Editorial

# Hepatocellular carcinoma mutation landscape and its differences between Asians and Whites

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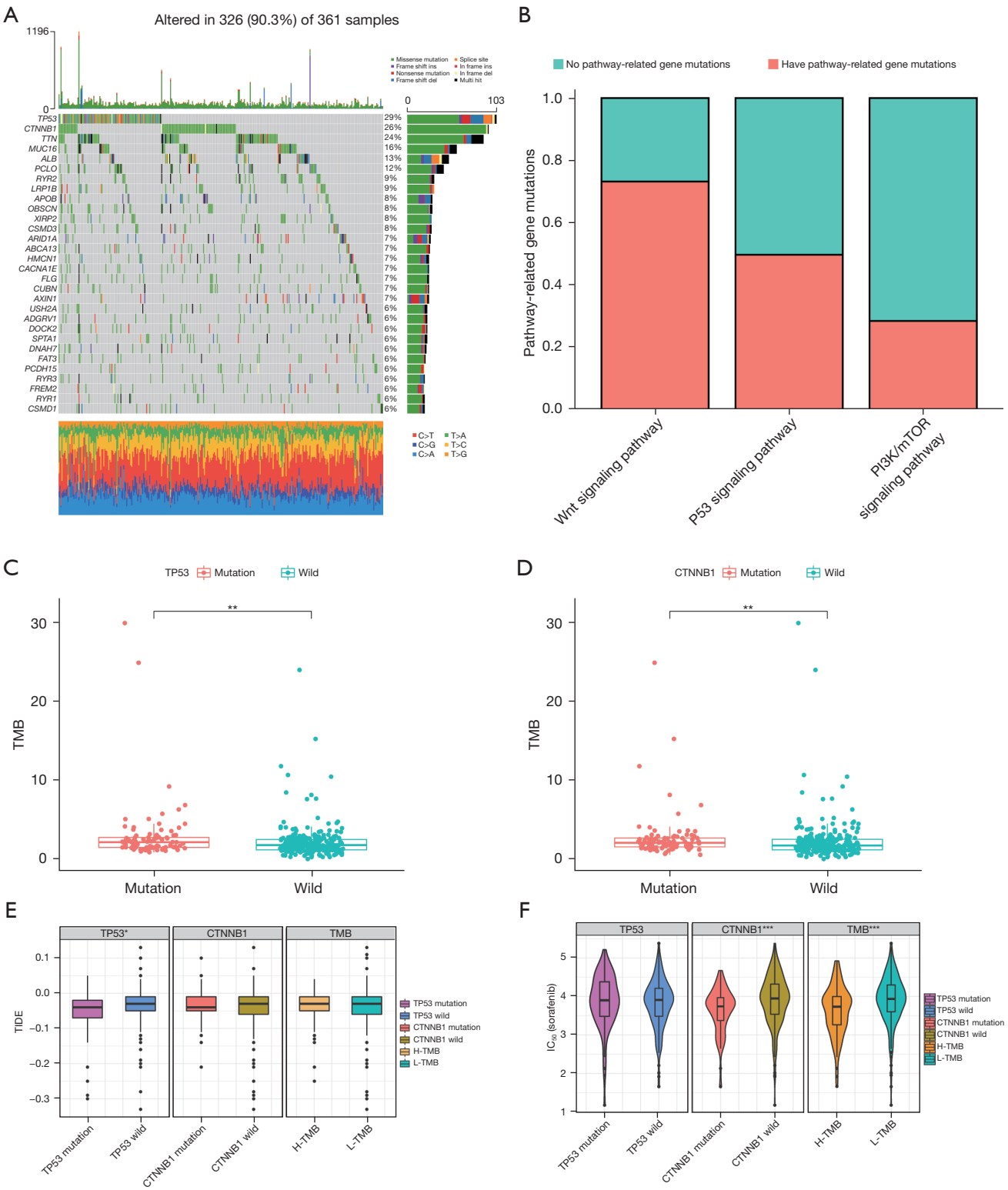
Hepatocellular carcinoma (HCC) is one of the most common malignancies around the world and accounts for 85% to 90% of the pathological types of primary liver cancer (1). In total, 905,677 patients die from HCC, which was the third leading cause of cancer-related death worldwide in 2020 (2). Despite significant advancements achieved in early detection, liver transplantation, surgical technique, and local and systemic treatment, the overall prognosis of HCC remains dismal with a 5-year relative survival rate of 18.4% (3). Data revealed that about half of the newly diagnosed HCC occurred in China annually, as well as half of new death of HCC per year (1,2). Different from the West, HCC in China has its unique characteristics, and the most common cause of HCC is hepatitis B virus infection (1). But contributing to the widespread vaccination against hepatitis B by the Chinese government, the disease spectrum of HCC is changing greatly, which needs corresponding adaptation in the management of HCC (1).

HCC generally results from a unique synergistic combination of genetic alterations mixed with epigenetic modifications (4,5). Heterogeneity is manifested as interindividual heterogeneity and intratumoral heterogeneity, and the latter also manifests as temporal and spatial heterogeneity, which shed light on the individualized and precise treatment for HCC. Owing to the advance in genomics, proteomics, and transcriptomics, plenty of molecular pathogenesis, drivers, and molecular and immune classes of HCC have been identified and many novel agents either molecular targets or immune checkpoint inhibitors (ICIs) have been developed and marked with promising results (6,7). Nonetheless, data revealed that only 25% of tumors harbor one druggable target mainly due to tumor heterogeneity (4,8). In addition, off-target and treatment resistance are also dilemmas after marking (4,6,7). As a result, the understanding of oncogenic drivers and molecular classes has not yet ceased.

In order to understand the underlying mechanisms of cancers and identify potential targets for treatment, bioinformatics analysis is one of the most effective strategies. Recently, Wang *et al.* (9) constructed a mutational profile based on next-generation sequencing from Chinese HCC patients and then explored its relevance to clinicopathology. However, the cohort included only Chinese patients with HCC and lacked comparisons with other races. Public datasets are often used to perform bioinformatics analysis, among which TCGA is the most commonly used dataset. We used the recently published data from TCGA to verify the findings in Wang *et al.* report. A total of 391 HCC samples were eligible to conduct further analysis, and somatic mutation occurred in 326 patients (90.3%). As depicted in *Figure 1A*, the top five mutation genes were *TP53* (29%), *CTNNB1* (26%), *TTN* (24%), *MUC16* (16%), and *ALB* (13%), respectively. Different from the results of Wang *et al.*, the incidence of TERT mutation was as low as 0.26%. The top three signaling pathways were Wnt, P53, and PI3K/mTOR, with the corresponding rate of 73.1%, 49.6%, and 28.3%, respectively (*Figure 1B*). TMB is the pan-cancer biomarker for ICIs, and the median



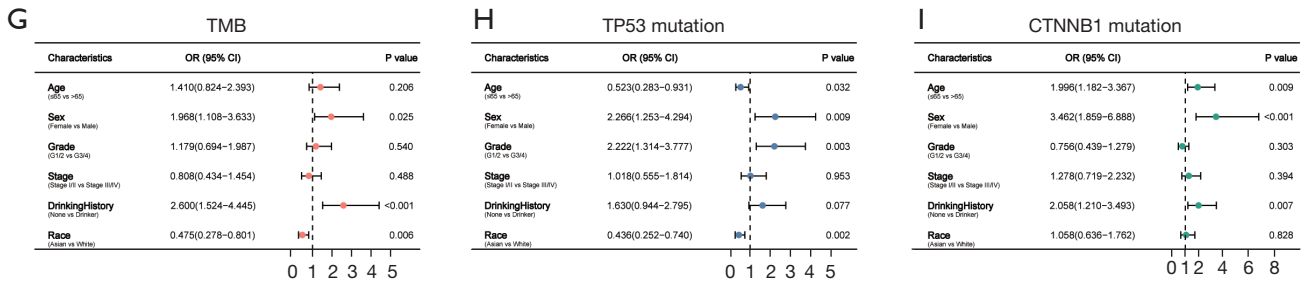
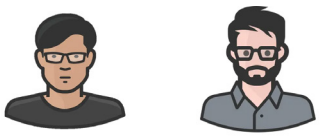



**Figure 1** HCC mutation information in TCGA cohort. (A) Waterfall plot showing the landscape of mutation profiles. (B) Stacked histogram on the proportion of mutations in pathway-related genes in HCC patients. (C,D) The distribution of TMB values between mutated and wild groups of TP53 and CTNNB1. (E,F) The differences of TIDE score and IC50 of sorafenib between the mutant and wild groups of the two genes TP53 and CTNNB1 and between the high- and low-TMB groups. (G-I) Forest plot showing the effect of clinicopathological characteristics on high- and low-TMB status, TP53 and CTNNB1 mutation status. *, P<0.05; **, P<0.01; ***, P<0.001. TIDE, Tumor Immune Dysfunction and Exclusion; HCC, hepatocellular carcinoma.

TMB among 391 HCC patients was 1.816. As shown in *Figure 1C*,*1D*, TMB in the TP53 mutation group and CTNNB1 mutation group were significantly higher than those in the wild group (both P<0.05). TIDE score is a score of tumor immune dysfunction and exclusion, which is often used to evaluate the tumor immune microenvironment. Generally, the higher TIDE score, the poorer response to ICIs. *Figure 1E* revealed a significant difference in TIDE score between TP53 mutation and wild, but no significant difference was observed stratified by CTNNB1 and TMB, which suggested that TP53 but not TMB should be taken as a biomarker for ICIs. Sorafenib is the cornerstone of systemic treatment for HCC. Drug sensitivity analysis exhibited that the IC50 in the CTNNB1 mutation group was significantly lower than that in the CTNNB1 wild group, and a significant difference was observed between high- and low-TMB group, but not between groups of TP53 mutation and wild (*Figure 1F*). These findings indicated that CTNNB1 and TMB could be taken as potential biomarkers for sorafenib. And then logistic regression analysis showed that race was an influencing factor of TMB (*Figure 1G*) and TP53 mutations (*Figure 1H*), but not CTNNB1 mutations (*Figure 1I*).

Furthermore, *Figure 2* illustrated the differences between Asians and Whites. Briefly, the most common mutated genes in Asians were TP53 (34%), CTNNB1 (26%), and TTN (24%), which were all significantly higher than those in the White (all P<0.05). A similar tendency was observed in terms of Wnt-, P53-, and PI3K/mTOR-signaling pathway-related gene mutations, as well as the median TMB. Among the White, significant differences in TIDE score were observed stratified by TMB and TP53, but no difference was observed among Asians, which indicated that TMB and TP53 could only be taken as predictive markers of immunotherapy response for Whites. Drug sensitivity analysis exhibited a significant difference in IC50 of sorafenib stratified by TMB and CTNNB1 among Asians, were as a significant difference was only observed stratified by CTNNB1 among Whites, which indicated that CTNNB1 could be taken as a common biomarker of sorafenib response both in Asians and Whites, while TMB could only be taken for Asians. Of note, all the findings in the present study should be taken with cautious.

In China, the 5-year survival rate of HCC is as low as 12.5% (1), which is proposed to improve by 15% in the outline of the Healthy China 2030 Plan (10). Hence, it is time to construct a biological database of Chinese to explore the unique underlying mechanism for HCC in China and then develop the corresponding strategies, considering the great divergence between the West and East. Moreover, it is also essential to build, share and connect data in the future.



| Item | Race | |
|---|---|---|
| | Asian | White |
| Mutation frequency of top three mutated genes | | |
| TP53 | Higher | Lower |
| CTNNB1 | Higher | Lower |
| TTN | Higher | Lower |
| Mutations in genes involved in signaling pathways | | |
| Wnt signaling pathway | Higher | Lower |
| P53 signaling pathway | Higher | Lower |
| PI3K/mTOR signaling pathway | Higher | Lower |
| Median TMB (Muts/Mb) | Higher | Lower |
| Whether is a predictive marker of immunotherapy response | | |
| TMB | No | Yes |
| TP53 mutation | No | Yes |
| CTNNB1 mutation | No | No |
| Whether is a predictive marker of sorafenib response | | |
| TMB | Yes | No |
| TP53 mutation | No | No |
| CTNNB1 mutation | Yes | Yes |

**Figure 2** Summary of differences in mutation status between Asian and White.

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*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-22-364/coif). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## References


1. Xie DY, Ren ZG, Zhou J, et al. 2019 Chinese clinical guidelines for the management of hepatocellular carcinoma: updates and insights. Hepatobiliary Surg Nutr 2020;9:452-63.
2. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71:209-49.
3. Falette Puisieux M, Pellat A, Assaf A, et al. Therapeutic Management of Advanced Hepatocellular Carcinoma: An Updated Review. Cancers (Basel) 2022;14:2357.
4. Llovet JM, Pinyol R, Kelley RK, et al. Molecular pathogenesis and systemic therapies for hepatocellular carcinoma. Nat Cancer 2022;3:386-401.
5. Braghini MR, Lo Re O, Romito I, et al. Epigenetic remodelling in human hepatocellular carcinoma. J Exp Clin Cancer Res 2022;41:107.
6. Jin H, Qin S, He J, et al. New insights into checkpoint inhibitor immunotherapy and its combined therapies in hepatocellular carcinoma: from mechanisms to clinical trials. Int J Biol Sci 2022;18:2775-94.
7. Ng CKY, Dazert E, Boldanova T, et al. Integrative proteogenomic characterization of hepatocellular carcinoma across etiologies and stages. Nat Commun 2022;13:2436.
8. Llovet JM, Montal R, Sia D, et al. Molecular therapies and precision medicine for hepatocellular carcinoma. Nat Rev Clin Oncol 2018;15:599-616.
9. Wang S, Shi H, Liu T, et al. Mutation profile and its correlation with clinicopathology in Chinese hepatocellular carcinoma patients. Hepatobiliary Surg Nutr 2021;10:172-9.
10. Central People's Government of PRC [Internet]. Circular of the Central Committee of the Communist Party of China and the State Council of PRC on Printing and Issuing the Plan for a Healthy China 2030; c2016. Available online: http://www.gov.cn/gongbao/2016-11/20/content_5133024.htm


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