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Identifying and Characterizing the Mutational Landscape of Noncirrohotic Hepatocellular Carcinoma

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Identifying and Characterizing the Mutational Landscape of Noncirrhotic Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) is the 5th highest diagnosed cancer type worldwide, and with the 2nd highest mortality rate, it contributes to 750,000 cancer related deaths per year. Cirrhotic HCC, which comprises of 80% of all cases, is strongly associated with hepatitis B/C infection, alcohol abuse, and fatty liver disease. Noncirrhotic HCC, making up the remainder 20% of HCC cases, can occur with no known underlying liver disease. Because the liver maintains normal functionality, noncirrhotic tumors are often detected at a more advanced stage, and have a high recurrence rate.

To understand the genomic landscape of noncirrhotic HCC, whole genome and transcriptome sequencing was performed on a discovery cohort consisting of 26 matched tumor/normal noncirrhotic HCC samples, as well as 3 matched tumor/normal cirrhotic samples. Analysis on the discovery set focused on structural variation (SV), gene fusion, copy number variation (CNV), loss of heterozygosity (LOH), and differential expression. Custom targeted capture sequencing was performed on another 87 HCC samples, and the total of 116 samples were analyzed for single nucleotide variants (SNVs) and insertions and deletions (INDELS).

Recurrent losses were observed in 6q, 8p, 13q, and 17p, with LOH of 8p being associated with lymphovascular space invasion (LVSI) and a shorter recurrence free survival. Copy number deletions at 2q were associated with a shorter overall survival. Recurrent SVs occurred at DNA repair genes (*MACROD2*), nuclear receptor signaling genes (*NCOR1*), cell adhesion genes (*CNTN1*), and microtubule organization genes (*CEP57L1*). Novel fusions involving *NR1H4* were found in 2/29 HCC samples, and mutations in *CTNNB1*, *FRAS1*, *RPS6KA3*, *RB1*, and *C5* were associated with shorter overall and/or shorter recurrence free survival.

We conclude that several genes and mutational events are potentially implicated in HCC development and progression. However, these mutational events largely do not appear to be specific to noncirrhotic HCC.