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A novel hotspot and rare somatic mutation p.*A138V*, at *TP53* is associated with poor survival of pancreatic ductal and periampullary adenocarcinoma patients

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Abstract

Background: Pancreatic Ductal Adenocarcinoma (PDAC) is a cancer of the exocrine pancreas and 5-year survival rates remain constant at 7%. Along with PDAC, Periampullary Adenocarcinoma (PAC) accounts for 0.5–2% of all gastrointestinal malignancies. Genomic observations were well concluded for PDAC and PACs in western countries but no reports are available from India till now.

Methods: Targeted Next Generation Sequencing were performed in 8 (5 PDAC and 3 PAC) tumour normal pairs, using a panel of 412 cancer related genes. Primary findings were replicated in 85 tumour samples (31 PDAC and 54 PAC) using the Sanger sequencing. Mutations were also validated by ASPCR, RFLP, and Ion Torrent sequencing. IHC along with molecular dynamics and docking studies were performed for the *p.A138V* mutant of *TP53*. Key polymorphisms at *TP53* and its associated genes were genotyped by PCR-RFLP method and association with somatic mutations were evaluated. All survival analysis was done using the Kaplan-Meier survival method which revealed that the survival rates varied significantly depending on the somatic mutations the patients harboured.

Results: Among the total 114 detected somatic mutations, *TP53* was the most frequently mutated (41%) gene, followed by *KRAS*, *SMAD4*, *CTNNB1*, and *ERBB3*. We identified a novel hotspot *TP53* mutation (*p.A138V*, in 17% of all patients). Low frequency of *KRAS* mutation (33%) was detected in these samples compared to patients from Western counties. Molecular Dynamics (MD) simulation and DNA-protein docking analysis predicted *p.A138V* to have oncogenic characteristics. Patients with *p.A138V* mutation showed poorer overall survival ($p = 0.01$). So, our finding highlights elevated prevalence of the p53*p.A138V* somatic mutation in PDAC and pancreatobiliary PAC patients.

Conclusion: Detection of *p.A138V* somatic variant in *TP53* might serve as a prognostic marker to classify patients. It might also have a role in determining treatment regimes. In addition, low frequency of *KRAS* hotspot mutation mostly in Indian PDAC patient cohort indicates presence of other early drivers in malignant transformation.

Keywords: Pancreatic ductal adenocarcinoma, Periampullary adenocarcinoma, Novel somatic hotspot mutation, Frequently mutated genes, Next generation sequencing

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