Dear reviewers and editor

Re: Manuscript ID:66269 and Title: **A case of autosomal dominant tubulointerstitial kidney disease with a novel heterozygous missense mutation in the uromodulin gene**

Thank you for your letter and the reviewers'comments concerning our manuscript entitled "**A case of autosomal dominant tubulointerstitial kidney disease with a novel heterozygous missense mutation in the uromodulin gene**" (**ID:66269**). Those comments are valuable and very helpful. We have read through comments carefully and have made corrections. Based on the instructions provided in your letter, we uploaded the file of the revised manuscript. Revisions in the text are shown using red highlight for additions. The responses to the reviewer's comments are marked in red and presented following.

We would love to thank you for allowing us to resubmit a revised copy of the manuscript and we highly appreciate your time and consideration.

Sincerely.

Liling Zhang.

Reviewer #1:

Q1. It is still possible to achieve a renal biospsy in an 8.3 cm kidney which is the 3 cm below the average lenth. Findings from renal biopsy in patients with ADTKD-UMOD could have shown aggregates of uromodulin in the enoplasmic reticulum and disruption of the epithelial cells of the thick ascending limb (TAL) of the loop of Henle. After considering ADTKD as a probable diagnosis, urine uromudolin would have been helpful while awaiting genetic sampling.

Response：First of all, We are grateful for the valuable suggestions of the reviewer. Secondly, we are sorry that we did not describe it clearly in the article: Actually, we also had a kidney biopsy plan when we get the patient's kidney B-ultrasound results, However, the patients were overly worried about the risks related to renal biopsy and refused it, furthermore, we have to admit that the technical limitations of renal biopsy in our hospital also played a certain role. we will learn from this lesson, and improve renal biopsy-related techniques, and give patients more positive advice in the future. For the second suggestion, It is very regrettable that our hospital currently does not carry out the test of urine uromudolin.

Reviewer #3:

Q1. About “DNA analyses”, the authors should provide more minute explanation of its method.

Response： We apologize for the ignorance of the method in the manuscript. we have provided more details to describe the method of the Whole-exome sequencing (WES) analysis as the following: The peripheral blood was sent to CIPHER GENE to perform the whole exome sequencing by Illumina HiSeq. The raw data were converted into a.fastq file through bcl2fastq and reads were aligned to the Human Reference genome (GRCh38/hg38) using the BWA ,Samtools and Picard software. The Genome Analysis Toolkit (GATK) was used to remove the repeated sequence and detected the mutation. ANNOVAR was then used for variant annotation.The principles of screening pathogenic mutation sites:(1)Variants located in the exonic region and the non-synonymous mutation sites were screened. (2) the variant site that Normal individuals do not carriage or the carriage rate less than 5% were identifited through ExAC_EAS, ExAC_ALL, 1000Genomes and gnomAD databases. (3) The pathogenic variant sites were evaluated with reference to dbSNP, OMIM, HGMD, ClinVar and other databases. (4) The SIFT, Polyphen2, LRT, MutationTaster, FATHMM and other protein function prediction software were used to predict protein function caused by gene variation. The pathogenic variants were screened according to the ACMG classification guidelines and the clinical phenotype of the patients.

All of the potential disease-causing variants that were identified genome wide were confirmed by Sanger sequencing.

Q2. Description concerning genetic counseling is totally lacking. The authors should explain this aspect of issue within genetic examination.

Response： We are extremely grateful to reviewer for pointing out this problem. we have added a brief description as follows: The conclusion of the genetic test is “Variants of unknown clinical significance” according to ACMG genetic variation classification standards and guidelines, the variation site is heterozygous, and the zygote type can explain the patient’s disease.

Reviewer #2 and 4:

This report represents an effort to accomplish this, as these data will most likely prove to be a unique resource well into the future. I think this paper should be published.

I would like to congratulate the article written by Santao Ou et al. The article is well written, presenting genetic and pathophysiological aspects of a unique condition, and is very well documented. We recommend the publication of the paper

Thanks for your comment.