PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Comprehensive Screening for PRSS1, SPINK1, CFTR, CTRC and CLDN2 Gene Mutations in Chinese Pediatric Patients with Idiopathic Chronic Pancreatitis
AUTHORS	Liao, Zhuan; Wang, Wei; Sun, Xiao-Tian; Weng, Xiao-Ling; Zhou, Dai-Zhan; Sun, Chang; Xia, Tian; Hu, Liang-Hao; Lai, Xiao-Wei; Ye, Bo; Liu, Mu-Yun; Jiang, Fei; Gao, Jun; Bo, Lu-Min; Liu, Yun; Li, Zhaoshen

VERSION 1 - REVIEW

REVIEWER	Jianjun Shi Research Associate The Scripps Research Institute USA No conflict of interest
REVIEW RETURNED	12-May-2013

THE STUDY	1. Supplemental Table 1: please mark forward/reverse primer for related mutation/variant. About CLDN2 gene mutations, there are eight primers, but no info for four primers. 2. Supplemental Figure 1 should be mentioned in the results to show the reliability of the methods and results. In Supplemental Figure 1B, the numbers standing for position of amino acids of PRSS1 are in wrong positions. In Supplemental Figure 1D, the legend(G to A) is not consist with the picture(C to T). In Supplemental Figure 1E, the legend(G to A) is not consist with the picture(C to T). In Supplemental Figure 1G, the legend(A to C) is not consist with the picture(T to G).
RESULTS & CONCLUSIONS	In table 3 and , the rate of pancreatic pseudocyst is significantly lower than in patients with a SPINK1 gene IVS3+2T>C mutation than that of patients without IVS3+2T>C. The related description in the results and conclusion/abstract is not consistent with it(significantly higher)

REVIEWER	Dr. Nageshwar Reddy D Chairman Asian Institute of Gastroenterology, There are no competing interests
REVIEW RETURNED	15-May-2013

THE STUDY	Appropriate controls have to be included in the study for meaningful associations of the studied genes to the disease

REVIEWER	Whitcomb, David University of Pittsburgh
REVIEW RETURNED	14-Jul-2013

RESULTS & CONCLUSIONS	The manuscript describes a candidate gene study of known pancreatitis-associated gene mutations in a pediatric Han population within China. The findings confirm that PRSS1, SPINK1 and CFTR variants are common etiologies in children, and report that the common SPINK1 mutation is that of Asians rather than Europeans. The study is done well and the results are convincing. The issue of PRSS1 CNV is not discussed. Specifically they report a reduced CN in 5 children with pancreatitis, whereas loss of PRSS1 activity is predicted to protect from pancreatitis. This needs to be addressed with further investigation or a rational and convincing argument of why reduced CN is a risk. Abstract, line 25, the word “unmoral” should be changed to “abnormal”

VERSION 1 – AUTHOR RESPONSE

Reviewer #1:
1. Supplemental Table 1: please mark forward/reverse primer for related mutation/variant. About CLDN2 gene mutations, there are eight primers, but no info for four primers.
Response: We accept the comment and we have marked forward/ reverse primers, respectively. And Exon 2 of CLDN2 was divided into 3 segments in order to be completely sequenced.

2. Supplemental Figure 1 should be mentioned in the results to show the reliability of the methods and results. In Supplemental Figure 1B, the numbers standing for position of amino acids of PRSS1 are in wrong positions. In Supplemental Figure 1D, the legend(G to A) is not consist with the picture(C to T). In Supplemental Figure 1E, the legend(G to A) is not consist with the picture(C to T). In Supplemental Figure
1G, the legend(A to C) is not consist with the picture(T to G). In table 3 and , the rate of pancreatic pseudocyst is significantly lower than in patients with a SPINK1 gene IVS3+2T>C mutation than that of patients without IVS3+2T>C. The related description in the results and conclusion/abstract is not consistent with it(significantly higher)
Response: Yes, we accept these suggestions and make changes accordingly in the revised manuscript.

Reviewer #2:
Appropriate controls have to be included in the study for meaningful associations of the studied genes to the disease.
Response: Thanks for your reasonable suggestion. In the present study, we did not include appropriate controls just because of the two reasons followed bellow.
First, there are only a few genetic studies of the chronic pancreatitis in mainland Chinese. Meanwhile, the genes genotyped in this study have already confirmed to be the causal genes in previous studies. So we did not use a case-control method to detect the genetic susceptibility. Instead, our initial objective was to investigate the genetic characters in our ICP patient cohort.

Second, except CFTR polymorphisms, most of the mutations screened in the study are seldom detected in healthy population according to the previous studies.

Reviewer #3:
The manuscript describes a candidate gene study of known pancreatitis-associated gene mutations in a pediatric Han population within China. The findings confirm that PRSS1, SPINK1 and CFTR variants are common etiologies in children, and report that the common SPINK1 mutation is that of Asians rather than Europeans. The study is done well and the results are convincing. The issue of PRSS1 CNV is not discussed. Specifically they report a reduced CNV in 5 children with pancreatitis, whereas loss of PRSS1 activity is predicted to protect from pancreatitis. This needs to be addressed with further investigation or a rational and convincing argument of why reduced CNV is a risk.
Abstract, line 25, the word “unmoral” should be changed to “abnormal”.
Response: Thank you for your important comments. Some recent studies have reported that increased CNV play a role in the development of pancreatitis. Our study cannot show reduced CNV is a risk but we proved some patients with ICP also had lower CNV than normal. And we will explore the role of CNV in the development of ICP further in the future.