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Identification of Common Molecular Subtypes of Asian Hepatocellular Carcinoma and Cholangiocarcinoma.

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Identification of Common Molecular Subtypes of Asian Hepatocellular Carcinoma and Cholangiocarcinoma.

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Hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) are clinically disparate primary liver cancers (PLC) with etiological and biological heterogeneity and are the primary cause of cancer mortality in Thailand. The Thailand Initiative in Genomics and Expression Research for Liver Cancer (TIGER-LC) consortium was established to identify genomic factors related to PLC risk, genetic susceptibility, and progression. We determined molecular subtypes among PLC patients by systematic integration of genomic, transcriptomic, and metabolic profiles. Genome wide profiling of 398 surgical specimens derived from 199 PLC patients was performed by Affymetrix HTA2.0 (transcriptome), Affymetrix Genome-Wide Human SNP Array 6.0 (somatic copy number alterations) and Metabolon's DiscoveryHD4 platform (metabolome). Unsupervised Consensus Clustering (cCluster), Subclass Mapping (SM), Gene Set Enrichment Analysis (GSEA), class comparison, loss of heterozygosity and minimum segmentation, Pearson and rank correlation algorithms were used to analyze and validate omics data in 852 Asian and Caucasian PLC cases. Thai HCC and ICC consisted of several stable molecular subtypes linked to similar prognosis that were validated in 247 Chinese HCC, 156 Asian American HCC and 182 Japanese ICC, but not in 163 European American HCC or 104 Caucasian ICC patients. While ICC and HCC share recurrently mutated genes, including *TP53*, *ARID1A*, and *ARID2*, mitotic checkpoint anomalies distinguish the C1 subtype with key drivers *PLK1* and *ECT2*, whereas the C2 subtype is linked to obesity, T-cell infiltration and bile acid metabolism. Thus, Asian ICC and HCC, while clinically treated as separate entities, share common molecular subtypes with similar actionable drivers to improve precision therapy.