

Responses to reviewers

Reviewer's code: 00188507

Thank you for your kind suggestions.

The authors would like to compare the ethnic differences between European and Asian with previous European and Asian reports, because PFIC is very rare in the world and rarer in Asia. In addition, because the patients were sorted from 47 infants with cholestasis based on the clinical courses and genetic studies, we thought that the article might be considered as a retrospective study.

Other points

1. Although there are significant differences of the frequency of SNPs in the coding lesion of ABCB11 genes in various populations, Korean SNPs in the coding lesion of ABCB11 genes have not established yet because of its rarity. So we estimated the characters of the found mutations using PolyPhen-2 (prediction of functional effects of human nsSNPs, <http://genetics.bwh.harvard.edu/pph2/>) and also estimated the functions of the amino acid substitutions using SIFT program (<http://sift.jcvi.org/>). And we described the results on the article.
2. Thank you for your excellent comments. The case 5 had a significantly high level of AFP. In that case, there was no hepatic mass on liver USG and the level of AFP had slightly decreased after 1 month. But we could not decide the meaning of the high AFP in case 5. However, decline of AFP and negative findings on liver USG could be helpful to exclude the development of hepatic tumor. So we described the previous mentions as follows in the discussion. "In patient 5, significantly high level of AFP was noted on the first laboratory examination. There was no evidence of hepatic mass on liver USG and inborn error of metabolisms on laboratory examination. The level of AFP was decreased into 530,000 ng/mL after 1 month. The decline of AFP and no occurrence of hepatic mass on liver USG could be ruled out the development of hepatic tumor in patient 5. Therefore, increment of serum AFP and hepatic image can be useful modalities for early detection of hepatic tumors in a patient with PFIC2."
3. As you mentioned, the number of the patient is too low to discuss the ethnic differences in SNPs in ABCB11. So we mentioned the low number and necessity of further study as follows. In the discussion, 'But further study was needed because the number of mutations in the Korean patients with PFIC2 was too low.' In abstract, 'The transmembranous alterations of bile salt export pump in the Korean infants were different from previous reported mutations in Chinese, Japanese, Taiwanese and European patients.'
4. I corrected the misspelling periprotal to periportal. Thank you.

Reviewer's code: 00724887

Thank you for your kind suggestions.

The authors would like to compare the ethnic differences between European and Asian with previous European and Asian reports, because PFIC is very rare in the world and rarer in Asia. In addition, because the patients were sorted from 47 infants with cholestasis based on the clinical courses and genetic studies, we thought that the article might be considered as a retrospective study.

We described the histopathologic findings in more detail especially in patient 1 as follows; Cellular atypia with trabecular and acinar type was shown. Microvascular invasion was not identified

According to the reference 1 (**Harris MJ**, Le Couteur DG, Arias IM. Progressive familial intrahepatic cholestasis: Genetic disorders of biliary transporters. *J Gastroenterol Hepatol* 2005;20:807-817), 'Portal and peri-portal fibrosis, cirrhosis and cholestasis are common findings in the later stages of liver disease'

Reviewer's code: 00013491

Thank you for your kind comments.

We revised the conclusions as your comments as follows.

In the discussion, 'But further study was needed because the number of mutations in the Korean patients with PFIC2 was too low.' In abstract, 'The transmembranous alterations of bile salt export pump in the Korean infants were different from previous reported mutations in Chinese, Japanese, Taiwanese and European patients.'