Original Article

# Evaluating the Role of GAB2 and ALDH1 as a Biomarker in Non-Small Cell Lung Carcinoma and Its Clinico-Pathological Correlations

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## Abstract

**Background:** This article will summarize the study's focus on the expression of GAB2 and ALDH1 in NSCLC, which is based on RT-qPCR and IHC. Identifying molecular markers influencing its progression and prognosis is crucial for targeted therapy and personalized medicine. This review focuses on the expression of Growth factor receptor-bound protein 2- associated binding protein 2 (GAB2) and Aldehyde dehydrogenase 1 (ALDH1) in NSCLC, investigating their potential roles as prognostic markers and their correlations with clinico- pathological parameters and aims to summarize the current knowledge on the roles of GAB2 and ALDH1 in NSCLC, focusing on their expression profiles, correlations with clinico-pathological features, and potential implications for diagnosis and treatment. This review seeks to contribute to the ongoing quest for effective biomarkers and therapeutic strategies in NSCLC management by exploring these aspects.

**Keywords:** NSCLC, GAB2, ALDH1, RT-PCR, IHC, Expression, Clinical correlation, Lung Cancer.

**Received: 21 September 2025** **Revised: 25 October 2025** **Accepted: 10 November 2025** **Published: 08 December 2025**

## Introduction

### 1. Overview of Non-Small Cell Lung Carcinoma (NSCLC): Prevalence and Types

Lung cancer remains a leading cause of cancer-related mortality worldwide. Despite advances in early detection and treatment, NSCLC continues to present challenges due to its heterogeneity and resistance to therapy. Non-small cell lung carcinoma (NSCLC) is the most prevalent subtype of lung cancer, accounting for approximately 85% of all cases. Lung cancer is a significant health concern in India. It ranks among the top five most frequent cancers in the country.[1] Recent World Health Organization (WHO) statistics indicate that lung cancer is the leading cause of cancer-related deaths worldwide, with around 1.8 million people dying from it each year.[2] It is more frequently diagnosed in older adults, with smoking being the primary risk factor, though non-smokers can also develop the disease. The global incidence varies, with higher rates observed in industrialized countries.[3] Due to advancements in early detection and targeted therapies, survival rates have improved, but prognosis remains poor for advanced-stage cases. Non-Small Cell Lung Cancer (NSCLC) can be caused by a combination of genetic, environmental, and lifestyle factors. Some of the key causes and risk factors include-

**Smoking:** The most significant risk factor, as tobacco smoke contains carcinogens that damage lung cells. Exposure to harmful substances: Radon gas, asbestos, and metal or mineral dust Can increase the risk. Air pollution: Prolonged exposure to polluted air may contribute to lung cancer development. Radiation therapy: Previous radiation treatments to the chest or breast can be a risk factor. Family history: A genetic predisposition may play a role. Underlying health conditions: Chronic obstructive pulmonary disease (COPD) and pulmonary fibrosis are associated with a higher risk.[4]

**Lung cancer is broadly classified into two main types:**

Non-Small Cell Lung Carcinoma (NSCLC) is the most common type, accounting for approximately 85% of cases. It includes three major subtypes:

Adenocarcinoma is the most common subtype, often occurring in non-smokers and from mucus-secreting glandular cells. It is typically found in the outer regions of the lung and tends to grow more slowly than other subtypes.

Squamous Cell Carcinoma: Strongly associated with smoking, this type originates from the flat cells lining the airways and is usually located near the central part of the lungs. It often presents with symptoms such as coughing and airway obstruction.

**Large Cell Carcinoma:** A less common but more aggressive form of NSCLC, large cell carcinoma can develop in any part of

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**DOI:**
10.21276/amit.2025.v12.i3.229

**How to cite this article:** Tripathi P, Tomar S, Bajpai J, Verma RK, Verma A, Kumar N. Evaluating the Role of GAB2 and ALDH1 as a Biomarker in Non-Small Cell Lung Carcinoma and Its Clinico-Pathological Correlations. Acta Med Int. 2025;12(3):1068-1071.

the lung and tends to grow and spread rapidly, making it more difficult to treat.

**Small Cell Lung Carcinoma (SCLC) –** A more aggressive and rapidly growing cancer that accounts for about 15% of cases, strongly associated with smoking, and tends to spread early.[5]

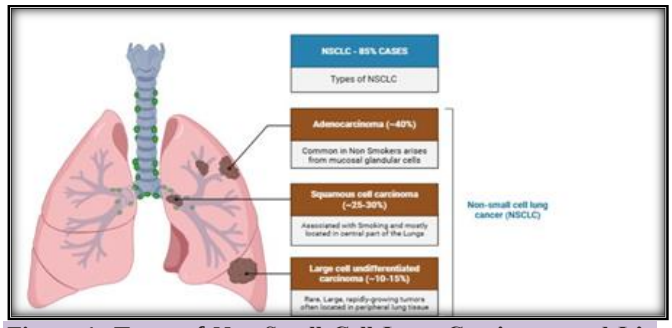


**Figure 1: Types of Non-Small Cell Lung Carcinoma and It's Locations inLung**

The pathogenesis of NSCLC involves complex genetic and molecular alterations, which have been the focus of extensive research to identify novel biomarkers and therapeutic targets. In recent studies, two genes that garnered significant attention are Grb2-Associated Binding Protein 2 (GAB2) and Aldehyde Dehydrogenase 1 (ALDH1). GAB2, a proto-oncogene located at chromosome 11q14.1, has been implicated in the development of lung squamous cell carcinoma, particularly in non-smokers. Studies have shown that GAB2 amplification is more prevalent in non-smokers, suggesting its potential role as a biomarker for lung squamous cell carcinoma (SCC) in this population.

Immunohistochemical analyses have further supported this notion by demonstrating higher GAB2 protein expression in non-smoker tissues compared to smoker tissues. On the other hand, ALDH1 on 9q21.13 is recognized as a marker for cancer stem cells (CSCs) and has been associated with recurrence and resistance to therapy in various cancers, including NSCLC. The expression of ALDH1 has been linked to improved disease-specific survival (DSS) in NSCLC patients, although its prognostic value remains controversial. ALDH1 expression varies across different histological subtypes of NSCLC, with higher levels observed in SCC, compared to adenocarcinoma.[6,7]

Understanding the expression patterns and clinico-pathological correlations of GAB2 and ALDH1 in NSCLC is crucial for developing targeted therapies and improving patient outcomes. 6 Studies on GAB2 Expression have stated that Immunohistochemistry IHC has shown that GAB2 protein is expressed in more NSCLC than normal lung tissues. For instance, one study found that GAB2 was positively expressed in 62.5% of squamous cell carcinomas and 51.35% of adenocarcinomas, with only 12% expression in normal lung tissues.[8-10] Molecular analyses like Quantitative real-time PCR (RT-qPCR) and western blot analyses have confirmed the overexpression of GAB2 mRNA and protein in NSCLC tissues. These findings support the potential role of GAB2 in lung cancer development. ALDH1 expression is often characterized by its ability to self-renew and differentiate, contributing to tumour heterogeneity and therapy resistance. In IHC, ALDH1 expression is significantly lower in adenocarcinoma compared to squamous cell carcinoma, indicating a potential correlation with histological subtype. Which could influence tumour stage.[8-10]

**Importance of Molecular Markers in NSCLC.**

Molecular markers play a critical role in the Diagnosis, Prognosis, and Treatment of NSCLC. Identifying specific biomarkers has led to the development of targeted therapies, improving patient outcomes. Key molecular markers such as EGFR, ALK, KRAS, and PD-L1 have guided treatment decisions and enabled personalized therapeutic approaches. GAB2 and ALDH1 have emerged as significant biomarkers in NSCLC, with their expression levels correlating with tumour progression, metastasis, and therapy resistance—their potential as predictive and prognostic markers may contribute to enhanced patient stratification and tailored treatment strategies. The treatment and prevention of lung cancer are major unmet needs that can most likely be addressed with a better understanding of the disease's molecular origins and evolution. Markers are associated with enhanced tumour-initiating capacity, increased resistance to therapy, and the ability to undergo epithelial-mesenchymal transition. This process enables cancer cells to acquire invasive and migratory properties.[7] GAB2 - Structure: GAB2 is a scaffolding protein that facilitates protein-protein interactions, playing a crucial role in signalling pathways. Its structure includes a pleckstrin homology domain for membrane localization, proline-rich regions for SH3 domain interactions, and multiple tyrosine residues that serve as docking sites for signalling molecules upon phosphorylation.[8]

Function: GAB2 acts as a signalling hub, linking RTKs to downstream effectors such as SHP2, PI3K, PLCγ, CRK, SHC, and SHIP. This function is critical for cell growth, differentiation, migration, and apoptosis. GAB2's role in promoting oncogenic signalling pathways in cancer contributes to tumour progression. GAB2 is involved in signal transduction pathways. Role in Cancer: GAB2 has been implicated in various cancers, including Lung Carcinoma, leukaemia, breast cancer, ovarian cancer, melanoma, and colorectal cancer. Its overexpression or aberrant activation drives malignant processes such as proliferation, migration, and immune evasion. For instance, in HER2-overexpressing cancers, GAB2 ablation can reverse stemness and inhibit tumour growth.[8] ALDH1- Structure: ALDH1 is a cytosolic enzyme that oxidizes intracellular aldehydes. It plays a role in the oxidation of retinol to retinoic acid during early stem cell differentiation. ALDH1 is recognized as a marker for CSCs due to its high activity in stem cell populations. Function: ALDH1's primary function is detoxification, contributing to stem cell maintenance and differentiation. Its enzymatic activity is crucial for protecting cells from oxidative stress and has been linked to chemoresistance in cancer cells. Role in Cancer: ALDH1 is associated with CSCs in various cancers, including NSCLC. In some studies, its expression is related to tumour recurrence, therapy resistance, and poor prognosis. However, its prognostic value remains controversial, with some studies indicating improved DSS in NSCLC patients. ALDH1-positive cells, such as cisplatin, exhibit enhanced resistance to chemotherapy and are characterized by stem-like properties.

ALDH1 is an enzyme that functions in oxidative stress response, and high ALDH1 expression has been reported in NSCLC and is associated with aggressive tumour behaviour, chemoresistance, and poor survival outcomes. It plays a critical role in maintaining stemness properties in cancer cells, making it a valuable marker for prognosis and targeted therapy.[9]

**Clinico-Pathological Correlations:** Several studies have analysed the correlation between GAB2 and ALDH1 expression with clinico-pathological features such as tumour size, lymph node metastasis, histological subtype, and patient survival. High expression of these markers is often linked to advanced tumour stage, greater metastatic potential, and decreased overall survival. Identifying their expression patterns may aid in stratifying patients based on risk and guiding therapeutic decisions. Additionally, their overexpression appears more prevalent in specific NSCLC subtypes, such as adenocarcinoma, suggesting a possible role in subtype differentiation. Patients with high GAB2 and ALDH1 expression levels often exhibit reduced overall survival rates and poor prognosis, emphasizing their potential as prognostic biomarkers. Identifying these expression patterns may help stratify patients into risk categories, refine therapeutic approaches, and improve personalized treatment strategies. While specific studies on GAB2's correlation with tumour stage and histology in NSCLC are limited, its role in oncogenic signalling pathways suggests that it could influence tumour progression and histological characteristics. Increased GAB2 expression has been linked to enhanced metastatic potential, making it a promising therapeutic target. It is an essential adaptor protein involved in oncogenic signalling pathways associated with cell survival, proliferation, migration, and invasion. GAB2 expression correlates with clinico-pathological features in lung adenocarcinomas and squamous cell carcinomas, such as tumour size and UICC staging. This correlation suggests that GAB2 may be a prognostic marker for predicting patient outcomes. The expression of ALDH1 in NSCLC has been correlated with various clinico-pathological features, although specific correlations can vary depending on the study. Generally, ALDH1 expression is linked to aggressive tumour behaviour and poor response to therapy. For instance, high ALDH1 levels have been associated with advanced tumour stages and lymph node metastasis in some studies.

The expression of ALDH1 in NSCLC tissues can influence treatment strategies, as ALDH1-positive cells may exhibit enhanced resistance to conventional therapies such as chemotherapy and radiation. Targeting ALDH1 or pathways associated with CSCs may offer new therapeutic avenues for overcoming resistance and improving treatment outcomes.[10] GAB2 has shown promise as a biomarker for lung SCC, particularly in non-smokers. Studies have identified GAB2 amplification and overexpression in non-smoker SCC tissues compared to smoker tissues, suggesting its potential role in distinguishing between these two groups. This distinction is crucial because the molecular mechanisms driving lung SCC in non-smokers differ significantly from those in smokers. GAB2 could help in early detection and personalized treatment strategies for non-smoker SCC patients. While ALDH1's prognostic value in NSCLC is controversial, it has been correlated with improved DSS in some studies. As a biomarker, ALDH1 could help identify patients at higher risk of recurrence or therapy resistance, guiding more aggressive or targeted treatment approaches.[8-10]

Targeted Therapies Based on GAB2 and ALDH1 Expression: Targeting GAB2 Given GAB2's role in oncogenic signalling pathways, therapies targeting GAB2 could potentially inhibit tumour growth and progression. Strategies might include:

1. Inhibition of GAB2-Mediated Signalling: Disrupting GAB2 interactions with downstream effectors like PI3K/AKT could limit tumour cell proliferation and survival.
2. Combination Therapies: Pairing GAB2 inhibitors with other targeted therapies could enhance efficacy in NSCLC treatment.

**TargetingALDH1**

Targeting ALDH1 could help eliminate CSCs, reducing tumour recurrence and therapy resistance:

1. ALDH1 Inhibitors: Developing drugs that inhibit ALDH1 activity could selectively target CSCs, improving treatment outcomes.
2. Stem Cell-Directed Therapies: Strategies to reduce CSC populations, such as using ALDH1 inhibitors in combination with conventional chemotherapy, may enhance treatment efficacy.

**Future Directions:** GAB2 and ALDH1 in NSCLC: Future Directions: Understanding the roles of GAB2 and ALDH1 in NSCLC is crucial for developing targeted therapies. GAB2's involvement in oncogenic signalling pathways and ALDH1's association with CSCs make them promising and helpful targets for intervention. Future studies can focus on elucidating their interactions with other molecular pathways and exploring therapeutic strategies that target these proteins to improve treatment outcomes for NSCLC patients. Recent studies have highlighted the potential of GAB2 and ALDH1 as targets for improving diagnostic accuracy and therapeutic outcomes in NSCLC. Emerging trends include personalized and precision medicines, Targeted cancer stem cells, combination therapies, understanding of tumor heterogeneity, and resistance to treatment.

## Conclusion

In conclusion, the expression of GAB2 and ALDH1 in NSCLC presents opportunities for improving diagnosis, prognosis, and treatment strategies. Future studies should focus on translating these findings into clinical applications to enhance patient care and outcomes in NSCLC.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

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