Reviewer Report

Title: **Advances in Genomic Hepatocellular Carcinoma Research**

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Reviewer name: **Eric Letouze**

Reviewer Comments to Author:

In this work, Huang et al. review and summarize most of the NGS studies related to HCC in the last few years.The study is nicely conducted and well written, and will be very useful to easily access and integrate the high number of data sets generated by many teams around the world.I have a few comments below.1. The following references are missing and should be added :- Zhang et al., Gastroenterology 2017, 49 WGS of aflatoxin B1-related HCC: https://www.ncbi.nlm.nih.gov/pubmed/28363643- Ng et al., Sci Transl Med 2017, WES of 98 HCC from Taiwan with a high contribution of aristolochic acid: https://www.ncbi.nlm.nih.gov/pubmed/29046434- Letouzé et al., Nat Commun 2017, WGS of 45 liver cancers from Europe with diverse etiological backgrounds: https://www.ncbi.nlm.nih.gov/pubmed/29101368- Chaudhary et al., Clin Cancer Res 2018, Meta-analysis of 1,494 HCC: https://www.ncbi.nlm.nih.gov/pubmed/302420232. The precise criteria used by the authors to include a gene in Table 2 should be specified, especially if the authors present this list as a reference of HCC driver genes. I would suggest to order genes according to a criteria (e.g. alteration frequency in HCC) to see the main drivers in the first lines.Also, the reason why the authors discuss in detail ALB, ARID2, RB1, BRD7 and RPL22 rather than other genes is not clear to me.Finally, although several genes harbor both mutations, SVs and CNAs, it may be worth to present separately genes that are primarily affected by SVs and CNAs (e.g. FGF19/CCND1, CCNE1, CDKN2A…). Otherwise they are a bit "drowned" in the sea of candidate drivers from mutations.3. It has been shown that very highly expressed genes (like ALB or APOB) display a striking accumulation of indels, likely due to the collision of the transcription and replication machineries (Letouzé et al., Nat Commun 2017). The authors should mention this alternate hypothesis to explain the recurrence of alterations in highly expressed liver genes.4. HBV insertions in CCNA2 were also reported (Wang et al., Nature 1990 and Fujimoto et al., Nat Genet 2016) and should be mentioned.5. Fujimoto et al. identified 7 signatures but 10 have been identified in a meta-analysis (Letouzé et al., Nat Commun 2017) and another signature related to cisplatin treatment was recently described (Boot et al., Genome Res 2018). I would suggest to mention these studies in the "mutational signature" paragraph, as well as the in-depth analyses of the aflatoxin B1 (Zhang et al., Gastroenterology 2017) and aristolochic acid (Ng et al., Sci Transl Med 2017) signatures.

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