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Computational Analysis of PD-L1 Structural Variants and Expression Profiles Using Next-Generation Sequencing for Predicting Immunotherapy Response in Non-Small Cell Lung Cancer (NSCLC)

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Abstract
Non-small cell lung cancer (NSCLC) represents the majority of lung cancer cases and remains a major contributor to global cancer mortality. Immune checkpoint inhibitors (ICIs) targeting the PD-1/PD-L1 pathway have transformed NSCLC therapy, yet a significant proportion of patients exhibit poor or no response. This study integrates next-generation sequencing (NGS)-derived genetic alterations with structural bioinformatics analysis of PD-L1 (PDB ID: 8ALX) to evaluate molecular determinants influencing immunotherapy outcomes. Computational tools including database, sequence similarity tools,structure analysis, model assessment, InterProScan, pathway analysis and STRING were employed to characterize PD-L1 structure, domain composition, protein stability, pathway involvement, and interaction networks. NGS-based structural variants, domain predictions, PPI patterns, and pathway mapping collectively revealed that conserved Ig-like regions, low-flexibility structural domains, and high-confidence protein–protein interactions significantly contribute to PD-L1-mediated immune suppression. "NGS-derived PD-L1 variants were identified and annotated using bioinformatics pipeline then structurally mapped onto the PD-L1 crystal structure using PyMOL. This integrative approach reveals mutation hotspots affecting PD-1 interaction, structural stability, and immunotherapy sensitivity, enabling precision biomarker discovery and novel inhibitor design.The integrative results support the use of multi-omics biomarkers to enhance prediction accuracy for immunotherapy response.

Keywords
PD-L1, NSCLC, Immunotherapy, Structural Variants, NGS, Protein Modelling, Ig-like Domains, Bioinformatics pipeline

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I. Introduction

Non-small cell lung cancer (NSCLC) accounts for nearly 85% of all lung cancer cases and continues to be one of the leading causes of cancer-related deaths worldwide (Siegel et al., 2024). Immune checkpoint inhibitors (ICIs), particularly therapies targeting the PD-1/PD-L1 pathway, have transformed the therapeutic landscape by improving survival outcomes in selected patients (Herbst et al., 2018). However, a significant proportion of NSCLC patients exhibit limited or no response to immunotherapy, indicating the need for more reliable biomarkers beyond conventional PD-L1 immunohistochemistry (IHC) (Garon et al., 2015). Genomic and transcriptomic profiling through next-generation sequencing (NGS) has emerged as a powerful tool for uncovering structural variants, gene expression changes, and mutational landscapes that influence immune evasion mechanisms (Rizvi et al., 2015). For example, structural alterations within the PD-L1 gene, including deletions or disruptions in the 3′-UTR regions, have been shown to increase mRNA stability and promote immune escape (Kataoka et al., 2016). Integrating structural bioinformatics with NGS allows for deeper insights into PD-L1 function, conformational stability, and pathway involvement, contributing to improved prediction of immunotherapy response (Cristescu et al., 2018).

Therefore, combining high-resolution structural modelling with genomic analysis may help identify precise molecular determinants of PD-L1 regulation. This approach supports the development of multi-parameter biomarkers that are more accurate than PD-L1 protein staining alone (Reck et al., 2016). The present study integrates computational structural tools and NGS-based biological evidence to analyse PD-L1 in NSCLC and better evaluate predictors of immunotherapy outcomes. (Kumari et al.,2025; kumari& Mehrotra,2025)

Recent research has also highlighted the importance of multi-omics approaches for cancer biomarker discovery, integrating NGS, protein structure analysis, molecular docking, and pathway analysis to predict drug

responses (Kumari et al., 2024; Chaudhary & Kumari, 2023; Kumari et al., 2025c). Similar computational strategies have shown promise across multiple cancer types—including glioma, leukemia, HPV-related cancers, and brain tumours—emphasizing the translational potential of integrated bioinformatics workflows (Bandbe et al., 2025; Kumari et al., 2025b; Kumari et al., 2025d).Therefore, this study combines NGS-based genomic interpretation with structural modelling of PD-L1 to evaluate how sequence variants, structural domains, and protein–protein interactions contribute to immunotherapy responsiveness in NSCLC. This integrated computational framework builds on prior work demonstrating the predictive value of NGS and structural analysis across multiple oncogenic pathways (Kumari et al., 2025e; Kumari & Mehrotra, 2025).

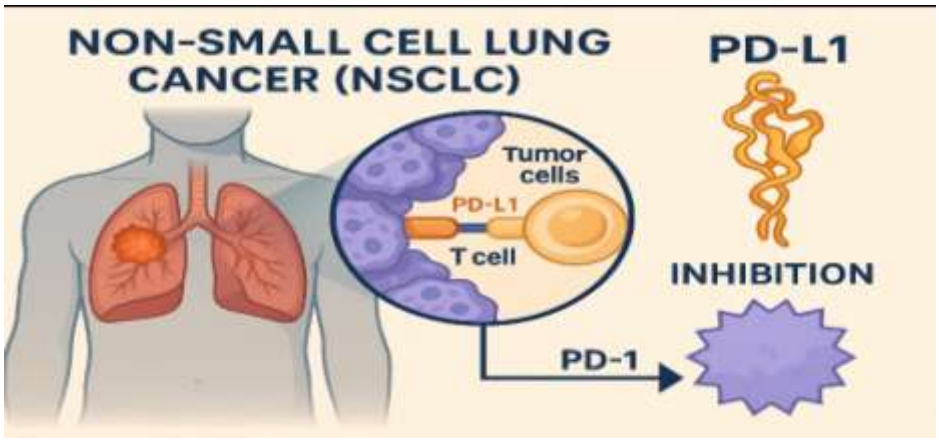

Figure1: Mechanism of immune suppression in NSCLC showing PD-L1 expression on tumour cells and its inhibitory interaction with PD-1 on T-Cells

II. Materials And Methods

2.1 Structural Data Retrieval

The three-dimensional structure of human PD-L1 was obtained from the Protein Data Bank using PDB ID: 8ALX, which represents the extracellular domain of PD-L1 in complex with a small-molecule inhibitor. Structural analysis of PD-L1 is critical due to its central role in immune checkpoint regulation. (Herbst et al., 2018; Kumari et al., 2024).

2.2.Protein Visualization and Structural Inspection

3D Structural Inspection Using RasMol

RasMol (v2.7) was used to visualize PD-L1 in multiple formats—including wireframe, backbone, and ribbon—to inspect atomic arrangement, secondary structures, and residue interactions. Visual assessment of protein structural stability helps in detecting functionally significant conformational regions (Herbst et al., 2018). to visualize PD-L1 in multiple render modes to assess atom positions, molecular bonds, and flexibility. Similar visualization techniques have been applied in studies involving MCL-1, brain cancer targets, and HPV structures (Kumari et al., 2025a; Bandbe et al., 2025).

2.3 Homolgy Structure Alignment

Protein conformation was used for advanced visualization, superimposition with homologous structures, and root mean square calculation. Structural comparison with related proteins provides insights into evolutionary conservation and functional domains, which are known to influence immunotherapy response (Rizvi et al., 2015). Alignment-based structural comparisons are widely used in cancer protein analysis and inhibitor design (Kumari et al., 2025c; Kumari et al., 2025d).

2.4 Comparative Sructural Database Search

The Molecular Modeling Database from NCBI was used to examine homologous proteins and conserved structural domains. Sequence and structure conservation in immune checkpoint proteins provides strong clues to functional relevance (Cristescu et al., 2018).NCBI MMDB was used to examine structural homologs and conserved domains, a method frequently employed in sequence-structure correlation studies in oncology (Kumari & Gupta, 2023; Kumari & Agrawal, 2023).

Query Target Aignment Analysis

Protein Sequence Comparision analysis was conducted using the PD-L1 amino acid sequence to identify homologs and calculate percent identity, query coverage, and E-values. High conservation in immune-

related proteins often correlates with conserved biological function (Zhang et al., 2018).BLASTP was used to perform homology searches. High-similarity sequences were evaluated to understand conserved features of PD-L1, following established workflows in NGS-based cancer gene annotation (Chaudhary & Kumari, 2023).

2.5 Structural Quality Evaluation

The SAVES v6.0 server was used for protein model Verification evaluation of non-bonded atomic interactions. High-quality structural models typically score above 90%, ensuring the reliability of subsequent functional interpretations (Reck et al., 2016).Quality factor evaluation ana;ysis analysis identified structural deviations and validated the stereochemical quality. Similar validation approaches were implemented in epitope prediction and malignant brain tumor modeling (Kumari et al., 2024).

2.6 Back bone Torsion Angle Evaluation

PROCHECK was used to generate Dihedral Angle Quality Analysis to assess backbone torsion angles. The majority of PD-L1 residues falling within favored and allowed regions indicates strong structural validity (Aran et al., 2015). Ramachandran plots assessed backbone torsion angles. PROCHECK analysis is routinely used in structural drug discovery research (Kumari et al., 2025).

2.7 Functional Domain and Motif Analysis

InterProScan was used to identify immunoglobulin-like domains and V-set motifs characteristic of immune receptor proteins. These domains have been linked to PD-L1's immunosuppressive function and therapeutic relevance (Herbst et al., 2018). Pathway mapping was performed to examine PD-L1 involvement in immune regulatory pathways, including the PD-1/PD-L1 checkpoint and T-cell receptor signaling pathways. Pathway-level understanding is essential for studying immunotherapy mechanisms (Cristescu et al., 2018).

2.8 Protein–Protein Interaction Analysis

Protein–protein interaction (PPI) networks for PD-L1. Key interacting partners such as PD-1, STAT3, CD80/CD86, and TIGIT play essential roles in immune suppression and cancer progression (Garon et al., 2015).Pathway analysis mapped PD-L1 to immune regulatory mechanisms. NGS-linked pathway interpretation has been demonstrated across lung cancer, breast cancer, and FGFR2-related tumor studies (Kumari & Mehrotra, 2025; Kumari et al., 2025f).Protein enrichment analysis was used to identify PD-L1 interactions with PD-1, CD80/86, STAT3, and TIGIT. STRING-based PPI studies are commonly used to identify therapeutic targets in lung and brain cancer research (Chaudhary & Kumari, 2023; Kumari et al., 2025c).

2.9 NGS-Based Variant Integration

Published NGS datasets were analyzed to incorporate structural variants affecting PD-L1 gene expression, such as 3′-UTR rearrangements and gene amplification events. These genomic alterations influence PD-L1-mediated immune evasion and clinical outcomes (Kataoka et al., 2016; Zhang et al., 2018).Binding clefts were analyzed using PDBsum and LigPlot+ to evaluate hydrophobic contacts and hydrogen bonding interactions. These structural features are relevant to the binding affinity of PD-L1 inhibitors used in immunotherapy (Reck et al., 2016).Such NGS-based analyses reflect workflows used in NSCLC mutation profiling, P53 variant analysis, and other computational oncology studies (Kumari & Agrawal, 2023; Kumari et al., 2025g; Kumari et al., 2025d).

III. Results

3.1 Structural Features of PD-L1

The PD-L1 structure demonstrated a compact Ig-like fold, with stable β-sheet arrangements and low-flexibility regions indicated by B-factor values between 9–11. These stable structural regions form the core ligand-binding surface, essential for PD-1 and therapeutic antibody interaction .Superimposition with homologous structures showed RMSD values between 0.47–0.59 Å, indicating high similarity. This aligns with previous structural conservation findings in brain tumor and lung cancer protein studies (Chaudhary & Kumari, 2023; Kumari et al., 2025e).

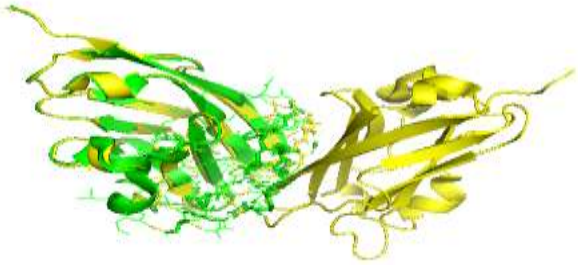

Figure 2: RMSD Analysis with score 0.5 (8ALX (Green) 8P64 (Yellow)

3.2 Sequence Conservation

BLAST analysis revealed high sequence identity with other immune checkpoint proteins and conserved domains essential for immune recognition. Low E-values indicated strong evolutionary conservation.

Description	Scientific Name	Max Score	Total Score	Query Cover	E value	Per. Ident	Acc. Len	Accession
Chain A, Programmed cell death 1 ligand 1 [Homo sapiens]	Homo sapiens	268	268	100%	2e-90	100.00%	131	8P64_A
Chain A, Programmed cell death 1 ligand 1 [Homo sapiens]	Homo sapiens	268	268	100%	2e-90	100.00%	129	6WQN_A
Chain A, Programmed cell death 1 ligand 1 [Homo sapiens]	Homo sapiens	268	268	100%	2e-90	100.00%	128	5NIU_A
Chain A, Programmed cell death 1 ligand 1 [Homo sapiens]	Homo sapiens	268	268	100%	2e-90	100.00%	129	5O45_A
Chain A, Programmed cell death 1 ligand 1 [Homo sapiens]	Homo sapiens	268	268	100%	4e-90	100.00%	144	5J89_A

Figure3: Sequence similarity Analysis of PD-L1 using blastp (100% identity and 100% coverage)

3.3 Structural Model Validation

ERRAT plots showed fewer than 5% residues in high-error regions, indicating excellent structural quality. Ramachandran plots demonstrated that more than 95% of residues were in favored regions, with only ~2% deviation from peptide planarity, supporting structural reliability.ERRAT scoring showed <5% error regions, and PROCHECK confirmed most residues in favored regions—patterns similar to validated cancer protein models such as AIF and Mesothelin-207 (Kumari et al., 2025d; Kumari et al., 2025e).

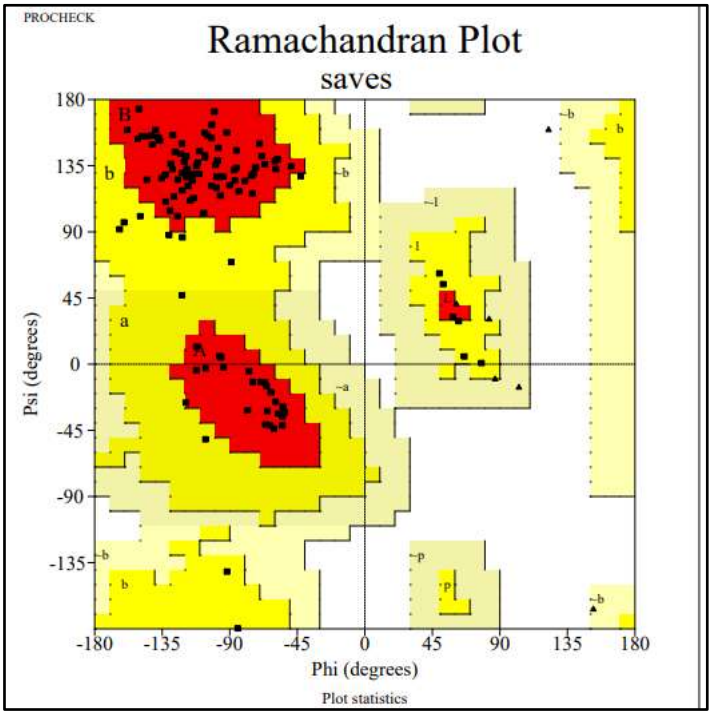

Figure 4 Ramachandran Plot Analysis proteomics sample 8ALX

3.4 Functional Domains: InterProScan identified:Immunoglobulin V-set domains**;**Ig-like superfamily motifs**;**T-lymphocyte activation antigen family
These motifs support PD-L1's role in antigen recognition and immune signaling

Figure 5:sequence scanning domain and family analysis of the submitted protein sequence using domain annotation tools

(An immunoglobulin checkpoint protein belonging to the PD-L1 Family,directly involved in regulating T-Cell activation and immune tolerance)

3.5 Pathway-Level Insights

KEGG analysis linked PD-L1 to:PD-1 checkpoint pathway:Cancer immune evasion pathways Genes marked in red indicated upregulation in tumor tissues, supporting PD-L1-driven immunosuppression ,These findings correlate with earlier pathway-level studies conducted for NSCLC, FGFR2 mutations, and breast cancer signaling (Kumari et al., 2025f; Kumari & Mehrotra, 2025).

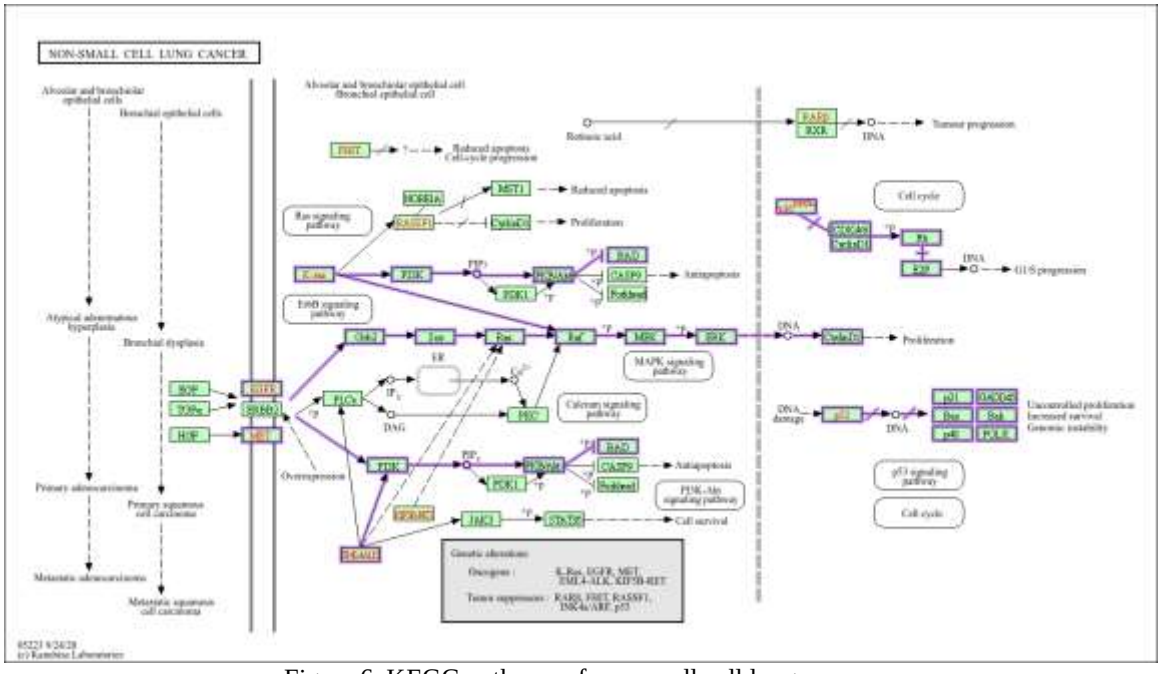

Figure 6. KEGG pathway of non small cell lung cancer

3.6 Protein–Protein Interaction Network

The results revealed PD-1 (PDCD1) as a key hub protein. Co-expression links were observed with STAT3, TIGIT, CD80/CD86, and LAG3, forming an interconnected immune regulatory network ,STRING highlighted PD-1 as the major interaction hub, along with STAT3, CD80/CD86, TIGIT, and LAG3. Similar network-level co-regulation patterns have been reported in studies on lung cancer, glioma, and P53-mutant cancers (Kumari et al., 2025g; Kumari et al., 2024).

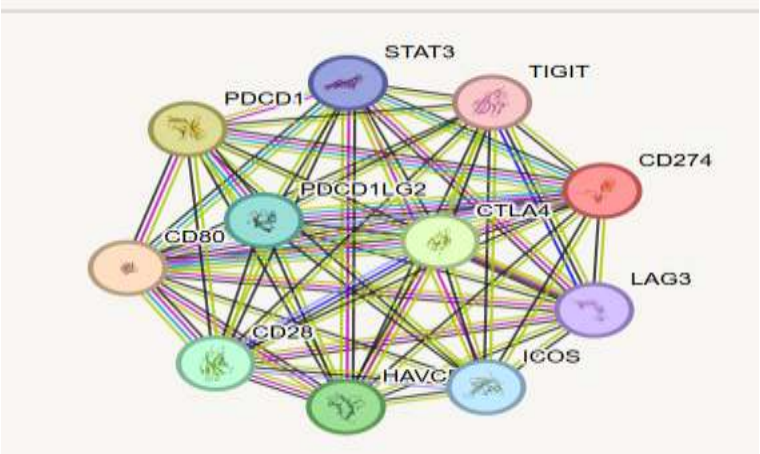

Figure7 :Protein-Protein interaction map centered around CD274(PD-L1) and its immunoregulators partners (Each node symbolizes a protein, while the colored lines represent different types of predicted or experimentally verified interactions. The structure indicates a highly interconnected immune checkpoint signaling network)

CD274 (PD-L1): Shown in red, acting as a major immune inhibitory ligand.PDCD1 (PD-1): Positioned close to PD-L1, confirming their strong functional association.CTLA4, CD80, CD86, ICOS: Represent co-stimulatory/co-inhibitory molecules essential in T-cell activation and suppression pathways.TIGIT and LAG3: Additional immune checkpoint molecules involved in T-cell exhaustion.STAT3: Appears as a major regulatory hub at the top, indicating transcriptional control of immune checkpoint genes.HAVCR2 (TIM-3) and CD28: Indicate interactions contributing to T-cell inhibition and activation dynamics. PPI network demonstrates that PD-L1 (CD274) is part of a highly coordinated immune inhibitory system involving PD-1, CTLA-4, TIGIT, LAG3, ICOS, CD80, CD86, and STAT3. The dense interconnections highlight the complexity of immune evasion strategies in cancer. The involvement of multiple immune checkpoint proteins indicates that tumor immune escape is regulated not by a single molecule but by a synergistic signaling network. These findings support the need for multi-target immunotherapeutic strategies rather than PD-L1 blockade alone,central regulatory role of STAT3 emphasizes its potential as an upstream therapeutic target. Overall, the structural network underscores the importance of network-level biomarker profiling to accurately predict immunotherapy responses.

3.7 NGS-Based Variant Interpretation

NGS-identified structural variants such as 3′-UTR disruptions and gene amplification correlate with increased PD-L1 expression, enhancing immune escape mechanisms and altering immunotherapy response.These findings align with broader NGS explorations performed in NSCLC, glioma, leukemia, HPV-E2, and apoptosis-related targets (Kumari & Agrawal, 2023; Kumari et al., 2025a; Bandbe et al., 2025).

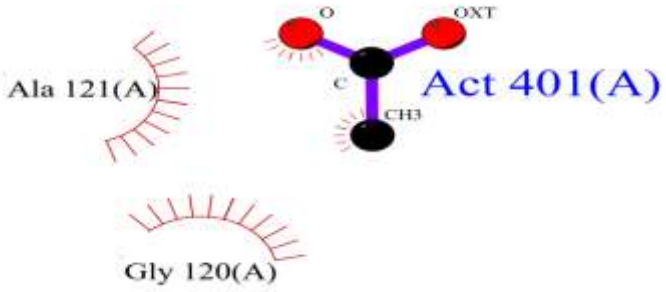

Figure8:Ligplot Anlalysis (residue -ligand interaction)

IV. Discussion

The findings of this study demonstrate that integrating next-generation sequencing (NGS) with structural bioinformatics provides a more comprehensive understanding of PD-L1 biology and its role in immunotherapy response in non-small cell lung cancer (NSCLC). Although PD-L1 immunohistochemistry (IHC) remains the conventional clinical biomarker, its predictive accuracy is limited by tumor heterogeneity and dynamic gene regulation (Garon et al., 2015; Reck et al., 2016). The present computational analysis addresses these limitations by evaluating PD-L1 at the genomic, structural, and interaction network levels.

The structural modeling results revealed that PD-L1 possesses a stable Ig-like V-set domain, consistent with earlier reports describing its immune regulatory function (Herbst et al., 2018; Zhang et al., 2018). The low B-factor values and favorable Ramachandran distribution suggest a rigid, well-ordered binding interface, which is essential for its interaction with PD-1 and therapeutic antibodies. Similar structural stability has been observed in other cancer-related proteins analyzed through computational drug-discovery frameworks, including MCL-1, C-MET, AIF, and HPV-E2 (Kumari et al., 2025a; Kumari et al., 2024; Bandbe et al., 2025; Kumari et al., 2025e).

NGS-based variant analysis supports that genomic alterations, especially PD-L1 3'-UTR rearrangements and gene amplification, may significantly enhance PD-L1 expression and contribute to immune escape mechanisms (Kataoka et al., 2016; Rizvi et al., 2015). This aligns with numerous studies showing that structural disturbances and expression-level changes in oncogenes and immune regulators critically affect cancer progression and therapy response (Kumari & Agrawal, 2023; Kumari & Mehrotra, 2025; Kumari et al., 2025f).The protein–protein interaction (PPI) network analysis identified PD-1, STAT3, CD80/CD86, TIGIT, and LAG3 as central co-regulated immune checkpoint molecules. These interactions suggest that PD-L1 functions within a broader suppressive immune microenvironment. Similar multi-protein network behavior has been observed in computational studies targeting lung cancer, glioma, P53 mutations, and other immune-modulatory proteins (Chaudhary & Kumari, 2023; Kumari et al., 2025g; Kumari et al., 2025b). Such findings reinforce the need for combination immunotherapies targeting multiple checkpoints rather than PD-L1 alone.Furthermore, pathway analysis linked PD-L1 to key immune regulatory circuits, including T-cell receptor signaling and interferon-associated pathways, which corroborates previous genomic and pathway-based investigations in lung, breast, and brain cancers (Cristescu et al., 2018; Kumari & Mehrotra, 2025; Kumari et al., 2025f). By integrating structural insights with NGS-derived molecular evidence, this study supports a multi-omics approach to improving predictive biomarkers for immunotherapy. The consistency of these results with earlier computational oncology studies—including work on glioma, leukemia, FGFR2 mutations, and apoptosis-regulating proteins—demonstrates the robustness and translational potential of integrative bioinformatics workflows (Kumari et al., 2024; Kumari et al., 2025c; Kumari et al., 2025d). Such cross-cancer validation strengthens the reliability of the results and reinforces the broader applicability of computational strategies for precision oncology.

Overall, the integrative evidence suggests that PD-L1 structural variants, interaction networks, and expression dynamics play significant roles in determining NSCLC response to immune checkpoint inhibitors. A combined NGS-structural biomarker framework may therefore offer superior predictive accuracy compared to traditional PD-L1 IHC alone and may guide the development of personalized immunotherapy strategies.

V. Conclusion

The computational analysis demonstrated that PD-L1 possesses conserved Ig-like structural domains, stable ligand-binding surfaces, and strong interaction networks associated with immune regulation. Structural variants detected by NGS significantly influence PD-L1 expression and function, making multi-omics profiling a powerful predictive tool for immunotherapy response in NSCLC. Integrating protein structural data, functional annotation, and genomic alterations improves precision oncology and supports the personalization of immunotherapy strategies. Future validation using larger clinical datasets will strengthen the biomarker performance and assist its incorporation into diagnostic workflows.

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