Demographic and Genetic Insights Into ARID1A Mutations in Hepatocellular Carcinoma: Implications for Prognosis and Treatment

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Liver cancer is the third leading cause of cancer-related deaths worldwide, with hepatocellular carcinoma (HCC) as the most common type. HCC shows disparities across race, gender, and ethnicity, highlighting the need to understand how demographics shape tumor biology. In this study, I analyzed genomic data from 2,351 HCC patients, focusing on ARID1A, a frequently mutated gene in HCC. ARID1A mutation disrupts chromatin remodeling and DNA repair mechanisms. Patients with ARID1A-mutated HCC had significantly shorter median survival, with the highest mutation rates in males compared to females, Black patients among races, and individuals under 30 or over 70 across ages. Black patients also showed the poorest survival outcomes. ARID1A-mutated tumors exhibited widespread genomic instability, including enriched mutations across multiple cellular pathways. In Black patients, immune pathway mutations and lymphocyte depletion suggest a less immunogenic tumor microenvironment and possible immunotherapy resistance, positioning ARID1A mutation as a potential biomarker for race-informed therapies. I hypothesized that gene co-mutations associated with extended survival in ARID1A-mutated HCC patients may drive cancer cell vulnerability and reveal new therapeutic strategies. Examining disease-free ARID1A-mutated HCC patient tumors, I identified 26 gene co-mutations, with POLQ, a DNA repair gene, as the top candidate. Notably, patients with both ARID1A and POLQ mutations had prolonged life with no adverse survival events, suggesting a synthetic lethal relationship. While ARID1A and POLQ are strongly co-expressed in normal liver, their correlation weakens in cancer, hinting at a compensatory mechanism. These findings position POLQ as a promising therapeutic target in ARID1A-mutated HCC.

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