

PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 75056

Title: Correlation of molecular alterations with pathological features in hepatocellular carcinoma: literature review and experience of an Italian center

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 01206150

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Chief Doctor

Reviewer's Country/Territory: China

Author's Country/Territory: Italy

Manuscript submission date: 2022-01-14

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-01-15 03:37

Reviewer performed review: 2022-01-15 09:08

Review time: 5 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No



**Baishideng
Publishing
Group**

7041 Koll Center Parkway, Suite
160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
<https://www.wjgnet.com>

Peer-reviewer statements	Peer-Review: [<input checked="" type="radio"/>] Anonymous [<input type="radio"/>] Onymous Conflicts-of-Interest: [<input type="radio"/>] Yes [<input checked="" type="radio"/>] No
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SPECIFIC COMMENTS TO AUTHORS

Generally, this paper was written well, but the language need to be polished. there were some apparent grammar errors such as: 1.The reactivation of TERT can be explained not also by the aforementioned 2. β -catenin the protein is translocated into the nucleus. 3.most significant in commonest human cancers, 4.that TERT more frequent mutations fall in a promoter region usually not covered by the exome sequencing studies. 5.correlated high alpha-feto protein (AFP) serum levels.

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Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 02540709

Position: Editorial Board

Academic degree: BSc, PhD

Professional title: Research Scientist, Teaching Assistant

Reviewer's Country/Territory: Spain

Author's Country/Territory: Italy

Manuscript submission date: 2022-01-14

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-01-28 08:33

Reviewer performed review: 2022-02-03 11:31

Review time: 6 Days and 2 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
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Peer-reviewer statements	Peer-Review: [<input checked="" type="radio"/>] Anonymous [<input type="radio"/>] Onymous Conflicts-of-Interest: [<input type="radio"/>] Yes [<input checked="" type="radio"/>] No
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SPECIFIC COMMENTS TO AUTHORS

I have carefully read your manuscript entitled “Correlation of molecular alterations with pathological features in hepatocellular carcinoma: literature review and experience of an Italian center”. This is a good review pointing out the utility of molecular characterization of HCC. Some minor revisions in language and references are needed. For example, ref. 59 is incomplete; ref 64 is a review evaluating the geographical differential distribution of TERT mutations in HCC, but is inserted in page 10, in the paragraph summarizing the relationship of HBV and aflatoxin B1 exposure with TP53 mutations. Please revise.

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Title: Correlation of molecular alterations with pathological features in hepatocellular carcinoma: literature review and experience of an Italian center

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 04737230

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: Mexico

Author's Country/Territory: Italy

Manuscript submission date: 2022-01-14

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-02-01 15:26

Reviewer performed review: 2022-02-10 19:52

Review time: 9 Days and 4 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input checked="" type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

Peer-reviewer statements	Peer-Review: [<input checked="" type="radio"/>] Anonymous [<input type="radio"/>] Onymous Conflicts-of-Interest: [<input type="radio"/>] Yes [<input checked="" type="radio"/>] No
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SPECIFIC COMMENTS TO AUTHORS

Thank you so much for this review. I find the aim of the review appealing and attractive, however, I believe that the authors did not comprehensively delve into the correlation between their three genes of interest and the pathological and molecular characteristics of HCC. Some key etiological factors contribute to HCC, and the authors mention them, however, they do not achieve to classify the frequency of TERT, CTNNB1, and TP53 mutations in these etiological factors. For example, they mention the frequency of TERT mutations in patients with cirrhosis, but they do not mention and delve into the frequency of these mutations in people with fatty liver, diabetes, genetic diseases such as hemochromatosis, or Wilson's disease. I believe that this might be compensated with better figures: some correlate the molecular characteristics to the etiological factors (e.g. DOI: 10.1158/0008-5472.CAN-09-1089, <https://doi.org/10.1073/pnas.1807305115>). I recommend redesigning the figures, trying to prioritize and graph what is discussed in the section "MOLECULAR HCC SUBTYPE CLASSIFICATION" and "MOLECULAR HCC SUBTYPES AND PATHOLOGICAL FEATURES", instead of illustrating the activation mechanism of the three molecules, since that is something that readers can find in other reviews. The authors explain nicely the canonical Wnt/ β -catenin pathway however, this activation mechanism is not present in every HCC, since (DOI: 10.1158/0008-5472.CAN-09-1089) The activation of the Wnt/ β -catenin pathway by the means of TGF-beta have been tightly related to HCC. It would be appreciated if the authors add this to the CTNNB1 section. About Hepatocellular Adenoma (HCA) Authors provide very interesting data, maybe authors could provide the mutation frequency of the mutations in HCA, as well as the frequency of HCA that transform into

HCC. It would be interesting if the authors could classify their findings in the etiological/ molecular classification and show it in an integrative figure. Mind the font size in the images, the actual it is hard to read, especially in the last image. In summary, I suggest redesigning the figures and showing the aim of the review which is to show the “Correlation of molecular alterations with pathological features in hepatocellular carcinoma:” and not showing the activation pathways that can be found in any other review.