Response to reviewers

Dear Editors and Reviewers:

Thank you for your comments concerning our manuscript entitled：polycystic kidney and hepatic disease 1 gene mutations in von meyenburg complexes：case report . Those comments are all valuable and very helpful for revising and improving our paper. We have studied comments carefully and have made correction according to your comments. which we hope meet with approval. The main corrections in the paper and the point to point responds to the reviewer’s comments are as following:

Reviewer 1

Review Date:2018-04-01 16:58

Comment1:I recommend to write numbers with letters when they are less than 10, for example, to write "two" instead of "2" .In methods it says that samples were extracted from 11 individuals. In results, it says that family members studied were 10. It is not clear.

Response:As the Reviewer's good advice, numbers in manuscript which are less than 10 have been changed to letters. We are very sorry for our unclear report in sample content, we took in 11 individuals and all members received gene sequencing.

Reviewer2

Review Date:2018-04-10 03:07

Comment2:This is an interesting/noval observation of potential correlation between PKHD1 gene and VMCs (bile duct microhamartomas); which VMCs have been reported to be associated with ADPKD, than ARPKD. However, I have several suggestions for investigators in order to improve their manuscript. 1. Please add a table summarized on the The clinical presentation of Von Meyenburg complexes: Please see PMID: 22110302 PMCID 2. Please discuss

more on the previously known/correlated ADPKD/ADPLD and VMCs; PMID: 12500201, PMID: 3811921 3. Any family member/offspring in pedigree died or had clinical full-blown ARPKD at all? 4. Some grammatically errors: -Introduction: Mutations of the polycystic kidney and hepatic disease 1 (PKDH1) gene have been proved to cause autosomal recessive polycystic kidney disease (ARPKD), a severe type of DPMs. Epigenetic changes in the liver and bile ducts "varies" from different exon mutation regions of PKHD1. Herein, we reported the PKHD1 gene sequences in two families of VMCs. Suggest to change to Mutations of the polycystic kidney and hepatic disease 1 (PKDH1) gene have been proved to cause autosomal recessive polycystic kidney disease (ARPKD), a severe type of DPMs. Epigenetic changes in the liver and bile ducts "vary" from different exon mutation regions of PKHD1. Herein, we reported the PKHD1 gene sequences in two families of VMCs. -case information Pedigree 2 (VMC2)： Proband B was a previously healthy 57-year-old woman (Fig.F, III:2), and abdominal ultrasonography displayed intrahepatic diffuse lesions (Fig.G), with no kidney cysts seen. Laboratory tests showed 34 U/L ALT, 32U/L AST, 10.8 μmol/L total bilirubin, 3.8 ng/ml AFP, 1310.95 IU/ml HBsAg, 0.02 s/co HBeAb, 11.57 s/co HBeAb, < 500 copies/ml HBV- DNA viral load. She was finally diagnosed "as" VMCs, congenital hepatic fibrosis (CHF) and HBeAg-negative chronic hepatitis B after MRI and histopathological examinations. Suggest to change to She was finally diagnosed "with" VMCs, congenital hepatic fibrosis (CHF) and HBeAg-negative chronic hepatitis B after MRI and histopathological examinations. In discussion: -In our previous study, the prevalence was 0.35% in patients who underwent liver biopsy for diagnostic purposes [6]. Mutations of the PKHD1 gene have been demonstrated to cause ARPKD, a type "of of" DPM [7]. There are 2 "of", please remove one.

Response:

1.According to your helpful advice, we have attached a table(table 2) summarized on the The clinical presentation of Von Meyenburg complexes

according to PMID: 22110302

2.Benifit from your valuable advice,we further attach address the relationship between the previously known/correlated ADPKD/ADPLD and VMCs in the section of discussion according to PMID: 12500201, PMID: 3811921

3.None of family member/offspring in pedigree died or had clinical full-blown ARPKD at all.

4.Thank you very much to point out the sentence structure and grammatical issues in our manuscript. We have carefully corrected this phrase throughout the manuscript according to your comment.

Reviewer3

Review Date:2018-04-09 22:22

Comment3:There is limited data on the association of PKHD1 with VMC (e.g. Courcet et al. (Am J Med Genetics, 2015). Suggestions: - There are some minor grammatical errors - With regard to Pedigree 1: Please clairify if Proband A is HIV positive as the wording looks ambigious (positive hepatitis C virus (HCV) and human immunodeficiency virus (HIV) antibodies") - Consider re-phrasing the the conclusion in the abstract ("The protein component encoded by exon 28-32 of PKHD1 gene may have closer correlation with the development of bile duct than with renal tubules.") as the data presented in this paper does not establish strong evidence for this hypothesis.

Response:Thank you for your careful reading of our manuscript. We are very sorry for our ambigious statement in the abstract. We have corrected it in the new manuscript. Furthermore，as you suggested that the data presented in this paper does not establish strong evidence for the hypothesis("The protein component encoded by exon 28-32 of PKHD1 gene may have closer correlation with the development of bile duct than with renal tubules.") .In the newly submitted manuscript, we have put forward a new hypothesis that PKHD1 gene mutations may be responsible for the development of VMCs. .

We tried our best to improve the manuscript and made some changes according to reviewer's comments. Here we did not list the changes but marked in yellow in revised paper.

We appreciate for Editors/Reviewers' warm work earnestly, and hope that the correction will meet with approval.

Once, again, thank you very much for your nice comments and suggestions.

Best regards,

Yueyong Zhu, MD. Ph.D

Liver Research Center

2018.04.27