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GENOMIC ANALYSIS OF COMBINED HEPATOCELLULAR-CHOLANGIOCARCINOMA REVEALS COMMON LINEAGE OF TUMOR COMPONENTS WITH UNIQUE GENE EXPRESSION PROFILE

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Background : Combined hepatocellular-cholangiocarcinoma (cHCC-CCA) is a rare primary liver cancer that exhibits both hepatocytic and biliary differentiation. cHCC-CCA is associated with prognosis worse than hepatocellular carcinoma (HCC) and similar to intrahepatic cholangiocarcinoma (iCCA), partly due to misdiagnosis and wrong-directed treatment. The aim of this study was to investigate genomic alterations for accurate diagnosis of cHCC-CCA.

Methods : We performed whole exome sequencing for 31 histologically defined cHCC-CCA in both hepatocytic and biliary tumor components and matched normal tissues. In total, 90 samples were analyzed. The mutational profile of hepatocytic and biliary tumor components were compared. Identified mutations were further correlated with known hotspot mutations of HCC and iCCA.

Results : Among 58 samples of tumor components, 718 pathogenic or likely pathogenic mutations were identified. The mutation profile of hepatocytic and biliary components showed 86.6% match, suggesting a common lineage despite different phenotypic expression. The most commonly mutated genes included TP53 (25/58, 43.1%) and TERT promoter (22/58, 37.9%). Missense and stop-gained variants in RB1 (4/58, 6.9%), PIK3CA (2/58, 3.4%), PTEN (2/58, 3.4%), and frameshift mutations in ATM (2/58, 3.4%) were also identified. None of the mutations were expressed in corresponding normal tissues. The identified mutations in TP53 and TERT promoter were different from the known hotspot mutations in HCC and iCCA, suggesting a unique genomic landscape in cHCC-CCA.

Conclusions : The common mutational profile in hepatocytic and biliary components of cHCC-CCA suggests a monoclonal origin. As mutations in cHCC-CCA were not previously reported in either HCC or iCCA, they could be utilized as potential molecular markers for diagnosis.

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