

Dear reviewers and editors,

Grateful to the editor for dominating the review and the valuable comments of the reviewers.

The author has carefully answered the questions one by one according to the requirements of reviewers, and made serious modifications to the article. The article was modified using Microsoft Word Track Changes.

Thanks to your suggestions, the revised articles are better and readers can get more valuable information.

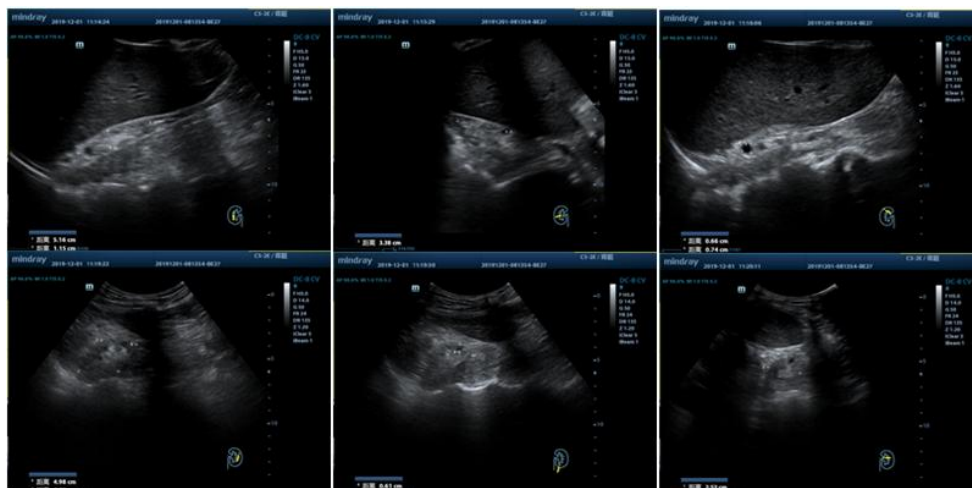
Thanks again to editors and reviewers for their concern.

The responses are as follows

To reviewer #1:

Thanks to your suggestions, the revised article is better and readers can get more valuable information. The following changes are made according to your comments.

To question 1: The ultrasound examination of the proband revealed bilaterally small kidneys (left kidney, 52x34 mm; right kidney, 50x25 mm) with multiple 5-7 mm medullary cysts as we mentioned in the part of “**Imaging examination**”. The image is showed below. We did not add it into the article due to space limitations. Because the patient was CKD5 with small kidneys, we did not give him additional CT scan. We have also added some content of differential diagnosis in discussion.



To question 2: Since we reviewed patients diagnosed with TBS with renal manifestations, some earlier published literatures were included. We accepted the suggestions and summarize the result of a recent studie in 2021^[1].

To question 3: We have send the revised manuscript to the Nature Publishing Group Language Editing and provided a new language certificate along with the manuscript.

To reviewer #2:

Thanks for the comments, no revision is required.

To reviewer #3:

Thanks to your suggestions, the revised article is better and readers can get more valuable information. The following changes are made according to your comments.

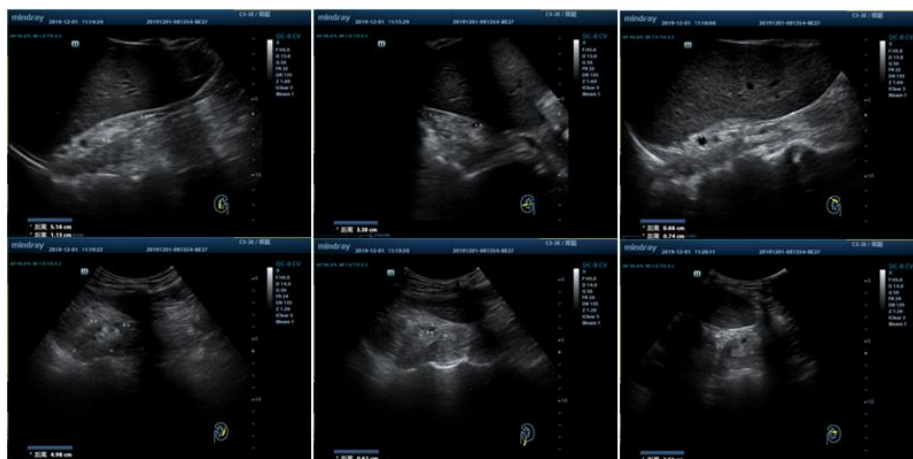
To question 1: We have added some details to the photographs to make these abnormalities more clear.

To question 2: We have added these suggestions about consultation which were mentioned by the reviewer. The treatment for the kid has been supplemented, too.

To reviewer #4:

Thanks to your suggestions, the revised articles are better and readers can get more valuable information. The following changes are made according to your comments.

To question 1: The ultrasound examination of the proband revealed bilaterally small kidneys (left kidney, 52x34 mm; right kidney, 50x25 mm) with multiple 5-7 mm medullary cysts as we mentioned in the part of “**Imaging examination**”. The image is showed below. We did not add it into the article due to space limitations. Because the patient was CKD5 with small kidneys, we did not give him additional CT scan. We mainly focused on the injury of kidney in this manuscript, so the cause of ear problems are not described.



Question 2: Heart defects including TF and ventricular wall defects are amongst the presenting features of this syndrome. An echocardiography could easily diagnose the potential cardiac defects in the proband and the other affected individuals in the pedigree.

To question 2: That's a good idea to assess the patient with an echocardiography. Unfortunately, due to the fact that the patient's family members were not in Hangzhou, they mainly underwent blood test and genetic test. We were unable to conduct cardiac ultrasound for them due to some objective reasons. We will improve these examinations during follow-up visits.

To reviewer #5:

Thanks to your meticulous suggestions, the revised article is better and readers can get more valuable information. The following changes are made according to your comments.

To question 1: About 4 articles mentioned patients received kidney transplantation and one of the patients had graft rejection. We have added these data into the revised manuscript.

To Question 2: We have added the content about DACT1 in the revised manuscript.

To question 3: Thanks to your good advice. We have added some content of these differential diagnosis in discussion.

1. Beaudoux O, Lebre AS, Doco Fenzy M, Spodenkiewicz M, Canivet E, Colosio C, and Poirsier C. Adult diagnosis of Townes-Brocks syndrome with renal failure: Two related cases and review of literature. *Am J Med Genet A* 2021; **185**(3): p. 937-944 [PMID: 33438842 DOI: 10.1002/ajmg.a.62050]