RESEARCH ARTICLE

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

Gourab Saha¹⁺, Richa Singh¹⁺, Argha Mandal²⁺, Subrata Das³⁺, Esita Chattopadhyay¹, Prasun Panja¹, Paromita Roy⁴, Navonil DeSarkar⁵, Sumit Gulati⁶, Supriyo Ghatak⁶, Shibajyoti Ghosh⁷, Sudeep Banerjee⁴, Bidyut Roy¹, Saurabh Ghosh¹, Dipankar Chaudhuri², Neeraj Arora⁴, Nidhan K. Biswas³ and Nilabja Sikdar^{1*}

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.

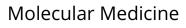
Results: Among the total 114 detected somatic mutations, *TP53* was the most frequently mutated (41%) gene, followed by *KRAS*, *SMAD4*, *CTNNB1*, and *ERBB3*. We identified a novel hotspot *TP53* mutation (p.A138V, in 17% of all patients). Low frequency of *KRAS* mutation (33%) was detected in these 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 p53p.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



© The Author(s). 2020 **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.



Open Access

^{*} Correspondence: snilabja@isical.ac.in; snilabja@gmail.com

[†]Gourab Saha, Richa Singh, Argha Mandal and Subrata Das contributed equally to this work.

¹Human Genetics Unit, Indian Statistical Institute, 203, B. T. Road, Kolkata 700108, India

Full list of author information is available at the end of the article