historical reasons (one child family plan), many Chinese families are quite simple. For this family, in fact, there are no siblings for both the proband and his father. The child didn’t show typical clinical manifestations of ADTKD-UMOD, the uremic father was not examined in detail and was considered to be due to “chronic nephritis” by his doctor, thus the proband was not considered to be this disease at the beginning. The diagnosis was made only when the results of exome sequencing came out and his father was re-examined and re-considered to be a typical case of ADTKD-UMOD. We have added some information such as exact serum levels of creatinine and uric acid of his father in the text, and also added a sentence “Other family members have no clinical manifestation of gout, CKD” in Page 4, line 15. Since the family was very simple and has been described in word, pedigree diagram was omitted in the text to save space. Of course it can be added to the paper if needed.

2. The urinary Umod level would be a useful addition.
Response: Yes, uromodulin is normally the most abundant protein in urine, detection of urinary Umod levels might have some value in the study of this disease. But urinary Umod was not a diagnostic marker for ADTKD-UMOD, the levels of Umod varied greatly even in patients with ADTKD-UMOD. Since the detection of urinary uromodulin was not commercially available in China, we regret that we are unable to provide the data in this manuscript at present time.