Dear editor,
Thank you for considering our manuscript and for the constructive suggestions and comments, which greatly helped us to improve the manuscript. We have tried our best to revise the manuscript. We hope that your comments have been addressed accurately. If there are any additional questions, please tell us and we can further try to resolve them. The revised portions of the manuscript are marked with red color and the point-to-point responses are given below. Thanks again.

We are looking forward to your final decision.

Sincerely,
Penghui Yang

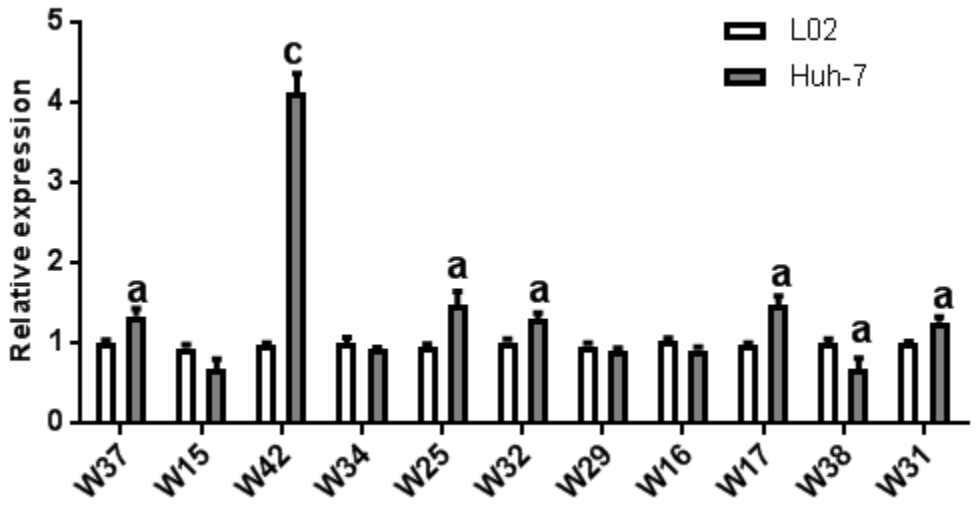
Response to reviewers' comments (60935 **)**

Reviewer #1:

1. Please add more explanations on the reasons why you select the non-coding long RNA W42 for analysis and the background on this important fact.

Response: Thank you for your comments. We have included more detailed information about lncRNA W42 in the Results section of the revised manuscript. Based on our previous bioinformatics analysis, we chose another 10 candidate lncRNAs and re-validated their expression in normal liver cell line LO2 and the human HCC cell line Huh7 (Supplementary Fig. 1A). Subsequently we re-validated the expression of lncRNA W42 in 25 pairs of HCC tissues and paired adjacent noncancerous tissues. The results showed that lncRNA W42 was the most differentially expressed among these lncRNAs. Hence, we chose lncRNA W42 as a candidate lncRNA for HCC in the following study.

Supplementary Fig. 1A



Based on our previous bioinformatics analysis, we chose another 10 candidate lncRNAs and re-validated their expression in normal liver cell line LO2 and the human HCC cell line Huh7. $^{a}p<0.05$, $^{c}P < 0.001$.

2. Are there any other non-coding RNAs involved in the development of hepatocellular carcinoma? If any references on non-coding RNAs related on the development of HCC have been reported to date, please list them up, and if possible, please add a new table on the manuscripts that have been reported to date. In addition, please add your own opinion on the future possibilities and perspectives on this important fact in the Discussion section.

Response: Thank you for your comments. We have included this part in the Discussion of the Revised Manuscript. "Particularly, some HCC star lncRNAs , such as HULC[1], P53[2], MCM3AP-AS1[3] ,ATB[40], HOTAIR[4] and lnc00624[5], have been reported, and Lots evidences showed that further investigation on the relationship between Lnc RNA and HCC might provide potential targets for targeted therapy of HCC."

Reference

1 Xin X, Wu M, Meng Q, et.al. Long noncoding RNA HULC accelerates liver cancer by inhibiting PTEN via autophagy cooperation to miR15a. Mol Cancer. 2018 Jun 12;17(1):94. [PMID: 29895332; PMCID: PMC5998602 Doi: 10.1186/s12943-018-0843-8.]

2 Qin G, Tu X, Li H, et.al. Long Noncoding RNA p53-Stabilizing and Activating RNA Promotes p53 Signaling by Inhibiting Heterogeneous Nuclear Ribonucleoprotein K deSUMOylation and Suppresses Hepatocellular Carcinoma. Hepatology. 2020 Jan;71(1):112-129. [PMID: 31148184. doi:

10.1002/hep.30793. Epub 2019 Aug 12.]
3 Wang Y, Yang L, Chen T, et.al. A novel lncRNA MCM3AP-AS1 promotes the growth of hepatocellular carcinoma by targeting miR-194-5p/FOXA1 axis. Mol Cancer. 2019 Feb 19;18(1):28. [PMID: 30782188; PMCID: PMC6381672. doi: 10.1186/s12943-019-0957-7.]
4 Li W, Kang Y. A new Lnc in metastasis: long noncoding RNA mediates the prometastatic functions of TGF-β. Cancer Cell. 2014 May 12;25(5):557-9. [PMID: 24823634; PMCID: PMC4091806. doi: 10.1016/j.ccr.2014.04.014.]
5 Wong CM, Tsang FH, Ng IO. Non-coding RNAs in hepatocellular carcinoma: molecular functions and pathological implications. Nat Rev Gastroenterol Hepatol. 2018;15:137-151. PMID: 29317776. Doi: 10.1038/nrgastro.2017.169.
6 Li Z, Lu X, Liu Y, et. al. Gain of LINC00624 Enhances Liver Cancer Progression by Disrupting the HDAC6-TRIM28-ZNF354C Corepressor Complex. Hepatology. 2020 Sep 1. [PMID: 32869873. doi: 10.1002/hep.31530. Epub ahead of print.]

3. Is the non-coding long RNA W42 really one of triggers for hepatocellular carcinoma carcinogenesis? Factors different from carcinogenesis or genetic and epigenetic factors related to the flow from chronic hepatitis to liver cirrhosis or from focal hepatocellular carcinoma carcinogenesis in the liver to multi-organ metastasis. For example, consider possible involvement in inflammation, fibrosis, viral hepatitis such as HBV, HCV, fatty liver, race, age, gender differences, etc., and add your own thoughts and considerations to the section of Dicussion.

Response: Thank you for your comments. We have included this part in the Discussion of the Revised Manuscript. “Furthermore, factors different from carcinogenesis or genetic and epigenetic factors related to the flow from chronic hepatitis to liver cirrhosis or from focal hepatocellular carcinoma carcinogenesis in the liver to multi-organ metastasis. As shown in Table1, we observed that lncRNA W42 expression was closely associated with liver cirrhosis and tumor recurrence, but no obvious differences were observed in age, gender, tumor size, HBV and AFP levels. Of course, the relationship between lncRNA W42 and the etiology of HCC (HCV, HBV, NAFLD, alcohol, etc) needed to be validated in a much larger cohort. “

4. For example, recently, miRNA and ctDNA are detected in blood and body fluids such as urine, are useful for screening for the presence diagnosis of various cancers. Is it possible that non-coding RNA W42 or part of it can be detected in peripheral blood? Please add your own

opinions and considerations on the expectations and usefulness of this method for future clinical diagnosis and screening for hepatocellular carcinoma detection.

Response: Thank you for your comments. We have included this part in the Discussion of the Revised Manuscript. "Several studies showed that miRNA and ctDNA are detected in blood and body fluids such as urine, are useful for screening for the presence diagnosis of various cancers [7-8]. Similarly, the abundant mRNA, circRNA, and lncRNA in human blood could be utilized as potential biomarkers for the diagnosis of various cancers, which were revealed by extracellular vesicles long RNA sequencing [9]. However, whether LncRNA W42 could be detected in peripheral blood needs to be investigated in our subsequently studies."

Reference

7 He Q, Fang Y, Lu F, Pan J, Wang L, Gong W, Fei F Cui J, Zhong J, Hu R, Liang M, Fang L, Wang H, Yu M, Zhang Z. Analysis of differential expression profile of miRNA in peripheral blood of patients with lung cancer. J Clin Lab Anal 2019; 33: e23003. [PMID: 31541491 PMCID: PMC6868404 DOI: 10.1002/jcla.23003]

8 Patel H, Okamura R, Fanta P, Patel C, Lanman R, Raymond V, Kato S, Kurzrock R. Clinical correlates of blood-derived circulating tumor DNA in pancreatic cancer. J Hematol Oncol 2019;12:130. [PMID: 31801585 PMCID: PMC6894333 DOI: 10.1186/s13045-019-0824-4]

9 Li Y, Zhao J, Yu S, Wang Z, He X, Su Y, Guo T, Sheng H, Chen J, Zheng Q, Li Y, Guo W, Cai X, Shi G, Wu J, Wang L, Wang P, He X, Huang S. Extracellular Vesicles Long RNA Sequencing Reveals Abundant mRNA, circRNA, and lncRNA in Human Blood as Potential Biomarkers for Cancer Diagnosis. Clin Chem 2019; 65: 798-808. [PMID: 30914410 DOI: 10.1373/clinchem.2018.301291]

Reviewer #2:

1. More data is needed to explain why the authors focus their research on lncRNA W42?

Response: Thank you for your comments. We have included more detailed

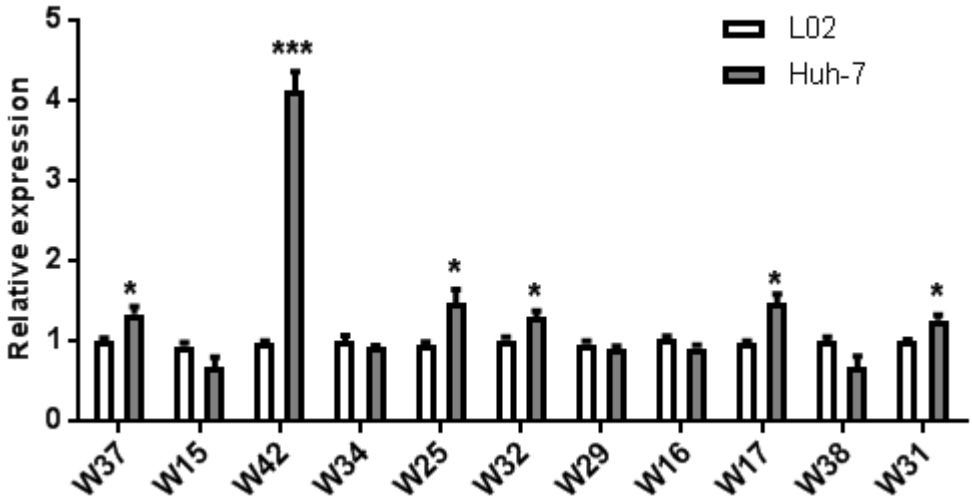
information about lncRNA W42 in the Results section of the revised manuscript. Based on our previous bioinformatics analysis, we chose another 10 candidate lncRNAs and re-validated their expression in normal liver cell line LO2, the human HCC cell line Huh7 (Supplementary Fig. 1A). Subsequently we re-validated the expression of lncRNA W42 in 25 pairs of HCC tissues and paired adjacent noncancerous tissues. The results showed that lncRNA W42 was the most differentially expressed among these lncRNAs. Hence, we chose lncRNA W42 as a candidate lncRNA for HCC in the following study.

2. The authors need to provide more information about lncRNA W42 in the main text.

Response: Thank you for your comments. We have included more detailed information about lncRNA W42 in the revised manuscript. Based on our previous bioinformatics analysis, we chose another 10 candidate lncRNAs and re-validated their expression in normal liver cell line LO2, the human HCC cell line Huh7, and we sequenced full-length of lncRNA W42 and found that its length was 1598 nt and that it was located on chromosome 7q: 94423057-94429430 and shares a transcript with the COL1A2 gene (Supplementary Fig. 1).

Supplementary Figure 1

A



B

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121  TCCCTGGCTC  GAGAGGTGAA  CGTGGTCTAC  CAGGTGTTGC  TGGTGCTGTG  GGTGAACCTG
181  GTCCTCTTGG  CATTGCCGGC  CCTCCTGGGG  CCCGTGGTCC  TCCTGGTGCT  GTGGGTAGTC
241  CTGGAGTCAA  CGGTGCTCCT  GGTGAAGCTG  GTCGTGATGG  CAACCCTGGG  AACGATGGTC
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361  GTCCCGTTGG  TGCTGCAGGT  GCACCTGGTC  CTCATGGCCC  CGTGGGTCCT  GCTGGCAAAC
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661  CTGCTGGTCC  TTCTGGCCCT  GCTGGAAAAG  ATGGTCGCAC  TGGACATCCT  GGTACAGTTG
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1261 TCATGCGCCT  GCTGGCCAAC  TATGCCTCTC  AGAACATCAC  CTACCACTGC  AAGAACAGCA
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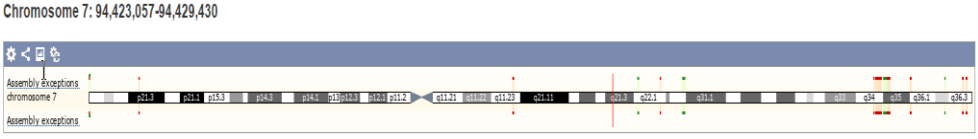
C



Replies to EDITORIAL OFFICE'S COMMENTS

1. I found the authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s);
Response: Thank you for your comments. We have provided the approved grant application forms.

2. I found the authors did not provide the original figures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor;
Response: Thank you for your comments. We have provided the original figures using PowerPoint.

3. I found the authors did not write the "article highlight" section. Please write the "article highlights" section at the end of the main text
Response: Thank you for your comments. We have added the "article highlights" section at the end of the main text.

4. please don't include any *, #, †, §, ‡, ¥, @….in your manuscript; Please use superscript numbers for illustration; and for statistical significance, please use superscript letters. Statistical significance is expressed as aP <0.05, bP <0.01 (P > 0.05 usually does not need to be denoted). If there are other series of P values, cP <0.05 and dP <0.01 are used, and a third series of P values is expressed as eP <0.05 and fP <0.01.
Response: Thank you for your comments. We have modified them according to your comments in the Results of the Revised Manuscript.