Peer Review File

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Reviewer

This study describes WES in a cohort of 18 patients with ADPLD. Pathogenic variants were found in known genes, PRKCSH (2x), GANAB (1x), and PKHD1 (1x), and ADPKD genes, PKD2 (2x), PKD1 (1x) and possible digenic disease (PKHD1 and PKD1). In particular, the case with PKHD1 pathogenic variant is described in more detail.

Comment 1: The paper should describe all of the patient not just the family with a novel PKHD1 change. PKD1 and PKD2 have not been classified as ADPLD genes, and this part should be expanded to describe these cases. The digenic case also sounds interesting.

Reply 1: We thank the Editor for giving us an opportunity to explain this issue. In our research, we reported some patients with isolated polycystic liver disease, which included one case with PKD1 mutation and two cases with PKD2 mutation. Just as you mentioned, PKD1 and PKD2 used to be classified as ADPKD genes. As far as we know, there is no report mentioning PKD1/2 mutations causing isolated polycystic liver disease. Reviewing the medical records of the three cases, we found that they were all about forty years of age. Polycystic liver/kidney diseases are age-cumulative, meaning that the number of cysts can increase with age; therefore, we assumed that these patients did not yet show a significant polycystic kidney phenotype because of their relatively young age. We will continue to follow up these patients and observe phenotypic changes.

Changes in the text: We have modified our manuscript as advised. (See page 10, line 174-180)

Comment 2: A Table showing phenotypic and genotypic details of all the patients including the number of liver and kidney cysts and the liver volume needs to be included.

Reply 2: We are very grateful to Editor for pointing out this important issue, and we added a table in the page 17 as you requested. There are some points we want to explain about the table we add. As we all know, only seven genes were identified to be associated with high risk of developing ADPLD, and more than 50% of patients still lack clear genetic attributes. 8 of 18 patients were identified with clear mutation, two PRKCSH, two PKD2, one PKHD1 and PKD1, one GANAB, one PKHD1 and one PKD1 mutation. The causative gene of other patients were unclear. Therefore, we listed the phenotypic and genotypic details of those five patients.

Changes in the text: We added a table showing phenotypic and genotypic details.

Comment 3: Images of all the patients' livers and kidneys should be shown.

Reply 3: We thank the Editor for giving us an opportunity to explain this issue. These 18 ADPLD patients were all enrolled in the HIS system of Peking Union Medical College Hospital. Some phenotypic details were based on the record of cases, the image data was not available. Besides, we have listed the images of the proband's family. We have submitted all the images we found in the supplement materials.

Changes in the text: We submitted some data in supplement materials.

Comment 4: The definition of ADPLD is very lax. How many had symptomatic liver disease and/or significant hepatomegaly?

Reply 4: We are really grateful to this opinion and the opportunity to improve our manuscript. The definition of ADPLD were revised as "multiple simple liver cysts (generally more than four cysts) with or without fewer than three renal cysts, when excluding infectious etiology." In addition, we searched with ((polycystic liver disease) OR (autosomal dominant polycystic liver disease)) AND ((clinical feature) OR (clinical profile) OR (clinical characteristic)) as the keywords, and did not find any research reporting the proportion of symptomatic cases among all ADPLD patients. Some

researches demonstrated that 23.7%-59.4% of PCLD patients suffered from complications such as abdominal pain, esophageal reflux, dyspnea, and portal hypertension. Then we reviewed the medical records of all our patients and reported the proportion of the cases with symptomatic liver disease and/or significant hepatomegaly among all the ADPLD patients involved in the present research.

Changes in the text: We have modified our manuscript as advised. (See page5, line 67-71; page 8, line 138-143)

Comment 5: How was the WES screened for variants?

Reply 5: Response: We thank Reviewer for giving us the opportunity to explain our methodology further. DNA libraries were sequenced as paired-end reads. Once they were confirmed as with high quality, they would be compared with the human reference genome sequence from the UCSC database. In this way, variants would be detected.

Changes in the text: We have modified our manuscript as advised. (See page 7-8, line 125-131)

Comment 6: How was the PKD1 variant confirmed (PKD1 is a duplicated locus).

Reply 6: We thank Editor for giving us the opportunity to explain this issue. As you comment, PKD1 is a duplicated locus, we found it was hard to be recognized in WES. Sanger sequencing was used in all samples to verify whether the ADPLD patients had PKD1 mutation.

Changes in the text: We have modified our manuscript as advised. (See page 8, line 132-133)

Comment 7: The Conclusions are longer than the Results!

Replay 7: We are really thankful to Editor for pointing it out and we apologize for our mistake. We incorrectly wrote a “discussion” section instead of a “conclusion” section. We have re-organized the construction of our manuscript.

Changes in the text: We have revised our manuscript as advised. (See line 135-220)