

REVIEW OPEN ACCESS

Mapping Mutations and Signaling Network Interactions to Guide Precision Therapy in Gallbladder Cancer

Nisha Manav¹  | Akanksha Kashyap¹  | Lakshay Malhotra²  | Chethan Rajegowda¹  | Chandra Prakash Prasad¹ 

¹DR. B.R.A. IRCH, AIIMS, New Delhi, India | ²Department of Biochemistry, Sri Venkateswara College, University of Delhi, New Delhi, India

Correspondence: Chandra Prakash Prasad (researchchandra@gmail.com)

Received: 17 December 2025 | **Revised:** 14 August 2026 | **Accepted:** 21 September 2026

Keywords: gallbladder cancer | mutations | oncogene | oncogenic signalling | therapeutics | tumor suppressor proteins | tumorigenesis

ABSTRACT

Background: Gallbladder cancer (GBC) is a biologically complex malignancy arising from the epithelial lining of the gallbladder, with adenocarcinoma constituting the major histological subtype. Early detection is challenging because of vague clinical manifestations and the organ's deep-seated anatomical location, resulting in diagnosis at advanced stages and limited treatment options. Consequently, patients often experience poor prognosis with low 5-year survival rates. Clinical and translational studies have demonstrated marked biological heterogeneity in GBC, primarily driven by diverse molecular alterations that fuel tumor initiation and progression.

Methods: In the present study, we investigated recurrently mutated genes in GBC using The Cancer Genome Atlas (TCGA) and Catalogue of Somatic Mutations in Cancer (COSMIC) gallbladder cohorts, focusing on genes with a mutation frequency above a pre-specified threshold ($\geq 5\%$ in at least one dataset). We then cross-referenced these genes with published literature till date in GBC and other solid tumors where the same variants have been functionally characterized as loss-of-function or gain-of-function. “Likely loss of function” was assigned only when mutations were annotated in OncoKB/COSMIC as truncating/nonsense or as missense variants with experimental or strong computational evidence of functional impairment.

Results: Evaluation and the functional impact of prominent mutations viz. TP53, SMAD4, PIK3CA, CDKN2A, ARID1A, ARID2, KRAS, ELF3, ERBB3, ERBB2, STK11, and CTNNB1 on key cellular signaling pathways that regulate GBC initiation and progression. These alterations influence various oncogenic mechanisms, including cell proliferation, survival, apoptosis evasion, and metastatic potential, by disrupting pathways. By comparing the mutational patterns observed in GBC with those reported in other malignancies sharing analogous molecular signatures, we delineate potential therapeutic vulnerabilities.

Conclusions: Mutation-guided therapeutic approaches hold great promise for advancing precision medicine in GBC. By tailoring treatments to the specific molecular alterations driving tumor development, this could pave the way for more effective interventions and improved patient outcomes in a disease long constrained by limited therapeutic options.

1 | Introduction

Gall bladder cancer (GBC) is the most prevalent malignancy of the biliary tract, originating from the epithelial lining of the gall bladder, affecting a considerable portion of the population every year [1]. Among all its histological subtypes,

adenocarcinoma accounts for nearly 90% of GBC cases, while the less frequently reported subtypes include undifferentiated, squamous cell, mucinous, and neuroendocrine carcinomas, each associated with distinct morphological and clinical characteristics [2]. GBC often remains clinically silent during its early course due to its deep anatomical location

This is an open access article under the terms of the [Creative Commons Attribution](https://creativecommons.org/licenses/by/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2026 The Author(s). *Cancer Reports* published by Wiley Periodicals LLC.